Original Report

Oocyte Cryopreservation in Adolescent Women

Heather S. Hipp MD [1,*], Lisa M. Shandley MD, MSCR [1], D. Austin Schirmer MD [1], Laurie McKenzie MD [2], Jennifer F. Kawwass MD [1]

[1] Emory Reproductive Center, Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Atlanta, Georgia
[2] Division of Reproductive Endocrinology and Infertility, Baylor College of Medicine, Houston, Texas

A B S T R A C T

Study Objective: To describe oocyte cryopreservation (OC) cycles in adolescent women (<20 years of age) performed at Society for Assisted Reproductive Technology member clinics in the United States from 2012 to 2016.
Design: Retrospective cohort study.
Setting: Not applicable.
Participants: OC cycles from the Technology Clinic Outcome Reporting System database.
Interventions: OC cycles from 2012 to 2016 among adolescent women were compared with cycles in older women.
Main Outcome Measure: Number of oocytes retrieved.
Results: From 2012 to 2016, OC cycles in women younger than 20 years of age accounted for 1.5% of OC cycles in all women. The absolute number has increased over the 5-year period, parallel to the increase in older women. OC cycles in adolescent women were most likely performed for fertility preservation for impending gonadotoxic treatment. The women were most likely to be non-Hispanic white and reside in the Northeast. Ten percent of the cycles were cancelled, most commonly for low response, compared with 6.6% of cycles in other age groups. There was no difference in mean oocytes retrieved in women younger than 20 years (n = 18.0) compared with women 20-29 years (n = 18.4). Complications, including ovarian hyperstimulation syndrome, were very rare.
Conclusion: OC cycles in adolescent women are similar with regard to stimulation characteristics and oocyte yield to those in women of other age groups. There is, however, a higher likelihood of cancellation because of poor response.
Key Words: Adolescent, Egg freezing, Fertility preservation, Oocyte cryopreservation

Introduction

Fertility preservation in adolescent women (defined as younger than 20 years of age) is very rare and typically performed secondary to impending or previous gonadotoxic therapy for oncologic or nononcologic conditions, such as a stem cell transplantation, planned oophorectomy, or impending gonadal failure. In 2012, the American Society for Reproductive Medicine removed the experimental designation previously assigned to mature oocyte cryopreservation (OC).[1] This change allowed many women without male partners a viable method of fertility preservation, which resulted in a marked increase in number of OC cycles in subsequent years.[2] Fertility preservation is a key survivorship issue for women with a cancer diagnosis, and offering gamete or embryo cryopreservation before gonadotoxic treatment is currently standard of care.[3] Most published outcome data, however, is in older reproductive-aged women.[4–6] Adolescent women are much more likely than older women to not have started or completed childbearing. If confronted with a cancer diagnosis, they are therefore more likely to have a need for OC technology. Other fertility preservation modalities are still either considered experimental, as is the case for ovarian tissue cryopreservation[3,7] or have conflicting data regarding efficacy (eg, Gonadotropin-releasing hormone [GnRH] agonist suppression).[8,9]

Questions remain regarding outcome data for these OC cycles. Although the women are postmenarchal, it is unknown whether conventional ovarian stimulation is as effective in much younger women compared with older reproductive-aged women. Specifically, knowledge gaps exist as to whether younger women respond similarly to gonadotropin exposure or have similar cycle outcomes, such as mature oocyte yield. Published data in adolescent women are currently limited to case series[10–13]; one of these reports (n = 8 women) suggested that younger women might require higher gonadotropin doses compared with women of other age groups.[10] The authors hypothesized that adolescent women have differences in oocyte maturity and development because of their proximity to puberty that might alter their gonadotropin response.

We used a national surveillance system to characterize OC cycles and outcomes in women younger than 20 years of age from 2012 to 2016. Our primary outcome was number of oocytes retrieved. We also describe national trends of women who underwent these cycles and cycle characteristics, including gonadotropin dosing, stimulation protocols, and complications.

The authors indicate no conflicts of interest.

* *Address correspondence to:* Heather S. Hipp, MD, Emory Reproductive Center, Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, 550 Peachtree St, Suite 1800, Atlanta, GA 30308; Phone (404) 778-3401; fax: 404-686-4956
E-mail address: hhipp@emory.edu (H.S. Hipp).

