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Surgical treatment for hydrosalpinx prior to *in-vitro* fertilization embryo transfer: a network meta-analysis

A. TSIAMI*, A. CHAIMANI†, D. MAVRIDIS†‡, M. SISKOU*, E. ASSIMAKOPOULOS* and A. SOTIRIADIS*

**Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Thessaloniki, Greece; †Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; ‡Department of Primary Education, University of Ioannina School of Education, Ioannina, Greece*

KEYWORDS: aspiration; hydrosalpinx; IVF; network meta-analysis; salpingectomy; tubal occlusion

ABSTRACT

Objective *The presence of hydrosalpinx impairs the outcome of* in-vitro *fertilization embryo transfer (IVF-ET). Surgical methods to either aspirate the fluid or isolate the affected Fallopian tubes have been attempted as a means of improving outcome. The aim of this network meta-analysis was to compare the effectiveness of surgical treatments for hydrosalpinx before IVF-ET.*

Methods *An electronic search of MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (Central) and the US Registry of clinical trials for articles published from inception to July 2015 was performed. Eligibility criteria included randomized controlled trials of women with hydrosalpinx before IVF-ET comparing ultrasound-guided aspiration of the fluid, tubal occlusion, salpingectomy or no intervention. Ongoing pregnancy was the primary outcome and clinical pregnancy, ectopic pregnancy and miscarriage were secondary outcomes. A random-effects network meta-analysis synthesizing direct and indirect evidence from the included trials was carried out. We estimated the relative effect sizes as risk ratios (RRs) and obtained the relative ranking of the interventions using cumulative ranking curves. The quality of evidence according to GRADE guidelines, adapted for network meta-analysis, was assessed.*

Results *Proximal tubal occlusion (RR, 3.22 (95% CI, 1.27–8.14)) and salpingectomy (RR, 2.24 (95% CI, 1.27–3.95)) for treatment of hydrosalpinx were superior to no intervention for ongoing pregnancy. For an outcome of clinical pregnancy, all three interventions appeared to be superior to no intervention. No superiority could be ascertained between the three surgical methods for any of the outcomes. In terms of relative ranking, tubal occlusion was the best surgical treatment followed by salpingectomy for ongoing and clinical pregnancy rates. No significant statistical inconsistency was detected; however, the point estimates for some inconsistency factors and their CIs were relatively large. The small study number and sizes were the main limitations. The quality of evidence was commonly low/very low, especially when aspiration was involved, indicating that the results were not conclusive and should be interpreted with caution.*

Conclusions *Proximal tubal occlusion, salpingectomy and aspiration for treatment of hydrosalpinx scored consistently better than did no intervention for the outcome of IVF-ET. In terms of relative ranking, proximal tubal occlusion appeared to be the most effective intervention, followed by salpingectomy. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Tubal disease is responsible for 25–30% of all female factor infertility, and the prevalence of hydrosalpinx is as high as 30% in women with tubal pathology[1]. Although *in-vitro* fertilization (IVF) was first developed to treat tubal infertility, it was soon observed that patients with hydrosalpinx had a poor outcome after IVF treatment[2].

The rationale behind surgical treatment of hydrosalpinx prior to IVF embryo transfer (ET) is to eliminate the detrimental effect of the hydrosalpingeal fluid, either by aspirating it (ultrasound-guided aspiration), by removing the Fallopian tubes altogether (salpingectomy) or isolating them from the uterine cavity (laparoscopic proximal occlusion or hysteroscopic proximal occlusion using Essure®). The latter approach has not yet been evaluated in randomized controlled trials (RCTs) and was therefore not included in this meta-analysis.

Correspondence to: Dr A. Sotiriadis, Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, 92 Tsimiski Street, 54622 Thessaloniki, Greece (e-mail: asotir@gmail.com)

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A meta-analysis published in 2010, assessing the effectiveness of surgical treatments for tubal disease, reported that laparoscopic occlusion of the affected Fallopian tube prior to IVF increased clinical and ongoing pregnancy rates[3]. Another meta-analysis failed to detect differences between salpingectomy and proximal tubal occlusion on clinical pregnancy[4]. There are some concerns about salpingectomy, including its invasiveness, its potential non-feasibility in cases of dense adhesions, its permanent nature, which precludes any possibility of spontaneous conception in the future in cases of bilateral salpingectomy[5], and its potential negative effect on the ovarian blood flow and subsequent reduction of ovarian response to gonadotropin stimulation[6–8]. Aspiration of hydrosalpinx fluid is less invasive, safer, easier to perform in cases of dense adhesions and requires shorter hospitalization. Its main disadvantages are the high recurrence rate of hydrosalpinx[9] and the risk of pelvic infection.

The aim of this network meta-analysis was to compare the efficiency of ultrasound-guided aspiration of hydrosalpinx fluid, salpingectomy, proximal tubal occlusion or no intervention in the management of patients with hydrosalpinx before IVF-ET.

PATIENTS AND METHODS

This meta-analysis was performed according to the PRISMA statement for network meta-analyses[10].

Eligibility criteria

Types of studies

RCTs comparing the following hydrosalpinx treatments prior to IVF-ET with each other or with no intervention were considered eligible for inclusion: ultrasound-guided aspiration of hydrosalpinx fluid, salpingectomy or proximal tubal occlusion. No language, country or publication date restrictions were imposed.

Types of participants

Inclusion criteria were women aged < 40 years with hydrosalpinx visible on ultrasound who were due to undergo IVF. Women due to undergo assisted insemination were excluded.

Types of intervention

The interventions being assessed included ultrasound-guided aspiration of hydrosalpinx fluid, salpingectomy, proximal tubal occlusion or no intervention prior to IVF-ET.

Types of outcome measures

The primary outcome measure was live birth; ongoing pregnancy was used as a surrogate when live birth was not reported and ongoing pregnancy was reported. Secondary outcomes measured were: (i) clinical pregnancy rate, defined as the presence of intrauterine gestational sac detected by transvaginal ultrasound; (ii) miscarriage, as defined by the study authors; and (iii) ectopic pregnancy.

Although reported in some studies, the implantation rate (defined as the number of gestational sacs visible by ultrasound, divided by the number of embryos transferred, including ectopic pregnancies) was not reported in the meta-analysis because the denominator for this outcome (number of embryos transferred) was not randomized.

Search methods for identification of studies

Eligible studies were identified by a predefined search strategy of electronic databases. We searched the literature for RCTs comparing ultrasound-guided aspiration of the hydrosalpinx fluid, tubal occlusion or salpingectomy with no intervention or with each other, prior to IVF-ET. MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (Central) and the US Registry of clinical trials (www.clinicaltrials.gov) were searched from inception to July 2015 using combinations of the terms 'aspiration', 'hydrosalpinx', 'IVF', 'salpingectomy', 'no intervention' and 'fluid'. These searches were complemented by perusal of the references of the retrieved articles and additional automated search using PubMed's 'search for related articles' function. All studies were carefully compared to avoid inclusion of duplicate or overlapping samples. In case of overlap, the study with the largest number of cases was included. The detailed search strategy of one database is presented in Appendix S1.

Study selection

Two reviewers independently assessed the eligibility of all identified citations according to the abovementioned criteria. Disagreements between reviewers were resolved by consensus.

