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REPRODUCTIVE PHYSIOLOGY AND DISEASE

Long-term hormonal contraceptive use is associated with a reversible suppression of antral follicle count and a break from hormonal contraception may improve oocyte yield

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Abstract
Purpose Unlike infertility, patients presenting for fertility preservation (FP) are often using combined hormonal contraceptives (CHC). We studied whether long-term (≥6 months) CHC use is associated with reversible suppression of antral follicle count (AFC).
Methods This is a longitudinal study of FP cycles from 2012 to 2016. We studied three groups: those without CHC exposure (NO CHC), those with CHC usage with a CHC break (BREAK), and without a break (NO BREAK) prior to ovarian stimulation. We assessed ovarian reserve by AFC at initial consultation and discussed the possibility of CHC suppression of AFC. Patients chose between ovarian stimulation with no CHC break versus ovarian stimulation after a CHC break. AFC was measured serially in the BREAK group. We assessed whether AFC suppression was reversed in the BREAK group. Total oocyte yield was compared among the NO CHC, BREAK, and NO BREAK groups. *T* tests, ANOVA, and linear/logistic regressions were used.
Results Seven hundred forty-three women underwent FP. Twenty-one percent (n = 154) were taking long-term CHC (≥6 months). AFC suppression was more likely with CHC use (OR 1.6, 95% CI 1.1–2.4, P = 0.011). The BREAK group (n = 79) stopped CHC for an average of 4 months. AFC improvement started at 1 month and plateaued at approximately 6- to 7-month break. The BREAK group had approximately twice as many oocytes per initial AFC as NO BREAK (2.8 ± 3.8 vs. 1.4 ± 0.9, $P < 0.001$).
Conclusions When women present for FP on CHC, AFC may be suppressed. A CHC break of several months is associated with an increase in AFC and a potential improvement in overall egg yield.

Keywords Fertility preservation · Hormonal contraception · Ovarian reserve · Antral follicle count · Ovarian stimulation

Introduction

As we seek to optimize fertility preservation (FP) protocols, we must recognize that patients seeking FP—for elective reasons or cancer—differ in some key ways from those who have traditionally utilized in vitro fertilization [1–3]. Namely, women seeking oocyte or embryo cryopreservation are often not actively attempting to conceive. Many, in fact, are utilizing combined hormonal contraception (CHC) at the time of their initial oocyte cryopreservation consultation [4]. Since women seeking elective oocyte cryopreservation have usually not taken a significant break from CHC (e.g., to try to conceive), the physiology of the hypothalamic-pituitary-ovarian axis may be altered as compared to women presenting for infertility evaluation [5].

A few weeks of short-term CHC exposure, which is often used in traditional IVF cycle preparation, is unlikely to be detrimental to oocyte yield [6–8]. However, longer-term CHC use may lead to significant suppression of gonadotropins, and—in turn—follicle development. After as few as 3 months of estrogen- and progestin-containing CHC use, for example, pituitary response to gonadotropin-releasing hormone is blunted [9–11].

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If hypothalamic-pituitary suppression from CHC prevents progression of follicle development to the antral stage, it may also lower the number of follicles susceptible to exogenous follicle-stimulating hormone (FSH) stimulation for oocyte collection. Prior studies in infertile patients (not on CHC) have shown that antral follicle count (AFC) is directly correlated with oocyte yield [12–14]. Certainly, in some cases, low AFC may be related to lower primordial follicle reserve in the ovary. However, some women with low AFC in the setting of long-term CHC use may actually have normal ovarian potential, but progression to the antral follicle stage may be blunted by CHC use. Since antral follicles represent those follicles that are susceptible to gonadotropin-induced ovarian stimulation, lower antral follicle counts may correlate with lower oocyte yield.

We hypothesize that long-term CHC use is associated with a reversible suppression of AFC. In other words, long-term CHC use may mask the "true biological potential" of the ovaries and possibly results in suboptimal oocyte yield. To address this hypothesis, we chose to systematically examine our clinical data. First, we evaluated whether long-term CHC use is associated with less-than-expected AFC. Second, we examined whether a break from CHC is associated with a reversal of AFC suppression. Third, we plotted out the relationship between onset of AFC return versus length of break from CHC. Finally, we explored the potential for improved oocyte yield after a break from CHC.

