

Early menopause in cancer survivors: Fertility options

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Recent diagnostic and therapeutic advances in oncology have led to greater survival in girls and reproductive-age women with malignancies. However, such treatments often lead to infertility, early menopause, and long-term health problems related to early ovarian failure. This review summarizes the scope of the problem, gonadotoxic cancer treatment, fertility-sparing methods, and fertility options after cancer treatment.

Cancer risk and survivorship

In the United States, the incidence of cancer in women younger than 50 years is increasing by 0.75% per year.¹ The American Cancer Society estimates almost 700,000 newly diagnosed cases of cancer in women in 2008.² Despite

these statistics, improvements in treatment have significantly increased the number of survivors over the past 25 years.³ In women, the 5-year survival for all cancers has increased from 57% to 64% over the last quarter century, most notably for breast cancer, whose survival rate has increased from 75% to 90% in the same timeframe.⁴ For childhood cancers, the 5-year survival rate for all cancers has improved from 68% to 81%, with the largest increases observed in hematologic cancers.⁴ It is estimated that 1 in 1000 adults in their thirties is a survivor of childhood cancer.⁵ The increasing number of survivors has highlighted the need for clinicians to consider survivorship issues from early menopause to fertility preservation in the care of this population.

Importance of fertility to survivors

The ability to lead full reproductive lives is very important to young cancer survivors. Women who have not completed their families are particularly susceptible to reproductive stress. In a recent survey of cancer survivors aged

37 to 45 years who were diagnosed with cancer 5 to 10 years earlier, reproductive concerns in infertile women resulted in significantly higher levels of cancer-specific stress, lower psychological and physical well-being, and poorer coping efforts.⁶ In a study of young women with breast cancer, one-third stated that infertility concerns influenced their treatment decisions. Sadly, however, only 51% of cancer survivors surveyed felt that their concerns were addressed adequately, highlighting the need for counseling efforts focused on fertility preservation and treatment.⁷

Gonadotoxicity of cancer treatments

The ovary is particularly sensitive to the adverse effects of chemotherapy because of its finite number of non-renewable germ cells.^{8,9} Cancer treatments that cause follicular atresia can lead to premature menopause and infertility.¹⁰ The irreversible gonadotoxic effects of some chemotherapeutic agents are well documented, particularly for alkylating agents, such as cyclophosphamide and busulfan, which

CONTINUED ON PAGE S3

IN THIS ISSUE

S2 From the editor

■ Nanette F. Santoro, MD

S7 Skeletal implications of premenopausal decline in ovarian reserve?

■ Lubna Pal, MBBS, MRCOG, MS

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FROM THE EDITOR



In this issue of *Menopausal Medicine*, we are reminded that ovarian reserve—critical for reproduction—can be threatened unexpectedly in women who consider themselves too young to have such problems.

Dr Su, Lin, and Gracia provide an exciting overview of the new field of “oncofertility,” part of a holistic approach to the cancer patient. For many individuals, when a life-threatening cancer has just been diagnosed, reproduction becomes a secondary concern that recedes into the background, only to resurface as a priority later, when the cancer has been brought to bay. Instead of looking myopically at the immediate problem and sacrificing future fertility potential, a cadre of physicians—led by their patients—have become devoted to taking a longer view. By looking to the postsurvival years of their cancer patients, they hope to provide the very best possible quality of life for cancer survivors.

We are also reminded that ovarian reserve is not only about reproduction. Dr Pal provides insight into the “behind-the-scenes” role of the ovary in maintaining skeletal health. Even in the absence of overt ovarian failure, women with reduced ovarian reserve have lower bone density than those with normal ovarian reserve, leading to more years of life at risk of osteoporosis and possibly fracture. It is easy, when focused on fertility, to ignore the “collateral damage” that low ovarian reserve may produce.

In both of these cases, the threat to health can be managed, but first it must be recognized. Hats off to Dr Su and her colleagues and to Dr Pal, who point the way to more sophisticated management of our patients with impending and untimely menopause.

