Outcomes of Pregnancies and Deliveries of Patients Who Underwent Fertility-Preserving Surgery for Early-Stage Epithelial Ovarian Cancer

Shin Nishio 1,*, Takayo Takeno 2, Takeshi Fukuda 3, Ayumi Shikama 4, Hidekatsu Nakai 5, Hiroko Nakamura 6, Hideki Tokunaga 7, Kazuaki Takahashi 8, Emi Okuma 9, Masahiko Mori 10, Yasuhisa Terao 11, Kimio Ushijima 1 and Nobuo Yaegashi 7

1 Department of Obstetrics and Gynecology, School of Medicine, Kurume University, Kurume 830-0011, Japan
2 Department of Obstetrics and Gynecology, Kagoshima City Hospital, Kagoshima 890-8760, Japan
3 Department of Obstetrics and Gynecology, School of Medicine, Osaka Metropolitan University, Osaka 545-8856, Japan
4 Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tsukuba, Tsukuba 305-8576, Japan
5 Department of Obstetrics and Gynecology, Faculty of Medicine, Kindai University, Sayama 589-8511, Japan
6 Department of Obstetrics and Gynecology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure 737-0023, Japan
7 Department of Obstetrics and Gynecology, School of Medicine, Tohoku University, Sendai 980-8574, Japan
8 Department of Obstetrics and Gynecology, School of Medicine, The Jikei University, Tokyo 105-8471, Japan
9 Department of Obstetrics and Gynecology, Faculty of Medicine, Saga University, Saga 849-8501, Japan
10 Department of Gynecologic Oncology, Aichi Cancer Center Hospital, Nagoya 464-0021, Japan
11 Department of Obstetrics and Gynecology, Faculty of Medicine, Juntendo University, Tokyo 113-0033, Japan

* Correspondence: shinshin@med.kurume-u.ac.jp; Tel.: +81-942-31-7573

Abstract: Some studies have shown increased risks of preterm birth, low birth weight, and cesarean delivery after oncologic treatment; others have shown the opposite. We evaluated the outcomes of pregnancies and deliveries of patients who underwent fertility-preserving surgery (FSS) for early-stage epithelial ovarian cancer (EOC) and examined their perinatal prognosis. This retrospective study included women with a history of stage IA or IC ovarian cancer reported in our previous study. The primary outcome was preterm birth after cancer diagnosis was considered. Secondary outcomes were neonatal morbidity and severe maternal morbidity. Thirty-one children were born to 25 women who had undergone FSS. The mean number of weeks at delivery was 38.7 ± 0.7, and the mean birth weight of infants was 3021 ± 160 g. With respect to pregnancy outcomes, 5 patients had preterm labor and 26 had full-term labor. The delivery mode was vaginal delivery in 18 patients and cesarean delivery in 13. Complications during pregnancy included placenta previa (one case) and pelvic abscess (one case). Except for three preterm infants with low birth weight, there were no other perinatal abnormalities. Pregnancy after fertility preservation in EOC has an excellent perinatal prognosis, although the cesarean delivery rate is high.

Keywords: early-stage epithelial ovarian cancer; fertility-preserving surgery; perinatal prognosis; preterm birth

1. Introduction

The National Cancer Institute predicted that women younger than 45 years would account for approximately 12% of the predicted 21,410 new cases of ovarian cancer in 2021 in the United States [1]. As childbirth is increasingly delayed [2], the likelihood that a woman will be diagnosed with ovarian cancer and have a current or future desire to conceive also increases [3], and fertility-sparing surgery (FSS) is considered safe for carefully selected women with early-stage ovarian cancer [4,5]. Although a fertility-sparing...
treatment approach has a positive effect on quality of life [6,7], cancer survivors are less likely to conceive than their peers, even when their ability to do so is preserved [8,9], and this may be related to the fear of pregnancy and adverse obstetric outcomes [7].

Some population-based studies have shown increased risks of preterm birth [10–14], low birth weight [11–14], and cesarean delivery [12] after oncologic treatment; contrarily, others have demonstrated only some or none of these effects [15,16]. Moreover, it is unclear to what extent these studies can be extrapolated to patients with ovarian cancer because the majority of these studies have jointly analyzed all reproductive cancers [10,17] or included a few ovarian cancer patients [10,13], whereas other studies have not stratified patients by cancer type [12,14], or they have focused on survivors of childhood cancers [14,17].

