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PERSPECTIVE

Ovarian Damage During Chemotherapy in Autoimmune Diseases: Broad Health Implications beyond Fertility

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Abstract: Women with autoimmune diseases such as lupus, scleroderma, and vasculitis receiving cyclophosphamide for severe disease manifestations risk primary ovarian insufficiency (POI) due to gonadotoxicity of this therapy. In addition to loss of reproductive potential, POI is associated with increased risk of morbidity and mortality. Practitioners caring for women requiring gonadotoxic therapies should be familiar with long-term health implications of POI and strategies for ovarian preservation. Accumulating evidence supports the effectiveness of adjunctive gonadotropin releasing hormone analog (GnRH-a) for ovarian protection during gonadotoxic therapy in cancer and autoimmune populations. GnRH-a is less costly and invasive than assisted reproductive technologies used for achievement of future pregnancies, but is not Food and Drug Administration approved for ovarian preservation. This review focuses on POI comorbidities and strategies for mitigation of related sequelae, which can accumulate over decades of hypoesteogenism. These issues are arguably more pronounced for women with chronic autoimmune diseases, in whom superimposed POI further heightens risks of cardiovascular disease and osteoporosis. Therefore, even if future pregnancy is not desired, ovarian protection during gonadotoxic therapy should be a major goal of disease management.

Keywords: primary ovarian insufficiency, autoimmune diseases, cyclophosphamide, fertility preservation

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Introduction

Severe manifestations of autoimmune diseases, such as systemic lupus erythematosus (SLE), systemic sclerosis, and vasculitis, often require treatment with gonadotoxic immunosuppressive medications, particularly cyclophosphamide (CYC). While CYC administration prolongs survival in these diseases, it is associated with significant toxicity, including an unacceptably high incidence of primary ovarian insufficiency (POI) in female patients, with consequent irreversible amenorrhea and infertility.[1–3] Beyond reproductive implications, POI is associated with broad and long lasting detrimental effects on general health, quality of life, and life expectancy.[4–6] With autoimmune diseases often affecting women during their reproductive years,[7] it is imperative that the risks of prolonged hypoestrogenemia associated with gonadotoxic therapies are adequately recognized when formulating treatment plans. These issues have been rigorously addressed in the field of oncology, as is evidenced by the development of practice guidelines for fertility preservation in the cancer population.[8] In comparison, rheumatologists have yet to develop similar practice guidelines for fertility preservation in rheumatic disease patients undergoing treatment with gonadotoxic chemotherapy.

In this broad overview, we aim to: (a) increase awareness and understanding of potential health consequences, beyond infertility, of gonadotoxic therapies in young women; and (b) highlight potential strategies for mitigation of such risks and resulting comorbidities, including methods for ovarian protection.

Triple Threat of Primary Ovarian Insufficiency, Underlying Autoimmune Disease, and Treatment Side Effects

Menopause before the age of 40 years is considered to be premature.[5] The term "primary ovarian insufficiency," rather than "primary ovarian failure" or "premature menopause," is the currently preferred term, as it is less stigmatizing and allows the condition to be viewed as a continuum of impaired ovarian function as opposed to a dichotomous state.[9–11] POI has become recognized as "a serious and incurable chronic disease," the diagnosis of which requires a woman to be less than 40 years old, have experienced amenorrhea for 4 months or more, and she has to have two serum follicle stimulating hormone levels obtained at least 1 month apart in the menopausal range.[5] Unlike natural menopause, which occurs on average at age 50 years,[12] 50% of women with POI still have variations in ovarian function, and 5%–10% conceive and deliver a child after receiving the diagnosis.[5,13,14]

While sequelae apply to all causes of POI (which is most frequently considered to be idiopathic, affecting 1% of women under the age of 40 years),[15,16] symptoms are compounded in women with autoimmune diseases. Both the underlying autoimmune/inflammatory processes and their treatments (eg, corticosteroids) are associated with many serious long-term consequences of hypoestrogenism, most notably cardiovascular disease and loss of bone mineral density.[17–21] These potential long-term consequences of ovarian damage, beyond infertility, may be overlooked in women with autoimmune diseases requiring CYC (often on an urgent or semi-urgent basis), and particularly among patients who may not be concerned with future childbearing.