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Materials and Methods

We queried the Society for Assisted Reproductive Technology (SART) Clinic Outcome Reporting System (SART CORS) database for this retrospective cohort study. Data are entered annually by member assisted reproductive technology clinics in the United States. Data were collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The data in the SART CORS are validated annually with some clinics having on-site visits for chart review on the basis of an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. Ten of 11 data fields selected for validation were found to have discrepancy rates of 5% or less.[14] The primary use of the SART CORS database is to track pregnancy outcomes from assisted reproductive technology, and thus has a necessary 2-year delay in data release. The most recent cycles included are from 2016.

This study was reviewed and deemed exempt by the Emory University institutional research board. After review by a research committee, SART CORS released a deidentified file containing cycle information and research identification numbers for each woman who underwent a treatment cycle between January 1, 2012 and December 31, 2016. We included OC cycles. We did not analyze future thaw outcomes or embryo transfer cycles, oocyte donation cycles (including for banks), and research cycles. Data were analyzed per cycle.

We assessed trends in the number of OC cycles in women younger than 20 years and as a percentage of OC cycles in all women. We abstracted demographic information, including age, body mass index (BMI), geographic location, race/ethnicity, and ovarian reserve data (anti-Müllerian hormone [AMH]). We also collected cycle data, including stimulation protocol, gonadotropin dose, cancellation data, reason for OC, and complications. We reported these demographic and cycle data in women younger than 20 years and in older women (20-29, 30-34, and 35 years and older). Last, we compared number of oocytes retrieved in women younger than 20 years with that in women in older age groups. Number of mature oocytes (cryopreserved) was only available as a field entry between 2014 and 2016. A subgroup analysis to assess percentage of mature oocytes was performed for these years among women younger than 20 years old compared with their older counterparts.

Linear regression was performed to assess whether a relationship existed between the number of annual OC cycles and the percentage of OC cycles in each age group over the years 2012-2016 and to test whether a linear relationship existed with a non-zero slope. The distributions of each demographic characteristic and OC cycle characteristic were compared between the age groups (<20 years, 20-29 years, 30-34 years, and 35 years or older) using χ^2 tests or Fisher exact test when cell sizes were less than 5. The mean number of oocytes retrieved and oocytes cryopreserved were compared among the age groups using analysis of variance. Data were then transposed and linked on the basis of patient identification number to calculate the average number of cycles per patient in each age group. These group means were compared using analysis of variance.

Results

We first described national trends in number of OC cycles on an annual basis from 2012 to 2016. There was an increase in annual number of cycles in women younger than 20 years, from 48 cycles in 2012 to 131 in 2016. Over the same 5-year period, there was an increase in OC cycles in women of all ages, with 2927 cycles in 2012 to 8890 in 2016. OC cycles in women younger than 20 years accounted for approximately 1.5% of all OC cycles during the 5-year study period (1.64% in 2012, 1.39% in 2013, 1.57% in 2014, 1.55% in 2015, and 1.47% in 2016.). Figure 1 shows these percentages according to age group of women (<20, 20-29, 30-34, and >35 years). Between 2012 and 2016, there was a slight increase in the percentage of cycles among women ages 30-

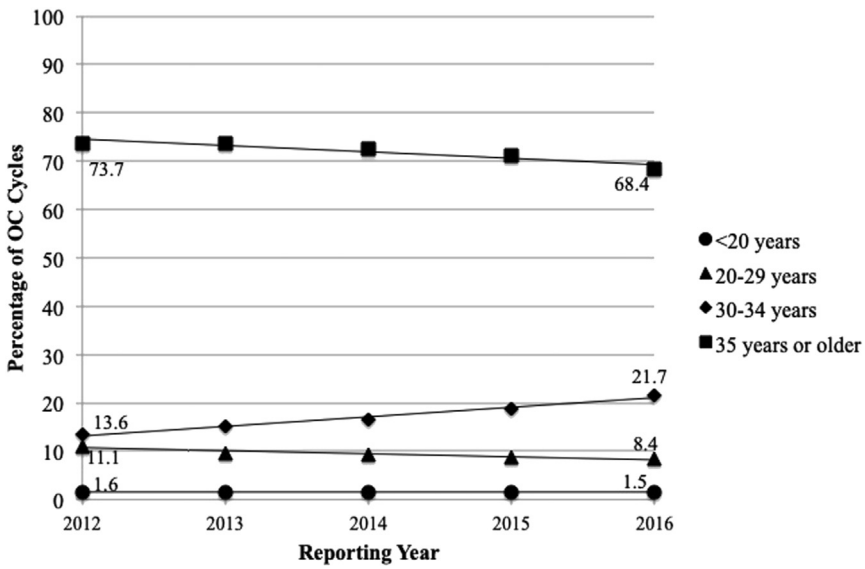

Fig. 1. Trends in percentage of oocyte cryopreservation (OC) cycles in different age groups among cycles in women of all ages (2012-2016).

