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FERTILITY PRESERVATION

Oncologic oocyte cryopreservation: national comparison of fertility preservation between women with and without cancer

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Abstract

Purpose The majority of data regarding oocyte cryopreservation (OC) outcomes focuses on healthy women. We compare trends, cycle characteristics, and outcomes between women freezing oocytes for fertility preservation due to cancer versus elective and other medical or fertility-related diagnoses.

Methods Retrospective cohort using national surveillance data includes all autologous OC cycles between 2012 and 2016. Cycles were divided into 4 distinct groups: cancer, elective, infertility, and medically indicated. We calculated trends and compared cycle and outcome characteristics between the 4 groups. We used multivariable log-binomial models to estimate associations between indication and gonadotropin dose, hyperstimulation, and cancelation and used Poisson regression models to estimate associations between indication and oocyte yield and maturity.

Results The study included 29,631 autologous OC cycles. Annual total (2925 to 8828) and cancer-related (177 to 504) cycles increased over the study period; the proportions remained constant. Compared to elective, cancer-related cycles were more likely to be performed among women < 35 years old, with higher BMI, living in the South, using an antagonist protocol. Compared to elective OC cycles, gonadotropin dose (aRR 0.89, 95%CI 0.80–0.99), cancelation (aRR 0.90, 95%CI 0.70–1.14), and hyperstimulation (aRR 1.46, 95%CI 0.77–2.29) were not different for cancer-related cycles. Oocyte yield and percent maturity were comparable in both groups.

Conclusion The number of OC cycles among women with cancer has increased; however, the percentage OC cycles for cancer have remained stable. While patient demographic characteristics were different among those undergoing OC for cancer indication, cycle outcomes were comparable to elective OC. The outcomes of the subsequent oocyte thaw, fertilization, and embryo transfer cycles remain unknown.

Keywords Cancer · Fertility preservation · Oocyte (egg) freezing · Oocyte maturity · Outcomes

Introduction

With increasing awareness of the importance of future fertility counseling at the time of cancer diagnosis and the availability of oocyte cryopreservation (OC) as a fertility preservation option, more reproductive-aged women diagnosed with cancer have the opportunity to consider freezing oocytes [1, 2], and the total number of oocyte cryopreservation cycles in the USA has increased annually [3].

Unlike embryo freezing, OC allows women to preserve fertility independent of relationship status and broadens the pool of individuals who may be candidates for fertility preservation. As OC is not covered by insurance in most states and may require a delay in cancer treatment, women considering oocyte freezing must actively weigh the risks and benefits of moving forward with preservation. Currently, the majority of

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data regarding stimulation outcomes for oocyte cryopreservation focuses on women electively freezing eggs for nonmedical indications, termed as planned fertility delay [4, 5]. However, there is limited information on whether women with active cancer respond differently to controlled ovarian stimulation compared to their healthy counterparts.

Studies published to date that aim to better characterize oocyte freezing among cancer patients are limited by relatively small sample sizes and heterogeneous comparison groups [5]. A 2018 meta-analysis that included 10 studies (713 women with cancer who underwent 722 cycles) revealed no impact of cancer diagnosis on oocyte yield between women diagnosed with cancer and controls [6]. However, the majority of the comparison groups in the included studies were comprised of women undergoing in vitro fertilization (IVF) for tubal factor or male factor infertility rather than women electively freezing eggs [6]. A recent small single-center study compared outcomes between newly diagnosed breast cancer patients and elective OC cycles and found no differences in oocyte yield [7]. In contrast, another recent small retrospective cohort study comparing outcomes between oocyte cryopreservation for cancer and IVF for male factor infertility found cancer-associated cycles to be associated with higher medication doses and increased likelihood of cancelation [8]. Data regarding outcomes following oocyte thaw and fertilization are scant; a small single-center study from 2016 revealed comparable live birth rates following frozen embryo transfers using cryopreserved oocytes comparing those who cryopreserved for cancer versus those who cryopreserved electively [9].

