

RELEVANCE OF OVARIAN PRESERVATION IN YOUNG WOMEN WITH EARLY-STAGE ENDOMETRIAL CANCER AFTER HORMONAL AND SURGICAL TREATMENT: A COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT

Relevance: Ovarian preservation in young women with early-stage endometrial cancer after surgical treatment has been conventionally associated with complications. Nevertheless, recent randomized studies suggest a different perspective.

The study aimed to clarify the occurrence of complications, in particular relapses, associated with ovarian preservation in young women after hormonal and surgical treatment for early-stage endometrial cancer.

Methods: The analysis included articles published in full text over the past 10 years. We identified relevant observations from studies using a comprehensive search in the following databases: PubMed, Medline, Embase, and Cochrane Library. The search strategy included terms related to endometrial cancer: premenopausal, young woman, endometrial cancer, ovarian conservation. The study followed the PRISMA guidelines for systematic reviews.

Results: A total of 178 articles were studied, of which 111 articles (literature reviews and meta-analyses) (62%) described the cases of ovarian preservation. Of these, 84 were excluded for various reasons; 29 eligible articles were included in this analysis. Notably, factors such as younger age ($P < 0.0001$), later year of diagnosis ($P = 0.03$), residence in Central and Southern Europe and the United States ($P = 0.02$), and lower-grade tumors in Asian countries ($P < 0.002$) correlated with the desire of women to preserve their ovaries. The conducted literature review showed that ovarian preservation did not significantly affect cancer-specific survival (risk ratio (HR) = 0.78, 95% CI 0.17-2.74) or overall survival (HR = 0.78, 95% CI 0.24-1.75).

This study's results remained practically unchanged even after excluding women after radiation and hormone therapy.

Conclusion: This literature review revealed no statistically significant difference in relapse-free survival between patients after ovarian preservation at stage IA and partially at stage II compared to those after bilateral salpingo-oophorectomy.

Keywords: Ovarian preservation, endometrial cancer, recurrence-free survival, lymphadenectomy, premenopausal women.

Introduction: Endometrial cancer is the fifth most prevalent cancer among women globally [1]. The incidence rates have steadily increased, with similar trends observed in developed and developing countries [2]. While the majority of diagnoses occur in post-menopausal women, it is worth noting that 15-25% of patients are premenopausal, and 5% are younger than 40 years old [3]. Several recognized risk factors encompass age, hyperestrogenic status linked to obesity and childbearing, obesity, and metabolic disorders.

Early-stage endometrial cancer cases often involve poorly differentiated tumors of the endometrioid subtype, which primarily affect the endometrial lining [4]. The RIAC classification system for endometrial cancer further categorizes it into two clinicopathological types: type 1, which is the estrogen-dependent endometrioid type often associated with obesity and accounting for up to 85% of endometrial cancer cases, and type 2, encompassing

non-endometrioid subtypes such as serous, clear cell, undifferentiated carcinomas, and malignant mixed Müllerian tumors, which are not typically linked to obesity. Tumor size and myometrial invasion tend to increase with age, posing a particularly poor prognosis for older patients [5].

Regarding treatment based on histological type, the standard approach for endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy (BSO), a strategy that yields excellent survival outcomes, particularly for low-grade endometrioid tumors [6].

However, the established standard surgical staging, which has remained unchanged since 1988, involves a total abdominal hysterectomy with pelvic and para-aortic lymphadenectomy as necessary, regardless of patient age or tumor stage. Removing both ovaries in premenopausal women often results in distressing menopausal symptoms, loss of fertility, and an elevated risk of cardiovascular disease, significantly impacting the quality of postoperative life [7].

Recent research has revealed that the incidence of ovarian metastases is approximately only 5% in patients with clinically early-stage endometrial cancer and may be inconsequential when intraoperative signs of disease progression are absent [8]. Some studies have examined the cancer prognosis in patients with early ovarian-sparing endometrial cancer and found no statistically significant difference in overall survival [9]. Since no prospective studies have been conducted on this matter, and only a few retrospective studies with large sample sizes exist, conducting a systematic review and meta-analysis could provide valuable insights. In light of this, we have undertaken a comprehensive review of relevant literature and conducted a meta-analysis to ascertain whether preserving both ovaries offers additional survival advantages for young women diagnosed with early-stage endometrial cancer.

