International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 14, No. 2, February 2025 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_14.2.2025.114

Original Research

Safety of Ovarian Preservation in Premenopausal Women with Endometrial Cancer

[1]Dr. Mona Naman Shah, [2]Dr. Shaileshkumar C Banker, [3]Dr. Sakshi Dhingra Gajjar

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Swaminarayan Institute of Medical Sciences and Research (SIMSR),Kalol, Gandhinagar, Gujarat, India
[2]Assistant Professor, Department of Obstetrics and Gynaecology , Swaminarayan Institute of Medical Sciences and Research (SIMSR),Kalol, Gandhinagar, Gujarat, India
[3]Senior Resident, Department of Obstetrics and Gynaecology , Swaminarayan Institute of Medical Sciences and Research (SIMS),Kalol, Gandhinagar, Gujarat, India

Corresponding Author
Dr. Shaileshkumar C Banker
Assistant Professor, Department of Obstetrics and Gynaecology , Swaminarayan Institute of Medical Sciences and Research (SIMSR),Kalol, Gandhinagar, Gujarat, India
Email- drshailesh2112@gmail.com

Received: 12 January, 2025 Accepted: 31 January, 2025 Published: 22 February, 2025

Abstract
Aim: The Aim of this study to evaluate the long-term sequelae of estrogen deprivation in women .and safety of ovarian preservation in young women with endometrial cancer who underwent hysterectomy.
Methods: We include the women ≤ 50 years of age with stage I endometrial cancer recorded from 2022 to 2024.We prepared Cox proportional hazards models and Kaplan-Meier curves to compare women who underwent oophorectomy with those who had ovarian preservation.
Results: A total of 3,200 women, including 400 patients (12%) who had ovarian preservation, were identified. Younger age ($P < .0001$), later year of diagnosis ($P = .04$), residence govt. medical college , gynaecology department ($P = .02$), and low tumor grade ($P < .0001$) were associated with ovarian preservation. In a multivariate Cox model, ovarian preservation had no effect on either cancer-specific (hazard ratio [HR] = 0.55; 94% CI, 0.12 to 2.40) or overall (HR = 0.68; 95% CI, 0.34 to 1.35) survival.
Conclusion: Ovarian preservation in premenopausal women with early-stage endometrial cancer is safe and not associated with an increase in cancer-related mortality.

Introduction

Hysterectomy is the most common gynecologic procedure performed in India, with more than 600,000 procedures performed each year. Complications of hysterectomy vary based on route of surgery and surgical technique. The uterus should be removed vaginally or abdominally has been the subject of controversy. concluded that compared with abdominal hysterectomy (AH) and laparoscopic assisted vaginal hysterectomy (LAVH), VH scored the most points in terms of patient satisfaction and well-being.[1,2]In randomised study showed that vaginal hysterectomy should be considered the primary method for hysterectomy.The most common complications of hysterectomy can be categorized as infectious, venous thromboembolic, genitourinary (GU) and gastrointestinal (GI) tract injury, bleeding, nerve injury, and vaginal cuff dehiscence.[3]Infectious complications after hysterectomy are most common, ranging from 10.5% for abdominal hysterectomy to 13.0% for vaginal hysterectomy and 9.0% for laparoscopic hysterectomy. laparoscopic compared to vaginal hysterectomy (odds ratio 2.07, confidence interval 1.12–3.81). Neuropathy after hysterectomy is a rare but significant event, with a rate of 0.2–2% after major pelvic surgery.[4] Vaginal cuff dehiscence is estimated at a rate of 0.39%, and it is more common after total laparoscopic hysterectomy (1.35%) compared with laparoscopic-assisted vaginal hysterectomy (0.28%), total abdominal hysterectomy (0.15%), and total vaginal hysterectomy (0.08%). With an emphasis on optimizing surgical technique, recognition of surgical complications, and timely management, we aim to minimize risk for women.

