Systematic Review and Meta-Analysis

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Reproductive and oncological outcomes of fertility-sparing surgery in patients with stage I epithelial ovarian cancer

A systematic review and meta-analysis

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Abstract

Objective: We meta-analyzed available evidence on fertility, survival, and cancer recurrence in patients with stage I epithelial ovarian cancer (EOC) after fertility-sparing surgery (FSS).

Methods: We systematically reviewed PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials to identify studies reporting reproductive and oncological outcomes of patients with stage I EOC who underwent FSS. Random-effects models were used to calculate pooled rates of disease outcomes, along with 95% confidence intervals (CIs). Subgroup and sensitivity analyses were conducted to identify sources of heterogeneity in the data.

Results: We included 23 observational retrospective studies involving 1126 patients. The pooled pregnancy rate was 30% (95% CI, 0.26–0.34), while the pooled natural conception rate was 26% (95% CI, 0.20–0.33). The pooled live birth rate was 27% (95% CI, 0.22–0.32). The pooled rate of EOC recurrence was 12% (95% CI, 0.09–0.14), which did not differ significantly from the rate among patients who underwent radical surgery (odds ratio, 0.77; 95% CI, 0.45–1.33).

Conclusions: FSS is associated with good oncological outcomes but less than satisfactory reproductive outcomes. All in all, the procedure appears to be a safe alternative to radical surgery for EOC patients who want to preserve fertility.

Abbreviations: CI = confidence interval, CENTRAL = Cochrane Central Register of Controlled Trials, DFS = disease-free survival, EOC = epithelial ovarian cancer, FIGO = International Federation of Gynecology and Obstetrics, FSS = fertility-sparing surgery, MINORS = Methodological Index for Non-Randomized Studies, NCCN = National Comprehensive Cancer Network, OS = overall survival, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses

Keywords: epithelial ovarian cancer, fertility-sparing surgery, live birth, pregnancy, tumor recurrence

1. Introduction

Ovarian cancer is one of the most prevalent gynecological malignancies throughout the world.[1] In 2020 alone, 313,959 women worldwide were diagnosed with ovarian cancer and 207,252 died.[2] The most common type of ovarian tumor is epithelial ovarian cancer (EOC).[3] EOC outcomes are better when patients are younger or have a lower-grade disease, lower-volume residual disease, good performance status, or less aggressive histology.[4] Approximately 92% of EOC patients with the early-stage disease remain recurrence-free at least 5 years after treatment.[5]

EOC patients are typically treated by total hysterectomy and bilateral adnexectomy including pelvic and para-aortic lymph node dissection,[3] and these radical procedures usually render the patient infertile. Medical advances and social trends have led clinicians and patients to try to preserve fertility and enhance the quality of life of patients of childbearing age. For example, the American Society of Clinical Oncology recommends discussing all options to preserve fertility when ovarian cancer patients are of reproductive age.[6]

The European Society for Medical Oncology recommends unilateral salpingo-oophorectomy for young EOC patients who

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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want to preserve their fertility because the uterus and contralateral ovary are retained. However, that Society recommends this procedure only for women with unilateral stage IA or IC disease involving mucinous, serous, endometrioid, or mixed histology.[7]

Another option may be fertility-sparing surgery (FSS),[8] which can offer a similar prognosis for patients with stage I EOC as radical surgery, regardless of tumor stage, grade, or histology.[9,10] FSS retains at least part of 1 ovary and the uterus to preserve fertility.[3] Whether FSS alters fertility and the risk of EOC recurrence is unclear. Therefore, we systematically reviewed and meta-analyzed available evidence on these questions for patients with stage I EOC.

2. Methods

This meta-analysis was performed based on recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement, and it was registered in PROSPERO (CRD42020199295). All analyses were based on previously published studies. Thus, no ethical approval and patient consent are required.

2.1. Search strategy

We systematically examined the electronic databases PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their respective inceptions to August 31, 2021, to identify studies on fertility-sparing treatments for EOC. The following search strings were used, both separately and in combination, to identify relevant studies on EOC: "epithelial ovarian cancer", "epithelial ovarian neoplasm", "epithelial ovarian carcinoma", "epithelial ovarian tumor", "epithelial cancer of the ovary", "epithelial neoplasm of the ovary", "epithelial carcinoma of the ovary", and "epithelial tumor of the ovary". In addition, the following search strings were used, both separately and in combination, to identify relevant studies on fertility-sparing treatments: "fertility sparing therapy", "fertility sparing surgery", "fertility sparing treatment", "conservative therapy", "conservative surgery", and "conservative treatment".

Reference lists in relevant articles were also searched manually to ensure that eligible papers were not overlooked. If multiple studies analyzed overlapping patient populations, only the largest study was retained.

