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Analysis of assisted reproductive outcomes for gynecologic cancer survivors: a retrospective study

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Abstract

Objective To examine the reproductive outcomes of assisted reproductive technology (ART) in gynecologic cancer patients and to assess maternal and neonatal complications.

Methods Women diagnosed with gynecologic cancer who underwent their first in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment between 2013 and 2021 at Shanghai Ji Ai Genetics and IVF Institute were included in this study. Infertile women without any history of cancer were matched to the cancer group. The primary outcome was the cumulative live birth rate. Baseline and follow-up data were compared between groups using Student's t-tests for normally distributed variables and with Chi-square test for categorical variables. A propensity score-based patient-matching approach was adopted to ensure comparability between individuals with and without specific cancer type.

Results A total of 136 patients with a history of gynecologic cancer and 241 healthy infertile controls were included in this study. Endometrial cancer constituted 50.70% of the cases and cervical cancer constituted 34.60% of the cases. The cancer group exhibited significantly shorter duration of stimulation, lower levels of estradiol, lower number of retrieved oocytes, day-3 embryos, and blastocysts compared to the control group ($P < 0.05$). The cumulative live birth rate of the gynecologic cancer group was significantly lower than that of the control group (36.10% vs. 60.50%, $P < 0.001$). Maternal and neonatal complications did not significantly differ between the groups ($P > 0.05$). The endometrial cancer and cervical cancer groups showed significantly lower cumulative live birth rates than their matched controls (38.60% vs. 64.50%, $P = 0.011$ and 24.20% vs. 68.60%, $P < 0.001$, respectively).

Conclusions These findings highlight the decreased occurrence of pregnancy and live birth in female gynecologic cancer patients undergoing ART, particularly in endometrial cancers and cervical cancers. These findings have important implications for counseling and managing gynecologic cancer patients undergoing ART.

Keywords Gynecologic cancer, Endometrial cancer, Cervical cancer, Live birth, In vitro fertilization, Assisted reproductive technology

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Introduction

Gynecologic malignancies comprise approximately 13% of female cancer diagnoses [1, 2], and oncological treatments such as surgery, chemotherapy, abdominal or pelvic radiotherapy, and hormonotherapy may induce infertility, premature ovarian failure, or early menopause, resulting in a loss of reproductive potential [3–5]. As the population of long-term cancer survivors continues to rise, concerns surrounding fertility and pregnancy outcomes have become increasingly critical for these young women [6]. Despite international guidelines recommending fertility consultation and prompt referral to fertility specialists for all reproductive-age cancer patients [7, 8], the provision of fertility information by oncology specialists is often inadequate due to a lack of relevant research and insufficient information.

Assisted reproductive technology (ART) has emerged as an important option for cancer patients undergoing treatment, but the reproductive outcomes of ART among gynecologic cancer survivors remain poorly understood [9, 10]. Therefore, this study aimed to examine the impact of a history of gynecologic cancer on pregnancy outcomes among cancer patients undergoing ART, by comparing their results with those of infertile women without a prior cancer diagnosis.

Materials and methods

Study population and design

The study was conducted at Shanghai Ji Ai Genetics and IVF Institute, Shanghai, China. Women who had been diagnosed with gynecologic cancer and subsequently underwent their first in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment between 2013 and 2021 were retrospectively screened in the institutional database. Infertile women without any history of cancer were matched to the cancer group based on key factors such as maternal age at oocyte retrieval, pregestational body mass index (BMI), antral follicle count (AFC), and fertilization method. Women were excluded if they had a history of repeated IVF/ICSI attempts, recurrent spontaneous abortion, chromosomal abnormalities, or incomplete data. The study was approved by the Institutional Review Board of Shanghai Ji Ai Genetics and IVF Institute (JIAI E2023-10). As data were deidentified and all analyses were retrospective, the requirement for informed consent was waived.

