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

Chelsea W. Fox, M.D.,[a] Jamie Stanhiser, M.D., M.S.C.R.,[b] and Alexander M. Quaas, M.D., Ph.D.[b]

[a] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Diego, La Jolla, California; and [b] Reproductive Partners Fertility Center/University of California, San Diego, California

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

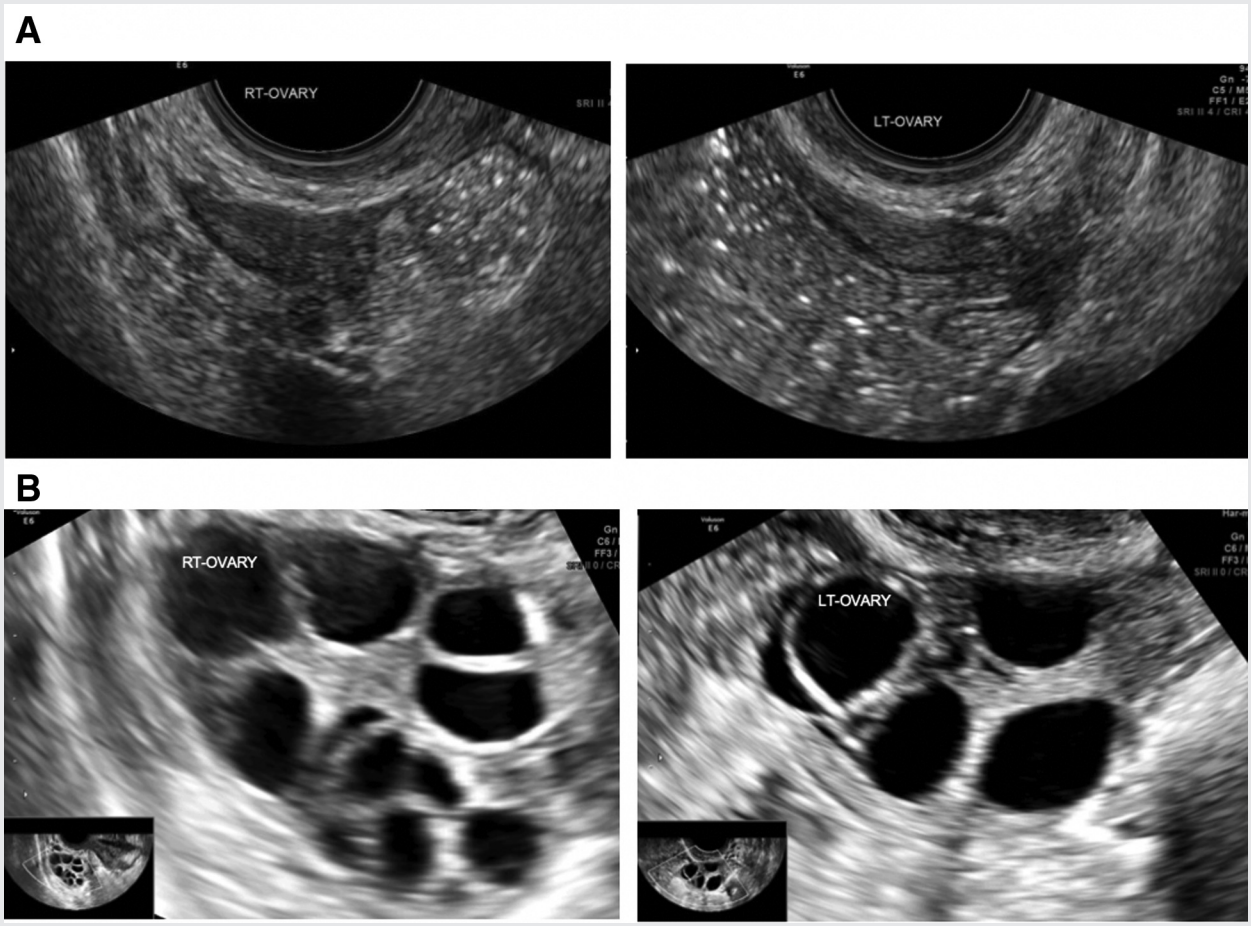
Since the removal of the "experimental" label for its use by the American Society of Reproductive Medicine, more and more reproductive age females take advantage of oocyte cryopreservation as a means of fertility preservation. Many patients present to fertility providers after long periods of continuous 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

Received March 18, 2020; revised May 14, 2020; accepted May 19, 2020.
C.W.F. has nothing to disclose. J.S. has nothing to disclose. A.Q. is a speaker and consultant for Ferring Pharmaceuticals.
Supported by the National Institutes of Health (grant number T32 HD007203 to C.W.F.).
Reprint requests: Alexander Quaas, M.D., Ph.D., Reproductive Partners Fertility Center, 9850 Genesee Ave, Suite 800, La Jolla, CA 92037 (E-mail: aquaas@health.ucsd.edu).

Fertil Steril Rep® Vol. 1, No. 2, September 2020 2666-3341

https://doi.org/10.1016/j.xfre.2020.05.007

FIGURE 1



Transvaginal ultrasound of the ovaries (**A**) at initial presentation in March 2019 and (**B**) prior to the second oocyte cryopreservation cycle in September 2019.

Fox. Stark reversible ovarian suppression. Fertil Steril Rep 2020.

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/m^2. 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.

TABLE 1

Timeline of ovarian reserve testing/oocyte retrieval cycle parameters.