2.2. Eligibility criteria

We included English-language studies that reported sufficient data on reproductive and oncological outcomes of fertility-sparing treatments for patients diagnosed with stage I EOC. Reproductive outcomes included rates of pregnancy, live birth, natural conception, assisted reproductive treatment, and spontaneous abortion. Oncological outcomes included recurrence, 5-year overall survival (OS), and 5-year disease-free survival (DFS).

We excluded studies for which accessible data were inadequate. We also excluded reviews, study protocols, commentaries, and letters.

2.3. Study selection

Two reviewers (YFZ and YF) independently screened potentially eligible studies first based on titles and abstracts, then based on full-text review. All disagreements were resolved through discussion. The quality of included studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS).[11]

2.4. Data extraction and calculation of outcomes

The following data were extracted from each study by 2 reviewers (YFZ and YF) working independently: author names, year of publication, study design, sample size, median age of patients, International Federation of Gynecology and Obstetrics (FIGO) stage, cancer histology, reproductive and oncological outcomes, and length of follow-up.

For each study, the following rates were calculated: pregnancy rate, where the pregnancy was defined as conception; the rate of live birth, defined as the birth of at least 1 healthy infant; the rate of natural conception, defined as spontaneous conception; the rate of assisted reproductive treatment, defined as the proportion of patients who conceived with the aid of such treatment; the rate of spontaneous abortion, defined as the rate of women experiencing 1 or more spontaneous abortions after FSS; and recurrence rate. The denominator in these calculated rates was the total number of women who underwent FSS. Rates of DFS and OS at 5 years were extracted directly from the studies.

2.5. Statistical analysis

Meta-analysis was performed using Stata 14.0 (StataCorp, College Station, TX, USA). We calculated rates using the double arcsine transformation and meta-analyzed them using a random-effects model and the DerSimonian–Laird method.[12,13] We also calculated pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to describe the risk of recurrence in the FSS group relative to patients who underwent radical surgery. Meta-analyses were also performed for subgroups stratified by cancer stage, country, year of publication, or follow-up time. Forest plots were created for each outcome to depict rates or OR and 95% CI.[14] Results associated with $P < .05$ were considered significant.

Heterogeneity in outcome data was assessed using the I^2 statistic,[15] and $I^2 > 50\%$ was considered high heterogeneity. Sensitivity analysis was performed by systematically removing studies one by one and then repeating the meta-analysis, to assess the effect of each study on the pooled results. Publication bias was assessed using Begg–Mazumdar rank correlation and funnel plots.[16]

3. Results

3.1. Characteristics of included studies

A total of 3,326 studies were identified in the databases and manual searches. In the end, 23 unique studies were included in the meta-analysis (Fig. 1),[17–39] all of which had a retrospective design (Table 1). Sample sizes ranged from 11 to 240 patients. The studies involved patients in the following countries: Japan (n = 6), China (n = 3), South Korea (n = 3), Italy (n = 3), France (n = 2), Argentina (n = 1), Australia (n = 1), Egypt (n = 1), India (n = 1), Sweden (n = 1), and the United States (n = 1).

3.2. Quality assessment of included studies

We assessed the quality of all included studies using MINORS (Fig. 2). Although all studies had a clear aim, they did not use a blind approach to assess disease outcomes, nor did they prospectively estimate a minimal sample size. A total of 20 studies consecutively enrolled patients, 16 collected data prospectively based on research protocols developed before the study began, and 20 defined endpoints that were appropriate for study aims. Only 12 of the 23 studies reported follow-up data for at least 5 years, which is the duration recommended by the National Comprehensive Cancer Network (NCCN) for stage I EOC patients.[9] Two studies reported >5% loss to follow-up.[21,29]

