Short-term Effects of Opportunistic Salpingectomy on Ovarian Reserve: A Postprint Meta-Analysis of Randomized Controlled Trials Based on the GRADE Evidence Grading System

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Abstract

Background: Opportunistic salpingectomy (OS) can serve as a primary prevention measure for ovarian cancer (OC); however, due to the shared blood supply system between the ovaries and fallopian tubes, OS may cause damage to ovarian function, thereby increasing the risk of ovarian aging and premature menopause. Objective: To evaluate the short-term effects of OS on ovarian reserve based on the GRADE evidence grading system. Methods: In September 2022, CNKI, Wanfang Data Knowledge Service Platform, VIP, PubMed, Web of Science, and Scopus were searched for literature evaluating the short-term effects of OS on ovarian reserve, with the search period from inception to September 10, 2022. Two researchers independently screened the literature and extracted data, the Jadad scale was used to evaluate literature quality, Stata 17.0 software was used for data processing and meta-analysis, and GRADEpro 3.2 software was used to assess the evidence quality of the meta-analysis results. Results: A total of 9 randomized controlled trials (RCTs) were included, comprising 482 patients, with 238 in the OS group and 244 in the non-OS group. The Jadad risk assessment scale results showed that all included RCTs were of high quality. Meta-analysis results indicated that compared with the non-OS group, the OS group showed no statistically significant differences in pre- and postoperative changes in AMH [WMD=-0.07, 95%CI (-0.28, 0.13), P=0.13], FSH [WMD=-0.03, 95%CI (-1.65, 1.59), P=0.24], LH [WMD=-0.39, 95%CI (-1.62, 0.83), P=0.08], or E2 [WMD=3.08, 95%CI (-4.26, 10.43), P=0.35] (P>0.05). GRADEpro software evaluation of the meta-analysis results showed that evidence for anti-Müllerian hormone (AMH) was of high quality, evidence for follicle-stimulating hormone (FSH) was of moderate quality, and evidence for estradiol (E2) and luteinizing hormone (LH) was of low quality. Conclusion: In the short term, ovarian reserve function indicators in premenopausal women who underwent OS for be-

nign diseases showed no significant differences compared with women who did not undergo OS. It is reasonable for parous premenopausal women to prevent OC through OS; however, this conclusion remains to be validated by RCTs with longer follow-up periods, more rigorous designs, and larger sample sizes.

Full Text

Short-term Effects of Opportunistic Salpingectomy on Ovarian Reserve: A Meta-analysis of Randomized Controlled Trials Based on the GRADE Evidence Grading System

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Abstract

Background: Opportunistic salpingectomy (OS) can be used as a primary prevention strategy for ovarian cancer (OC). However, due to the shared homologous blood supply system between the ovaries and fallopian tubes, OS may cause impairment of ovarian function, thereby increasing the risk of ovarian aging and premature menopause.

Objective: To evaluate the short-term effects of OS on ovarian reserve based on the GRADE evidence grading system.

Methods: In September 2022, CNKI, Wanfang Data, VIP, PubMed, Web of Science, and Scopus were searched for literature assessing the short-term effects of OS on ovarian reserve from inception to September 10, 2022. Two investigators independently screened the literature and extracted data. The Jadad scale was used to evaluate literature quality, Stata 17.0 software was used for data processing and meta-analysis, and GRADEpro 3.2 software was used to assess the evidence quality of the meta-analysis results.

Results: A total of 9 randomized controlled trials (RCTs) involving 482 patients were included, with 238 cases in the OS group and 244 in the non-OS group. The Jadad risk assessment scale results showed that all included RCTs were of high quality. Meta-analysis results indicated that compared with the non-OS group, the OS group showed no statistically significant differences in pre- and postoperative changes in anti-Müllerian hormone (AMH) [WMD=-0.07, 95%CI (-0.28, 0.13), P=0.13], follicle-stimulating hormone (FSH) [WMD=-0.03, 95%CI (-1.65, 1.59), P=0.24], luteinizing hormone (LH) [WMD=-0.39, 95%CI (-1.62, 0.83), P=0.08], or estradiol (E2) [WMD=3.08, 95%CI (-4.26, 10.43), P=0.35] (all P>0.05). The GRADEpro software assessment of the meta-analysis results showed high-quality evidence for AMH, moderate-quality evidence for FSH, and low-quality evidence for E2 and LH.

