GYNECOLOGY

Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicenter study

Satoshi Tamauchi, MD; Hiroaki Kajiyama, MD, PhD; Masato Yoshihara, MD; Yoshiki Ikeda, MD; Nobuhisa Yoshikawa, MD, PhD; Kimihiro Nishino, MD, PhD; Fumi Utsumi, MD, PhD; Kaoru Niimi, MD, PhD; Shiro Suzuki, MD, PhD; Fumitaka Kikkawa, MD, PhD

BACKGROUND: Malignant ovarian germ cell tumors usually occur in young women. Until the 1970s, before establishment of systemic chemotherapy, malignant ovarian germ cell tumors had a very poor prognosis. Recently, prognosis has improved, and fertility-sparing treatment is being adopted in patients who desire to become pregnant. However, the number of malignant ovarian germ cell tumor survivors who actually became pregnant remains unknown.

OBJECTIVE: The present study aimed to clarify the reproductive outcomes in malignant ovarian germ cell tumor survivors by using data from a multicenter database and an additional survey on reproductive outcomes.

STUDY DESIGN: The study used the Tokai Ovarian Tumor Study Group database on ovarian cancer patients. We assessed the database from 1986 through 2016 and selected malignant ovarian germ cell tumor patients <40 years of age who received fertility-sparing treatment. Questionnaires on reproductive outcomes were sent to the registered facilities. The following data were collected and used in this study: age, date of onset, surgical procedure, chemotherapy regimen, tumor type, International Federation of Gynecology and Obstetrics stage, survival outcome and period, number of pregnancies and childbirths, marital status, childbearing desire, method of pregnancy, gestational weeks at delivery, birthweight of the baby, obstetric complications, and menstrual status after fertility-sparing treatment.

RESULTS: A total of 110 malignant ovarian germ cell tumor patients who received fertility-sparing treatment were identified. The median follow-up period was 10.4 years. Five patients were excluded because of death or loss of fertility after treatment for recurrence. Thus, 105 patients were finally included. The additional survey revealed that 42 of 45 patients who desired childbirth became pregnant. The total number of pregnancies was 65, and 56 babies were born to 40 malignant ovarian germ cell tumor survivors.

CONCLUSION: The reproductive outcomes of malignant ovarian germ cell tumor survivor are promising with fertility-sparing treatment. Malignant ovarian germ cell tumor survivors can become pregnant and give birth if they desire.

Key words: bleomycin/etoposide/cisplatin therapy, cancer survivor, fertility-sparing treatment, malignant ovarian germ cell tumor, reproductive outcome

Introduction

Malignant ovarian germ cell tumors (MOGCTs) usually occur in young women,[1] and they account for 1−2% of all ovarian malignancies.[2] Until the 1970s, before establishment of systemic chemotherapy, MOGCTs had a very poor prognosis. However, after the introduction of chemotherapy consisting of bleomycin, etoposide, and cisplatin (BEP) for MOGCT treatment, the prognosis dramatically improved.[3] Moreover, as BEP therapy has little effect on ovarian function, most MOGCT patients treated with BEP were able to remain fertile and give birth.[4−16] However, the number of MOGCT survivors who actually became pregnant remains unknown, as there is a relatively long period from MOGCT treatment to pregnancy because age at first marriage or childbirth is increasing, especially in Japan.[17] The present study aimed to clarify the reproductive outcomes in MOGCT survivors by using data from a multicenter database and an additional survey on reproductive outcomes.

Materials and Methods

The Tokai Ovarian Tumor Study Group includes Nagoya University Hospital and 13 other institutions, and its database has been collecting ovarian cancer patient data since 1986, with approval from our ethics committee. All surgical specimens were pathologically reviewed by specialist gynecological pathologists blinded to the clinical data of patients. We screened the database from 1986 through 2016 and selected MOGCT patients <40 years of age. We further identified patients who underwent fertility-sparing treatment (FST). In this study, FST was defined as preservation of the uterus and at least 1 ovary during surgery with any chemotherapy regimen but without adjuvant radiation therapy to the entire pelvis. To obtain additional data on MOGCT patients who underwent FST, questionnaires on reproductive outcomes were sent to the registered facilities in December 2016, and all completed questionnaires were collected. The following data were collected and used in this study: age, date of onset, surgical procedure, chemotherapy regimen, tumor type, International Federation of Gynecology and Obstetrics (FIGO) stage, survival outcome and period, number of pregnancies and childbirths, marital status, childbearing desire, method of pregnancy, gestational weeks at delivery, birthweight of the baby, obstetrical complications, and menstrual status after FST.