Materials and methods

We performed a longitudinal, observational study. For this type of study, formal consent is not required. All study procedures were approved by University of California, San Francisco (UCSF) Committee on Human Research.

Study population

An electronic chart review was performed to select all patients from our clinic who had undergone a cycle of ovarian stimulation for FP from January of 2012 to September of 2016. January of 2012 was chosen as a starting point because that is when we began to suspect that CHC could be leading to ovarian suppression. This observation led us to offer patients to take a break from CHC prior to ovarian stimulation. Inclusion criteria for the study included ages 18 to 44 years old, first ovarian stimulation cycle, elective oocyte cryopreservation, or oocyte/embryo cryopreservation prior to cancer treatment (chemotherapy, radiation, or pelvic surgery). Results of the first ovarian stimulation cycle were recorded. Every patient underwent an antagonist-based ovarian stimulation cycle and egg retrieval.

Based on history of long-term CHC exposure, the study population was divided into three groups: NO CHC, NO BREAK, and BREAK. The NO CHC group did not have a history of long-term CHC exposure. Long-term CHC exposure was defined as six or more consecutive months of CHC exposure that was continued until within 1 month of FP consultation. The NO BREAK group had a history of long-term CHC exposure and continued CHC until the onset of ovarian stimulation. The BREAK group took a break from CHC for one or more months prior to ovarian stimulation. Patients awaiting urgent cancer treatment were advised not to delay their cancer care for ovarian stimulation or CHC break.

Assessment of antral follicle count

We assessed ovarian reserve by measuring AFC at the initial FP consultation. Transvaginal ultrasound was performed by an experienced clinician and follicles measuring between 2 and 10 mm (by clinician measurement, not automated calculation) were counted in both ovaries to account for the AFC.

Statistical analysis

Electronic medical record data were extracted and de-identified. Statistical analyses were performed using Stata version 14 (Stata Corp, College Station, Tx). Statistical significance was defined by two-sided P values <0.05. T tests, ANOVA, and linear or logistic regressions were used as appropriate to compare demographic data. Further statistical analysis will be discussed in the four study questions below.

Question 1: Is long-term CHC use associated with lower ovarian reserve?

We compared the AFC of women on long-term CHC and NO CHC against that of women in the general population. We performed logistic regression to assess whether long-term CHC use (NO BREAK + BREAK) was associated with increased odds of presenting with a "lower-than-expected" AFC as compared to women in the NO CHC group. To address whether a given patient's AFC was lower-than-expected, we used the age-stratified 50th percentile of AFC from the Ovarian Aging Study (OVA) as an estimate of "expected AFC." OVA was a longitudinal assessment of ovarian reserve. OVA was conducted in a cohort of women from the general population who were not taking hormonal contraception [15, 16]. The 50th percentile reference cutoffs from OVA were AFC of 21 for ages 30 years old or younger, AFC of 15 for ages 31 to 35, AFC of 13 for ages 36–40, and AFC of 6 for ages 41 and up. Those with an age-based AFC less than the OVA study, 50th percentile were considered to have a "lower-than-expected" AFC.

Question 2: Is a break from CHC associated with a reversal of AFC suppression?

Women in the BREAK group were followed with multiple AFC measurements, in order to assess for AFC improvement over time. We compared the difference between initial and final AFC's using a paired *T* test. The BREAK group was created primarily from women with a lower-than-expected initial AFC. When possible, women on CHC who had a lower-than-expected AFC at their initial consult were advised to take a break from CHC. In those who agreed to take a break, CHC was stopped for one or more months prior to ovarian stimulation (BREAK). These patients underwent ultrasound monitoring to assess for potential ovarian recovery during their break from CHC (Fig. 1). The BREAK group had periodic assessments of AFC (every 1–3 months). Ovarian stimulation started either when the AFC rose to at least the OVA-based 50th percentile for age ("normalized") or after the third AFC measurement if there was a plateau. So, the BREAK group had an initial AFC, one or more interval AFCs, and a final AFC prior to ovarian stimulation.

Question 3: How long does it take to improve AFC?