Conclusion: In the short term, ovarian reserve function indicators in premenopausal women who underwent OS for benign diseases showed no significant differences compared with those who did not receive OS. It is reasonable for premenopausal women who have completed childbearing to use OS for OC prevention, but this conclusion remains to be validated by RCTs with longer follow-up periods, more rigorous designs, and larger sample sizes.

Keywords: Salpingectomy; Opportunistic salpingectomy; Ovarian neoplasms; Ovarian reserve; Meta-analysis

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Introduction

Ovarian cancer (OC) is a common malignant tumor of the female reproductive system, with increasing incidence and mortality rates [1]. Recent reports suggest that preserving ovaries until age 65 is beneficial for long-term survival in women undergoing hysterectomy for benign diseases [2], while other researchers believe that opportunistic salpingectomy (OS) can serve as an effective primary prevention strategy for OC [3]. Although the American College of Obstetricians and Gynecologists has investigated the safety of concurrent hysterectomy and salpingectomy, demonstrating that OS does not increase complications such as rehospitalization or need for transfusion, the homologous blood supply shared by ovaries and fallopian tubes raises concerns that OS in premenopausal women may damage ovarian function and increase risks of ovarian aging and premature menopause [4-5]. Given the strong associations between premature menopause and cardiovascular disease, cognitive impairment, and osteoporosis [6-7], the potential risks of OS may outweigh its benefits in OC prevention.

To investigate whether OS affects ovarian reserve in the short term, this study selected indicators that reflect ovarian reserve function: anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2). We conducted a meta-analysis of published literature examining changes in these indicators before and after OS to determine whether concurrent OS during surgery for benign diseases impairs ovarian reserve, aiming to provide evidence-based medical evidence for clinical practice.

Methods

1.1 Search Strategy We systematically searched CNKI, Wanfang Data, VIP, PubMed, Web of Science, and Scopus from inception to September 10, 2022, for relevant literature. The English search strategy included terms: "ovarian cancer" or "hysterectomy" or "cesarean section" and "opportunistic salpingectomy" or "salpingectomy" or "ovarian reserve" or "ovarian function" and "randomized controlled trial," with no language or regional restrictions. The Chinese search strategy included: “卵巢癌”or “子宫切除术”or “剖宫产”and “机会性输卵管切除术”or “输卵管切除术”or “卵巢储备”or “卵巢功能”or “激素”and “随机对照试验.” Two researchers independently used Endnote X9.1 software to screen and select literature according to inclusion and exclusion criteria, with disagreements resolved through discussion or consultation with other researchers.

1.2 Inclusion and Exclusion Criteria **Inclusion criteria:** (1) Study subjects were premenopausal women undergoing OS for benign indications; (2) Interventions were divided into OS and non-OS groups based on whether OS was performed concurrently; (3) Outcome measures were ovarian reserve indicators, specifically changes in AMH, FSH, LH, and E2 before and after surgery; (4) Study type was randomized controlled trial (RCT).

Exclusion criteria: (1) Studies with sample size <10; (2) Studies where clinical data could not be extracted; (3) Non-RCT studies; (4) Studies derived from computer models or animal models; (5) Patients who underwent concurrent non-reproductive system surgery or had other malignant tumors; (6) Case reports, commentaries, letters, reviews, or books.

1.3 Quality Assessment and Evidence Grading The modified Jadad scale was used to evaluate the quality of included RCTs. The scale totals 7 points, comprising random sequence generation, allocation concealment, blinding, and withdrawals/dropouts. Two raters independently scored each component, with scores >4 considered high-quality literature [8]. Additionally, GRADEpro 3.2 software was used to rate the evidence quality level of meta-analysis results, with high quality indicated by and very low quality by .

1.4 Data Extraction Two researchers independently extracted data according to inclusion and exclusion criteria, with disagreements resolved through discussion with other researchers. Extracted information included: (1) Basic trial characteristics (author, publication year, country, number of patients per group, surgical approach, follow-up duration); (2) Basic patient characteristics (age, menstrual regularity, presence of malignant tumors); (3) Outcome indicator data for this study.

