

Measuring ovarian function after cancer treatment

► H. IRENE SU, MD, MSCE

In the United States, 2% of girls and young women will develop an invasive cancer by age 40.¹ With improvements in diagnosis and treatment, the probability of surviving cancer is high (TABLE 1). In this population, overall survival at 10 years from diagnosis is estimated to be 75%.

Ovarian function is an important issue in cancer survivorship, because it impacts cancer outcome, cancer treatment decisions, fertility options, bone health, and other estrogen-related processes.

Ovarian reserve refers to the

quantity and quality of eggs remaining in the ovary. Some cancer treatments can damage the finite ovarian reserve in young patients.

The threat to ovarian function varies by patient age, cancer type, treatment regimen, and other patient-specific characteristics. In clinical care, questions commonly arise regarding menopausal status and fertility potential. It is therefore important to understand how ovarian function is measured in young cancer survivors and the current limitations of these measures.

This article reviews how to assess ovarian function and ovarian reserve in young women who have been exposed to gonadotoxic therapy.

Clinical measures of ovarian function

Menstrual pattern, follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), and antral follicle count (AFC) are the most common clinical measures of ovarian function in young cancer survivors (TABLE 2). Fewer data are available on inhibin B and dynamic ovarian reserve tests, such

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Disclosures

Dr Su reports no commercial or financial relationships relevant to this article.

TABLE 1 Most common types of invasive cancer and 5-year relative survival rates in females, birth to 39 years of age

TYPE OF CANCER	INCIDENCE IN FEMALES, BIRTH TO 39 YEARS	5-YEAR RELATIVE SURVIVAL RATES
Breast	1 in 207	90%
Melanoma	1 in 353	93%
Cervical	1 in 656	72%
Leukemia	1 in 759	54%
Hodgkin disease	1 in 1000	88%
Non-Hodgkin lymphoma	1 in 1179	69%
Colon	1 in 1272	63%
Uterine	1 in 1423	84%

Data from Siegel et al,¹ and National Cancer Institute.²⁰

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The ASRM is pleased to acknowledge the generous contribution of Pfizer toward the publication of this newsletter.



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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.² 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.³ 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.⁴ 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
CANCER TREATMENT			
Gonadotoxic chemotherapy	↑	↓	↓
Tamoxifen	↓	↔	↔
GnRH agonist	↓	↓ ↔	↔
SURVIVORSHIP			
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,⁵ half of these women resumed bleeding in the following 3 years.⁴ 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,^{6,7} 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.³ FSH rises acutely in response to gonadotoxic therapy, often to postmenopausal levels.⁸ 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.⁷ 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.^{9,10} 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.¹¹

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.¹² In premenopausal women, FSH levels are similar or lower with tamoxifen use.^{7,9}

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.¹³

In young women with cancer,

AMH levels decrease with chemotherapy⁸ and are lower in regularly menstruating cancer survivors compared with controls.⁹ Early data suggest that AMH levels are not affected by tamoxifen use.⁷ 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.¹⁴ 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.¹⁵

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,¹⁶ is lower in regularly menstruating cancer survivors than in controls, and potentially provides additive information on ovarian function along with FSH and AMH levels.¹⁷ 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.¹⁸

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.¹⁹ 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. ■

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Racial and ethnic differences in sex steroids in aging women

► LAUREN W. ROTH, MD, GINA BOLNET, MD, AND ALICIA Y. ARMSTRONG, MD, MHSCR

Racial and ethnic differences in physiology and disease states have been noted in all fields in medicine. The importance of this area of health is illustrated by the recent establishment of a National Institute of Minority Health and Health Disparities at the National Institutes of Health (NIH).

This article reviews our current knowledge about ethnic differences in sex steroid metabolism in postmenopausal women and explores how these differences may explain differences in menopausal symptoms and menopausal disorders.

Evidence for racial and ethnic differences in sex steroid metabolism

Menopausal symptoms

Several studies show racial and ethnic differences in the symptoms experienced during the menopausal transition.¹⁻³ Our objective is to answer the

question, *Are these differences associated with ethnic differences in sex steroid metabolism?*

The Study of Women's Health Across the Nation (SWAN) evaluated symptoms in white, African American, Chinese, Japanese, and Hispanic women.¹ In this analysis, African American women experienced the most vasomotor symptoms, and Japanese and Chinese women, the least.¹ White and Hispanic women reported similar frequency of vasomotor symptoms: less than African American but more than Chinese and Japanese women.¹ White women reported the most psychosomatic symptoms, while Chinese and Japanese women reported the least.¹

Im and colleagues surveyed white, Hispanic, African American, and Asian women regarding their menopausal symptoms.² The symptom most frequently reported by white, Hispanic, and African American women was feeling hot or cold, whereas Asian women most frequently reported decreased sexual interest.²

The disparate menopausal experiences reported by different racial and ethnic groups may be secondary to cultural differences, but they may also be explained by differences in sex steroid metabolism. The **TABLE** summarizes the evidence for racial and ethnic differences in sex steroids.

