Reproductive outcome of FIGO stage IA and IC ovarian cancer after fertility-sparing surgery: A retrospective cohort study*

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ABSTRACT

Background: Early stage ovarian cancer may be managed with fertility-sparing surgery, to preserve the uterus and contralateral ovary, thus preserving future reproductive function. The aim of this study was to determine the reproductive outcome of early stage ovarian cancer managed conservatively by unilateral salpingooophorectomy, and to compare the survival and recurrence rate among those who had and did not have pregnancy after treatment.

Methodology: A retrospective cohort study was conducted on 34 patients with early stage ovarian cancer who underwent fertility-sparing surgery from January 2005 to December 2018. Fertility outcome following treatment was determined. Survival and recurrence rate was analyzed between those who had and did not have pregnancy after surgery.

Results: A total of 34 out of 661 (5.14%) new cases of ovarian cancer who underwent fertility-sparing surgery were analyzed, with a mean age of 23.71 ± 5.57 years (range: 12-36 years old), with the most common complaints of increasing abdominal girth (11/34, 32.35%) or palpable abdominal mass (11/34, 32.35%). Successful pregnancy was seen in 9 cases (26.47%), with 2 of them currently pregnant. Overall recurrence and survival rates were 14.71% and 91.18%, respectively. There was no statistically significant difference in the survival rate (88.89% vs 92%, p-value 0.7778) and rate of recurrence (22.22% and 12%, p-value 0.4578) between those who got pregnant after fertility-sparing surgery for early stage ovarian cancer, FIGO Stage IA and IC, compared to those who did not get pregnant.

Conclusions: Fertility-sparing surgery can be effectively offered to young patients with early stage ovarian cancer, to preserve reproductive function, with 26.47% successful pregnancy rate. Pregnancy had no significant effect on recurrence and survival among FIGO stage IA and IC ovarian cancer who underwent fertility-sparing surgery by unilateral salpingooophorectomy.

Keywords: early-stage ovarian cancer, fertility-sparing surgery, fertility outcome

INTRODUCTION

Ovarian cancer is the eighth most common female cancer and also the eighth most common cause of cancer death among women worldwide, based on the 2018 GLOBOCAN database for 185 countries and 36 cancers.[1] The world rate for ovarian cancer is estimated to be 10.6 per 100 000 women. In the Philippines, a total of 5, 069 new cases of ovarian cancer were diagnosed in 2018, making it the 5th most common malignancy among Filipino women.[2]

Ovarian cancer is rare among women younger than 40 years of age.[3] It is staged surgically and differs primarily on the type of histology. Most tumors, in general, are comprised of malignant epithelial tumors in more than 90% of the cases, followed by the much less frequent malignant germ cell tumors (3% of ovarian malignancy; dysgerminomas, yolk sac tumors and immature teratomas), and malignant sex cord stromal tumors (1-2% of ovarian cancers; mainly granulosa cell tumors,).[4] However, majority of women in the younger age group have germ cell tumor as the most common histology.[3] In 2014, the International Federation of Gynecology and Obstetrics (FIGO) released a revised staging of ovarian cancer. Stage I ovarian cancer was divided into stage IA (tumor limited to one ovary with capsule intact), IB (tumor limited to two ovaries with capsule intact) and stage IC. Stage IC was further subdivided into 3 groups: IC1 (surgical spill intraoperatively), IC2 (capsule rupture before surgery or tumor on ovarian/fallopian tube surface), and IC3 (positive ascitic fluid or peritoneal washings).[4,5]

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Conservative management for stage I ovarian carcinoma has been previously recommended for early stage ovarian cancer with stage IA disease, adequately staged and desiring to preserve fertility, and also in some cases of stage IC tumors. Its goal was to preserve the reproductive and endocrine function by conserving the uterus and the contralateral ovary while treating the disease.[6-8]

Fertility-sparing surgery in the form of unilateral salpingoophorectomy has been shown to be a safe procedure for young women, with early stage ovarian cancer, stage IA and IC. It has a relapse rate of 9% to 29% and with good survival documented at 83% to 100%.[9, 10]

This study was conducted among patients with early stage ovarian cancer, Stage IA and IC, who had fertility-sparing surgery, and presented at our institution from January 2005 to December 2018. This aimed to determine the reproductive outcome of early stage ovarian cancer managed with unilateral salpingooophorectomy, and to compare the survival and recurrence rate among those who had and did not have pregnancy after treatment.

