Oxytocin and vasopressin V1A receptors as new therapeutic targets in assisted reproduction

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Introduction

- IVF/ET: averaging at about 30% live births per treatment cycle
- Embryo transfer is an independent factor affecting the outcome of the treatment
- The determinants of success of embryo transfer involve the *quality of embryo(s) and uterine receptivity, the quality of the intrauterine environment*

- Uterine contractions constitute one of and the most fundamental components of uterine receptivity → important role in embryo implantation
- Excessive uterine contractions → might expel embryos from the uterus
- Up to date, treatment strategies to reduce uterine contractions before embryo transfer such as the use of beta agonists or non-steroid anti-inflammatory drugs have not been shown to provide sufficient benefit

- Oxytocin and vasopressin V1A antagonists represent a novel class of drugs developed for patients experiencing threatened premature birth.
- decrease intrauterine production of PGF2a → reduction of uterine contractions and improvement of uterine blood supply → potentially beneficial for embryo implantation.
- This paper presents a review of what is known about the application of oxytocin/vasopressin V1A antagonists for implantation support in assisted reproduction

Oxytocin, vasopressin and their receptors

- Oxytocin receptors (OTR) have been found in ovary, testis, blood vessels, heart myocytes, pancreas and kidney as well as on several types of cancer cells
- Oxytocin : important mediator in the central nervous system, with significant roles in maternal, sexual and social behavior
- Vasopressin : V1A subtype receptor is found in the uterus, being responsible for contractile responses.
- V1A receptors are also found in vascular smooth muscle cells, platelets and hepatocytes where they mediate contraction, proliferation, hypertrophy of cells and platelet aggregation

- Oxytocin and V1A vasopressin receptors share similar structures as they both belong to the class I family of G-coupled receptors
- Binding stimulates phospholipase C activity → releases triphosphoinositol and diacyloglycerol, inducing mobilization of intracellular calcium.
- Calcium triggers phosphorylation of light myosin chains, which in turn promotes contractile activity
- In myometrial cells, activation of OTR → phosphorylation and activation of mitogen-activated protein kinase → increase in cyclooxygenase-2 production → enhances uterine contractions.

- Oxytocin evokes the calcium influx through receptor-coupled calcium channels.
- Braileanu et al. (2001) : vasopressin acting through V1A receptors also increases phospholipase C activity
- In the uterus, oxytocin remains closely associated with another strong uterotonin, PGF2a
- In endometrial stromal and glandular cells, oxytocin enhances the secretion of PGF2a and the expression of PGF2a receptor

- Oxytocin is locally synthesized in the endometrium and in fetal membranes where it stimulates uterine contractions → through action on its own receptors and by increasing PGF2a synthesis
- In the animal model, the administration of oxytocin stimulates uterine PGF2a expression → reduction in endometrial blood supply → reduced embryonic survival rate
- Synthesis of oxytocin is strongly influenced by oestradiol
- Oxytocin and vasopressin plasma concentrations increase during the follicular phase, reaching the maximum around the time of ovulation while they decrease during the luteal phase

- Oxytocin mRNA in the endometrium follows a similar pattern and also reaches its maximum in the mid-cycle phase
- A relative increase in oestradiol concentrations stimulates the synthesis of oxytocin receptors in the myometrium before labour
- Kimura et al. (1996): a 300-fold increase in the production of OTR mRNA in pregnant myometrium near term.
- Expression of vasopressin V1A receptors and concentrations of vasopressin do not seem to be affected by steroids and are not altered in pregnancy

- Both oxytocin and vasopressin are involved in induction and maintenance of uterine contractions during labour
- Similarities between oxytocin, vasopressin and their receptors may explain cross reactivity of oxytocin to V1A receptors.
- It has been shown that oxytocin may still exert its actions even when OTR are blocked, through action upon the V1A receptors

