RESEARCH ARTICLE

Pregnancy Outcomes after Conservative Surgery for Early-Stage Ovarian Neoplasms

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Abstract

Objective: This retrospective, single institute study aimed to evaluate pregnancy and oncologic outcomes in reproductive-age Thai women with early-stage ovarian neoplasms undergoing conservative surgical treatment. **Methods:** Medical records of 84 women of reproductive age (15-45 years) with histologically confirmed early-stage (IA-IIC) borderline ovarian tumors or cancers who had undergone conservative surgery between January 2003 and December 2012 were retrospectively reviewed. **Results:** The mean age of patients at diagnosis was 28.0 years (SD 7.2). Histologically, 30 (35.7%) had borderline ovarian tumors, 28 (33.3%) epithelial cancers, 22 (26.2%) malignant germ cell tumors, and 4 (4.8%) sex cord stromal tumors. Thirty-five women (41.7%) had complete surgical staging performed, whereas 49 (58.3%) underwent an incomplete staging procedure. Thirty-four patients (40.5%) received postoperative chemotherapy. Among 29 patients subsequently attempting pregnancy, 15 conceived successfully (51.7%). Pregnancy outcomes were one spontaneous abortion and 14 viable births. There were no serious adverse obstetric and neonatal outcomes among women with documented live births and no reported fetal abnormalities. Pregnancy rates were not impacted by surgical staging (53.8% vs 50.0%, p=0.837) or adjuvant chemotherapy (55.6% vs 50.0%, p=0.782). The 5-year disease-free survival was 91.0% and pregnancy after conservative surgery did not affect progression-free survival (p=0.194). **Conclusion:** Conservative surgery with or without appropriate adjuvant chemotherapy can be offered to young women with early-stage ovarian neoplasms who wish to preserve their fertility potential.

Keywords: Pregnancy outcome- conservative surgery- early-stage- ovarian tumor

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Introduction

Of all the gynecologic malignancies, ovarian cancer represents the greatest clinical challenge. It is the seventh most common cancer in women worldwide and is the leading cause of death among gynecologic malignancies in the Western World, killing more women than uterine and cervical cancer combined. In Thailand, it is the second most common cancer of the female genital tract after cervical cancer with an annual incidence and a death rate of 6.8 and 4.0 per 100,000 women per year, respectively (Globocan, 2012). Due to the often asymptomatic nature of the early stages of disease, many cases of ovarian cancer present in advanced stage for which the 5-year survival is around 30% (Memarzadeh and Berek, 2001). Whereas total hysterectomy plus bilateral salpingo-oophorectomy, infracolic omentectomy, peritoneal biopsy and lymph node sampling remains the cornerstone of treatment for early-stage ovarian cancer, maximal cytoreductive surgery followed by chemotherapy is the standard treatment for advanced ovarian cancer. It is predominantly a disease of postmenopausal women, with a median age at diagnosis of 63 years. However, approximately 12% of cases occur in women aged less than 45 years (Howlader et al., 2014; Siegel et al., 2016). The World Health Organization (WHO) classifies ovarian neoplasms by the most probable tissue of origin: epithelial, germ cell, and sex cord. The majority of primary ovarian cancers (90%) are derived from tissues that come from the coelomic epithelium or mesothelium. Others malignant tumors of the ovary consist of germ cell (5%) or sex cord tumors (5%) (Chen et al., 2003). Approximately 15% of epithelial ovarian tumors are further classified as low malignant potential (LMP), or borderline tumors (Chen et al., 2003; Skirnisdottir et al., 2008). These tumors are characterized by a younger age at diagnosis, an earlier stage at presentation, longer survival, and late recurrences. Approximately half of such diagnoses are made in women younger than the age of 40 (Gotlieb et al., 1998; Skirnisdottir et al., 2008). Since women tend to give birth to their first child at an older age nowadays, there has been an increasing demand to preserve their reproductive capability among young women diagnosed with early-stage ovarian neoplasms. Caring for these young women can be problematic for physicians who have to balance the patient's desire for fertility with a conservative surgical plan and the treatment outcomes.