Data collection process and items

Data extraction and assessment of study quality were performed independently by two authors (A.T. and A.S.). The study characteristics of each included study were assessed according to a predefined data extraction form. A detailed list of the items assessed during data extraction is presented in Appendix S2. In case of disagreement, a consensus was reached after discussion between the two authors.

Risk of bias in individual studies

The risk of bias in individual studies was assessed using the Cochrane 'risk of bias' tool[11]. We assessed the following risk of bias items: random sequence generation, allocation concealment, blinding of participants, personnel and assessors, incomplete outcome data and selective reporting. We also considered non-comparable baseline patient and cycle characteristics as other sources of risk of bias. We subsequently classified studies as being at overall low risk of bias when none of these items was rated as high risk and fewer than four were rated as unclear risk, and at moderate risk of bias when one item was rated as high risk or none was rated as high risk but four or more were rated as unclear risk. In all other cases, studies were considered as being at overall high risk of bias. Specifically for blinding, we considered the risk of bias as being low despite a lack of blinding because the objective nature of the outcomes makes it very unlikely that either the outcomes *per se* or their ascertainment was affected by the lack of blinding[11].

Geometry of the network

A network diagram was constructed using the *networkplot* command of the *network graphs* package[12] in Stata (Stata 13.0, Statacorp LP, College Station, TX, USA). Treatments are represented by nodes and head-to-head comparisons with edges. The size of the node and the thickness of the edges are proportional to the number of studies evaluating each intervention and the direct comparison, respectively.

Assessment of transitivity

Transitivity is the fundamental assumption of network meta-analysis and implies that one can validly compare two treatments via a connected indirect route involving one or more intermediate comparators. Transitivity can be evaluated statistically by comparing the distribution of the potential effect modifiers across the available direct comparisons in the network[13,14]. Details on patient and study characteristics that could act as effect modifiers were recorded, as described in Appendix S2.

Statistical analysis

A standard random-effects meta-analysis was performed initially for outcomes when data for direct comparisons were available. Direct estimates were derived using a comparison-specific random-effects model on Open Meta-Analyst (http://www.cebm.brown.edu/open_meta/). We then performed a random-effects network meta-analysis in order to compare simultaneously the relative effectiveness of all interventions[15]. We assumed a common heterogeneity (τ) across all comparisons and compared it with previously derived empirical distributions for heterogeneity[16]. For all possible pairwise comparisons, summary risk ratios (RRs) with 95% CIs were estimated using the multivariate meta-analysis approach that treats the different comparisons in studies as different outcomes and properly accounts for the correlation introduced by multiarm trials[17]. We ran the network meta-analysis models using the *network* package in Stata[18]. Analyses were performed as per intention to treat.

Prediction intervals (PrIs), which indicate the interval within which the relative effect of a future study is expected to lie[19,20], were estimated and plotted in order to aid interpretation of the random-effects network meta-analysis. This was performed using the *network graphs* package in Stata. The PrI plot gives information about the extent and impact of the common heterogeneity on each relative treatment effect[21].

For each treatment, we estimated the ranking probabilities of assuming any possible rank, plotted the cumulative ranking curves and calculated the surface under them (SUCRA). SUCRA is a percentage that shows how much effectiveness a treatment achieves in comparison with a theoretical treatment that is always the best without uncertainty. The larger the SUCRA value, the better the rank of the treatment[21,22].

Contribution plots were constructed in order to assess the influence of every direct comparison to each network estimate and to the entire network[21,23].

Assessment of inconsistency

The consistency of treatment effects, i.e. the agreement of direct and indirect evidence, was assessed by constructing an inconsistency plot using the *ifplot* command in Stata. In each loop, we estimated the inconsistency factor as the ratio of the two risk ratios (RRRs) from direct and indirect evidence for one comparison in the loop; RRR values close to 1 mean that the two different sources of evidence are in statistical agreement[21]. Significant inconsistency is identified in a loop if the 95% CI for RRR does not include the unity. We performed this approach assuming a common heterogeneity parameter across all loops in the network as this was estimated from the network meta-analysis model.

Assessment of small-study effects

The potential for small-study effects, which are usually seen as a proxy for publication bias, was assessed using a comparison-adjusted funnel plot, which accounts for the fact that studies estimate effects for different comparisons across the network[21]. It should be noted that, as in standard funnel plots with a small number of studies (e.g. fewer than 10), the graph is not informative as funnel-plot asymmetry cannot be assessed. We also needed to make some assumptions regarding the direction of small-study effects[24] in each comparison, and therefore we assumed that small studies are expected to favor treatments in order of invasiveness, i.e. salpingectomy, tubal occlusion, aspiration and, last, no intervention.

Additional analysis

None planned.

Quality of the evidence

We assessed the quality of the evidence for the primary outcome (ongoing pregnancy) and the most important secondary outcome (clinical pregnancy). We used an approach that extends the GRADE system (http://www.gradeworkinggroup.org/publications/JCE_series.htm) into network meta-analysis based on the contributions of the direct comparisons to the network estimates[25]. Specifically, the quality was assessed separately for the confidence in specific pairwise comparisons and for the confidence in treatment ranking. The assessment regarding pairwise comparisons involved five domains, i.e. study limitations, indirectness (joint consideration of indirectness and intransitivity), inconsistency (joint consideration of statistical heterogeneity and statistical inconsistency), imprecision and publication bias[25]. The assessment for treatment ranking involved three domains, i.e. study limitations, indirectness and inconsistency[25].

RESULTS

Study selection

All RCTs reporting on IVF-ET outcomes in women with hydrosalpinx visible on ultrasound who were treated by aspiration of the hydrosalpinx fluid, salpingectomy, proximal tubal occlusion or received no intervention before they underwent IVF-ET were considered eligible for inclusion in this meta-analysis.

The electronic search initially retrieved 556 records. After exclusion of duplicates ($n = 229$), 327 records remained and were screened based on their title and abstract. Of these, 295 were consequently excluded. The full text of the remaining 32 articles was retrieved to assess for eligibility. Of these, 25 studies were excluded, with the reasons for exclusion summarized in Table S1. In total, seven articles were included in the meta-analysis[9,26–31]. The flowchart of the selection procedure is shown in Figure 1. Characteristics of the included studies are presented in Table S2.

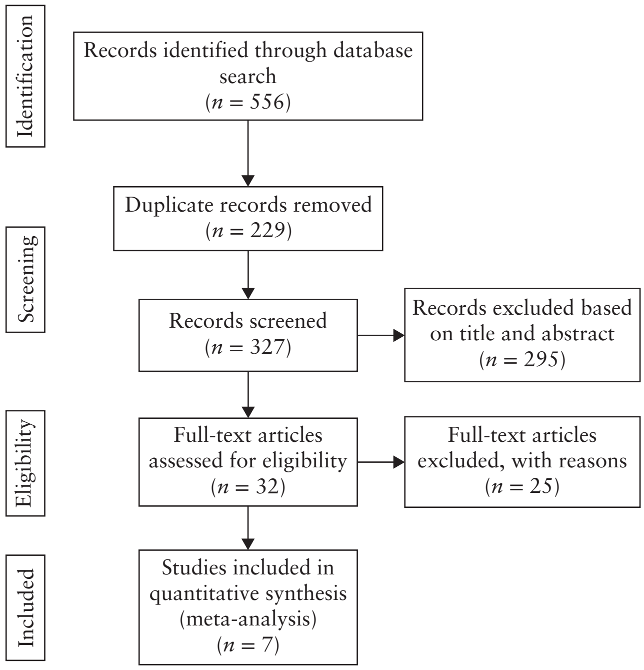

Figure 1 Flowchart of study selection of randomized controlled trials for network meta-analysis.