In order to better assess this question, we used national surveillance data to report trends in cancer-related and elective OC from 2012, when national surveillance of oocyte cryopreservation cycle collection began, through 2016. We compare cycle and outcome characteristics between women freezing oocytes due to a recent cancer diagnosis and those freezing eggs for elective reasons. We also compare cancer-related OC cycle outcomes to those performed for other medical or fertility-related diagnoses.

Materials and methods

The data used for this study were derived from the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System (SART CORS), a national surveillance system that has been collecting assisted reproductive technology (ART) patient and cycle characteristics and outcomes data since 1985 [10]. Reporting of all ART procedures in the USA to the Centers for Disease Control and Prevention has been federally mandated since 1992 [11]. Currently, SART CORS data encompasses 80% of all fertility clinics in the USA, and approximately 95% of all ART cycles performed in the USA. Data are validated annually with select clinics undergoing in-person on-site chart review. The primary purpose of SART CORS is pregnancy outcome surveillance. As a result, the most recent complete cycles are from 2016.

We included autologous oocyte cryopreservation cycles (ovarian stimulation, oocyte retrieval, and oocyte cryopreservation only) from SART CORS that occurred between 2012 and 2016. Oocyte thaw, fertilization, and subsequent embryo transfers were not included. Donor oocyte cryopreservation cycles and embryo cryopreservation cycles were excluded. Included cycles were divided into 4 distinct groups by indication: (1) cancer only, (2) elective only (planned fertility delay), (3) infertility-indicated, and (4) medically indicated. If more than one indication was reported, the cycle was placed in the most heterogeneous group; both the cancer only and elective groups are as clean as possible in that these patients did not have a secondary diagnosis. Cancer only cycles specifically indicated a cancer diagnosis or "banking prior to gonadotoxic treatment" as the reason for cryopreservation. Elective only cycles were specifically indicated as having been performed for elective, social family planning reasons. Infertility-related cycles are those in which an infertility diagnosis, such as ovulatory disorder or tubal factor, was assigned. The medically indicated group included medical reasons for preserving fertility such as Fragile X carrier status, history of prior oophorectomy, and BRCA carrier status (see Table 1). Multiple imputations were used to characterize cycles with a missing indication for fertility preservation (32.3%), race/ethnicity (47.2%), and body mass index (22.0%). Five imputed datasets were used, utilizing the fully conditional specification method. The distribution of those missing an indication for OC is shown in Supplemental Table 1. Variables for age at cryopreservation, body mass index, stimulation protocol, geographic region of residence, and race/ethnicity were included in the imputation procedure. The robustness of the multiple imputation approach has been previously validated [12, 13].

Trends in absolute number and proportion of cycles within each group were analyzed over time using linear regression. Chi-squared analyses were used to compare cycle and outcome characteristics between the 4 groups. Subsequently, multivariable log-binomial models were used to estimate pooled unadjusted and adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) for associations between indication for cryopreservation and ovarian hyperstimulation syndrome, gonadotropin dose, and cycle cancelation. Poisson regression models were used to estimate oocyte yield among non-canceled cycles. Models controlled for age at cryopreservation, body mass index (BMI), stimulation protocol, geographic region of residence, and race/ethnicity. Variables were selected a priori based on clinical evidence that each could impact outcomes. Elective cryopreservation cycles were the referent group as these cycles included women without known infertility or disease. p values < 0.05 where considered statistically significant. SAS 9.4 software was used for all analyses.

This study was reviewed and deemed exempt by the Emory University Institutional Research Board.

