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Ovarian function, fertility, and menopause occurrence after fertility-sparing surgery and chemotherapy for ovarian neoplasms☆,☆☆

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HIGHLIGHTS

- Chemotherapy for nonepithelial ovarian cancer affects ovarian function.
- Patients with epithelial ovarian cancer can safely receive chemotherapy.
- Fertility rates are satisfactory among all group of patients.
- Fertility preservation can be safely offered to young women with ovarian neoplasms.

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ABSTRACT

Background. The effect of chemotherapy exposure (CE) on ovarian function in young women with ovarian neoplasms undergoing fertility-sparing treatment (FST) remains unclear. We investigated whether CE is correlated with the *outcomes* (*1*) during-treatment and (*2*) post-treatment amenorrhea, (*3*) conception rate, (*4*) pregnancy outcome, and (*5*) spontaneous menopausal age.

Patients and methods. Eligibility criteria were patients with a diagnosis of epithelial (EOC) or nonepithelial (no-EOC) invasive ovarian neoplasm, premenopausal age, undergoing FST ± CE, histopathology confirmation, and adequate follow-up. The groups' *outcomes* were compared by logistic and linear regression analysis.

Results. A total of 548 patients diagnosed during 1980 and 2014 were included, 198 in the EOC group and 350 in the no-EOC group, and 44% received chemotherapy, with a median follow-up of 15.9 years. In no-EOC patients, CE conferred a higher risk for *Outcomes* 1 (adjusted OR [aOR] 27; 95% CI 12 to 61; $P < .0001$) and 2 (aOR 5.42; 95% CI 1 to 24; $P = .0256$) and was associated with a younger menopausal age (adjusted β −5.52; 95% CI −10.53 to −0.52; $P = .0313$). Overall, 57% of patients attempted pregnancy, with a conception rate of 89%. In EOC patients, no association between CE and a decreased fertility was demonstrated (aOR, 3.05; 95% CI 0.72 to 12.88; $P = .1298$).

Conclusions. CE in no-EOC was associated with an increased risk of during-treatment amenorrhea, post-treatment amenorrhea, and earlier spontaneous menopausal age; CE in EOC was not associated with any item at study. Patients undergoing FST had reassuringly high conception rates and low premature ovarian failure rates; however, in pretreatment counseling, the risks of this approach in such young population should be discussed.

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1. Introduction

Fertility-sparing treatment (FST) for premenopausal women with early-stage ovarian neoplasms consists of surgical removal of ovarian neoplasm, sparing the unaffected gynecological apparatus, and adjuvant chemotherapy according to risk factors. This experimental approach has been proved to be safe for different ovarian neoplasm subtypes: malignant germ cell tumors (MGCT) [1,2], sex cord-stromal tumor (SCST) [1,3] and early-stage epithelial ovarian cancer (EOC) [4–6]. Nevertheless, as controversies regarding high-risk cases remain unsolved, inclusion criteria are very strict [5]. Moreover, the rarity of this condition limits the knowledge of the impact of FST on the residual ovarian function and fertility potential. The question is pivotal because fertility is considered of outmost interest among factors affecting the quality of life in young patients [7]. Reports on childhood cancer survivors showed that premature ovarian failure (POF) occurred more frequently in patients undergoing anticancer therapy with an increased risk of 30% than in their healthy siblings [8]. Nationwide reports observed higher infertility rates [9–10] after irradiation and chemotherapy.

The gonadotoxic effect of chemotherapy during the fertile age is far-reaching, thereby affecting equally primordial follicles and granulosa cells, with short- and long-term effects, including acute ovarian failure (<5 years from the primary treatment), POF (menopause <40 years), infertility, and younger menopausal age [11].