IVF/ICSI treatment

All patients underwent IVF/ICSI treatment with an appropriate ovarian stimulation protocol tailored to their ovarian reserve. Patients treated with the long protocol received a long-acting gonadotropin-releasing hormone (GnRH) agonist at mid-luteal phase of the previous cycle. Once downregulation was achieved, gonadotropins (Gn) were administered for ovarian stimulation, with the dose adjusted based on follicle growth and serum hormone levels. Patients treated with the short protocol were administered a short-acting GnRH agonist and Gn simultaneously starting from cycle days 2–3 (CD2-3). In patients treated with the antagonist protocol, ovarian stimulation was initiated from CD2-3. The administration of a GnRH antagonist was initiated from day 6 of ovarian stimulation till the day of the ovulation trigger. In the mild stimulation protocol, patients were administered oral letrozole for five consecutive days from CD2-5 followed by low-dose Gn for ovarian stimulation. Patients treated with the progestin-primed ovarian stimulation protocol received oral dydrogesterone 20 mg/day and Gn simultaneously from CD2-3 until the trigger day.

Oocyte retrieval was performed 34-36 h after triggering with human chorionic gonadotropin (hCG), a GnRH agonist or combined hCG and GnRH agonist under transvaginal ultrasound guidance. Fertilization assessment was performed about 16–18 h post-insemination. On Day 3 after oocyte retrieval, an embryo with at least seven cells and Grades 1 and 2 was defined as good quality. Embryos with at least six cells and fragments < 50% were frozen. Women who had more than six good-quality embryos on Day 3 were counselled for extended culture and blastocyst transfer. Fresh embryo transfer (ET) was performed based on clinical practice, and any surplus embryos were cryopreserved for subsequent frozen-thawed embryo transfer (FET). Luteal support was provided after ET.

Data collection and outcome measures

Patient data were extracted from electronic medical records. Time to IVF was determined by considering the intervals between the initiation of tumor treatment and the start of oocyte retrieval. Ongoing pregnancy was defined as a viable intrauterine pregnancy lasting at least 12 weeks confirmed by ultrasound. Live birth was defined as the delivery of at least one live-born infant irrespective of gestational duration. The primary outcome of the study was the cumulative live birth rate, which was calculated based on the fresh ET and all subsequent FETs resulting from the initial stimulation.

All patients were interviewed by phone on their expected date of delivery to follow-up on details regarding the pregnancy outcomes and any complications. Obstetrical and neonatal complications were assessed for all live births following the ET cycles. Obstetrical complications included hypertensive disorders in pregnancy, gestational diabetes, placenta previa, preterm premature rupture of the membranes, postpartum hemorrhage, and Cesarean delivery. Neonatal complications included

twin pregnancy, gestational age, birth weight, and birth defects.

Statistical analyses

Quantitative data with a normal distribution were presented as means (standard deviations) and compared with Student's t-tests. Non-normally distributed data were presented as medians (range). Qualitative data were presented as numbers (percentages) and the between-group differences were analyzed with the Chi-square test. Logistic regression was employed to explore the factors influencing pregnancy outcomes. Potential confounders were adjusted based on univariate analyses, previous studies, and biological plausibility.

Furthermore, a propensity score-based patient-matching (PSM) approach was adopted to ensure comparability between individuals with and without specific cancer type. The propensity scores were estimated through a binary logistic regression analysis. In the case of cervical cancer survivors, patients were matched based on factors such as maternal age, BMI, and the number of embryos transferred. For endometrial cancer survivors, BMI and the number of embryos transferred were included in the matching analysis. All statistical analyses were conducted with R v 4.2.2. A two-sided P of less than 0.05 was considered statistically significant. In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

Results

Patient characteristics

A total of 136 patients with a history of gynecologic cancer and 241 healthy infertile controls were included in this study. The demographic characteristics of the two groups, including maternal age at oocyte retrieval, BMI, AFC, infertility type, and infertility duration, were found to be similar (Table 1). Among the 136 cancer survivors, endometrial cancer emerged as the predominant tumor type, comprising a significant proportion of cases at 50.70%. Cervical cancer constituted 34.60% of the cases, while ovarian cancer accounted for a modest 5.88%. Gestational trophoblastic disease was also observed in 5.88% of cases. The co-occurrence of ovarian and endometrial cancer represented smaller fractions at 2.94%.

