The effect of salpingectomy on the ovarian reserve and ovarian response in ectopic pregnancy

A systematic review and meta-analysis

Jiaqi Luo, MD\textsuperscript{a}, Yu Shi, MD\textsuperscript{b}, Dan Liu, MS\textsuperscript{a}, Danni Yang, MD\textsuperscript{a}, Jiahui Wu, MD\textsuperscript{a}, Lijuan Cao, MD\textsuperscript{a,c}, Lan Geng, MS\textsuperscript{a}, Zhenhui Hou, MD\textsuperscript{a}, Hongbo Lin, MD\textsuperscript{a}, Qiuju Zhang, MD\textsuperscript{a}, Xuefeng Jiang, MD\textsuperscript{c}, Weiping Qian, MD, PhD\textsuperscript{b}, Zhiling Yu, MD\textsuperscript{d}, Xi Xia, MD, PhD\textsuperscript{a,e}

Abstract

Background: Salpingectomy is routinely performed in ectopic pregnancy (EP). However, the effect of the surgery on the ovarian reserve and ovarian response in EP patients is still uncertain and has not been systematically evaluated. Therefore, we conducted this meta-analysis to provide a comparison of the ovarian reserve and ovarian response between the pre-salpingectomy and post-salpingectomy in EP patients.

Methods: Pubmed, Embase, and Cochrane Library were searched for all relevant articles published up to December 2018. We retrieved the basic information and data of the included studies. The data was analyzed by Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK).

Results: A total of 243 articles were extracted from the databases, and 7 studies were included in the meta-analysis. The ovarian reserve including anti-Mullerian hormone (inverse variance [IV] = 0.7 [95% confidence interval [CI] = 0.63, 0.49]), antral follicle count (IV 1.7 [95% CI = 2.02, 5.42]) and basal follicle stimulating hormone (IV 0.02 [95% CI = 0.63, 0.68]) was comparable between the pre-salpingectomy group and the post-salpingectomy group. The amount of gonadotropin was significantly higher in the post-salpingectomy group when compared with that in the pre-salpingectomy group (IV = 212.65 [95% CI = 383.59, 41.71]). There was no significant difference in the left parameters of the ovarian response including the duration of gonadotropin stimulation (IV = 0.32 [95% CI = 0.76, 0.12]), the estrogen level on the human chorionic gonadotropin triggering day (IV = 4.12 [95% CI = 236.27, 228.04]) and the number of retrieved oocytes (IV 0.35 [95% CI = 0.76, 1.46]) between 2 groups.

Conclusions: The current results suggest that salpingectomy has no negative effect on the ovarian reserve and ovarian response.

Abbreviations: AFC = antral follicle count, AMH = anti-Mullerian hormone, CI = confidence intervals, E2 = estrogen, EP = ectopic pregnancy, FSH = follicle stimulating hormone, hCG = human chorionic gonadotropin, IV = inverse variance, IVF = in-vitro fertilization, NOS = Newcastle–Ottawa scale, SD = standard deviation.

Keywords: ectopic pregnancy, ovarian reserve, ovarian response, salpingectomy
1. Introduction

Ectopic pregnancy (EP) accounts for almost 2% of pregnancies.[1–3] Salpingectomy is a routine treatment in EP patients especially in the following circumstances such as high serum human chorionic gonadotropin (hCG) concentration, the mass at the fallopian tube greater than 4 cm, and hemodynamically unstable.[2] However, with the removal of the affected oviduct in salpingectomy, Chan et al demonstrated that ovarian stromal blood flow of the operated side seemed to be relatively impaired compared to the nonoperated side and they speculated that the less blood supply might result in the decreased ovarian function.[4] Gelbaya et al observed a significant alteration in the basal follicle stimulating hormone (FSH) level and the estrogen (E2) concentration on the day of hCG injection in the salpingectomized group, which might suggest a compromised ovarian response to in-vitro fertilization (IVF) treatment after salpingectomy.[5] On the contrary, in a prospective study including 102 patients, Lass et al noted that salpingectomy had no detrimental effect on the total number of retrieved oocytes during the IVF performance although the retrieved oocytes from the operated ipsilateral ovary were fewer than that from the contralateral ovary.[6] Dar et al also concluded that the surgery did not alter ovarian response in IVF cycles.[7] Is there demonstrable variation in practice regarding the population of women evaluated in the studies? Till now, no meta-analysis towards the effect of salpingectomy due to EP on the ovarian reserve and ovarian response during controlled ovarian stimulation in patients undergoing IVF has been reported. Given the inconsistency of the prior articles, we conducted this meta-analysis to provide a comparison of the ovarian reserve and ovarian response between the pre-salpingectomy and post-salpingectomy in EP patients.

