Systematic Review and Meta-Analysis

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Effect comparison of salpingectomy versus proximal tubal occlusion on ovarian reserve

A meta-analysis

Shuxie Wu, MD, Qiong Zhang, MD, Yanping Li, MD*

Abstract

Introduction: The women with hydrosalpinx have lower pregnancy rates in assisted reproductive technology, and only laparoscopic salpingectomy and tubal occlusion has proven to be effective to improve the outcome of in vitro fertilization. The main objective of the present meta-analysis was to assess and compare the ovarian reserve after salpingectomy or proximal tubal occlusion (PTO) in the published literature.

Material and methods: We considered all published cohort (retrospective and prospective) and cross-sectional studies as well as randomized controlled trials that investigated changes in serum anti-Müllerian hormone (AMH), follicle-stimulating hormone levels or antral follicle count (AFC) following salpingectomy or PTO. Two investigators (SW, QZ) independently screened the full text of all identified articles to assess relevance to our meta-analysis.

Results: In total, 648 patients were included in 5 studies. In the analysis of comparative studies. In the analysis of comparative studies, the follicle-stimulating hormone of salpingectomy had no significant difference with that of PTO (WMD 0.46IU/L, 95% CI [-0.14,1.05]). The AMH and AFC of salpingectomy were significantly higher than that of PTO (AFC: WMD -0.80IU/L, 95% CI [-1.46, -0.14]; AMH: WMD -1.01IU/L, 95% CI [-1.28, -0.74]).

Conclusions: Salpingectomy did more harm to ovarian reserve than PTO in the short-term. However, the long-term effects on ovarian reserve remains uncertain.

Abbreviations: AFC = antral follicle count, AMH = anti-Müllerian hormone, ART = assisted reproductive technology, FSH = follicle-stimulating hormone, IVF = in vitro fertilization, PTO = proximal tubal occlusion, RCTs = randomized controlled trials.

Keywords: assisted reproductive technology, hydrosalpinx, laparoscopic salpingectomy, meta-analysis, ovarian reserve, proximal tubal occlusion

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Ethics approval and consent to participate was not applicable. Our manuscript does not involve human data or tissue.

The manuscript was approved by all authors for publication. I would like to declare that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Tubal infertility, which is the main indication of in vitro fertilization (IVF)-embryo transfer accounts for about 25% to 35% of female infertility.[1] The most severe manifestation of women suffering from tubal disease is hydrosalpinx. It is now accepted that women with hydrosalpinx have lower pregnancy rates in assisted reproductive technology (ART), as combination of mechanical and chemical factors.[2] The current treatment options for hydrosalpinx mainly includes: salpingectomy, tubal proximal ligation, transvaginal aspirationat and salpingostomy, but only laparoscopic salpingectomy and tubal occlusion has proven to be effective to improve the outcome of IVF.[3] Currently, laparoscopic salpingectomy and tubal occlusion seem to be helpful to improve the success rate of IVF. Reproductive surgery is still necessary as a complementary treatment for optimizing IVF outcomes for patients with not only hydrosalpinges but also select cases of endometriomas and myomas. In order to prevent signs or suspicions of hydrosalpinx, the National Institutes of health and Clinical Excellence has recommended laparoscopic salpingectomy before ART.As the anatomical position of the blood vessels and nerves supplying for the oviduct and ovary are close to each other, interruption of the blood supply of the ovary may occur after laparoscopic surgery, which lead to poor ovarian reserve.[4–6] A fertility specialist should take quantitative ovarian reserve into account for patients requiring treatment with ART. With the increasing success rate of IVF, the potential deleterious impact of salpingectomy and proximal tubal occlusion (PTO) on success rates became more apparent.

However, salpingectomy is a feasible, sure surgical procedure and an expert surgeon could minimize ovarian and tubal blood vessel injuries.Thus, it is worthwhile to search the actual benefits/harms of laparoscopic salpingectomy and tubal occlusion before IVF to ovarian reserve in women with hydrosalpinx. The main objective of the present meta-analysis was to assess and compare the ovarian reserve after salpingectomy or PTO in the published literature. It will help both the clinician and the patient when they face the choice between PTO and salpingectomy to pretreat hydrosalpinx.