Cite this article as: Tamauchi S, Kajiyama H, Yoshihara M, et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicenter study. Am J Obstet Gynecol 2018;219:385.e1-7.

0002-9378
© 2018 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.ajog.2018.07.021

AJOG at a Glance

Why was this study conducted?

To describe the reproductive outcomes of survivors of malignant ovarian germ cell tumor (MOGCT).

Key findings

Over 90% of survivors of MOGCT <40 years of age who received fertility-sparing treatment and desired pregnancy became pregnant and gave birth.

What does this add to what is known?

This study demonstrated favorable reproductive outcomes for survivors of MOGCT, including women with advanced stage diagnoses.

Results

Among 5057 patients with any ovarian cancer in the database, 135 patients with MOGCTs, who were aged <40 years, were selected. Of these patients, 25 were excluded because they did not receive FST. Thus, 110 patients who received FST were identified. Table 1 summarizes the patient characteristics. The median patient age was 22.8 years, and the median follow-up period was 10.3 years. Among the patients, 14 had a history of childbirth before FST. The tumor types were as follows: 42 immature teratomas, 37 dysgerminomas, 31 yolk sac tumors. Recurrence was noted in 11 patients. One survivor of dysgerminoma recurrence received radiation therapy to the entire pelvis for the recurrence, and she lost fertility. Additionally, 4 patients died from MOGCTs. Thus, 105 MOGCT survivors who underwent FST were finally assessed (Figure 1).

The menstrual status after FST is summarized in Table 2. Regular menstruation recovered in 57 of 72 patients who received adjuvant chemotherapy. The median time to menstruation recovery was 6 months. At the time of the additional survey, 3 patients had premature ovarian failure at <40 years of age. The characteristics of these 3 patients are summarized in Table 3.

The obstetric outcomes after FST are summarized in Table 4. Among the 105 survivors, 45 attempted to become pregnant. Of these 45 patients, 42 achieved pregnancy, and 40 patients had successful deliveries. Seven patients received infertility treatment, but only 2 patients needed assisted reproductive technology.

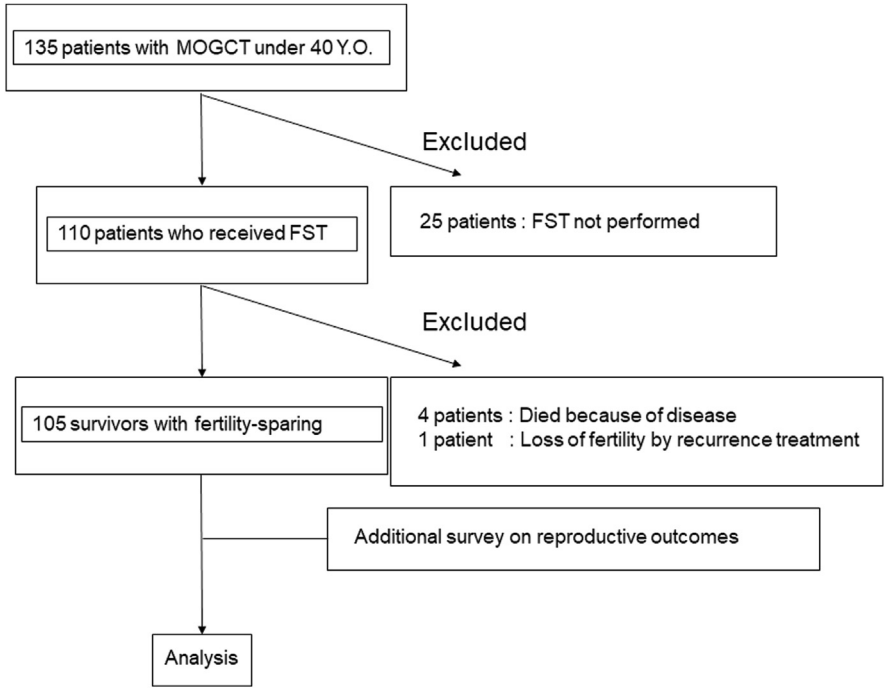
TABLE 1
Characteristics of patients who received fertility-sparing treatment (n = 110)