IVF/ICSI outcomes

Analysis of the first-cycle ovarian stimulation outcome is presented in Table 2. The cancer group exhibited a significantly shorter duration of stimulation (9.92 ± 2.77 days vs. 10.80 ± 2.20 days, $P = 0.003$) in comparison to the control group. Additionally, the cancer group displayed a significantly lower level of estradiol (3494 ± 2401 pg/ml vs. 4559 ± 2311 pg/ml, $P < 0.001$) on the trigger day. There was a significant difference in both the fertilization method and fertilization rate between the

Table 1 Demographic characteristics of the cancer and control groups

	Cancer group ($n = 136$)	Control group ($n = 241$)	P value
Maternal age at oocyte retrieval (years), mean (SD)	33.0 (4.46)	32.2 (4.11)	0.091
BMI (kg/m^2), mean (SD)	23.1 (3.72)	22.6 (3.09)	0.091
Duration of infertility (years), mean (SD)	4.05 (2.77)	4.00 (3.18)	0.870
Infertility type, n (%)			0.062
Primary	86 (62.50%)	130 (53.90%)	
Secondary	50 (36.80%)	111 (46.10%)	
AFC, mean (SD)	13.7 (8.45)	15.2 (6.47)	0.090
Cancer type, n (%)			-
Cervical	47 (34.60%)	-	
Endometrial	69 (50.70%)	-	
Ovarian	8 (5.88%)	-	
Endometrial + Ovarian	4 (2.94%)	-	
Gestational trophoblastic disease	8 (5.88%)	-	
Treatment manner, n (%)			-
Surgery	43 (31.60%)	-	
Chemotherapy	75 (55.10%)	-	
Surgery + Chemotherapy	16 (11.80%)	-	
Time to IVF (months), median (range)	23 (0–267)	-	-

Abbreviations: AFC Antral follicle count, *BMI* Body mass index, *IVF* in vitro fertilization, *SD* Standard deviation

Table 2 Ovarian stimulation and assisted reproductive outcomes in the cancer and control groups

	Cancer group	Control group	*P* value
Ovarian stimulation outcomes			
Gonadotropin consumption (IU), mean (SD)	2363 (1177)	2155 (1165)	0.106
Days of stimulation, mean (SD)	9.92 (2.77)	10.8 (2.20)	**0.003**
Estradiol level at hCG day (pg/ml), mean (SD)	3494 (2401)	4559 (2311)	**< 0.001**
Fertilization method, n (%)			**0.004**
IVF	100 (73.50%)	164 (68.00%)	
ICSI	31 (22.80%)	77 (31.90%)	
No. of oocyte retrieved, mean (SD)	9.99 (7.07)	12.2 (6.04)	**0.002**
Fertilized rate (%), mean (SD)	81.9 (18.30)	77.4 (19.10)	**0.023**
Cleavage rate (%), mean (SD)	95.3 (14.70)	94.1 (16.80)	0.454
No. of day-3 embryos, mean (SD)	5.50 (4.17)	6.80 (4.18)	**0.004**
No. of blastocysts, mean (SD)	1.85 (2.89)	1.21 (2.64)	**0.034**
Pregnancy outcomes			
No. of embryo transfer, mean (SD)	1.50 (0.78)	1.53 (0.75)	0.719
No. of embryos transferred, mean (SD)	2.21 (1.45)	2.69 (1.40)	**0.006**
Ongoing pregnancy rate, n (%)	42 (38.90%)	118 (60.50%)	**< 0.001**
Cumulative live birth rate, n (%)	39 (36.10%)	118 (60.50%)	**< 0.001**
Obstetrical complications			
Hypertensive disorders in pregnancy, n (%)	7 (17.90%)	12 (10.20%)	0.255
Gestational diabetes, n (%)	3 (7.69%)	16 (13.60%)	0.408
Placenta previa, n (%)	1 (2.56%)	1 (0.85%)	0.436
Preterm premature rupture of the membranes, n (%)	0 (0.00%)	4 (3.39%)	0.573
Postpartum hemorrhage, n (%)	1 (2.56%)	5 (4.24%)	1.000
Cesarean delivery, n (%)	28 (71.80%)	97 (82.20%)	0.327
Neonatal outcomes			
Twin pregnancy	4 (10.30%)	29 (24.80%)	0.090
Gestational age (weeks), mean (SD)	37.4 (2.17)	37.8 (2.38)	0.387
Preterm birth, n (%)	31 (79.5%)	91 (78.4%)	1.000
Birth weight (g), mean (SD)	3006 (625)	3214 (656)	0.081
Birth defect, n (%)	2 (5.13%)	0 (0.00%)	0.061

Abbreviations: hCG Human chorionic gonadotropin, *ICSI* Intracytoplasmic sperm injection, *IVF* In vitro fertilization, *SD* Standard deviation

two groups, with a higher prevalence of IVF and a higher fertilization rate observed in the cancer group ($P<0.05$). Moreover, we observed a significantly lower number of retrieved oocytes, day-3 embryos, and blastocysts in the cancer group, as compared to the control group ($P<0.05$).