Results

Between 2012 and 2016, 29,631 autologous oocyte cryopreservation cycles were reported to SART CORS. The total number of OC cycles performed for any indication increased from 2925 to 8828 cycles from 2012 to 2016 (Fig. 1). The number of cancer-related cycles increased from 177 to 504 cycles and comprised a similar proportion (range 5.6–6.1% annually) of all OC cycles performed in the USA over the study period (Fig. 2). Elective/Social family planning cycles increased from 1038 to 2246 but comprised a significantly smaller proportion of all OC cycles performed, decreasing from 35.5 to 25.4% ($p = 0.03$). Medically indicated cycles increased from 539 to 1242 in the same period. There was a nonsignificant decrease in the proportion of cycles performed for a medical indication from 18.4% to 14.1% of total cycles ($p = 0.07$). Combined non-cancer indications (groups 2–4) increased nonsignificantly from 2209 (75.5%) to 7082 (80.2%) cycles ($p = 0.09$).

Compared to purely elective OC cycles, cycles completed for a cancer diagnosis were more likely to be performed among women under 35 years old, with a higher BMI, living in the South, and were more likely to use an antagonist protocol (Table 2, Supplemental Table 1). Compared to all other groups, OC cycles performed for medical indications were more likely to be in individuals > 38 years, in individuals who reside in the northeast, to use a non-gonadotropin protocol, to be canceled, and to retrieve 5 or fewer eggs. Cycles performed in individuals with an infertility diagnosis were generally similar to the elective family planning group but did tend to yield fewer oocytes.

Compared to elective OC, rates of cycle cancelation (aRR 0.90, 95% CI 0.70–1.14) and hyperstimulation (aRR 1.46, 95% CI 0.77–2.29) were not different for cancer-related cycles (Table 3). Gonadotropin dose was marginally lower among cancer cycles than elective OC cycles (aRR 0.89, CI 0.80–0.99). Compared to elective OC, there was no difference in oocyte yield for cycles completed for a cancer diagnosis (Beta coefficient 0.02, 95% CI 0.00–0.04). The estimated adjusted oocyte yield, approximately 16 (95% CI 14.5–16.5), and percent maturity, approximately 80% (95% CI 79.3–82.7), were comparable in both groups. Oocyte cryopreservation performed for medical indications was associated with higher gonadotropin dose (aRR 1.22, 95% CI 1.12–1.33), higher likelihood of cancelation (aRR 1.68, 95% CI 1.46–1.92), and lower oocyte yield (Beta coefficient − 0.30, 95% CI − 0.33, − 0.26) compared to elective OC.

Discussion

The number of oocyte cryopreservation cycles among women with a cancer diagnosis has increased over the past 5 years; however, the percentage OC cycles for cancer has remained stable as the total number of oocyte cryopreservation cycles increased over the study period. While patient demographic

Table 1 Group categorization

Group	Name	Description
1	Cancer	Cancer group*
2	Elective/family planning preservation	Elective, planned fertility delay preservation group
3	Infertility	Infertility diagnosis listed including endometriosis, ovulatory dysfunction, polycystic ovary syndrome, tubal disease or occlusion, recurrent pregnancy loss, functional hypothalamic amenorrhea, **male factor infertility**, **unexplained infertility**, need for preimplantation genetic testing, premature ovarian failure, secondary amenorrhea, uterine septum, or other malformation
4	Medical	Medical indication listed, including **diminished ovarian reserve**, Turner syndrome, Fragile X, prior oophorectomy, BRCA, diabetes, hyperprolactinemia, lupus, same sex couple, gender dysphoria, seizure disorder, history of organ transplantation, Mayer-Rokitansky-Küster-Hauser syndrome, HIV discordance, migraine, IgA nephropathy, nephrotic kidney disease, thalassemia, cervical stenosis, hypothyroidism, balanced translocation or other genetic mutation, aplastic anemia, heart disease, autoimmune hepatitis, Addison's disease, Fanconi's anemia, multiple sclerosis, psoriatic arthritis, unspecified immunological disease, antiphospholipid syndrome without RPL or other thrombophilia, history of hysterectomy, bipolar disorder, Wegener's granulomatosis, Wilson's disease, stiff person syndrome, chronic fatigue syndrome, sickle cell disease, history of fetal anomaly, and **unspecified medical egg freeze**