Materials and methods: Articles published over the last 10 years were included in the study. In the Republic of Kazakhstan, there are not many scientific works conducted by domestic authors in the whole study of preservation of the ovary during early-stage endometrial cancer in young women. Therefore, articles (literary review, meta-analysis) written in English were given priority for research. Even though many studies are currently being conducted abroad on ovarian preservation in endometrial cancer in young women, it remains one of the most pressing problems. The study followed the PRISMA guidelines for systematic reviews. We identified relevant obser-

vational studies using a comprehensive search in the following databases: PubMed, Medline, Embase, and the Cochrane Library. A search strategy includes terms related to endometrial cancer (premenopausal, young woman, endometrial cancer, carcinoma, endometrial neoplasm, endometrial cancer, hysterectomy, simultaneous ovarian bleeding), patient age (premenopausal, young and reproductive age), tumor stage (early stage), and treatment (conservation of ovaries).

The literature search was conducted from 2013 to November 2022. We also surveyed collections of full papers and conference proceedings from 2013 to 2022 to identify forthcoming studies. To ensure the inclusivity of our research, we performed a recursive literature search by examining the reference lists of all confirmed relevant studies.

The initial search yielded 178 records, of which 111 were closely related but excluded from further evaluation (Fig. 1, 2). Of them, 84 were excluded for various reasons, leaving 29 retrospective cohort studies eligible for inclusion in this literature review [10, 11]. Some studies had to be excluded from the meta-analysis because they did not provide sufficient data for risk measurement, making it impossible to calculate the necessary risk inputs [12]. As such, their data was not included in the meta-analysis. It is important to note that all selected studies were assessed using the Newcastle-Ottawa scale (NOS), a tool designed to evaluate retrospective cohort studies.

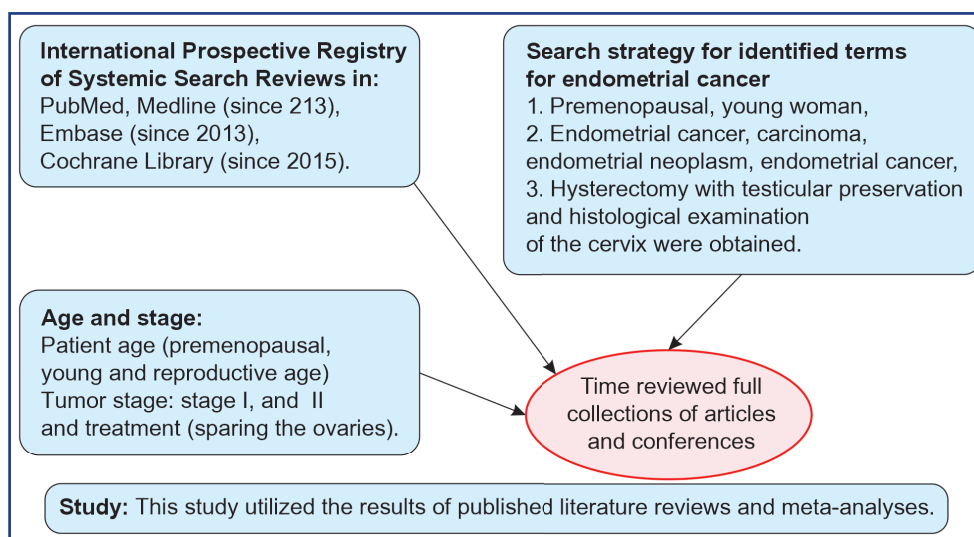


Figure 1 – General study design

Results: Our study included a total of 178, of which 111 articles were literature reviews and meta-analyses (62%) describing cases of ovarian preservation. Of these, 84 were excluded for various reasons: the study was not fully studied, the age category did not match, and the treatment of endometrial cancer was conservative. This left us with 29 articles eligible for inclusion in our review. Notably, factors such as younger age ($P < 0.0001$), later year of diagnosis ($P = 0.03$), residence in Central and Southern Europe and the United States ($P = 0.02$), and lower grade tumors grade of malignancy in Asian countries ($P < 0.002$) correlated with the desire of women to preserve their ovaries.