Network structure and geometry

None of the included studies reported live birth rate and therefore ongoing pregnancy rate was used as its proxy. Five studies[26–28,30,31] reported on the impact of aspiration or salpingectomy prior to IVF-ET on the primary outcome of ongoing pregnancy. Of these, two studies[30,31] compared salpingectomy *vs* no treatment, one study[28] compared salpingectomy *vs* tubal occlusion *vs* no treatment, one study[26] compared aspiration *vs* salpingectomy and one study[27] compared aspiration *vs* no treatment (Figure 2a). For the outcome of ongoing pregnancy, the most common tested modality was salpingectomy ($n = 276$), followed by no intervention ($n = 188$), aspiration ($n = 135$) and tubal occlusion ($n = 50$). Both studies on aspiration were performed by the same group[26,27].

Six studies[9,26–30] provided data on clinical pregnancy rate. Of these, two studies[9,27] compared aspiration *vs* no treatment, one study[30] compared salpingectomy *vs* no treatment and two studies[28,29] compared salpingectomy *vs* tubal occlusion *vs* no treatment. Salpingectomy was the most commonly tested treatment ($n = 306$), followed by no intervention ($n = 258$), aspiration ($n = 167$) and tubal occlusion ($n = 128$) (Figure 2b).

Risk of bias within studies

The within-studies risk of bias was assessed by the 'risk of bias' tool by the Cochrane Collaboration and the results are presented in Table S3. As shown in the table, the risk of bias was low for most of the studies. In two studies[9,27], the patients were given the option of salpingectomy before entering the study. One trial was terminated early, before the required sample size was reached[9]. In one study comparing aspiration and salpingectomy, four patients had proximal tubal occlusion but no separate data were provided for them[26]; however, this is technically not a problem in the context of intention-to-treat analysis.

Results of individual studies

The results of individual studies for primary and secondary outcomes are presented in Table S4.

Assessment of transitivity

We were unable to evaluate properly the plausibility of the transitivity assumption due to lack of sufficient data as only one or two studies were available for almost all direct comparisons in our network. However, we did not find any important discrepancies in study and participant characteristics or in the definition of interventions and outcomes between trials that compared different sets of

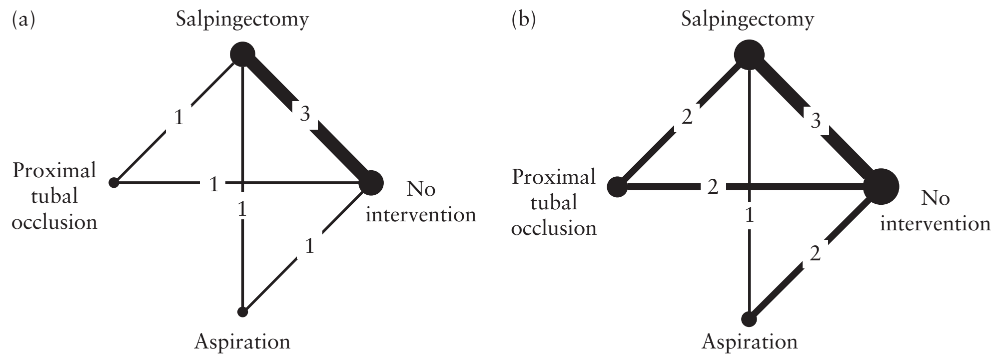

Figure 2 Network plot for ongoing pregnancy (a) and clinical pregnancy (b). Nodes represent the competing interventions in the network and lines represent pairwise comparisons evaluated directly in at least one study. Both nodes and lines have been weighted according to the number of studies involving each intervention and comparison, respectively.

treatments and therefore we can assume that transitivity is likely to hold in our dataset.

Synthesis of results

Primary outcome

For the outcome of ongoing pregnancy, proximal tubal occlusion (RR, 3.22 (95% CI, 1.27–8.14)) and salpingectomy (RR, 2.24 (95% CI, 1.27–3.95)) prior to IVF-ET appeared to be superior to no treatment, whereas for aspiration *vs* no treatment we could not ascertain which strategy provided a better outcome (RR, 1.84 (95% CI, 0.83–4.07)). The differences between the three interventions failed to reach statistical significance (Table 1, Figure 3a). The comparison of the estimated heterogeneity ($\tau = 0.08$) with the respective empirical distribution suggested that the former was low. The PrIs could not be estimated for this outcome due to the small number of studies per comparison (Figure 3a). Proximal tubal occlusion had the highest SUCRA value (90.2%), followed by salpingectomy (62.8%) and aspiration (44.2%) (Figure 4).

Secondary outcomes

For the outcome of clinical pregnancy, all three interventions appeared to be superior to no intervention (RR for salpingectomy, 2.12 (95% CI, 1.36–3.31); RR for occlusion, 2.64 (95% CI, 1.51–4.62); RR for aspiration, 1.73 (95% CI, 1.02–2.95)). However, the PrIs were wide enough to suggest that the direction of the relative effect may change in a future study (Figure 3b). The differences between the three interventions failed to reach statistical significance (Table 1, Figure 3b), so we could not ascertain which intervention provided a better outcome. Compared with the respective empirical distribution, the estimated heterogeneity ($\tau = 0.05$) was also low for this outcome. Similar to ongoing pregnancy, proximal tubal occlusion had the highest SUCRA value (92.1%), followed by salpingectomy (64.7%) and aspiration of the hydrosalpinx fluid (42.4%) (Figure 4).

Six studies[9,26–28,30,31] reported on the outcome of miscarriage (Figure S1). For the comparisons of salpingectomy *vs* no treatment (RR, 0.51 (95% CI, 0.23–1.12)), occlusion *vs* no treatment (RR, 0.38 (95% CI, 0.09–1.67)) and aspiration *vs* no treatment (RR, 0.70 (95% CI, 0.28–1.71)), we could not ascertain which modality was better. Similarly, there were no significant differences between the three interventions (Figure S2). The heterogeneity estimate was zero. In terms of relative ranking, proximal tubal occlusion (77.0%) and salpingectomy (67.8%) had the highest SUCRA value, followed by aspiration (43.2%) (Figure S3).

Six studies[9,26–28,30,31] reported on the outcome of ectopic pregnancy (Figure S1). We did not find statistically significant differences for salpingectomy *vs* no treatment (RR, 0.57 (95% CI, 0.14–2.26)), occlusion *vs* no treatment (RR, 0.22 (95% CI, 0.01–5.54)) or aspiration *vs* no treatment (RR, 0.82 (95% CI, 0.11–6.16)), or between the three interventions (Figure S2), so we could not ascertain which intervention was better. However, the data were limited in number, especially given the low prevalence of ectopic pregnancy. The heterogeneity estimate was zero. Tubal occlusion had the highest SUCRA value (77.3%), followed by salpingectomy (56.1%) and then aspiration (39.5%) (Figure S3).

