

Case for combined hormonal contraception holiday in fertility preservation patients

As fertility preservation, particularly elective oocyte and embryo cryopreservation, increases, it is important to remember these patients differ in important ways from traditional infertility patients seeking assisted reproductive treatment. These women have not been trying to conceive and many are using combined hormonal contraception (CHC). Although a few weeks of CHC is typical with traditional in vitro fertilization protocols, women who are on CHC for a much longer period of time have been shown to have depressed antimüllerian hormone (AMH) levels, elevated follicle-stimulating hormone (FSH) levels, and depressed antral follicle counts (AFC).

AMH and AFC levels have been shown to be as much as 30% lower in patients who have completed a long course of CHC (1) partly because the pituitary response to gonadotropin-releasing hormone is blunted after only 3 months of CHC (2). The depressed hypothalamic-pituitary axis inhibits the development of preantral and antral follicles and ultimately the follicles that can respond to exogenous gonadotropins. There are data that show a CHC holiday can restore some of these parameters to varying degrees, however, there are not a significant amount of data surrounding the actual oocyte yield differences before and after CHC suppression.

That is why the case report and review of the literature by Fox et al. (3) in this issue of *F&S Reports* is of interest. In it, they describe a patient undergoing elective fertility preservation who was on CHC and had depressed AMH, elevated FSH, and depressed AFC. She underwent an oocyte retrieval after 4 months off of CHC and had a modest number of oocytes retrieved. After 2 additional months off of CHC, for a total of a 6-month holiday, there were improvements seen in AMH level, day 3 FSH level, and AFC count, as well as a significant improvement in oocyte yield after in vitro fertilization stimulation. The authors conclude that patients, with profound ovarian suppression while on CHC, can present as having severely diminished ovarian reserve. This is reversible with time off of suppression but it may take a full 6 months in some cases. This is consistent with other studies that have shown that a CHC break for 6 months can improve AMH and AFC (1, 4). Letourneau et al. (4) suggested CHC breaks when the AFC does not meet age-adjusted medians from the Ovarian Aging study. This includes AFC <21 for ages 30 years-old or younger, AFC <15 for ages 31 to 35, AFC <13 for ages 36 to 40, and AFC <6 for ages 41 and up. In this particular case report, there was a dramatic improvement in oocyte yield after controlled ovarian

hyperstimulation once a full 6-month CHC holiday was achieved as compared with 4 months.

It is interesting to note some studies have not shown parenteral contraception in the form of levonorgestrel intrauterine device or combined hormonal vaginal ring causes a change in AFC. Moreover, the same study showed that the vaginal ring did not cause changes in AMH levels (5), as opposed to this particular case report. It is possible that this particular patient had additional suppression due to her being a high-performance athlete as noted by the authors. Certainly, more studies are needed in this regard.

In summary, the article by Fox et al. (3) serves as a good reminder that patients undergoing elective fertility preservation may present quite differently than the traditional patient with infertility. Those that are on CHC may present with signs of diminished ovarian reserve in the form of depressed AMH and AFC as well as elevations in FSH. It is prudent to give them a CHC holiday, which may be required for up to 6 months. It is possible that some may return to baseline sooner, in which case perhaps ultrasound and blood work assessment every 1 to 2 months up to 6 months until an age appropriate AFC and AMH are achieved may be reasonable once other factors, such as the patient's age, are considered.

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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. Wan LS, Ganguly M, Weiss G. Pituitary response to LHRH stimulation in women on oral contraceptives: a follow up dose response study. *Contraception* 1981;24:229–34.
3. Fox CW, Stanhiser J, Quaas A. 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. *Fertil Steril Rep* 2020;1:94–8.
4. Letourneau JM, Cakmak H, Quinn M, Sinha N, M IC, 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.
5. Landersøe 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.