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# Epithelial ovarian cancer

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The incidence of epithelial ovarian cancer in women aged 40 years and younger is 3–17%. The management of these women is challenging and requires balancing the need to treat epithelial ovarian cancer adequately and preserving reproductive potential. Fertility-sparing surgery, especially for early stage epithelial ovarian cancer, seems to be associated with equivalent clinical and cancer outcomes while preserving reproductive potential. A complete staging and cytoreductive procedure retaining the uterus, and at least one grossly normal ovary, is the minimum recommended procedure. Adjuvant chemotherapy with a platinum-taxane combination is recommended as clinically indicated, and is associated with better cancer and survival outcomes. Adjuvant treatment does not seem to increase the risk of congenital anomalies in subsequent pregnancies. Targeted therapy and ovarian cryopreservation are largely experimental and cannot be recommended as part of the clinical standard of care.



## Introduction

Epithelial ovarian cancer is a common gynaecologic cancer in developed countries, and is either the most common or second most common gynaecologic malignancy. Age-standardised risk ranges from 7–17 per 100,000 population per year.[1]

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Epithelial ovarian cancer accounts for up to 90% of all ovarian cancer. Evidence suggests that epithelial ovarian tumours develop along two distinct molecular pathways leading to different clinical presentations and end points. Type I tumours arise from the ovarian epithelium and inclusions of the germ cell layers of the Müllerian system, and are thought to give rise to endometrioid, mucinous, clear cell and well-differentiated serous tumours. The tumourigenesis of these lesions is often more indolent and has been postulated to be the result of 'multi-hit oncogenesis'. Type II tumours are thought to arise from Fallopian tubular epithelial origins, which give rise to poorly differentiated serous carcinomas. These are thought to be the product of p53 mutations.[2,3] These tumours tend to be more clinically aggressive and account for a larger proportion of widely metastatic ovarian cancers. Epithelial ovarian cancer spreads primarily by exfoliating from the primary organ to seed the entire peritoneal cavity and alternatively by lymphatic spread via the retroperitoneal lymph nodes. Because of the primary mode of spread and the lack of distinct symptomatology in early disease, multiple organ systems are usually involved when a diagnosis of an ovarian malignancy is made.[4]

The standard of care for the optimal treatment of metastatic epithelial ovarian cancer involves surgical debulking of all visible or gross disease followed by adjuvant combination chemotherapy with a platinum and a taxane. The uterus, adnexae and pelvic peritoneum are often involved in bulky pelvic disease, which is removed *en bloc* along with involved portions of other intraperitoneal organs. As the peak age incidence of epithelial ovarian cancer is in the fifth and sixth decades of life, and fertility is no longer a consideration, removal of the uterus, fallopian tubes and ovaries has been accepted as a necessary part of the standard surgical regimen.

The incidence of epithelial ovarian cancer in women aged 40 years and younger has been reported to be between 3 and 17%.[5–8] Demographically, women in countries in which epithelial ovarian cancer incidence is highest are also the most likely to delay childbearing, and these women will most likely be interested in retaining their fertility. The prognosis that follows a particular treatment course will also be an important consideration to women in this age group. The confluence of these factors creates the dilemma that confronts cancer specialists who have to provide care to women who have a diagnosis of epithelial ovarian cancer and who may want to retain their fertility. Although the standard of care for epithelial ovarian cancer is supported by ample evidence, considerably fewer data are available to guide the management of epithelial ovarian cancer in a woman of reproductive age in whom fertility is to be preserved. This review of the available literature, specifically of recent publications, will hopefully serve as a guide to providing sound clinical care to preserving fertility in women living with epithelial ovarian cancer (Table 1).