OBJECTIVES

General Objective:

To determine the reproductive outcome of early stage ovarian cancer, FIGO stage IA and IC, managed with fertility-sparing surgery (FSS) by unilateral salpingooophorectomy, and to analyze the effect of pregnancy on recurrence and survival.

Specific objectives:

1. To determine the fertility outcome of early stage ovarian cancer, FIGO Stage IA and IC, following FSS
2. To compare the overall survival and recurrence rate of early stage ovarian cancer between those who had and did not have pregnancy after FSS

METHODOLOGY

Study Population

A retrospective, epidemiological, observational, analytical cohort study was conducted among women in their reproductive years, aged 40 years old and younger, with early stage ovarian cancer, FIGO (International Federation of Gynecology and Obstetrics) Stage IA and IC, who underwent fertility-sparing surgery, comprising of unilateral salpingoophorectomy with or without complete surgical staging, and who presented at a single institution from January 2005 until December 2018.

Our institution is a referral center for gynecologic malignancy and all patients seen here during the study period, even if operated at another institution were included in the study. The following patients who underwent unilateral salpingooophorectomy were included in the analysis: (1) intraoperative referral from our institution for complete surgical staging after a malignant frozen section (FS) or with grossly malignant tumor, (2) patients with final histopathology of ovarian malignancy but had no surgical staging because of a benign FS results or intraoperative findings of grossly benign tumor, and (3) diagnosed case of ovarian cancer from another institution after unilateral salpingooophorectomy referred either for adjuvant treatment, cancer monitoring or further evaluation for possible re-exploration and completion of surgical staging.

Patients excluded from the study are: (1) those with other malignancies or synchronous tumors, (2) those with spread of cancer to other organs, (3) those who had completion surgery after initial operation which included subsequent removal of the uterus and/or contralateral ovary.

Medical records of these patients including outpatient clinic records, operative and histopathology report, and chemotherapy records were reviewed. The general and clinical data were collected including age, civil status, employment status, co-morbidities, smoking and family history. Obstetrical history, menarche, use of contraceptive pills and chief complaint were also recorded. Details of her surgery and histopathologic findings were gathered including the procedure performed, frozen section results, stage, tumor grade, histology, and peritoneal fluid cytology. Adjuvant chemotherapy given to the patients were also documented.

After treatment, follow-up consults of these patients were reviewed including clinical examinations, assessment of tumor markers, ultrasonography and periodic computed tomography results. Documented tumor recurrences as well as the treatment and course of the disease were collected. Any pregnancies after surgery were recorded including date of conception and delivery, outcome or any complications. The patients were followed-up until the date of last consult, or last known alive, or date of death. Some patients lost to follow-up were also contacted by telephone calls or online messages to document current status.

Fertility-sparing surgery (FSS) was defined as an operation that resulted in preservation of the uterus and the contralateral ovary, involving removal on only one ovary, unilateral salpingooophorectomy.[11]

Complete surgical staging in ovarian cancer comprised of systematic abdominal exploration, sampling of peritoneal cavity washings, careful inspection and palpation of all peritoneal surfaces, biopsy and resection of suspicious lesions, removal of primary ovarian tumor, unilateral salpingooophorectomy (USO) in young patients, infracolic omentectomy (IO) or infragastric omentectomy

if with gross omental involvement, random peritoneal biopsies, with or without systematic lymphadenctomy and/or appendectomy. Young patients with early stage ovarian cancer, FIGO Stage IA-IC, with good histologic type, grade 1 or 2 disease, and wanting to retain their fertility may undergo FSS by unilateral salpingooophorectomy with frozen section (FS), followed by complete surgical staging.[11,12]

Primary endpoint of the study were the fertility outcome, the overall survival and recurrence rate between those who had and did not have pregnancy. Fertility was measured with documented pregnancies regardless of outcome and the live births after fertility-sparing surgery. Pregnancy rate was computed as the number of pregnancies after FSS regardless of pregnancy outcome divided by the total number of patients who underwent fertility sparing surgery.

Statistical Analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Chi-square test was used to determine the significance of pregnancy in the recurrence rate and survival.