Another retrospective study from China involving 638 patients revealed that ovarian-conserving surgery was performed in 33 patients (5.2%). Most of these endometrial cancer cases were grade 1 (87.1%). Among the 33 ovarian-sparing patients, both ovaries were preserved in 31, while one ovary was spared in two. With informed consent regarding unknown risks, at least one ovary was retained during hysterectomy, with bilateral salpingectomy performed, sometimes including lymph node dissection [14]. Patients in the ovarian preservation group were notably younger than those in the BSO group (median age = 45 ± 6.18 years vs. 40 ± 7.01 years), had less myometrium invasion, and un-

derwent fewer lymphadenectomies. Importantly, the ovarian-sparing group exhibited no relapses throughout the

follow-up period, and recurrence rates did not significantly differ between the ovarian-sparing and BSO groups [15].

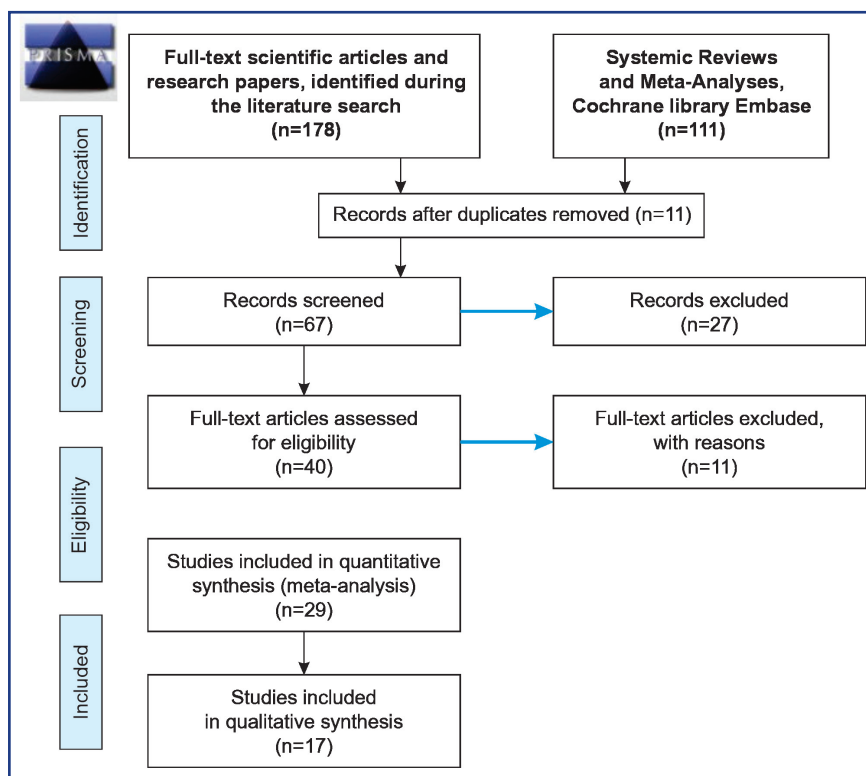


Figure 2 – The final sample structure – PRISMA 2009 Flow Diagram [13]

To gather observational studies assessing the impact of ovarian sparing surgery versus BSO in young patients with early-stage endometrial cancer, we conducted searches across multiple databases, including Medline, Embase, Cochrane Library, Chinese Biomedical Literature Database, Chinese Scientific Journal Full Text Database, and Wanfang Database. The literature search encompassed studies up to March 2017, and we identified ten retrospective cohort studies that met our criteria. Both random and fixed effect models indicated that ovarian preservation was associated with improved overall survival (RR=0.75, 95% CI 0.57-0.99, P=0.044). Importantly, ovarian preservation was not associated with lower relapse-free survival in premenopausal patients with early-stage endometrial cancer (RR 1.22, 95% CI 0.32-4.72, P=0.648; RR=1.11, 95% CI 0.59-2.10, P=0.745) (Table 1). This suggests that ovarian preservation is a safe

option offering significant benefits in this low-risk population, particularly when coupled with thorough preoperative and intraoperative assessments [16].