Medications used in Autoimmune Diseases Associated with POI and Common Sequelae

Alkylating agents

Alkylating agents such as CYC and chlorambucil are immunosuppressive medications used to treat severe manifestations of autoimmune diseases, including SLE, systemic sclerosis, and vasculitis, and they are used as part of chemotherapeutic regimens for both hematologic malignancies and solid tumors. Even as potentially less toxic alternatives for CYC therapy become more widely applied (eg, mycophenolate mofetil),[22,23] CYC is still indicated in patients with organ-threatening manifestations of severe autoimmune disease. In humans, CYC-induced ovarian damage is generally regarded as cumulative and irreversible, due in part to the progressive reduction of a limited number of primordial follicles.[1–3] Among female patients treated with CYC for rheumatic disease or malignancy, POI develops in 12% to 83%, depending on variables including patient age, mode of administration, and cumulative CYC dose, all of which are strong predictors of POI.[2,3,24–27] CYC may also contribute directly to bone loss, even beyond its potential to induce a hypoestrongenic state.[28,29] In animal models, CYC decreases the number of osteoclasts and osteoblasts on bone surfaces, and exerts adverse effects on epiphyseal growth plates.[30,31]

Glucocorticoids

Large cumulative doses of glucocorticoid therapy (GC), either by intravenous bolus dosing or through prolonged daily oral therapy, have been associated with side effects including accelerated atherosclerosis and osteoporosis.[20,21,32–35] Although glucocorticoid therapy is a cornerstone of treatment for patients with autoimmune diseases, efforts are continually being made to decrease cumulative exposure by maintaining patients on immunosuppressive "steroid-sparing" agents such as methotrexate, azathioprine, and mycophenolate mofetil. At high intravenous doses (eg, >250 mg), the most common immediate side effects of glucocorticoid therapy include elevation of diastolic blood pressure, cardiac arrhythmia, hyperglycemia, and flushing.[36] Long-term, moderate daily doses of prednisone, defined as >7.5 mg to 30 mg a day for more than 2–3 months are associated with a range of adverse outcomes, including myopathy, glaucoma, cataracts, infections, avascular necrosis, weight gain, and various mood disturbances including depression, anxiety, and even psychosis.[37–39] Even at low daily doses (less than 7.5 mg/day), side effects of glucocorticoids such as acne, easy bruising, weight gain, and cataracts are seen in patients who are treated for more than 90 days,[40–43] although the actual frequency of adverse events at low doses is not as well characterized as that associated with higher dose therapy.[38] Physicians caring for patients treated with glucocorticoids at any dose must be aware of these risks, many of which are compounded in patients with POI. In particular, patients with POI may be at risk for decreased bone density if they lose estrogen during their twenties and thirties, when spinal bone mineral density (BMD) increases significantly, peaking in the mid-thirties.[44] (Rodin et al 1990) Exposure to medications that deplete BMD and induce a hypoestrogenic state prior to or during these years may prevent young women from reaching a normal BMD.

Comorbidities Associated with POI

All-cause mortality

All-cause mortality has been shown to increase twofold with early menopause.[45] Large observational studies of women who experience idiopathic menopause at an age of less than 50 years have revealed significantly increased age-adjusted risk of death compared to women experiencing natural menopause at an age greater than 50 years.[4,46] Similarly, mortality has been shown to be significantly higher in women who undergo oophorectomy before age 45 versus referent women.[47] Recently, prospective data from a large, homogenous population-based study evaluating the risk of fracture and mortality associated with age at menopause revealed that at 34 years of follow-up, women undergoing menopause before age 47 had increased risks of mortality, fragility fractures, and osteoporosis at age 77.[48]

Cardiovascular disease

POI of any cause may also be associated with increased morbidity and mortality from cardiovascular disease (CVD) due to premature loss of the protective effects of estrogen.[45,46] Data from several large cohort studies confirm the presence of a heightened CVD risk among women who had a bilateral oophorectomy before age 40 compared to after age 45, and the effect of exogenous estrogen was not necessarily protective.[49,50] The Mayo Clinic Cohort Study of Oophorectomy and Aging, which included over 2,000 cases of unilateral or bilateral oophorectomy compared to over 2,300 referent women who did not undergo oophorectomy, found increased mortality from CVD associated with bilateral oophorectomy if patients were not treated with HT until or past the age of 45 (HR 1.84, 95% CI 1.27–2.68).[51] Large scale epidemiologic studies of women with POI demonstrate CVD occurring at higher rates and at younger ages in women with POI than in control women, although not all results reached statistical significance.[45,52–57] For example, Snowden et al[4] found an increased risk of death, though this did not reach statistical significance, from coronary heart disease (adjusted OR 1.59, 95% CI 0.58–4.40) and stroke (adjusted OR 1.87, 95% CI 0.51–6.92) in women experiencing natural menopause at an age younger than 40 years as compared to those experiencing menopause at older than 50 years.