•Top 2 most common indications in **bold**

*The most common cancer diagnoses were (1) unspecified cancer – "pretreatment before chemotherapy," "cancer," "oncofertility" ($n \sim 800$). (2) Breast cancer (~550). (3) Lymphoma/leukemia (~ 250)

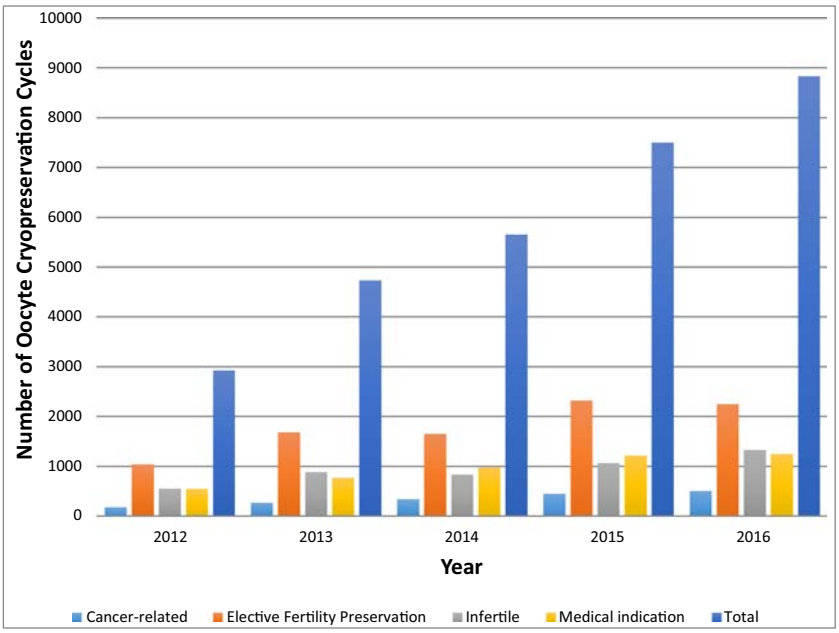

Fig. 1 National trends in absolute number of oocyte cryopreservation by indication, 2012–2016

characteristics were different among those freezing eggs for fertility preservation due to cancer, the cycle outcomes were comparable to elective cryopreservation cycles after controlling for potential confounding.

Our findings, specifically related to oocyte yield and percentage maturity, are reassuring to women freezing eggs for fertility preservation due to an active cancer diagnosis requiring cancer treatment and delay of conception. The findings