2. Material and methods

The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Meta-analysis Of Observational Studies in Epidemiology guidelines.

We considered all published cohort (retrospective and prospective) and cross-sectional studies as well as randomized controlled trials (RCTs) that investigated changes in serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH) levels or antral follicle count (AFC) following salpingectomy or PTO.

2.1. Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria were used to perform the systematic review. A literature search in EMBASE, PubMed, Cochrane Library and Web of Science from January 2000 to January 2019 was performed by the first author (SW) and (QZ) aiming to identify all studies that evaluated the effect of both bilateral salpingectomy and PTO on ovarian reserve as estimated by changes in serum AMH, FSH levels or AFC. The following search strategy was used occurring in the title and the abstract: (laparotomy OR salpingectomy OR tubal occlusion) AND (ovarian function OR ovarian reserve OR anti-Mullerian hormone OR follicle-stimulating hormone OR AFC).

2.2. Selection of studies

2.2.1. Inclusion and exclusion criteria. Studies had to fulfill all the following criteria for eligibility:

(1) published cohort (retrospective and prospective) and RCTs;
(2) diagnosis of hydrosalpinges had to be confirmed at hysterosalpingography or laparoscopy;
(3) outcomes including serum FSH concentration or AFC or serum AMH following bilateral salpingectomy or PTO and before surgery.

Reviews and case report, duplicated data, and longitudinal studies referring to intrauterine insemination were exluded. Two investigators (SW, QZ) independently screened the full text of all identified articles to assess relevance to our meta-analysis.

2.3. Data Extraction

All retrieved articles were assessed according to standardized Newcastle-Ottawa scale.

Data extraction was performed independently by 2 reviewers (SW, QZ). The following data were recorded from each of the eligible studies: demographic data, age and number of patients, methodology (study design), surgical intervention, AMH, AFC, FSH, postoperative duration, and other outcomes. AMH, AFC, FSH, and surgical intervention were the major outcomes. Postoperative duration, demographic data, age and number of patients, methodology (study design) and other outcomes were the secondary outcomes. The parameters of ovarian response include number of AMH, AFC, FSH, and postoperative duration. When reaching a consensus was difficult, the third author (YL) made the final decision on the eligibility of the study and the data extraction.

2.4. Data analysis

The continuous variables from each of the studies eligible for meta-analysis were expressed as a weighted mean difference (WMD) with 95% CI.An $I^2 > 50\%$ was indicative of signifificant heterogeneity between studies. When heterogeneity was significant, a random-effect model was used for meta-analysis. Fixed effect meta-analysis was used when there was no significant heterogeneity. Meta-analysis was performed using RevMan Software (version 5.1.; The Cochrane Collaboration, 2011).

2.5. Risk of bias in individual studies

The results of methodologic bias assessment of 3 retrospective analysis were using the standardized Newcastle-Ottawa scale. Each article was scored according to 3 categories including selection (maximum 3 stars), comparability (3 stars), and outcomes (2 stars). Selection was rated according to recruitment bias, case-cohort representative and ascertainment of exposure. Comparability was assessed based on adjustment of analysis for 3 confounders including women's age (<40 years), baseline serum AMH (≥1.0 ng/mL) and laterality of surgery. Outcome was scored according to duration of follow-up and outcome assessment. The results of methodologic bias assessment of 2 RCTs were using the Cochrane bias risk assessment and will include the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

3. Results

Twenty-three studies identified through the electronic search were screened for relevance, of which 5 were deemed eligible for the meta-analysis. (Fig. 1)

3.1. Characteristics of all Included Studies

Characteristics of the studies included in the meta-analysis are presented in Table 1. Eligible studies were published between 2000 and 2019 and included 648 patients. There were 3 retrospective cohort and two RCTs. Details of the 5 included studies are shown in Table 1.