Conservative surgery, leaving behind the uterus

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with one or both healthy adnexa in the treatment of young women with early-stage ovarian neoplasms has been evaluated since the mid-1980s (Schwartz et al., 1984; Zanetta et al., 1997; Morris et al., 2000; Morice et al., 2001; Samldone et al., 2010; Chaopotong et al., 2015). However, the recommended indications for such treatment remain controversial. Subsequent studies have confirmed that early-stage ovarian borderline tumor and invasive cancer may be safely treated with fertility-sparing surgery (Suh-Burgmann, 2006; Chan et al., 2008; Cheng et al., 2012; Fruscio et al., 2013; Uzan et al., 2014; Zapardiel et al., 2014; Ditto et al., 2015; Vasconcelos et al., 2015; Fruscio et al., 2016). The aim of this study was to evaluate the pregnancy and oncologic outcomes in reproductive-age Thai women with early-stage ovarian neoplasms undergoing conservative surgical treatment.

Materials and Methods

After the approval of research project by our institutional review board, women with histologically confirmed early-stage borderline ovarian tumors and ovarian cancers who underwent conservative surgery at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, between January 2003 and December 2012 were evaluated. All information was obtained by chart review. Criteria for inclusion were as follows: age between 15 and 45 years at the time of initial diagnosis, stage IA to IIC ovarian neoplasms, and receiving conservative surgical surgery. We excluded women with a prior history of tubal sterilization procedures, pelvic or abdominal radiation therapy either pre- or postoperatively. For the purpose of this study, conservative surgery was defined as any procedure in which the uterus and at least some ovarian tissues were left intact. Both borderline and malignant ovarian neoplasms were grouped together and stage IIC was used as a cutoff because these patients still had disease limited to the pelvis and therefore had low risk for recurrence. Pregnancy rates were determined for those women attempting conception after the conservative surgical management. The tumor stage and histological diagnosis of each case were determined according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) and the histological typing system of the World Health Organization (WHO), respectively. For the epithelial ovarian cancers, tumors were graded as well (G1), moderately (G2), or poorly (G3) differentiated.

Data were analyzed using descriptive statistics, Fisher exact test and $\chi 2$ analyses. Survival analysis was performed with Kaplan-Meier estimates.

Results

Between January 2003 and December 2012, 84 patients with histologically confirmed early-stage borderline ovarian tumors and ovarian cancers treated with conservative surgery were included. The mean age of patients at diagnosis was 28.0 years (SD 7.2). Histologically, 30 (35.7%) patients were borderline ovarian tumor, 28 (33.3%) epithelial cancer, 22 (26.2%) malignant germ cell tumor, and 4 (4.8%) sex cord stromal tumor. Thirty-five women (41.7%) had complete surgical staging performed, whereas 49 women (58.3%) received incomplete staging procedure. More than half of the women (57.1%) had stage IA disease, the remaining women had stage IB (4.8%), IC (34.3%) or IIC (3.6%) disease. Among

Table 1. Obstetric and Fetal/Neonatal Outcomes

	All cell type n (%)	Borderline n (%)	Epithelial n (%)	Germ cell n (%)	Sex-cord stromal n (%)
All patients	84 (100)	30 (35.7)	28 (33.3)	22 (26.2)	4 (4.8)
Attempt to conception	29 (34.5)	12 (40)	7 (25)	8 (36.4)	2 (50)
Pregnancy	15	5	4	4	2
Obstetric outcomes					
Miscarriages	1	1	0	0	0
Live birth	14	4	4	4	2
Term pregnancy	13	3	4	4	2
Route of delivery					
Normal delivery	9	3	1	4	1
Cesarean section	5	1	3	0	1
Complications					
Antepartum	0	0	0	0	0
Intrapartum	1	0	1	0	0
Fetal/neonatal outcomes					
Mean birth weight (±SD), grams	3138 ±348	3030 ±336	3097 ±396	3203 ±71	3320 ±736
1-min Apgar score (median)	9	9	7	9	8
5-min Apgar score (median)	10	10	9	10	10
NICU admission	0	0	0	0	0
Congenital anomalies	0	0	0	0	0

Table 2. Patients with Early-Stage Ovarian Neoplasm Who Developed Recurrence

Pt	Age	Cell type	Surgical staging	FIGO stage	Grade	Precedure	Status	Follow up (months)
1	30	Epithelial	Incomplete	Ic	1	B/L cystectomy	NED	12
2	38	Epithelial	Incomplete	Ic	3	Oophorectomy	AWD	15a
3	30	Epithelial	Incomplete	Ic	3	Oophorectomy+C/L cystectomy	DOD	19
4	30	Epithelial	Incomplete	Ic	n/a	Oophorectomy+C/L cystectomy	NED	128
5	26	Germ cell	Incomplete	Ia	-	Oophorectomy	AWD	15
6	19	BOT	Incomplete	Ia	-	B/L cystectomy	NED	47
7	35	BOT	Incomplete	Ib	-	B/L cystectomy	NED	76