To answer this question, we created two Kaplan Meier survival curves, which assessed time to AFC recovery in patients in the BREAK group with less-than-expected AFC's. One curve was created to track the cumulative proportion of those in the BREAK group whose AFC had begun to rise by a given number of months break from CHC. A second survival curve was created to display the cumulative proportion of women who "normalized" their AFC (to the 50th percentile or greater) by a given number of months break from CHC.

Question 4: Is there potential for improved oocyte yield after a break from CHC?

We compared the number of oocytes collected per initial AFC from the NO CHC, NO BREAK, and BREAK groups using ANOVA. We calculated the "oocytes per initial AFC" metric as number of oocytes collected divided by the initial AFC. We split the analysis into those whose initial AFC was "less-than-expected" compared to those with an initial AFC that was "as expected" (at or above the 50th percentile based on the OVA study).

Results

Patient characteristics

A total of 743 patients were included in our study, and 21% (n = 154) were using long-term CHC at the time of presentation. Age, BMI, duration of ovarian stimulation, and dose of gonadotropins were similar across the NO CHC, NO BREAK, and BREAK groups (Table 1). There were no unplanned pregnancies in our BREAK group, as alternative methods of contraception were used (Paraguard or barrier methods). Of the 743 women, 268 underwent FP for newly-diagnosed cancer, 20 underwent FP for health issues other than cancer (BRCA gene mutation or benign ovarian tumors), and the remaining 455 underwent elective oocyte cryopreservation. Of the patients with cancer, 66% had been diagnosed with breast cancers and 34% with other types of cancer (including leukemia, Hodgkin's disease, Non-Hodgkin lymphoma, gastrointestinal cancer, gynecologic cancer, and thyroid cancer). Thirty-seven patients with a history of cancer were using CHC at their initial presentation. The majority (n = 27) went on to immediate ovarian stimulation, without a CHC break. By the virtue of their cancer treatment plan, a minority of patients (n = 10) came off of hormonal contraceptives at diagnosis, but waited for one or more months prior to ovarian stimulation. Of those 20 women who underwent FP for health issues other than cancer, three were using long-term CHC, and all of them underwent FP due to impending bilateral salpingectomy for BRCA-carrier status. One of these three took a break from CHC prior to ovarian stimulation and the other two did not. Initial AFC for patients with a recent cancer diagnosis was similar to those without a cancer diagnosis (cancer 14.9 ± 9.9 vs. 14.6 ± 8.7, P = 0.64).

Long-term CHC use is associated with lower ovarian reserve

When compared to the OVA Study population of reference AFC's, 70% in the CHC group (NO BREAK + BREAK) had a lower-than-expected initial AFC, whereas only 58% of the NO CHC group had a lower-than-expected AFC. The odds of observing lower-than-expected AFC was significantly greater among the women who had been taking long-term CHC versus those who had not (OR 1.6, 95% CI 1.1–2.4, P = 0.011).

A break from CHC is associated with a reversal of AFC suppression

Fifty-one percent (n = 79) of women entered the BREAK group, with an average pre-stimulation break from CHC of 4 ± 2 months (range 1 to 13 months). Forty-nine percent of CHC users (n = 75) did not take a break (NO BREAK). Reasons for not taking a break included personal time constraints and cancer treatment time constraints. AFC appeared more likely to rise in the 61 women in the BREAK group who started with a less-than-expected AFC. In these 61 women, AFC nearly doubled after the CHC break, from 8.5 ± 4.7 to 14.2 ± 7.4, (P < 0.001; Table 2A). Among those with expected