3.2. Intervention

Five studies were associated with laparoscopic bilateral salpingectomy.[9–13] Two studies were associated with laparoscopic PTO.[11,12] Three studies were associated with laparoscopic PTO and salpingostomy.[9,10,13] One study was associated with salpingostomy.[9] One study was associated with laparoscopic

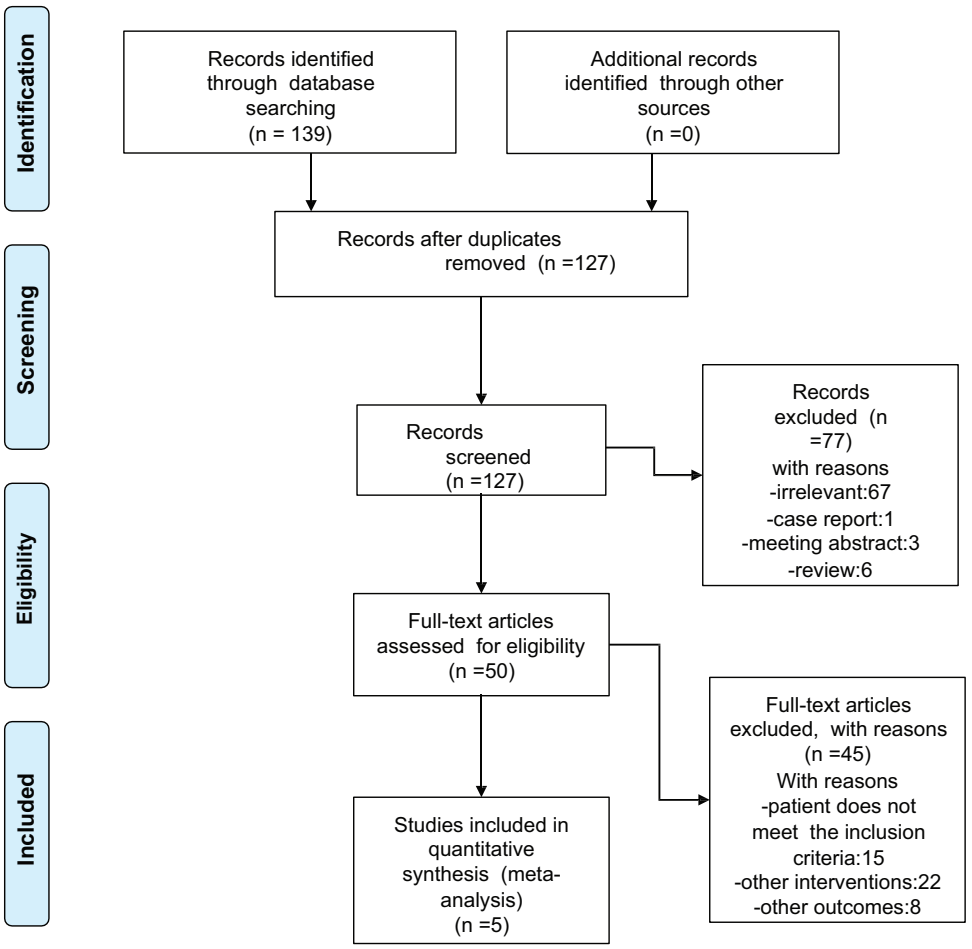

Figure 1. Studies included in qualitative synthesisStudies included in qualitative synthesis. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. PRISAMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

unilateral salpingectomy, PTO and salpingostomy[10] which would not be considered into the final result as 2 of the 3 surgical methods could both affect ovarian reserve. However, we classified patients who have conducted both PTO and salpingostomy as PTO group, with the consensus that salpingostomy wouldn't hurt ovarian reserve.[14]

3.3. Length of follow up after laparoscopy

The length of follow up after laparoscopy was 3 months in 3 studies,[9–11] 2 months in 1 study[12] and 1 months in 2 study.[10,13] One study reported 2 postoperative measurements at 1 month and at 3 months.[10]Those whose length were not specific were not included.

Table 1

Characteristics of the 7 studies included in the meta-analysis.