## The management of epithelial ovarian cancer in young women

In stage I epithelial ovarian cancer, irrespective of grade of tumour, women who undergo fertility-sparing surgery can expect to have the same overall survival and disease-free survival as women undergoing standard surgical treatment. In the management of FIGO Stage I epithelial ovarian cancer, fertility-sparing surgery is an option.[9]

The Fertility Task Force of the European Society of Gynaecologic Oncology laid out five considerations in the conservative management of epithelial ovarian cancer[10]: (1) fertility-sparing surgery should be discouraged in women older than 40 years of age. The fertility rates in this group of women are low and the main objective of conservative management is to promote subsequent fertility; (2) full disclosure to the woman of possible cancer outcomes and fertility outcomes of conservative management; (3) patient engagement and co-operation in complying with the follow-up regimen; (4) histological diagnosis should be clearly made and preferably by a gynaecologic pathologist. This is important as histological features such as subtype and grade are major prognostic factors in epithelial ovarian cancer; and (5) the surgical findings of exploratory surgery should be described exhaustively to provide a clear clinical picture of the state and extent of disease at the time of diagnosis. This is important to prognosis and in guiding management.

**Table 1**
Recent studies in fertility preservation in epithelial ovarian cancer.

| Study | Year | *N* | Median age (years) | Stage | *N* | % | Adjuvant | | Recurrence Disease-free survival | | Mortality Overall survival | | Median follow up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *N* | % | *N* | % | *N* | % | |
| Kajiyama et al.[9] | 2011 | 74 | ≤ 40 | IA | 36 | 48.6 | 54 | 73 | ? | 87.9 | ? | 90.8 | 62.5 |
| | | | | IB | 1 | 1.4 | Platinum and taxane | 29.7 | | | | | |
| | | | | IC | 37 | 50 | Platinum-based | 43.2 | | | | | |
| Hu et al.[13] | 2011 | 94 | 28.3 | IA | 46 | 48.9 | 48; all stage IB and | 51% | 9; most | 91.4 | ? | 92.3% | 58.7 |
| | | | | IB | 8 | 8.5 | above treated with | | recurrences in | | | | |
| | | | | IC | 28 | 29.8 | platinum-based | | stages II and III | | | | |
| | | | | II | 1 | 1.1 | adjuvant chemotherapy | | | | | | |
| | | | | III | 11 | 11.7 | | | | | | | |
| Schlaerth et al.[35] | 2009 | 20 | 27 | IA | 11 | 55 | 10; | 50 | 3 | 84 | 3 | 84 | 122 |
| | | | | IC | 9 | 45 | Oral alkylating agent 2 | 10 | | | | | |
| | | | | | | | Platinum-based | 40 | | | | | |
| | | | | | | | chemotherapy 8 | | | | | | |
| Wright et al.[26] | 2009 | 432 | < 50 | IA | 370 | 85.7 | NA | NA | NA | NA | ? | 94 | NA |
| | | | | IC | 62 | 14.4 | | | | | | | |
| Park et al.[14] | 2008 | 62 | 26 | IA | 36 | 58.1 | 48 | 77.4 | ? | 80 | ? | 88 | 56 |
| | | | | IB | 2 | 3.2 | | | | | | | |
| | | | | IC | 21 | 33.9 | | | | | | | |
| | | | | II | 1 | 1.6 | | | | | | | |
| | | | | III | 2 | 3.2 | | | | | | | |

## Clinical considerations

*Age at diagnosis as a prognostic factor*

Thigpen et al.[11] looked specifically at age as a prognostic factor in epithelial ovarian cancer. Six studies by the Gynaecologic Oncology Group in advanced ovarian cancer with a pooled database of more than 2000 women were analysed for important prognostic factors, and specifically for age as a determinant of eventual clinical outcome. Women older than 69 years of age had a poorer prognosis than younger women, having corrected for stage, residual disease and performance status.

One of the early studies looking at epithelial ovarian cancer in reproductive age women was published by Duska et al.[12] They studied clinical outcomes of epithelial ovarian cancer in women younger than 40 years. One-half of the women in the study group had borderline tumours and one-half had carcinoma. As expected, women with borderline ovarian tumours tended to have early stage disease, were able to have fertility-sparing surgery (54.3%) with optimal cytoreduction (defined as residual disease less than 2 cm), and therefore successful pregnancies (14 live births) after treatment. Women with carcinoma tended to have advanced disease at time of diagnosis (63% FIGO Stage III and IV), and consequently fewer women were candidates for fertility-sparing surgery (13%), with only one woman having two live births after treatment. In this study, age younger than 40 years alone was not associated with a better prognosis.[12]

