Follicular flushing during oocyte retrieval: a systematic review and meta-analysis

Matheus Roque · Marcos Sampaio · Selmo Geber

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Abstract

Purpose The purpose of this systematic review and meta-analysis was to examine the literature and identify randomized controlled trials (RCTs), in order to answer if performing follicular flushing during the oocyte retrieval may improve the assisted reproductive technologies (ART) outcomes.

Methods An exhaustive electronic search was performed using MEDLINE and EMBASE databases. Only RCTs comparing follicular flushing to aspiration only during ART, were included. We included 5 trials, with a total of 482 patients randomized, with median ages ranging from 30.5 to 37.1.

Results The data analyses did not show significant differences regarding live birth rate, clinical pregnancies rates, and the number of oocytes retrieved. The duration of oocyte retrieval was significantly increased in the follicular flushing group.

Conclusions The results from this systematic review and meta-analysis suggest that there is no advantage to use of routine follicular flushing during OR in an unselected group of patients.

Keywords Follicular flushing · Oocyte retrieval · Single/double-lumen needle

Capsule Follicular flushing is performed to increase the number of oocyte retrieved. This systematic review and meta-analysis suggest that there is no advantage to use this method in routine basis.

M. Roque · M. Sampaio · S. Geber
Origen – Center for Reproductive Medicine,
Belo Horizonte, Brazil

S. Geber (✉)
Medical School of the Universidade Federal de Minas Gerais,
Av. Contorno 7747 – Lourdes,
Belo Horizonte, MG CEP 30 110 120, Brazil
e-mail: selmogeber@origen.com.br

Introduction

Up to the early 1980s, oocyte retrieval during the assisted reproductive technologies (ART) was performed via laparoscopy, which was an expensive process requiring general anesthesia [12, 16, 24]. This was replaced by ultrasound-guided transvaginal oocyte retrieval, first described in 1981 [16]. This is a simple and effective method for oocyte retrieval and is the gold standard for ART treatments nowadays [20].

It is possible to perform oocyte retrieval with single or double-lumen needles. The last one has one channel to withdraw follicular fluid and another to instill saline fluid into the follicle. It is used for intermittent flushing of ovarian follicles, in an attempt to overcome the potential oocyte retention within the follicle during direct aspiration or in the collection system [12, 18] and maximize the number of oocytes recovered [5]. The rationale of follicular flushing is to retrieve more oocytes and subsequently obtain more embryos [28]. However, there is divergent opinion about the use of double lumen needle during the OR. Initial reports showed that the use of double-lumen needles and flushing could recover 20 % more oocytes compared with direct aspiration [27], but other studies did not find differences in the number of retrieved oocytes, fertilization rates, embryo quality or pregnancy rates ([14, 15, 26]). The contrary opinion to perform the follicular flushing is due to no evidence of better ART outcomes, longer operative time and increased amounts of anesthetics required [26, 28].

The purpose of this systematic review and meta-analysis was to examine the literature and identify randomized controlled trials (RCTs), in order to answer if performing follicular flushing during the oocyte retrieval in patients submitted to IVF treatment may improve the ART outcomes.

Table 1 Quality assessment of included trials

Study (reference)	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data
[25]	Unclear	Unclear	Unclear	YES
[14]	Unclear	Unclear	NO	YES
[26]	Unclear	YES	NO	YES
[18]	YES	YES	YES	YES
[9]	YES	YES	YES	YES

Methods

The study was exempt from institutional Review Board approval because this was a systematic review and meta-analysis. We utilized the preferred reporting items for systematic reviews and meta-analysis (PRISMA statement) to report the results of this systematic review [22].

Search strategy

An exhaustive electronic search was performed using MEDLINE and EMBASE databases, the Cochrane Central Register of Controlled Trials, the main ongoing

clinical trials registers (controlled-trials.com, clinical-trials.gov and the International Clinical Trials Registry Platform from the World Health Organization) until March 2012. The search combined terms and descriptors related to in vitro fertilization with or without ICSI AND follicular flushing, double lumen needle, oocyte retrieval. We restricted the search to articles published in English. We also searched among the references of the identified articles.

Eligibility criteria and data extraction

The review included only RCTs of women undergoing in vitro fertilization, submitted to oocyte retrieval with double-lumen needle and the addition of flushing compared to women with oocyte retrieval with single lumen needle with aspiration only. We extracted outcome results per women randomized. In a first screening, two independent authors (S.G.; M.R.) assessed all the abstracts retrieved from the search, and then they obtained the full manuscripts of citations that fit with inclusion criteria. They evaluated the studies eligibility, quality and extracted data, and any discrepancies were solved by agreement, and if needed, reaching consensus with a third author (M.S.)