A subsequent study examined a cohort of 3,269 women, with 402 patients (12%) opting for ovarian preservation. Notably, factors such as younger age (P<0.0001), a more recent year of diagnosis (P=0.04), residence in the Eastern United States (P=0.02), and a lower tumor grade (P<0.0001) were all correlated with the choice of ovarian preservation (Table 2).

Importantly, these results remained consistent even when excluding women who had received pelvic radiotherapy. This research consensus suggests that ovarian preservation in premenopausal women diagnosed with early-stage endometrial cancer may indeed be a safe option without an associated increase in cancer-related mortality (Table 2) [17].

Table 1 – Summary of selected studies over the past ten years (systematic literature reviews)

Reference	Year	Country	Data source	Study period	Final/initial study sample	Mean age (range)	FIGO stage	Histological grade	Type of treatment	Follow-up (m)	Quality score
Gonthier C. [1]	2017	USA	Surveillance, Epidemiology End Results (SEER) Pubmed	2007-2017	96/849	≤45	la	G2 90% G3 10%	Hysterectomy with ovarian preservation	0-352	9
Matsuo K. [2]	2916	USA	SEER	2006-2016	1034/8076	≤50	la 87% lb 3% INOS 10%	G1	Hysterectomy	0-360	9
Obermair A. [3]	2020	Australia	SEER	2016-2020	35/25	≤40	I	G1 82% G2 18%	Hysterectomy	36	7
Wang Y. [4]	2017	China	Pubmed	2009-2017	25/76	≤45	la 87% lb 13%	G1 75% G2 21% G3 40%	Hysterectomy	3-72	7

Table 2 – General characteristics of analyzed studies (cohort studies and case series)

Reference	Year	Country	Study design	Subjects with EEC	Mean age (range)	Type of treatment	Subjects with complete response (%)	Mean follow-up in months (range)	Quality score
Cappelletti E. [5]	2022	Germany	Cohort study	10	34.3 (30.2-7.9)	Progestins (O)	5 (50%)	16.7 (4-40)	6
Ayhan et al. [7]	2020	Turkey	Cohort study	30	32 (20-45)	Progestins (O and/or IU) + Hysteroscopic resection	22 (73.3%)	55.5 (6-133)	7
Chen et al [8]	2016	China	Cohort study	37	32 (21-41)	Progestins (O)	27 (73%)	54 (4-148)	9
Falcone et al. [9]	2017	Italy	Cohort study	27	36 (25-40)	Progestins (O or IU) + Hysteroscopic resection	26 (96.3%)	96 (6-172)	9
Raffone et al. [10]	2021	Italy	Cohort study	6	35.5 (NK-44)	Progestins (IU) + Hysteroscopic resection	2 (33.3%)	NK (12-NK)	6
Tamauchi et al. [11]	2018	Japan	Cohort study	9	34 (19-45)	Progestins (O)	8 (88.9%)	52 (16-128)	6
Tock et al. [12]	2018	Belgium	Cohort study	8	30.4 (18-38)	Hysteroscopic resection + GnRH agonists	5 (62.5%)	25.3 (5-72)	8
Yamagami et al. [13]	2018	Japan	Cohort study	97	35 (19-44)	Progestins (O)	88 (90.7%)	71.3 (4.5-208.7)	3
Zhou et al. [14]	2015	China	Cohort study	19	30.4 (20-40)	Progestins (O)	15 (78.9%)	32.5 (10-92)	6
Atallah et al. [6]	2021	Lebanon	Case series	6	NK (NK-40)	Progestins (O) + Hysteroscopic resection + GnRH agonists	6 (100%)	NK (12-NK)	4
Casadio et al. [15]	2018	Italy	Case series	3	35.7 (32-38)	Progestins (O) + Hysteroscopic resection + GnRH agonists	3 (100%)	60 (60)	4
Casadio et al. [16]	2020	Italy	Case series	36	33.1 (NK-45)	Progestins (O) + Hysteroscopic resection	35 (97.2%)	30 (24-60)	6
Giampaolino et al. [17]	2019	Italy	Case series	14	35.1 (NK-44)	Progestins (IU) + Hysteroscopic resection	11 (78.6%)	NK (12-24)	6
Gungor et al [18]	2016	Turkey	Case series	6	34.3 (30-40)	Progestins (O or O+IU)	5 (83.3%)	45 (3-75)	6
Maggiore et al. [19]	2019	Italy	Case series	16	33.4 (NK)	Progestins (IU)	13 (81.3%)	85.3 (NK)	6
Ohyagi-Hara et al. [20]	2015	Japan	Case series	16	NK	Progestins (O)	11 (68.8%)	NK	6
Wang et al. [21]	2015	China	Case series	6	29.5 (25-34)	Progestins (O) + Hysteroscopic resection	6 (100%)	48.5 (26-91)	7
Wang et al. [22]	2017	China	Case series	11	27.3 (25-39)	Progestins (O or IM) + Hysteroscopic resection	9 (81.8%)	82.3 (15-152)	8
Yang et al. [23]	2019	Taiwan	Case series	6	33.7 (30-36)	Progestins (O) + Hysteroscopic resection	6 (100%)	32 (4-49)	5
Zhang et al. [24]	2019	China	Case series	6	30.5 (NK-40)	GnRH agonists + aromatase inhibitors	6 (100%)	48 (15-84)	7