In our previous study, the results suggested that fertility-preserving treatment may be safe for patients with stage IA epithelial ovarian cancer (EOC), clear cell carcinoma, and stage IC EOC, with or without adjuvant chemotherapy [18]. We are currently conducting a prospective non-randomized validation study to expand the indications for fertility-preserving treatment for EOC in JCOG 1203 for stage IA, clear cell, stage IC, and non-clear cell cancers [19]. In our previous study [18], we reported that 54 out of 84 (64.3%) patients who tried to conceive became pregnant, and 56 healthy children were born. However, no detailed studies exist on the perinatal period, including the background, means of conception, and pregnancy outcomes in pregnant cases. To evaluate fertility-preserving treatment, assessing both treatment and pregnancy outcomes is necessary. Therefore, the present study aimed to clarify the perinatal outcomes of patients who underwent FSS for EOC, in order to provide useful information for patients receiving this treatment.

2. Materials and Methods

This study was a preplanned secondary analysis of the dataset from a previous retrospective observational study performed between 1995 and 2007 [16]. The previous study was conducted by the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG-GCSG), and it was a multicenter retrospective observational study examining FSS for stage IA EOC, clear cell carcinoma, and stage IC EOC, with or without adjuvant chemotherapy, at 11 JCOG-GCSG-affiliated institutions. The study was hosted by the Kurume University School of Medicine (institutional review board approval registration number: 17229). Each participating center obtained ethical committee approval. The requirement for informed consent was waived, owing to the retrospective nature of the present study.

We collected the following data on pregnancy outcomes and perinatal outcomes:
(1) age (at the beginning of pregnancy (years and months)); (2) height and weight at the time of pregnancy; (3) history of smoking, alcohol consumption, and oral contraceptive use; (4) marital status (never married, married, never remarried after divorce, never remarried after bereavement); (5) number of births, number of pregnancies; (6) age at menarche, menstrual cycle before treatment (regulated, irregular, unknown); (7) histological type (a. serous, b. mucinous, c. endometrioid, d. clear cell, e. others); (8) surgery type; (9) adjuvant chemotherapy (none, yes), chemotherapy regimen, number of cycles; (10) post-treatment menstrual cycle (restored to regularity, irregular but restored, not restored, unknown); (11) marital status after treatment (same as before treatment, married, divorced, bereaved, unknown); (12) time to pregnancy after treatment; (13) forms of pregnancy after treatment (natural pregnancy, methods of assisted reproductive technology (ART); (14) post-treatment period until the start date of ART; (15) date of return of pregnancy after treatment, duration of pregnancy (miscarriage, preterm labor, full-term labor); (16) perinatal events (presence or absence of cervical suture), delivery mode (vaginal delivery, cesarean delivery and indications), course of delivery, and presence or absence and type of uterine contraction inhibitors; (17) maternal complications during pregnancy after treatment (pregnancy-related complications (gestational hypertension, gestational diabetes, fetal failure to thrive, abnormal placental position, other maternal complications, and psychiatric disorders) and outcomes; (18) neonatal information (congenital diseases and other complications); and (19) date
of last confirmed survival (disease-free survival (date of confirmed recurrence, with or without treatment of recurrence), treatment).

Comparison of continuous variables was performed using Student’s t-test. Fisher’s exact test was used for categorical variables, as appropriate, for each category size. Statistical significance was set at \( p < 0.05 \), unless otherwise stated. For survival analysis, data on progression-free survival (PFS) were censored from the date of surgery to the date of the last follow-up if disease progression had not occurred. An event was defined as death from any cause, disease relapse, or disease progression. Data on overall survival (OS) were censored from the date of surgery to the date of the last follow-up. An event was defined as death occurring from any cause. Oncologic outcomes, PFS, and OS were analyzed using the Kaplan–Meier method.

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and the revised version 2.7.0.