Authors	Year	Country	Design	Patients (n)	Age (yr) mean ± SD	Intervention of participants	Rate	Follow up (mo)	Outcomes
Li et al	2010	China	Retrospective cohort	111	28.6 ± 3.32	A:Ostomy B:PTO+ostomy C:Bilateral salpingectomy	A:48/111 B:33/111 C:30/111	3	FSH,AFC
Lv et al	2013	China	Retrospective cohort	88	NR	A:PTO+ostomy B:Unilateral salpingectomy +PTO+ostomy C:Bilateral salpingectomy	A:30/88 B:28/88 C:30/88	1 and 3	FSH,AFC
Vignarajan et al	2014	India	Randomized controlled trial	72	NR	A:Bilateral salpingectomy B:PTO	A:35/72 B:37/72	3	FSH,AMH,AFC
Vignarajan et al	2015	India	Randomized controlled trial	165	A:29.3 ± 2.6 B:29.4 ± 3.2	A:PTO B:Bilateral salpingectomy	A:83/165 B:82/165	2	FSH,AMH,AFC
Xie et al	2018	China	Retrospective cohort	288	A:32.5 ± 6.8 B:33.0 ± 7.0	A:Bilateral salpingectomy B:PTO+ostomy	A:102/288 B:186/288	1	FSH,AFC

AFC = antral follicle count, AMH = anti-Müllerian hormone, E2 = estradiol, FSH = follicle-stimulating hormone, PTO = proximal tubal.

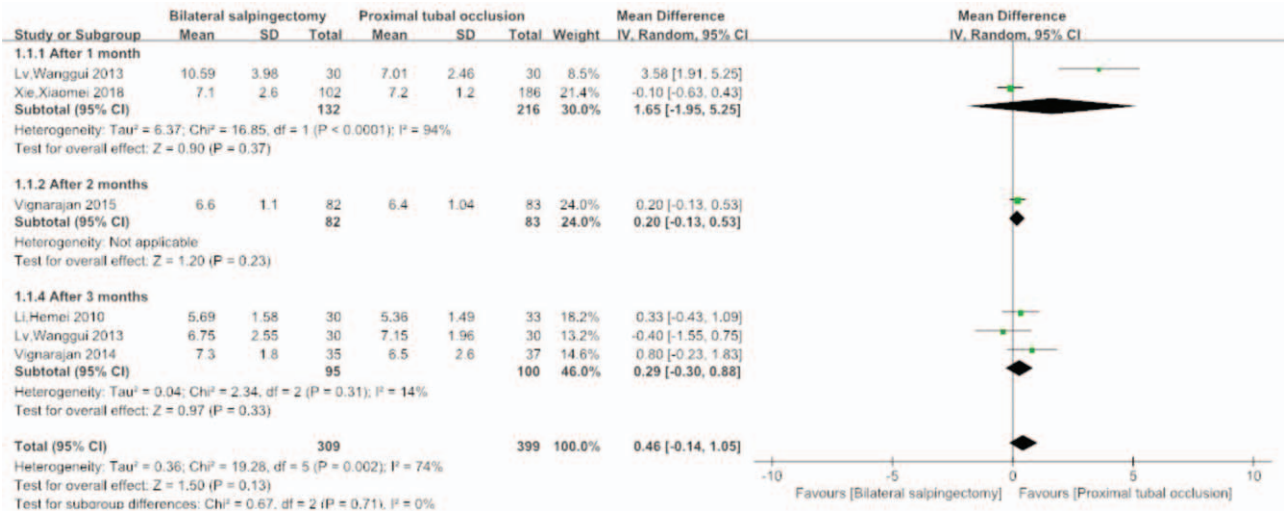

Figure 2. Weighted mean difference in serum follicle-stimulating hormone concentrations after salpingectomy or proximal tubal occlusion: pooled results for all 7 studies.

3.4. Quality Assessment of Studies

The results of methodologic bias assessment of 3 retrospective analysis were using the standardized Newcastle-Ottawa scale (Table 2). The results of methodologic bias assessment of 2 RCTs were using the Cochrane bias risk assessment (Fig. 5).