Discussion: While endometrial cancer is generally considered a disease that primarily affects post-menopausal women, there is a concerning trend of increasing incidence in younger women. Evans-Metcalf et al. reported that as much as 14-15% of endometrial cancer cases occur in premenopausal women. Standard surgical interventions, including hysterectomy and BSO, often followed by lymphadenectomy, result in surgical menopause, elevate the risk of cardiovascular disease and osteoporosis and significantly reduce the quality of life for these young women.

The safety of ovarian preservation raises two theoretical concerns: the potential coexistence of ovarian malignancies and the impact of ovarian estrogen stimulation on residual microscopic endometrial cancers. Studies have

produced varying results concerning the incidence of coexisting ovarian malignancies in early-stage endometrial cancer. For instance, Pan et al. reported that among 976 patients with stage I endometrial cancer, only 20 were histologically diagnosed with coexisting ovarian cancer. Conversely, Lin et al. found that microscopic ovarian involvement occurred in 0.8% of endometrial cancer patients. However, Walsh et al. reported that 25% of young patients with endometrial carcinoma had coexisting epithelial ovarian tumors. These findings underscore the need for careful consideration when deciding whether to preserve the ovaries in young women.

Furthermore, the potential risk of estrogen stimulation in patients with endometrial cancer remains controversial.

A prospective study conducted by Barakat et al. involving 1236 patients who received estrogen replacement therapy showed an absolute recurrence rate of 2.1% and a low incidence of new malignancies. Comparable control studies and retrospective reviews also suggest that estrogen replacement therapy does not appear to increase recurrence or mortality rates among endometrial cancer survivors.

In many studies, ovarian preservation did not significantly affect recurrence rates or survival, which is consistent with previous research [18,19]. Gonthier et al. found that ovarian preservation was not associated with reduced disease-specific or overall survival in young women with grade 2 or 3 endometrial adenocarcinomas limited to the endometrium. A recent meta-analysis [19] indicated that

ovarian preservation was linked to improved overall survival and did not lead to reduced relapse-free survival in premenopausal patients with early-stage endometrial cancer.

In a retrospective analysis of 144 young and premenopausal women with early-stage endometrial cancer, ovarian involvement was associated with deep myometrial invasion, lymphatic metastases, LVIS, and grade (G2-G3) according to the univariate analysis results. A multivariate analysis revealed deep myometrial invasion as an independent risk factor for developing ovarian malignancies. Therefore, ovarian preservation can be safely considered for premenopausal women with stage Ia endometrial carcinoma (odds ratio-12.81, P=0.046) (Table 3).