- Treatment cycles induce an abundant increase in oestradiol concentrations (about 10–20 nmol/l) at the end of ovarian stimulation as compared with less then 2 nmol/l before the ovulation in the natural cycle
- Supraphysiological concentrations of oestradiol → induce local (endometrial) production of oxytocin → formation of oxytocin receptors, and – indirectly – formation/ release of PGF2a → similar to the prelabour status.
- It has been shown that uterine contractile activity in IVF cycles is increased by approximately 6-fold when measured before embryo transfer as compared with the situation before ovulation in the natural cycle

Uterine contractions in treatment cycles

- Uterine contractions play an important role in human reproduction → rapid and directed sperm transport and high fundal embryo implantation
- In IVF/ET treatments, a progressive decrease in uterine contractions is observed after the egg collection, reaching nearly a quiescent status at the time of blastocyst transfer (5–6 days after egg collection)
- Such a decrease in contractile activity is thought to further augment the higher implantation rates achieved with blastocyst transfers
- However, the majority of embryos are still transferred on day 2 or 3 after fertilization, during periods of noticeable uterine contractile activity.

- The embryo transfer procedure itself is expected to increase the local oxytocin and prostaglandins release
- Any additional manipulation of the vagina or cervix, such as the use of a tenaculum, provides an additional stimulus for oxytocin/prostaglandin release → increases in uterine contractions
- Mansour et al. : in more than half of patients having mock embryo transfer with methylene blue dye, the dye was seen to be transported into the vagina after the procedure
- It was also demonstrated that less then 50% of transferred embryos remained in the uterus 1 h after transfer and about 15% of embryos could be found in the vagina after embryo transfer

- Considering the above: uterine contractile activity at the time of embryo transfer and especially fundo-cervical contractions → expel embryos from the uterus
- Fanchin et al. (1998): about 30% of patients undergoing ET have pronounced uterine contractions.
- In that group, success rates of IVF/ET treatment were up to 3-fold less compared with the population of patients with 'silent' uteri (16% versus 53% of clinical pregnancies).
- That could imply that pharmacological inhibition of increased contractions at the time of embryo transfer could be an attractive target for potential treatment

Oxytocin and vasopressin V1A receptors as a novel target in fertility treatments

- Inhibition of oxytocin and vasopressin V1A receptors → improve uterine receptivity by decreasing uterine contractions, interfering with PGF2a/oxytocin systems and possibly improving endometrial perfusion
- Selective blockade of oxytocin receptors directly halts contractions and decreases PGF2a release in human uterine smooth muscle cells
- Blocking both vasopressin V1A receptors and OTR may be an optimal approach as oxytocin exerts a relatively strong effect on V1A receptors

- Currently, only atosiban, which is a combined oxytocin/ vasopressin V1A antagonist, is registered for human use
- Only two other antagonists, the peptidyl, long-acting selective oxytocin antagonist barusiban (FE200440) and the non-peptidyl, orally active, mainly V1A vasopressin antagonist relcovaptan (SR49059) have reached the level of clinical trials.
- Other drugs or drug candidates of that group are either not progressing in clinical research or at far earlier stages of development.

Atosiban and barusiban

- Atosiban: for threatened premature birth
- Although it is commonly said to be an ‘oxytocin antagonist’, its affinity to vasopressin V1A receptors is higher than to oxytocin receptors (4.7 nmol/l versus 397 nmol/l, respectively)
- Barusiban is a new-generation, peptidyl, OTR-specific antagonist.
- 300-fold more selective for the human oxytocin receptors than the vasopressin V1A receptors
- Its plasma half-life varies between 2.2 and 2.8 h

- In preclinical studies: potency, longer duration of action and reversibility as compared with atosiban
- In monkeys, it was effective in maintaining low intrauterine pressure near the end of pregnancy, suppressing oxytocin induced premature contractions and preventing early delivery
- However, in a second-phase clinical trial of women experiencing premature labour, it was not shown to be of satisfactory clinical effectiveness
- In mice, barusiban was confirmed to support embryo implantation (Figure 1).