Median age, y (range)	22.8 (5.0–39.0)
Median follow-up, y (range)	10.3 (1.3–30.3)
Pregnancy history before FST, n	
Nullipara	71
Multipara	14
Unknown	25
Histological type, n	
YST	31
IMT	42
DYS	37
FIGO stage, n	
I	79
II	10
III	20
IV	1
Residual tumors, n	
Yes	14
Adjuvant chemotherapy, n	
Yes	76
Recurrence, n	11
Death because of disease, n	4

DYS, dysgerminoma; *FIGO*, International Federation of Gynecology and Obstetrics; *FST*, fertility-sparing treatment; *IMT*, immature teratoma; *YST*, yolk sac tumor.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

FIGURE 1
Flowchart of patient inclusion



Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

TABLE 2
Menstrual status after fertility-sparing treatment (n = 105)

Adjuvant chemotherapy, n (%)	
Yes	72 (68.6)
Regimen, n (%)	
BEP/BEC	46 (63.9)
PVB	22 (30.6)
PVAC/VAC	3 (4.2)
Other	1 (1.4)
Menstrual recovery after chemotherapy, n (%)	
Yes	57 (79.2)
No	2 (2.8)
Unknown	13 (18.1)
Median time to menstrual recovery, mo (range)	6 (1−19)
Premature ovarian failure age <40 y, n (%)	3 (2.9)

BEC, bleomycin/etoposide/carboplatin; *BEP*, bleomycin/etoposide/cisplatin; *PVAC*, cisplatin/vincristine/actinomycin D/cyclophosphamide; *PVB*, cisplatin/vinblastine/bleomycin; *VAC*, vincristine/actinomycin D/cyclophosphamide.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

A total of 56 babies were born to the patients, and 54 (96.4%) babies were delivered at term. There were no remarkable obstetric complications related to MOGCT treatment. However, 12 (17.4%) miscarriages were recorded in 10 patients. On the other hand, 60 patients did not attempt to become pregnant. Among these patients, 36 were unmarried and 4 already had children before FST.

Cancer-related information of the patients who became pregnant is presented in Table 5. The median time to pregnancy was 4.4 years. Among the 40 patients, 8 had MOGCTs of FIGO stage II or III. About 75% of patients had received chemotherapy before pregnancy. Two patients had a history of recurrence before delivery (Tables 5 and 6).

Supplementary Figure 1 is a scatter plot showing the relationship between onset and pregnancy period. The horizontal axis shows the MOGCT onset age, and the vertical axis shows the period from surgery to first child delivery. Together, Supplementary Figure 2 and Table 3 indicate that the important factor related to the duration to achieving pregnancy was not adjuvant chemotherapy but marital status at FST.

TABLE 4
Reproductive outcomes after fertility-sparing treatment (n = 105)

Attempts to conceive	45 (42.9)
Patients who conceived after FST	42 (93.3)
Total pregnancies	65
Fertility treatment	7 (15.6)
Conservative medical treatment	5 (11.1)
In vitro fertilization	2 (4.4)
Patients who successfully delivered after FST	40 (95.2)
Outcome of pregnancies	
Live-born babies	56 (86.2)
Term delivery	54 (83.1)
Preterm delivery	2 (3.1)
Miscarriage	12 (18.5)
Unknown	1 (1.5)

All values are n (%).

FST, fertility-sparing treatment.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

Comment

MOGCTs occur in young women, and it is now possible to achieve cure and fertility preservation; therefore, reproductive outcomes are considered important. However, there are sporadic reports on reproductive outcomes in MOGCT survivors.[4−16] This is because MOGCT is a relatively rare cancer, and only about 30 years have passed since the dramatic improvement in prognosis with BEP therapy. Furthermore, there is usually a gap of >5 years between onset age and pregnancy age (Supplementary Figure 2), making it difficult to accumulate data on pregnancy outcomes in survivors. In this study, we assessed the reproductive outcomes of 105 survivors after assessing >5000 patients included in a database over a period of 30 years. To our knowledge, this study included the largest number of MOGCT patients in whom reproductive outcomes were examined.