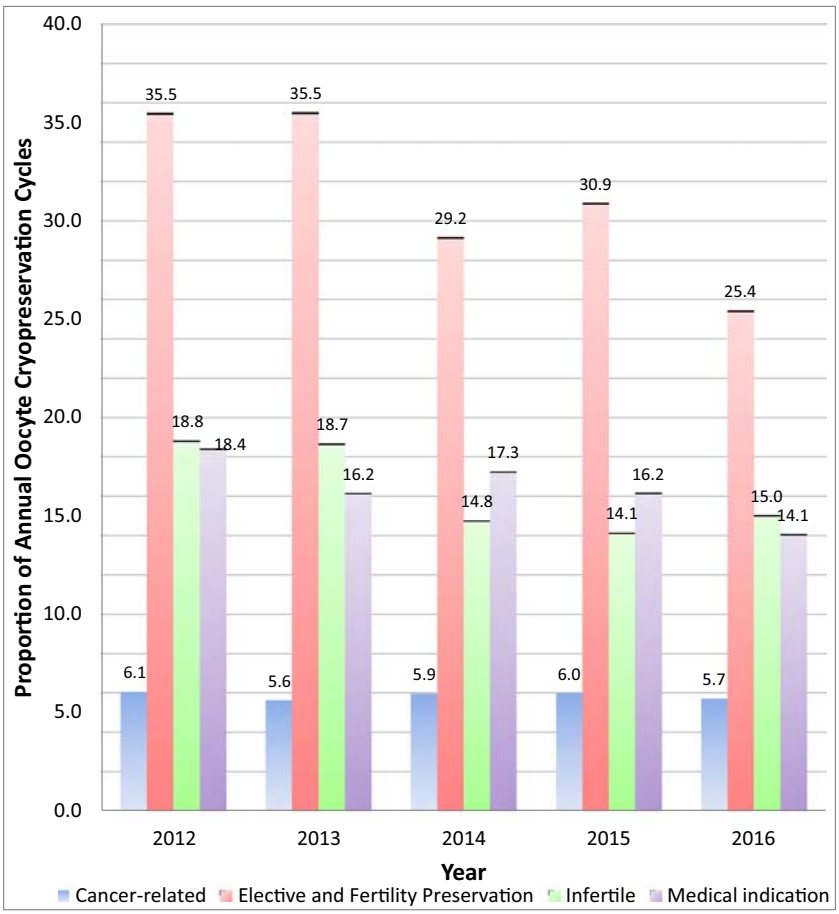

Fig. 2 National trends in proportion of oocyte cryopreservation by indication, 2012–2016

Table 2 Oocyte cryopreservation patient and cycle characteristics: cancer-related versus elective versus infertile versus medically indicated cycles, 2012–2016 (imputed data)[a]

	Cancer (group 1)		Elective and social family planning (group 2)		Other infertile (group 3)		Medical indication (group 4)		
	N 2715	% 9.16	*N* 13,626	% 45.99	*N* 6863	% 23.16	*N* 6427	% 21.69	*p* value[b]
Female Characteristics									
Age (years)									< 0.0001
< 35	1722	63.43	4086	29.99	1794	26.14	896	13.94	
35–37	591	21.78	4898	35.95	2160	31.46	1494	23.24	
38–40	310	11.42	3609	26.49	19,145	27.90	1997	31.07	
41–42	61	2.25	753	5.52	542	7.89	935	14.55	
>42	30	1.12	280	2.05	453	6.59	1105	17.19	
Body Mass Index (kg/m^2)									0.020
<18.5	144	5.31	639	4.69	313	4.56	267	4.15	
18.5–24.9	1637	60.30	9429	69.20	4466	65.07	4606	71.66	
25–29.9	578	21.28	2441	17.91	1386	20.20	1086	16.89	
> 30.0	356	13.11	1117	8.20	698	10.17	469	7.29	
Geographic Location (defined by US Census data)									< 0.0001
Northeast	828	30.48	5199	38.16	2571	37.47	3253	50.62	
South	836	30.81	3008	22.08	1501	21.86	1100	17.11	
West	683	25.16	4198	30.81	2330	33.96	1603	24.95	
Midwest	368	13.55	1220	8.96	461	6.71	471	7.32	
Race/ethnicity									0.0074
Non-Hispanic White	2008	73.97	9450	69.35	4353	63.43	4077	63.44	
Non-Hispanic Black	191	7.03	819	6.01	575	8.38	457	7.11	
Asian/Pacific Islander	329	12.12	2475	18.16	1460	21.28	1453	22.61	
Hispanic/Latino	139	5.13	560	4.11	328	4.79	296	4.61	
Other [c]	47	1.74	322	2.36	146	2.13	143	2.23	
Cycle Characteristics									
Stimulation Protocol									< 0.0001
Antagonist	2235	82.31	10,273	75.39	4557	66.40	3307	51.46	
Standard agonist	123	4.55	1014	7.44	533	7.77	319	4.96	
Agonist flare	68	2.51	1011	7.42	489	7.13	611	9.51	
Mixed/other [d]	289	10.63	1329	9.75	1283	18.70	2190	34.07	
Gonadotropin dose (International units)									< 0.0001
None	91	3.36	702	5.15	1100	16.03	1305	20.31	
1–2000	565	20.82	2343	17.19	1137	16.57	1147	17.85	
2001–4000	1354	49.85	6230	45.72	2572	37.48	1814	28.23	
4001–6000	582	21.45	3459	25.39	1563	22.78	1523	23.70	
> 6000	123	4.52	893	6.55	490	7.15	637	9.92	
Cancelation									< 0.0001
Yes	127	4.66	759	5.57	470	6.84	624	9.71	
No	2588	95.34	12,867	94.43	6393	93.16	5803	90.29	
Oocyte yield (*n*)[e]									< 0.0001
≤ 5	272	10.50	1801	14.00	1339	20.94	2569	44.28	
6–10	530	20.47	3243	25.20	1679	26.26	1579	27.22	
11–20	991	38.29	4959	38.54	2198	34.37	1204	20.74	
21–30	556	21.48	1995	15.51	808	12.64	337	5.80	
> 30	240	9.26	869	6.76	370	5.79	114	1.97	
Hyperstimulation									0.076