Pt, patient; B/L, bilateral; C/L, contralateral; BOT, borderline ovarian tumor; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; n/a, not applicable

the epithelial ovarian cancer, tumor grade was G1 in 17 (60.7%) patients, G2 in 1 (3.5%), and G3 in 5 (17.9%). Eight (9.5%) patients underwent ovarian cystectomy with or without other procedures on the contralateral ovary, whereas 76 (90.5%) had oophorectomy with or without other procedures on the contralateral ovary. Thirty-four patients (40.5%) received adjuvant chemotherapy with a mean number of chemotherapy cycles of 4.8 (range 2-6 cycles). Patients with malignant ovarian germ cell tumor and sex cord stromal tumor received the combination of cisplatin, etoposide, and bleomycin, whereas those with epithelial ovarian cancer had carboplatin plus paclitaxel. Eight (9.5%) patients had prophylactic removal of the remaining ovary with or without hysterectomy after the initial conservative surgery.

Twenty-nine patients (34.5%) attempted pregnancy after the conservative surgical treatment of ovarian neoplasms. Fifteen patients successfully conceived, producing a pregnancy rate of 51.7% for those attempting conception. Obstetric and neonatal outcomes were examined for 15 patients (17.9%) who had received conservative surgery (Table 1). Pregnancy outcomes included one spontaneous abortion and 14 viable births with a mean birth weight of 3,138 grams (SD 348) and median Apgar scores of 9 at 1 minute and 10 at 5 minutes. There were no serious adverse obstetric and neonatal outcomes among women with documented live births and no fetal abnormalities in the offspring of these women have been reported. There were no significant differences in pregnancy rates between patients who had complete surgical staging and those who had incomplete procedure (53.8% vs 50.0%, p=0.837) and between patients who received adjuvant chemotherapy and those who had not (55.6% vs 50.0%, p=0.782).

Median follow-up time was 43.0 months, with a range of 6.0-148.0 months and median overall survival was not reached. There were seven tumor recurrences (8.3%) during the follow-up period (Table 2). Four recurrences occurred in patients with stage 1C epithelial ovarian cancer, 2 with borderline tumor and 1 with germ cell tumor. There were two deaths (2.4%) among our study population. One patient with stage 1C, G3 epithelial ovarian cancer who had undergone right salpingo-oophorectomy with left ovarian cystectomy and received 6 cycles of carboplatin plus paclitaxel after the surgery. She attempted pregnancy but failed to conceive. She had recurrent pelvic tumor with multiple intra-abdominal lymphadenopathies 14 months after her last chemotherapy. The patient failed to respond to subsequent treatment and died from her disease. The other one with stage 1A, G1 epithelial ovarian cancer had died from non-cancer related conditions. All patients who had tumor recurrence and who had died from the disease had incomplete surgical staging. The 5-year disease-free survival was 91.0% and pregnancy after conservative surgery did not affect the progression-free survival (p=0.194).

Discussion

It has been generally accepted that the surgical treatment of choice for early-stage ovarian cancer consists of aspiration of ascites or peritoneal lavage, total hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, selected peritoneal biopsy, bilateral pelvic and para-aortic lymph node sampling. Hysterectomy and bilateral salpingo-oophorectomy are crucial because uterine serosa and endometrium are often sites of occult metastasis and the prevalence of synchronous endometrial carcinoma is also relatively high. Moreover, the possibility of occult metastasis in the normal appearing contralateral ovary may vary from 2 to 12% depend on histological cell type, grade, and stage of disease (Zanetta et al., 1997; Benjamin et al., 1999; Morice et al., 2001; Park et al., 2008). Although ovarian cancer is a disease of postmenopausal women, approximately 12% of women with ovarian cancer were younger than 45 years old when the disease was diagnosed (Howlader et al., 2014; Siegel et al., 2016). Conservative surgery may be an option for selected patients with younger age who want to preserve their potential fertility function. Conservative therapy raises problems about the risks of tumor recurrence and whether or not postoperative chemotherapy should be given, and what adverse effects the remaining ovary and/or future fetus may suffer as a result of cytotoxic drugs. Therefore gynecologic oncologists must balance between fertility desire and treatment outcome. The recommended indications for conservative surgery in the treatment of young women with early-stage ovarian neoplasms remain controversial. According to the 2007 guidelines of the American College of Obstetrics and Gynecology (ACOG) and the 2008 guidelines of the European Society for Medical Oncology (ESMO), such treatment has been adopted for patients with stage IA epithelial ovarian cancer and non-clear cell histology G1 and G2 (ACOG

2007; Aebi and Castiglione, 2008). Recently, the Fertility Taskforce of the European Society of Gynecologic Oncology (ESGO) has recommended that conservative surgery should not be offered to patients with G3 epithelial ovarian cancer (Morice et al., 2011).