In this study, >90% of the 45 survivors who desired to bear children became pregnant. Most patients lost 1 ovary because of surgery and received adjuvant chemotherapy, but these did not cause much disadvantage in terms of pregnancy, as reported previously.[13−16] With regard to the effect on long-term ovarian function, 3 cases of premature

TABLE 3
Premature ovarian failure after fertility-sparing treatment

	Case 1	Case 2	Case 3
Age at FST, y	31	27	13
Age at POF, y	39	39	38
Duration from FST to POF, y	8	12	25
Gestation before FST	G1P1	G1P1	G0P0
Tumor type	Dysgerminoma	Immature teratoma	Immature teratoma
FIGO stage	IC	IC	IIIC
Surgical procedure	HSO	HSO	HSO
Adjuvant chemotherapy	BEP	None	PVAC
Gestation after FST	G1P0SA1	G2P2	G2P2

BEP, bleomycin/etoposide/cisplatin; *FIGO*, International Federation of Gynecology and Obstetrics; *G*, gravida; *HSO*, hemilateral salpingo-oophorectomy; *P*, para; *POF*, premature ovarian failure; *PVAC*, cisplatin/vincristine/actinomycin D/cyclophosphamide; *SA*, spontaneous abortion.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

TABLE 5
Backgrounds of patients who gave birth (n = 40)

Median age at FST, y (range)	25.1 (11.2–32.8)
Median age at first pregnancy after FST, y (range)	30.1 (22.1–40.0)
Median duration from FST to first delivery, y (range)	4.4 (1.3–19.2)
Married at FST	2.8 (1.3–5.9)
Unmarried at FST	6.6 (2.0–19.2)
Histological type, n (%)	
IMT	20 (50.0)
YST	10 (25.0)
DYS	12 (30.0)
FIGO stage, n (%)	
I	34 (85.0)
II	3 (7.5)
III	5 (12.5)
IV	0 (0.0)
Adjuvant chemotherapy, n (%)	30 (75.0)
BEP	20 (50.0)
PVB	7 (17.5)
PVAC/VAC	3 (7.5)
Pregnancy after recurrent MOGCT	2 (5.0)

BEP, bleomycin/etoposide/cisplatin; *DYS*, dysgerminoma; *FIGO*, International Federation of Gynecology and Obstetrics; *FST*, fertility-sparing treatment; *IMT*, immature teratoma; *MOGCT*, malignant ovarian germ cell tumor; *PVAC*, cisplatin/vincristine/actinomycin D/cyclophosphamide; *PVB*, cisplatin/vinblastine/bleomycin; *VAC*, vincristine/actinomycin D/cyclophosphamide; *YST*, yolk sac tumor.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

TABLE 6
Delivery after recurrent malignant ovarian germ cell tumor

	Case 1	Case 2
Age at FST, y	23	30
Surgical procedure	HSO	HSO
Tumor type	Yolk sac tumor	Immature teratoma
FIGO stage	IA	IIIB
Adjuvant chemotherapy	BEP	BEP
Recurrence-free interval, mo	6	6
Recurrence site	Omentum	Peritoneal dissemination
Treatment of recurrence	Omentectomy, TIP	Peritoneal resection, TC
Timing of marriage	After remission of recurrence	After remission of recurrence
Duration from recurrence treatment to pregnancy, y	1	4
Disease-free survival, y	10	15

BEP, bleomycin/etoposide/cisplatin; *FIGO*, International Federation of Gynecology and Obstetrics; *FST*, fertility-sparing treatment; *HSO*, hemilateral salpingo-oophorectomy; *TC*, paclitaxel/carboplatin; *TIP*, paclitaxel/ifosfamide/cisplatin.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

menopause age of <40 years were recorded. However, as the median age at the time of additional survey was 33.5 years, this finding is difficult to discuss. In MOGCT patients, the influence of chemotherapy on long-term ovarian function requires further investigation.

Although MOGCT is expected to be curable with BEP therapy, this therapy is not easy. Cisplatin has a high risk for chemotherapy-induced nausea and vomiting.[18] In addition, BEP therapy is associated with several adverse effects, such as neutropenia and fever.[19,20] In young women, depilation by etoposide and bleomycin is an anxious side effect. Low-dose intensity and compliance with the administration schedule have been reported to affect prognosis; thus, the treatment should not be changed or delayed due to temporary side effects.[21] In MOGCT patients, in addition to a desire for cure, a desire to become pregnant in the future may improve treatment compliance, as shown in the present study.

In previous studies, it was shown that FST did not affect cancer prognosis in patients with advanced-stage MOGCTs.[8,10,16,22,23] However, the numbers of pregnancies and childbirths after FST for advanced MOGCTs were unclear. In the present study, 8 of 40 patients with successful deliveries had FIGO stage II or III MOGCTs. Taken together, these findings suggest that it is not necessary to give up fertility preservation because of advanced tumor stage at diagnosis. Moreover, 2 patients gave birth after tumor recurrence. Thus, the possibility of fertility preservation at the time of recurrence can be explored.