### 3. Results

We obtained information regarding age, EOC stage, histological characteristics of the tumor, treatment details, and follow-up period from 25 patients in the present study. In 25 patients with unilateral stage I EOC, the distribution of stages was as follows: stage IA, \( n = 17 \); stage IC1, \( n = 2 \); stage IC2, \( n = 3 \); and stage IC3, \( n = 3 \). Table 1 summarizes the main characteristics of patients and tumors. The mean patient age was \( 26.7 \pm 5.9 \) years (range, 19–39 years). The median follow-up duration was 90 months (range, 18–160 months) from the initial FSS (Table 1).

**Table 1. Patient characteristics and oncologic outcomes (\( n = 25 \)).**

| Factor                                | \( n \) (%)       |
|---------------------------------------|-------------------|
| **Age, mean (range), years**          | \( 26.7 \pm 5.9 \) (19–39) |
| FIGO stage (2014)                     |                   |
| IA                                    | 17 (68)           |
| IC1                                   | 2 (8)             |
| IC2                                   | 3 (12)            |
| IC3                                   | 3 (12)            |
| **Histology**                         |                   |
| Mucinous                              | 16 (64)           |
| Serous                                | 7 (28)            |
| Clear                                 | 2 (8)             |
| **Surgery**                           |                   |
| Unilateral salpingo-oophorectomy      | 25                |
| Contralateral ovarian biopsy          | 13                |
| Omentectomy                           | 13                |
| Pelvic lymph node biopsy              | 4                 |
| Pelvic lymphadenectomy                | 1                 |
| Pelvic lymphadenectomy + para-aortic  | 3                 |
| lymphadenectomy                       |                   |
| No pelvic lymph node retrieval        | 17                |
| **Adjuvant therapy**                  |                   |
| None                                  | 7 (28)            |
| Yes (chemotherapy)                    | 18 (72)           |
| **Regimen**                           |                   |
| Cyclophosphamide + cisplatin          | 6                 |
| Cyclophosphamide + doxorubicin + cisplatin | 5             |
| Paclitaxel + carboplatin              | 3                 |
| Weekly paclitaxel + carboplatin       | 1                 |
| Cyclophosphamide + carboplatin        | 1                 |
| Irinotecan + cisplatin                | 1                 |
| Fluorouracil                          | 1                 |

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.
All 25 patients underwent unilateral salpingo-oophorectomy. Surgical staging included careful inspection and palpation of peritoneal surfaces with biopsies of any suspected lesions and peritoneal washing cytology. No patients underwent endometrial curetage during surgery, although most patients underwent endometrial cytology or biopsy before surgery. If optimal surgical staging required at least omentectomy, in addition to unilateral salpingo-oophorectomy, all 25 patients were considered to be optimally staged.

Platinum-based adjuvant chemotherapy was administered to 18 (72%) patients, with a mean number of four cycles (range, three to six cycles). The most common chemotherapy regimens were cyclophosphamide + cisplatin (six of 18; 33.3%), cyclophosphamide + doxorubicin + cisplatin (five of 18; 27.8%), and paclitaxel + carboplatin (three of 18; 16.7%). The remaining four patients who received adjuvant chemotherapy were administered paclitaxel + carboplatin, cyclophosphamide + carboplatin, irinotecan + cisplatin, and fluorouracil, respectively. Seven (28%) patients received no adjuvant treatment after initial surgery (Table 1).

Recurrence was not identified in any patient during the follow-up period. The median follow-up duration for this group was 79 months. Twenty-five patients showed rates of 100% for 5-year PFS and OS. The median follow-up duration for these patients was 78 months.

In total, 31 children were born to the 25 women after surgery, with or without adjuvant chemotherapy, with a mean interval of 34 (8–48) months from cancer treatment to pregnancy. Five women (20%) in the total cohort who underwent FSS received ART treatment, according to medical records.

The mean maternal age at the time of delivery was 31.7 ± 2.1 years. All deliveries were singleton and occurred at full-term, at a mean gestational age of 38.7 ± 0.7 weeks. Eighteen (58.1%) of the vaginal deliveries were induced, and five of the planned cesarean deliveries were induced. Eight children were delivered via unplanned cesarean delivery. No congenital malformations were registered, and the mean birth weight was 3021 ± 160 g (Table 2). Tables 3 and 4 provide details on pregnancy-related and fetal outcomes, respectively.