All valid data was included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

Patient Profile and Characteristics

A total of 661 new cases of ovarian cancer was seen at our institution from January 2005 until December 2018 (Figure 1). Of these cases, 34 patients (5.14%) diagnosed with early stage ovarian cancer who underwent fertility-sparing surgery were analyzed and included in the study. They had a mean age of 23.71 ± 5.57 years (range: 12-36 years old), and 85.29% were single during the time of surgery. Majority (70.59%) were unemployed, with no co-morbidities (94.12%), and non-smoker (85.29%) at the time of diagnosis. There were 10 women with a positive family history for cancer, with seven and three women having a history of breast and ovarian cancer respectively. The patients consulted for complaints of increasing abdominal girth (32.35%), abdominal mass (32.35%) or abdominal pain (23.53%), with four women who knew of having an ovarian mass through incidental findings on routine check-up or for other conditions. The average age of menarche in these patients was 12.29 ± 1.36 years old, 70.59% were nulligravid and 94.12% had no history of oral contraceptive use (Table 1).

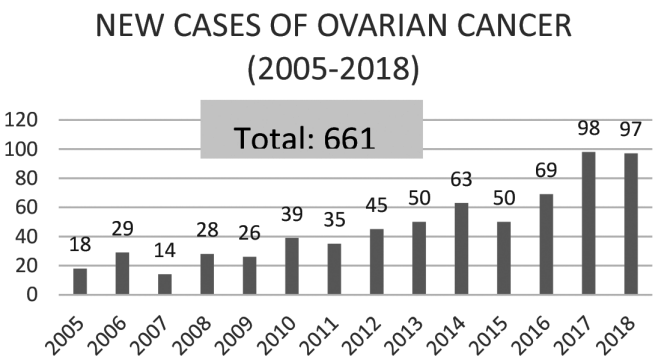

Figure 1. Annual number of new cases of ovarian cancer seen at a single institution from January 2005 to December 2018

Clinical Findings

A total of 23 (67.65%) women were classified as having Stage 1A disease and 11 (32.35%) with Stage 1C, predominantly with well-differentiated or grade 1 tumor (44.12%). Frozen section was performed on 21 patients, with results showing malignancy in 13 patients (38.24%), low malignant or borderline tumor in 3 patients (8.82%) and benign in 5 cases (14.71%). There were 12 cases who have clinically benign tumor pre-operatively and grossly benign intraoperatively, and no frozen section was done. However, final histopathology reported malignant findings. There was 1 case who underwent an outright complete surgical staging for a grossly malignant ovarian new growth. Complete surgical staging was performed only in 16/34 patients (47.06%) with FS of malignant (12), low malignant potential (3) and a grossly malignant tumor (1). Non-epithelial tumors was seen on final biopsy in 52.94% of cases. The most common histology was mucinous carcinoma in 11 patients (68.75%), followed by dysgerminoma in 5 cases (27.78%). One patient had malignant peritoneal fluid cytology (Table 2).

Adjuvant treatment

The median follow-up from the time of surgery was 31.5 months (range: 1-117). Adjuvant treatment in the form of chemotherapy was given in fourteen patients (41.18%). The chemotherapeutic agent used were bleomycin-etoposide-cisplatin (BEP), etoposide-cisplatin (EP), carboplatin-paclitaxel, and cisplatin cyclophosphamide regimens (Table 2).

Fertility Outcome

There were nine patients who conceived after the surgery, with time to first conception of 18 ± 14.18 months from surgery. Six of the nine patients had their first live birth on their first pregnancy after surgery, delivered via normal spontaneous delivery, one had an abortion and the other two are currently pregnant. There was a total of eight live births and 2 miscarriages from 7 patients (Table 3). Four of these patients delivered to term and live babies. The

Table 1. Demographic characteristics of patients with early stage ovarian cancer (n = 34)

	Frequency (%); Mean ± SD
Age at surgery	23.71 ± 5.57
Civil status	
Single	29 (85.29)
Married	5 (14.71)
Employment status	
Unemployed	24 (70.59)
Employed	6 (17.65)
Student	4 (11.76)
Comorbidity	
No	32 (94.12)
Yes	2 (5.88)
Smoking history	
Never	29 (85.29)
Currently smoking	3 (8.82)
Previous	2 (5.88)
Family history of cancer	10 (29.41)
Breast cancer	7 (70)
Ovarian cancer	3 (30)
Cervical cancer	1 (10)
Lung cancer	1 (10)
Leukemia	1 (10)
Chief complaint	
Abdominal enlargement	11 (32.35)
Abdominal mass	11 (32.35)
Abdominal pain	8 (23.53)
Incidental finding	4 (11.76)
Menarche	12.29 ± 1.36
Parity	
0	24 (70.59)
≥1	10 (29.41)
Gravity	
0	24 (70.59)
≥1	10 (29.41)

