Evidence of profound ovarian suppression on combined hormonal contraception resulting in dramatically different ovarian reserve testing and oocyte retrieval outcomes: case report and review of the literature

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Objective: To describe a case report and demonstrate that degree of ovarian suppression with continuous combined hormonal contraception (CHC) may be more profound than previously described and may present similarly as decreased ovarian reserve.

Design: Case report and review of the literature.

Setting: Private practice in vitro fertilization center.

Patient(s): A 36-year-old single gravida 0 presenting for oocyte cryopreservation on CHC.

Intervention(s): Discontinuation of vaginal ring combined hormonal contraceptive for 6 months.

Main Outcome Measure(s): Antral follicle count, antimüllerian hormone, day 3 follicle-stimulating hormone, total oocytes, and mature oocytes retrieved before and after discontinuation of CHC.

Result(s): After a 6-month break from CHC, our patient’s antimüllerian hormone level increased from undetectable levels to 3.45 ng/mL, day 3 follicle-stimulating hormone level decreased from 14.9 IU/mL–6.17 IU/mL, and antral follicle count improved from 0–28. In addition, the number of oocytes retrieved after a 4-month CHC break and 6-month break increased from 8 to 29, respectively.

Conclusion(s): In patients on long-term combined continuous hormonal contraception, profound ovarian suppression can result in a clinical picture of diminished ovarian reserve and extremely poor response to high-dose stimulation, which may be reversed by more time off from suppression. (Fertil Steril Rep® 2020;1:94–8. ©2020 by American Society for Reproductive Medicine.)

Key Words: Fertility preservation, elective oocyte cryopreservation, ovarian reserve, combined hormonal contraception

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Since the removal of the “experimental” label for its use by the American Society of Reproductive Medicine, more and more reproductive age females take advantage of oocyte cryopreservation as a means of fertility preservation. Many patients present to fertility providers after long periods of continuous combined hormonal suppression, which in most studies has been reported to only modestly influence ovarian reserve markers, including a decrease in antral follicle count (AFC) and antimüllerian hormone (AMH) of up to 30% (1). It previously has been demonstrated that AMH may not be reflective of the primordial follicle pool, but rather of the growing follicular pool.
responsive to gonadotropins (2) and AMH concentrations may be unstable, such as in the case of idiopathic hypogonadotropic hypogonadism. In these cases, taking a break from combined hormonal contraception (CHC) of up to 6 months has been shown in retrospective studies to improve AMH and AFC (3). In addition, oocyte yield after a CHC break appears to improve when compared with predicted oocyte yield based on initial AFC (3). To our knowledge, there is no study to date evaluating actual oocyte yield longitudinally during a CHC break. Herein, we describe a case of profound ovarian suppression (undetectable AMH and elevated follicle-stimulating hormone [FSH]) from prolonged continuous CHC in a former two-time Olympic gold medalist undergoing fertility preservation, resulting in dramatically different ovarian reserve testing, ovarian stimulation characteristics, and outcomes of oocyte retrieval cycles following a CHC break. We highlight this case to demonstrate that degree of ovarian suppression with continuous CHC may be more profound than previously described and may present similarly as decreased ovarian reserve (DOR).

SUBJECT AND METHODS
A 36-year-old single gravida 0 presented to our clinic in March 2019 with a desire for fertility preservation. She was a two-time Olympic gold medalist with more than two decades spent as a competitive endurance athlete. Her medical history was remarkable only for 14 years of continuous combined hormonal suppression using the vaginal ring for the purposes of period suppression during her athletic career and for contraception. At the time of presentation, the vaginal ring was in place. Her gynecologic history was negative, and there was no clinical suspicion for a diagnosis of endometriosis. Her height was 6 feet 2 inches and her weight 180 lb, for a body mass index (BMI) of 23.1 kg/m². Upon initial assessment, no antral follicles were seen in either ovary on transvaginal ultrasound (Fig. 1A). Her serum AMH concentration was undetectable (<0.015 ng/mL) on March 11, 2019. Written informed consent was obtained from the patient for participation in this case report.
Given the patient’s desire to proceed with elective oocyte cryopreservation, she was advised to discontinue the use of the vaginal ring at the time of initial presentation on March 11, 2019. Following discontinuation of combined hormonal contraception, repeat ovarian reserve testing on cycle day 3 on April 23, 2019 revealed a serum FSH level of 14.9 IU/mL with an E2 level of 29 pg/mL, and an AMH concentration of 0.114 ng/mL (Table 1).