Bone density

Osteoporosis is associated with hypoestrogenism due to ovarian insufficiency or natural menopause.[58] Both the time since the onset of menopause and increased chronological age are associated with lower bone density,[59] underscoring the well-recognized risk to bone health that accumulates over decades after early menopause.[58,60,61] In a population-based prospective

study of Swedish women that were followed from the age of 48 years onwards, the authors reported that by age 77, a significantly higher proportion of women who had undergone early menopause had osteoporosis (BMD by dual energy X-ray absorptiometry of hip and lumbar spine) compared to women with late or natural menopause (56% versus 30%, respectively, $P = 0.01$).[48] Other cross sectional studies support the findings of significantly lower BMD in women undergoing oophorectomy prior to menopause as compared to women undergoing natural menopause.[62,63] Osteoporotic fracture rates before the age of 70 are also significantly higher among women with early menopause.[64–67] This problem is compounded in women with autoimmune diseases who experience early menopause, as they have underlying risks for osteoporosis not only due to chronic steroid use, but due to proinflammatory cytokines that drive their underlying inflammatory disease.[33,68–71] Furthermore, women with SLE have further increased risk factors for low bone density, as they often have low vitamin D levels, which are associated with sun avoidance (related to photosensitivity) and with periods of active lupus disease activity.[72–74]

Mental health and neurocognition

The distress associated with POI differs from that experienced by women with natural menopause, which may be due, in part, to the abrupt and unexpected nature of the diagnosis.[75–77] In a study of 100 women with idiopathic POI, 84% of women felt both unprepared emotionally for their diagnosis, and that the diagnosis had created moderate to severe suffering in their lives.[75] Beyond the initial stress of the POI diagnosis, many studies have documented increased rates of anxiety, depression, somatization, negative affect, hostility, or sensitivity among women with POI.[76,78–80] A number of studies have also examined the effects of POI on a woman's sense of self, and have found a significant association with POI and lowered self-esteem, as well as with a feeling of loss of femininity.[76,81–84]

Neurocognitive deficits in women with POI have also been reported, including higher rates of cognitive impairment, dementia, and Parkinson's disease in women with oophorectomy when compared with controls.[85–87] Some of these conditions may have a cumulative effect in women with autoimmune diseases such as SLE, for example, in whom preexisting rates of depression and cognitive dysfunction are increased compared with healthy controls.[88,89] These associations were stronger for those undergoing oophorectomy at a younger age, supporting the hypothesis that estrogen may have a protective effect against the neurodegenerative processes associated with natural aging.

Quality of Life

Vasomotor and sexual dysfunction

Classic symptoms of natural menopause such as hot flashes and night sweats are also prevalent among women with POI, and can be more severe in women who experience menopause at a younger age.[87] In a report by Mar Fan,[90] 51.4% of 41 women with chemotherapy-induced POI experienced moderate to severe hot flashes, as compared with only 19.3% of 57 women undergoing natural menopause, at 1-year follow-up. Besides the immediate discomfort, these episodes of vasomotor instability can disturb sleep and interrupt daily life, leading to impaired mood and frustration.[91] These symptoms represent the most common reason that women request treatment with HRT, which effectively relieves hot flashes for a majority of patients.