Mechanisms of action differ by compound type, with the alkylating agents platinum derivatives and anthracyclines carrying the highest gonadotoxic risk [11]. Bleomycin and etoposide have also been identified as gonadotoxic compounds, especially in combination regimens [12]. For patients affected by ovarian malignancy, the scenario is even more complex: along with chemotherapy, gonadal surgery can also affect ovarian function due to the surgical ablation of the healthy ovarian tissue [13]. In this perspective, the gonadotoxic effect of FST by itself in ovarian neoplasms is largely unknown: data on conception and pregnancy rates are satisfactory after chemotherapy exposure [14–16]; however, no long-term observations have ever been performed comparing treated and untreated women.

In this study, we examine the residual ovarian function in women undergoing FST with separate analysis for EOC and MCGT grouped with SCST in the no-EOC group. Specific outcomes were evaluated. In particular, the association of chemotherapy exposure (CE) and surgical procedures with the occurrence of (*1*) during-treatment amenorrhea, (*2*) post-treatment amenorrhea, (*3*) conception, (*4*) pregnancy outcome, and (*5*) spontaneous menopausal age, henceforth called *outcomes* were analyzed.

2. Patients and methods

All clinical data including ovarian function as menstrual cycles and fertility details of patients consecutively treated at San Gerardo Hospital (Monza) between 1980 and 2014 were retrospectively and prospectively collected and analyzed. Our institutional review board approved the study. Patients diagnosed before the age of 45 years and treated with FST (primary surgery, restaging surgery after referral from external institutions, or adjuvant treatment) with the conservation of at least one ovary and the uterus regardless of chemotherapy exposure as adjuvant or relapse treatment were included.

For statistical analysis, continuous variables were represented as the median and interquartile range (IQR: Q1–Q3), whereas categorical variables were represented as the frequency and percentage of subjects who were in each treatment group. Chi-square (or Fisher, as appropriate) and Wilcoxon tests were performed to compare categorical and continuous variables, respectively. The median and IQR of the follow-up period were calculated with the reverse Kaplan–Meier (KM) method. The relapse-free survival (RFS) was defined as the time from surgery to the date of relapse or death from any cause. Patients known to be alive and relapse-free at the time of analysis were censored at their last follow-up date. The RFS rate at 5 and 10 years was calculated with the KM method.

Detailed information about inclusion criteria, the population used for the analysis of each outcome, and statistical methods can be found in the supplementary material available online.