2. Materials and methods

2.1. Literature search and study selection

The study was performed in accordance with the PRISMA guidelines. Data searches were conducted on Pubmed, Embase, and Cochrane Library with the end date of December 2018. The searched terms were “ectopic pregnancy,” “salpingectomy,” “anti-Mullerian hormone (AMH),” “antral follicle count (AFC),” “FSH,” “E2,” and “inhibin.” The primary measured outcome was the ovarian reserve, including AMH, AFC, basal FSH, and basal E2. The second measured outcome was the ovarian response, including gonadotropin doses, gonadotropin stimulation days, E2 concentration on the hCG triggering day and the number of retrieved oocytes. Identified studies were included if they meet the following criteria:

(1) underwent salpingectomy because of EP;
(2) had a retrospective, prospective or randomized controlled design;
(3) examined at least 1 of the aforementioned parameters;
(4) patients served as their own controls before and after the salpingectomy;
(5) parameters were reported in mean and standard deviation (SD).

Case reports, review articles, animal models, and studies published as abstracts only were excluded since the unavailability of the detailed data to make a specific analysis.

2.2. Data extraction and quality assessment

There was no contact with the authors of the included articles for additional information. All analyses were based on previous studies. Therefore, no ethical approval was required. We retrieved characteristics of each study, including the first author’s name, year of publication, geographic location, type of study design, number of the participants, and the mean and SD of parameters. All relevant data were independently collected by 2 working researchers (JQ Luo and JH Wu) and then checked for any error or missing data. When the opinions were inconsistent, the solution was discussed with a third party. Quality assessment of the retrospective and prospective studies was performed by the Newcastle–Ottawa scale (NOS) where scores were given in terms of stars. A maximum number of 9 stars demonstrated a low risk of bias.

2.3. Statistical analysis

After extraction, the data was analyzed by Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). As for the continuous data, we chose the inverse variance (IV) as the statistical method. The mean difference and the 95% confidence intervals (CI) were calculated using either the fixed-effect model or the random-effect model. The fixed-effect model was applied when there was no heterogeneity. Heterogeneity was identified and quantified by the I² statistics. According to Higgins et al, the value of I² on the order of 25%, 50%, and 75% might be considered as low, moderate, and high heterogeneity.[8] When heterogeneity was found, the random-effect model was conducted for the meta-analysis. Also, subgroup analysis and even sensitivity analysis could be performed. When necessary, publication bias would be assessed by visual inspection of funnel plots. Results were presented as IV and 95% CI.

2.4. Ethics

No ethical or board review approval was required for this meta-analysis.

3. Results

3.1. Literature search

A flow diagram of the study selection was shown in Figure 1. Two hundred forty-three articles were extracted from the 3 databases. One hundred fifty-six articles were left after removing the duplicates (n = 87). Then, no full articles (n = 10), case reports (n = 43), animal models (n = 1), irrelevant studies (n = 72), review articles (n = 9), no control group (n = 11), and not self-control (n = 3) were excluded. Thus, 7 articles were considered eligible for the meta-analysis.

3.2. Study characteristics

The 7 articles included 2 prospective studies and 5 retrospective studies. The basic characteristics of the 7 articles were summarized in Table 1. Since the basal E2 was only assessed in Xi’s study, we did not include this parameter in the measured outcome. Quality assessment of the included studies ranged from 6 to 7 stars by NOS scoring system.
3.3. Meta-analysis

3.3.1. Ovarian reserve

3.3.1.1. AMH. Two studies reported the AMH level\cite{9,10}. None found any significant difference between the pre- and post-salpingectomy group. Because the result of the $I^2$ index ($I^2 = 0\%$) did not suggest heterogeneity, a fix-effect model was used for the meta-analysis. There was no evidence of difference in the AMH level when comparing the pre- and post-salpingectomy group ($IV -0.7$ [95\% CI $-0.63, 0.49$]) (Fig. 2A).