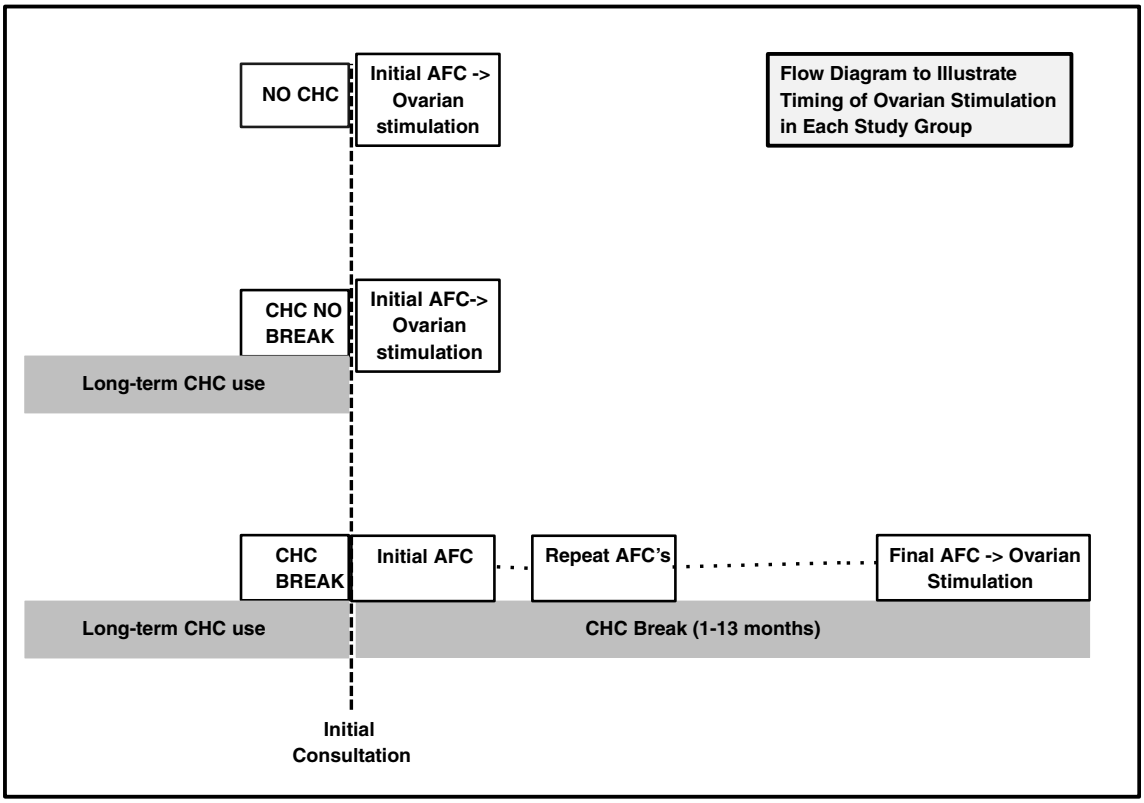

Fig. 1 Study group diagram. Fig. 1 shows the three study groups (NO CHC, NO BREAK, and BREAK), including how they differ regarding CHC exposure and time elapsed between initial AFC and ovarian stimulation/oocyte retrieval

initial AFC ($n = 18$), AFC did not change after the CHC break (19.2 ± 8.7 vs. 20.2 ± 7.8 AFC, $P = 0.84$; Table 2B).

It takes up to about 6 months to improve AFC

Two Kaplan-Meier survival curves were created to assess the timing of AFC recovery among those in the BREAK group with a lower-than-expected initial AFC. Overall, AFC increased in approximately 80% of women (Fig. 2, red line). Approximately 60% of women ultimately noted "normalization" of AFC (improvement in AFC to the 50th percentile or above; Fig. 2, blue line). By 2 months, 25% had noted at least some increase in AFC. By 4 months, 50% had noted such a rise. By 6 months, the proportion of women noting any AFC rise began to plateau. Once AFC began to rise, normalization was not immediate. For instance, it took 5 months for 25% to have normalization of AFC and 6 to 7 months for 50% to do so. Overall, the proportion of women who noted an initial improvement in AFC or a normalization of AFC started to plateau around 6 months.

A break from CHC prior to FP has potential to improved oocyte yield

Taking a break from CHC appears likely to improve oocyte yield for women with a less-than-expected AFC (Table 2A), but does not appear likely to improve oocyte yield for women with an initial "expected" AFC (Table 2B). Among women with a lower-than-expected initial AFC, those in the BREAK group had an oocyte yield per initial AFC twice that of those in the NO BREAK group (2.8 ± 3.8 vs. 1.4 ± 0.9, $P < 0.001$; Table 2A). This difference remained significant after