Table 1
Oocyte Cryopreservation Cycle and Outcome Characteristics Among Women Younger than 20 Years Old Compared With Women 20-29 Years, 30-34 Years, and 35 Years or Older, 2012-2016

Years of Age	Younger than 20		20-29		30-34		35 or Older		*P**
	n	%	n	%	n	%	n	%	
Women's characteristics	449	1.5	2707	9.1	5364	18.1	21,113	71.3	
Age, years									
Younger than 14	19	4.2							
14-15	53	11.8							
16-17	121	26.9							
18-19	256	57.0							
BMI									
Less than 18.5	22	4.9	86	3.2	207	3.9	755	3.6	<.0001
18.5-24.9	200	44.5	1320	48.8	2954	55.1	11247	53.3	
25-29.9	67	14.9	444	16.4	820	15.3	2973	14.1	
30 or more	39	8.7	258	9.5	393	7.3	1366	6.5	
Missing	121	27.0	599	22.1	990	18.5	4772	22.6	
Geographic location (defined according to US Census data)									<.0001
Northeast	161	35.9	874	32.3	1806	33.7	8946	42.4	
South	108	24.1	845	31.2	1374	25.6	4143	19.6	
West	88	19.6	638	23.6	1638	30.5	6492	30.8	
Midwest	92	20.5	350	12.9	545	10.2	1532	7.3	
Missing	0	0.0	0	0.0	1	0.02	0	0.0	
Race/ethnicity									
Non-Hispanic white	193	43.0	1187	43.9	2005	37.4	7288	34.5	<.0001
Non-Hispanic black	16	3.6	158	5.8	181	3.4	854	4.0	<.0001
Asian/Pacific Islander	19	4.2	156	5.8	498	9.3	2503	11.9	<.0001
Hispanic	24	5.4	144	5.3	142	2.7	545	2.6	<.0001
American Indian/Alaskan Native	1	0.2	3	0.1	5	0.1	34	0.2	.62†
Patient not asked/refused	205	45.7	1103	40.8	2591	48.3	10108	47.9	
Anti-Müllerian hormone, ng/mL									<.0001
Less than 1.0	55	12.2	275	10.2	556	10.4	3159	15.0	
1.0-5.0	87	19.4	638	23.6	1525	28.4	4864	23.0	
5.1-10.0	18	4.0	219	8.1	379	7.1	675	3.2	
Missing	289	64.4	1575	58.2	2904	54.1	12415	58.8	
Cycle characteristics									
Mean number of cycles‡	1.31	0.77	1.35	0.91	1.48	0.95	2.13	2.62	<.0001§
Stimulation Protocol									
Antagonist	375	83.5	2186	80.8	4129	77.0	14375	68.1	<.0001
Standard Lupron	18	4.0	194	7.2	482	9.0	1898	9.0	<.0001
Agonist Flare	17	3.8	120	4.4	307	5.7	1865	8.8	<.0001
Gonadotropin dose (International units)									<.0001
0-2,000	117	26.1	695	25.7	1105	20.6	3255	15.4	
2,001-4,000	194	43.2	1219	45.0	2516	46.9	8049	38.1	
4,001-6,000	81	18.0	469	17.3	1047	19.5	5545	26.3	
>6,000	31	6.9	119	4.4	272	5.1	1726	8.2	
Missing	26	5.8	205	7.6	424	7.9	2538	12.0	
Cancellation									<.0001
Yes	45	10.0	132	4.9	253	4.7	1553	7.4	
No	404	90.0	2575	95.1	5111	95.3	19560	92.6	
Oocyte Yield (n)‖									<.0001
≤5	49	12.1	264	10.3	557	10.9	5085	26.0	
6-10	69	17.1	439	17.1	1174	23.0	5354	27.4	
11-20	139	34.4	908	35.3	2004	39.2	6315	32.3	
21-30	89	22.0	613	23.8	938	18.4	2060	10.5	
>30	58	14.4	351	13.6	438	8.6	746	3.8	
Hyperstimulation									<.0001†
Yes	4	0.9	17	0.6	21	0.4	42	0.2	
No	445	99.1	2690	99.4	5343	99.6	21071	99.8	