Table 3 – Summary of selected studies (research longer than ten years)

Study	Year	Country	Data Source	Study period	Final/initial study sample	Mean age (range)	FIGO stage	Histological grade	Type of histology	Follow-up (m)	Quality score
Gallup D.G. [25]	2014	USA	SEER	1983-2014	96/849	≤45	Ia	G2 90% G3 10%	Endo	0-352	9
Nasioudis D. [26]	2017	USA	SEER	1983-2017	1034/8076	≤50	Ia 87% Ib 3% INOS 10%	G1	Endo	0-360	9
Shin W. [27]	2020	Korea	Korean group	1997-2020	176/319	PRE	Ia 89% Ib 5% II 6%	G1 78% G2 18% G3 4%	Endo	6-208	8
Lyu T. [28]	2019	China	Tongji Hospital	2000-2019	34/132	≤45	Ia 93% Ib 7%	G1 66% G2 21% G3 13%	Endo 97%	27-122	8
Akgor U. [29]	2022	USA	SEER	1960-2022	20/153	≤45	I	N	N	0-480	7
Shen F. [30]	2017	China	Pubmed	1999-2017	20/55	≤40	Ia 69% Ib 31%	G1 71% G2 25% G3 4%	Endo	0.3-160	8
Xu J. [31]	2021	China	SPTH	2008-2021	35/25	≤40	I	G1 82% G2 18%	Endo	36	7
Wang [32]	2016	China	Pubmed	2009-2016	25/76	≤45	Ia 87% Ib 13%	G1 75% G2 21% G3 40%	Endo 99%	3-72	7
Jia P. [33]	2017	China	Pubmed	2005-2017	25/47	≤45	Ia 90% Ib 10%	G1 78% G2 13% G3 9%	Endo	7-131	8

In recent studies, the incidence of ovarian metastases approached 5% in patients with early-stage endometrial cancer, which could be insignificant with no intraoperative signs of progression [34]. Some studies have evaluated the prognosis of cancer in patients with early-stage endometrial cancer after ovarian preservation and found no significant differences compared to BSO. A systematic review and meta-analysis could provide valuable insights since there have been no prospective studies on this subject and only a few retrospective studies with large sample sizes. Our review of the relevant literature and subsequent meta-analysis aimed to investigate whether bilateral salpingo-oophorectomy conferred any additional benefit on the survival of young women with early-stage endometrial cancer.

Conclusion: This literature review revealed no significant difference in recurrence-free survival in patients with preserved ovaries at stage IA and partial stage II and those after bilateral salpingo-oophorectomy. This study suggests that ovarian preservation in early-stage endometri-

al cancer in premenopausal women may be a safe choice, providing a comprehensive explanation of potential risks and a thorough preoperative assessment. However, this study's limitations should be considered when interpreting our results.

Firstly, some studies had inadequate sample sizes, leading to an absence of significant differences in recurrence rates between the ovarian preservation and BSO groups. Secondly, we did not differentiate between laparotomy and laparoscopic treatments but focused on treatment outcomes. Therefore, we recommend future research to analyze laparoscopic and laparotomy procedures separately for a more comprehensive assessment.

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АНДАТПА

ХИРУРГИЯЛЫҚ ЖӘНЕ ГОРМОНАЛЬДІ ЕМНЕН КЕЙІНГІ ЕРТЕ ЭНДОМЕТРИЙ ІСІГІ БАР ЖАС ӘЙЕЛДЕРДЕ АНАЛЫҚ БЕЗДІ САҚТАУДЫҢ ӨЗЕКТІЛІГІ: ӘДЕБИЕТТЕРДІ ЖАН-ЖАҚТЫ ШОЛУ

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Өзектілігі: Дәстүрлі түрде, онкология қоғамының мәліметі бойынша, хирургиялық емдеуден кейін ерте сатыдағы эндометрия қатерлі ісігі бар жас әйелдерде аналық безді сақтау дәстүрлі түрде асқынулармен байланысты болды. Дегенмен, соңғы рандомизацияланған сынақтар басқа перспективаны ұсынады.

Зерттеудің мақсаты – ерте эндометрия ісігін гормональді және хирургиялық емдеуден кейін жас әйелдерде аналық бездердің сақталуына байланысты асқынулардың, атап айтқанда қайталанудың пайда болуын мұқият зерттеу үшін әдебиеттерге кең шолу жасау.

Әдістері: Зерттеуге соңғы 10 жылда толық жазылған мақалалар кірді. Біз келесі дерекқорларды жан-жақты іздеу арқылы зерттеулерден тиісті бақылауларды анықтадық: PubMed, Medline, Embase және Cochrane кітапханасы. Іздеу стратегиясы эндометриялық қатерлі ісікке (менопауза алдындағы кезең, жас әйел, эндометрия ісігі, карцинома, эндометриялық ісік, ерте кезеңі және емдеу, аналық безді сақтау) қатысты терминдерді қамтыды. Зерттеу жүйелі шолуларға арналған PRISMA нұсқауларына сәйкес жүргізілді.