Evaluation of inconsistency

The analysis for inconsistency for all outcomes is shown in Figure S4. There was no significant inconsistency for any of the outcomes (the 95% CIs for RRRs included 1.0); however, the mean RRR was relatively large for the loop of no intervention–occlusion–salpingectomy in all outcomes, and for the loop of aspiration–no intervention–salpingectomy in ongoing pregnancy, indicating that the estimates of direct and indirect comparisons may have differed substantially.

Small-study effects

Due to the small number of included studies and the small number of studies per comparison, we could only draw a comparison-adjusted funnel plot for the outcome of clinical pregnancy. The graph (Figure S5) appears asymmetric, suggesting that small studies tended to favor the more invasive interventions.

Table 1 Direct pairwise and network estimates for primary and secondary outcomes

Outcome	Studies (n)	*Direct meta-analysis* RR (95% CI)	Events (n)/total (N)	I^2 (%)	*Network meta-analysis* RR (95% CI)
Ongoing pregnancy					
Aspiration *vs* no treatment	1	3.00 (1.17–7.68)	15/55 *vs* 5/55	—	1.84 (0.83–4.07)
Salpingectomy *vs* no treatment	3	1.83 (1.18–2.86)	62/196 *vs* 22/133	0	2.24 (1.27–3.95)
PTO *vs* no treatment	1	6.90 (1.01–46.93)	23/50 *vs* 1/15	—	3.22 (1.27–8.14)
PTO *vs* aspiration	—	—			1.75 (0.67–4.55)
Salpingectomy *vs* aspiration	1	1.53 (0.94–2.49)	29/80 *vs* 19/80	—	1.22 (0.63–2.33)
Salpingectomy *vs* PTO	1	0.74 (0.45–1.21)	17/50 *vs* 23/50	—	0.69 (0.33–1.45)
Clinical pregnancy					
Aspiration *vs* no treatment	2	2.11 (1.17–3.82)	27/87 *vs* 13/89	0	1.73 (1.02–2.95)
Salpingectomy *vs* no treatment	3	2.09 (1.11–3.95)	83/226 *vs* 32/169	53.4	2.12 (1.36–3.31)
PTO *vs* no treatment	2	3.41 (1.83–6.34)	57/128 *vs* 10/81	0	2.64 (1.51–4.62)
PTO *vs* aspiration	—	—			1.54 (0.82–2.86)
Salpingectomy *vs* aspiration	1	1.45 (0.93–2.27)	32/80 *vs* 22/80	0	1.23 (0.75–2.00)
Salpingectomy *vs* PTO	2	0.86 (0.64–1.17)	44/110 *vs* 57/128	0	0.81 (0.53–1.22)
Miscarriage					
Aspiration *vs* no treatment	2	0.68 (0.24–1.93)	6/31 *vs* 4/13	0	0.70 (0.28–1.71)
Salpingectomy *vs* no treatment	3	0.52 (0.22–1.25)	9/86 *vs* 7/51	0	0.51 (0.23–1.12)
PTO *vs* no treatment	1	0.23 (0.04–1.33)	3/26 *vs* 1/2	—	0.38 (0.09–1.67)
PTO *vs* aspiration	—	—			0.54 (0.11–2.94)
Salpingectomy *vs* aspiration	1	0.69 (0.15–3.09)	3/32 *vs* 3/22	—	0.74 (0.27–2.00)
Salpingectomy *vs* PTO	1	0.87 (0.16–4.70)	2/20 *vs* 3/26	—	1.35 (0.31–5.88)
Ectopic pregnancy					
Aspiration *vs* no treatment	2	0.53 (0.05–6.21)	0/87 *vs* 1/89	0	0.82 (0.11–6.16)
Salpingectomy *vs* no treatment	3	0.67 (0.15–2.88)	3/196 *vs* 3/133	—	0.57 (0.14–2.26)
PTO *vs* no treatment	1	0.31 (0.01–15.2)	0/50 *vs* 0/15	—	0.22 (0.01–5.54)
PTO *vs* aspiration	—	—			0.26 (0.01–10.0)
Salpingectomy *vs* aspiration	1	0.33 (0.01–8.06)	0/80 *vs* 1/80	—	0.69 (0.08–5.88)
Salpingectomy *vs* PTO	1	3.00 (0.13–71.92)	1/50 *vs* 0/50	—	2.63 (0.12–50.0)

Aspiration, aspiration of hydrosalpinx fluid; PTO, proximal tubal occlusion; RR, risk ratio.

Quality of the evidence

The quality of the evidence was assessed as per GRADE criteria adapted for network meta-analysis[25].

Study limitations

Figure 5 presents the ratings for the domain of study limitations for every direct comparison as well as for the network estimates and the relative ranking. The latter were obtained by combining the ratings for the direct comparisons using their percentage contribution to the estimation within the network (Figure S6). We downgraded by one level all network estimates for which 50% or more of the information came from studies at moderate or high risk of bias. According to Figure 5, for both outcomes of ongoing and clinical pregnancy, the three relative effects between aspiration and each of the other interventions are of moderate quality with respect to study limitations, whereas the remaining relative effects and relative ranking appear to be of high quality.

Indirectness

Although the baseline characteristics of the patients did not differ substantially between the included studies, we were not able to assess properly the transitivity assumption due to lack of sufficient data and we had to rely on our clinical experience in the field and understanding of the condition for its plausibility. Thus, we downgraded the quality of the evidence for all relative effects and relative ranking by one level.

Inconsistency

Heterogeneity was low for both outcomes and we did not find significant inconsistency for any loop so we did not downgrade the quality of the evidence for this domain.

Imprecision

Considering the CIs of the relative effects in Figure 3, we downgraded all relative effects between two active interventions by one level for imprecision. The rankograms in Figure 4 suggest that the relative ranking for both outcomes of ongoing and clinical pregnancy is quite precise and needs no downgrading.

Publication bias

We could not assess small-study effects for ongoing pregnancy due to lack of sufficient data, whereas the comparison-adjusted funnel plot appeared asymmetric for clinical pregnancy. However, as we implemented an extensive search strategy, substantially lowering the likelihood for missed eligible studies, we downgraded