DOI: 10.69605/ijlbpr_14.2.2025.114

each year, endometrial cancer develops in about 142 000 women worldwide, and an estimated 42 000 women die from this cancer.[5,6] the typical age-incidence curve for endometrial cancer shows that most cases are diagnosed after the menopause, with the highest incidence around the seventh decade of life. the appearance of symptoms early in the course explains why most women with endometrial cancer have early-stage disease at presentation. for all stages taken together, the overall 5-year survival is around 80%. there is a substantial prognostic difference between the histological types of endometrial cancers.[7]It is estimated that 40,100 cases of endometrial cancer will be diagnosed in the United States in 2008 and that 7,470 deaths will result from the disease.Endometrial cancer is traditionally considered a disease of postmenopausal women. However, previous work has suggested that up to 14% of women with endometrial cancer are premenopausal. A recent population-based analysis noted that 4% of endometrial cancers occurred in women aged 40 years or younger.Although prior data has been somewhat conflicting, many studies have found that young women with endometrial cancer have a more favorable prognosis than older patients. Premenopausal women with endometrial cancer often have low-grade, early-stage tumors that may in part explain the differential survival.In a series of more than 50,000 patients, the 5-year disease-specific survival was 93% in women younger than 40 years of age as compared with 86% in older patients. The improved survival persisted when separate analyses for early- and late-stage disease were performed.[8]

Treatment for endometrial cancer typically involves hysterectomy and salpingo-oophorectomy, often accompanied by lymphadenectomy. Hysterectomy results in loss of fertility and is often unacceptable to women of childbearing age. Conservative, uterine-preserving treatment with progestational agents has been proposed as an alternative for women unwilling to undergo hysterectomy.Progestin treatment is associated with a reasonable success rate, particularly in women with low-grade tumors.[9]

The most common lesions (type 1) are typically hormone sensitive and low stage and have an excellent prognosis, whereas tumours of type 2 are high grade with a tendency to recur, even in early stage. the cornerstone of treatment for endometrial cancer is surgery, which not only is important for staging purposes but also enables appropriate tailoring of adjuvant treatment modalities that benefit high-risk patients only. we review current concepts about epidemiology, pathology, pathogenesis, risk factors and prevention, diagnosis, staging, prognostic factors, treatment, and follow-up of endometrial cancer.the epidemiology, prevention, diagnosis, treatment, prognosis, and new international federation of gynecology and obstetrics staging system of endometrial carcinoma are reviewed.[10] endometrial cancer has increased 21% in incidence since 2008, and the death rate has increased more than 100% over the past two decades. precursor lesions of complex hyperplasia with atypia are associated with an endometrial carcinoma in more than 40% of cases.[11]endometrial cancer in white women occurs at twice the incidence as in black women, but, stage for stage, black women have a less favorable prognosis. preoperative imaging cannot accurately assess lymph node involvement. gross examination of depth of myometrial invasion does not have the sensitivity, specificity, positive predictive value, or negative predictive value to select women who can have lymphadenectomy safely omitted from the surgical procedure. although surgical staging remains the most accurate method of determining the extent of disease, the therapeutic value of pelvic lymphadenectomy has not been established. the anatomical extent of lymphadenectomy and the number of lymph nodes removed to establish prognostic and therapeutic benefit are controversial.[12] Research efforts are directed at identifying women with early stage endometrial cancer who only require total hysterectomy and bilateral salpingo-oophorectomy. minimally invasive surgical techniques have become established as standard therapy for treating women with endometrial cancer. women with a family history of hereditary nonpolyposis colorectal cancer are at increased risk for endometrial cancer. conservative treatment to allow for childbearing is possible in select situations. women with endometrial cancer should be managed by physicians experienced in the complex multimodality treatment of this disease.A largely unanswered question is the safety of ovarian preservation in young women with endometrial cancer. Oophorectomy is typically performed in conjunction with hysterectomy to exclude occult ovarian metastases and to decrease estrogen production, given that endometrial cancer is an estrogen-responsive tumor. Despite these theoretic benefits of oophorectomy, the procedure results in surgical menopause and places patients at risk for the long-term sequelae of estrogen deprivation. Although prior reports have examined the risk of ovarian metastases in young women with endometrial cancer, there are no data to describe the safety of ovarian conservation. The goal of this study was to determine the safety of ovarian preservation in young women with endometrial cancer and to examine the effect of ovarian conservation on mortality.[13]

Study Material:

Data from the Govt . Medical college , Gynaecology department and End Results database were analyzed. A population-based cancer registry that includes approximately 25% of the India population.