Table 2. Clinical characteristics of patients with early stage ovarian cancer (n = 34)

	Frequency (%); Mean ± SD
Stage	
1A	23 (67.65)
1C	11 (32.35)
Tumor	
Grade 1	15 (44.12)
Grade 2	3 (8.82)
Grade 3	5 (14.71)
Not indicated	11 (32.35)
Frozen section	
Not done	12 (35.29)
Benign	5 (14.71)
Low malignant potential	3 (8.82)
Malignant	13 (38.24)
Grossly malignant	1 (2.94)
Complete surgical staging	
No	18 (52.94)
Yes	16 (47.06)
Histology	
Epithelial	*16 (47.06)*
Mucinous	11 (68.75)
Serous	4 (25)
Endometrioid	1 (6.25)
Non-epithelial	*18 (52.94)*
Dysgerminoma	5 (27.78)
Sertoli Leydig	4 (22.22)
Immature Teratoma	4 (22.22)
Endodermal sinus	3 (16.67)
Granulosa cell	2 (11.11)
Presence of malignant ascites	1 (2.94)
Median time to follow-up from surgery	31.5 (1 – 117)
With adjuvant chemotherapy	14 (41.18)
Chemotherapeutic agent	
Bleomycin-Etoposide-Cisplatin (BEP) >1	7 (50)
Carboplatin-Paclitaxel	4 (28.57)
Etoposide-Cisplatin	2 (14.29)
Cisplatin- Cyclophosphamide	1 (7.14)

other two who had adjuvant chemotherapy delivered prematurely at 30 and 32 weeks age of gestation (AOG) to live babies. One of them had two more pregnancies, one abortion and one term pregnancy delivered via cesarean section. Three of them received adjuvant chemotherapy and conceived at 7, 18 and 38 months after the last cycle of treatment. One patient had spontaneous abortion 7 months after her surgery but again conceived 16 months later. She delivered via cesarean section to a live term baby. During exploration, the omentum was noted to have multiple firm, ovoid nodules ranging from 0.5 to 2.0 cm and was positive for malignant cells. A left renal mass was also noted on computed tomography scan after delivery measuring 18.0 x 8.0 x 12.0 cm. The other two of the nine patients who conceived after FSS are currently pregnant with no known evidence of disease, at 14 weeks and 30 weeks AOG, respectively (Table 4). The time to first live birth was 30.43 ± 9.74 months from surgery. Five of the nine patients had non-epithelial tumor (Table 3).

The overall recurrence rate after FSS was 14.71%. There was no statistically significant difference in the recurrence rate (22.22% and 12.00%, p-value 0.4578) between those who got and did not get pregnant after FSS for early stage ovarian cancer (Table 5).

The overall survival rate after FSS was 91.18%. Likewise, no statistically significant difference in the survival rate (88.89% vs 92%, p-value 0.7778) was seen

Table 3. Fertility outcomes of patients with early stage ovarian cancer (n = 34)

	Frequency (%); Mean ± SD; Median (Range)
Patients with first pregnancy after surgery	9 (26.47)
Patients with live birth after surgery	7 (20.59)
Number of live births after surgery 1 ≥2	 6 (75.00) 2 (25.00)
Time to pregnancy, months	18 ± 14.18 13 (1 – 41)
Time to live birth, months	30.43 ± 9.74 31 (18 – 44)
Mode of delivery of live births after surgery 1 ≥2	N = 8 6 (75.00) 2 (25.00)

Table 5. Comparison of recurrence rate and survival rate among early stage ovarian cancer patients who had and did not have pregnancy

	With recurrence n (%)	**No recurrence n (%)**	**p-value**
With pregnancy (9)	2 (22.22)	7 (77.78)	0.4578
No pregnancy (25)	3 (12.00)	22 (88.00)	
Total (34)	5 (14.71)	29 (85.29)	
	Alive n (%)	**Expired n (%)**	**p-value**
With pregnancy (9)	8 (88.89)	1 (11.11)	0.7778
No pregnancy (25)	23 (92.00)	2 (8.00)	
Total (34)	31 (91.18)	3 (8.82)	

between those who got pregnant after FSS for early stage ovarian cancer, compared to those who did not get pregnant. Pregnancy had no effect on the recurrence and survival of early stage ovarian cancer, FIGO stage IA and IC, after fertility-sparing surgery (Table 5).