Hormonally sensitive cancers

Much of the evidence for ethnic differences in sex steroid metabolism comes from the study of hormonally sensitive cancers. Racial and ethnic disparities in hormonally sensitive cancers have been well documented in the onco-

logic literature. Endometrial cancer, for example, is more common in white than in black women, but mortality is 80% higher in black women.⁴ These findings suggest a differing biology in endometrial cancer in black compared with white women.

Similar differences are noted in breast cancer. African American women have the highest rates of premenopausal breast cancer compared with other racial groups.⁵ In the Multiethnic Cohort Study, which followed more than 100,000 menopausal women, postmenopausal breast cancer rates were highest in Native Hawaiians, followed by Japanese, whites, African Americans, and then Hispanics.⁶ Compared with women of other racial and ethnic groups, African American women are more likely to be diagnosed with the aggressive "triple negative tumors."⁷ African American women also present with larger tumors and more advanced disease when compared with women of other races and ethnicities.^{5,7} African American women have a 32% higher death rate from breast cancer than do white women.⁷

Although these findings are influenced by many factors, racial and ethnic differences in sex steroids may play a role. A study from the National Cancer Institute showed that postmenopausal women with the highest estrogen and androgen levels had twice the relative risk of developing breast cancer as those with the lowest levels.⁸

Hypothalamic-pituitary-gonadal-adrenal axis

There are not a great deal of data regarding ethnic differences in gonad-

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Disclosures

The authors report no commercial or financial relationships relevant to this article. Dr Bolnet reports that her spouse/partner is employed by Globelmmune.



TABLE Evidence for racial and ethnic differences in sex steroids

MEASURE	EVIDENCE	AUTHORS (YEAR)	COMMENTS
Menopausal symptoms	Survey studies, observational studies	Avis et al ¹ (2001) Im et al ² (2010)	Correlations identified, literature does not document cause-and-effect relationship
Hypothalamic-pituitary-gonadal-adrenal axis	Prospective cohort studies, observational studies	Avis et al ¹ (2001) Setiawan et al ⁶ (2006) Lee et al ¹² (2010) Huddleston et al ¹³ (2010)	Data limited on postmenopausal women
Estrogen	Prospective cohort studies, observational studies	Setiawan et al ⁶ (2006) Randolph et al ¹⁶ (2003) Randolph et al ¹⁷ (2004)	SWAN studies have the largest cohorts
Progestin	Prospective cohort studies	Pinheiro et al ⁵ (2005) Manson et al ¹⁹ (2001)	No racial differences seen
Androgens	Prospective cohort studies	Setiawan et al ⁶ (2006) Randolph et al ¹⁷ (2004) Crawford et al ¹⁸ (2009)	Differences are noted but research on clinical correlates is needed

ototropin-releasing hormone (GnRH) and gonadotropin secretion.⁶ However, clinical evidence does indicate that differences may exist.^{1,2,9} Although additional factors are likely involved in the racial and ethnic disparity in age at onset of puberty, a difference in GnRH secretion is suggested, with African American and Hispanic girls entering puberty earlier than white girls.¹⁰ In addition, one study showed that whites have higher levels of adrenocorticotrophic hormone (ACTH) and cortisol compared with blacks in response to stress.¹¹ This suggests a racial difference in the hypothalamic-pituitary-adrenal (HPA) axis.¹¹

Multiple authors have noted differences in response to exogenous gonadotropins for ovarian stimulation that may be related to ethnic differences in the hypothalamic-pituitary-gonadal axis.^{12,13} The complexity and expense of studies of GnRH and gonadotropin secretion, however, limit the number of both studies and subjects.¹⁴

Some studies suggest that racial and ethnic differences exist in the hypothalamic-pituitary-ovary axis. Significant differences in the prevalence

of menopausal symptoms were reported for 9 ethnic groups of Asian women participating in the Pan-Asia Menopause (PAM) study. Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol were compared between the 9 ethnic groups and noted to be different.¹⁵ The clinical significance of these differences was not investigated.