### Table 2. Obstetrical outcomes of 25 women who gave birth (31 children) after FSS.

| Factor                                         | n (%)     |
|------------------------------------------------|-----------|
| Age at the time of pregnancy, mean, years      | 31.7 ± 2.1|
| Pregnancy method, n (%)                        |           |
| Spontaneous                                    | 26 (73.9) |
| Assisted reproductive technology               | 5 (16.1)  |
| Delivery mode, n (%)                           |           |
| Vaginal                                        | 18 (58.1) |
| Planned cesarean delivery                      | 5 (16.1)  |
| Unplanned cesarean delivery                    | 8 (25.8)  |
| Births, n                                      |           |
| Single                                         | 29        |
| Twins                                          | 2         |
| Gestational age at birth (weeks), mean         | 38.7 ± 0.6|
| Child weight at birth (g), mean                | 3021 ± 160|
| Sex of child, n (%)                            |           |
| Male                                           | 21 (67.7) |
| Female                                         | 10 (32.3) |
| Delivery outcomes, n (%)                       |           |
| Preterm                                        | 5 (16.1)  |
| Term                                           | 26 (83.9) |
| Complications during pregnancy, n (%)          | 2 (6.5)   |
| Placenta previa, n                             | 1         |
| Pelvic abscess, n                              | 1         |
| Complications among children, n (%)            | 4 (12.9)  |
| Low birth weight infant, n                     | 4         |
Table 3. Pregnancy-related outcomes.

| Number | Maternal Age at the Time of Pregnancy | Time from Surgery to Pregnancy | Pregnancy Method | Gestational Age at Birth (Weeks) | Delivery Mode | Indication for C/D | Complications during Pregnancy |
|--------|--------------------------------------|-------------------------------|-----------------|---------------------------------|--------------|-------------------|-------------------------------|
| 1      | 37y6mo                               | 2y4mo                         | ART             | 39w4d                           | Vaginal      | None              |                               |
| 2      | 33y4mo                               | 13y1mo                        | ART             | 40w4d                           | C/D          | Delivery arrest   | None                          |
| 3      | 29y8mo                               | 9y8mo                         | Spontaneous     | 37w2d                           | Vaginal      | None              |                               |
| 4      | 31y6mo                               | 8y7mo                         | Spontaneous     | 39w2d                           | Vaginal      | None              |                               |
| 5      | 32y0mo                               | 3y5mo                         | Spontaneous     | 38w6d                           | Vaginal      | None              |                               |
| 6      | 40y7mo                               | 2y3mo                         | Spontaneous     | 38w2d                           | Vaginal      | None              |                               |
| 7      | 32y0mo                               | 3y5mo                         | Spontaneous     | 38w6d                           | Vaginal      | None              |                               |
| 8      | 25y3mo                               | 2y0mo                         | Spontaneous     | 39w6d                           | C/D          | Delivery arrest   | None                          |
| 9      | 29y1mo                               | 1y4mo                         | Spontaneous     | 40w5d                           | C/D          | Delivery arrest   | None                          |
| 10     | 33y10mo                              | 1y4mo                         | Spontaneous     | 39w4d                           | C/D          | Previous C/D      | None                          |
| 11     | 37y11mo                              | 3y5mo                         | Spontaneous     | 38w3d                           | C/D          | Previous C/D      | None                          |
| 12     | 37y2mo                               | 5y7mo                         | ART             | 39w6d                           | Vaginal      | None              | Threatened miscarriage       |
| 13     | 40y3mo                               | 2y3mo                         | Spontaneous     | 38w6d                           | Vaginal      | None              | Vasa previa                  |
| 14     | 22y6mo                               | 2y9mo                         | Spontaneous     | 39w5d                           | Vaginal      | None              |                               |
| 15     | 27y8mo                               | 2y8mo                         | Spontaneous     | 38w6d                           | Vaginal      | None              |                               |
| 16     | 36y2mo                               | 6y0mo                         | Spontaneous     | 38w4d                           | Vaginal      | None              |                               |
| 17     | 28y3mo                               | 5y2mo                         | Spontaneous     | 39w4d                           | Vaginal      | None              |                               |
| 18     | 39y3mo                               | 1y6mo                         | Spontaneous     | 39w3d                           | C/D          | Fetal distress    | None                          |
| 19     | 30y0mo                               | 5y5mo                         | Spontaneous     | 36w1d                           | C/D          | DD twin           | Threatened labor              |
| 20     | 30y0mo                               | 5y5mo                         | Spontaneous     | 36w1d                           | C/D          | DD twin           | Threatened labor              |
| 21     | 24y2mo                               | 1y2mo                         | Spontaneous     | 39w3d                           | Vaginal      | None              |                               |
| 22     | 29y11mo                              | 1y2mo                         | Spontaneous     | 39w6d                           | Vaginal      | None              |                               |
| 23     | 40y4mo                               | 1y4mo                         | Spontaneous     | 37w5d                           | Vaginal      | None              |                               |
| 24     | 31y6mo                               | 3y10mo                        | Spontaneous     | 39w6d                           | Vaginal      | None              |                               |
| 25     | 33y5mo                               | 3y7mo                         | Spontaneous     | 36w6d                           | Vaginal      | None              |                               |
| 26     | 28y11mo                              | 2y2mo                         | Spontaneous     | 39w1d                           | C/D          | Delivery arrest   | Threathened miscarriage       |
| 27     | 34y4mo                               | 5y3mo                         | Spontaneous     | 39w6d                           | Vaginal      | None              |                               |
| 28     | 23y4mo                               | 1y7mo                         | Spontaneous     | 39w3d                           | Vaginal      | None              |                               |
| 29     | 24y9mo                               | 5y6mo                         | Spontaneous     | 38w0d                           | C/D          | Delivery arrest   | None                          |
| 30     | 23y10mo                              | 1y9mo                         | Spontaneous     | 40w5d                           | C/D          | CPD               | None                          |
| 31     | 40y11mo                              | 1y8mo                         | ART             | 34w1d                           | C/D          | Placenta previa   | Threatened labor/placenta previa |