3.5. Study design

In all studies, patients were diagnosed with hydrosalpinx by ultrasound or laparoscopy. Two studies clarified the diagnostic criteria for hydrosalpinx with a hydrosalpinx > 3.0 cm,[11,12] and the remaining 3 did not specify. Four studies identify patient age < 40 years old.[9,11–13] Patients with a history of endometriosis, previou surgery on the ovaries, polycystic ovary syndrome, and such uterine conditions as adenomyosis and uterine synechiae were excluded in all studies. Patients with any contraindications for laparoscopic surgery before were excluded in 4 studies.[9–12] Patients with AMH<1.1ng/mL were excluded in two studies.[11,12]

3.6. Salpingectomy surgery

In all studies, operations were performed laparoscopically. None of the surgeons mentioned.

3.7. AMH kits

In two studies, AMH was measured by enzyme-linked immunosorbent assay (AMH Gen II ELISA; Beckman Coulter, Brea, CA).[11,12]

3.8. Outcome analysis

FSH outcome of 2 surgical approaches. Among the 5 studies included in the analysis, 2 of them reporting the FSH level and AFC at 1 month after surgery,[10,13] 1 of them also reported it at 3 months after surgery,[10] and 3 of them reported it at 3 months after surgery.[9–11] There were no statistically significant differences in FSH level between the salpingectomy group and the PTO group at 1 month after surgery (132 VS 216, WMD 1.65IU/L, 95% CI[-1.95,5.25]). Similarly, no statistically significant differences at 2 months (82 VS 83, WMD0.20IU/L, 95% CI [-0.13,0.53]) and 3 months (95 VS 100, WMD 0.29IU/L, 95% CI [-0.30,0.88]) after surgery. The pooled analysis showed no statistically significant difference between the salpingectomy group and the PTO groups (309 VS 399, WMD 0.46IU/L, 95% CI [-0.14,1.05]). (Fig. 2)

AFC outcome of 2 surgical approaches. For all the 5 studies included in the meta-analysis, 2 of them reported the AFC at 1 month after surgery,[10,13] 1 of them reported it at 2 months after surgery,[12] and 3 of them reported it at 3 months after surgery.[9–11] There were no statistically significant differences in AFC between the salpingectomy group and the PTO groups at 1 month after surgery (132 VS 216, WMD -0.82, 95% CI [-1.65,0.01]). Similarly, no significant differences at 3 months after surgery (95 VS 100, WMD -0.28, 95% CI [-0.99,0.43]). But the statistically significant differences was shown at 2 months after surgery (82 VS 83, WMD -1.90, 95%CI [-2.54,-1.26]). Pooled analysis showed a significant difference between the salpingectomy group and the PTO groups (309 VS 399, WMD -0.80IU/L, 95% CI [-1.46, -0.14]). (Fig. 3).

Table 2

Risk of bias using standardized Newcastle-Ottawa scale.

Author	Year	Selection (***)	Comparability (***)	Outcome (**)	Overall
Li et al	2010	**	**	**	6
Lv et al	2013	**	*	**	5
Xie et al	2018	**	**	**	6