Studies have consistently shown that women with POI experience greater rates of sexual dysfunction than control women of comparable ages. Vaginal dryness and associated dyspareunia are commonly reported symptoms of sexual dysfunction among women with idiopathic POI, oophorectomy, chemotherapy-induced POI, and diminished ovarian reserve.[16,78,92–95] These symptoms can lead to a variety of related problems such as difficulty with sexual arousal, satisfaction, and difficulty reaching orgasm, often translating into emotional distress and impaired intimacy, or avoidance of sexual contact.[16,75]

Interpersonal relationships

Sexual dysfunction can affect the experience of a woman's partner as well, and some data suggests that it could lead to sexual impairment in males.[81] In cases where a woman's partner may be desiring children, the loss of fertility may also place an added burden on the relationship.[97] The experience of menopause at a young age has also been described as creating a disconnect between a young woman and her peers,

making her feel older and less able to relate to mates of similar ages.[91]

When POI occurs in the context of chronic illness, it is difficult to assess the impact of ovarian function alone on quality of life. The studies assessed in this review represent a variety of populations and control groups, yet the consistency of results across the studies of POI suggests that it significantly impacts quality of life regardless of underlying health and prognosis. Short versus long-term effects of POI may also confound quality of life assessments. Symptoms in idiopathic POI that impact quality of life may begin months before amenorrhea or the actual diagnosis of menopause, making it difficult to accurately assess women's perceptions of the effects of POI. Some quality of life outcomes may also capture short-term consequences that may not last more than a few months after the onset of menopause. Therefore, the overall impact of POI on the perception of quality of life may be confounded by the duration of symptoms.

Mitigation of Ovarian Damage after Cyclophosphamide

Alternatives to use of bolus CYC

In an effort to reduce exposure to CYC, several newer therapeutic options have been investigated for the treatment of severe manifestations of autoimmune diseases. The use of CYC as induction therapy for lupus nephritis (LN) is declining since the introduction of induction therapy with mycophenolate mofetil (MMF), which may be an adequate initial therapy for mild LN, is well-tolerated,[23,97] and is not associated with gonadotoxicity. A subset of LN patients may also respond to the "Euro-lupus" regimen, consisting of six doses of 500 mg CYC given every 2 weeks, followed by azathioprine.[98] The resulting total CYC exposure of 3 grams is much lower than cumulative doses given in standard 6-month courses for LN. However, patients with severe proliferative LN with renal insufficiency, and those who do not respond initially to MMF, will still require standard monthly intravenous CYC therapy. Similarly, use of the anti-CD20 monoclonal antibody, rituximab, may be an effective alternative to CYC in some patients with systemic vasculitis,[99] further expanding treatment options beyond cyclophosphamide for patients with autoimmune diseases.

Ovarian protection

A number of assisted reproductive technologies exist (eg, oocyte, embryo, or ovarian tissue cryopreservation), which may increase the chances of future childbearing for women undergoing gonadotoxic therapy; however, these "high-tech" reproductive strategies do not address the preservation of ovarian function and its attendant health benefits, which can be extremely costly, and usually requires a delay in medical treatment.

Adjunctive oral contraceptive use during gonadotoxic therapy has been proposed for the preservation of ovarian function, but convincing evidence regarding its efficacy for this purpose is lacking.[100] However, the accumulating data from our group and others suggest that adjunctive treatment with gonadotropin releasing hormone analog (GnRH-a) during CYC therapy protects against the loss of the ovarian reserve, as measured by gradations in anti-Mullerian hormone, a biomarker of the ovarian reserve.[101] Currently, we are conducting an National Institutes of Health-sponsored multicenter randomized controlled trial of GnRH-a for ovarian protection in women with autoimmune diseases receiving CYC, in order to more definitively assess the efficacy of the GnRH-a regimen in this patient population. GnRH-a therapy is far less costly and invasive than other potential methods for fertility preservation. If confirmed as efficacious, the health benefits beyond fertility preservation would make this an important adjunctive therapy to consider regardless of childbearing intentions. If the efficacy of GnRH-a is not confirmed in randomized controlled trials, future interventions should be developed with the preservation of ovarian function as a primary therapeutic strategy.

Management of POI in Women with Rheumatic Diseases

In 2012, the North American Menopause Society addressed the issue of hormone therapy (HT) for women with POI in a position statement on the use of HT in post-menopausal women.[102] The authors advised that in general, women who experience premature menopause—because of their increased risk of osteoporosis, possible increased CVD risk, and their more intense hypoestrogenemic symptoms—should take HT until at least the median age of menopause. While the authors acknowledged that no comparative