Abbreviations: y, years; mo, months; ART, assisted reproductive technology; C/D, cesarean delivery; DD, dichorionic diamniotic; a, b, c, d, e, and f are identical patients.

Table 4. Fetal outcomes.

| Number | Child Weight at Birth (g) | Sex | Delivery Mode | Complications of Children |
|--------|---------------------------|-----|---------------|----------------------------|
| 1      | 2952                      | Male| Vaginal       | None                       |
| 2      | 2828                      | Female| C/D          | None                       |
| 3      | 3022                      | Male| Vaginal       | None                       |
| 4      | 2226                      | Male| C/D          | Low birth weight infant    |
| 5      | 2710                      | Male| Vaginal       | None                       |
| 6      | 3162                      | Male| Vaginal       | None                       |
| 7      | 3674                      | Female| Vaginal      | None                       |
| 8      | 3716                      | Female| C/D          | None                       |
| 9      | 2818                      | Male| C/D          | None                       |
| 10     | 3561                      | Male| C/D          | None                       |
| 11     | 2810                      | Male| C/D          | None                       |
| 12     | 3375                      | Male| Vaginal       | None                       |
| 13     | 3785                      | Male| Vaginal       | None                       |
| 14     | 3109                      | Male| Vaginal       | None                       |
| 15     | 3216                      | Male| Vaginal       | None                       |
| 16     | 3429                      | Female| Vaginal     | None                       |
| 17     | 2977                      | Female| Vaginal      | None                       |
| 18     | 3362                      | Male| C/D          | None                       |
Table 4. Cont.