Nanette F. Santoro, MD

are common components of polychemotherapy for breast cancer, leukemia, and lymphomas.¹¹⁻¹⁴ By cross-linking DNA and introducing single-stranded DNA breaks, alkylating agents destroy cells in a dose-dependent, non-cell cycle specific fashion, leading to decreased follicles, absent follicles, and stromal fibrosis.¹⁵⁻¹⁸ The risk of ovarian failure after chemotherapy varies by both treatment and age. For Hodgkin disease, approximately two-thirds of women treated before age 30 can expect to develop premature ovarian failure (POF), compared with 13% of women treated before age 15.¹⁹ After cyclophosphamide-based adjuvant therapy, breast cancer patients who are older than 40 years experience rates of amenorrhea from 61% to 97%, whereas patients who are younger than 40 years have rates from 18% to 61%.²⁰

Radiation therapy is used in conjunction with polychemotherapy in childhood cancers or directed toward the pelvis for multiple gynecologic cancers. Total body irradiation (TBI) for several solid and hematologic cancers results in POF in more than 80% of patients treated in childhood.²¹ Abdominopelvic irradiation for Hodgkin lymphoma with subdiaphragmatic disease or advanced cervical cancer can expose ovaries to large radiation doses on the order of 2000-4000 cGy and invariably results in ovarian failure.²² Using mathematical models assuming age at natural menopause to be 51 years, 2000 cGy represents a critical dose at which 50% of primordial oocytes are destroyed and ovarian failure risk is increased.²³ In addition to ovarian toxicity, radiation therapy affects the uterus. Following TBI, uterine volume is significantly smaller and the endometrial lining is thinner than in healthy controls.^{24,25} There is some evidence to suggest increased obstetrical risks from preterm birth to low birth weight after pelvic irradiation.²⁶ Finally, it is important to keep in mind that cranial irradiation can affect the hypothalamic-pituitary-ovarian axis, with changes in gonadotropin secretion leading to precocious or delayed puberty, ovarian failure, and infertility.

TABLE

Options for Fertility Preservation in Cancer Patients

Before Cancer Treatment

Medical	GnRH agonist concurrent with chemotherapy
Surgical	Oophorectomy prior to pelvic irradiation
Cryopreservation	Embryo cryopreservation* <ul style="list-style-type: none"> • Standard IVF protocols • Tamoxifen and FSH, or letrozole in breast cancer Oocyte cryopreservation Ovarian tissue cryopreservation

After Cancer Treatment

IVF*	Standard IVF protocols Tamoxifen and FSH, or letrozole in breast cancer
Donor oocyte*	

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; IVF, in vitro fertilization.

*Established procedures.

Pregnancy outcomes in cancer survivors

A large-scale epidemiology study (Childhood Cancer Survivor Study, CCSS) encompassing more than 20,000 childhood cancer survivors offers some optimism about pregnancy outcomes. Cancer survivors had a small but significant decrease in live births compared to their siblings (relative risk, 0.52-0.87). Survivors were more likely to choose termination of pregnancy, perhaps because of concerns about pregnancy outcome or maternal medical effects. However, stillbirth risk was not increased, and no specific chemotherapy agent contributed more to adverse pregnancy outcomes. Radiation to ovaries resulted in a higher risk of miscarriage but had no effect on live births. Survivors did have a 2-fold increased risk of low birth weight infants (<2500 g). This appears to be related primarily to an increase in preterm births.²⁶ Women with a history of pelvic radiation have the highest risk for low birth weight, small-for-gestational-age, and preterm birth outcomes. Radiation is thought to decrease the size and compliance of the uterus, perhaps adversely affecting vascular supply, implantation, and fetal and placental growth. More reassuringly, risk of major congenital malformations does not appear increased compared with

the general population.²⁷⁻³⁰ Further, the concern that offspring of cancer survivors will have a higher risk of developing cancer themselves has also not been validated.³¹ The prenatal and obstetrical care of the cancer survivor should be multidisciplinary, because the spectrum of medical complications resulting from cancer treatment would certainly benefit from diverse expertise.

Options for preserving fertility prior to gonadotoxic therapy

Options available to cancer patients seeking to preserve their fertility appear in the TABLE.

