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## Sex hormone metabolism, cancer, and menopause

Menopause can occur in women of all ages, including young women who receive chemotherapy for cancer. As science and medicine make great strides in allowing these women to survive their cancers, we as providers strive to answer our patients' questions about reproduction in cancer survivors. Does an elevated follicle-stimulating hormone (FSH) level or amenorrhea really mean menopause forever? Or is there hope in these cases for future fertility?

In this issue of *Menopausal Medicine*, H. Irene Su, MD, MSCE, describes various ways of assessing ovarian function after cancer treatment so that we can be better prepared to answer these questions.

And what about differences between individual women? It appears that ethnicity and race play a significant but underappreciated role in hormone-dependent cancers arising in postmenopausal women. Are there differences between women with regard to the metabolism of sex steroids after menopause? If so, does this account for differences in cancer incidence and in menopause symptoms between racial and ethnic groups?

Lauren W. Roth, MD, Gina Bolnet, MD, and Alicia Y. Armstrong, MD, MHSCR, tackle the complex issue of linking ethnicity and race to sex hormone metabolism.

Our patients, particularly those who are cancer survivors, will be better prepared to face the future.

**Cynthia K. Sites, MD**



as the exogenous FSH ovarian reserve test (EFORT).

### Menstrual pattern

The menstrual pattern is an integral component of staging natural ovarian aging.<sup>2</sup> In the general population, menopause is diagnosed retrospectively after 12 months of amenorrhea. In young cancer survivors, menstrual pattern is also considered the standard against which other measures are compared.<sup>3</sup> For common cancer treatments in young girls and women, there are estimated risks of amenorrhea in the literature and some clinical calculators (<http://savemyfertility.org/>). However, there are unique considerations to interpreting this measure after chemotherapy.

Amenorrhea or menstrual disturbance occurs frequently after exposure to chemotherapy; this has been termed chemotherapy-induced or chemotherapy-related amenorrhea (CRA). While CRA is closely related to ovarian failure, it is not synonymous with it. Physiologically, the changes in menstrual pattern occur when chemotherapy destroys not only cancer cells, but also the growing ovarian follicle pool. If ovarian reserve is not completely depleted, then ovulation and menses ensue when the residual ovarian follicles enter the menstrual cycle.

Clinically, the shorter the duration of amenorrhea, the more likely that menstrual cyclicity will return. This is best seen in the Menstrual Cycle Maintenance and Quality of Life after Breast Cancer Treatment Study, the largest prospective cohort study of menstrual pattern after cancer.<sup>4</sup> The study followed 466 breast cancer patients who kept bleeding calendars after diagnosis. Participants were younger than 45 years (median age, 39) with regular periods at diagnosis. After exposure to

**TABLE 2 Common ovarian reserve tests used during cancer treatment and survivorship**

	FSH	AMH	AFC
<b>CANCER TREATMENT</b>			
Gonadotoxic chemotherapy	↑	↓	↓
Tamoxifen	↓	↔	↔
GnRH agonist	↓	↓ ↔	↔
<b>SURVIVORSHIP</b>			
COCP	↓	↔	↓
COCP (pill-free interval)	↔ ↓	↔	↔
Amenorrhea	↑	↓	↓
Fertility	↑ 0	↓ 0	0
<small>AFC, antral follicle count; AMH, anti-Müllerian hormone; COCP, combined oral contraceptive pills; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone.            ↑, increased levels; ↓, decreased levels; ↔, unchanged levels; 0, minimal or no data.            More than one symbol reflects conflicting data.</small>			

gonadotoxic chemotherapy regimens (most containing cyclophosphamide), the risks of prolonged amenorrhea and return of menses varied by the definition of amenorrhea. In the first 6 months following start of chemotherapy, 41% of women were amenorrheic. Although 6 months of amenorrhea meets the criteria for a diagnosis of secondary amenorrhea,<sup>5</sup> half of these women resumed bleeding in the following 3 years.<sup>4</sup> After 12 months of amenorrhea (29% of participants), one-third of women resumed bleeding in the ensuing 3 years. After 2 years of amenorrhea (23% of participants), 10% of patients resumed bleeding in the following 3 years, though none resumed regular periods.

These data suggest that for young breast cancer patients who become amenorrheic after starting chemotherapy, 2 years of amenorrhea may be more accurate in diagnosing ovarian failure. Importantly, while prolonged amenorrhea can reflect ovarian failure, there are currently no studies cor-

relating menstrual pattern with fertility in this population.

Hormonal therapy, including gonadotropin-releasing hormone (GnRH) agonists, tamoxifen, and hormonal contraception, affects the interpretability of menstrual pattern in young cancer survivors. GnRH agonists may be administered during chemotherapy for fertility preservation or as adjuvant hormone therapy in breast cancer. While on GnRH agonists, patients are amenorrheic. Recovery of menstruation from depot GnRH agonist should occur within 3 months after the last dose. Tamoxifen, a selective estrogen receptor modulator, has also been associated with amenorrhea,<sup>6,7</sup> although many premenopausal women retain regular periods on treatment. Because tamoxifen is often initiated following adjuvant chemotherapy, it is not entirely clear that chemotherapy does not contribute to the menstrual disturbance observed with tamoxifen exposure.