The present study has several limitations. This was a retrospective, multicenter study; thus, there might be differences in the details of surgery and chemotherapies. Additionally, this study did not include pediatric MOGCT patients, as the assessed database registered only patients treated at gynecological facilities. Moreover, as the median patient age at the additional survey was 33.5 years, the numbers of pregnancies and childbirths were not stable. Furthermore, the effects of FST on ovarian function might manifest later in life.

In conclusion, we showed that MOGCT survivors could become pregnant and give birth if they desire. Advanced tumor stage or recurrence should not be used as indicators for avoiding fertility preservation. We believe that the results of the present study will encourage patients to overcome MOGCTs with FST. ■

Acknowledgment

We sincerely thank Tokai Ovarian Tumor Study Group members for collaborating in data collection.

References

1. Norris HJ, Jensen RD. Relative frequency of ovarian neoplasms in children and adolescents. Cancer 1972;30:713–9.
2. Quirk JT, Natarajan N. Ovarian cancer incidence in the United States, 1992-1999. Gynecol Oncol 2005;97:519–23.
3. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the gynecologic oncology group. J Clin Oncol 1994;12:701–6.
4. Williams SD. Ovarian germ cell tumors: an update. Semin Oncol 1998;25:407–13.
5. Williams SD, Blessing JA, DiSaia PJ, et al. Second-look laparotomy in ovarian germ cell tumors: the gynecologic oncology group experience. Gynecol Oncol 1994;52:287–91.
6. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. Gynecol Oncol 1994;55:S62–72.
7. Peccatori F, Bonazzi C, Chiari S, et al. Surgical management of malignant ovarian germ-cell tumors: 10 years' experience of 129 patients. Obstet Gynecol 1995;86:367–72.
8. Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol 2007;25:2938–43.
9. Gershenson DM, Miller AM, Champion VL, et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: a gynecologic oncology group study. J Clin Oncol 2007;25:2792–7.
10. Chan JK, Tewari KS, Waller S, et al. The influence of conservative surgical practices for malignant ovarian germ cell tumors. J Surg Oncol 2008;98:111–6.
11. Gershenson BDM. Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumors. Am Soc Clin Oncol 2016;6:270–5.
12. Mitchell PL, Al-Nasiri N, A'Hern R, et al. Treatment of nondysgerminomatous ovarian germ cell tumors: an analysis of 69 cases. Cancer 1999;85:2232–44.
13. Brewer BM, Gershenson DM, Herzog CE, et al. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. J Clin Oncol 2017;17:2670–5.
14. Kanazawa K, Suzuki T, Sakumoto K. Treatment of malignant ovarian germ cell tumors with preservation of fertility: reproductive performance after persistent remission. Am J Clin Oncol 2000;23:244–8.
15. Segelov E, Campbell J, Ng M, et al. Cisplatin-based chemotherapy for ovarian germ cell malignancies: the Australian experience. J Clin Oncol 1994;12:378-4.
16. Tangir J, Zelterman D, Ma W, et al. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. Obstet Gynecol 2003;101:251–7.
17. Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future. Gerontologist 2011;51:425–32.
18. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016;27:v119–33.
19. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 1989;7:387–91.
20. Nichols BCR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B study. J Clin Oncol 1998;16:1287–93.
21. Satoh T, Aoki Y, Kasamatsu T, et al. Administration of standard-dose BEP regimen (bleomycin + etoposide + cisplatin) is essential for treatment of ovarian yolk sac tumor. Eur J Cancer 2015;51:340–51.
22. Patterson DM, Murugaesu N, Holden L, et al. A review of the close surveillance policy for stage I female germ cell tumors of the ovary and other sites. Int J Gynecol Cancer 2008;18:43–50.
23. Park JY, Kim DY, Suh DS, et al. Analysis of outcomes and prognostic factors after fertility-sparing surgery in malignant ovarian germ cell tumors. Gynecol Oncol 2017;145:513–8.