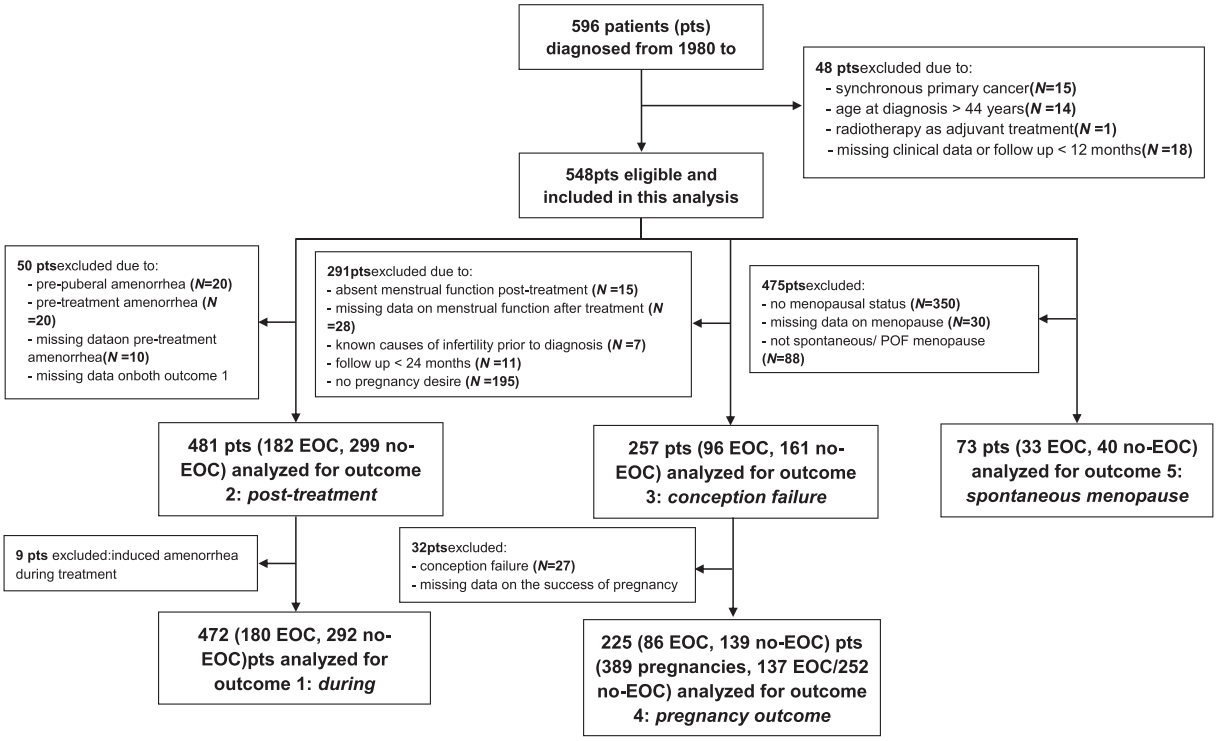

Fig. 1. Flowchart of eligible population for outcomes at study.

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3. Results

Among 596 patients treated with FST, 48 were excluded; therefore, 198 EOC and 350 no-EOC patients constituted the study cohort (Fig. 1). During a median follow-up of 15.9 years, 121 EOC and 184 no-EOC patients underwent FST with no chemotherapy exposure (no-CE) and 77 EOC and 166 no-EOC patients with CE (Tables 1 and S1).

In the EOC group, median age was 30.9 years, which as similar between the CE and no-CE groups. No differences were observed in surgical procedures. Relapses occurred in 16.8% of cases, with a higher incidence in the CE group than in the no-CE group (26.0% vs. 10.8%, $P = .005$).

In addition, patients in the CE group were younger than those in the no-CE group (20.9 vs. 24.6 years, $P < .0001$) and had a lower prior pregnancy rate (13.3% vs. 25.5%, $P = .0039$). No differences were detected in surgical procedures. Relapses occurred in 14.4% of cases, with a higher incidence in the CE group (22.0% vs. 8.0%, $P = .0003$).

Specific treatment regimens are reported in Table S2. Among patients in the CE group, 73 (94.8%) EOC and 153 (92.2%) no-EOC patients received adjuvant chemotherapy, while 4 and 13 patients, respectively, were exposed at relapse. A total of 86.3% of patients in the EOC group received single-platinum treatment, and 92.2% of those in the no-EOC group received platinum-bleomycin-etoposide or vinblastine (PEB and PVB) (Table S3).

3.1. During-treatment amenorrhea

Among 292 no-EOC patients, 10 (6.3%) of them in the no-CE and 98 (73.7%) in CE groups had during-treatment amenorrhea ($P < .0001$). Amenorrhea lasted for 7 months (IQR: 5 to 10) in the no-CE and 5 months (IQR: 4 to 7) in CE groups. At multivariable analysis, CE in no-EOC patients increased the risk of during-treatment amenorrhea (adjusted OR [aOR] 27.06; 95% CI 11.97–61.14; $P < .0001$). No association was observed between *Outcome 1* and surgical procedures (Table 2). Only one EOC patient had an event for *Outcome 1*; therefore, no logistic analysis was performed.

3.2. Post-treatment amenorrhea

Among 299 no-EOC patients, 3 (1.9%) of them in the no-CE group and 7 (5.0%) in the CE group had post-treatment amenorrhea ($P = .1967$). At multivariable analysis, CE in no-EOC patients increased the risk of post-treatment amenorrhea (aOR 5.42; 95% CI 1.23–23.91; $P = .0256$). No association was observed between *Outcome 2* and surgical procedures (Table 3). No events were observed in EOC patients.