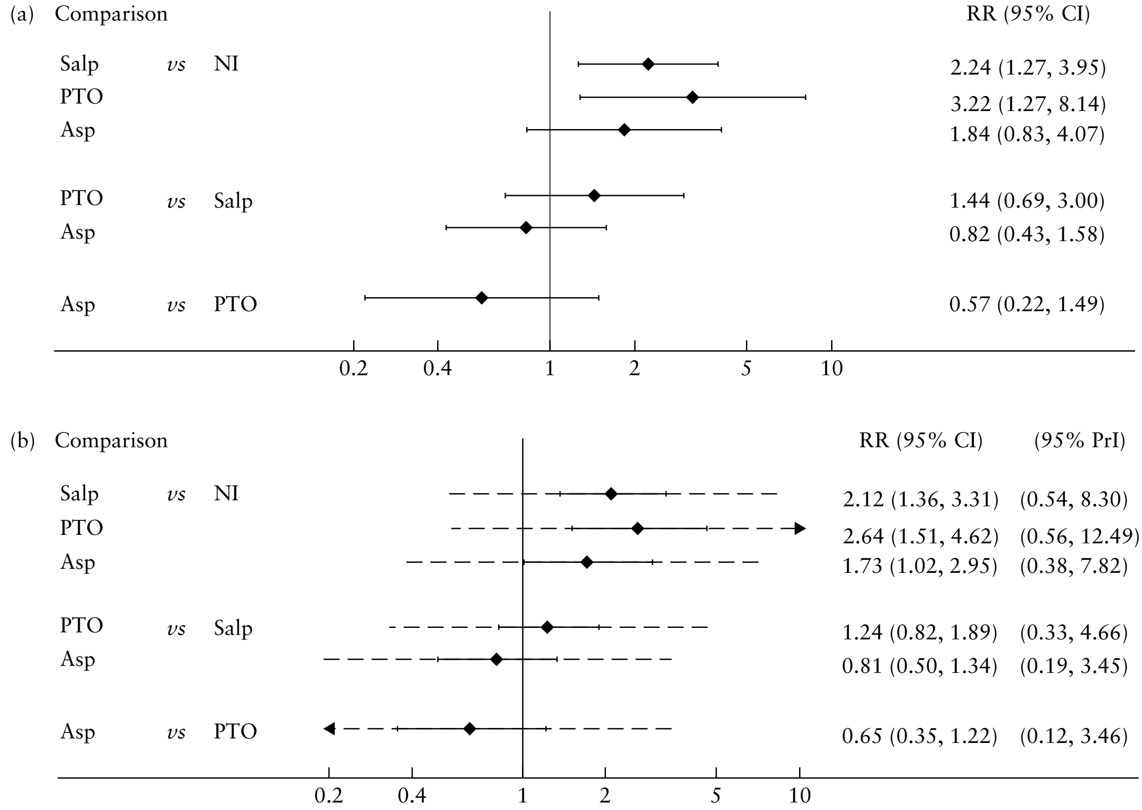

Figure 3 Risk ratios (RRs) for ongoing pregnancy (a) (heterogeneity SD = 0.08) and clinical pregnancy (b) (heterogeneity SD = 0.05) as estimated from the network meta-analysis for every possible pair of interventions for hydrosalpinx performed prior to *in-vitro* fertilization embryo transfer. Solid lines represent 95% CIs and dashed lines represent 95% prediction intervals (PrIs). PrIs were not estimable for ongoing pregnancy due to the small number of studies per comparison. Asp, aspiration; NI, no intervention; PTO, proximal tubal occlusion; Salp, salpingectomy.

the quality of evidence by one level for clinical pregnancy only.

The summary of findings for clinical and ongoing pregnancy is presented in Table 2. The details for within-study risk of bias, along with justifications, can be found in Table S3.

DISCUSSION

In this network meta-analysis, we compared four different strategies (i.e. salpingectomy, tubal occlusion, hydrosalpinx fluid aspiration and no intervention) for managing sonographically visible hydrosalpinx before IVF-ET. We found that proximal tubal occlusion and salpingectomy were superior to no intervention for the outcome of ongoing pregnancy. For the outcome of clinical pregnancy, all three interventions were superior to no intervention. No differences were found for the outcomes of miscarriage and ectopic pregnancy. No significant differences between the three treatments were found in network pairwise comparisons using summary RRs. In terms of probabilistic analysis by relative ranking probabilities, the two best options for the outcomes of ongoing and clinical pregnancy were proximal tubal occlusion and salpingectomy. Occlusion and salpingectomy were the best options for reducing ectopic pregnancy and miscarriage; however, we should emphasize the small size of available evidence for this outcome. No intervention (i.e. doing nothing) before IVF-ET scored consistently as the least effective strategy. The quality of evidence according to GRADE recommendations was moderate to low for comparisons of interventions with no intervention and low to very low for comparisons of two interventions. This essentially indicates that there is a high degree of uncertainty about which indication works better, and this is particularly true for aspiration, the evidence about which is of the lowest quality.

The rationale for intervention in the presence of hydrosalpinx arose from the observation that implantation, pregnancy and delivery rates after IVF were significantly lower in the presence of uni- or bilateral hydrosalpinges in retrospective studies[32–34], which was soon confirmed in a meta-analysis[2]. The first RCTs comparing salpingectomy *vs* no intervention were published in the late 1990s, reporting improved success rates in the group of women who had undergone salpingectomy before IVF[30,31]. Interestingly, in their publication, Strandell *et al.* discussed whether a less radical approach than salpingectomy would be more appropriate, based on the non-reversibility of salpingectomy and the (mostly theoretical) concern of the risk for impairment of ovarian function after salpingectomy[30]. Proximal tubal occlusion appeared as

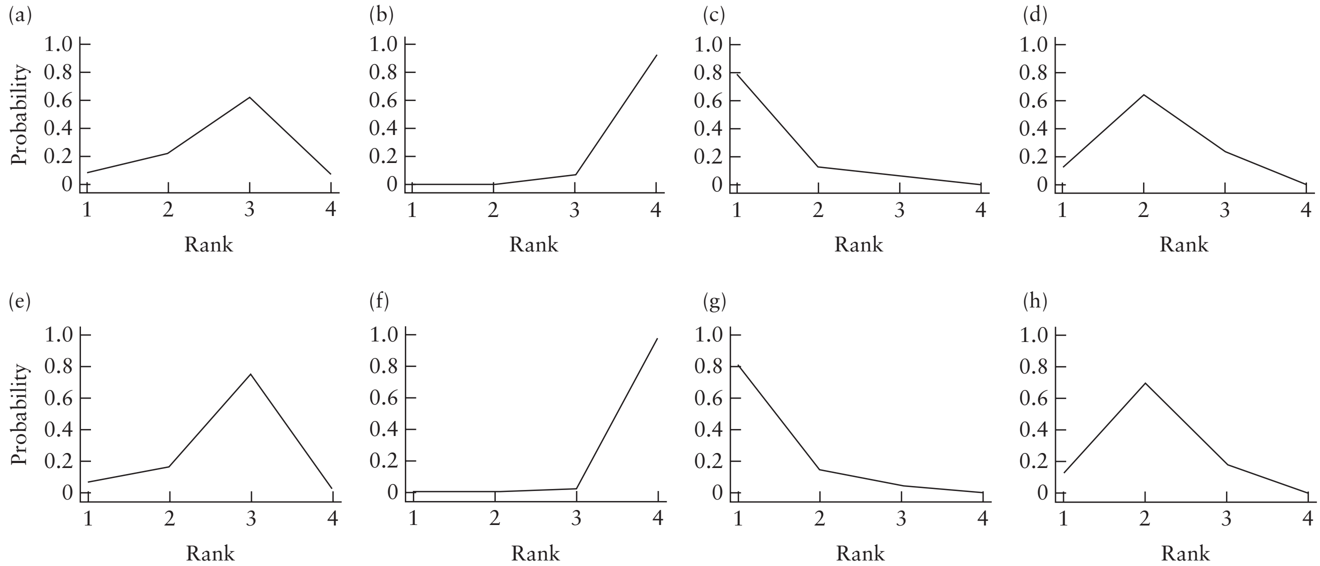

Figure 4 Rankograms for ongoing pregnancy (upper row) and clinical pregnancy (lower row) and the surface under the cumulative ranking curve (SUCRA) for each intervention for hydrosalpinx, performed prior to *in-vitro* fertilization embryo transfer: (a) aspiration (SUCRA = 44.2%); (b) no intervention (SUCRA = 2.7%); (c) proximal tubal occlusion (SUCRA = 90.2%); (d) salpingectomy (SUCRA = 62.8%); (e) aspiration (SUCRA = 42.4%); (f) no intervention (SUCRA = 0.8%); (g) proximal tubal occlusion (SUCRA = 92.1%); (h) salpingectomy (SUCRA = 64.7%). Horizontal axis shows possible ranks and vertical axis shows probability that an intervention is at each rank.

a suitable alternative, as it isolates the hydrosalpingeal fluid without actually removing the tubes, and it has been tested in several retrospective studies and two RCTs[28,29]. Transvaginal aspiration of the hydrosalpingeal fluid was proposed as a less invasive option for women with difficult surgical access to the Fallopian tubes or for cases in which hydrosalpinges are first detected after the commencement of IVF treatment[9]. Finally, Essure®, a hysteroscopically inserted device for tubal occlusion, originally developed for sterilization, has been tried for this purpose, but only in a small retrospective series[35].