Hu et al.[13] published the results of their multi-centre retrospective study on women aged 40 years or younger with epithelial ovarian cancer. They studied 94 women who received fertility-sparing surgery with a median follow up of 58.7 months. Fertility-sparing surgery was defined as conservation of one ovary and the uterus after staging procedures, which included removal of the affected ovary, peritoneal washings, omentectomy, pelvic and para-aortic lymphadenectomy. The median age in the study group was 28 years. Only 11 out of 94 women had FIGO Stage III disease and only one woman had a high-grade histology. The study population can therefore be characterised as young, with a diagnosis of early stage, low-grade epithelial ovarian cancer. A total of 17 pregnancies with seven live births took place, with most of these resulting from spontaneous conception. The elective abortion rate in this report was almost 30% (five out of 17 electing termination). Almost 90% of these women, however, resumed normal menstrual periods and by extension their reproductive potential. Chemotherapy did not affect reproductive potential in these young women.

Conservative surgery did not adversely affect survival, which was found to be comparable to other studies unrestricted by age. Survival was ultimately a function of disease stage, tumour grade and histology, and not necessarily of age.[13]

## Common clinical presentations of epithelial ovarian cancer in reproductive age women

Young women with epithelial ovarian cancer most commonly present with abdominal distention and pain. Complaints of an increase in abdominal girth resulting in the discovery of a pelvic mass is also a common presentation. Although less common, complaints of dyspareunia should also be investigated for a pelvic mass.[12,14]

It is important to remember that even young women can present with advanced epithelial ovarian cancer and that the symptoms described above are often associated with the constellation of symptoms in the premenstrual phase. It is therefore prudent to maintain a low index of suspicion for any woman presenting with these symptoms.

## The standard of care for fertility preservation surgery for epithelial ovarian cancer

The minimum staging surgery that has been described in most studies as fertility-sparing is unilateral salpingo-oopherectomy with conservation of the uterus and contralateral ovary (presumably grossly normal), omentectomy and lymphadenectomy. These have variously been described as involving the ipsilateral pelvic nodes only, also including the para-aortic lymph nodes, and an appendectomy in cases of mucinous tumours.[15–18] The practice of carrying out a wedge biopsy on a grossly normal contralateral ovary should be discouraged. The benefit of such a practice is unclear,

and evidence shows that wedge biopsies of normal-appearing ovaries negatively affects subsequent ovarian function.[19–21] Once the decision has been made to proceed with fertility-preservation, all efforts should be made to ensure that reproductive potential is optimised.

The clinical rationale for completion surgery involving removal of the uterus and the remaining ovary or ovarian tissue derives (1) from the standard of care for epithelial ovarian cancer; (2) from the possibility of a concurrent endometrial cancer, especially when the histology of the ovarian primary is endometrioid; and (3) the concern about occult ovarian metastases in a grossly normal ovary is reported to be up to 12%.[22–24]

## Common histological subtypes

The most common histologies encountered in epithelial ovarian carcinoma are endometrioid, serous, mucinous and clear cell. In young women who have epithelial ovarian cancer, a particular histological type does not seem to predominate. A histological diagnosis of a clear-cell tumour of the ovary, however, is associated with a poorer prognosis.[25] This finding is reflected in the analysis of Surveillance, Epidemiology and End Results data,[26] with women less likely to be given the option of fertility preservation if the histology was either that of a poorly differentiated tumour or if the histology were suggestive of a clear-cell carcinoma, despite an apparent early stage.

## The standard of care in adjuvant chemotherapy in epithelial ovarian cancer in reproductive age women

When considering chemotherapeutic options for women of reproductive age with epithelial ovarian cancer, it is important to remember that 'non-standard' surgery has been carried out and that the treatment regimen should not negatively affect reproductive potential.

Gynecologic Oncology Group-111, the Intergroup trial, and a handful of other trials in the 1990s, [27–32] defined a combination of platinum and taxane as the chemotherapeutic standard of care for epithelial ovarian cancer. Further experience showed the use of carboplatin to be just as effective as cisplatin and with less neurotoxicity.