Assisted reproductive outcomes

Pregnancy outcomes are summarized in Table 2. Women with gynecologic cancer tended to have a lower number of embryos transferred compared to the control group ($P<0.05$). For a complete cycle, which encompassed the outcomes from fresh ET and all FETs following one ovarian stimulation, the ongoing pregnancy rate and cumulative live birth rate of the cancer group were significantly lower than those of the control group (38.90% vs. 60.50%, $P<0.001$; 36.10% vs. 60.50%, $P<0.001$, respectively). The cumulative live birth rate following every ET procedure is show in Fig. 1. Regarding obstetrical and neonatal outcomes (Table 2), no significant differences were observed ($P>0.05$).

Analysis of endometrial cancer survivors

A total of 44 patients with a history of endometrial cancer and 76 matched controls were subjected to analysis, as presented in Table 3. The endometrial cancer cohort had a higher prevalence of primary infertility compared to the control group ($P=0.001$), while other demographic characteristics were found to be comparable ($P>0.05$). The endometrial cancer group exhibited a significantly lower level of estradiol (3427 ± 1934 pg/ml vs. 5000 ± 2300 pg/ml, $P<0.001$) on the trigger day. A significantly higher number of blastocysts was observed in the endometrial cancer group, as compared to the control group ($P<0.001$). Despite similar numbers of ET

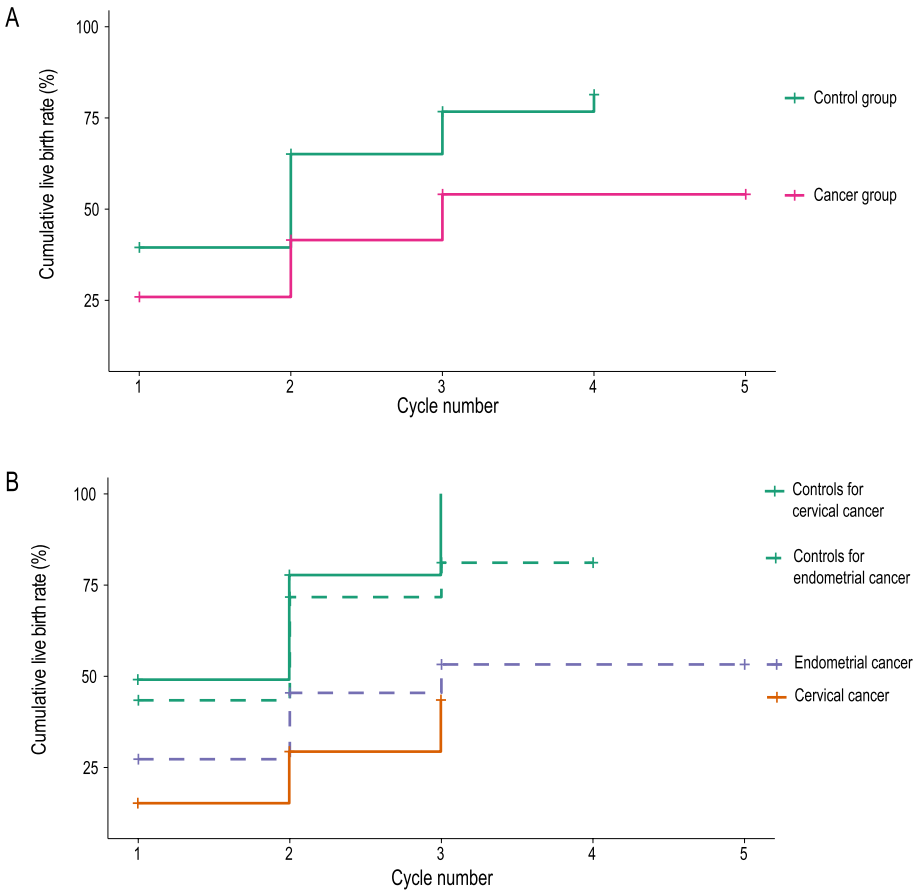

Fig. 1 Cumulative live birth rate in the cancer and control groups. **A** The cumulative live birth rate for the cancer and control groups are respectively represented with red and green lines. The difference between the two groups was significant ($P < 0.001$). **B** The cumulative live birth rate for women with endometrial cancer and matched control are respectively represented with purple and green dotted lines. The difference between the two groups was significant ($P = 0.014$). The cumulative live birth rate for women with cervical cancer and matched control are respectively represented with orange and green solid lines. The difference between the two groups was significant ($P < 0.001$)