1.5 Statistical Analysis Stata 17.0 software was used for data analysis. All data were continuous variables, so weighted mean difference (WMD) and 95% confidence interval (CI) were used as effect measures. Heterogeneity among included trials was assessed using ^{2} test and Higgins I^2 test. $P \geq 0.05$ indicated no heterogeneity, and a fixed-effects model was used. I^2 values <25%, 25-50%, and >50% indicated mild, moderate, and severe heterogeneity, respectively [9]. When heterogeneity was present, sources were analyzed through subgroup or sensitivity analysis. If heterogeneity sources remained unclear after these analyses, a random-effects model was employed. Funnel plots were used to assess publication bias.

Results

2.1 Literature Search Results The initial search yielded 274 articles from the selected databases. After strict application of inclusion and exclusion criteria and quality assessment, 9 RCTs were ultimately included in the meta-analysis, all published in English [10-18]. The literature search flowchart is shown in [Figure 1: see original paper].

2.2 Baseline Data of Included Studies The 9 included RCTs comprised 482 patients, with 238 in the OS group and 244 in the non-OS group [10-18]. Baseline characteristics of each study are shown in , and Jadad risk assessment scale results are presented in , demonstrating that all included RCTs were high-quality studies.

2.3 Meta-analysis Results

2.3.1 AMH Six studies reported changes in AMH before and after surgery, with 368 patients included in this analysis [10-13, 16-17]. Heterogeneity testing indicated severe heterogeneity among studies (I^2=64.0%, P=0.016), so a random-effects model was used. Results showed no statistically significant difference in AMH changes between OS and non-OS groups [WMD=-0.07, 95%CI (-0.28, 0.13), P=0.13], as shown in [Figure 2: see original paper]A.

2.3.2 FSH Three studies reported changes in FSH before and after surgery, with 114 patients included [14-15, 18]. Heterogeneity testing showed significant heterogeneity (I^2=56.9%, P=0.098), so a fixed-effects model was applied. Meta-analysis revealed no statistically significant difference in FSH changes between groups [WMD=-0.03, 95%CI (-1.65, 1.59), P=0.24], as shown in [Figure 2: see original paper]B.

2.3.3 E2 Two studies reported E2 changes before and after surgery, including 74 patients [14-15]. Heterogeneity testing indicated homogeneity (I^2=0%, P=0.688), so a random-effects model was used. Results showed no statistically significant difference in E2 changes between groups [WMD=3.08, 95%CI (-4.26, 10.43), P=0.35], as shown in [Figure 2: see original paper]C.

2.3.4 LH Three studies reported LH changes before and after surgery, with 114 patients included [14-15, 18]. Heterogeneity testing indicated severe heterogeneity (I^2=59%, P=0.087), so a fixed-effects model was applied. Meta-analysis showed no statistically significant difference in LH changes between groups [WMD=-0.39, 95%CI (-1.62, 0.83), P=0.08], as shown in [Figure 2: see original paper]D.

2.3.5 Bias Analysis Publication bias analysis of the meta-analysis results indicated no significant publication bias among included studies (P>0.05), as shown in [Figure 3: see original paper].

2.3.6 Sensitivity Analysis Sensitivity analysis for AMH meta-analysis results was performed by sequentially removing each included study and re-running heterogeneity tests and result pooling. This showed that while heterogeneity decreased, the overall direction of results remained unchanged, as shown in [Figure 4: see original paper].

2.4 Evidence Level Based on GRADEpro System The meta-analysis results were rated using the GRADEpro system. AMH was classified as high-quality evidence, FSH as moderate-quality evidence, and E2 and LH as low-quality evidence. Detailed quality assessments are shown in .

Discussion

BEHNAMFAR et al. [18] first proposed OS for ovarian cancer prevention in 2006 and strongly recommended the procedure in subsequent research. However, concerns about postoperative ovarian reserve may negatively impact OS adoption. OS carries the risk of disrupting ovarian microcirculation, potentially advancing menopause. As ovarian reserve indicators decline with age, they serve as predictors of menopausal age [3,19]. However, this damage may be subtle: reduced ovarian perfusion affects steroid secretion and follicular development but may not immediately reflect changes in ovarian reserve indicators. Since all-cause mortality increases with earlier menopause, exploring OS effects on ovarian reserve indicators and menopausal age is crucial [20-21].