More recently, Gynecologic Oncology Group -172 compared outcomes for intravenous paclitaxel followed by intraperitoneal paclitaxel and cisplatin chemotherapy and the standard intravenous platinum-taxane combination. Median progression-free survival was 23 months in the intraperitoneal chemotherapy group compared with 18 months in the intravenous group. The authors concluded that intraperitoneal chemotherapy with a platinum and taxane improved survival significantly in optimally debulked FIGO Stage III epithelial ovarian cancer.[33] Most women who are likely to be offered or are considering fertility-sparing surgery, and who require adjuvant chemotherapy, are likely to be suitable candidates for intra-peritoneal chemotherapy. The effect of intraperitoneal chemotherapy on ovarian function in a pre-menopausal woman is, however, unknown. This adjuvant treatment option and its relative benefits and the unknown effect on future fertility should be discussed preoperatively with all young women with a possible ovarian malignancy presenting with a pelvic mass.

There is no evidence that modulating the dose intensity of adjuvant chemotherapy in epithelial ovarian cancer based on age improves tolerability.[11] Furthermore, a relative dose intensity of less than 70% in adjuvant treatment has been associated with poorer outcomes in epithelial ovarian cancer.[34]

Targeted therapy uses agents or drugs that 'target' or act on a specific molecules or parts of molecular pathways that are important for tumour growth and spread. Molecular tumour profiling has been used to individualise targeted therapy, making it more specific by individualising the agents used based on the tumour profile to reduce tumour resistance. Tumour resistance is still the primary limitation of targeted therapy.

## Fertility after treatment and the risk of congenital anomalies

The objective of fertility preservation is to retain reproductive potential, which ultimately culminates in a live birth for the woman. Although most studies use resumption of normal menses as a proximate measure for the return of reproductive function, fewer studies look specifically at live

births and reproductive outcomes in pregnancies after treatment. Duska et al.[12] reported two live births from one woman with stage I disease in a cohort of six women who had epithelial ovarian cancer. Hu et al.[13] reported on 94 women with a median age of 28 years who underwent fertility-sparing surgery for epithelial ovarian cancer, 40% of whom were nulliparous at the time of diagnosis. A total of 17 pregnancies took place (of which 14 pregnancies were spontaneous conceptions), which resulted in seven live births.[13] Park et al.[14] reported on their cohort of 62 patients with a median age of 23 undergoing fertility sparing surgery for epithelial ovarian cancer. A total of 19 women ultimately attempted pregnancy resulting in 22 live births.[14] Schlaerth et al.[35] reported on 20 women who had fertility-sparing surgery; three of them died of recurrent disease and six of the remaining 17 women had nine live births. The study by Hu et al.[13] is one of the few contemporary studies that report specifically on the mode of conception in women who have fertility-sparing surgery for epithelial ovarian cancer. In their study, the rate of assisted reproduction was reported as 17% (three out of 17 women; two women had in-vitro fertilization and one had intrauterine insemination).[13] The available data are scant on rates of congenital anomalies in pregnancies that follow fertility-sparing surgery and adjuvant chemotherapy for epithelial ovarian cancer. The available data suggest no increase in risk of congenital anomalies in such pregnancies compared with the general population.

## Recurrent disease and role of adjuvant chemotherapy

In most studies, recurrence rates of 12–15% have been reported for women with stage I disease who received fertility-sparing surgery.[36–42] In these studies, however, a fair amount of variation took place in the adjuvant treatment for these women, first in whether adjuvant treatment was offered and second in the agents that were used. Recurrence is an important consideration especially given the 'non-standard' nature of the surgical treatment, the age of the patient, and the effect on prognosis of a diagnosis of recurrent epithelial ovarian cancer. Considering the available evidence, it seems that only women with adequately staged FIGO Stage I with no apparent risk factors should be expectantly managed with observation. Risk factors would include tumour histology that is poorly differentiated or consistent with a clear-cell type, capsular breach either spontaneously or iatrogenically, capsular surface excrescences, or positive cytology.