Cryopreservation

Embryo cryopreservation. The most successful option for fertility preservation in women with cancer is embryo cryopreservation for future transfer, performed prior to gonadotoxic therapy. In the general in vitro fertilization (IVF) population, embryo cryopreservation yields a pregnancy rate of 30% to 40%.³² This option requires time for ovarian stimulation and oocyte retrieval, which delay cancer treatment 2 to 5 weeks.³³ Further, younger patients are at higher risk of ovarian hyperstimulation syndrome, which occurs in 5% of all IVF patients. Embryo cryopreservation is currently the preferred option

for patients who have male partners or who would accept donor sperm. Patients with early-stage breast cancer represent a group especially appropriate for embryo cryopreservation because of the usual 4- to 6-week delay between breast surgery and radiation therapy. A prospective cohort of 383 breast cancer survivors followed for a median period of 13 years showed that pregnancy did not increase cancer recurrence rates (hazard ratio, 0.7; 95% confidence interval, 0.25-1.95; $P = 0.49$).³⁴ It is unclear whether transiently elevated estradiol levels in ovarian stimulation affect breast cancer prognosis. There are currently multiple protocols to minimize the estradiol peak in breast cancer patients undergoing IVE, the most promising of which involves administering letrozole and low-dose follicle-stimulating hormone (FSH).³⁵

Oocyte cryopreservation. Freezing oocytes rather than embryos is an option for cancer patients who do not have a partner, decline use of donor sperm, or have objections to embryo freezing and storage. Unfortunately, the technique of oocyte freezing is challenging because of large cellular volume, meiotic spindle fragility, and zona hardening. Although recent protocol improvements have increased mature oocyte (MII) survival rates to 70% to 85% and implantation rates to 5% to 14%, the process is still very inefficient.^{36,37} Fewer than 200 babies have been born using this experimental technique. Using the most optimistic of results, 2% of frozen-thawed mature oocytes will give rise to a pregnancy.³⁶ Therefore, oocyte cryopreservation should be performed only under investigational protocol.³⁸ Cryopreservation of immature oocytes could represent an advantage, since it avoids trauma to the sensitive meiotic spindle of MII oocytes. However, only 1 live birth derived from frozen immature oocytes has been reported to date.³⁹

Ovarian tissue cryopreservation. Ovarian tissue cryopreservation for subsequent transplantation or in vitro maturation offers the advantages of preserving thousands of primordial follicles at one time and potentially restoring temporary endocrine function to cancer survivors who develop

POF.⁴⁰ Autotransplantation may be orthotopic or heterotopic, although, to date, live births have only resulted from orthotopic transplants, in which cryopreserved ovarian fragments are transplanted back to their original anatomic site in the pelvis.⁴¹⁻⁴⁴ This technique faces multiple challenges, including oocyte atresia from both ischemia at the time of biopsy and the freeze-thaw process,⁴⁵ altered hormonal profiles compared to normal ovaries,^{40,46} short transplant survival (reported from 9 months to 3 years) requiring repeat transplantation,^{33,47} and potential reintroduction of cancer cells. Cancer recurrence or reseeding has not been seen in human procedures reported thus far or in experiments where ovarian tissue from lymphoma patients was grafted onto immunodeficient mice.^{48,49} Although these case reports are exciting, clearly, more success must be demonstrated through Institutional Review Board (IRB)-approved protocols before ovarian tissue cryopreservation can be considered a feasible option for women with cancer.

GnRH analogues

The administration of gonadotropin-releasing hormone (GnRH) agonists and antagonists with gonadotoxic chemotherapy is hypothesized to protect oocytes. The theory follows observations that young, premenarchal girls exposed to chemotherapy were less susceptible to POF than were their older, postmenarchal counterparts. By establishing a quiescent follicular metabolic state with GnRH analogues, the resting primordial follicles and oocytes are thought to be spared. Multiple studies with significant methodologic limitations have reported resumption of ovulation, improved hormonal profiles, and pregnancies in girls and women who received GnRH agonists during chemotherapy.⁵⁰⁻⁵⁵ However, the biological plausibility of this approach is somewhat questionable. It is not obvious how GnRH agonists can protect primordial follicles (which constitute the bulk of a woman's ovarian reserve) when these follicles are not known to express gonadotropin receptors and their initial stages of growth

appear to be gonadotropin-independent. To date, the only randomized, controlled trial used busarelin and noted ovarian failure in 4 of 8 treated women compared to 6 of 9 untreated women receiving chemotherapy for Hodgkin lymphoma.⁵⁶ A randomized, controlled trial is much needed to adequately judge the role of GnRH agonists as ovarian protectants.