This meta-analysis included only RCTs to provide the highest level of evidence regarding OS effects on premenopausal ovarian reserve and menopause. We selected static ovarian reserve indicators (FSH and LH) and reproductive endocrine markers (AMH and E2) to comprehensively reflect OS impact on ovarian reserve from a hematological perspective. Our results did not show any short-term abnormalities in indicators representing ovarian reserve function.

Ovarian reserve is influenced by multiple factors, and our selected indicators reflect changes only from a hematological perspective. Studies show that decreased AMH and increased FSH may be closely associated with diminished ovarian reserve, with changes in these hormones potentially heralding earlier menopause [22]. However, no definitive research reveals relationships between E2, LH and age, making them poor indicators of ovarian reserve changes and unreliable for predicting menopausal age [22]. Although AMH is currently the best indicator for estimating ovarian reserve and predicting menopausal age, it can fluctuate with contraceptive use and is a weak predictor of menopause onset in older women, requiring cautious interpretation [23-24]. Additionally, FSH exhibits strong cyclicity and high intra-cycle variability, making it relatively insensitive as a predictive factor [25]. FSH only begins to increase in the final decade before menopause, serving as a late predictor and thus poorly reflecting ovarian reserve [22]. Studies also indicate that FSH and LH are influenced by both age and BMI, suggesting these factors should be included in subgroup analyses in future research [18]. Furthermore, dynamic ovarian reserve indicators (predicted follicle count and single ovulation stimulation tests) also reflect ovarian reserve, warranting cautious interpretation of our results and indicating that more comprehensive indicators should be used in future studies examining OS effects on ovarian reserve.

SEZIK et al. [14] conducted a small-sample RCT (n=24) in 2007 using FSH, LH, and E2 as surrogate markers of ovarian reserve, finding no differences between OS and non-OS groups. MORELLI et al. [26] performed a larger retrospective study (n=158) in 2013, similarly showing no significant differences in AMH, FSH, antral follicle count, or mean ovarian diameter between groups. Our results align with these findings, further confirming that OS has acceptable short-term impact on ovarian reserve.

Due to concerns about surgical disruption of tissue architecture and blood supply, VENTURELLA et al. [27] studied the effects of extensive resection of soft tissues adjacent to ovaries and fallopian tubes during laparoscopic bilateral OS on ovarian reserve and surgical outcomes. Results indicated that even with mesosalpinx removal, OS did not impair ovarian reserve. Additionally, the study found no significant differences in perioperative outcomes such as blood loss or hospital stay [27]. However, PING et al. [28] explored AMH and ovarian reserve changes in women under 40 undergoing in vitro fertilization and embryo transfer after OS, finding that OS was positively associated with AMH decline in this population.

Most women undergoing OS are aged 35-45, meaning they require several years before reaching menopause, and collection of such clinical data requires at least a decade. The follow-up periods in our included studies were relatively short, preventing objective reflection of long-term ovarian reserve changes. Currently, trials NCT0386080 and NCT04757922 are comparing OS versus tubal ligation as contraceptive methods and their effects on menopausal age, with results expected in 20 years [29].

Despite this meta-analysis's strict inclusion/exclusion criteria and statistical processing, several limitations exist: (1) The relatively small number of included studies reduces evidence strength; (2) Some studies measured few ovarian reserve indicators, affecting meta-analysis credibility; (3) Although all included studies were RCTs, short follow-up durations and small sample sizes remain shortcomings.

In summary, based on current evidence, premenopausal women undergoing OS for benign diseases show no statistically significant differences in ovarian reserve compared with those not receiving OS in the short term. Therefore, OS is reasonable for OC prevention in premenopausal women who have completed childbearing, though this conclusion requires validation by RCTs with longer follow-up, more rigorous designs, and larger sample sizes.

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Author Contributions: ZHAO Li conceptualized the research direction and wrote the initial draft, taking overall responsibility for the article; YANG Chunyan conducted database searches and preliminary screening; ZUO Manyun performed final study selection and data extraction; YANG Hongmei conducted statistical analysis using software and created forest plots.

Conflict of Interest: The authors declare no conflicts of interest.

Note: Figure translations are in progress. See original paper for figures.