There are two previous meta-analyses on the subject[3,4]. A Cochrane meta-analysis from 2010 reported an increase in ongoing and clinical pregnancy rates with salpingectomy *vs* no intervention (OR, 2.14 (95% CI, 1.23–3.73) and OR, 2.31 (95% CI, 1.48–3.62), respectively) and an increase in clinical pregnancy rate with occlusion *vs* no intervention (OR, 4.66 (95% CI, 2.47–10.01))[3]. A more recent meta-analysis did not detect a difference in the clinical pregnancy rates between salpingectomy and tubal occlusion[4]. In terms of completeness, our approach ensures superior utilization of data, as (i) it includes two new studies[26,27], of which one compared aspiration with salpingectomy[26] (this comparison was not included in the Cochrane meta-analysis) and (ii), most importantly, it has a completely different statistical basis, utilizing both direct and indirect evidence. As a result, it improves the accuracy of comparisons, which is particularly useful in a setting with sparse data, and it goes beyond pairwise comparisons providing a relative ranking of treatments, which is clinically relevant when there are multiple options and is unique among the published meta-analyses.

A concern specific to aspiration is that reaccumulation of the hydrosalpingeal fluid might eventually hamper its effectiveness. Indeed, rapid (i.e. within 2 weeks) reaccumulation of the fluid was observed in 22–32% of the women in the RCTs[9,26,27]. Current theories about the mechanisms by which hydrosalpinx impairs the success of IVF-ET postulate that it is mainly through mechanical flushing of the endometrial cavity and impairment of endometrial receptivity rather than through direct toxic action on the developing human embryo[1,36]. Therefore, the reaccumulation of fluid would, if anything, impair implantation. Indeed, the implantation and clinical pregnancy rates were significantly higher in women who underwent salpingectomy compared with those with rapid reaccumulation of fluid after aspiration (43% *vs* 19% for clinical pregnancy rate, respectively) in a randomized trial[26], although this was not confirmed in a smaller study[9]. Moreover, there was no long-term harm after the establishment of pregnancy (presence of embryonic cardiac beats). In our analysis, salpingectomy was the only treatment that significantly improved implantation rates over no intervention. However, the three interventions were not found to differ significantly in network pairwise comparisons.

A finding that probably merits consideration is that the point estimates of occlusion may favor it compared with the other treatments in terms of ongoing pregnancy, clinical pregnancy, miscarriage and ectopic pregnancy rates. However, proximal tubal occlusion is the least studied method and the CIs for the network pairwise comparisons with salpingectomy and aspiration are wide. Generally speaking, the PrIs, which indicate the area within which the treatment effect is expected to lie with 95% probability in a new trial[22], are quite wide for all

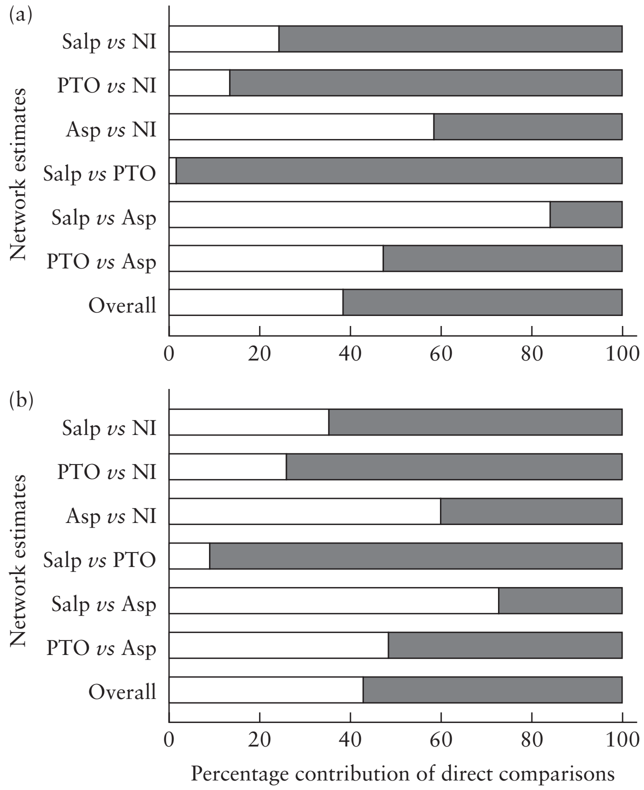

Figure 5 Study limitations bar graphs for ongoing pregnancy (a) and clinical pregnancy (b) in women undergoing intervention or no intervention for hydrosalpinx prior to *in-vitro* fertilization embryo transfer, showing the percentage of information coming from studies with moderate (□) (Asp *vs* NI, Salp *vs* Asp) or low (■) (Salp *vs* NI, PTO *vs* NI, Salp *vs* PTO) risk of bias for every network estimate and overall in the network. No studies were at high risk of bias. Asp, aspiration; NI, no intervention; PTO, proximal tubal occlusion; Salp, salpingectomy.

pairwise comparisons. This means that (i) a new study may show a different direction of effect than the existing ones and (ii) in the light of lack of a definitive advantage of one treatment method *vs* the others, individual circumstances and clinical judgement may be the main determinants for method of choice.

Regarding the comparisons involving no treatment, the PrIs, unlike the 95% CIs for the summary estimate, include zero, suggesting that there could be study settings where the active intervention is not beneficial compared with no treatment. This could be a genuine fact or it could be attributed to the fact that heterogeneity is overestimated due to the small number of studies in the network meta-analysis.

Limitations

The main limitation of our analysis was the small sample sizes for most of the comparisons, of which many were mostly based on indirect data, and the comparison of tubal occlusion *vs* tubal fluid aspiration was solely based on indirect data. This results in wide CIs for the RRs and even wider 95% PrIs. This highlights the uncertainty of existing evidence, as the publication of a study pointing to the different direction of effect is likely for all outcomes and comparisons. The power of our analysis is particularly limited for the outcomes of miscarriage and ectopic pregnancy due to the small numbers and low prevalence of these events, especially ectopic pregnancy (rate, 1.1%).