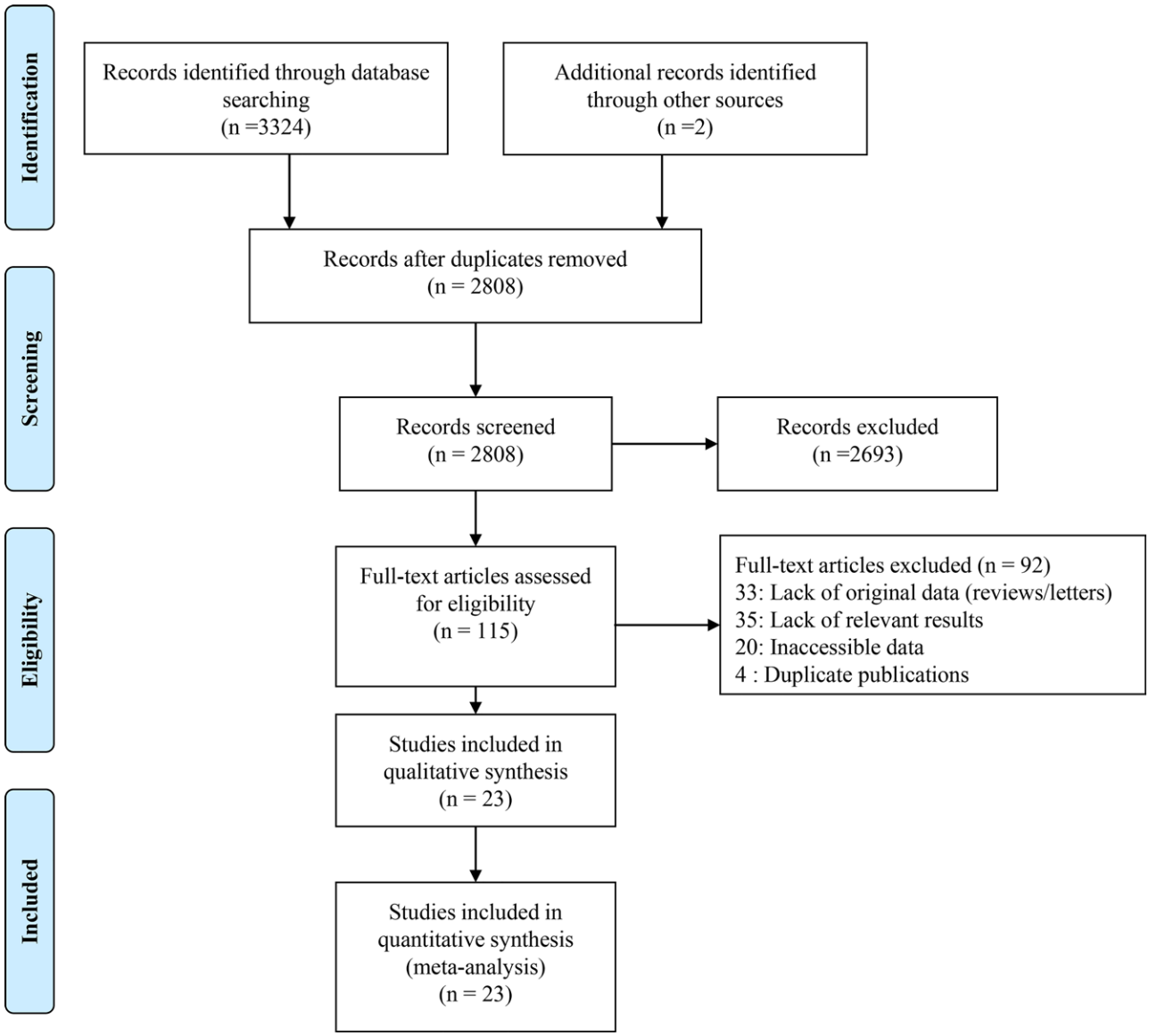

Figure 1. Flow diagram of study selection.

3.3. Reproductive outcomes after FSS

3.3.1. Pregnancy rate. Twenty-three studies involving 1126 patients reported pregnancy rates, and 343 women of reproductive age conceived at least once after FSS, resulting in a pooled pregnancy rate of 30% (95% CI, 0.26–0.34, P =.005; Fig. 3A).[17–39] Data for this outcome showed high heterogeneity across studies (I^2 = 56.8%, P < .001). Subgroup analyses showed no significant differences from the meta-analysis of all available data. Sensitivity analyses identified 1 study as a potential source of heterogeneity.[23] Excluding it reduced heterogeneity substantially (I^2 = 40.5%, P =.026) and gave results similar to the meta-analysis of all available data (28%, 95% CI, 0.25–0.32, P = .003; Figure 1, SupplementaryDigital Content, http://links.lww.com/MD/G957).

3.3.2. Live birth rate. Sixteen studies involving 806 patients reported live birth rates, and 224 women gave birth to at least 1 healthy infant.[17–20,22–25,27–29,32,33,35,37,38] Thus, the pooled live birth rate was 27% (95% CI, 0.22–0.32, P = .005; Fig. 3B), and data for this outcome showed high heterogeneity across studies (I^2 = 55.8%, P = .004). Subgroup analyses showed no significant effects. Sensitivity analyses identified 1 study as a potential source of heterogeneity.[23] Excluding this study led to a significant reduction in heterogeneity (I^2 = 18.2%, P =.251), and the result was similar (25%, 95% CI, 0.21–0.29, P = .001; Figure 2, Supplementary Digital Content, http://links.lww.com/MD/G957).

3.3.3. Natural conception rate. Twelve studies involving 512 patients reported natural conception rates, and 135 patients conceived naturally.[18–21,25,28–30,32,33,37,38] The pooled natural conception rate was 26% (95% CI, 0.20–0.33, P = .007; Fig. 3C), and data for this outcome showed high heterogeneity across studies (I^2 = 59.3%, P = .005). Subgroup analyses could not identify the cause of the high heterogeneity. Sensitivity analyses identified 1 study as a potential source of heterogeneity.[21] Excluding this study led to a significant reduction in heterogeneity (I^2 = 23.7%, P = .218), and the pooled natural conception rate was 24% (95% CI, 0.19–0.28, P = .001; Figure 3, Supplementary Digital Content, http://links.lww.com/MD/G957).