Author and article information

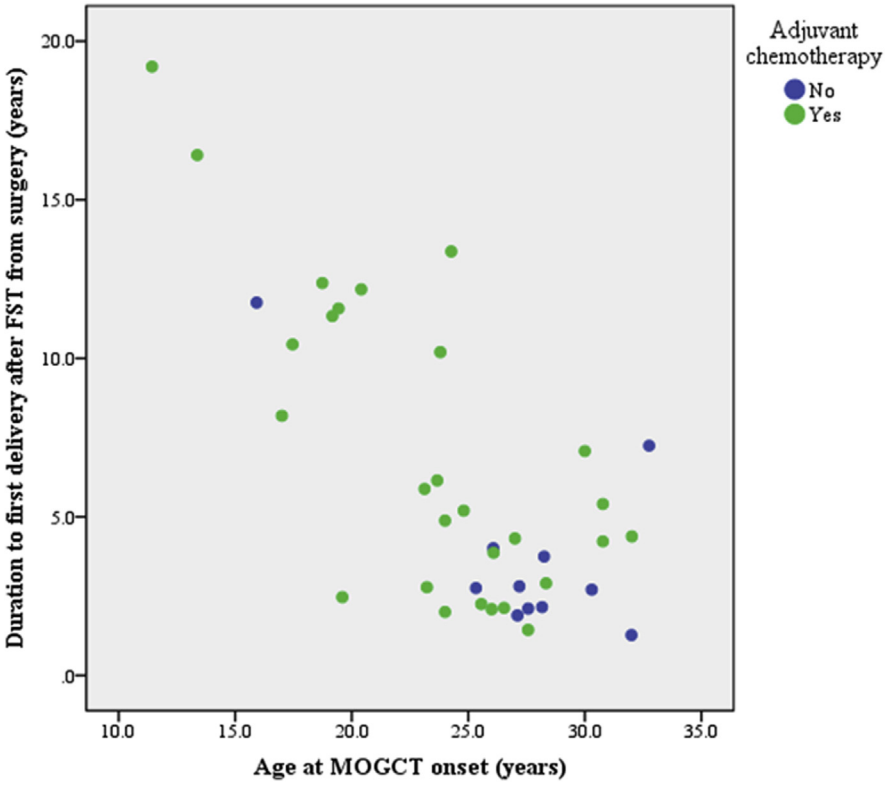
From the Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Received May 18, 2018; revised July 8, 2018; accepted July 24, 2018.

The authors report no conflict of interest.

Corresponding author: Hiroaki Kajiyama, MD, PhD. kajiyama@med.nagoya-u.ac.jp

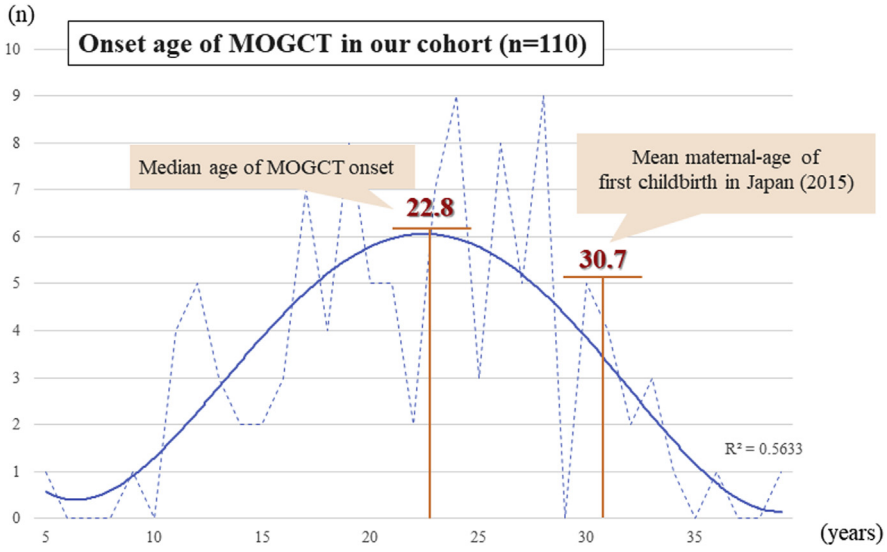
SUPPLEMENTARY FIGURE 1
Duration achieving pregnancy after fertility-sparing treatment



Duration achieving pregnancy after fertility-sparing treatment (FST) of malignant ovarian germ cell tumor (MOGCT). *Green dots* indicate those who received adjuvant chemotherapy, and *blue dots* indicate those who did not receive the treatment.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.

SUPPLEMENTARY FIGURE 2
The divergence between onset age and first childbearing age in Japan



Onset age of malignant ovarian germ cell tumor (MOGCT) in our cohort.

Tamauchi et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors. Am J Obstet Gynecol 2018.