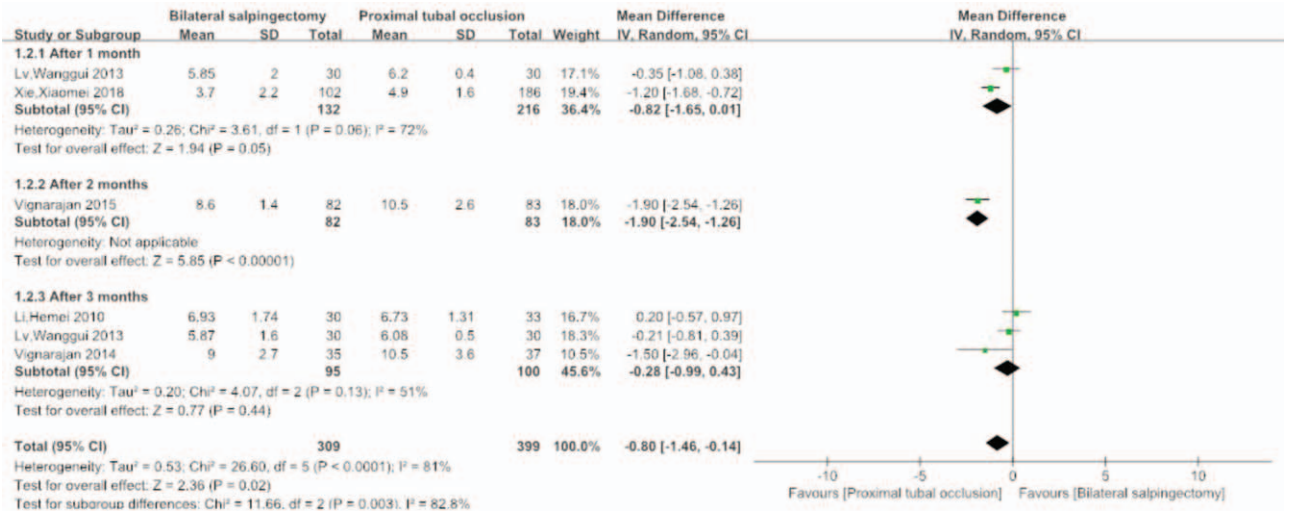

Figure 3. Weighted mean difference in antral follicle count concentrations after salpingectomy or proximal tubal occlusion: pooled results for all 6 studies.

AMH outcome of 2 surgical approaches. For the 5 studies included in the analysis, 1 of them reported the AMH at 2 month after surgery,[12] and one of them reported it at 3 months after surgery.[11] There were statistically significant differences in AMH between the salpingectomy group and the PTO groups both at 2 months (82 VS 83, WMD -1.10, 95% CI[-1.42,-0.78]) and at 3 months after surgery (35 VS 37, WMD -0.80, 95% CI [-1.29,-0.31]). Pooled analysis showed significant difference between the salpingectomy group and the PTO groups (117 VS 120, WMD -1.01IU/L, 95% CI [-1.28, -0.74]). (Fig. 4).

4. Discussion

To the best of our knowledge, this is the first meta-analysis to compare the impact of salpingectomy and PTO on ovarian reserve. In the present study, we evaluated studies comparing ovarian reserve in patients treated with laparoscopic salpingectomy or PTO month by month. We demonstrated that there were no significant differences in FSH between the laparoscopic salpingectomy and PTO groups. Compared with the salpingectomy group, significantly higher AFC were achieved in the 2 months subgroup and in total of the PTO group, and significantly higher AMH were achieved in each time-specific subgroup of the PTO group, also in total.

Several retrospective studies have shown that hydrosalpinx may significantly reduce the rate of embryo implantation and clinical pregnancy and improve the rate of abortion and ectopic pregnancy.[15,16] The mechanism of hydrosalpinx affecting the success rate of IVF is still not completely clear. It is mainly believed that there are several reasons from the following aspects: hydrosalpinx fluid could return to the uterine cavity and may affect endometrial receptivity, cause an embryotoxic agent, mechanical hindrance to implantation and simply wash out embryos and so on.[17] Thus, it is generally believed that patients with unilateral or bilateral hydrosalpinges would be better to have pretreatment of hydrosalpinx before their IVF treatment.

It has been proved that PTO or salpingectomy performed as a pretreatment could significantly increase the rate of successful implantation and for clinical and ongoing pregnancy.[18,19] Nevertheless, both of them involve some certain surgical risks. Ovarian blood supply mainly comes from the arterial arch in the ovarian artery and the mesosalpinx. Tubal excision may damage the arch of the artery, while tubal ligation at the proximal end and distal salpingostomy may cause less damage to the mesangium.[20] Then the continuity of blood vessels between the oviduct and ovary is damaged, resulting in insufficient blood supply to the ovary and dysfunction, especially in women with previous abdominal surgery and/or extensive pelvic adhesions,