3.3.4. Assisted reproductive treatment rate. Twelve studies involving 512 patients reported assisted reproductive treatment rates, and 16 patients received such treatment.[18–21,25,28–30,32,33,37,38] The pooled assisted reproductive treatment rate was 2% (95%

Table 1

Characteristics of included studies.

Study	Country	Study design	Median age (y)	Patients	FIGO stage, n (%)	Histology, n (%)	Median follow-up (months)
Anchezar 2009[17]	Argentina	Retrospective	NRA	16	IA 11 (68.7); IC 5 (31.3)	Muc 8 (50.0); Serous 1 (6.3); Endo 5(31.3); Clear cell 2 (12.5)	96
Bisseling 2009[18]	Australia	Retrospective	36.5	23	IA-IC 23 (100.0)	NRA	NRA
Chen 2020[19]	China	Retrospective	23.5	36	IA/IB 7 (19.4); IC 29 (80.6)	Muc 32 (88.9); Serous 3 (8.3); Endo 1 (2.8)	47
Ditto 2014[20]	Italy	Retrospective	31.1	18	IA 12 (66.7); IB 1 (5.5); IC 5 (27.8)	Muc 6 (33.3); Serous 1 (5.6); Clear cell 1 (5.6); Endo 7 (38.9); Undif 3 (16.6)	108
Fakhr 2013[21]	Egypt	Retrospective	NRA	32	IA 32 (100.0)	Muc 6 (18.8); Serous 24 (75.0); Endo 2 (6.2)	58.5
Fruscio 2013[22]	Italy	Retrospective	32	240	IA 130 (54.2); IB 2 (0.8); IC 108 (45.0)	Muc 99 (41.3); Serous 62 (25.8); Endo 60 (25.0); Clear cell 17 (7.1); Undif 2 (0.8)	108
Jiang 2017[23]	China	Retrospective	25	52	IA-B 19 (36.5); IC 33 (63.5)	Muc 38 (73.1); Serous 1 (1.9); Endo 11 (21.2); Clear cell 2 (3.8)	60
Jobo 2000[24]	Japan	Retrospective	26.8	11	IA 6 (54.5); IC 5(45.5)	Muc 8(72.7); Serous 2(18.2); Endo 1(9.1)	112
Johansen 2020[25]	Sweden	Retrospective	29	36	IA 27 (75.0); IC 9 (25.0)	Muc 18(50.0); Serous 3 (8.3); Endo 10 (27.8); Clear cell 3(8.3); Mixed 2 (5.6)	63
Kajiyama 2010[26]	Japan	Retrospective	30	60	IA 30 (50.0); IB 1 (1.7); IC 29 (48.3)	Muc 34 (56.7); Serous 5 (8.3); Endo 11 (18.3); Clear cell 10 (16.7)	54.7
Kashima 2013[27]	Japan	Retrospective	28.5	18	IC 18 (100.0)	Muc 9 (50.0); Serous 2 (11.1); Endo 3 (16.7); Clear cell 4 (22.2)	78
Kwon 2009[28]	South Korea	Retrospective	26.7	21	IA 17 (81.0); IC 4 (19.0)	Muc 16 (76.2); Serous 1 (4.8); Endo 2 (9.5); Clear cell 2 (9.5)	43
Morice 2001[29]	France	Retrospective	24	25	IA 19 (76.0); IC 6 (24.0)	NRA	47
Morice 2005[30]	France	Retrospective	27	33	IA 30 (90.9); IC 3 (9.1)	Muc 21 (63.6); Serous 3 (9.1); Endo 5 (15.1); Clear cell 2 (6.1); Mixed 2 (6.1)	47
Park 2008[31]	South Korea	Retrospective	26	60	IA 36 (60.0); IB 2 (3.3); IC 22 (36.7)	Muc 39 (65.0); Serous 7 (11.7); Endo 8 (13.3); Clear cell 4 (6.7); Mixed 2 (3.3)	56
Park 2016[32]	South Korea	Retrospective	33.5	18	IA 6 (33.3); IC 12 (66.7)	Muc 7 (38.9); Serous 3 (16.7); Endo 5 (27.8); Clear cell 3 (16.6)	47.3
Satoh 2010[33]	Japan	Retrospective	29	211	IA 126 (59.6); IC 85 (40.3)	Muc 126 (59.6); Serous 27 (12.8); Endo 27 (12.8); Clear cell 30 (14.2); Mixed 1 (0.4)	78
Schilder 2002[34]	India	Retrospective	26	52	IA 42 (80.8); IC 10 (19.2)	Muc 25 (48.1); Serous 20 (38.5); Clear cell 5 (9.6); Mixed 2 (3.8)	78
Schlaerth 2009[35]	USA	Retrospective	27	20	IA 11 (55.0); IC 9 (45.0)	Muc 11 (55.0); Serous 1 (5.0); Endo 6 (30.0); Clear cell 1 (5.0); Undif 1 (5.0)	122
Watanabe 2020[36]	Japan	Retrospective	27.2	29	IA 14 (48.3); IC 15 (51.7)	Muc 16 (55.2); Serous 5 (17.2); Endo 5 (17.2); Clear cell 3 (10.3)	60.6
Yin 2019[37]	China	Retrospective	28	38	IA 11 (28.9); IC 27 (71.1)	Muc 17 (47.4); Serous 4 (10.5); Endo 7 (18.4); Clear cell 10 (26.3)	54
Yoshihara 2019[38]	Japan	Retrospective	36.2	21	IA-IC 21 (100.0)	Clear cell 21 (100.0)	55.6
Zanetta 1997[39]	Italy	Retrospective	29	56	IA 32 (57.1); IB 2 (3.6); IC 22 (39.3)	Muc 23 (41.1); Serous 18 (32.1); Endo 13 (23.2); Undif 2 (3.6)	94
Total				1126		Muc 560 (51.9); Serous 193 (17.9); Endo 189 (17.5); Clear cell 119 (11.0); Mixed 9 (0.9); Undif 8 (0.8)	