The scarcity of data and comparisons did not allow us to assess properly the transitivity assumption. The presence of consistency between direct and indirect evidence is an underlying assumption for the validity of network meta-analysis and we assessed it for all outcomes as described elsewhere[21]. There was no significant inconsistency observed for any of the outcomes, as the 95% CIs for the RRRs always included unity. However, the point estimates for RRRs were commonly large, indicating a significant difference between direct and indirect evidence. Large point estimates usually involved the loop of tubal occlusion–no intervention–salpingectomy. A potential reason for this would be that the success rate in the no-intervention group of the study by Kontoravdis *et al.*[28], from which nearly all direct estimates for occlusion were derived, was lower for most outcomes than the respective overall rate for all women receiving no treatment. For example, the ongoing pregnancy rate in the no-intervention group was 2/36 (6%) in the study by Kontoravdis *et al.*[28] *vs* 1.1% in the whole sample; therefore, it is reasonable that the direct RR for occlusion was 6.90 *vs* 3.22 for the network RR. In fact, although inconsistency is commonly seen as threatening the validity of network meta-analysis, it may also serve in highlighting areas of spuriously distorted evidence.

Similarly, the small number of studies in each comparison did not allow us to assess formally the distribution of effect modifiers across comparisons and were based on clinical criteria, i.e. the similarity of studies assessing different treatments. Finally, the included studies cover a 15-year period, during which the IVF procedures have changed, potentially leading to improved results anyway. The impact of this effect is likely to be low, but the small number of studies prevented a formal exploration through cumulative meta-analysis.

Quality of evidence

We assessed the quality of evidence for ongoing and clinical pregnancy, according to the GRADE guideline[37] adapted for network meta-analyses[25]. We downgraded all comparisons involving aspiration by one level for study limitations. We also downgraded all comparisons by one level for indirectness, as the assessment for transitivity was limited by insufficient data, despite the fact that the baseline characteristics of the patients did not differ across studies. Adding to that the potential for imprecision, arising from the suboptimal information size and/or the presence of 95% CI including the unit, the quality of evidence is of moderate to low quality when comparing interventions with no intervention, and low to very low quality for the comparisons between two active

Table 2 GRADE summary of findings on relative effects of salpingectomy, proximal tubal occlusion, aspiration of hydrosalpingeal fluid or no intervention prior to *in-vitro* fertilization embryo transfer on ongoing and clinical pregnancy rates

Intervention	*Events (n) (studies (N))*	*Relative effect (RR (95% CI))*	*Rate per 1000 cycles*	*NNT (95% CI)*	*Quality of evidence (GRADE)*	*Comment*
Aspiration *vs* no intervention						
Ongoing pregnancy	110 (1)					
Direct evidence		3.00 (1.17–7.68)	91	5.5 (1.6–64.6)	NA (one study)	
Network MA		1.84 (0.83–4.07)	91	NA	Low	1,2,4
Clinical pregnancy	176 (2)					
Direct evidence		2.11 (1.18–3.82)	146	6.2 (2.4–40.3)	Low	1,3,4
Network MA		1.73 (1.02–2.95)	146	9.4 (3.5–342)	Low	1,2,4
Salpingectomy *vs* no intervention						
Ongoing pregnancy	329 (3)					
Direct evidence		1.83 (1.17–2.86)	165	7.3 (3.3–35.6)	Moderate	3,4
Network MA		2.24 (1.27–3.95)	165	4.9 (2.1–22.4)	Moderate	2,4
Clinical pregnancy	395 (3)					
Direct evidence		2.09 (1.11–3.95)	189	4.9 (1.8–48.1)	Moderate	3,4
Network MA		2.12 (1.36–3.31)	189	4.7 (2.3–14.7)	Moderate	2,4
Tubal occlusion *vs* no intervention						
Ongoing pregnancy	65 (1)					
Direct evidence		6.90 (1.01–46.93)	133	1.3 (0.2–752)	NA (one study)	–
Network MA		3.22 (1.27–8.14)	133	3.4 (1.1–27.8)	Moderate	2,4
Clinical pregnancy	209 (2)					
Direct evidence		3.41 (1.83–6.34)	123	3.4 (1.5–9.8)	Moderate	3,4
Network MA		2.64 (1.51–4.62)	123	4.9 (2.2–15.9)	Moderate	2,4
Tubal occlusion *vs* salpingectomy						
Ongoing pregnancy	100 (1)					
Direct evidence		1.35 (0.83–2.21)	340	NA	NA (one study)	–
Network MA		1.44 (0.69–3.00)	340	NA	Low	2,3,4
Clinical pregnancy	238 (2)					
Direct evidence		1.16 (0.86–1.56)	391	NA	Moderate	3,4
Network MA		1.24 (0.82–1.89)	391	NA	Low	2,3,4
Tubal occlusion *vs* aspiration						
Ongoing pregnancy	No direct data					
Direct evidence		—	—	—	—	
Network MA		1.75 (0.67–4.55)	252*	NA	Very low	1,2,3,4
Clinical pregnancy	No direct data					
Direct evidence		—	—	—	—	
Network MA		1.54 (0.82–2.86)	293*	NA	Very low	1,2,3,4
Salpingectomy *vs* aspiration						
Ongoing pregnancy	160 (1)					
Direct evidence		1.53 (0.94–2.49)	238	NA	NA (one study)	
Network MA		1.22 (0.63–2.32)	238	NA	Very low	1,2,3,4
Clinical pregnancy	160 (1)					
Direct evidence		1.45 (0.93–2.27)	275	NA	NA (one study)	
Network MA		1.23 (0.75–2.00)	275	NA	Very low	1,2,3,4
Ranking of treatments						
Outcome: ongoing pregnancy		NA	NA	NA	Low	1,2,4,5
Outcome: clinical pregnancy		NA	NA	NA	Low	1,2,4,5

(1) Study limitations: downgraded by one level because proportion of information from studies at moderate/high risk of bias was sufficient to affect interpretation of results (Figures S5 and S6). (2) Indirectness: downgraded by one level because we were not able to assess properly the transitivity assumption due to lack of sufficient data, despite baseline characteristics of patients not differing substantially between included studies. (3) Imprecision: downgraded by one level due to CIs of effect sizes. For direct meta-analysis: 95% CIs including the unit or optimal information size not reached. (4) Publication bias: formal assessment was not feasible due to the small number of studies. However, based on the other four criteria described in the GRADE Handbook (experimental design, similar study size, no lag bias, comprehensive search strategy), we did not downgrade for publication bias. (5) Imprecision for ranking of treatments: not downgraded because rankograms (Figure 4) suggested that the relative ranking for both outcomes was quite precise. *Pooled rate from all studies involving aspiration. MA, meta-analysis; NA, not applicable; NNT, number needed to treat; RR, risk ratio.

interventions. This indicates that the true effect is likely to be substantially different from the estimate of effect, and this particularly affects aspiration, as the respective studies were all of moderate quality. Our confidence for the relative ranking of treatments is slightly stronger, as the rankograms are not suggestive of imprecision. Still, the quality of the evidence for relative ranking is low, indicating that the true effect may be substantially different from the estimate of the effect. In any case, further research is clearly needed.

Conclusions

Evidence from this network meta-analysis indicates that proximal tubal occlusion, salpingectomy and aspiration of the hydrosalpingeal fluid prior to IVF-ET improve clinical pregnancy rates compared with no intervention. Tubal occlusion and salpingectomy also improve ongoing pregnancy rates. Proximal tubal occlusion ranks highest for most of the outcomes assessed, whereas no intervention scores consistently as the least effective strategy for all outcomes. The PrIs are wide for all comparisons and the level of evidence as per GRADE is commonly low/very low, especially when aspiration is involved, indicating that results are not conclusive and should be interpreted with caution. As a future direction, a large RCT comparing the three active interventions is needed.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Network plot for miscarriage and ectopic pregnancy rates.