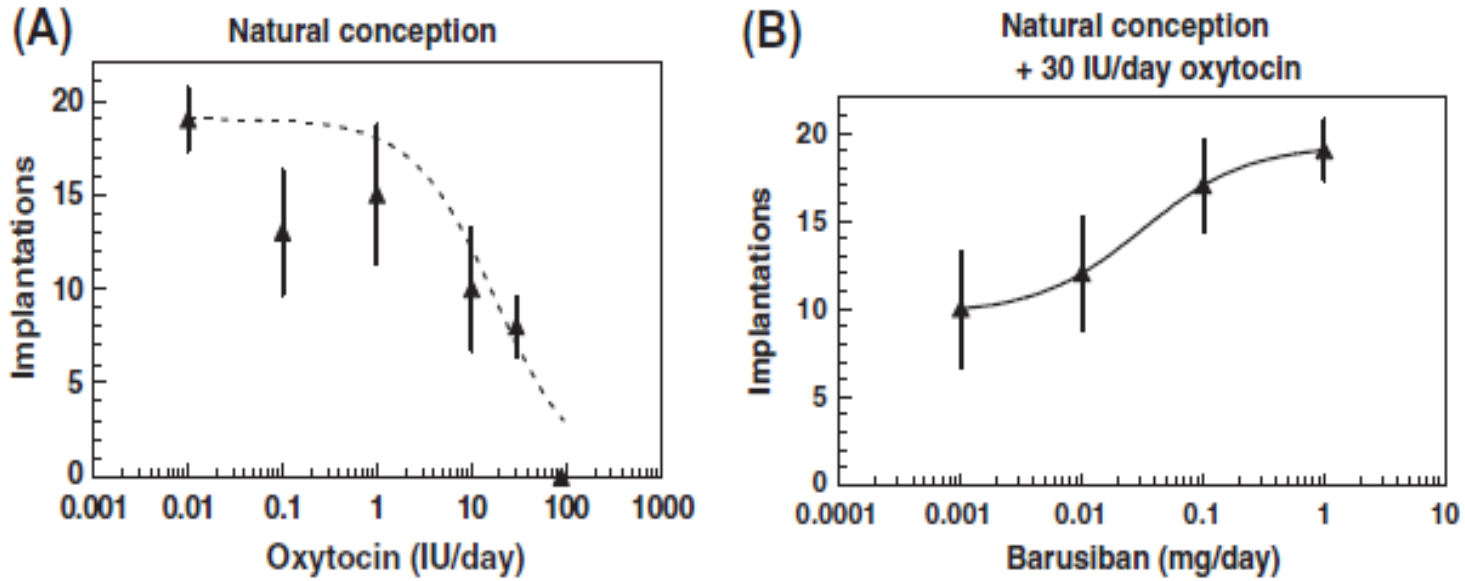

Figure 1 Influence of oxytocin and the selective oxytocin antagonist barusiban on implantation rate in mice. (**A**) Implantations were dose-dependently inhibited by oxytocin. (**B**) Embryo implantations were dose-dependently restored by barusiban.

- The original concept of the novel application of atosiban in embryo transfer recipients was first developed in 2004.
- before considering the clinical application it was decided to verify its embryotoxic potential.
- The preclinical study involved the application of two embryotoxicity techniques : Both failed to detect an embryotoxic effect of atosiban in concentrations up to 50-fold therapeutic blood concentrations.
- Tests performed on human spermatozoa also failed to show an adverse influence.

- The very first case of clinical application of atosiban prior to embryo transfer was published in 2007
- a 42-year-old patient who had previously undergone 8 embryo transfers involving a total number of 12 good-quality embryos.
- Atosiban was administered in intravenous infusion lasting 3 h as per license conditions
- As its plasma steady state is reached within the first hour of infusion → embryo transfer was carried out 60 min from the start of the drug administration.
- uterine contractions decreased from 11 contractions per 4 min to 7 contractions per 4 min and decrease in their amplitude (Figure 2).
- Therapeutic success (healthy twins delivered 8 months later) encouraged further investigations.