Нәтижелері: Барлығы алынған мәліметтер негізінде 178 мақала зерттелді, оның ішінде 111 мақала (әдебиет шолулары және мета-талдаулар) (62%) аналық бездердің сақталуы жағдайын сипаттады. Атап айтқанда, жасы ($P < 0,0001$), диагноз кешігіп қойылған жылдары ($P = 0,03$), Орталық және Оңтүстік Еуропа мен АҚШ-та тұру ($P = 0,02$) және Азия елдеріндегі төменгі дәрежедегі ісіктер ($P < 0,002$) сияқты факторлар әйелдердің қалауымен аналық безді сақтаумен байланысты болды.

Бұл зерттеуде нәтижелер әсіресе сәуле және гормондық терапия алған әйелдерді алып тастағаннан кейін де тұрақты болып қалды.

Қорытынды: жүргізілген әдебиеттік шолу мен мета-талдаулардың нәтижелері екі жақты сальпинго-оофорэктомия жасалынған науқастармен салыстырғанда ІА сатысы мен аналық безі ішінара ІІ сатысы кезеңдегі консервациядан өткен пациенттер арасында рецидивсіз өмір сүрудің статистикалық маңызды айырмашылығын көрсетпеді.

Түйінді сөздер: Аналық безді сақтау, эндометрия ісігі, аурусыз өмір сүру, лимфаденэктомия, менопауза алдындағы әйелдер.

АННОТАЦИЯ

АКТУАЛЬНОСТЬ СОХРАНЕНИЯ ЯИЧНИКОВ У МОЛОДЫХ ЖЕНЩИН С РАННИМ РАКОМ ЭНДОМЕТРИЯ ПОСЛЕ ГОРМОНАЛЬНОГО И ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ: КОМПЛЕКСНЫЙ ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: Сохранение яичников у молодых женщин с ранними стадиями рака эндометрия после хирургического лечения традиционно связывают с осложнениями. Тем не менее, недавние рандомизированные исследования предлагают другую точку зрения.

Цель исследования – тщательно провести широкий обзор литературы с целью выяснения возникновения осложнений, в частности рецидивов, связанных с сохранением яичников у молодых женщин после гормонального и хирургического лечения рака эндометрия на ранней стадии.

Методы: В исследование вошли статьи, написанные в полном объеме за последние 10 лет. Мы выявили соответствующие наблюдения из исследований, используя всесторонний поиск в следующих базах данных: PubMed, Medline, Embase и Cochrane Library. Стратегия поиска включала термины, связанные с раком эндометрия: менопауза, молодая женщина, рак эндометрия, сохранение яичников. Исследование проводилось в соответствии с рекомендациями PRISMA по систематическим обзорам.

Результаты: Всего на основе полученных данных изучено 178 статей, из них в 111 статьях (обзоры литературы и метаанализы) (62%) описан случай сохранения яичников. Из них 84 были исключены по разным причинам, в результате чего у нас осталось 29

статей, подходящих для включения в наш анализ. Примечательно, что такие факторы, как более молодой возраст ($P < 0,0001$), более поздний год постановки диагноза ($P = 0,03$), проживание в Центральной и Южной Европе и США ($P = 0,02$) и опухоли более низкой степени злокачественности в азиатских странах ($P < 0,002$), коррелировали с желанием женщин сохранить яичники.

Результаты этого обзорного исследования остались практически неизменными даже после исключения женщин, получавших лучевую и гормональную терапию.

Заключение: Результаты проведенного обзора литературы демонстрирует отсутствие статистически значимой разницы в безрецидивной выживаемости между пациентками, перенесшими сохранение яичников на стадии IA и частично на стадии II, и теми, кто перенес двустороннюю сальпинго-офорэктомию.

Ключевые слова: Сохранение яичников, рак эндометрия, безрецидивная выживаемость, лимфаденэктомия, женщины в пременопаузе.

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