GnRH antagonists (antide or cetrorelix), with immediate hypothalamic-pituitary-gonadal axis suppression, would avoid the initial "flare" effect of agonists. However, human studies are lacking in this area. A large multicenter trial (OPTION) is under way to assess the efficacy of GnRH antagonists for ovarian protection in estrogen receptor-negative breast cancer patients. In addition, a protocol combining GnRH antagonists and agonists is being tested in the hopes of achieving ovarian suppression within 96 hours, so that chemotherapy can be started without delay.⁵⁷ Until more experience is gained with GnRH antagonists, their routine adjunctive use in chemotherapy cannot be recommended.

Oophoropexy

Women who undergo pelvic radiation therapy are at very high risk of POF. Ovarian transposition or oophoropexy surgically displaces ovaries outside anticipated radiation fields, thereby reducing radiation exposure to oocytes. This surgery has been described for Hodgkin lymphoma requiring abdominopelvic radiation and for gynecologic tumors such as ovarian dysgerminomas.^{58,59}

Most oophoropexies are now performed laparoscopically. Either medial or lateral laparoscopic transposition can be used, depending on the extent of the irradiated field. Medial oophoropexy pulls ovaries from their lateral position to medially behind the uterus, while lateral oophoropexy anchors ovaries to the lateral peritoneum at the level of the anterior superior iliac spines⁶⁰ or even higher in the paracolic gutters.⁵⁹ CT images show that medial transposition left the majority of the ovaries in the field of radiation, whereas lateral transposition adequately excluded the ovaries

from the field.⁶¹ Besides the routine risks associated with surgery, complications of oophoropexy include localized pain and failure of the ovaries to remain transposed. Therefore, it is important to perform oophoropexy close to the time of planned radiation therapy in order to avoid this relatively common outcome.

Spontaneous or IVF pregnancies following oophoropexy have reportedly been normal.^{62,63} Repositioning of the ovaries to their original pelvic loci is not required in order to achieve spontaneous pregnancy, nor is it absolutely necessary for oocyte retrieval and IVF depending on accessibility.⁵⁹

Assisted reproductive technology after cancer therapy

Predicting ovarian function

The ability to predict when ovarian failure might occur would be helpful in determining the need for sex steroid replacement in achieving normal puberty, the window of fertility for family planning, and the onset of menopause for bone and cardiovascular health. Taking into account age at treatment and radiation doses ranging from 3 to 9 cGy, Wallace et al devised a table for predicting age of ovarian failure and the maximum doses at any age that would render the patient sterile.⁶⁴ Currently, no such tool exists to predict ovarian function after chemotherapy.

In infertility treatment, hormonal and ultrasound measures of ovarian reserve such as FSH and antral follicle count (AFC) are used to anticipate response to ovulation induction. Multiple studies of both childhood and adult cancer survivors have reported diminished ovarian reserve in survivors.⁶⁵⁻⁶⁷ Survivors had higher FSH, lower inhibin B, lower anti-Mullerian hormone, and lower AFC than did healthy controls. In cancer survivors, the exact relationship between these measures and response to ovulation induction is unclear.

IVF after cancer therapy

In women who have not chosen to pursue embryo cryopreservation prior to gonadotoxic therapy, IVF may be the most efficient way for these patients to achieve pregnancy with their own

gametes after chemotherapy has been completed. Only 1 study has reported IVF outcomes in cancer patients after treatment. Women with systemic chemotherapy had a poorer response to gonadotropins and lower delivery rates than did women treated for local disease.⁶⁸ In approaching breast cancer survivors, reproductive endocrinologists should consider protocols (as cited above) to maximize oocyte yield with the lowest rise in estradiol, because the effect of even transiently elevated estradiol on their cancer is not known.

Oocyte donation

After a woman has undergone cancer treatment, the option with the highest chance of a delivering a liveborn infant is oocyte donation, with typical live birth rates of 40% to 50% per transfer (www.cdc.gov/ART/ART2005/index.htm). Although this option is not acceptable to all women, many women are grateful for the opportunity to achieve pregnancy with their partner even if it is not genetically their own. This method may actually be preferable to some women whose cancer has a strong genetic component. As with any donor oocyte recipient, both overall medical health and the health of the uterus should be evaluated before attempting pregnancy.