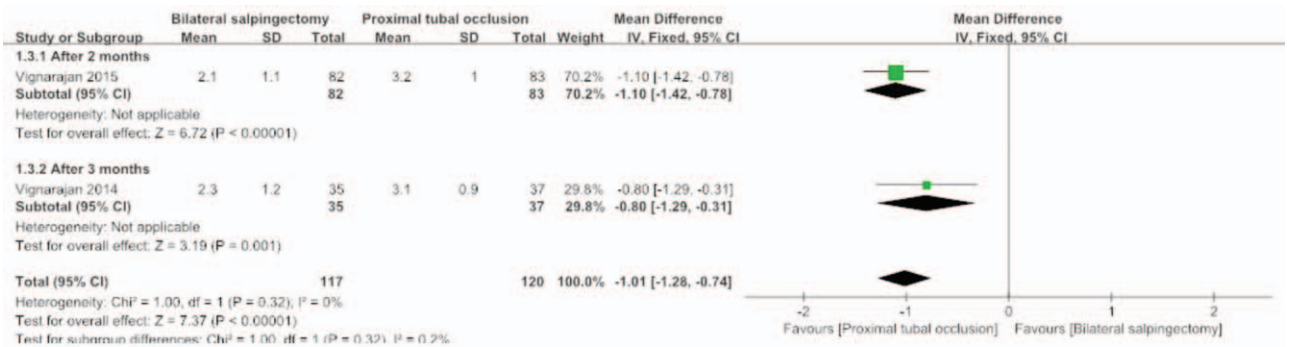

Figure 4. Weighted mean difference in serum anti-Müllerian hormone concentrations after salpingectomy or proximal tubal occlusion: pooled results for all 2 studies.

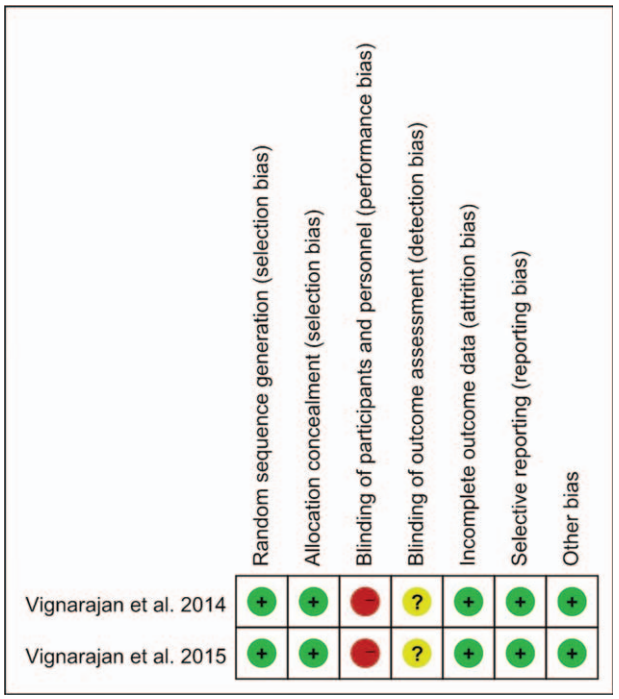

Figure 5. Risk of bias using Cochrane bias risk assessment.

which might result in a subsequently reduced efficacy of ovarian reserve.

Li[9] had proved that blood pressure would relieve and ovarian function would prove in the immediate postoperative period when hydrosalpinx was drained, the period mentioned was 3 months. But the long-term postoperative ovarian function still needs further study. Xu's meta-analysis[21] shown that patients treated by laparoscopic surgery including PTO and salpingectomy had better clinical pregnancy rate, implantation rate, live birth rate and less miscarriage rate than Essure, while salpingectomy and PTO had no significant differences in clinical pregnancy rate, implantation rate and live birth rate. Nakagawa proved that PTO can preserve ovarian reserve.[8] It was believed that PTO shall not hurt ovarian function, but salpingectomy will need further evaluation.[7,22,23] Chan et al had demonstrated that salpingectomy would impair ovarian blood flow and reduce AFC shortly after the operation, but the long-time performance was not mentioned.[24]

This meta-analysis is consistent with the above results. On the whole, the serum AMH level and AFC of PTO were significantly higher than those of salpingectomy, and the serum FSH level of PTO were no significant difference. The result realved that salpingectomy produced much damage to ovarian reserve than PTO.