Table 1 Patient characteristics

	NO CHC ($n = 589$)	NO BREAK ($n = 75$)	BREAK ($n = 79$)	*P* value
Age	35.6 ± 4.5	34.5 ± 4	35 ± 3.3	0.08
BMI	23.2 ± 4.3	23 ± 3.6	23.3 ± 3.5	0.94
Days of stimulation	9.9 ± 1.8	10.1 ± 1.7	10.2 ± 1.6	0.6
Total gonadotropin dose (IU)	2396 ± 1068	2401 ± 1015	2401 ± 972	0.99

BMI body mass index, *IU* international units

Table 2 Description of initial AFC, final AFC, and oocytes per initial AFC

	NO CHC	NO BREAK	BREAK
(A) Women with lower-than-expected AFC for age: AFC and ovarian stimulation results[a]			
Initial AFC	9.7 ± 4.2	11.6 ± 5.1	8.5 ± 4.7
Final AFC			14.2 ± 7.4
Oocytes Retrieved	13.1 ± 8.2	14.9 ± 7.5	17.9 ± 9.7
Oocytes per initial AFC	1.4 ± 1.1	1.4 ± 0.9	2.8 ± 3.8[c]
(B) Women with expected AFC for age: AFC and ovarian stimulation results[b]			
Initial AFC	23.1 ± 10.1	21.1 ± 7.3	19.2 ± 8.7
Final AFC			20.2 ± 7.8
Oocytes retrieved	24.2 ± 12.6	21.6 ± 10.5	21.8 ± 9.4
Oocytes per initial AFC	1 ± 0.4	1 ± 0.4	1.3 ± 0.5[d]

[a] Women with AFC in the lower-two quartiles from the reference AFC from the OVA Study

[b] Women with AFC in the upper-two quartiles from the reference AFC from the OVA Study

[c] AFC per initial AFC was doubled in the BREAK group versus the NO CHC group and the CHC BREAK group ($P < 0.001$)

[d] No significant differences noted on ANOVA ($P = 0.09$)

controlling for the presence of patients with a history of cancer, using general linear modeling ($P = 0.035$, linear model coefficient = 1.4). A break from CHC did not appear likely to improve oocyte yield in those with an initial "expected" AFC (NO BREAK = 1 ± 0.4 vs. BREAK = 1.3 ± 0.5 oocytes per initial AFC, $P = 0.08$).

For those presenting on CHC with an initial AFC that was less-than-expected, the average number of collected oocytes was similar (within 3) to the number of initial AFC, if a break from CHC was not undertaken (Table 3). However, the longer the break from CHC, the greater the difference that was seen between the number of oocytes collected and the initial AFC. After adjustment for age and initial AFC, waiting: 1- to 3-month break was associated with an estimated 3.8 ± 2.2 ($P = 0.082$) additional oocytes (vs. NO BREAK); 4- to 6-month break was associated with an estimated 6.7 ± 2.3 ($P = 0.004$) additional oocytes (vs. NO BREAK); 7- to 9-month break was associated with an estimated 9.2 ± 3.8 ($P = 0.018$) additional oocytes (vs. NO BREAK).

Discussion

In this study, we investigated whether CHC use was associated with a reversible suppression of AFC. The main findings are that long-term CHC use is significantly associated with reversible AFC suppression and that such suppression is generally maximally reversed within 6 to 7 months of CHC stoppage. When a patient presenting