Endo = endometroid, FIGO = International Federation of Gynecology and Obstetrics, Muc = mucinous; NRA = not reported/available, Undif = undifferentiated.

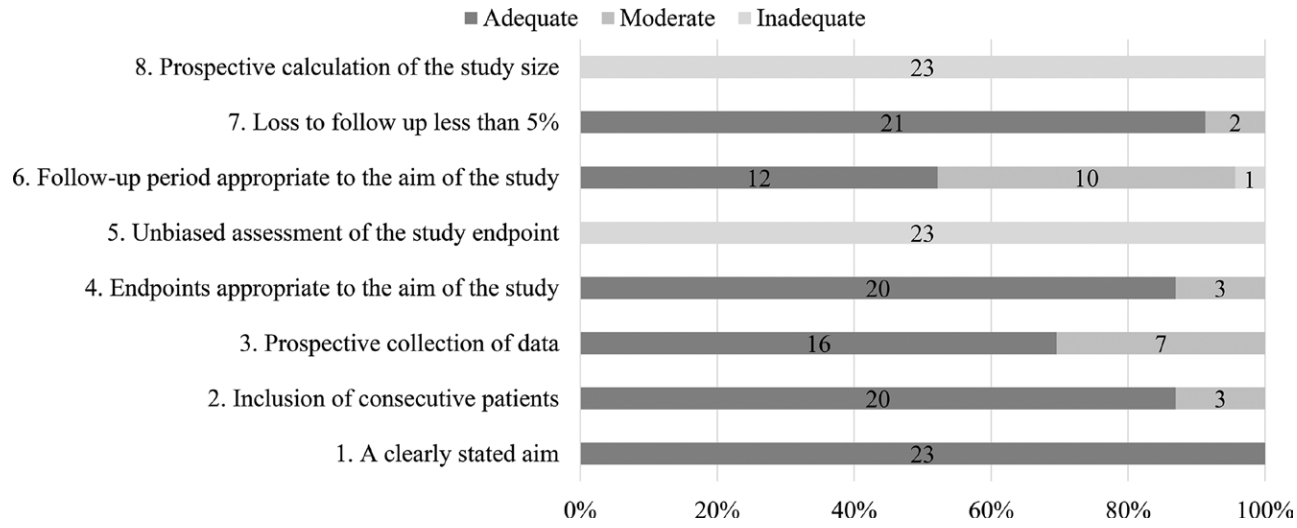

Figure 2. Quality assessment of included studies.