Table 2 (continued)

	Cancer (group 1)		Elective and social family planning (group 2)		Other infertile (group 3)		Medical indication (group 4)		
	N 2715	% 9.16	*N* 13,626	% 45.99	*N* 6863	% 23.16	*N* 6427	% 21.69	*p* value[b]
Yes	17	0.63	42	0.31	15	0.22	10	0.15	
No	2698	99.37	13,584	99.69	6848	99.78	6417	99.85	

BMI body mass index, *FSH* follicle stimulating hormone

[a] All N's and percentages are calculated as an average among the 5 imputed datasets. All N's are rounded to the nearest whole number

[b] All *p* values are calculated using combined chi-squared test from the five imputed datasets

[c] Other Race includes American Indian, Alaskan Native, or mixed race including two or more selected races

[d] Mixed/other stimulation protocol includes Clomid ± FSH, aromatase inhibitors ± FSH, unstimulated cycle, mixed cycle incorporating more than one protocol

[e] Only includes cycles that were not canceled

affirm those of prior smaller studies that found no difference in oocyte yield between individuals with and without cancer [7], even among women with BRCA gene mutations [14]. Admittedly, the study would be strengthened by inclusion of outcome data regarding subsequent thaw, fertilization, and live birth. Such a study will be more feasible in the future when more time has elapsed from time of oocyte cryopreservation. Women treated for cancer in 2012 that required chemotherapy, surgery, and possible continued endocrine therapy are likely just now approaching a time when conception may be feasible. A portion of these women may conceive on their own without using previously frozen oocytes. A small single-center 2016 study did suggest comparable live birth rate between women with and without cancer at time of OC [9]. A future larger study on the topic could affirm the generalizability and accuracy of the findings.

Previous studies have hypothesized that women with cancer will have a poor response to ovarian stimulation due to the inflammatory burden of their disease [15]; the results of our study suggest that the response to medication appears similar to women without cancer. In fact, the total gonadotropin dose among cancer patients was lower than that in the elective group, perhaps as a result of the overall younger age or potentially out of a heightened effort to avoid ovarian hyperstimulation. Our results may even underestimate the similarity between cancer and non-cancer outcomes as the cancer group could, in theory, include women with previous history of cancer treated with gonadotoxic treatment that lessened their potential response.

The increased prevalence of obesity in the cancer group may reflect the increased risk of cancer among overweight women and may also reflect clinic policies to allow for the use of ART independent of BMI in women with cancer. Many clinics have BMI cutoffs that may be waived for cancer patients given the urgency and finality of the opportunity to freeze oocytes in a narrow timeframe. In all groups, the majority of patients undergoing treatment were non-Hispanic Whites; an opportunity remains to expand access to all fertility treatment, particularly fertility preservation for cancer; while 13% of the US population self-identifies as non-Hispanic Black, only 7% of the study population identified as such [16, 17].

Women who underwent oocyte cryopreservation due to medical illness were more likely to require higher medication doses and to be canceled. Several of the medically indicated cryopreservation diagnoses, such as Fragile X carrier status and Turner Syndrome, are associated with diminished ovarian reserve and may have contributed to the findings. The group is, however, heterogeneous and also contains individuals with medical diagnoses that are not associated with diminished ovarian reserve.