BMI, body mass index.
* All *P* values are calculated using χ^2.test except where stated otherwise.
† Calculated with Fisher exact test because the cell size is less than 5.
‡ If an individual had more than 1 oocyte retrieval and these occurred in 2 different age groups, they were classified according to age at first oocyte retrieval (total affected, n = 180).
§ *P* value calculated using analysis of variance.
‖ Percentages are of patients who did not experience a cancellation for their cycle (n = 404 for those <20 years, n = 2575 for those 20-29 years, n = 5111 for those 30-34 years, n = 19,560 for those ≥35 years).

34 (P = .0023) and a slight decrease among women older than 35 years (P = .0192) and 20-29 years (P = .0095). Throughout the 5 years, however, the largest percentage of cycles were in women older than 35 years.

The characteristics of the cycles in women younger than 20 years compared with the cycles in women in older age groups (20-29, 30-34, and >35 years) between 2012 and 2016 are shown in Table 1. There were 449 cycles in women younger than 20 years of age. Most of these (n = 256) were in women 18-19 years of age (57.0%). On average, women went through a mean of 1.31 ± 0.77 cycles. There were 39 women younger than 20 years who went through more

Table 2
Reasons for Cancellation of Oocyte Cryopreservation Cycle, 2012-2016

Reason for Cancellation	Age Group, years							
	Younger than 20 (n = 45)		20-29 (n = 132)		30-34 (n = 253)		35 and Older (n = 1553)	
	n	%	n	%	n	%	n	%
High response*	0	–	<5	<2.0	5	2.0	45	2.9
Low response	33	73.3	86	65.2	203	80.2	1314	84.6
Concurrent illness	0	–	17	12.9	5	2.0	12	0.8
Withdrawal because of family reasons*	0	–	<5	<2.0	0	–	<5	<1.0
Withdrawal because of financial reasons*	<5	<3.0	<5	<2.0	<5	<2.0	8	0.5
Withdrawal because of psychological reasons*	<5	<3.0	<5	<2.0	<5	<2.0	9	0.6
Withdrawal for other reason	10	22.2	23	17.4	32	12.6	156	10.1

* Cells with "n" fewer than 5 were suppressed for anonymity.

than 1 cycle. In this adolescent age group, women predominantly had a normal BMI, lived in the northeast or south region of the United States, and were of non-Hispanic white race/ethnicity. These same patterns were true in cycles among women of all ages with the exception of geographic location, with cycles in women aged 30 years or older more likely to be in the northeast or the west.

In all age groups, the most common stimulation protocol was an antagonist protocol, including in women younger than 20 years. With regard to gonadotropin dosing, on average, women younger than 20 years used a mean dose of 3183 ± 1742 IU compared with 3027 ± 1584 IU in women 20-29 years, 3199 ± 1558 IU in women 30-34 years, and 3636 ± 1781 IU in women aged 35 years or older. A higher proportion of cycles were cancelled in women younger than 20 years (45 of 449 total cycles; 10.0%) than in other age groups (1,938 of 29,184 total cycles; 6.6%). Most cycles, 33 of 45, were cancelled because of low response (73.3%) in women younger than 20 years (Table 2). A small percentage were cancelled for other reasons (eg, high response, concurrent illness, family reasons, financial reasons, psychological reasons).

In cycles that were not cancelled, the number of oocytes retrieved is presented in Table 1. Compared with cycles in women ages 20-29 years, a similar percentage of cycles had retrieval of 5 or fewer, 6-10, 11-20, 21-30, and greater than 30 oocytes. Women older than 35 years had fewer eggs retrieved. We compared mean number of oocytes retrieved in women younger than 20 years with women 20-29 and 30-34 years, because it is more likely that women older than 35 years have confounding age-related diminished ovarian reserve. On average, women younger than 20 years retrieved a mean of 18.0 oocytes compared with 18.4 oocytes in women aged 20-29 years and 16.0 oocytes in women aged 30- 34 years ($P < .001$). Table 3 has a subgroup analysis with a specific focus on maturity rate for cycles during 2014-2016, when data were available for number of oocytes cryopreserved. The percent mature was similar across all age groups: 82.5% in women younger than 20 years, 80.7% in women aged 20-29 years, 81.1% in women aged 30-34 years, and 81.5% in women aged 35 years or older ($P = .23$).