and embryos transferred, the ongoing pregnancy rate and cumulative live birth rate of the endometrial cancer group were significantly lower than those of the control group (30.30% vs. 68.60%, $P = 0.021$; 38.60% vs. 64.50%, $P = 0.011$, respectively). Figure 1 shows the cumulative live birth rate following every ET procedure. In terms of obstetrical and neonatal outcomes (Table 3), no significant differences were observed ($P > 0.05$).

Analysis of cervical cancer survivors

In this study, a cohort of 33 patients with a history of cervical cancer and 51 matched controls were examined. As shown in Table 4, both groups were similar with respect to demographic characteristics and ovarian stimulation outcomes ($P > 0.05$). Despite comparable numbers of ET and embryos transferred, the cervical cancer group exhibited significantly lower ongoing pregnancy rates and cumulative live birth rates than the control group (30.30% vs. 68.60%, $P = 0.001$; 24.20% vs. 68.60%, $P < 0.001$, respectively). Figure 1 shows the cumulative live birth rate following every ET procedure. Notably, there were no significant differences in obstetrical and neonatal outcomes, as presented in Table 4 ($P > 0.05$).

Discussion

In this retrospective study, we observed a decreased occurrence of pregnancy and live birth among female patients with a history of gynecologic malignancy undergoing IVF/ICSI, when compared to their control counterparts. This disparity was further highlighted in specific cancer types, including endometrial and cervical cancers.

The findings of several cohort studies indicate that female cancer survivors have lower rates of pregnancy and live birth compared to the general population [11]. However, there is a scarcity of literature evaluating the reproductive outcomes of ART in gynecologic cancer patients. A meta-analysis reviewed ten studies regarding ovarian performance of 731 patients with breast cancer,

Table 3 Comparison between women with endometrial cancer and matched controls

	Endometrial cancer (*n* = 44)	Control group (*n* = 76)	*P* value
Maternal age at oocyte retrieval (years), mean (SD)	32.1 (4.27)	32.2 (3.65)	0.896
BMI (kg/m^2), mean (SD)	23.5 (3.12)	23.3 (2.73)	0.648
Duration of infertility (years), mean (SD)	3.86 (2.56)	4.39 (3.18)	0.325
Infertility type, n (%)			**0.001**
Primary	35 (79.50%)	39 (51.30%)	
Secondary	8 (18.20%)	37 (48.70%)	
AFC, mean (SD)	15.9 (7.90)	16.3 (5.86)	0.787
Histology			-
Grade 1	41 (95.18%)	-	
Grade 2	2 (4.55%)	-	
Treatment manner, n (%)			-
Hormone treatment	43 (97.70%)	-	
Time to IVF (months), median (range)	17.5 (0–94)	-	-
Ovarian stimulation outcomes			
Gonadotropin consumption (IU), mean (SD)	2361 (1196)	2338 (951)	0.914
Days of stimulation, mean (SD)	10.3 (3.35)	11.1 (2.13)	0.190
Estradiol level at hCG day (pg/ml), mean (SD)	3427 (1934)	5000 (2300)	**< 0.001**
Fertilization method, n (%)			0.621
IVF	34 (77.30%)	52 (68.40%)	
ICSI	10 (22.70%)	23 (30.30%)	
IVF + ICSI	0 (0.00%)	1 (1.32%)	
No. of oocyte retrieved, mean (SD)	12.3 (7.85)	12.8 (5.72)	0.734
Fertilized rate (%), mean (SD)	81.9 (17.30)	79.9 (16.00)	0.524
Cleavage rate (%), mean (SD)	95.2 (8.91)	96.9 (5.70)	0.257
No. of day-3 embryos, mean (SD)	6.77 (4.16)	7.53 (3.65)	0.320
No. of blastocysts, mean (SD)	2.80 (3.13)	1.25 (2.60)	**0.007**
Pregnancy outcomes			
No. of embryo transfer, mean (SD)	1.57 (0.90)	1.47 (0.72)	0.554
No. of embryos transferred, mean (SD)	2.39 (1.71)	2.63 (1.37)	0.421
Ongoing pregnancy rate, n (%)	18 (40.90%)	49 (64.50%)	**0.021**
Cumulative live birth rate, n (%)	17 (38.60%)	49 (64.50%)	**0.011**
Obstetrical complications			
Hypertensive disorders in pregnancy, n (%)	4 (23.50%)	6 (12.20%)	0.267
Gestational diabetes, n (%)	2 (11.80%)	6 (12.20%)	1.000
Placenta previa, n (%)	1 (5.88%)	1 (2.04%)	0.452
Preterm premature rupture of the membranes, n (%)	0 (0.00%)	1 (2.04%)	1.000
Postpartum hemorrhage, n (%)	1 (5.88%)	1 (2.04%)	0.452
Cesarean delivery, n (%)	14 (82.40%)	41 (83.70%)	1.000
Neonatal outcomes			
Twin pregnancy	2 (11.80%)	11 (22.40%)	0.488
Gestational age (weeks), mean (SD)	38.0 (1.22)	37.8 (2.63)	0.611
Preterm birth, n (%)	15 (88.2%)	40 (81.6%)	0.714
Birth weight (g), mean (SD)	3156 (399)	3323 (603)	0.209
Birth defect, n (%)	1 (5.88%)	0 (0.00%)	0.258