Of note, a small proportion of young survivors may experience

amenorrhea as a consequence of *hypogonadotropic*, rather than *hypergonadotropic*, hypogonadism. Hypogonadotropic hypogonadism is a known consequence of intracranial surgery or radiation. While possible, the occurrence of hypothalamic amenorrhea secondary to stress or malnutrition in this population is not well characterized.

Menstrual pattern (while not on hormonal therapy) is a standard measure of ovarian function in young cancer survivors. The initial menstrual pattern after the start of chemotherapy strongly predicts the subsequent menstrual pattern over the ensuing few years; prolonged amenorrhea with chemotherapy is strongly correlated with ovarian failure. More data are needed on the duration of amenorrhea required to diagnose ovarian failure in patients who initially retain cyclic menses and then develop prolonged amenorrhea. Finally, the association between menstrual pattern and fertility is not well characterized.

### Follicle-stimulating hormone

FSH is secreted by the anterior pituitary and is subject to feedback from the ovary. FSH measurement is the primary ovarian reserve test used clinically in cancer patients.<sup>3</sup> FSH rises acutely in response to gonadotoxic therapy, often to postmenopausal levels.<sup>8</sup> After the period of acute exposure to chemotherapy, FSH may decrease, although it generally does not return to prechemotherapy levels.

Among cancer survivors, FSH is associated with menstrual pattern; levels are higher in amenorrheic than in menstruating young survivors.<sup>7</sup> In addition, FSH may help to identify cancer survivors who have decreased ovarian reserve even in the setting of regular periods. Regularly menstruating cancer survivors have been shown to have higher FSH levels than healthy

controls.<sup>9,10</sup> While these data suggest that FSH can reflect impaired ovarian reserve after cancer therapy, it is not known if FSH can predict fertility. For example, in early experiences with ovarian transplantation, FSH levels can remain high and are not associated with probability of pregnancy.<sup>11</sup>

FSH levels are also impacted by hormonal treatments, including GnRH agonists, tamoxifen, and hormonal contraception. In postmenopausal women, FSH levels are lower with tamoxifen exposure.<sup>12</sup> In premenopausal women, FSH levels are similar or lower with tamoxifen use.<sup>7,9</sup>

### FSH may help to identify cancer survivors who have decreased ovarian reserve even in the setting of regular periods.

To date, FSH measurement is the most commonly used ovarian reserve test in cancer patients. Measuring FSH may help identify ovarian function in young survivors, but levels need to be interpreted with caution in women on hormone therapy and with respect to timing relative to cancer treatment. There are no validated cut points in FSH levels for fertility or menopause in survivorship. As well, more data are needed to determine if FSH levels prior to cancer treatment can predict post-treatment fertility or time to menopause.

### Anti-Müllerian hormone

AMH is a glycoprotein made by the granulosa cells of primary, secondary, pre-antral, and early antral follicles. Increasingly, AMH has been used as a measure of ovarian reserve that is associated with reproductive outcomes, from successful in vitro fertilization (IVF) to time to menopause.<sup>13</sup>

In young women with cancer,

AMH levels decrease with chemotherapy<sup>8</sup> and are lower in regularly menstruating cancer survivors compared with controls.<sup>9</sup> Early data suggest that AMH levels are not affected by tamoxifen use.<sup>7</sup> It is not known if AMH levels are affected by concurrent ovarian suppression by GnRH agonists.

Recently, a cohort study showed that pretreatment AMH, but not FSH, inhibin B, or antral follicle count, can be predictive of continuing menses 4 to 5 years later.<sup>14</sup> In addition, a separate cohort study identified an AMH level cut point of 1.2 ng/mL for poor response in IVF stimulation in breast cancer survivors.<sup>15</sup>

Although these findings are preliminary, they suggest that AMH may be a more versatile marker for measuring ovarian function in young cancer patients than FSH.

### Antral follicle count

The AFC is the sum of ovarian follicles between 2 and 10 mm in size. Assessed by ultrasound, both AFC and ovarian volume (OV) have been studied as measures of ovarian reserve in patients undergoing gonadotoxic therapy. AFC has been a more consistent marker than OV.

AFC decreases in a dose-dependent manner with gonadotoxic treatments,<sup>16</sup> is lower in regularly menstruating cancer survivors than in controls, and potentially provides additive information on ovarian function along with FSH and AMH levels.<sup>17</sup> Although tamoxifen treatment can result in simple follicular cysts on the ovaries, AFC does not appear to vary by tamoxifen exposure in multiple studies.

More data are needed to determine whether pretreatment AFC can predict post-treatment ovarian function and whether post-treatment AFC is associated with fertility or time to menopause.