Four months after initial presentation, she underwent a cycle of oocyte cryopreservation using an antagonist protocol with estrace priming and high-dose gonadotropin stimulation at a dose of 525 U daily along with 100 mg of clomiphene citrate daily. A total of eight follicles were seen on the day of trigger (six follicles >15 mm; largest, 22 mm), and the peak E2 level was 1,288 pg/mL. A total of eight oocytes were retrieved, of which six were mature and were cryopreserved as MII oocytes.

Table 1

| Date          | Discontinuation of CHC (vaginal ring) use | AFC, n | AMH concentration (ng/mL) | FSH concentration (IU/mL) | E2 concentration (pg/mL) | Peak E2 during stimulation (pg/mL) | Total oocytes retrieved, n | Mature oocytes retrieved, n |
|---------------|------------------------------------------|--------|---------------------------|---------------------------|--------------------------|-----------------------------------|---------------------------|---------------------------|
| March 11, 2019|                                          | 0      | <0.015                    | 0.114                     | 14.9                     | 29                                | 1,288                     | 8                         | 6                         |
| April 22, 2019|                                          | 12     | 6.17                      | <11                       | 4,723                    |                                   | 29                        | 27                        |
| July 22, 2019 |                                          | 28     | 3.45                      | 4,723                     | 29                       |                                   | 29                        | 27                        |
| July 31, 2019 |                                          |        |                           |                           |                          |                                   |                           |                           |
| August 2, 2019|                                          |        |                           |                           |                          |                                   |                           |                           |
| August 14, 2019|                                         |        |                           |                           |                          |                                   |                           |                           |
| September 18, 2019|                                   |        |                           |                           |                          |                                   |                           |                           |
| September 25, 2019|                                      |        |                           |                           |                          |                                   |                           |                           |
| September 28, 2019|                                     |        |                           |                           |                          |                                   |                           |                           |
| September 30, 2019|                                   |        |                           |                           |                          |                                   |                           |                           |

Note: AFC = antral follicle count; AMH = antimüllerian hormone; CHC = combined hormonal contraception; FSH = follicle-stimulating hormone.

RESULTS

The authors of a 2019 prospective cohort study performed serial ovarian reserve evaluations on 68 women with a history of long-term CHC use over a 4-month period after discontinuing CHC (5). Over the first 2 months after CHC discontinuation, AMH level increased by 53% and AFC level by 41%, before reaching a plateau. Landerse et al. (8) concluded that ovarian reserve testing can be considered accurate 2 months after CHC discontinuation. A recent retrospective study by the same group aimed to assess differences in ovarian reserve markers in 983 Danish non–hormonal contraception users and 565 women using different types of hormonal contraception including the progestin-only pill (POP), the levonorgestrel-releasing intrauterine system (LNG-IUS), the combined oral contraceptive (COC) pill, and the contraceptive vaginal ring. Although COC users, POP users, and LNG-IUS users had statistically significant AMH reductions compared with non–hormonal contraceptive users (31.1%, 35.6%, and 17.1%, respectively), no significant AMH reduction was observed in users of the contraceptive vaginal ring. The AFC level was significantly lower in COC and POP users, but not in LNG-IUS and vaginal ring users. In the setting of oocyte cryopreservation, a longitudinal study of 743 fertility preservation cycles between 2012 and 2016 examined patients with and without CHC exposure, and compared those within the CHC-exposed group according to whether there was a break in CHC use prior to ovarian stimulation or not (3). In the patients with a break (n = 79; with a mean break interval of 4 months), approximately twice as many oocytes per initial AFC were retrieved compared with patients who started stimulation immediately after discontinuation of CHC use (2.8 ± 3.8 vs. 1.4 ± 0.9; P<.001).