Fig. 1 Flow chart for the trial identification and selection process

Table 2 Characteristics of the clinical trials included in the review

Study ID	Patients	Age, mean years (Flushing/ aspiration only)	Interventions	Outcomes
[25]	44 IVF patients	Not given	Single lumen needle (Swe-Med); Double-lumen needle (Swe-Med); follicular flushing with 1–3 mL of heparinized Dulbecco's solution	*Number of follicles aspirated *Number of oocytes retrieved *Incidence of fractured zone
[14]	34 IVF patients	30.5/31 years	Double channel needle (JP6L); follicular flushing with 10 ml Earle's balanced solution supplemented with pyruvate, bicarbonate and buffered with HEPES	*Number of oocytes retrieved; *Procedure time *Fertilization and pregnancy rates
[26]	100 IVF patients	32.5/32 years	JP6L double-lumen channel needle (Casmed, Chem, UK); follicular flushing medium was injected (1.5 mL) up to 6 times	*Number of follicles aspirated *Number of oocytes retrieved *Procedure time *Fertilization and clinical pregnancy rates
[18]	30 poor responders undergoing IVF	37.1/36.2 years	Cook Echotip single-lumen (K-J-ANC-16R-35) and double lumen (K-OPSD-1635-B-S) retrieval needles; follicular flushing with 2 mL sterile PBS	*Number of oocytes retrieved; *Number of mature oocytes retrieved; *Fertilization and implantation rate; *Ongoing pregnancy rate; *Procedure time
[9]	274 IVF patients	30.75/30.58 years	Single-lumen needle with 17-gauge (Cook Ireland Ltd, Limerick, Ireland) and a 17-gauge double lumen needle; follicular flushing with 2 mL of flush medium once	*Number of oocytes retrieved; *Number of mature oocytes retrieved; *Procedure time; *Fertilization, clinical and live birth rates

Outcome measures

The primary outcome of interest for this systematic review included: live birth rate per women randomized. Secondary outcomes included: clinical pregnancy rate per women randomized; the number of oocytes retrieved yield and the duration of oocyte retrieval. Clinical pregnancy was defined by the observation of fetal heart beat by 7 weeks of gestation.

Risk of bias assessment

The risk of bias from included studies following was assessed following the guidance suggested by the Cochrane Collaboration [11]. We evaluated the generation of the sequence generation, allocation concealment, and blinding and incomplete outcome data for each trial included in the

review. A low risk of bias was considered when a judgment of “yes” for all domains was obtained, whereas a high risk of bias was considered when a judgment of “no” for one or more domains was obtained. An unclear risk of bias was defined when an “unclear” judgment in any domain was considered. The results are shown in Table 1.

Analysis

We pooled data for dichotomous outcomes from original studies, to obtain the relative risk (RR) for the occurrence of an outcome event and for continuous outcomes the mean differences (MD) $\pm$ SD and the inverse variance (IV), presented with their corresponding 95 % confidence intervals. We used the intention to treat principle to extract the event data. Statistical significance was set at a *P* value <0.05. We

Fig. 2 Forest plot comparing the live birth rate in the follicular flushing group versus aspiration only group

Fig. 3 Forest plot comparing the clinical pregnancy rate in the follicular flushing group versus aspiration only group

pooled the outcome data from each study using a random effects model. To quantify statistical heterogeneity, we used the I^2 statistic in order to describe variations across trials that are due to heterogeneity and not to sampling error [10]. We used the Review Manager 5 software to conduct the meta-analysis.

Results

The search strategy yielded 18 articles related to the topic. After the screening of titles and abstracts we excluded 13 articles because they did not fulfilled the selection criteria. Among the excluded studies, two were review articles [12, 28], five studies did not have comparison group [3, 6, 13, 17, 29], one was a retrospective study (Knight et al., 2001), five were not RCTs [1, 5, 19, 21, 27]. Five RCTs met the inclusion criteria and were included in this review. The flow chart of the trials included in the meta-analysis is shown in Fig. 1.

Description of included studies

Five prospective, randomized, controlled trials evaluating the use of follicular flushing during oocyte retrieval in IVF/ICSI cycles versus aspiration only met the inclusion criteria. Their sample sizes range from 30 to 274 patients, with a total of 482 patients randomized, with median ages ranging from 30.5 to 37.1. In one of the studies [25] the median age was not given. One of the studies [18], included only low responders patients, determined by a cumulative ovarian follicle count of four to eight follicles ≥ 12 mm with at least two follicles

achieving ≥ 16 mm on the day of HCG administration. The characteristics of the studies included in the review are shown in Table 2.