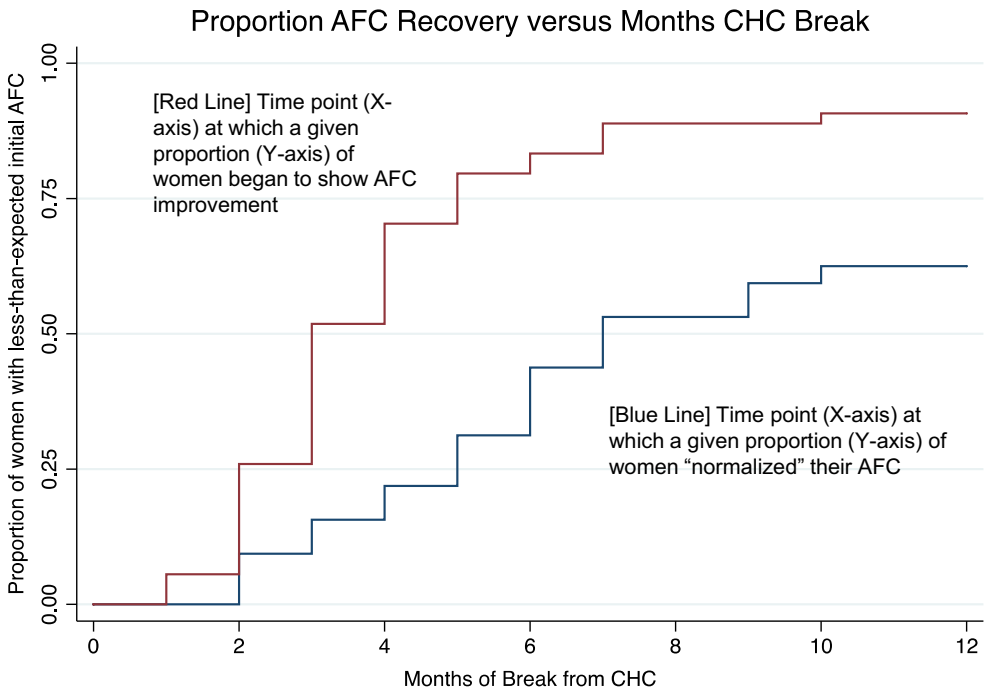

Fig. 2 Proportion of women who have recovered AFC after CHC Break. The *red line* indicates the proportion of women who noted their first improvement in AFC by a given time. By 2 months, for example, 25% had noted a rise in AFC and by 4 months, 50% had noted such a rise. By 6 months, the proportion with an initial rise in AFC began to plateau. The *blue line* represents proportion of women who normalized to "expected AFC" (at least the 50th percentile for age) by a given time. It took 5 months for 25% to notice normalization of AFC and 6 to 7 months for 50% to do so

Table 3 Oocytes collected for those with a lower-than-expected AFC

	NO BREAK (n = 40)	1 to 3 months break (n = 25)	4 to 6 months break (n = 21)	7 to 9 months break (n = 6)
Initial AFC	11.6 ± 5.1	9.5 ± 3.2	8.9 ± 6.3	5.3 ± 3.6
Oocytes collected	14.9 ± 7.5	17.4 ± 4[a]	19.5 ± 10.6[b]	20.8 ± 8.1[c]
Difference between initial AFC and oocytes collected	2.8 ± 6.9	7.9 ± 7.2	10.9 ± 12.4	15.5 ± 8.4

The 10–13-month break group had insufficient numbers for analysis (n = 2) and was not included in the table

[a] After controlling for age and initial AFC, general linear modeling predicts 3.8 ± 2.2 (P = 0.082) additional oocytes for a 1- to 3-month break (vs. NO BREAK)

[b] 6.7 ± 2.3 (P = 0.004) additional oocytes for a 4- to 6-month break (vs. NO BREAK)

9.2 ± 3.8 (P = 0.018) additional oocytes for a 7- to 9-month break (vs. NO BREAK)

for elective cryopreservation has a low AFC on hormonal contraceptives, the extent of CHC suppression versus the role of the patient's own biological potential must be questioned. Interestingly, it appears that for women with an initial AFC at the median for age or above, it may be appropriate to immediately proceed to ovarian stimulation, without a break from CHC. However, for women with low initial AFC, waiting several months after stopping CHC before ovarian stimulation resulted in improved AFC and potentially an increase in oocyte yield.

Our study showed a reduction in AFC with long-term CHC use, with a potential for AFC increase with a break from CHC, which is in agreement with prior studies. Existing evidence suggests that combined CHC use can suppress measures of ovarian reserve, including Anti-Mullerian Hormone (AMH), ovarian volume, and AFC, via suppression of follicle--stimulating hormone (FSH) [17–19]. Work by Bentzel and colleagues suggests that AFC and AMH are 30% lower among women who had just completed a long-term course of CHC as compared to those who had not [18]. A recent study revealed that ovarian reserve markers, including AFC, could recover after discontinuation of CHC. This prior study included 25 participants with an average age of 26 years. After stopping long-term CHC use for 2 months, the authors noted an average increase in AFC of 4 [20].