## The role of the oral contraceptive pill

The Cancer and Steroid Hormone Study was conducted by the US Centers for Disease Control in the early 1980s. The study concluded that users of contraceptive pills had a lower lifetime risk of epithelial ovarian cancer, 40% lower overall and as much as 80% in women who had used the pill for 10 years or more. More recent studies have concluded that that there is no significant difference in the level of protection for epithelial ovarian cancer between 'high-dose progestogen' oral contraceptive pills and the low-dose preparations in current use.[43,44] The number of lifetime ovulatory cycles at the time of diagnosis of epithelial ovarian cancer has been shown to be an important prognostic factor.[45] Consideration should, therefore, be given to the use of contraceptive pills in young women who have successfully undergone fertility preservation and for whom conception is not imminent or between pregnancies.

## Ovarian cryopreservation

Ovarian cryopreservation is the process of harvesting ovarian tissue and, more specifically, the ovarian cortex to freeze and store the tissue for later reimplantation, with the ultimate objective of harvesting viable oocytes from the reimplanted tissue. The harvested oocytes could then be fertilised for implantation in a retained uterus or more likely in a surrogate. This is largely still an experimental process, and virtually no data are available on outcomes, with only case reports describing the procedure. In the context of epithelial ovarian cancer, this procedure would ostensibly be applicable in a situation in which advanced disease required the removal of both ovaries and the uterus. Grossly normal ovarian tissue would be harvested and cryopreserved. Concerns with ovarian cryopreservation in epithelial ovarian cancer have been raised. First, the possibility of occult metastasis in grossly normal

ovarian tissue, especially in advanced disease, is not inconsequential. In studies looking at the incidence of occult metastases in a grossly normal contralateral ovary, the incidence of occult disease was reported to be 7–12%.[46,47] Second, a strategy of aggressive surgical and chemotherapeutic extirpation of disease rendering the woman disease free, only to reimplant possibly diseased tissue is clinically and ethically suspect. At present, ovarian cryopreservation cannot be recommended as a fertility-preserving option in the management of epithelial ovarian cancer.

## Conclusion

Epithelial ovarian cancer most commonly affects women in the fifth and sixth decades of life. The incidence in women aged 40 years and younger, however, is significant, and clinicians who care for women living with cancer should be familiar with the available data on the clinical management of epithelial ovarian cancer in reproductive-age women. Fertility-preserving surgery that spares the uterus and at least one ovary while ensuring removal of all gross disease produces equivalent cancer outcomes to comprehensive extirpative surgery, with the added advantage of conserving reproductive potential. Adjuvant chemotherapy is recommended for all advanced disease and in early stage disease with risk factors of extra-ovarian disease, high histological grade and clear-cell subtypes. Although adjuvant chemotherapy improves overall and disease-free survival, it is not associated with an increased risk of congenital anomalies in subsequent pregnancies. The use of targeted therapy and cryopreservation cannot be recommended as part of routine clinical practice as there is insufficient evidence on efficacy and safety.

### Practice points

- Epithelial ovarian cancer is not uncommon in women under 40 years, and clinicians delivering women's cancer care should be familiar with the issues surrounding the care of women of reproductive age with a diagnosis of epithelial ovarian cancer.
- Patient autonomy and the right to self-determination should be respected when considering fertility preservation in the management of epithelial ovarian cancer. Women should be empowered with the necessary information to make informed decisions about their treatment and future fertility.
- Fertility-preserving surgery should be considered in women aged 40 years and younger with a preoperative diagnosis of epithelial ovarian cancer.
- The uterus and at least one ovary are retained as part of fertility-preserving surgical management.
- Surgical staging should be as complete as possible and should include peritoneal cytology, peritoneal biopsies, pelvic and para-aortic lymphadenectomy, and an omentectomy.
- Adjuvant chemotherapy with a platinum and a taxane should be considered in all women with advanced disease or early disease with risk factors.
- Risk factors in early disease include positive cytology, capsular breach, surface excrescences, poorly differentiated tumours and clear-cell tumour type.
- Consideration should be given to the use of oral contraceptive pills when women are not actively trying for pregnancy.

### Research agenda

- The relationship between regular oral contraceptive pill use and the incidence of epithelial ovarian cancer in women aged 40 years and younger.
- Intraperitoneal chemotherapy and its effect on ovarian reserve and reproductive potential.
- The safety of ovarian cryopreservation in women with epithelial ovarian cancer.

## Conflict of interest

None declared.

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