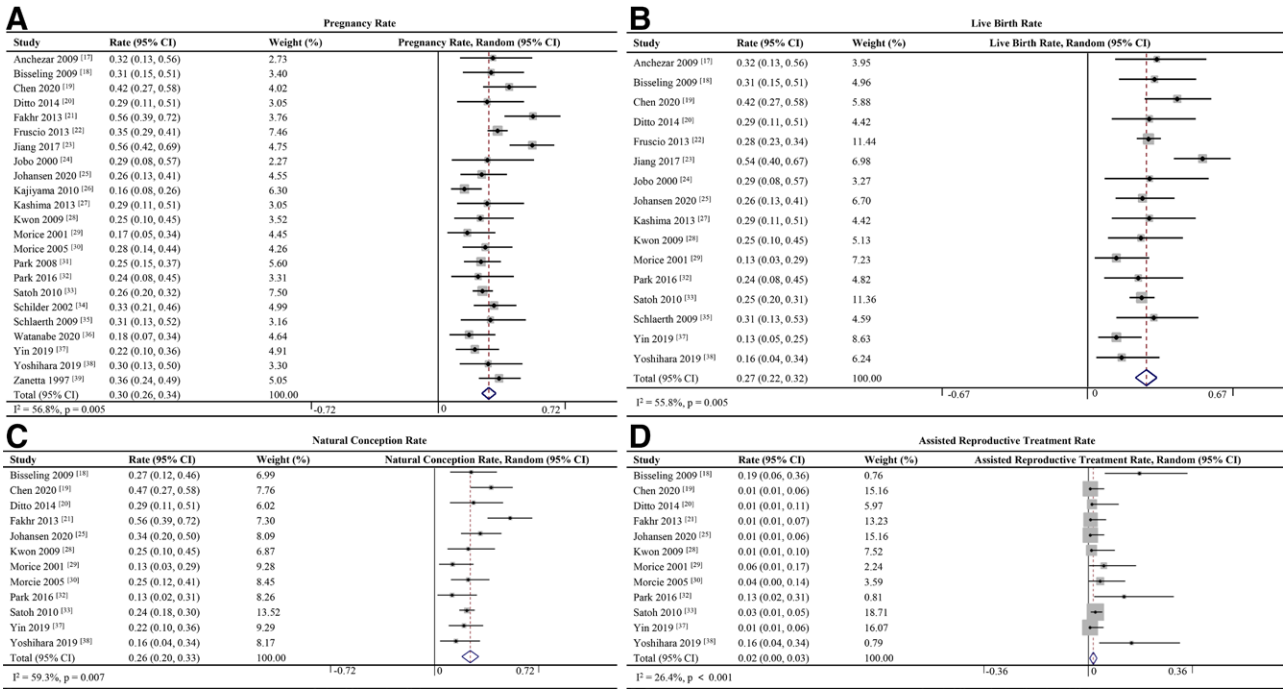

Figure 3. Forest plot of meta-analyses of (A) pregnancy rate, (B) live birth rate, (C) natural conception rate, and (D) assisted reproductive treatment rate in stage I epithelial ovarian cancer patients who underwent fertility-sparing surgery.

CI, 0.00–0.03, $P < .001$; Fig. 3D), and data for this outcome showed low heterogeneity across studies ($I^2 = 26.4\%$, $P = .185$).

3.3.5. Spontaneous abortion rate. Nineteen studies involving 856 patients reported spontaneous abortion rates, and 47 patients had 1 or more.[17–26,29–32,34,36–39] The pooled spontaneous abortion rate was 4% (95% CI, 0.03–0.06, $P < .001$; Fig. 4), and data for this outcome showed low heterogeneity across studies ($I^2 = 37.0\%$, $P = .054$).

3.4. Oncological outcomes after FSS

3.4.1. Recurrence rate. Twenty-three studies involving 1,126 patients reported recurrence rates, and 134 patients experienced recurrence, giving a pooled recurrence rate of 12% (95% CI 0.09–0.14, $P = .001$; Fig. 5A).[17–39] Data for this outcome showed low heterogeneity across studies ($I^2 = 35.5\%$, $P = .048$). Eight studies involving 661 patients reported recurrence rates among patients who underwent FSS (10.8%, 27/250) or radical surgery (15.3%, 63/411).[19,20,23–25,35,38,39] The rates did not differ significantly between the 2 groups (OR 0.77, 95% CI, 0.45–1.33, $P = .353$; $I^2 = 0.0\%$, $P = .630$; Figure 4, Supplementary Digital Content, http://links.lww.com/MD/G957).

3.4.2. Five-year OS rates. Eight studies involving 498 patients reported 5-year OS rates.[19,22,23,25,29,31,35,36] The pooled 5-year OS rate was 94% (95% CI, 0.91–0.96, $P < .001$; Fig. 5B), and data for this outcome showed low heterogeneity across studies ($I^2 = 16.4\%$, $P = .301$).

3.4.3. Five-year DFS rates. Six studies involving 229 patients reported 5-year DFS rates.[19,23,25,29,31,35] The pooled 5-year DFS