Outcomes

Live birth rate per women randomized

Only one of the included studies reports data on live birth rate [9]. There was no statistically difference among the follicular flushing group versus aspiration only group. ($RR=1.04$, 95 % CI 0.76–1.43) (Fig. 2).

Clinical pregnancy per women randomized

Four of the included trials [9, 14, 18, 26] reported data about clinical pregnancy rates. There was no evidence of a statistically difference in clinical pregnancy rate ($RR=1.09$, 95 % CI 0.87–1.37) (Fig. 3).

Oocytes retrieved

Three studies [9, 18, 25] presented data regarding the mean $\pm$ SD of oocytes retrieved. There was no evidence of statistically difference in the number of oocytes retrieved between the groups of follicular flushing versus aspiration only ($IV=-0.37$, 95 % CI -1.06 – 0.33) (Fig. 4).

Procedure time

Four studies reported data showing a significant increase in the procedure time in the follicular flushing group. Only two of these studies reported the mean $\pm$ SD retrieval time [9,

Fig. 4 Forest plot comparing the number of oocytes retrieved in the follicular flushing group versus aspiration only group

Fig. 5 Forest plot comparing the procedure time in the follicular flushing group versus aspiration only group

18]. There was a statistically difference in the procedure time with a significant decrease in the aspiration only group ($IV=3.55$, 95 % CI 2.59–4.52). The other two studies reporting the procedure time, reported median data only [14]. reported a median time of 20 min for the aspiration only group and 35 min for the follicular flushing group ($p < 0.001$) [26]. reported a median time of 15 and 30 min for aspiration only and follicular flushing groups, respectively ($p < 0.01$) (Fig. 5).

Discussion

This systematic review and meta-analysis did not demonstrate a beneficial effect of oocyte retrieval with follicular flushing compared to oocyte retrieval with aspiration only, regarding live birth rate, clinical pregnancy rate and the number of oocytes retrieved in unselected ART patients. Furthermore, there is an increase in the procedure time that may be related with an increase in the total amount of analgesic drugs used.

The quality of the available evidence that supports these results is moderate [7]. The results may have some imprecision, since there were a limited number of eligible trials and most of the studies' results were based on low number of patients. Nowadays, the live birth rate would be the outcome of interest in all reproductive trials, but in this meta-analysis only one of the included trials followed women up to obtain data on live birth rate [9].

The use of a double lumen needle during oocyte retrieval with a follicular flushing was developed to overcome the possibility of oocyte retention within the follicle or in the aspiration system [8, 12]. It was suggested that with its use, it would be retrieved more oocytes during follicular aspiration. Once, the number of embryos that are obtained during ART cycles are dependent on the number of retrieved oocytes, it would be expected more embryos in the treatments with the use of follicular flushing and improvements in the ART outcomes.

Some reports found that the follicular flushing resulted in the recovery of 20 % more oocytes [27]. Another study found that about 40 % of oocytes were retrieved with aspiration only, while with the first four flushes a further 57.3 % of oocytes were recovered [1]. Mendez Lozano et al., showed 46.8 % of oocyte recovery with follicular

aspiration only compared to 84.6 % recovery with additional follicular flushing in poor responder patients [21]. In another study, Lozano et al., reported higher implantation rates and number of superior grade embryos in semi-natural cycles when the follicular flushing was used [19]. These results are different from those that we found in our meta-analysis, which did not show improvements in the number of oocytes retrieved neither in ART outcomes.

Although frequently used, there are no evidence that follicular flushing is superior to aspiration only [18], the total number of mature oocytes recovered did not differ among the two groups, and the number of cryopreserved embryos are the same in normal responders [9]. The clinical pregnancy rates are not superior when the OR is performed with double lumen needle [9, 14, 18, 26].

We believe that the best improvements achieved with the use of follicular flushing would specifically occur in a subgroup of poor responders, in patients submitted to natural ART cycles or ART cycles with minimal ovarian stimulation. Some studies reported a high frequency of failure to obtain the oocyte in the OR in poor responders submitted to minimal ovarian stimulation, ranging from 15 % to 40 % [2, 4, 21, 23]. In this subgroup, even a small and discrete variation in the number of oocytes collected, could be beneficial for the patient. However, there is a paucity of randomized clinical trials evaluating the effects of follicular flushing in this subgroup of patients. We found only one RCT comparing the follicular flushing versus aspiration only, among poor responders patients and this was small study evaluating only 15 patients in each group [18].

The results from this systematic review and meta-analysis suggest that there is no advantage to use a routine follicular flushing during the OR in an unselected group of patients. There is no evidence that performing the follicular flushing increase the chance of clinical pregnancy or the number of oocytes retrieved. Further RCTs with a larger sample size are necessary to evaluate the real effect of follicular flushing, mainly in poor responders patients.

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