3.3. Conception rate

Even though there is no demonstrated deterministic cause–effect relation between hypofertile conditions and conception success, to conduct a reliable evaluation of fertility outcome, patients with minimal

Table 1
Demographic and clinical characteristics of patients included in the analysis according to chemotherapy exposure ($N = 548$).

	EOC			no-EOC		
	no-CE $N = 121$	CE $N = 77$	Chi-square *P*-value	no-CE $N = 184$	CE $N = 166$	Chi-square *P*-value
Follow-up (years)	16.5	13.7		15.8	17.0	
Median (Q1–Q3)	(10.8–21.7)	(9.8–18.6)		(11.2–22.0)	(10.5–23.9)	
Age at surgery (years)	30.7	31.9	.2507[a]	24.6	20.9	<.0001[a]
Median (Q1–Q3)	(26.2–34.6)	(28.2–35.5)		(18.6-31.7)	(17.2–26.3)	
Previous pregnancies	48 (40.0)	21 (28.0)	.0882	47 (25.5)	22 (13.3)	.0039
Missing	1	2		0	0	
Histotype			<.0001			<.0001
Epithelial, low grade	108 (89.3)	29 (37.7)		–	–	
Epithelial, high grade	13 (10.7)	48 (62.3)		–	–	
MGCT	–	–		114 (62.0)	149 (89.8)	
SCST	–	–		70 (38.0)	17 (10.2)	
Stage			–			<.0001
I/II	121 (100)	77 (100)		184 (100)	103 (62.8)	
III/IV	0 (0.0)	0 (0.0)		0 (0.0)	61 (37.2)	
Missing	0	0		0	2	
Surgical procedure			.3449			.0544
Oophorectomy	87 (71.9)	60 (77.9)		151 (82.5)	148 (89.7)	
Cystectomy	34 (28.1)	17 (22.1)		32 (17.5)	17 (10.3)	
Missing	0	0		1	1	
Gonadal surgery laterality			.7127			.3741
Monolateral	77 (63.6)	47 (61.0)		149 (81.4)	128 (77.6)	
Bilateral	44 (36.4)	30 (39.0)		34 (18.6)	37 (22.4)	
Missing	0	0		1	1	
Additional ovarian surgeries	24 (19.8)	22 (28.6)	.1559	6 (3.3)	5 (3.0)	.8940
Relapse	13 (10.8)	20 (26.0)	.0055	14 (8.0)	33 (22.0)	.0003
Missing	1	0		8	16	
Number of treatment lines						
1	–	68 (88.3)		–	156 (94.0)	
2	–	9 (11.7)		–	9 (5.4)	
3	–	0 (0.0)		–	1 (0.6)	
Patients' status at last follow-up			0.0199[b]			0.0004[b]
NED	118 (97.5)	68 (88.3)		180 (98.4)	154 (93.3)	
DOD	1 (0.8)	6 (7.8)		0 (0.0)	10 (6.1)	
Dead due to other cause	1 (0.8)	2 (2.6)		2 (1.1)	0 (0.0)	
AWD	1 (0.8)	1 (1.3)		1 (0.5)	1 (0.6)	
Missing	0	0		1	1	

Legend. EOC: epithelial ovarian cancer. no-EOC: nonepithelial ovarian cancer. CE: chemotherapy exposure. no-CE: no chemotherapy exposure. MGCT: malignant germ cell tumor. SCST: sex cord-stromal tumor. NED: no evidence of disease. DOD: died of disease. AWD: alive with disease. Q1-Q3: first to third quartile.

[a] Wilcoxon test *P*-value.

[b] Fisher test *P*-value.