DISCUSSION

Early stage ovarian cancer in young patients

Ovarian cancer is managed surgically with hysterectomy and bilateral salpingooophorectomy, with complete surgical staging as previously discussed. In young women, removal of the uterus and bilateral ovaries would mean loss of reproductive capability and estrogen deprivation, hence management of this special group of population remains a challenge for every gynecologist or oncologist. [11,12]

A total of 661 new cases of ovarian cancer presented at our institution and 34 patients who underwent conservative fertility-sparing surgery in the form of unilateral salpingooophorectomy, diagnosed with stage I disease were included. Studies have shown that fertility-sparing surgery is a safe and acceptable option for management of early stage ovarian cancer in patients who wishes to preserve their fertility[9,10].

Ovarian malignancy is not common among women younger than 40 years of age. In this study, the mean age is 23 years old with a range of 12 to 36 years old. The most common histology among young population with ovarian cancer are germ cell tumors.[3] However in this study, the most common histology was mucinous carcinoma in 68.75% of cases followed by dysgerminoma (27.78%). In a review of I. Zapardiel et al in 2014, mucinous histotype was also the most frequent among young patients, occurring in 53% out of the 793 patients analyzed from 10 publications.[9]

Surgical staging in early stage ovarian cancer

Complete surgical staging was performed in only 47.06% of the patients in the study. Complete surgical staging is important in the management of early stage ovarian cancer since it identifies the "real" early stage disease from the "perhaps" early stage ovarian cancer, with a likelihood of undiagnosed residual disease of 16-42% of cases.[11]

A strong recommendation and guidelines for staging and management of ovarian cancer exist, both for early and advanced stage of the disease. However, despite these guidelines, significant variation in lymph node dissection are still being practiced locally and in other countries.[13]

A study in 2009 showed that even in randomized trial like the European Organisation for Research Treatment of Cancer (EORTC) Adjuvant ChemoTherapy In Ovarian Neoplasm (ACTION) Trial, 295/448 (66%) were incompletely staged despite the strong recommendation for comprehensive surgical staging.[14] The patients included in this study were all patients who presented at our institution with stage I ovarian cancer who underwent fertility-sparing surgery, even if done in another institution. Since ours is a referral center for gynecologic cancer, post-operative cases were being referred to us for adjuvant treatment, cancer monitoring or possible re-exploration. Some referrals came from areas where there could have been no frozen section facilities or no gynecologic oncologist specialist available.

Table 4. Tabulation of patients who conceived after fertility-sparing surgery for early stage ovarian cancer (n = 9)

Patient ID number	Age in years	Surgical Staging	FIGO Stage	Histological Type	Grade	Adjuvant Treatment	Time from diagnosis to conception in months	Time from last chemotherapy to conception	Outcome of Pregnancy	Mode of delivery	Status
2	23	yes	IC	Mucinous	1	Cisplatin-Cyclophosphamide VI	42	38	preterm, alive	normal delivery	no evidence of disease for 84 months on last contact; lost to follow-up
5	17	no	IA	Dysgerminoma	not indicated	Advised chemotherapy, not given	7	N/A	abortion	dilatation and curettage	At 31 weeks from diagnosis, she had tumor recurrence (omentum and kidney) which was diagnosed during cesarean section of her second pregnancy (alive, term); last known alive at 33 months from diagnosis; lost to follow-up
13	27	yes	IA	Sertoli Leydig	3	Bleomycin-Etoposide-Cisplatin IV	27	18	preterm, alive; had 2 more pregnancy: 1 abortion and 1 term via CS	normal delivery	no evidence of disease for 55 months
15	19	no	IA	Dysgerminoma	not indicated	Advised chemotherapy, not given	23	N/A	term , alive	normal delivery	died of the disease at 37 months
27	27	yes	IA	Mucinous	not indicated	None	10	N/A	term, alive	normal delivery	no evidence of disease for 19 months
28	19	yes	IA	Immature teratoma	2	Bleomycin-Etoposide-Cisplatin IV	12	7	term, alive	normal delivery	no evidence of disease for 12 months
32	23	yes	IC	Serous	1	advised chemotherapy, not given	35	N/A	term, alive	normal delivery	with tumor recurrence, s/p left salpingoophorectomy at 13 weeks age of gestation (serous carcinoma, grade 1); for chemotherapy after delivery but patient did not follow-up despite advise
33	23	yes	IC	Serous	1	advised chemotherapy, not given	10	N/A	currently pregnant at 3-4 months age of gestation	N/A	no evidence of disease for 13 months
34	19	yes	IA	Granulosa cell	0	none	12	N/A	currently pregnant at 7-8 months age of gestation	N/A	no evidence of disease for 19 months