Less than 1% of women in all age groups experienced ovarian hyperstimulation syndrome, although there was a statistically increased risk in women younger than 20 years of age compared with older women. Other complications were exceedingly rare (<1%). In women younger than 20 years, 3 women (0.67%) were either hospitalized or developed an infection. There were no other complications listed. In older age groups, fewer than 1% of cycles had reported anesthetic complications, hemorrhage, hospitalization, infection, or psychological stress. There were no reports of deaths in any age groups.

Last, reasons for OC in cycles in women younger than 20 years and 20-29 years are listed in Table 4. We chose to focus on these 2 groups of women because they are likely to have similar reasons for OC. Approximately half of the cycles were performed for fertility preservation with no reason given in the reporting system in both age groups (229 of the 449 cycles (50.8%) in women younger than 20 years and 1455 of the 2707 cycles (53.7%) in those 20-

Table 3
Mature Oocytes Cryopreserved From OC Cycle Among Women Younger than 20 Years Old Compared With Women 20-29 Years, 30-34 Years, and 35 Years or Older, 2014-2016

Years of Age	Younger than 20 (n = 301)		20-29 (n = 1816)		30-34 (n = 4040)		35 or Older (n = 14,314)		P*
Oocytes retrieved, n (%)									<.0001
5 or fewer	31	10.3	193	10.6	416	10.3	3655	25.5	
6-10	53	17.6	305	16.8	946	23.4	3950	27.6	
11-20	105	34.9	652	35.9	1577	39.0	4634	32.4	
21-30	68	22.6	415	22.9	760	18.8	1521	10.6	
More than 30	44	14.6	251	13.8	341	8.4	554	3.9	
Oocytes cryopreserved, n (%)									<.0001
5 or fewer	45	15.0	283	15.6	700	17.3	4911	34.3	
36-10	67	22.3	421	23.2	1142	28.3	4438	31.0	
11-20	116	38.5	712	39.2	1555	38.5	3891	27.2	
21-30	52	17.3	293	16.1	502	12.4	856	6.0	
More than 30	21	7.0	107	5.9	141	3.5	218	1.5	

OC, oocyte cryopreservation.
* P value calculated using χ^2 test.

Table 4
Reasons for Oocyte Cryopreservation Among Women Younger than 20 and 20-29 Years

Reason for Oocyte Cryopreservation	Younger than 20 years		20-29 Years	
	n	%	n	%
Gonadotoxic treatment	141	30.7	712	26.3
Cancer-related	135	29.9	693	25.6
Aplastic anemia/sickle cell disease	5	1.1	7	0.3
Autoimmune disease	0	0	13	0.5
Fertility preservation, medical reason NOS	16	3.5	71	2.6
Fertility preservation NOS/no reason given	229	50.8	1455	53.7
Diminished ovarian reserve	36	8.0	179	6.6
Turner syndrome/mosaic Turner syndrome	11	2.4	<5	<0.1
Unexplained infertility	6	1.3	52	1.9
Gender dysphoria	6	1.3	<5	<0.1
Preimplantation genetic diagnosis*	<5	<1.0	29	1.1
Polycystic ovaries*	<5	<1.0	74	2.7
Tubal-related reason*	<5	<1.0	21	0.8
Male factor infertility*	<5	<1.0	116	4.3
Uterine factor*	<5	<1.0	15	0.6
Endometriosis*	<5	<1.0	66	2.4
Cysts in ovary*	<5	<1.0	0	0

NOS, not otherwise specified.
* Cells with fewer than 5 women suppressed for anonymity.

29 years of age). "Banking before gonadotoxic treatment" was not added as a field in the database until 2016. Of the cycles with reason listed, the most common reason was for impending gonadotoxic treatment ([64.1%; 141 of the 221 cycles] in women younger than 20 years and [56.9%; 712 of the 1,252 cycles] in women aged 20-29 years). A small percentage had other reasons listed, including gender dysphoria, diminished ovarian reserve, or infertility.

