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Review

Follicular flushing in patients with poor ovarian response: a systematic review and meta-analysis

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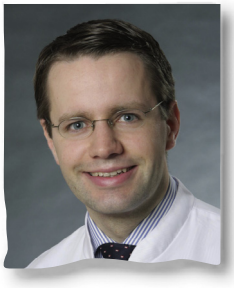

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KEY MESSAGE

A positive effect of flushing in poor response IVF patients could not be observed in published research.

A B S T R A C T

A systematic literature review and meta-analysis was conducted to evaluate the effect of follicular flushing on clinical outcomes (primary outcome: mean number of cumulus–oocyte–complexes [COC]) in poor-response IVF patients). The bibliographic databases *OvidMedline* (includes *Pubmed*), *Cochrane Library* and *Web of Science* were searched electronically for randomized controlled trials comparing follicular flushing with no flushing. Three randomized controlled trials with a total of 210 patients could be included. The mean number of COC did not increase with flushing (weighted mean difference: −0.45 COC, 95% CI −1.14 to 0.25, I^2 = 70%; three randomized controlled trials, n = 210). Mean number of metaphase II oocytes and the proportion of randomized patients having at least one COC retrieved were no different between groups. No difference was observed between groups for mean number of embryos, the proportion of randomized patients achieving embryo transfer, clinical pregnancy and live birth rates. Procedure duration was significantly increased with flushing (P = 0.0006). A positive effect of flushing on any of the investigated outcomes could not be observed in in patients with poor ovarian response. Flushing is unlikely to significantly increase the number of oocytes, and the routine use of follicular flushing should, therefore, be scrutinized.

Introduction

Transvaginal ultrasound-guided follicular aspiration is the routine procedure for oocyte retrieval in patients undergoing IVF (Gembruch et al., 1988; Ludwig et al., 2006). Flushing follicles with multiple aspirations from the same follicle is used to increase the number of cumulus–oocyte–complexes (COC) retrieved from a given number of follicles. For that purpose, double lumen needles consisting of one lumen for aspiration and a second lumen for flushing of the ovarian follicle were developed (Miller et al., 2004).

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As the number of COC available for IVF is a determinant of the cumulative chance of a patient to achieve pregnancy (Fatemi et al., 2013), it important to retrieve the maximum number of COC from a give number of follicles that have developed in response to stimulation with FSH. A fraction of patients will, despite high FSH doses, produce only a small number of growing follicles (Mehri et al., 2014). In case of extreme ovarian follicular depletion, mono-follicular growth may be the maximally achievable outcome of ovarian stimulation. In such patients, retrieval of at least one COC determines if embryo transfer (and thereby a chance of pregnancy achievement) may occur at all. Accordingly, in patients with poor ovarian response, the use of follicular flushing and double lumen needles has become popular for decreasing the risk of oocyte retention within the follicle. For the Austrian and German market, it is estimated from needle sales that up to 18% of oocyte retrieval procedures are carried out with flushing (Gynemed company, Lensahn, Germany; personal communication).

Apart from flushing, several approaches have been investigated to improve IVF outcomes of poor responders. For a few of these interventions, an indication of potential proof of benefit for patients exists, e.g. use of androgens in poor responders (Bosdou et al., 2012), addition of growth hormones to gonadotrophins in ovarian stimulation of poor responders (Kolibianakis et al., 2009), which is why poor response is still rather challenging in IVF treatment.

In normal responding patients, randomized studies and meta-analyses comparing flushing with double lumen needles with conventional follicular aspiration with single lumen needles failed to prove superiority of the concept of follicular flushing (Levy et al., 2012; Roque et al., 2012; Wongtra-Ngan et al., 2010). Neither meta-analysis found increased oocyte retrieval but agreed on prolonged procedure times when carrying out follicular flushing in normo-responders. In patients with poor ovarian response who might benefit the most from flushing, however, this intervention has remained popular despite negative evidence in normo-responders. In the latest Cochrane review (Wongtra-Ngan et al., 2010), only one, single, small, study in low-response patients was available, thus limiting definite inferences on the utility of flushing in this patient population.

The aim of the present review and meta-analysis, therefore, was to systematically evaluate the primary outcome mean number of COC retrieved from randomized clinical trials on follicular flushing in IVF patients with poor ovarian response.

Material and methods

Electronic literature search for identification of randomized controlled trials

The electronic literature search was built on the existing search strategy of the Cochrane library of Wongtra-Ngan et al. (2010). The electronic literature search of the present meta-analysis covered the time point until 2017 and was conducted in the databases *OvidMedline* (includes *PubMed*), *Cochrane Library* and *Web of Science*. The literature search aimed to identify randomized controlled trials from which comparative data on clinical outcome after follicular flushing versus no follicular flushing in poor ovarian response IVF patients were retrieved. The computerized literature search was conducted using various combinations of involved terminology and key words (**Supplementary Appendix**).

Selection criteria

Randomized controlled trials in IVF patients termed as poor ovarian responders by the investigators were considered for inclusion in this review. No exclusion criteria were set for patient number, number of follicles or relating to specific flushing techniques. Two review authors (KN, GG) independently scanned titles and abstracts identified from the searches. Potentially relevant trials were selected and independently assessed for inclusion in this review. A flowchart of identified and analysed trials based on PRISMA guidelines is presented in **Figure 1** (Moher et al., 2009).

Studies selected

Characteristics of the included randomized controlled trials are shown in **Table 1**.

Primary and secondary outcome, data extraction and analysis

As primary outcome criteria, mean number of COC aspirated on follicular puncture was chosen. The secondary outcome criteria were mean number of metaphase II oocytes, proportion of patients having at least one COC, mean number of embryos, proportion of patients achieving embryo transfer, clinical pregnancy rate, live birth rate and procedure time of follicle aspiration. Study features and results were assembled in tabular form, and a formal meta-analysis was conducted. The dichotomous data results for each study were expressed as a risk difference or relative risk with 95% confidence intervals. These results were combined for meta-analysis with the software RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), using the Mantel–Haenszel method. All outcomes were extracted based on the denominator patients randomized (intention-to-treat).

When the outcome of interest was of a continuous nature, the differences were pooled across the studies, which provided information on this outcome parameter, resulting in a weighted mean difference (WMD) with 95% confidence interval. The heterogeneity between studies was tested using the Q statistic (Zamora et al., 2006). Statistical heterogeneity was assessed by the measure of the I^2. An I^2 measurement greater than 50% was taken to indicate a substantial heterogeneity (The Cochrane Collaboration, 2011). If substantial heterogeneity was detected, a random effect model was used instead of a fixed effect model.

Results

Included studies

One study, identified in the clinical trial registry, had to be excluded, after contact with the principal investigator, as the study is still ongoing (Pirrello et al., 2011). Three studies fulfilled the inclusion criteria (**Table 1**). All three studies had the primary objective of testing for a difference in mean COC (Mok-Lin et al., 2013; von Horn et al., 2017) or mean metaphase II (MII) oocyte (Haydardedeoglu et al., 2017) numbers between flushing and no flushing; in all three trials the necessary sample size was determined a-priori. In the control group of all trials, a conventional single lumen needle was used. All trials were conducted between 2013 and 2017.

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