Several studies reveal racial and ethnic differences in estradiol levels that are not mirrored by similar differences in FSH, suggesting racial and ethnic differences in the pituitary-ovarian relationship.¹⁶⁻¹⁸ Because of the small amount of data, it is difficult to correlate variation of symptoms of menopause with ethnic differences in GnRH and gonadotropins.

Estrogen

Premenopausal African American and Asian women have higher estrogen levels than white women.⁵ This finding may help explain the higher rates of premenopausal breast cancer in African American women, but it does not explain the lower rates in Asian women.⁵ Interestingly, estrogen was

found to decrease at a steeper slope over time in African American women when compared with white women, which may help to explain the higher rate of vasomotor symptoms in African American women.^{1,18}

In contrast to the above studies, the baseline data from the SWAN study found no racial or ethnic differences in estradiol levels in premenopausal and early perimenopausal women.¹⁶

In the longitudinal data from the SWAN study, mid-life Chinese and Japanese women had the lowest estradiol levels, whereas there was no difference in estradiol levels among whites, Hispanics, and African Americans.¹⁷ The reason for these contrasting results may be the timing of the blood draws, as the former was drawn in the follicular phase and the latter in the luteal phase.

The Multiethnic Cohort Study discussed earlier correlated postmenopausal hormone levels with postmenopausal breast cancer. This study found that postmenopausal Native Hawaiians had the highest estradiol levels, followed by African Americans and Japanese, with white and Hispanic women having similarly lower levels.⁶

Progesterin

Very little data exist on racial and ethnic differences in circulating progesterins. No racial differences in progesterone levels were seen in a subset of regularly cycling women from the Nurses' Health Study 2 when comparing African American, white, and Asian women.⁵ Similarly, in the Daily Hormone Study of the SWAN study, there were no differences seen in progesterone levels during ovulatory cycles when evaluating African American, white, Japanese, Chinese, and Hispanic women.¹⁹

Androgens

There are notable racial and ethnic differences in androgens levels, but data are lacking on clinical correlates. It has been speculated that the differences in androgens in postmenopausal women help explain the racial disparities in breast cancer, because androgens act as a precursor for estrogens.⁶ Further research is needed to establish this link as well as to offer other clinical correlates.

Testosterone. As part of the SWAN study, Randolph et al showed that premenopausal and perimenopausal Hispanic and African American women had lower testosterone levels than white, Chinese, and Japanese women.¹⁶ In a different cohort of older, regularly cycling African American and white women, no racial difference in testosterone was established.¹⁸

Testosterone levels increase with increasing body mass index (BMI). One study showed a 2% increase in testosterone level with each unit increase in BMI in both African American and white women.⁸ It is important to control for BMI when comparing testosterone levels between races. When women with similar BMIs were examined, the racial and ethnic differences in testosterone levels were no longer seen.¹⁶

Dehydroepiandrosterone sulfate (DHEAS). DHEAS is thought

to decline steadily with increasing chronological age¹⁶ but to "bump" transiently with ovarian aging.¹⁸ In a SWAN study analysis, DHEAS was found to sharply increase for a period during the early and late menopausal transition and then decrease again in the late menopause in all of the racial and ethnic groups studied.¹⁸

In a study of regularly cycling older women, DHEAS was lower in African American than white women at several study points.¹⁸ In addition, the decline in DHEAS associated with increasing age was more significant in African American women, with a 5% decline in DHEAS level with each year of age.¹⁸ In contrast, the level remained relatively stable in the white cohort.¹⁸

Conclusion

Menopausal signs and symptoms are recognized to be disparate among racial and ethnic groups. In addition, racial and ethnic differences in circulating sex steroids in premenopausal, perimenopausal, and postmenopausal women are evident. Unfortunately, there is little research to link the differences noted in sex steroids with menopausal symptoms or disease states, such as endometrial and breast cancer.

Further, several issues arise in this field of research. First, sex steroids change with BMI and body composition.^{5,16,18} Although most studies control for BMI, none control for the different body types or fat mass of the study subjects in the different racial and ethnic groups. The second issue that arises is in the assignment of racial and/or ethnic groups. Many studies group all Asians together and all Hispanics together, but this is likely inadequate. The third issue is study expense, because large sample sizes and long time periods are needed.

Although there are clearly obstacles to investigating racial and ethnic disparities in the expression of menopause-

related symptomatology and health burden, this is an important field of research with large gaps in knowledge. ■

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