data exist, they state that potential benefits for women with POI may outweigh the risks associated with taking HT. Furthermore, the risks associated with POI may actually be fewer than those incurred by older women who commence HT at or beyond the median age of menopause; specifically, the heightened risks of cardiovascular events and breast cancer have been observed among post-menopausal women treated with HT as part of the Women's Health Initiative.[103] Results from the Women's Health Initiative, however, do not necessarily apply to the population of women with POI, who would receive HT as a replacement until the age of natural menopause, and not as supplementary therapy past the age when the body stops naturally producing gonadal hormones. However, HT is contraindicated in patients with increased thrombotic risk, including women with antiphospholipid antibodies either as a primary syndrome, or secondary to autoimmune diseases such as SLE. Hypercoagulability has also been documented in patients with granulomatosis with polyangiitis (formerly Wegener's).[104] Therefore, the best strategy to try to prevent the loss of naturally occurring gonadal hormones, as the best levels recommended for replacement and even the method of delivery of HT for patients with POI have not been well established.

Although few, the currently existing randomized controlled trials that address HT recommendations for women with POI have compared physiological sex steroid replacement versus standard HT (oral ethinylestradiol and norethisterone), and found that those women treated with the physiologic replacement had improved markers of CVD, including lower blood pressure, improved renal function, and less activation of the renin-angiotensin system, as well as improvement in markers of bone mineral density in the lumbar spine.[105,106] However, these studies focused on proxies of disease, and it remains unclear if this treatment simply replaces estrogen until the presumed natural menopause affords young women the same health benefits as the experience of premenopausal women. Even if personalized HT treatment strategies with favorable risk-benefit profiles are developed for women with POI, poor compliance with decades of HT is frequently observed. In one study, only 48% of women with POI were taking HT, with 85% citing increased risk of cancer, stroke, and heart attack as concerns regarding long-term HT.[107]

Conclusions

It has been our experience that long-term health consequences beyond the preservation of fertility (eg, the ability to conceive a child either in vitro or in vivo), including issues of psychosocial and sexual health related to POI are often overlooked in the rheumatic disease patient population. This may be due to the sense of urgency in treating the severe active disease, or to lack of awareness on the part of the practitioner. When faced with the decision to use CYC in premenopausal patients, the burden of disease resulting from POI beyond the loss of fertility must be considered, as it confers on our patients another chronic condition that must be managed in the context of their underlying autoimmune disease. With survival rates among patients with autoimmune diseases and many malignancies improving over time,[108,109] attention to long-term health and quality of life for patients facing gonadotoxic therapy during their reproductive years must be incorporated into their health care plan as early as possible. A broad focus on ovarian protection and related women's health issues, rather than a focus on fertility preservation as the singular goal, is the paradigm shift we have tried to emphasize in this review by describing the wide variety of deleterious outcomes beyond the loss of fertility that are associated with POI due to any cause.

Options for fertility preservation that also prevent POI (for example, the use of GnRH-a during CYC therapy) are increasingly advocated for use in rheumatic and some oncologic diseases.[101,110–117] Promising results in women with SLE treated with GnRH-a during CYC make this therapy attractive, and give GnRH-a a clear advantage over vastly more expensive, invasive, and inconvenient therapies such as cryopreservation of embryos or ovarian tissue. The extensive comorbidities associated with POI discussed in this article, compounded by poor compliance with HT, as well as contraindications for HT among patients with hypercoagulability, make prevention of POI the most attractive strategy. If ovarian protection can be achieved with simple, adjunctive GnRH-a therapy, prevention of POI-

related comorbidities over time would be clearly cost-effective, which is in contrast to assisted reproductive technologies, which are costly, labor intensive, and focus solely on fertility without addressing gonadal protection and long-term health issues associated with hypoestrogenism. We and others feel that GnRH-a has the best likelihood (among currently available options) of preventing POI in our patient population receiving CYC, and we have published our protocol detailing timing and dosing during CYC therapy.[116] However, in advance of results from ongoing clinical trials, such use of GnRH-a is considered "off label." Clearly, increased awareness of the health risks associated with POI is needed. Research efforts should continue to focus on prevention and mitigation of the chronic and complex sequelae of POI in this patient population.

Author Contributions

WM, MG wrote the first draft of the manuscript: WM, MG, SF, ECS Contributed to the writing of the manuscript. WM, MG, SF, ECS agree with manuscript results and conclusions. WM, SF, ECS jointly developed the structure and arguments for the paper. WM, SF, ECS made critical revisions and approved final version. All authors reviewed and approved of the final manuscript.

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