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REVIEW

The effect of peri-implantation administration of uterine relaxing agents in assisted reproduction treatment cycles: a systematic review and meta-analysis

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Abstract Sub-endometrial junctional zone peristalsis is increased by ovarian stimulation and traumatic embryo transfer, and is linked with decreased implantation and pregnancy rates in assisted reproduction treatments. Various agents have been used to inhibit uterine hyper-peristalsis at the time of embryo transfer with conflicting results. This systematic review aimed to identify if uterine relaxants administered in the peri-implantation period during assisted reproduction treatments could improve pregnancy outcomes through literature search with no language restrictions. The review reports on 3546 patients in 17 randomized controlled trials published between 1993 and 2014. Women undergoing assisted reproduction techniques who either received a uterine relaxant agent in the peri-implantation period versus placebo or no treatment were included. Primary outcome was live birth rate. The meta-analyses did not show statistically significant benefit of any uterine relaxing agents on live birth rate. Other meta-analyses did not show a significant effect on the clinical pregnancy, spontaneous abortion, ectopic pregnancy and multiple pregnancy rate. Most of the included studies were of low quality and lacked significant power to detect minimally important effect. Evidence is insufficient to recommend using these agents in routine practice. Further methodologically robust randomized controlled trials with more refined selection criteria might reveal a beneficial effect.

KEYWORDS: assisted reproduction, embryo transfer, oxytocin antagonists, prostaglandin synthetase inhibitors, uterine contractions

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Introduction

Successful embryo implantation in assisted reproduction technique cycles depends on embryo quality, endometrial receptivity and a non-traumatic embryo transfer. Difficult and traumatic embryo transfer has been strongly linked to lower pregnancy rates (Kovacs, 1999; Schoolcraft et al., 2001). It has been shown that difficult embryo transfer stimulates uterine junctional zone contractions (Lesny et al., 1998). This has been postulated to lead to non-adherence of the embryo(s) to the endometrium, expulsion of the embryos from the uterine cavity shortly after embryo transfer (Lesny and Killick, 2004; Lesny et al., 1998; Mansour et al., 1990), or both. Furthermore, it has also been shown in normal fertile women that sub-endometrial peristalsis of the junctional zone myometrium progressively increases during menstrual cycle reaching a peak at time of ovulation with the pattern changing from predominantly ante-grade (fundo-cervical) in the menstrual and proliferative phase to retrograde (cervico-fundal) or opposing contractions in the early luteal phase (Lyons et al., 1991; van Gestel et al., 2003). The frequency of sub-endometrial peristalsis has been shown to be higher in ovarian stimulation cycles compared with natural cycles but generally follows the same pattern as in natural cycles (Lesny et al., 1998; Zhu et al., 2012). Fanchin et al., showed that the pregnancy and implantation rates correlate negatively with the frequency of these contractions. Clinical, ongoing pregnancy and implantation rates decrease significantly in a stepwise manner with increasing frequency of uterine contractions at time of embryo transfer (Fanchin et al., 1998). The same findings has been reported in a small study in natural cycles (IJland et al., 1997). These findings from previous studies suggest that women with a background increase in the sub-endometrial peristalsis may have further increase in the frequency of contractions if embryo transfer is traumatic, decreasing the implantation potential. To decrease this detrimental impact of sub-endometrial hyper-peristalsis it is imperative to exercise utmost care by performing gentle atraumatic embryo transfer aiming to minimize trauma to the endometrium and avoid touching the uterine fundus.

The practitioner's ability to perform atraumatic embryo transfer and other patient-related factors such as endometriosis (Bulletti et al., 2002) or the presence of fibroids (Yoshino et al., 2010) may also affect uterine contractions. It has, therefore, been suggested that using pharmacological agents that inhibit uterine contractions around the time of embryo transfer may lead to an improvement in implantation and pregnancy rates. The potential candidate agents to exert this effect include: oxytocin receptor antagonists (ORA); these drugs act by antagonising naturally circulating and locally synthesized oxytocin as well as vasopressin at their receptors in the myometrium promoting uterine relaxation (Pierzynski, 2011); prostaglandin synthetase (cyclooxygenase) inhibitors (PGSI); these drugs act by reducing levels of various prostaglandins such as PGF2 alpha, PGE2 and thromboxane A2, which are implicated in the induction of myometrial contractions in non-pregnant and pregnant uteri (Hagenfeldt, 1987; Marjoribanks et al., 2010; Olson et al., 2003); nitric oxide donors; these drugs are potent smooth muscle relaxants which act by increasing levels of nitric oxide and nitrites in the myometrium. This helps with vasodilatation and may help by inducing relaxation of the smooth muscles of the myometrium as shown in pregnancy (Bisits et al., 2004; Lees et al., 1999); beta-adrenergic receptor agonists; these drugs act by stimulating beta-adrenergic receptors in the myometrium, promoting the relaxation of the smooth muscle in cases of preterm labour (Leveno et al., 1986) and in the non-pregnant uterus (Fedorowicz et al., 2012); anti-cholinergic agents; these drugs act by antagonising the effect of acetylcholine at the muscarinic receptor promoting relaxation of the myometrial smooth muscles (Kido et al., 2009; Nakai et al., 2008); and calcium channel blockers; these drugs inhibit the influx of calcium ions through the cell membranes of smooth muscle, inhibiting contractions. They have been used for tocolysis (Flenady et al., 2014) and treatment of dysmenorrhoea (Childress and Katz, 1994).

Many randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of these drugs when administered in the peri-implantation period of assisted reproduction technique cycles (Bernabeu et al., 2006; Dal Prato and Borini, 2009; Farzi et al., 2005; Firouzabadi et al., 2007; Hanevik et al., 2012; Moraloglu et al., 2010; Ng et al., 2014; Ohl et al., 2002; Pinheiro et al., 2003; Shaker et al., 1993; Tsirigotis et al., 2000; Zargar et al., 2013). The results of these trials, however, have been conflicting. Consequently, their use in routine clinical practice within assisted reproduction treatment is not recommended. The aim of our study was to conduct a systematic review to identify all relevant RCTs and summarize the effect of these drugs on live birth and clinical pregnancy rates after assisted reproduction technique cycles as well as the safety of these medications.

Materials and methods

The population of interest for our review were women undergoing assisted reproduction treatment cycles. The intervention of interest was administration of uterine relaxant drugs during the peri-implantation period of the assisted reproduction technique cycle. The peri-implantation period was defined as the period spanning from the day of oocyte retrieval until 3 days after embryo transfer in assisted reproduction technique cycles in humans, as this is the period when early events of the implantation process take place. The comparator intervention was placebo, no treatment or an alternative type of uterine relaxant drug. The primary outcome of interest was live birth rate. Secondary outcomes were clinical pregnancy rate, biochemical pregnancy rates, spontaneous abortion rates (including both biochemical pregnancy losses and clinical spontaneous abortions), ectopic pregnancy rates and multiple pregnancy rates. We also sought to identify any reports of side-effects or serious reactions to the agents used in the included trials to assess any potential harm.

Eligibility criteria

Studies were included if they were RCTs reporting on the use of any of the uterine relaxing agents in the peri-implantation period. Case reports, observational cohort studies, retrospective studies and non-randomized trials were excluded. Studies reporting only on surrogate outcomes (i.e.