## Fertility preservation prior to cancer treatment

Besides age and proposed treatment regimen, there are currently no other reliable predictors of postchemotherapy ovarian function or fertility. Therefore, medical providers are encouraged to inform patients of the possibility that infertility may result from cancer treatments.<sup>18</sup>

The standard of care in fertility preservation remains embryo freezing. In addition, ovarian shielding, ovarian transposition, cervical trachelectomy, and other conservative gynecologic surgeries are considered standard of care. Although egg freezing has improved with the vitrification technique, most fertility centers have not had long-standing experiences with egg banking, and this procedure remains investigational.

There has been a long-standing debate over the efficacy of ovarian suppression for fertility preservation. A recent randomized controlled trial in breast cancer patients, which used the GnRH agonist triptorelin for temporary ovarian suppression, demonstrated a significantly decreased risk of 12 months of amenorrhea in the patients treated with triptorelin during chemotherapy.<sup>19</sup> However, follow-up is limited, and fertility outcomes have not been published. Therefore, use of GnRH agonists is still not a standard treatment for fertility preservation.

## Summary

Cancer treatment can threaten a woman's finite ovarian reserve, resulting in infertility and premature ovarian insufficiency. In young women exposed to gonadotoxic therapy, studies have measured ovarian function by menstrual pattern, fertility attempts, basal hormone measures (FSH, AMH, inhibin B), dynamic hormone measures (EFORT), and ovarian mor-

phometry (AFC and OV).

While all of these measurements change with gonadotoxic therapy, menstrual pattern, FSH, AMH, and AFC appear to be the most sensitive. Menstrual pattern remains the standard outcome, but cancer survivors may recover menstrual cycling after significant lengths of amenorrhea. Even in young survivors with regular menses, ovarian reserve may be diminished and measurable by ovarian reserve testing.

FSH is the most commonly used hormone measure of ovarian reserve, but it can be subject to variation depending on hormonal treatments and cycle day. AMH may be a more versatile marker. Limited data support the use of AMH in predicting ovarian failure or poor IVF outcomes. Similar to AMH, AFC may have less variability than FSH.

Because of limitations in each marker, it may be clinically useful to consider measuring multiple markers to describe ovarian function. Overall, more longitudinal data are needed to validate these measures as *surrogates* of underlying ovarian function or *predictors* of ovarian failure or infertility in young cancer survivors.

Currently, there are no reliable predictors of future ovarian function in young female cancer patients. It is therefore important to discuss with patients whether planned cancer treatment would impact future fertility or result in early menopause. ■

## References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011;61(4):212-236.
2. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Climacteric.* 2001;4(4):267-272.
3. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 2006;24(36):5769-5779.
4. Sukumvanich P, Case LD, Van Zee K, et al. Inci-

- dence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. *Cancer.* 2010;116(13):3102-3111.
5. Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility.* 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
6. Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol.* 2006;24(7):1045-1051.
7. Su HI, Sammel MD, Green J, et al. Antimüllerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. *Cancer.* 2009;116(3):592-599.
8. Anderson RA, Themmen AP, Al-Qahtani A, et al. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Hum Reprod.* 2006;21(10):2583-2592.
9. Partridge AH, Ruddy KJ, Gelber S, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil Steril.* 2010;94(2):638-644.
10. Bath LE, Wallace WH, Shaw MP, et al. Depletion of ovarian reserve in young women after treatment for cancer in childhood: detection by anti-Müllerian hormone, inhibin B and ovarian ultrasound. *Hum Reprod.* 2003;18(11):2368-2374.
11. Janse F, Donnez J, Anckaert E, et al. Limited value of ovarian function markers following orthotopic transplantation of ovarian tissue after gonadotoxic treatment. *J Clin Endocrinol Metab.* 96(4):1136-1144.
12. Jordan VC, Fritz NE, Tormey DC. Endocrine effects of adjuvant chemotherapy and long-term tamoxifen administration on node-positive patients with breast cancer. *Cancer Res.* 1987;47(2):624-630.
13. La Marca A, Broekmans FJ, Volpe A, et al. Anti-Müllerian hormone (AMH): what do we still need to know? *Hum Reprod.* 2009;24(9):2264-2275.
14. Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. *J Clin Endocrinol Metab.* 2011;96(5):1336-1343.
15. Lee S, Ozkavukcu S, Heytens E, et al. Anti-Müllerian hormone and antral follicle count as predictors for embryo/ooocyte cryopreservation cycle outcomes in breast cancer patients stimulated with letrozole and follicle stimulating hormone. *J Assist Reprod Genet.* 2011;28(7):651-656.
16. Larsen EC, Muller J, Schmiegelow K, et al. Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. *J Clin Endocrinol Metab.* 2003;88(11):5307-5314.
17. Su HI, Chung K, Sammel MD, et al. Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. *Fertil Steril.* 2011;95(5):1857-1859.
18. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol.* 2006;24(18):2917-2931.
19. Del Mastro LB, Boni L, Michelotti A, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA.* 2011;306(3):269-276.
20. National Cancer Institute. DevCan: probability of developing or dying of cancer. Software VSRaABNCI, 2007. Available at: [www.srab.cancer.gov/devcan](http://www.srab.cancer.gov/devcan).