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Table 2
Effect of adjuvant chemotherapy on the absence of ovarian function during treatment in nonepithelial ovarian cancer patients ($N = 292$). Univariable and multivariable logistic regression models.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CE	41.71(19.75–88.09)	<.0001	27.06(11.97–61.14)	<.0001
Age at surgery (1-year increase)	0.93(0.90–0.96)	.0001	0.98(0.93–1.03)	.3815
MGCT histology (ref. SCST cell)	4.41(2.00–9.74)	.0002	1.80(0.65–5.02)	.2608
stage III/IV (vs. stage I/II)	13.58(6.27–29.41)	<.0001	2.17(0.91–5.18)	.0822
Surgical procedure: oophorectomy (vs. cystectomy)	2.09(0.98–4.45)	.0553	1.54(0.56–4.27)	.4032
Bilateral surgery	1.01(0.57–1.80)	.9613	–	–
Additional ovarian surgeries	0.48(0.10–2.34)	.3616	–	–

Legend. CE: chemotherapy exposure. MGCT: malignant germ cell tumor. SCST: sex cord-stromal tumor. OR: odds ratio. 95% CI: 95% confidence interval.

or absent fertility potential were excluded. Three women with a prior diagnosis of primary infertility and 4 women with a diagnosis of infertility after conception attempts (2 patients with tubal occlusion and 2 with azoospermia of the partner), were excluded.

Among 96 EOC patients, conception failure was reported in 4 (6.4%) patients in the no-CE group and 6 (18.2%) patients in the CE group ($P = .0715$). No impact of CE or surgical procedures for *Outcome 3* was identified in EOC patients (Table 4).

Among 161 no-EOC patients, conception failure was reported for 5 (6.3%) patients in the no-CE group and 12 (14.6%) in the CE group ($P = .0865$). At multivariable analysis, no association between CE and conception failure in the no-EOC subgroup was observed (Table 5).

3.4. Pregnancy outcome

Among 137 conceptions reported for 86 EOC patients, there have been 75 (75.0%) and 29 (78.4%) vital newborns, in the no-CE and CE groups, respectively ($P = .6814$). Among 252 conceptions reported for 139 no-EOC patients, there have been 99 (83.2%) and 108 (81.2%) vital newborns in the no-CE and CE groups, respectively ($P = .6805$), and 4 patients underwent successful assisted reproductive techniques.

In univariable analysis, CE was not associated with *Outcome 4* for EOC patients (OR 0.83; 95% CI 0.34–2.04; $P = .6817$) and no-EOC patients (OR 1.15; 95% CI 0.60–2.19; $P = .6806$). No other risk factors associated with *Outcome 4* were identified (Table S4).

3.5. Spontaneous menopausal age

EOC patients in menopausal status at last follow-up were 74/176 (42.0%). Thirty-nine (53.4%) and one (1.4%) patient underwent surgical or medical menopause, respectively, and for 1 patient, the information was not available. The number of patients with spontaneous menopause were 33 (45.2%), with a median age of 49 (IQR 45–49) years in the no-CE group ($N = 19$) and 46 (IQR 44–49) years in the CE group ($N = 14$) ($P = .2498$). POF occurred in one patient in the no-CE group and one patient in the CE group. In multivariable analysis, CE was not associated with menopausal age (adjusted β −1.49; 95% CI, −4.70–1.72; $P = .3520$) in EOC patients, and no associations were observed with surgical features (Table S5).

No-EOC patients in menopausal status at last follow-up were 94/342 (27.5%). For six patients, the cause of menopause was unknown, whereas 43 (48.9%) and 5 (5.7%) patients underwent surgical or medical menopause, respectively. The number of patients with spontaneous menopause were 40 (45.5%), with a median age of 47 (IQR 45–50) years in the no-CE group ($N = 17$) and 37 (IQR 31–48) years in the CE group ($N = 23$) ($P = .0149$). POF occurred in 2 patients in the no-CE group and 14 patients in the CE group ($P = .0017$). In multivariable analysis, CE was associated with younger menopausal age (aβ −5.52; 95% CI, −10.53–0.52; $P = .0313$) in no-EOC patients. No association was observed with surgical features (Table S6).