The observations from our study have the potential to significantly impact FP care, as providers can consider CHC stoppage in women based on the defined AFC cutoffs we have referenced. Based on the age-adjusted medians from the OVA Study, initial AFC's for considering a break from CHC prior to FP could include AFC less than 21 for ages 30 years old or younger, AFC less than 15 for ages 31 to 35, AFC less than 13 for ages 36–40, and AFC less than 6 for ages 41 and up. In our study, we observed that approximately 80% of such women had at least one additional AFC after a break from CHC. If patients and providers are willing to wait up to 6 months, they are likely to reach a maximum in AFC improvement. Some women may reach an improvement plateau sooner, so providers could consider repeating an ultrasound every 1 to-2 months off of CHC, and beginning ovarian stimulation after the AFC rises to at least the expected median for age (based on OVA Study data above) or after the third AFC measurement if there is a plateau.

If women had undergone stimulation prior to CHC break, they would have had a quantity of frozen oocytes consistent with their initial, suppressed AFC, as was seen in the CHC NO BREAK group with less-than-expected initial AFC. Others have also demonstrated a strong correlation between pre-stimulation AFC and oocyte yield [12]. In the CHC BREAK group, oocyte yield appeared to represent an improvement over what it may have been if stimulation began without a break at the time of the initial, suppressed AFC.

Among women with lower than expected initial AFCs, the majority appeared to recover AFC with a short break from CHC. Among those with a low initial AFC, our average improvement was approximately six AFC. It has been suggested that as few as eight to ten frozen oocytes are needed to achieve a pregnancy, [21] so the simple act of waiting for the potential of many more oocytes takes on an obvious, low-risk appeal.

Strengths, limitations, and future research

This study has several strengths and limitations. The study population is a large group of women from a single university medical center. The average age of our patients presenting for oocyte cryopreservation, and the proportion using CHC, are similar to other large studies in other settings [4, 21]. This supports the generalizability of our results. Limitations of this study include the retrospective nature, as well as the potential for bias among those who took a CHC break versus those who did not. While the measurements of AFC in the BREAK and NO BREAK groups were performed or directly supervised by one of two experienced clinicians, we did not directly assess, or control for, the possibility of inter-observer bias. Patients with a history of recent cancer diagnosis were included, which did not appear to affect antral follicle count or oocyte yield,

though whether cancer affects ovarian function remains a subject of ongoing debate [22–26].

Higher doses of ethinyl estradiol (30 μg or higher vs. 20 μg) may be associated with greater levels of suppression on follicle development [27]. We did not record the dose of ethinyl estradiol. Investigation of ethinyl estradiol dosing in the future may help to explain why some women noted an AFC improvement with a break from CHC and others did not. Similarly, we included women who had at least 6 months of CHC use, but did not stratify by route of administration or exact duration of use prior to initial oocyte preservation consultation. A negative linear association between duration of hormonal contraceptive use and ovarian reserve parameters was previously reported [18]. We also did not record the route of administration of CHC. However, most evidence suggests that route of administration (oral, vaginal, or transdermal) does not affect the rate of ovarian suppression [28, 29]. It would also be of interest for future research to assess improvement in other markers of ovarian reserve, such as AMH and FSH, with CHC stoppage prior to oocyte cryopreservation.

Conclusion

Nearly one-quarter of the women who present for FP are taking long-term CHC. Women who are taking such contraception are more likely to present with lower-than-expected ovarian reserve. However, the majority of women willing to wait at least a few months should see an improvement in AFC and likely an improvement in oocyte yield. It is not currently understood exactly how many eggs should be frozen to reasonably assure a chance at future pregnancy. However, it stands to reason that efficient oocyte collection, where egg yield is optimized with each cycle, should be our collective near-term goal [21]. The simple act of taking a break from hormonal contraception prior to ovarian stimulation may help us toward that goal.

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Authors' contribution Joseph Letourneau and Hakan Cakmak's roles included study design, data collection, data analysis, and manuscript writing. Molly Quinn and Nikita Sinha's roles included data collection and manuscript writing. Marcelle Cedars' roles included data analysis and manuscript writing. Mitchell Rosen's roles included study design, data analysis, and manuscript writing.

Compliance with ethical standards

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

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