Women 50 years of age or younger with endometrial cancer diagnosed between 2022 and 2024 were examined. Only women with tumors classified as endometrioid carcinoma (7071/3) and adenocarcinoma not otherwise specified (6190/3)

DOI: 10.69605/ijlbpr_14.2.2025.114

were included. Clinical and pathologic data, including age at diagnosis (< 30, 30 to 39, 40 to 50 years), marital status, tumor grade, and performance of lymphadenectomy, were collected. Receipt of radiation was classified as vaginal brachytherapy, external beam (with or without vaginal brachytherapy), none, or unknown. Staging information was derived from the American Joint Cancer Committee staging information and recorded extent of disease codes. Only patients with stage IA, IB, and IC tumors were analysed. All patients underwent simple hysterectomy. Patients were stratified on the basis of whether oophorectomy was performed (oophorectomy group) or whether the ovaries were retained (ovarian preservation group).

Each patient's vital status was recorded. Survival was calculated as the number of months from cancer diagnosis to date of death. Patients who were alive at last follow-up were censored. Both overall and cancer-specific survival were calculated for all patients.

Frequency distributions between categoric variables were compared using the χ^2 test. Logistic regression models were developed to describe predictors of receipt of ovarian preservation. In Cox proportional hazards analyses, we modelled the cancer-specific and overall mortality hazard ratios, comparing patients who underwent oophorectomy with those who did not, and controlling for the other predictive variables. Separate Cox models were generated that included only patients who did not receive radiation. Kaplan-Meier curves were generated to examine overall and cancer-specific survival based on performance of oophorectomy.

Results

A total of 3,200 women, including 400 patients (12%) who had ovarian preservation, were identified. The demographic characteristics of the study population are listed in Table 1. Women who had ovarian conservation were younger than those who had oophorectomy ($P < .0001$). Low-grade ($P < .0001$) and early-stage tumors ($P = .0003$) were more common in women who had ovarian preservation. Stage IA tumors were found in 64% of those who had ovarian preservation versus 54% of women who underwent oophorectomy ($P = .0003$). Patients who underwent oophorectomy were more likely to undergo lymphadenectomy (33% *v* 10%; $P < .0001$) and to receive adjuvant radiation (9% *v* 3%; $P = .0004$).

Characteristic	Oopho rectomy (n = 3200)		Ovarian Preservation (n = 400)		*P*
	No.	%	No.	%	
Age at diagnosis, years					**< .0001**
< 30	**78**	**2.8**	**26**	**6.2**	
30-39	**920**	**30.2**	**180**	**45.2**	
40-50	**1810**	**64.1**	**181**	**44.5**	
Year of diagnosis					**< .0001**
2022-2023	**574**	**20.0**	**71**	**17.7**	
2023-2024	**429**	**15.0**	**95**	**23.6**	
SEER registry					**.12**
Central	**657**	**22.9**	**75**	**18.7**	
East	**521**	**18.2**	**83**	**20.1**	
West	**1689**	**58.9**	**244**	**60.1**	
Marital status					**.29**
Married	**1573**	**54.9**	**224**	**55.7**	
Single	**1193**	**41.6**	**158**	**39.3**	
Unknown	**101**	**3.5**	**20**	**5.0**	
Tumor grade					**< .0001**
1	**1757**	**61.3**	**318**	**79.1**	
2	**780**	**27.2**	**58**	**14.4**	
3	**185**	**6.5**	**11**	**2.7**	
Unknown	**145**	**5.1**	**15**	**3.7**	
Radiation					**.0004**
No	**2575**	**89.8**	**386**	**96.0**	
External beam	**165**	**5.8**	**8**	**2.0**	
Vaginal brachytherapy	**78**	**2.7**	**2**	**0.5**	
Unknown	**49**	**1.7**	**6**	**1.5**	
Lymphadenectomy					**< .0001**
Performed	**933**	**32.5**	**38**	**9.5**	
Not performed	**1934**	**67.5**	**364**	**90.5**	
Stage					**.0003**
IA	**1536**	**53.6**	**258**	**64.2**	
IB	**1200**	**41.9**	**132**	**32.8**	