hematological malignancies, or other malignancies, showing that the number of retrieved oocytes among patients with cancer was not significantly different compared with age-matched healthy IVF patients [12]. A recent study of 27 cases of thyroid cancer, 26 cases of gynecologic cancer, and 5 cases of other cancers also

Table 4 Comparison between women with cervical cancer and matched controls

	Cervical cancer ($n=33$)	Control group ($n=51$)	*P* value
Maternal age at oocyte retrieval (years), mean (SD)	33.1 (3.59)	32.6 (4.09)	0.554
BMI (kg/m^2), mean (SD)	21.7 (3.21)	21.8 (2.79)	0.876
Duration of infertility (years), mean (SD)	3.64 (2.58)	3.57 (2.92)	0.912
Infertility type, n (%)			0.786
Primary	15 (45.50%)	26 (51.00%)	
Secondary	18 (54.50%)	25 (49.00%)	
AFC, mean (SD)	13.7 (7.74)	15.0 (5.80)	0.436
FIGO stage			-
0	12 (36.36%)	-	
IA1	1 (3.03%)	-	
IA2	2 (6.06%)	-	
IB1	14 (42.42%)	-	
Treatment manner, n (%)			-
Surgery	29 (87.90%)	-	
Surgery + Chemotherapy	4 (12.10%)	-	
Time to IVF (months), median (range)	25 (2–100)	-	-
Ovarian stimulation outcomes			
Gonadotropin consumption (IU), mean (SD)	2223 (755)	2424 (1114)	0.332
Days of stimulation, mean (SD)	10.1 (1.87)	10.7 (2.09)	0.137
Estradiol level at hCG day (pg/ml), mean (SD)	4334 (2953)	4851 (2039)	0.383
Fertilization method, n (%)			0.639
IVF	24 (72.70%)	39 (76.50%)	
ICSI	8 (24.20%)	11 (21.60%)	
IVF + ICSI	0 (0.00%)	1 (1.96%)	
No. of oocyte retrieved, mean (SD)	10.0 (5.10)	11.8 (6.17)	0.149
Fertilized rate (%), mean (SD)	81.5 (15.50)	81.9 (14.70)	0.894
Cleavage rate (%), mean (SD)	97.3 (6.48)	98.2 (5.06)	0.506
No. of day-3 embryos, mean (SD)	5.61 (3.94)	7.25 (4.40)	0.078
No. of blastocysts, mean (SD)	1.36 (2.74)	1.45 (2.90)	0.889
Pregnancy outcomes			
No. of embryo transfer, mean (SD)	1.52 (0.76)	1.33 (0.52)	0.231
No. of embryos transferred, mean (SD)	2.18 (1.29)	2.22 (0.83)	0.894
Ongoing pregnancy rate, n (%)	10 (30.30%)	35 (68.60%)	**0.001**
Cumulative live birth rate, n (%)	8 (24.20%)	35 (68.60%)	**< 0.001**
Obstetrical complications			
Hypertensive disorders in pregnancy, n (%)	0 (0.00%)	3 (8.57%)	1.000
Gestational diabetes, n (%)	0 (0.00%)	7 (20.00%)	0.315
Placenta previa, n (%)	0 (0.00%)	0 (0.00%)	-
Preterm premature rupture of the membranes, n (%)	0 (0.00%)	2 (5.71%)	1.000
Postpartum hemorrhage, n (%)	0 (0.00%)	2 (5.71%)	1.000
Cesarean delivery, n (%)	5 (62.50%)	29 (82.90%)	0.332
Neonatal outcomes			
Twin pregnancy	0 (0.00%)	12 (34.30%)	0.082
Gestational age (weeks), mean (SD)	36.8 (2.96)	37.3 (2.02)	0.639
Preterm birth, n (%)	6 (75.00%)	22 (62.9%)	0.692
Birth weight (g), mean (SD)	2807 (759)	3101 (675)	0.338
Birth defect, n (%)	1 (12.50%)	0 (0.00%)	0.186