4. Discussion

FST has been one of the most revolutionary aspects in gynecologic oncology. Even though it is a complex multidisciplinary approach, fertility reports have shown reassuringly positive data (Table S7). Possible ovarian function impairment resulting from the treatment was hypothesized from reports on other cancers [9,10]. Series from our center described favorable oncologic outcomes for FST [17,18]. Herein, we focus on the updated long-term residual ovarian function, thus covering a median follow-up time of 16 years.

We observed during-treatment amenorrhea in 23.1% of cases and post-treatment amenorrhea in 2.1% of cases. Among patients with pregnancy desire (57.5%), we observed a conception rate of 89.5%, out of which 97.0% of cases resulted from spontaneous conceptions, with successful pregnancy in 79.9% of cases. Median spontaneous menopausal age occurred at 47 years. Remarkably, an infertility rate of 10.5% is comparable to that obtained in the general population, reported with a prevalence rate of 9% (3.5–16.7%) [19], thus providing a strong rationale to FST.

Furthermore, parallel analyses for EOC and no-EOC were conducted to measure the impact of each treatment modality. For EOC, multivariable analysis showed no independent association of the outcomes of study (*1* to *5*) with CE or surgical features. For no-EOC, at multivariable

Table 3
Effect of chemotherapy exposure on the absence of ovarian function post-treatment in nonepithelial ovarian cancer patients ($N = 299$). Univariable and multivariable logistic regression models.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CE	2.78(0.70–10.94)	.1448	5.42(1.23–23.91)	.0256
Age at surgery (1-year increase)	1.11(1.02–1.22)	.0210	1.16(1.05–1.28)	.0046
MGCT histology (ref. SCST cell)	0.92(0.19–4.45)	.9166	–	–
stage III/IV (vs. stage I/II)	3.08(0.84–11.33)	.0896	–	–
Bilateral surgery	0.85(0.18–4.12)	.8440	–	–
Additional ovarian surgeries	3.90(0.44–34.60)	.2213	–	–

Note: Surgical procedure was not included in univariable and multivariable analyses because no woman without ovarian function after the end of treatment underwent cystectomy.
Legend. CE: chemotherapy exposure. MGCT: malignant germ cell tumor. SCST: sex cord-stromal tumor. OR: odds ratio. 95% CI: 95% confidence interval.

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Table 4
Effect of chemotherapy exposure on conception failure in epithelial ovarian cancer patients ($N = 96$). Univariable and multivariable logistic regression models.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CE	3.28(0.85–12.58)	.0715	3.05(0.72–12.88)	.1298
Previous pregnancies	1.29(0.34–4.93)	.7122	–	–
Age at surgery (1-year increase)	1.12(0.98–1.27)	.0891	–	–
Surgical procedure: oophorectomy (vs. cystectomy)	0.22(0.06–0.84)	.0266	0.26(0.06–1.16)	.0783
Bilateral surgery	1.87(0.50–6.96)	.3528	–	–
Additional ovarian surgeries	1.25(0.30–5.24)	.7635	–	–
Relapse	5.07(1.22–21.10)	0.0258	2.69(0.54–13.51)	.2296

Legend. CE: chemotherapy exposure. OR: odds ratio. 95% CI: 95% confidence interval.

analysis, *Outcomes 1*, *2*, and *5* were independently impaired by CE, whereas no impact on *Outcomes 3* and *4* was observed (Table 6).

It is known that PEB/PVB, the regimens used for no-EOC, may cause during-treatment amenorrhea, with a reported frequency of 12.5–95% [20]. After 1–5 months, 87.3–100% of patients recovered regular menstruations. In our cohort, we observed 5% rate of persistent amenorrhea, which is more frequent in the CE group than in the no-CE group (1.9 vs. 5%), with chemotherapy as the only associated factor. The same observation was made for *Outcome 5*, including POF occurrence; moreover, long-term hormonal impairment such as early menopause is possibly underestimated in such young population [21]. Swerdlow reported a higher risk of secondary amenorrhea and early menopause with the use of compounds including platinum and etoposide in Hodgkin Lymphomas [22], thereby causing diffuse DNA double-strand break damage and selective apoptosis to the follicles [23,24].