Embryo donation and adoption

Last, embryo donation and adoption remain possible options for the cancer survivor whose chances of having her own genetic child are reduced as a consequence of medical or surgical treatment. In women with prior pelvic irradiation, possible resultant uterine damage must be considered in the decision to carry a pregnancy.

Conclusion

Although dramatic improvements in treatment have prolonged survival for many reproductive-age women with cancer, such women often suffer from compromised fertility and premature menopause. Embryo cryopreservation prior to cancer treatment remains the most feasible solution for women of reproductive age with a partner, as long

as the cancer treatment itself can be safely delayed for ovarian stimulation and oocyte retrieval to be completed. While still considered experimental, other potential options for fertility preservation include cryopreservation of oocytes or ovarian tissue. Ovarian tissue cryopreservation also has the potential for reversing POF and the associated symptoms and long-term health risks, such as osteoporosis. Ovarian transposition may minimize the damaging effects of pelvic radiation. Studies on GnRH agonists and antagonists are methodologically limited and do not conclusively show that these agents are ovarian protectants. After cancer therapy, measures of ovarian reserve suggest diminished ovarian reserve in survivors compared to healthy controls. Oocyte donation offers the best chance for pregnancy after reproductive potential has been compromised by cancer therapy. Although many of these options have tremendous potential, clinicians should encourage cancer patients who consider any experimental approach to take part in IRB-approved protocols.

The use of any of these methods requires close collaboration among cancer patients and members of the medical community who care for them. A multifaceted "oncofertility" team approach that includes the expertise of a reproductive endocrinologist will culminate in the best treatment plan possible, encompassing not just cancer treatment but also fertility preservation. We are optimistic that more choices will soon be available to help cancer survivors lead full reproductive lives.

Disclosures

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Skeletal implications of premenopausal decline in ovarian reserve?

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Follicle-stimulating hormone (FSH) levels increase years before menopause and well before the first clinical signs of declining reproductive physiology are apparent.¹ Indeed, rising levels of this hormone reflect declining ovarian reserve and are one of the earliest manifestations of reproductive aging.²

Evidence of early menopause in premenopausal women diagnosed with reduced ovarian reserve indicates that these patients are experiencing accelerated reproductive aging, with implications beyond suboptimal reproductive performance.³⁻⁵ Proatherogenic lipid profiles⁶ and deteriorating renal function⁷ are associated with premenopausal declines in ovarian reserve. The emerging literature, which is reviewed here, describes the skeletal implications of “replete” versus “deplete” ovarian reserve.⁸⁻¹⁰

Disturbed reproductive hormone milieu and low BMD

Recent data demonstrate a significantly higher prevalence of low bone mineral density (BMD) and enhanced bone turnover in premenopausal infertile women with diminished ovarian reserve compared with women who have normal ovarian reserve.⁹ Further, these data demonstrate positive correlations between early follicular phase serum levels of FSH with bone turnover status (**FIGURE**). Peak bone accrual depends on normal gonadal activity, and skeletal attrition is exacerbated by reproductive aging.¹¹⁻¹⁴ Enhanced bone turnover

in the settings of FSH elevations, hypoestrogenism, and hypoandrogenemia implies that the disturbed reproductive hormone milieu plays a causative role in low BMD in this population.

Although ovarian estrogen is hailed as the critical gonadal determinant of skeletal health and maintenance, recent data challenge this assumption by supporting direct stimulatory effects of FSH on osteoclastogenesis.¹⁵ Positive correlations between bone turnover markers and urinary gonadotropins have been previously described in perimenopausal women.¹⁶ Recent *in vitro* data provide tantalizing evidence supporting a direct role of elevated FSH levels in the pathophysiology of age-related bone loss.¹⁵ Utilizing FSH receptor and FSH β null mice, Sun et al demonstrated skeletal preservation in the setting of severe hypogonadism. In contrast, increased skeletal mass and decreased bone resorption were observed in haploinsufficient FSH β (+/-) mice with normal ovarian function, suggesting that the skeletal actions of FSH are independent of circulating estrogen. These findings imply that elevations in FSH levels may be of pathophysiologic significance in modulating skeletal metabolism toward a net bone loss.