As for FSH, no obvious difference is revealed. It may attribute to the easily numerical fluctuation of FSH as the source of FSH is basophil of the anterior pituitary and itself has self-adjustment. It has been proved that AFC was a better prediction of poor ovarian response than FSH.[25] To illustrate the changes in FSH monthly, a larger sample size would be needed.

With regards of AFC, it was interesting to see there were only significant difference between two group in after 2 months group. It may be due to the possibility that although the blood supply to the ovaries was reduced after surgery, most of the surgery was completed at the 3rd-7th day after the end of menstruation. At this time, the antral follicles had formed already and the affect may not come up immediately. In the second month after surgery, the new antral follicles were highly influenced by the effects of ischemia on the ovary sustained all the month and truly reflected the impact of laparoscopic surgery on ovarian reserve. In the third month, the collateral circulation was established, which compensated for the impact of the surgery, thus reducing the gap between the 2 groups which was consistent with the points that the recovery of the laparoscopic surgery occurs in 12 to 14 weeks.[12] But, compared with PTO, salpingectomy was more harmful to the ovaries in all. But whether salpingectomy caused a permanent damage in ovarian reserve or just an ephemeral effect needed further researches.

We generally think that the results of AFC and AMH are directly proportional. From the results of AMH, salpingectomy has significantly more ovarian damage than PTO. This is fully consistent with the findings of the AFC group. Similarly, the long-term effects of surgery on the ovaries require advanced long-term follow-up studies.

As in younger women, tubal dysfunction could be often the only reason for sterility, it's difficult to think that the worsening of the ovarian reserve after tubal surgery significantly impacts the success rate of itself IVF procedure, Given to data of this meta-analysis, to minimize the reduction of ovarian reserve in case of IVF procedures after hydrosalpinx, in patients with poor ovarian reserve prior to surgery, pick-up could be performed with subsequent embryo freezing before both salpingectomy or proximal ligation, even if some authors, like Xu,[21] have demonstrated that salpingectomy and proximal tubal ligation were equally effective in restoring IVF success rates for women without hydrosalpinges. Moreover, a salpingectomy is not useful only to remove any source of inflammation and the release of pro-inflammatory cytokines, but it also plays a crucial role in the prevention of ovarian and tubal cancers. So it should almost always be considered, both in cases of good or bad ovarian reserve.

We acknowledged the limitations present in this meta-analysis. First, few studies were included and the duration follow up was short, resulting in difficulty of drawing objective conclusion and lack of the assessment of long-term impact. Second, there is heterogeneity among studies with regards to the surgical techniques and tubal pathologies. Third, the current study is not registered and there may be a small offset, but we still strictly follow the steps of the systematic review. Therefore, it is regretful that all articles did not mention the specific operator, which may lead to an increase in heterogeneity. Also, the studies included were heterogeneous in terms of study location, population, number of patients of different studies, basal condition. However, the studies with no difference in the patient's basic condition were included, and restricted the patient's basic condition to minimize heterogeneity. Despite of this, the quality and risk of bias assessment revealed was small, and retrospective analysis scored well on the Newcastle-Ottawa scale, achieving scores between 5 to 8. As well as RCTs both got low rick in Cochrane bias risk assessment. We don't have enough data about the long-term ovarian reserve. Therefore, further prospective studies are needed to evaluate this outcome and provide more accurate answers, although this meta-analysis may help to choose the best surgical approach for the patient based on her preoperative ovarian reserve.

5. Conclusion

Our primary endpoint was to assess the impact of laparoscopic salpingectomy and PTO on ovarian reserve. Available data suggested salpingectomy hurt ovarian reserve much more than PTO. As they had same effect on the improvement of the pregnancy outcome of IVF, PTO should be considered more than salpingectomy when dealing with hydrosalpinx, especially for patients with poor ovarian reserve.

Author contributions

SW analyzed and interpreted the patient data and finished writing manuscript.
QZ was a co contributor in writing the manuscript.
YL was a major contributor in writing the manuscript.
All authors read and approved the final manuscript.

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