Older age at the time of diagnosis also increased the risk for *Outcome 2*, in accordance with the observation that prepubertal and young ovaries are more resistant to adverse effects of chemotherapy [25].

It is not clear whether this translates in a lower impact of chemotherapy in nonfunctioning ovaries: studies showed that women using oral contraceptives during treatment fully recovered menstruations afterwards [26]. More recently, gonadal protection with GnRH during chemotherapy for breast cancer was demonstrated effective against post-treatment POF [27]. Investigating the effect of menstrual cycle inhibition to preserve functioning ovarian follicles is of extreme interest; however, because this population was negligible in this report, no conclusion could be drawn at this time.

Regarding fertility, no detrimental impact of CE or surgical procedures on *Outcomes 3* and *4* was observed. Considering large series in the literature (>25 patients) (supplementary references), conception attempts were 25–65% in the EOC group and 11–87% in the no-EOC group; successful conception rates were 52–80% in the EOC group and 42–95% in the no-EOC group; and successful pregnancy rates were 63–92% of conceptions. Some series with FST and chemotherapy also reported reliable results [15,25,26]. Additionally, in a GOG surveillance study [28], fertility outcomes were evaluated in MGCT patients treated with chemotherapy versus controls, and the results showed 37 pregnancies in 24 patients and 186 pregnancies in 92 patients. Authors concluded that such population was very likely to retain menstrual function and fertility after chemotherapy. Recently, Yang et al. [29] in a cohort of 148 patients treated with FST reported a conception rate of 79.5% (35/44) among patients undergoing PEB and 100% (5/5) among controls, with a successful pregnancy rate of 75%.

In our analysis, both treatment schedules used for the EOC group, platinum based in 86.3% of cases in the no-EOC group and PEB/PVB schedule in 92.2% of cases in the EOC group, did not add detrimental effect. No specific analysis could be performed for exposure of alkylating agents because of their minor use ($N = 12$).

For EOC patients, even though no factors for *Outcome 3* reached statistical significance, the high odds ratios for CE (aOR: 3.05 (0.72–12.88)), oophorectomy versus cystectomy (aOR: 0.26 (0.06–1.16)), and relapse (aOR: 2.69 (0.54–13.51)) need further comment. There is the possibility that cystectomy might be related to relapse and infertility, given that this procedure was related to a higher risk of recurrence (29.6% vs. 8.7%, $P = .0090$). Relapse by itself would reduce the time free from disease, the conception chance, and the possibility of another conservative surgery. As such, surgery might have some detrimental repercussion on residual ovarian function per se. In fact, some events were observed in unexposed patients: for *Outcome* 1 ($N = 10$), *Outcome 2* ($N = 3$), and POF (N = 3) (Table S2). Seven out of 16 women underwent multiple surgeries for restaging and follow-up. Following several reports, it is known that the extent of gonadal surgery [13], especially in bilateral lesions, [30] is directly proportional to the pool of residual follicles [31]. For this reason, the evaluation of lesions suspicious for relapse deserves extreme attention to avoid unnecessary surgeries for benign conditions.

Limitations of this analysis must be considered: the retrospective nature, the long period of observation, the fact that referral from other centers may have produced biases, and the lack of systematic assessment of hormonal levels for the evaluation of the ovarian function. However, the strength of the study is that cases were consecutively collected, enrollment for FST was formulated after case re-evaluation and often surgical re-staging, that amenorrhea and menopause were confirmed using plasmatic markers as clinically indicated [18] and follow-up was updated by using a direct questionnaire during clinical