Hypoestrogenism and hypoandrogenemia—observed in premenopausal infertile women with reduced ovarian reserve^{9,17}—are other plausible mechanisms for early skeletal compromise. Estrogens and androgens are both key players in maintaining an osteoblastic dominance relative to osteoclasts.^{11-14,18} Aromatization of circulating androgens to estrogen within the skeleton has been well described, supporting a major role for estrogens in maintaining skeletal health in men and women.¹⁸

Low BMD before menopause

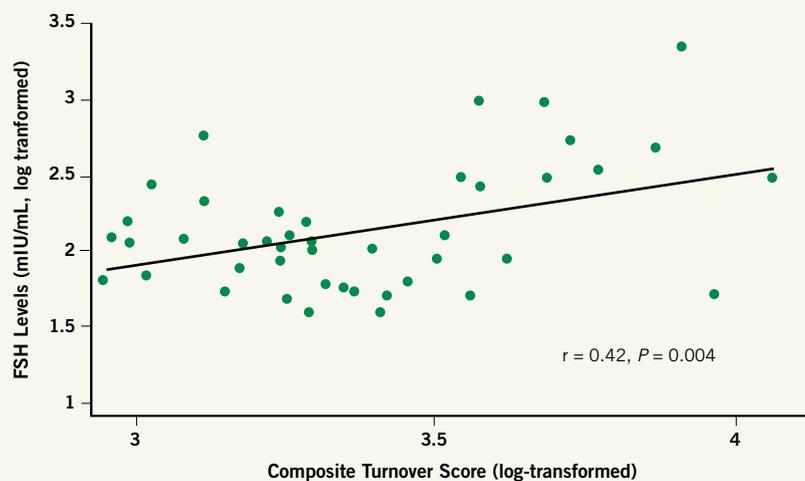
Osteoporotic fractures constitute a major morbidity of the postmenopausal period. The implications of low BMD in premenopausal women, while far less concerning,¹⁹ remain poorly understood. Indeed, short-term fracture risk for a young, albeit light, skeleton is nowhere near that of older bones of a comparable BMD. In terms of preventive care and lifetime risk assessment, however, it is important to realize that the light premenopausal skeleton is destined for progressive attrition concomitant with aging. Because “skeletal reserves” decline in parallel with ovarian reserves, one may posit that, failing vigilant care, premenopausal women identified with low BMD may be future cases of osteopenia and osteoporosis.

Appropriately designed longitudinal studies are much needed to better understand the cause-effect nature of the relationship between ovarian reserve and bone health, as well as the long-term implications of low skeletal reserves in a relatively young population. Meanwhile, diminished ovarian reserve may be added to the growing list of determinants of low BMD in premenopausal women.²⁰ To this end, ovarian reserve testing should be considered in women detected with low BMD and in those who sustain premenopausal fractures; this may provide insight into the pathophysiologic mechanisms at play. Conversely, premenopausal women diagnosed with reduced ovarian reserve will benefit from screening for low bone density and enhanced bone loss.

Preventive care for bone health

Although existing therapies are unable to slow the pace of ovarian attrition, simple interventions can translate to

Increasing FSH Levels Correlate With Enhanced Bone Turnover



FSH, follicle-stimulating hormone.

In a cross-sectional population of premenopausal infertile women (N=45), declining ovarian reserve (as reflected by increasing FSH levels) is accompanied by an upregulation of bone metabolism (reflected by increased serum levels of bone turnover markers). Composite bone turnover score reflects summation of serum levels of bone formation (bone-specific alkaline phosphatase) and bone resorption (N-telopeptide and tartrate-resistant acid phosphatase) markers.

improve skeletal health at any age.^{21,22} Lifestyle modifications, optimization of dietary calcium, vitamins (including D and K), and protein, regular weight-bearing physical activities, attainment of optimal goals for body mass (ie, weight gain in those with a low body mass index), and avoidance of exogenous insults such as smoking (skeletal and ovarian detriment!) are the essential minimums. These strategies are relatively innocuous yet effective in providing skeletal benefit.

Given the ambiguities about long-term fracture risk associated with low BMD during the premenopausal years, any pharmacologic intervention aiming to reduce fracture risk in this population must weigh heavily toward a potential for net benefit. Reduced bone turnover is a recognized noncontraceptive benefit of combination oral contraceptives.²³

This can be considered as an alternative management option for young women with low BMD who do not desire short term fertility.

Disclosures

Dr Pal reports no commercial or financial interests or other relationships with any company that provides medically related services.

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