3.3.1.2. AFC. Two studies reported the AFC\cite{11,12}. None found any significant difference between the pre- and post-salpingec-
tomy group. Because the result of the $I^2$ index ($I^2 = 41\%$) suggested heterogeneity, a random-effect model was used for the meta-analysis. There was no evidence of difference in the AFC when comparing the pre- and post-salpingectomy group ($IV 1.7 [95\% CI -2.02, 5.42]$) (Fig. 2B).

### 3.3.1.3. Basal FSH

Three studies reported the basal FSH level.

![Image](image_url)

**Figure 2.** (A) Forest plot comparing the AMH level before and after salpingectomy. (B) Forest plot comparing the AFC before and after salpingectomy. (C) Forest plot comparing the basal FSH level before and after salpingectomy. AMH = anti-Mullerian hormone, AFC = antral follicle count, FSH = follicle stimulating hormone.

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### Table 1

| Author      | Year | Location | Type of study | N | Outcomes | Pre-salpingectomy group | Post-salpingectomy group |
|-------------|------|----------|---------------|---|----------|-------------------------|--------------------------|
| Dar         | 2000 | Israel   | Prospective   | 26| Gonadotropin dose (IU) | $2709.75 \pm 1083.75$ | $2610.75 \pm 925.25$ |
|             |      |          |               |   | Duration of stimulation (d) | $10.81 \pm 2.45$ | $10.68 \pm 2.57$ |
|             |      |          |               |   | E2 on hCG d (pg/mL) | $1285 \pm 785$ | $1151 \pm 819$ |
|             |      |          |               |   | No. of oocytes retrieved (n) | $5.58 \pm 3.51$ | $4.87 \pm 3.96$ |
| Singer T    | 2011 | United State | Retrospective | 4| AMH (ng/mL) | $2.49 \pm 1.44$ | $2.20 \pm 1.7$ |
|             |      |          |               |   | No. of oocytes retrieved (n) | $16.75 \pm 10.97$ | $11.3 \pm 3.65$ |
| Xi          | 2011 | China    | Retrospective | 76| Basal E2 (pg/mL) | $41.1 \pm 11.5$ | $39.2 \pm 13.0$ |
|             |      |          |               |   | Basal FSH (IU) | $6.9 \pm 1.5$ | $7.2 \pm 1.6$ |
|             |      |          |               |   | Gonadotropin dose (IU) | $2124.5 \pm 590.3$ | $2370.8 \pm 614.5$ |
|             |      |          |               |   | Duration of stimulation (d) | $10.7 \pm 1.5$ | $11.1 \pm 1.8$ |
|             |      |          |               |   | E2 on hCG d (pg/mL) | $2663.5 \pm 1246$ | $2783.3 \pm 1281.3$ |
|             |      |          |               |   | No. of oocytes retrieved (n) | $11.1 \pm 5.4$ | $11.6 \pm 4.1$ |
| Wiser       | 2013 | Israel   | Retrospective | 22| AFC (N = 14) | $22.5 \pm 4.9$ | $17.2 \pm 12.1$ |
|             |      |          |               |   | Basal FSH (IU/mL) | $6.9 \pm 1.7$ | $6.2 \pm 1.5$ |
|             |      |          |               |   | Gonadotropin dose (IU) | $2813 \pm 1071$ | $2895 \pm 979$ |
|             |      |          |               |   | Duration of stimulation (d) | $9.1 \pm 2.7$ | $9.4 \pm 2.8$ |
|             |      |          |               |   | No. of oocytes retrieved (n) | $1059.1 \pm 648.2$ | $1064.6 \pm 621.5$ |
| Pereira     | 2015 | United State | Retrospective cohort | 22| Basal FSH (IU/L) | $13.4 \pm 9.5$ | $4.94 \pm 2.05$ |
|             |      |          |               |   | Gonadotropin dose (IU) | $4.8 \pm 2.75$ | $3126.4 \pm 1967.5$ |
|             |      |          |               |   | Duration of stimulation (d) | $2421.4 \pm 1468.8$ | $9.86 \pm 4.92$ |
|             |      |          |               |   | No. of oocytes retrieved (n) | $9.63 \pm 2.21$ | $10.2 \pm 4.23$ |
| Sahin       | 2016 | Turkey   | Prospective   | 61| AMH (ng/mL) | $2.10 \pm 1.74$ | $2.20 \pm 1.52$ |
| Pereira     | 2017 | United State | Retrospective cohort | 29| AFC (n) | $11.9 \pm 1.59$ | $11.2 \pm 2.01$ |