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					
April 23, 2019			0.114	14.9	29			
July 22, 2019		12						
July 31, 2019						1,288		
August 2, 2019							8	6
August 14, 2019				6.17	<11			
September 18, 2019		28						
September 25, 2019			3.45					
September 28, 2019						4,723		
September 30, 2019							29	27

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

Fox. Stark reversible ovarian suppression. Fertil Steril Rep 2020.

RESULTS

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. Two months later, she presented for a second cycle. Her BMI was unchanged at 23.1 kg/m^2. Her baseline antral follicle count was now 28 (Fig. 1B), and her AMH concentration on September 25, 2019 was 3.45 ng/mL. A second cycle with lower-dose gonadotropin stimulation at 375 U daily along with 100 mg of clomiphene citrate daily resulted in the growth of more than 25 follicles. Following a trigger at a peak E2 level of 4,723 pg/mL, a total of 29 oocytes were retrieved, of which 27 were mature and were cryopreserved as MII oocytes.

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%).

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. Landersoe 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 contraceptive 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; $P<.001$).

In this case report, we demonstrate the extent of ovarian suppression may be more profound than previously reported and can mimic DOR (elevated FSH level, low E2 level, and undetectable AMH level). After a 6-month break from CHC, our patient's AMH level increased from undetectable levels to 3.45 ng/mL, day 3 FSH level decreased from 14.9 IU/mL to 6.17 IU/mL, and AFC level 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.

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 after discontinuation of CHC use, and her BMI remained the same throughout her treatment. Taken together, these clinical circumstances are not in support of the hypothesis that current acute hypothalamic dysfunction was responsible for the profound ovarian suppression and the findings suggestive of DOR. However, it is feasible that her high-intensity athletic training over many years, concomitant with continuous ovarian suppression via CHC use, resulted in the delayed recovery of ovarian function. It is unclear whether the type of exercise impacted the extreme suppressive effect of long-term CHC use. Different types of elite training have varying effects on the hypothalamic-pituitary-ovarian axis, mediated by diverse training types and intensities resulting in heterogenous athlete-specific body compositions (15). 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.

REFERENCES

1. Bentzen JG, Forman JL, Pinborg A, Lidegaard O, Larsen EC, Friis-Hansen L, et al. Ovarian reserve parameters: a comparison between users and non-users of hormonal contraception. Reprod Biomed Online 2012;25:612–9.
2. Tran ND, Cedars MI, Rosen MP. The role of anti-mullerian hormone (AMH) in assessing ovarian reserve. J Clin Endocrinol Metab 2011;96:3609–14.
3. Letourneau JM, Cakmak H, Quinn M, Sinha N, Cedars MI, Rosen MP. 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. J Assist Reprod Genet 2017;34:1137–44.
4. Tran ND, Aghajanova L, Kao CN, Cedars MI, Rosen MP. Impact of pituitary suppression on antral follicle count and oocyte recovery after ovarian stimulation. Fertil Steril 2016;105:690–6.
5. Landersoe SK, Birch Petersen K, Sorensen AL, Larsen EC, Martinussen T, Lunding SA, et al. Ovarian reserve markers after discontinuing long-term use of combined oral contraceptives. Reprod Biomed Online 2019;40:176–86.
6. Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. Anti-mullerian hormone levels decrease in women using combined contraception independently of administration route. Fertil Steril 2013;99:1305–10.
7. D'Arpe S, Di Feliciantonio M, Candelieri M, Franceschetti S, Piccioni MG, Bastianelli C. Ovarian function during hormonal contraception assessed by endocrine and sonographic markers: a systematic review. Reprod Biomed Online 2016;33:436–48.
8. Landersoe SK, Forman JL, Birch Petersen K, Larsen EC, Nohr B, Hvidman HW, et al. Ovarian reserve markers in women using various hormonal contraceptives. Eur J Contracept Reprod Health Care 2020;25:65–71.
9. Birch Petersen K, Hvidman HW, Forman JL, Pinborg A, Larsen EC, Macklon KT, et al. Ovarian reserve assessment in users of oral contraception seeking fertility advice on their reproductive lifespan. Hum Reprod 2015;30:2364–75.
10. Kallio S, Aittomaki K, Piltonen T, Veijola R, Liakka A, Vaskivuo TE, et al. Anti-Mullerian hormone as a predictor of follicular reserve in ovarian insufficiency: special emphasis on FSH-resistant ovaries. Hum Reprod 2012;27:854–60.
11. Barron JL, Noakes TD, Levy W, Smith C, Millar RP. Hypothalamic dysfunction in overtrained athletes. J Clin Endocrinol Metab 1985;60:803–6.

12. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP, et al. American College of Sports Medicine position stand. The female athlete triad. Med Sci Sports Exerc 2007;39: 1867–82.
13. Pfeifer S, Patrizio P. The female athlete: some gynecologic considerations. Sports Med Arthrosc Rev 2002;10:2–9.
14. Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD. Effects of lifetime exercise on the outcome of in vitro fertilization. Obstet Gynecol 2006;108:938–45.
15. Cumming DC, Wheeler GD, Harber VJ. Physical activity, nutrition, and reproduction. Ann N Y Acad Sci 1994;709:55–76.
16. Wilson JM, Loenneke JP, Jo E, Wilson GJ, Zourdos MC, Kim JS. The effects of endurance, strength, and power training on muscle fiber type shifting. J Strength Cond Res 2012;26:1724–9.
17. Hvidman HW, Petersen KB, Larsen EC, Macklon KT, Pinborg A, Nyboe Andersen A. Individual fertility assessment and pro-fertility counselling; should this be offered to women and men of reproductive age? Hum Reprod 2015; 30:9–15.