DOI: 10.69605/ijlbpr_14.2.2025.114

IC	**131**	**4.6**	**12**	**3.0**	

Table: 1. Association Between Ovarian Preservation and Demographic and Clinical Variables

A logistic regression model of factors associated with ovarian preservation is displayed in Table 2. Women diagnosed in later years of the study and those residing in the eastern United States were more likely to have ovarian preservation. For example, patients in the eastern United States were 52% (odds ratio = 1.52; 95% CI, 1.08 to 2.15) more likely to have ovarian conservation than women in the central United States. In contrast, older women, those with grade 2 tumors, those who received pelvic radiotherapy and those who underwent lymphadenectomy were more likely to undergo oophorectomy. Compared with women younger than 30 years, patients aged 40 to 45 years were 68% (odds ratio = 0.32; 95% CI, 0.19 to 0.53) less likely to have ovarian preservation. There was no statistically significant association between stage and performance of oophorectomy in our multivariate logistic regression model.

Variable	**Ovarian Preservation**	
	OR	**95% CI**
Age, years		
< 30	Referent	
30-40	0.65	0.40 to 1.08
40-50	0.32	0.19 to 0.53
Year of diagnosis		
	Referent	
2022-2023	1.92	1.36 to 2.71
2023-2024	1.36	1.02 to 1.83
SEER registry		
Central	Referent	
Eastern	1.52	1.08 to 2.15
Western	1.30	0.99 to 1.74
Marital status		
Single	Referent	
Married	1.09	0.87 to 1.37
Unknown	1.57	0.89 to 2.65
Tumor grade		
1	Referent	
2	0.50	0.37 to 0.68
3	0.62	0.30 to 1.14
Unknown	0.63	0.35 to 1.08
Radiation		
None	Referent	
External beam	0.47	0.20 to 0.97
Vaginal brachytherapy	0.23	0.04 to 2.30
Unknown	1.01	0.04 to 0.78
Lymphadenectomy		
Not performed	Referent	
Performed	0.23	0.16 to 0.33
Stage		
IA	Referent	
IB	0.80	0.63 to 1.01
IC	1.27	0.62 to 2.52

Table: 2. Logistic Regression Model of Factors Associated With Ovarian Preservation

Likewise, 2-year survival was similar between the two groups (Table 3). Five-year survival was 98% for patients with IA endometrial tumors, regardless of whether the ovaries were preserved or removed. Among patients with IC endometrial cancer, survival was 89% (95% CI, 83% to 96%) in women who underwent oophorectomy as compared with 86% (95% CI, 63% to 100%) in those who had ovarian preservation.

DOI: 10.69605/ijlbpr_14.2.2025.114

Stage	Oophorectomy			Ovarian Preservation		
	No. of Patients	2-Year Survival (%)	95% CI	No. of Patients	2-Year Survival (%)	95% CI
IA	1,531	98	97 to 99	258	98	96 to 100
IB	1,400	96	95 to 97	132	100	95 to 100
IC	269	89	83 to 96	12	86	63 to 100

Table 3. 2-Year Survival Stratified By Stage and Ovarian Preservation

Table 4 displays multivariate Cox proportional hazards models of survival based on performance of oophorectomy. Ovarian preservation had no effect on either cancer-specific (hazard ratio [HR] = 0.58; 95% CI, 0.14 to 2.44) or overall (HR = 0.68; 95% CI, 0.34 to 1.35) survival. The most important factors for survival were tumor grade and stage. The radiation tolerance of normal ovaries is typically 20 to 30 Gy.Thus pelvic radiotherapy often results in loss of ovarian function. To account for the fact that pelvic radiation results in ovarian inactivation, we constructed separate Cox models and included only women who did not receive radiotherapy. Again, ovarian preservation had no effect on either cancer-specific (HR = 0.62; 95% CI, 0.14 to 2.63) or overall (HR = 0.71; 95% CI, 0.36 to 1.42) survival.