| Number | Child Weight at Birth (g) | Sex   | Delivery Mode | Complications of Children |
|--------|---------------------------|-------|---------------|----------------------------|
| 19     | 2448                      | Female| C/D           | None                       |
| 20     | 2044                      | Female| C/D           | None                       |
| 21     | 2877                      | Male  | Vaginal       | None                       |
| 22     | 2675                      | Female| Vaginal       | None                       |
| 23     | 2920                      | Male  | Vaginal       | None                       |
| 24     | 2795                      | Female| Vaginal       | None                       |
| 25     | 2905                      | Male  | Vaginal       | None                       |
| 26     | 3286                      | Male  | C/D           | None                       |
| 27     | 3320                      | Male  | Vaginal       | None                       |
| 28     | 2947                      | Male  | Vaginal       | None                       |
| 29     | 2698                      | Male  | C/D           | None                       |
| 30     | 3586                      | Male  | C/D           | None                       |
| 31     | 2418                      | Female| C/D           | Low birth weight infant    |

Notes: a, b, c, d, e, and f are identical patients. Abbreviation: C/D, cesarean delivery.

4. Discussion

Early-stage EOC is a relatively uncommon disease in young women; hence, this study adds to the current body of knowledge by reporting on both the safety and efficacy of FSS. The 100% PFS and OS rates at 5 years were in accordance with previously published data [20–22].

Compared to perinatal reports from Japan [23], in this study, women who conceived after FSS for stage IA or IC ovarian cancer did not have an increased risk of preterm birth, delivery of small-for-gestational-age (SGA) neonates, neonatal morbidity, or severe maternal morbidity; however, the rates of cesarean delivery were higher. In this study, the cesarean delivery rate was 42%, which is clearly higher than the rate of 18.5% in the general population [23]. In this study, the majority of cesarean deliveries were due to delivery arrest; nevertheless, the apparent reason for this was unclear.

Receipt of chemotherapy did not appreciably affect the proportion of adverse obstetric events. US guidelines have highlighted the importance of discussing fertility preservation with young cancer patients for at least a decade [24,25], but data regarding obstetric outcomes after FSS have been limited. Our study provides encouraging evidence that pregnancy after FSS in stage IA or IC ovarian cancer is generally safe.

Given the rarity of ovarian cancer, even studies that focused on patients with reproductive cancers who conceived included small numbers of ovarian cancer patients [10,26]. A systematic review of obstetric outcomes after reproductive cancers demonstrated that most studies were a case series with few births, and more than one-third of studies did not comment on the viability or gestational age at birth [26]. In another study, women with a history of reproductive cancer had a greater absolute risk of preterm birth than women in a matched control group, but this difference may have been driven by the 28% of cervical cancer survivors who delivered prematurely [10]. Furthermore, we included only patients who conceived after their treatment, unlike prior reports, which included patients who were diagnosed with cancer during pregnancy [11], a group that is likely at higher risk of adverse obstetric outcomes, iatrogenic or otherwise. Considering that the preterm birth rate in this study was 16.1% (five patients at 34–36 weeks), our results may be more applicable to women who are contemplating pregnancy after completion of ovarian cancer treatment.

Our results vary from prior data that suggested a possible increase in neonatal complications after treatment for early-stage ovarian cancer [14].

Data that guide the timing of pregnancy after cancer treatment are sparse. It has been suggested that cancer patients—particularly those receiving chemotherapy—postpone conception until 12–24 months after treatment completion [13], given the possible damage to oocytes and prolonged immunosuppression, which could predispose patients to preterm birth, SGA neonates, and miscarriage [27]. In the current study, we did not find that chemotherapy recipients, or those who delivered within a year of diagnosis, had higher
frequencies of adverse events, although these analyses were limited by sample size. Hence, these important questions should be investigated in future studies with longer follow-up periods.

This study had several limitations. First, the sample size was small; thus, the results must be interpreted with caution. Moreover, only half of the originally planned number of patients could be analyzed, due to the deliveries at another facility and lack of follow-up data. Second, several patients from more than 20 years ago were included, and there may be discrepancies with current treatment. Finally, the true impact of FSS on pregnancies is not known because only cases that resulted in live births were included, and there are no data on miscarriages.

In conclusion, our study results provide important insights to guide shared decision-making discussions regarding FSS for patients with early-stage ovarian cancer. These data may reassure patients considering FSS that pregnancy after ovarian cancer treatment is not associated with increased rates of preterm birth and neonatal morbidity, although the risk of cesarean delivery is higher.

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