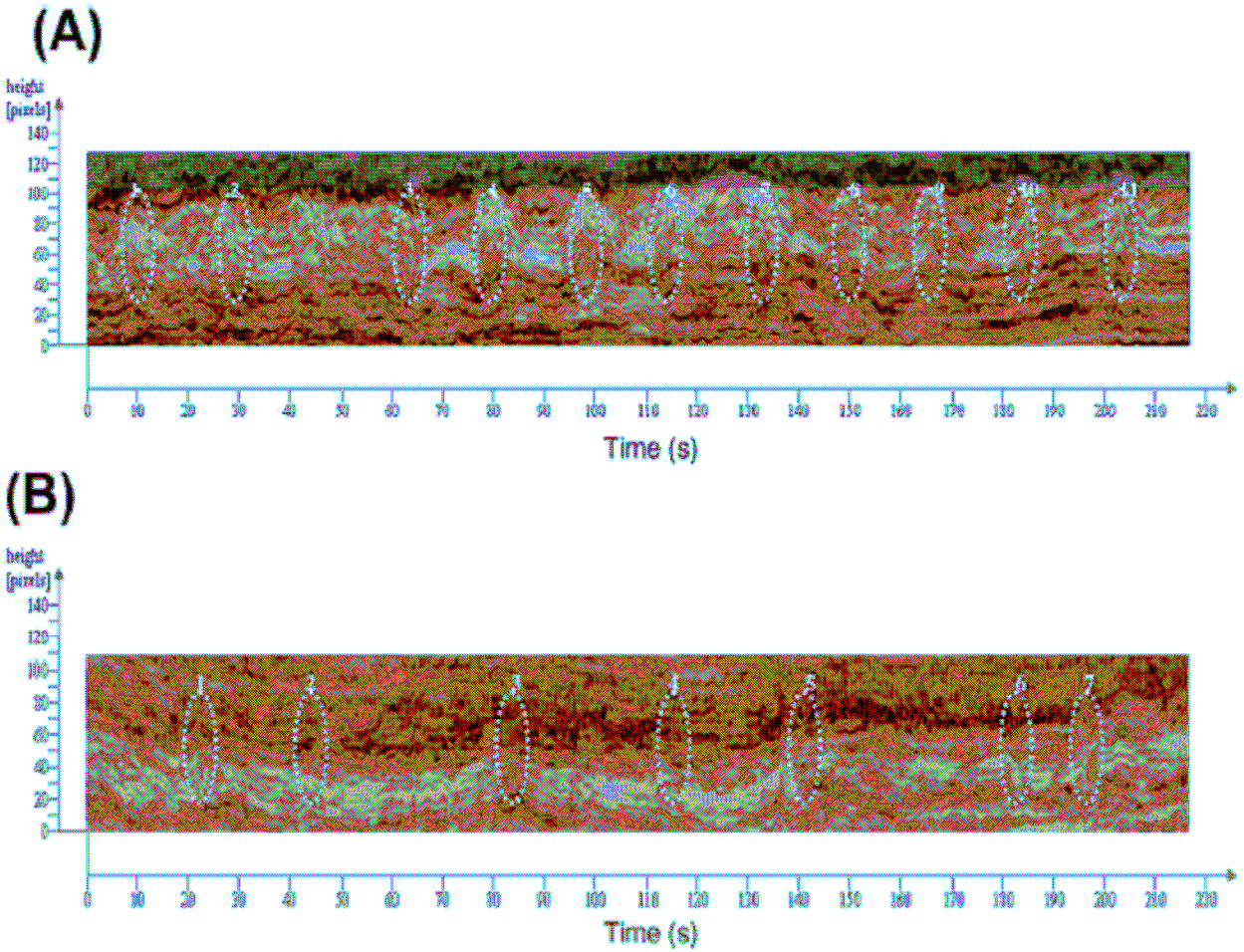

Figure 2 Effect of atosiban on uterine contraction waves in an embryo transfer recipient. (A) Four-minute recording of uterine contractions before the connection of atosiban infusion. (B) Recording of uterine contractions after 1 h of infusion. Dotted circles mark uterine contractions.