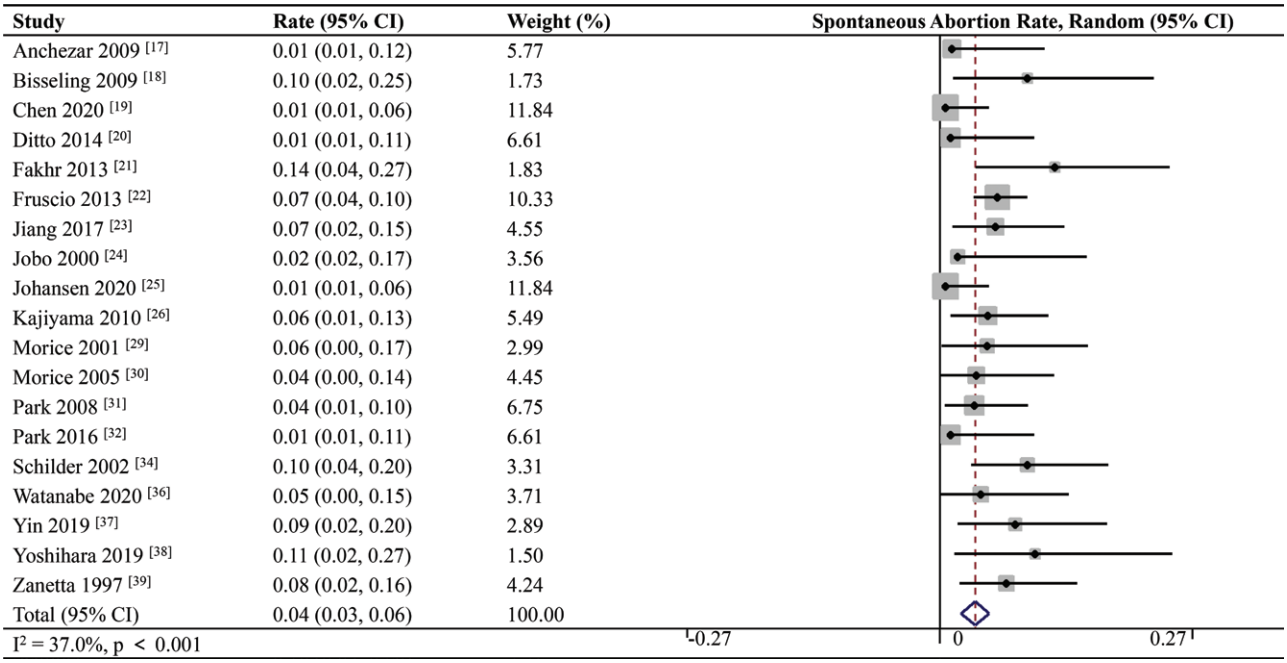

Figure 4. Forest plot of the meta-analysis of spontaneous abortion rate in stage I epithelial ovarian cancer patients who underwent fertility-sparing surgery.

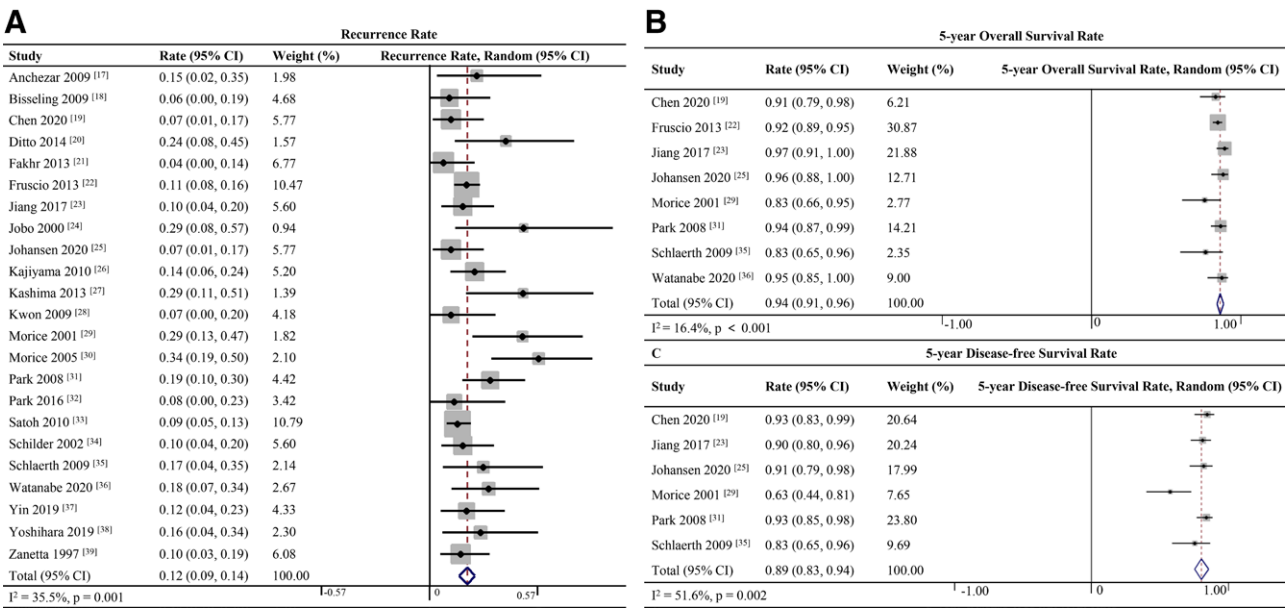

Figure 5. Forest plot of meta-analyses of (A) recurrence rate, (B) 5-year overall survival rate, and (C) 5-year disease-free survival rate in stage I epithelial ovarian cancer patients who underwent fertility-sparing surgery.

rate was 89% (95% CI, 0.83–0.94, P = .002; Fig. 5C), and data for this outcome showed high heterogeneity across studies (I^2 = 51.6%, P = .067). Subgroup analyses could not identify the cause of the high heterogeneity. Sensitivity analyses identified 1 study as a potential source of heterogeneity.[29] Excluding this study led to a significant reduction in heterogeneity (I^2 = 0.0%, P = .808), and the pooled 5-year DFS rate was 91% (95% CI, 0.88–0.95, P < .001; Figure 5, Supplementary Digital Content, http://links.lww.com/MD/G957).