AFC = antral follicle count, AMH = anti-Mullerian hormone, E2 = estrogen, FSH = follicle stimulating hormone, hCG = human chorionic gonadotropin.
difference in the basal FSH level when comparing the pre- and post-salpingectomy group (IV 0.02 [95% CI –0.63, 0.68]) (Fig. 2C).

3.3.2. Ovarian response

3.3.2.1. Gonadotropin doses. The amount of gonadotropin doses used in the IVF treatment was reported in 4 studies.\[^7,11,13,14\] One of them reported a significantly higher gonadotropin requirement in the post-salpingectomy group compared to the pre-salpingectomy group.\[^13\] Because the result of the $I^2$ index ($I^2 = 0\%$) did not suggest heterogeneity, a fix-effect model was used for the meta-analysis. The total doses of gonadotropin used in the post-salpingectomy group were significantly higher than those in the pre-salpingectomy group (IV 212.65 [95% CI 383.59, 41.71]) (Fig. 3A).

3.3.2.2. Duration of stimulation. Four studies reported the duration of gonadotropin in the IVF treatment.\[^7,11,13,14\] None found any significant difference between the pre- and post-salpingectomy group. Because the result of the $I^2$ index ($I^2 = 0\%$) did not suggest heterogeneity, a fix-effect model was used for the meta-analysis. There was no evidence of difference in the gonadotropin stimulation days when comparing the pre- and post-salpingectomy group (IV 0.32 [95% CI –0.76, 0.12]) (Fig. 3B).

3.3.2.3. E2 on hCG day. Three studies reported the E2 level on the hCG triggering day before and after salpingectomy.\[^7,11,13\] None found any significant difference between the pre- and post-salpingectomy group. Because the result of the $I^2$ index ($I^2 = 0\%$) did not suggest heterogeneity, a fix-effect model was used for the meta-analysis. There was no evidence of difference in the E2 concentration on the hCG triggering day when comparing the pre- and post-salpingectomy group (IV –4.12 [95% CI –236.27, –228.04]) (Fig. 3C).

3.3.2.4. Number of oocytes retrieved. Five studies reported the number of retrieved oocytes.\[^7,9,11,13,14\] None found any significant difference between the pre- and post-salpingectomy group. Because the result of the $I^2$ index ($I^2 = 0\%$) did not suggest heterogeneity, a fix-effect model was used for the meta-analysis. There was no evidence of difference in the number of retrieved oocytes when comparing the pre- and post-salpingectomy group (IV 0.35 [95% CI –0.76, 1.46]) (Fig. 3D).

4. Discussion

Salpingectomy is clinically performed in EPs, especially when there is evidence of rupture.\[^1–3\] When compared with salpingostomy, the advantages of salpingectomy involve almost
eliminating the risks of persistent EP and repeat EP. Some studies even stated that persistent EP after salpingostomy accounted for 4% to 15%. Moreover, it is required for shorter supervision of serum hCG in salpingectomy compared to salpingostomy, which means fewer hospital visits and venipunctures. Even though salpingectomy has the benefits mentioned above, clinicians would still worry that the descending blood flow along with the removed tube could impair the ovarian function. Theoretically, ovaries are supplied by the ovarian artery and the vascular arcade in the mesosalpinx which is derived from the uterine artery. Székely et al examined 24 patients who had total hysterectomy with or without bilateral salpingectomy and reported that complete removal of fallopian tubes had a deleterious effect on ovarian blood supply. Thus it could be postulated that the vascular arcade in the mesosalpinx took an important part in the ovarian blood supply. Especially in EP patients, the invasion of trophoblast at the fallopian tube increased the mesosalpinx blood flow. Hence, we inferred whether the abrupt reduction of the ovarian blood perfusion during salpingectomy for EP patients would impair the ovarian function.