DISCUSSION

Long-term use of CHC has been associated with a modest and reversible suppression of ovarian reserve markers including AFC and AMH (1–7). Bentzen et al. (1) conducted an age-adjusted comparison between 228 users and 504 nonusers of hormonal contraception. All measured ovarian reserve parameters were reduced significantly: serum AMH concentration by 29.8% (95% confidence interval [CI] 19.9%–38.5%), AFC by 30.4% (95% CI 23.6%–36.7%), and ovarian volume by 42.2% (95% CI 37.8%–46.3%).
We initially speculated this profound decrease and subsequent improvement of ovarian function may be attributable to the extended length of CHC use and/or use of vaginal CHC.

Although Bentzen et al. observed more pronounced decreases in ovarian reserve parameters with increasing duration of hormonal contraception (1), other studies evaluating the duration of CHC have not shown significant differences in the relative change in AMH or AFC levels after adjusting for age (5, 9). Furthermore, Kallio et al. (10) demonstrated serum markers of ovarian reserve (AMH, FSH, and E2 levels) decrease in women after 9 weeks of CHC treatment independently of administration route.

It is likely that the extended length of continuous CHC use in our patient did contribute to the marked ovarian suppression and to the extended 6-month duration of recovery of ovarian function, which is significantly longer than the 2 months recovery observed by Landersoe et al. (5). This case report also demonstrates that the vaginal ring can exert similarly suppressive effects on ovarian function as COCs, contrary to the findings of the recent Danish cross-sectional study (8). Possible explanations for this discrepancy include the duration of vaginal ring use, the fact that our patient was using it continuously without a “ring-free interval,” and the fact that the Danish study may have been underpowered to observe a significant reduction.

The described case begs the question whether the extended hormonal suppression acted in synergy with the patient’s history of long-term high-performance athletic activity. It is well known that strenuous training can induce hypothalamic dysfunction (11) and “the female athlete triad” of low energy availability (with or without an eating disorder), amenorrhea, and osteoporosis (12). Female athletes commonly use continued CHC for bone protection, to avoid menstrual periods during competitions, and to reduce the incidence of premenstrual syndrome and dysmenorrhea (13). In the setting of in vitro fertilization, Morris et al. reported worse treatment outcomes in women who exercised for 4 or more hours per week for 1 to 9 years, including a 40% reduction in the live birth rate, as well as statistically significant increases in cycle cancellation, implantation failure, and pregnancy loss (14).

Our patient retired from professional athletic activity 5 years prior to presentation, but still exercised at least an hour per day. She had no history of eating disorders and her BMI had been stable for many years. Her periods resumed 4 or more hours per week for 1 to 9 years, including a 40% reduction in the live birth rate, as well as statistically significant increases in cycle cancellation, implantation failure, and pregnancy loss (14). Our patient was an endurance athlete with a normal BMI, low body fat percentage, and a likely abundance of type I muscle fibers for aerobic activity (16). Establishing predictors of ovarian recovery in athletes after CHC-mediated suppression represents an intriguing area of future exploration.

A striking feature of the initial clinical picture suggestive of DOR was the elevated basal serum FSH concentration (14.9 IU/mL) 1 month after discontinuation of CHC. Studies evaluating the longitudinal effects of CHC on FSH values have shown a marked suppressive effect on gonadotropin secretion during CHC use with a subsequent increase and plateau at a median of 7.2 IU/L 1 week after discontinuation (8). Although our patient’s rebound in FSH is higher than the reported median, this case highlights the risk of falsely identifying women at risk of low ovarian reserve. False-positive predictions of DOR may lead to undue anxiety and overtreatment (17). Therefore, in select patients on long-term CHCs and at low risk of DOR, it may be prudent to consider extending waiting for a period up to 6 months (3) for ovarian markers to improve prior to undergoing fertility preservation.

In patients on long-term continuous CHC, profound ovarian suppression can result in a clinical picture of diminished ovarian reserve and extremely poor response to high-dose stimulation, which may be reversed by more time off from suppression. Providers may wish to consider more extended waiting periods prior to ovarian stimulation for oocyte cryopreservation in this clinical situation.

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