Table 5
Effect of chemotherapy exposure on conception failure in nonepithelial ovarian cancer patients ($N = 161$). Univariable and multivariable logistic regression models.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CE	2.54(0.85–7.57)	.0865	1.42(0.40–5.03)	.5872
Previous pregnancies	0.35(0.04–2.75)	.3160	–	–
Age at surgery (1-year increase)	0.91(0.84–0.99)	.0358	0.93(0.85–1.01)	.0936
MGCT histology (ref. SCST cell)	0.78(0.24–2.59)	.6903	–	–
stage III/IV (vs. stage I/II)	3.79(1.25–11.50)	.0188	2.63(0.74–9.34)	.1336
Surgical procedure: oophorectomy (vs. cystectomy)	3.56(0.45–28.02)	.2285	–	–
Bilateral surgery	1.26(0.38–4.17)	.7008	–	–
Additional ovarian surgeries	1.44(0.16–12.71)	.7441	–	–
Relapse	0.38(0.05–3.00)	.3559	–	–

Legend. CE: chemotherapy exposure. MGCT: malignant germ cell tumor. SCST: sex cord-stromal tumor. OR: odds ratio. 95% CI: 95% confidence interval.

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Table 6
Summary of the results for each outcome in the EOC and no-EOC groups.

Outcomes	EOC (198)			no EOC (350)		
	CE (77)	no-CE (121)	*P*	CE (166)	no-CE (184)	*P*
1: During-treatment amenorrhea (%)	1	0	N/A	73.7	6.3	<.0001
2. Post-treatment amenorrhea (%)	0	0	N/A	5	1.9	.0256
3: Conception rate (%)	18.2	6.4	.1298	14.6	6.3	.5872
4: Pregnancy outcome (vital newborns, %)	78.4	75.0	.6817	81.2	83.2	.6806
5: Spontaneous menopausal age (median age, years)	49	46	.2498	37	47	.0149

Underline values is statistically significant difference.

evaluation. The rate of patients' loss at follow-up proved to be low, thus ranging from 0% to 8% for the studied outcomes.

The infertility rate might be underestimated, especially in patients not attempting conception, as not all the patients systematically underwent fertility assessment tests. On the other hand, it is reported that in the general population, there is an underestimation of early conceptions, with approximately 22% of preclinical pregnancies not diagnosed or reported to physicians [32].

As a side comment, we observed that a significant fraction of patients (42.5%) did not consider pregnancy for different reasons (e.g., presence or fear of the disease, young age, or absence of the partner or stable relationship). Excluding social, relational, and medical reasons, the negative psychological impact of the diagnosis is extremely relevant in cancer survivors [9] and needs careful assessment during counseling.

To summarize, this analysis showed for the first time that, even though chemotherapy had a detrimental impact on residual follicles in no-EOC in terms of persistent amenorrhea and premature menopause, it did not have a negative effect on fertility in both EOC and no-EOC patients. The suggestion that residual follicles, especially in such young population, may still be viable for successful pregnancies is valuable and needs further study.

Pretreatment counseling should highlight and clarify the potential ovarian damage of chemotherapy. Moreover, to preserve the overall quality of life, early menopause should be promptly identified and treated, thereby avoiding the related morbidity [33].

Finally, the role of a multidisciplinary team to grant specific support to these young patients is once more underlined.

Conflict of interest statement

All authors disclose that there is no potential conflict of interest.

CRediT authorship contribution statement

Lorenzo Ceppi: Investigation, Project administration, Writing - original draft. **Francesca Galli:** Formal analysis, Methodology. **Maria Lamanna:** Investigation. **Sonia Magni:** Investigation. **Federica Dell'Orto:** Investigation. **Debora Verri:** Investigation. **Martina Delle Marchette:** Investigation. **Andrea Alberto Lissoni:** Conceptualization. **Federica Sina:** Conceptualization, Investigation. **Daniela Giuliani:** Conceptualization, Investigation. **Tommaso Grassi:** Investigation. **Fabio Landoni:** Supervision, Writing - review & editing. **Cristina Maria Bonazzi:** Conceptualization, Project administration. **Robert Fruscio:** Conceptualization, Project administration, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.11.032.

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