Conclusions

In this retrospective study using national data from the SART CORS database, we describe OC cycles in adolescent women and compare them with those in older women. We found an increasing trend of absolute number of OC cycles in adolescent women from 2012 to 2016, which paralleled the overall trends in OC cycles in women of all ages. Cycles in women younger than 20 years were similar in many demographic characteristics to older women except for geographic distribution, with a higher preponderance of cycles in the Midwest and less in the west. OC cycle characteristics were similar. Adolescent women did have higher cancellation rates. Fortunately, complication rates, including ovarian hyperstimulation syndrome, were rare (<1%) across all age groups.

We had hypothesized that oocyte yield in women younger than 20 years would be similar to a slightly older comparison group (20- to 29-year-old women) because ovarian reserve is likely similar and their reason for OC is similar. Women younger than 20 years had a mean of 18.0 oocytes retrieved compared with 18.4 oocytes in women 20-29 years of age, which was similar in our post hoc analysis (although significantly more than in cycles in women 30-34 years old). In addition, in the secondary analysis, maturity rate was similar across age groups (approximately 81%). Women younger than 20 years did have a higher cancellation rate with slightly higher gonadotropin doses used. The higher cancellation rate might be attributed to physician caution to avoid complications in adolescents (eg, ovarian hyperstimulation). There could also be inherent differences in ovarian physiology in adolescent women, particularly within a few years of pubertal onset.[15] In addition, adolescent women are more likely to be undergoing OC because of anticipated or previous gonadotoxic treatment. Previous studies in the oncology fertility preservation literature have shown lower oocyte yield in oncology patients before treatment, which was hypothesized to be due to lower gonadotropin dosing.[16,17] There might, however, be a blunted ovarian response in oncology patients,[18,19] perhaps because of malignancy-induced suppression of the hypothalamic-pituitary-gonadal axis or production of gonadotoxic cytokines.

Our study of OC cycles is more reassuring than previously published data in younger women, which were limited to case series. One previous study[10] included 8 girls who underwent OC before myeloablative chemotherapy for a bone marrow transplantation for sickle cell disease. Their mean dose of gonadotropins and number of oocytes retrieved was 2134.38 IU and 14.8, respectively, however, half of the women had fewer than 10 mature oocytes cryopreserved. The study authors had used a previously published adult gonadotropin dosing regimen on the basis of ovarian reserve data but had to increase the dose in 6 of the 8 women. Another study evaluated 5 women (3 with Turner syndrome and 2 with cancer) and reported a mean number of mature oocytes cryopreserved of 8.1 ± 3.4.[11] These studies had raised concern that adolescent women might have subpar results with OC, particularly in light of the number of oocytes projected to result in live birth.[4]

Information regarding young women's response to fertility treatment is crucial because young women are most likely to be pursuing OC because of impending gonadotoxic therapy. These young women are also the least likely to have completed childbearing. Future fertility is of significant concern for many adolescent and young cancer survivors.[20,21] This study provides reassuring data regarding a low complication rate and fairly equivalent oocyte yield in women younger than 20 years of age.

This study has a few strengths. To our knowledge, this is the largest cohort of OC cycles published to date in women

younger than 20 years. Previous data are limited to case series,[10,11,13] with the largest study including 11 women. Furthermore, we were able to include cycles from a national cohort, reflecting broader trends and national practice patterns. A large amount of demographic and cycle-specific descriptive data were included in the analysis.

There were also a couple of limitations to the study with missing data. There was a large proportion of missing AMH data (>50% of cycles). Women with lower AMH are more likely to receive a higher dose of gonadotropins, have higher cancellation rates,[22] and have fewer oocytes retrieved.[23] With the absent AMH data, we cannot determine if the oocyte yield results are secondary to differences in ovarian reserve or gonadotropin dosing (or both). Because of the urgency of fertility preservation with a newly diagnosed malignancy, it is likely that many cycles were started (and dosed) without AMH data guidance. Similar to all database studies, we are limited by inherent data entry issues (eg, BMI data, reason for OC cycle). The fields for oocyte maturity and, as a rationale for treatment, "banking for gonadotoxic treatment" were not added until 2014 and 2016, respectively. We do not believe, however, that these missing data would affect our primary outcome of number of oocytes retrieved or that missing data would be reflected disproportionately in one group compared with another.

Although OC cycles in adolescent women are rare (1.5% of all cycles), they are typically performed for fertility preservation before gonadotoxic therapy. The low complication rate and good oocyte yields provide reassuring guidance for clinicians caring for young women planning OC.

Acknowledgments

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