Factor	Cancer-Specific Survival		Overall Survival	
	HR	95% CI	HR	95% CI
Ovarian preservation				
Oophorectomy	Referent		Referent	
Ovarian preservation	0.58	0.14 to 2.44	0.68	0.34 to 1.35
Age, years				
< 30	Referent		Referent	
30-39	1.40	0.70 to 2.82	3.87	0.53 to 28.19
40-50	0.82	0.41 to 1.63	3.33	0.46 to 13.98
Race				
White	Referent		Referent	
Black	1.03	0.24 to 4.37	1.27	0.61 to 2.63
Asian	1.00	0.30 to 3.33	0.89	0.45 to 1.78
Other	2.48	0.85 to 7.20	2.13	1.13 to 4.00
Year of diagnosis				
	Referent		Referent	
2022-2023	0.56	0.19 to 1.63	0.78	0.45 to 1.36
2023-2024	0.99	0.43 to 2.29	1.05	0.63 to 1.75
SEER registry				
Central	Referent		Referent	
Eastern	1.31	0.42 to 4.07	0.93	0.54 to 1.61
Western	1.39	0.56 to 3.45	0.85	0.55 to 1.31
Marital status				
Single	Referent		Referent	
Married	0.59	0.28 to 1.17	0.76	0.52 to 1.10
Unknown	—		0.69	0.21 to 2.20
Tumor grade				
1	Referent		Referent	
2	1.92	0.86 to 4.26	1.07	0.69 to 1.64
3	5.42	2.18 to 13.44	2.27	1.29 to 3.97
Unknown	1.14	0.15 to 8.71	1.15	0.46 to 2.86
Radiation				
None	Referent		Referent	
External beam	1.18	0.39 to 3.50	0.95	0.48 to 1.87
Vaginal brachytherapy	—		0.23	0.03 to 1.63
Unknown	1.23	0.16 to 9.45	0.68	0.16 to 2.77
Lymphadenectomy				
Not performed	Referent		Referent	
Performed	1.21	0.57 to 2.59	1.37	0.88 to 2.11
Stage				
IA	Referent		Referent	

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IB	**1.60**	**0.75 to 3.40**	**1.92**	**1.28 to 2.86**
IC	**4.11**	**1.40 to 12.07**	**4.52**	**2.38 to 8.61**

Table 4. Cox Proportional Hazards Model of Factors Associated With Cancer-Specific and Overall Survival for Young Women With Stage I Endometrial Cancer

Discussion

Our findings suggest that ovarian preservation is safe in young women with early-stage, low-grade endometrial cancer. Ovarian conservation had no effect on either the cancer-specific or overall survival in our cohort. Further, the findings were unchanged, even after excluding patients who had received pelvic radiotherapy.

In addition to the immediate consequences of hot flashes and vaginal atrophy, surgical menopause in young women results in a number of long-term sequelae, including an increased risk of cardiovascular disease, osteoporosis, hip fracture, and cognitive dysfunction. In a recent meta-analysis, the relative risk of cardiovascular disease in women who had undergone bilateral oophorectomy was 2.62.[14] The risk of myocardial infarction is increased more than seven-fold in those who undergo bilateral oophorectomy before the age of 35 years. Perhaps even more importantly, early oophorectomy seems to have a direct effect on all-cause mortality. In a Markov model, Harper et al· demonstrated that women who underwent oophorectomy before age 55 years had an 8.6% excess mortality by age 80 years. A prospective, population-based cohort study found that women who underwent prophylactic bilateral oophorectomy before the age of 45 years had a 67% increase in mortality. Thus to avoid the short and long-term consequences of surgical menopause, there is a strong rationale for ovarian preservation in young women.[15]