Figure S2 Risk ratios for miscarriage and ectopic pregnancy as estimated from network meta-analysis for every possible pair of interventions for hydrosalpinx performed prior to *in-vitro* fertilization embryo transfer.

Figure S3 Rankograms for miscarriage and ectopic pregnancy and surface under the cumulative ranking curve for each intervention for hydrosalpinx, performed prior to *in-vitro* fertilization embryo transfer.

Figure S4 Inconsistency plots for ongoing pregnancy, clinical pregnancy, miscarriage and ectopic pregnancy in women undergoing intervention or no intervention for hydrosalpinx prior to *in-vitro* fertilization embryo transfer, presenting the ratio of risk ratio between direct and indirect estimates for each closed loop in the network.

Figure S5 Comparison-adjusted funnel plot for clinical pregnancy. Each point represents the difference between a study-specific estimate of *ln(RR)* and the direct summary estimate of the respective comparison.

Figure S6 Contribution plots for ongoing pregnancy, clinical pregnancy, miscarriage and ectopic pregnancy in women undergoing intervention or no intervention for hydrosalpinx prior to *in-vitro* fertilization embryo transfer, presenting the percentage contribution of each direct comparison to each network estimate and to the entire network.

Appendix S1 Search strategy.

Appendix S2 Items of data extraction.

Table S1 Characteristics of excluded trials

Table S2 Characteristics of included randomized controlled trials comparing salpingectomy, proximal tubal occlusions, aspiration of hydrosalpinx fluid and no intervention for treatment of hydrosalpinx prior to *in-vitro* fertilization embryo transfer

Table S3 Cochrane Collaboration – risk of bias tool for randomized controlled trials

Table S4 Results of individual studies

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Shireen Meher, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Ruben Dario Fernandez.

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Tratamiento quirúrgico de hidrosalpinx previo a la transferencia de embriones de fertilización *in-vitro*: un metaanálisis en red

RESUMEN

Objetivo La presencia de hidrosalpinx perjudica el resultado de la de transferencia de embriones de fertilización *in-vitro* (FIV/TE). Para mejorar el resultado se han empleado métodos quirúrgicos, ya sea aspirando el líquido o aislando las trompas de Falopio afectadas. El objetivo de este metaanálisis en red fue comparar la eficacia de los tratamientos quirúrgicos de hidrosalapinx antes de la FIV/TE.

Métodos Se realizó una búsqueda electrónica en MEDLINE, Scopus, el Registro Central Cochrane de Ensayos Controlados (Central) y el Registro de los EE.UU de ensayos clínicos de artículos publicados desde el inicio hasta julio de 2015. Los criterios de elegibilidad fueron ensayos controlados aleatorios de mujeres con hidrosalpinx antes de la FIV/TE que compararon la aspiración del fluido guiada por ultrasonido, la oclusión tubárica, la salpingectomía o la no intervención. El embarazo en curso fue el resultado primario y el embarazo confirmado ecográficamente, el embarazo ectópico y el aborto fueron los resultados secundarios. Se realizó un metaanálisis en red de efectos aleatorios de la síntesis de evidencia directa e indirecta de los ensayos incluidos. Se estimaron los tamaños de los efectos relativos como cocientes de riesgo (CR) y se obtuvo la clasificación relativa de las intervenciones mediante curvas de clasificación acumulativas. Se evaluó la calidad de la evidencia según las directrices de GRADE, adaptadas al metaanálisis en red.

Resultados La oclusión tubárica proximal (CR; 3,22; IC 95% 1,27–8,14) y la salpingectomía (CR; 2,24; IC 95% 1,27–3,95) para el tratamiento de hidrosalpinx fueron mejores para el embarazo en curso que la no intervención. En cuanto al resultado de embarazo confirmado ecográficamente, las tres intervenciones parecieron ser superiores a la no intervención. No se pudo determinar un superioridad entre los tres métodos quirúrgicos para cualquiera de los resultados. En cuanto a la clasificación relativa, la oclusión tubárica fue el mejor tratamiento quirúrgico, seguido por la salpingectomía, para las tasas del embarazo en curso y del confirmado ecográficamente. No se detectó ninguna inconsistencia estadística significativa, sin embargo las estimaciones puntuales de algunos factores de inconsistencia y sus IC fueron relativamente grandes. Las principales limitaciones fueron el reducido número de estudios y sus tamaños. La calidad de la evidencia fue típicamente baja o muy baja, especialmente cuando se empleó aspiración, lo que indica que los resultados no fueron concluyentes y se deben interpretar con precaución.

Conclusiones La oclusión tubárica proximal, la salpingectomía y la aspiración para el tratamiento de hidrosalpinx puntuaron regularmente mejor que la no intervención, en el resultado de la FIV/TE. En cuanto a la clasificación relativa, la oclusión tubárica proximal pareció ser la intervención más eficaz, seguido por la salpingectomía.

体外受精胚胎移植前手术治疗输卵管积水：一项网络荟萃分析

目的：输卵管积水会损害体外受精胚胎移植（in-vitro fertilization embryo transfer，IVF-ET）的结局。人们一直在尝试不同的手术方法——抽吸术或输卵管粘连松解术来改善结局。本篇网络荟萃分析的目的是比较 IVF-ET 前不同手术方法治疗输卵管积水的有效性。

方法：计算机检索 MEDLINE、Scopus、Cochrane 临床对照试验资料库（Central）和美国临床试验注册中心中的文献，检索时间从建库至 2015 年 7 月。纳入标准为对 IVF-ET 前输卵管积水的女性中超声引导下输卵管积水抽吸术、输卵管栓塞术、输卵管切除术或无干预措施进行比较的随机对照试验。主要结局为继续妊娠，次要结局为临床妊娠、异位妊娠和流产。进行随机效应网络荟萃分析，合并纳入试验的直接和间接证据。采用危险比（risk ratios，RRs）评估相对效应量，采用累积排序曲线获得各种干预方法的相对排序。评估根据适用于网络荟萃分析的 GRADE 指南进行的证据质量分级。

结果：在继续妊娠方面，近端输卵管栓塞术[RR，3.22（95% CI，1.27~8.14）]和输卵管切除术[RR，2.24（95% CI，1.27~3.95）]治疗输卵管积水优于无干预措施。在临床妊娠方面，三种干预措施似乎均优于无干预措施。对任一结局来说，三种手术方法比较无差异。根据相对排序，在继续妊娠率和临床妊娠率方面，输卵管栓塞术是最佳的手术方法，其次为输卵管切除术。未见明显的统计学不一致性，然而某些不一致因素的点估计值及其可信区间变异较大。研究数量少、规模小是主要局限性。证据质量通常低/极低，特别是采用输卵管积水抽吸术时，表明结果并不确定，应当谨慎处理。

结论：在 IVF-ET 结局方面，近端输卵管栓塞术、输卵管切除术和输卵管积水抽吸术治疗输卵管积水均优于无干预措施。根据相对排序，近端输卵管栓塞术可能是最有效的治疗方法，其次为输卵管切除术。