Based on our study, we concluded that salpingectomy did not impact the ovarian function in EP patients. The ovarian reserve including the AMH level, the AFC and the basal FSH and almost all parameters in the ovarian response including the duration of gonadotropin stimulation, the E2 level on the hCG triggering day and the number of retrieved oocytes were of no significant differences between the pre- and post-salpingectomy group. Given the potential surgical damage to arteries in the mesosalpinx, this result might due to the compensatory blood supply of the contralateral artery in the mesosalpinx. Lass et al noticed that the retrieved oocytes from the operated ipsilateral ovary were fewer than that from the contralateral ovary after salpingectomy. But the total number of retrieved oocytes in the IVF treatment was comparable with those patients not having salpingectomy. However, there is opposite speculation. According to the randomized controlled trial comparing standard salpingectomy and wide salpingectomy, Venturella et al reported that wide excision of the mesosalpinx in salpingectomy did not alter blood loss and the ovarian reserve. It might mean that the blood supply from the mesosalpinx took only a little part in the ovarian blood supply. Thus, wide excision of the mesosalpinx in salpingectomy might not compromise the ovarian function. This speculation was consistent with the previous results in hysterectomy combined with tubal removal. Findley et al found bilateral salpingectomy during hysterectomy did not have negative effect on ovarian reserve, as measured by the AMH level. In patients who had unilateral salpingectomy for tubal pregnancy before embarking on the IVF treatment, unilateral salpingectomy did not affect the ovarian response to stimulation by comparing 98 cycles in the surgery group and 134 cycles in the nonsurgery group. Overall, the reduction of the ovarian blood supply during salpingectomy for EP patients would not impair the ovarian function.

In a cross-sectional study including 71 infertile women, Grynerup et al noticed that 16 women after salpingectomy had a lower serum AMH level than those who preserved their oviducts. Similarly, in women with hydrosalpinx, basal FSH levels were significantly raised and the serum E2 levels on the hCG injection day were reduced considerably after salpingectomy when compared to the non-surgery group, according to Gelbaya et al. The results of the previous studies were different from the current result. It may result from the diversely selected population, limited sample size or patients not serving as their own control group in the previous studies. This meta-analysis addressed the above problems. It was the first study to evaluate the effect of salpingectomy on ovarian function in EP population. And in this study, patients were acted as their own control in the comparison between the pre-salpingectomy group and post-salpingectomy group, which minimized the individual differences and prevented the potential bias.

The only statistically significant parameter was the amount of gonadotropin used in the IVF treatment, which was higher in the post-salpingectomy group. Xi et al also observed the same increase in initial and total doses of gonadotropin after salpingectomy in EP patients. The same significant raise was also noticed in the control group involved 80 women without surgical intervention in that study. It means salpingectomy may not correlate with impairment on the ovarian function but partly due to clinicians’ concern to prevent poor ovarian response after the failure in the last cycles. The assessed interval between pre-salpingectomy and post-salpingectomy was another concern because age was negatively associated with ovarian reserve. Overall, other parameters in the present study were of little significant difference, which safely provided us the notion that the salpingectomy in EP patients was not harmful to the ovarian reserve and response.

The limitations of this study should also be recognized. First, the number of included studies available for this meta-analysis was limited and some of the included studies had a relatively small sample size. Second, most of the included studies were retrospective studies which could not prevent the potential bias and, to some extent, restricted the quality of the study. Last but not least, the present study could not compare the further pregnancy outcomes since the included studies did not provide such parameters.

In conclusion, the present study suggest that salpingectomy has no negative effect on the ovarian reserve and ovarian response. Clinicians could perform the surgery in EP patients without concerning too much about ovarian function damage.

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Author contributions
Conceptualization: Xi Xia.
Data curation: Jiaqi Luo, Jiahui Wu.
Formal analysis: Jiaqi Luo, Yu Shi, Dan Liu, Danni Yang, Liyuan Cao.
Methodology: Lan Geng, Zhenhui Hou, Hongbo Lin, Qiuju Zhang, Xuefeng Jiang.
Supervision: Weiping Qian, Zhiying Yu, Xi Xia.
Writing – original draft: Jiaqi Luo.
Writing – review & editing: Zhiying Yu, Xi Xia.

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