Abbreviations: AFC Antral follicle count, *BMI* Body mass index, *hCG* Human chorionic gonadotropin, *ICSI* Intracytoplasmic sperm injection, *IVF* In vitro fertilization, *SD* Standard deviation

showed no impact of malignancy history on ovarian response or live birth outcomes [13]. However, the opposite conclusion was demonstrated in another meta-analysis, showing a significantly lower number of retrieved oocytes among cancer patients even before radiotherapy or chemotherapy [14]. In a study exploring the impact of cancer type on ovarian response to stimulation for fertility preservation, a lower ovarian response was observed in patients with gynecologic cancers [15]. It is important to interpret these results with caution due to variations in sample size, types of malignancies, and patient age across different studies. Our study found a poor ovarian stimulation outcome in the patients with a history of gynecologic cancer in terms of significantly lower numbers of retrieved oocytes, day-3 embryos, and blastocysts. We also observed that women with gynecologic cancer tended to have lower ongoing pregnancy rate and cumulative live birth rate, consistent with previous research [16].

Specific cancer types can influence reproductive outcomes [17]. Previous studies on fertility preservation in gynecologic cancer patients have reported live birth rates ranging from 28 to 66% in patients with endometrial cancer after conservative oral progestin therapy [18, 19]. However, the studies on pregnancy outcomes following ART use are limited, mostly consisting of case reports. Elizur et al. reported a live birth rate of 50% in 8 endometrial cancer patients referred to IVF treatment [20]. Kim et al. demonstrated a cumulative pregnancy rate (27.3%) after the IVF procedure in 22 patients with early-stage endometrial cancer [21]. Our study, which included a relatively large number of 44 endometrial cancer patients, reported a decreased cumulative live birth rate (38.60% vs. 64.50%) compared to age-matched women undergoing IVF/ICSI. All endometrial cancer patients had received daily oral progestin therapy (megestrol acetate 160 mg) and underwent hysteroscopy assessments every 3 months until achieving complete response, with fertility treatment initiated after two consecutive evaluations and biopsies [22]. In the case of endometrial cancer, women might experience impaired endometrial response to infertility treatments because of their primary endometrial cancerous conditions, the post-high-dose progestin therapy status, and repeated hysteroscopy examinations or endometrial curettages [23]. The hysteroscopy or curettage procedures can lead endometritis, intrauterine adhesions, and endometrial thinning, exerting a damaging impact on the endometrial function.