The study is strengthened by its generalizability; it is larger in number and geographic breadth than previous studies aiming to compare outcomes between cancer and non-cancer oocyte cryopreservation. The ability to correct for potential confounders including age, body mass index, stimulation protocol, geographic region, gonadotropin dose, and race/ethnicity also strengthens the study. The use of multiple imputation to account for missing data allowed for analysis of the complete set of autologous oocyte cryopreservation cycles; multiple imputation has been shown to be a valid approach even when the proportion of missing data is large [12, 13]. The results are limited by the retrospective nature of the analysis, the reliance on the accuracy of individual clinic data entry, the inability to account for clustering by clinic, the evolution of indication specificity over time, the inability to control for anti-mullerian hormone level (though diagnosis of diminished ovarian reserve was included in the model), the lack of subsequent birth outcomes, and the potential for residual confounding, most likely due to age given the younger age of the women in the cancer group. When interpreting trends in oocyte cryopreservation indication over time, it is important to

Table 3 Medication dose, cancelation, oocyte yield, and cancelation between cancer-related oocyte cryopreservation cycles and elective, infertility-related, and medically indicated oocyte cryopreservation cycles, 2012–2016

	Unadjusted				Adjusted			
	Cancer	Elective fertility preservation	Other infertile	Medical	Cancer	Elective fertility preservation	Other infertile	Medical
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Gonadotropin dose > 4000 IU[a,b]	0.75 (0.67, 0.83)	Referent	0.91 (0.85, 0.98)	1.08 (1.00, 1.16)	0.89 (0.80, 0.99)	Referent	0.97 (0.90, 1.1)	1.22 (1.12, 1.33)
Cycle cancellation[c]	0.83 (0.66, 1.04)	Referent	1.25 (1.10, 1.41)	1.82 (1.61, 2.06)	0.90 (0.70, 1.14)	Referent	1.19 (1.05, 1.35)	1.68 (1.46, 1.92)
Hyperstimulation[c]	2.06 (1.11, 3.81)	Referent	0.71 (0.32, 1.56)	0.48 (0.20, 1.13)	1.46 (0.77, 2.79)	Referent	0.79 (0.35, 1.78)	0.71 (0.29, 1.74)
Total oocytes retrieved			Predicted[d]				Predicted[d]	
Poisson beta coefficient for number of eggs retrieved	0.13 (0.11, 0.14)	Referent	− 0.11 (− 0.13, − 0.09)	− 0.55 (− 0.58, − 0.52)	0.02 (0.00, 0.04)	Referent	− 0.04 (− 0.07, − 0.01)	− 0.30 (− 0.33, − 0.26)
Percentage mature oocytes[e]	79.8 (79.3, 80.3)	80.2 (79.6, 80.9)	80.9 (80.4, 81.5)	80.2 (79.7, 80.7)	81.1 (80.1, 82.0)	82.6 (80.6, 82.7)	82.2 (81.2, 83.2)	81.7 (80.8, 82.6)

IU International Units, *RR* risk ratio, *aRR* adjusted risk ratio, *95% CI* 95% confidence interval

[a] Adjusted for age, body mass index, stimulation protocol, geographic region, and race

[b] Compared to those who received 0–4000 IU gonadotropins

[c] Adjusted for age, body mass index, stimulation protocol, geographic region, gonadotropin dose, and race

[d] Poisson model for predicted number of oocytes retrieved excludes cycles that were canceled

[e] Analysis for percent mature does not include those who had cycle canceled or those who had 0 eggs retrieved

consider that those cycles missing an indication were not included in the trends analysis.

In our study, women freezing oocytes for oncologic reasons had similar oocyte yield and maturity as compared to those of women freezing oocytes electively. The outcomes of the subsequent egg thaw, fertilization, and transfer cycles remain unknown and warrant future study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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