Fertility outcome

Among the 34 patients, 9 patients (26.47%) were able to conceive after fertility sparing surgery, with 6 patients able to deliver successfully on their first pregnancy. The denominator on the fertility rate was the total number of patients in this study. The patients who were actually desirous of pregnancy or who have actually tried getting pregnant was not documented in this study.

Successful fertility outcome has been reported among early stage ovarian cancer after FSS. In a study among 240 patients with early stage ovarian malignancy managed by fertility-sparing surgery, 84 patients (85%) out of the 105 cases who tried to become pregnant were successful.[15] Adjuvant chemotherapy on some patients after surgery has shown no effect among early stage ovarian cancer. In a retrospective study among

94 patients with early stage ovarian cancer managed with FSS, 89% of 79 patients had normal menstruation two months after chemotherapy, with 69 patients menstruating regularly. Twelve patients conceived out of the 45 patients who desired pregnancy, 36 patients of which received chemotherapy perioperatively.[16]

There were fourteen patients who received adjuvant chemotherapy among the 34 patients included in the study. Three of these patients conceived (1) 7 months after receiving chemotherapy with Bleomycin-Etoposide-Cisplatin (BEP), (2) 18 months after BEP, and (3) 38 months after Cisplatin-Cyclophosphamide. In another study, the overall successful conception was seen in 74% of women desiring to get pregnant, with an overall abortion rate of 17%. There was no effect on the fertility or obstetrical outcome among patients who got pregnant after receiving adjuvant chemotherapy, with no congenital abnormalities reported.[9]

The relapse rate reported in one study was 11% (27 patients) at a median follow-up of 9 months, while 11 (5%) died of progressive disease. All patients with an ovarian relapse were given with successful second-line chemotherapy.[15] In our study , a recurrence rate of 14.71% and a survival rate of 91.18% were observed. Pregnancy was also shown to have no effect on the overall recurrence rate and survival rate of early stage ovarian cancer following fertility-sparing surgery.

A five-year local study conducted among 44 patients, 16-40 years old who underwent FSS reported restoration of menses 1-2 months after the initial surgery, even with administration of platinum-based chemotherapy in 7 patients. There was 15 pregnancies reported with 8 cases of tumor persistence/recurrence.[17]

This study showed that fertility-sparing surgery can be effective and safe for young patients with early stage ovarian cancer desirous of pregnancy.

CONCLUSION

Fertility-sparing surgery can be effectively offered to young patients with early stage ovarian cancer, with desire to preserve fertility, with 26.47% successful pregnancy rate. Pregnancy was shown to have no significant effect on recurrence and survival among FIGO stage IA and IC ovarian cancer who underwent fertility-sparing surgery by unilateral salpingooophorectomy.

LIMITATIONS

The study was limited by unavailability of some data including recent contact information of some patients. Difficulty in contacting these patients especially those lost to follow-up was encountered during the data collection.

The study was also limited with the unavailability of the data on who among the population were actually desirous of pregnancy.

RECOMMENDATIONS

Complete surgical staging is vital in the correct diagnosis and appropriate management of early stage ovarian cancer. It is recommended that adherence to complete surgical staging guidelines be observed during ovarian cancer surgery, preferably with a specialist in gynecologic cancer on board.

Further study on this topic is recommended to further analyze and understand the course and outcome of early stage ovarian cancer managed conservatively by fertility-sparing surgery. ■

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