- To verify its influence on uterine contractions, a multicentre, randomized, placebo-controlled trial has recently been performed on egg donors
- After ovarian stimulation and egg collection, the participants started luteal support (micronized progesterone) and had a mock embryo transfer (introduction of an empty embryo transfer catheter into the uterus, mimicking regular embryo transfer).
- The study compared the uterine contractions between patients receiving placebo and those receiving infusions of atosiban or barusiban.
- Both antagonists caused reductions in frequency and amplitude of uterine contractions
- Neither barusiban nor atosiban changed the endocrine profile at time of implantation

- Moraloglu et al. (2010) reported a randomized, placebo controlled trial: 37.5 mg i.v. of atosiban infused before and up to 2 h after the embryo transfer in 160 patients → significant improvement in both implantation rates and clinical pregnancies.
- Implantation rates per embryo transferred were 20.4% versus 12.6% and clinical pregnancy rates per cycle were 46.7% versus 28.9%
- Fewer early miscarriages (16.7% versus 24.4%)
- However, the authors did not evaluate uterine contractions.
- Large randomized, placebo controlled trial testing the effect of atosiban on uterine contractions and pregnancy and birth rates would provide a more definite answer to the value of this drug for this indication.

Relcovaptan

- Relcovaptan (SR49059) is a non-peptide, orally active vasopressin V1A/oxytocin antagonist
- Administered orally → used in patients with dysmenorrhoea or for prophylactic/ maintenance treatment of pre-term labour sufferers.
- Relcovaptan was shown to decrease myometrial contractions in vitro (Akerlund et al., 1999) as well as in vivo (Steinwall et al., 2004a).
- In a clinical study on pre-term labour patients, it significantly decreased uterine contractions as compared with placebo (Steinwall et al., 2005).
- Being predominantly a vasopressin V1A antagonist, relcovaptan has recently been tested in animal models of congestive heart failure

Other oxytocin antagonists

- there are cheaper (although less safe) and equally effective alternatives to oxytocin/vasopressin V1A antagonists such as nifedipine or beta agonists
- Currently, some initial reports on potential drug candidates list SSR126768A (Serradeil-Le Gal et al., 2004), GSK221149A (Liddle et al., 2008) and (2S,4Z)-N-[(2S)-2-hydroxy-2-phenylethyl]-4-(methoxyimino)-1-[(2-methyl[1,10-biphenyl]-4-yl)carbonyl]-2-pyrrolidinecarboxamide (Cirillo et al., 2003).
- However, their therapeutic applicability still needs to be determined.

Future prospects

- Initial trials indicated that oxytocin and oxytocin/vasopressin V1A antagonists may be clinically useful in supporting implantation following embryo transfer
- Clinical use of these compounds should be acceptable for IVF/ET patients, even when the drugs need to be administered intravenously.
- Introduction of oral (non-peptide) drugs from this group could enable testing on the longer-term effect of halting the uterine contractions on embryo implantation

- It is however controversial whether such a treatment should be used after the embryo implantation (occurring 1–3 days after the embryo transfer).
- The shorter plasma half-life of peptide antagonists such as atosiban as well as the limited duration of treatment should avoid embryonic exposure and therefore might be preferred.
- Further trials are needed to establish the clinical value of this class of medications in this novel indication.

- Maximal effect of oxytocin antagonists given at the embryo transfer is observed within the first 3 h after embryo transfer
- the average cost of atosiban treatment per patient would reach about 150 Euro, which should not vastly affect overall costs of IVF treatment (averaging at 3000–4000 Euro per treatment cycle).
- The safety profile of atosiban has been extensively studied prior to its licensing for pre-term labour
- Considering the shortness of treatment (3 h versus 2 days in the obstetric indication), the probability of significant side effects of atosiban would be largely reduced.

- For registration of any medication supporting embryo transfer, more preclinical (full embryo toxicity data) and clinical (efficacy) studies would be necessary.
- Only a randomized, placebo-controlled trial, comparing pregnancy outcome in patients treated with oxytocin or oxytocin/vasopressin V1A antagonists could provide a definitive answer on the value of this application.
- With more favourable data appearing on this indication, the academic community and research-oriented fertility centres could become a significant driving force in promoting further trials.

Thanks for your attention!