Our study demonstrated that selected patients with early-stage ovarian neoplasms who received conservative surgical treatment and appropriate adjuvant chemotherapy could have successful pregnancy outcomes with a pregnancy rate of 51.7% for those attempting conception. Furthermore, obstetric and neonatal outcomes among women with documented live births were favorable and no congenital anomalies in the offspring of these women were demonstrated. The results found in this study are in agreement with other previous reports on both early-stage ovarian cancer and borderline tumors (Suh-Burgmann, 2006; Chan et al., 2008; Cheng et al., 2012; Fruscio et al., 2013; Uzan et al., 2014; Zapardiel et al., 2014; Ditto et al., 2015; Vasconcelos et al., 2015; Fruscio et al., 2016). Chemotherapeutic agents, particularly alkylating agents, have a direct cytotoxic effect on the ovaries, which may result in premature ovarian failure and subsequent infertility (Byrne et al., 1992). In the present study, none of our patients received alkylating agents. Only the combination of cisplatin/etoposide/bleomycin and carboplatin/paclitaxel were given and no premature ovarian failure was found in our study cohort.

Rapid growth and recurrence of ovarian cancers have been found to be associated with pregnancy (Elit et al., 1999). However, subsequent studies have failed to show such a relationship (Morice et al., 2001; Seracchioli et al., 2001; Donnez et al., 2003). In our series, there were seven tumor recurrences and one cancer-related death among the 84 patients with early-stage ovarian neoplasms. The recurrence rate including one cancer-related death was 8.3% (7 of 84), falling within the range reported previously (Suh-Burgmann, 2006; Chan et al., 2008; Cheng et al., 2012; Fruscio et al., 2013; Uzan et al., 2014; Zapardiel et al., 2014; Ditto et al., 2015; Vasconcelos et al., 2015; Fruscio et al., 2016). Four patients with tumor recurrence had stage IC epithelial ovarian cancer, 3 of these had grade 3 disease and one had undetermined grade. Therefore, our study confirmed the American and European guidelines that conservative surgical treatment should not be recommended to patients who had stage IC tumor and unfavorable histology (ACOG 2007; Aebi et al., 2008; Morice et al., 2011). All of the patients with recurrence had incomplete surgical staging. Occult intra-abdominal metastasis including retroperitoneal lymph node involvement has been reported in patients with clinically apparent stage 1 ovarian cancer. Pelvic and/or para-aortic lymph node metastases appear in around 10-15% of such patients (Cass et al., 2001; Morice et al., 2003). Re-staging surgery of presumed early-stage ovarian cancer has demonstrated up to 30% upstaging rate and complete surgical staging has been shown to be an important prognostic factor for the patients' outcome (Young et al., 1983; Zanetta et al., 1998; Trimbos et al., 2003; Engelen et al., 2006; Grabowski et al., 2012). It is important to emphasize that patients selected for conservative surgery should have complete surgical staging, including pelvic/para-aortic lymph node sampling, multiple peritoneal biopsies, washings, and omentectomy (Smaldone et al., 2010).

Our study has several limitations. Data obtained from retrospective study are subject to significant potential bias. Secondly, we did not have systematic tumor registry in our institute until 2006 therefore it was difficult to determine the exact number of young women undergoing conservative surgery. Thirdly, we evaluated only women who visited our hospital and therefore this single institutional cohort might not reflect the real picture of the whole country.

In conclusion, the results of our study confirm that conservative surgical treatment with or without proper postoperative chemotherapy can be offered to young women with early-stage ovarian neoplasms who want to preserve their fertility capability. Such treatments do not have adverse effects on their obstetric, neonatal and oncologic outcomes. To achieve a high quality evidence, a randomized controlled trial may be warranted to compare conservative treatment with radical surgery for these particular patients. However, such trials may not be ethically feasible.

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