The decision to perform oophorectomy in premenopausal women with endometrial cancer is based on two theoretic risks of leaving the ovaries in situ. First, estrogen production from the ovaries may stimulate microscopic foci of residual endometrial cancer. In vitro data has suggested that estrogen stimulates the growth of endometrial cancer cells and upregulates the expression of estrogen receptors. To date, this concern has not been observed clinically. Several reports have examined the use of estrogen replacement therapy in postmenopausal women with endometrial cancer.[16] These studies have not demonstrated any increase in the risk of recurrence or death in women receiving estrogen replacement The largest report was a prospective trial of estrogen replacement therapy in more than 1,200 women with endometrial cancer conducted by the Gynaecologic Oncology Group. Although closed early, the absolute recurrence rate was only 2.1% (HR = 1.27; 95% CI, 0.92 to 1.77). The findings from these studies, as well as our data, suggest that the risk of estrogenic stimulation of residual endometrial cancer is quite low, particularly in women with early-stage, low-risk lesions.[17]

The second potential risk of ovarian conservation is the presence of a coexisting synchronous primary tumor within the ovaries. Synchronous primary tumors of the endometrium and ovary are reported in approximately 5% of women with endometrial cancer However, among young women with endometrial cancer, the incidence of coexisting ovarian tumors is increased and has been reported to range from 5% to 29%. Walsh et alreported a series of 102 women younger than 45 years of age with endometrial cancer. Twenty-six patients (25%) had coexisting epithelial ovarian tumors; 23 tumors were classified as synchronous primaries, whereas three tumors were metastatic. The preoperative ovarian imaging in the women with ovarian involvement was normal in 15% of patients. Of greater concern, of those with ovarian tumors, 15% had normal-appearing adnexa intraoperatively. The authors recommended a cautious approach when considering ovarian conservation in young women. Despite the potential for occult ovarian tumors in women who undergo ovarian preservation, survival was not compromised in our series.

Our findings are notable in that ovarian preservation was more commonly performed in women with low-grade and early-stage tumors. Encouragingly, we were unable to discern any racial disparities in ovarian conservation; 12% of white women and 14% of black women had their ovaries preserved. Numerous prior reports have demonstrated racial disparities in the treatment selection and outcome of women with endometrial cancer. Somewhat surprisingly, we noted marked regional differences in the performance of oophorectomy. Compared with women in the central United States, those residing in the eastern United States were more than 50% more likely to have ovarian preservation in our multivariate model.[18]

Although the present study benefits from the inclusion of a large number of patients, several inherent limitations must be recognized. We assumed that premenopausal women had not previously undergone oophorectomy. Although a small fraction of young women may have had a prior oophorectomy, the number of patients who would have undergone bilateral ovarian removal before the age of 45 years is likely small. Although our survival estimates suggest that ovarian conservation does not negatively impact outcome, it should be recognized that, based on the 95% CIs we calculated, it is also plausible that ovarian preservation may be associated with a two-fold or greater increase in mortality. It is therefore imperative that these findings be conveyed in the proper context when counseling patients. Despite the fact that our overall cohort is large, the number of women with stage IC tumors and those with grade 3

DOI: 10.69605/ijlbpr_14.2.2025.114

lesions who had ovarian conservation were small, and these results should be interpreted with caution. Finally, the performance of oophorectomy is highly individualized. Registry data are unable to account for patient and physician preferences that may have biased the decision to perform oophorectomy.

Conclusion

In this study we concluded ovarian preservation in premenopausal women with early-stage, low-grade endometrial cancer may be safe and not associated with an increased risk of cancer-related mortality. Given the potential consequences of surgical menopause, further research to examine the safety of ovarian conservation for young women with early-stage endometrial cancer is clearly warranted. At present, the long-term risks and benefits of ovarian preservation should be carefully discussed with young women with endometrial cancer before hysterectomy .

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