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REVIEW

The effect of intrauterine HCG injection on IVF outcome: a systematic review and meta-analysis

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Abstract In this systematic review and meta-analysis, the effect of intrauterine HCG infusion before embryo transfer on IVF outcomes (live birth rate, clinical pregnancy rate and spontaneous aboretion rate) was investigated. Searches were conducted on *MEDLINE*, *EMBASE* and The *Cochrane Library*. Randomized studies in women undergoing IVF and intracytoplasmic sperm injection comparing intrauterine HCG administration at embryo transfer compared with no intrauterine HCG were eligible for inclusion. Eight randomized controlled trials were eligible for inclusion in the meta-analysis. A total of 3087 women undergoing IVF and intracytoplasmic sperm injection cycles were enrolled (intrauterine HCG group: $n = 1614$; control group: $n = 1473$). No significant difference was found in the live birth rate (RR 1.13; 95% CI 0.84 to 1.53) and spontaneous abortion rate (RR 1.00, 95% CI 0.74 to 1.34) between women who received intrauterine HCG and those who did not receive HCG. Although this review was extensive and included randomized controlled trials, no significant heterogeneity was found, and the overall included numbers are relatively small. In conclusion the current evidence does not support the use of intrauterine HCG administration before embryo transfer. Well-designed multicentre trials are needed to provide robust evidence.

KEYWORDS: HCG injection, human chorionic gonadotrophin, intrauterine HCG

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Introduction

Embryo implantation remains low despite advances in asssted reprodction techniques (Norwitz et al., 2001). Although most of the causes of implantation failure are embryonic in origin, endometrial contribution cannot be underestimated (Macklon and Brosens, 2014). This has led investigators to propose several interventions to improve endometrial receptivity (Derks et al., 2009; Nastri et al., 2012). Among these interventions is intrauterine infusion of HCG before embryo transfer.

The role played by HCG in natural as well as in assisted conception is important. It is produced by the trophoblastic cells to facilitate implantation and its use has been extended as a substitute for LH surge to trigger ovulation in IVF when pituitary suppression is used. It also maintains progesterone production from the corpus luteum for luteal phase support and suppression of uterine myometrial contractility (Doheny et al., 2003).

Both animal and human studies have shown that HCG is implicated in the process of embryo implantation (Licht et al., 2001; Sherwin et al., 2007). It has been detected as early as 7 days after fertilization in culture media (Hay and Lopata, 1988), and results in the inhibition of insulin-like growth factor-binding protein 1, which could lead to prolongation of the window of endometrial receptivity (Licht et al., 1998). It also stimulates angiogenesis by increasing vascular endothelial growth factor release; modulate implantation by increasing leukemia inhibitory factor and tissue remodelling through stimulating endometrial matrix-metalloproteinases (MMP-9) (Licht et al., 1998; Paiva et al., 2011; Psychoyos, 1973). Additionally, evidence shows that HCG is secreted by the endometrium in the secretory phase and that full-length HCG receptors are expressed mostly in the mid-luteal phase (Zimmermann et al., 2009), suggesting that HCG produced by the endometrium has a paracrine role that can contribute to endometrial pre-decidualization (Licht et al., 2001).

These molecular functions have encouraged clinicians to investigate the effect of intrauterine HCG infusion at the time of embryo transfer on pregnancy rates in IVF programmes. To date, several studies have been conductd with conflicting results (Aaleyasin et al., 2015; Hong et al., 2014; Mansour et al., 2011; Santibáñez et al., 2014; Wirleitner et al., 2015; Zarei et al., 2014). The aim of this systematic review was to establish whether intrauterine infusion of HCG at the time of embryo transfer could improve IVF outcome.

Materials and methods

Literature search methodology

The following databases were searched for randomized controlled trials: *MEDLINE* (1950 to 31 August 2015), *EMBASE* (1980 to 31 August 2015), and *The Cochrane Library*. A combination of Medical Subject Headings (MeSH) and text words were used to generate two subsets of citations, one including studies of "intrauterine HCG" or "human chorionic gonadotrophin" or "HCG injection" and the second "IVF" or "implantation". These subsets were combined using "AND" to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by the electronic searches. No language restrictions were placed on any of our searches. The searches were conducted independently by AO and ME.

Study selection

Studies were selected if they were randomized, and the target population was women undergoing IVF and intracytoplasmic sperm injection (ICSI), who were given intrauterine HCG at the time of embryo transfer and were compared with women who had embryo transfer with no intrauterine HCG administration. The primary outcome measure was the live birth rate (LBR). Secondary outcomes were the clinical pregnancy (CPR) and the spontaneous abortion rates.

A two-stage process was used for study selection. First, two reviewers (AO and ME) scrutinized the titles and abstracts from the electronic searches independently and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent or complete versions were selected. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (TET).

Assessment of methodological quality and data extraction

Each study included was assessed for method of randomization, allocation concealment, blinding, and completeness of outcome data, intention to treat analysis, outcome reporting and other potential sources of bias. The selected studies were assessed for methodological quality by using the components of study design that are related to internal validity. Assessment of methodological quality was based on the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions v 5.1.0 (Julian PT Higgins and Sally Green). Two reviewers (AO and SD) completed data extraction and quality assessment (Berlin and Rennie, 1999).

Statistical analysis

From each study, two reviewers extracted outcome data. The relative risks with 95% confidence interval for dichotomous measures are calculated for each study and then these relative risks are pooled to get an overall relative risk. $P < 0.05$ is considered statistically significant. The results from individual studies were pooled using either a fixed effect (Mantel and Haenszel, 1959) or random effects model as appropriate (DerSimonian and Laird, 1986). Heterogeneity of the exposure effect was evaluated graphically using forest plots (Lewis and Clarke, 2001) and statistically using the I^2 statistic (Higgins and Thompson, 2002). If the I^2 value was greater than 50%, showing significant heterogeneity, a random effect model was used. A chi-squared test for heterogeneity was also performed and the *P*-values were presented. Exploration of causes of heterogeneity was planned using variations in