A review of cervical cancer patients who underwent fertility preservation surgeries reported a live birth rate of 39% and varying proportions of patients seeking ART treatment [24]. A study on early cervical lesions, including cervical intraepithelial neoplasia and early invasive cancer, revealed that cervical lesions were associated with lower ovarian reserve, reduced pregnancy rate, and decreased live birth rate [25]. The results of our study suggested that female patients with a history of early cervical cancer had similar ovarian stimulation outcomes but a decreased cumulative live birth rate (24.20% vs. 68.60%) compared with age-matched women undergoing IVF/ICSI. Fertility-sparing surgeries for early-stage cervical cancer patients included cervical conization, cervical excision, and radical trachelectomy [26]. Patients with intermediate-risk factors for recurrence post-surgery were advised to undergo comprehensive adjuvant therapy, typically comprising 3–6 cycles of the paclitaxel/cisplatin regimen [27]. In the case of cervical cancer, although early lesions are localized and treatments do not directly involve the ovaries, some research suggest that the deleterious impact on the reproductive outcome may be related to cervical treatments, human papilloma virus (HPV) infection, and the potential reproductive damaging effects of the tumor itself. The various types of fertility-saving procedures for cervical cancer, which differ in terms of surgical approach and extent of paracervical resection, can influence pregnancy outcomes [28, 29]. Additionally, cervical treatments can result in a shortened cervical length and abnormal cervical function, increasing the risk of miscarriage or preterm delivery [30]. Based on follow-up data among 149 cervical cancer patients attempting pregnancy post-surgery, 30 pregnancies occurred, resulting in 11 miscarriages and 19 successful deliveries, including 14 full-term births [31]. The efficacy of cervical cerclage was highlighted, with 12 out of 20 cases leading to full-term births compared to 3 out of 5 cases without cerclage experiencing second-trimester miscarriage or preterm birth [31]. As cervical cancer has clear association with HPV positivity, the impact of the HPV infection on reproductive function should not be ignored. Studies have reported a significant decreased pregnancy rate in IVF cycles in women with cervical HPV infection [32]. Furthermore, the diagnosis of HPV infection is associated with a marked increase in the risk of pregnancy loss [33]. However, more research is needed to reveal the underlying mechanisms and develop strategies to optimize fertility preservation in gynecologic cancer patients.

The obstetrical outcomes of cancer patients who achieve pregnancy after ART have received continuous attention, but available data are limited. Previous studies have shown that women with a history of cancer are at a greater risk of adverse pregnancy outcomes, such as miscarriage, preterm birth, and a rare occurrence of cardiomyopathy [34]. However, our study found no association between a history of gynecologic

malignancy and adverse pregnancy outcomes or pregnancy-related complications. Another study reported higher rates of preterm birth and low birth weight among cancer survivors, although the difference was not statistically significant [13]. Nevertheless, due to the limited statistical power of most studies, larger-scale studies are needed to investigate potential complications associated with an oncologic history. Still, long-term survival outcomes after ART among patients with a history of gynecologic cancer remain poorly understood, emphasizing the importance of ongoing obstetric surveillance and close follow-up for these patients.

The strengths of this study included its detailed information on reproductive outcomes and long follow-up time. However, some limitations must be recognized. Similar to other studies, our study was limited by the retrospective design in nature and small sample size of its patient cohort. Therefore, we were unable to consider other types of cancers such as ovarian cancer. In addition, the effect of cancer treatments was not evaluated specifically in the current study due to the limited number of patients and possible inconsistency in surgical operations.

Conclusions

Our findings indicate that a history of gynecologic cancer among infertile women pose a significantly negative impact on the IVF/ICSI outcomes, with a poor ovarian response and a lower live birth rate. Our findings underscore the challenges and complexities of achieving successful ART outcomes in patients with a history of gynecologic cancer.

This study provides data support for further exploration of the effects of endometrial cancer, cervical cancer, and other gynecologic cancers on fertility, advocating that oncologists and reproductive physicians pay more attention to these patients. Comprehensive ovarian function assessment, detailed counseling, individualized fertility guidance, and close follow-up after ART therapy are recommended for patients with gynecologic malignancy history. Further research of the long-term reproductive and oncological outcomes of cancer survivors should be conducted.

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Authors' contributions
J. L. and H. L. conceived and designed the protocols. T. Y., L. L., X. S., and H. L. collected data. J. L. and H. L. conducted the analysis and interpreted the results. J. L. drafted the original version of the manuscript. H. L. made critical revisions of the manuscript. All authors contributed to reviewing and editing multiple versions of the manuscript. X. S. and H. L. supervised the study.

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Availability of data and materials
All data sharing and collaboration requests should be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of Shanghai Ji Ai Genetics and IVF Institute, Obstetrics and Gynecology Hospital of Fudan University (JIAI E2023-10).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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