3.5. Publication bias

The Begg-Mazumdar rank correlation test showed no evidence of publication bias in the meta-analysis of pregnancy rates (P = .711), and the funnel plot was symmetrical (Figure 6, Supplementary Digital Content, http://links.lww.com/MD/G957).

4. Discussion

FSS during the early stages of EOC continues to be controversial, since improving survival may be more important than preserving fertility, especially in older patients.[40] FSS has been associated with worse survival and a greater risk of recurrence than radical surgery.[41,42] Nevertheless, some have suggested that FSS may lead to survival similar to radical surgery if the EOC is in stage IA or IC (grades 1 or 2).[43]

Our meta-analysis of oncological and reproductive outcomes after FSS in patients with stage I EOC shows a relatively low rate of recurrence (12%, 95% CI, 0.09–0.14), similar to that among patients treated by radical surgery (OR 0.77, 95% CI, 0.45–1.33). FSS was also associated with relatively good 5-year rates of OS (94%) and DFS (89%), comparable to the corresponding rates of 90% and 88% reported for stage I EOC patients treated in different ways.[44] Indeed, a recent meta-analysis concluded that OS and DFS rates for stage I EOC patients were similar after FSS or radical surgery.[10] Based on these results, we suggest that FSS is a safe alternative to radical surgery for young women with stage I EOC.

Our findings suggest that about one-third (30%) of stage I EOC patients can become pregnant after FSS, while 26% of patients can conceive naturally and 2% can conceive through assisted reproductive treatments. The relatively low pregnancy rate may be explained by several factors that can affect fertility, including acute stress, impaired ovarian or tubal functioning (unilateral or bilateral ovarian-salpingectomy), and the presence of adhesions after pelvic surgery.[45] Nevertheless, our findings suggest that up to 27% of stage I EOC patients who undergo FSS can give birth to a healthy infant, while 4% of pregnant patients experienced at least 1 spontaneous abortion; this success may still represent great promise for women who otherwise face complete loss of fertility during radical surgery. Another option for patients who have undergone FSS treatment and wish to conceive in the future is the cryopreservation of embryos and oocytes, which may be particularly helpful in the event of relapse or re-surgery.[46]

Our conclusions should be interpreted carefully in light of the limitations of the studies in our systematic review. We observed significant heterogeneity across studies in the data for several outcomes. This may reflect differences in eligibility criteria across the included studies. The retrospective design of the studies and the differences in their sample sizes could also be sources of bias. For example, the heterogeneity in 5-year DFS rates may reflect that few studies reported such data, and 1 study reported a much lower rate than the others.[29] The heterogeneity in rates of pregnancy, live birth, and natural conception may reflect variations in how many patients in each study attempted to conceive. We were able to identify individual studies that contributed substantially to heterogeneity, and repeating the meta-analysis without them led to similar results as the original meta-analysis. This suggests that even our more heterogeneous meta-analyses are reliable. We were unable to evaluate rates of ectopic pregnancies, preterm births, or fetal anomalies, all of which have been linked to FSS.[47] Across the 23 studies in our review, only 2 patients experienced an ectopic pregnancy, only 4 babies were born preterm, and no baby was reported with congenital anomalies. We may also have introduced bias by including only English-language studies. We were unable to stratify analyses by the histological type of EOC in our patients since most studies in our review did not report the necessary data. Future studies should examine whether the histological type influences outcomes after FSS.

Despite these limitations, the results of our meta-analysis suggest that FSS is associated with good oncological outcomes, even if reproductive outcomes may not be completely satisfactory. Nevertheless, patients may wish to opt for the reproductive opportunities offered by FSS in lieu of the sterility that results from radical surgery. As far as we know, this is the first systematic review and meta-analysis to evaluate the reproductive outcomes of early-stage EOC patients after FSS. Our study suggests that FSS is a safe alternative to radical surgery for women with early-stage EOC who want to preserve their fertility.

Author Contributions

Yu-fei Zhang: Conceptualization, Data curation, Writing-Original draft preparation; Yu Fan: Methodology, Software, Validation; Yi Mu: Methodology, Formal analysis; Peng Zhang: Visualization, Investigation; Meng-yao Wang: Supervision; Jin-ke Li: Writing - Review & Editing.

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