Medical Hypotheses 116 (2018) 49–53

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Exercise and chemotherapy-induced amenorrhea

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ABSTRACT

Chemotherapy-induced amenorrhea (CIA) is the temporary or permanent loss of menses experienced by premenopausal women undergoing chemotherapy treatment for cancer. Two possible mechanisms through which chemotherapy induces CIA have been identified: systemic endothelial dysfunction, resulting in decreased blood flow to the ovaries, and increased oxidative stress within the ovaries, both of which are proposed to lead to apoptosis of follicles. Endothelial dysfunction in ovarian arteries in women undergoing or who have undergone chemotherapy treatment is characterized by prothrombotic changes and thickening of the vascular wall. These changes result in occlusion of the blood vessels. Oxidative stress is increased and antioxidants decreased in the ovaries secondary to chemotherapy drugs, specifically cyclophosphamide. It is hypothesized that low to moderate intensity aerobic exercise during chemotherapy may prevent these changes and lessen the risk for developing CIA in premenopausal women. Low to moderate intensity aerobic exercise has been shown to improve endothelial function and blood flow in patients with cardiovascular disease—a disease state characterized by endothelial dysfunction and for which patients who have undergone chemotherapy are at increased risk. In mice, moderate intensity aerobic exercise has been shown to decrease the amount of oxidative stress within the ovaries, and in humans, chronic aerobic exercise has been shown to increase antioxidant production systemically. This hypothesis should be tested in both a mouse model, using sedentary and exercising mice treated with chemotherapy drugs that commonly result in CIA, as well as a human model to determine the effects of low to moderate intensity aerobic exercise on ovarian function in premenopausal women undergoing chemotherapy.

Introduction

More women are surviving cancer due to improved detection and treatment, with the total death rate for all cancers declining 23% since 1991 [1]. However, many cancer treatments are associated with a decreased quality of life and persistent adverse health outcomes. One side effect of chemotherapy in premenopausal women undergoing treatment for cancer is ovarian dysfunction and cessation of menses due to the toxicity of chemotherapeutic agents, including platinum based agents, alkylating agents, and anthracyclines [2–4]. Ovarian dysfunction can manifest as temporary chemotherapy induced amenorrhea (CIA), with women eventually resuming menses, or as permanent chemotherapy induced menopause (CIM) [5–8].

Rates of CIA in premenopausal women undergoing chemotherapy treatment for various cancers vary between 3% and 93.3%, depending on the cancer type and treatment regimen [8,9–13]. In premenopausal women with breast cancer undergoing chemotherapy, rates of CIA typically vary between 35% and 93% [7,10,14–16]. Risk factors for developing CIA include increased age at time of diagnosis [7,8,11–13,15], duration of chemotherapy [14], addition of tamoxifen [8,11], and initiating chemotherapy during the follicular phase of the menstrual cycle [14]. Rates will vary between studies due to inconsistencies in the definition and measurement of CIA among investigators. Frequently reported outcomes used to classify women as having developed CIA or CIM include: self-reported menstrual status; changes in estrogen, follicle stimulating hormone, luteinizing hormone, and anti-Müllerian hormone levels; and antral follicle count [5,9,17,18]. Additionally, the duration of the absence of menstruation used to classify women as having developed CIA ranges from 3 to 24 months [3]. To clarify the incidence of CIA and CIM, standard definitions and measurements need to be established. The authors of this paper propose that the presence of CIA be uniformly defined by the absence of menses for ≥3 months, serum FSH > 40 IU/L, and serum estrogen (E_2) < 10 pg/ml, which characterize women who experience

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https://doi.org/10.1016/j.mehy.2018.04.022
Received 13 February 2018; Accepted 24 April 2018

primary ovarian insufficiency and menopause [5,19]. CIA is the absence of menses and ovarian dysfunction and should be defined along the same parameters as both conditions in order to accurately characterize and identify women affected by CIA.

Due to the significant reduction in follicular count and changes in hormone levels to postmenopausal levels that characterize CIA, CIA is an indicator of infertility or impaired fertility [5]. For women contemplating pregnancy, the effect of chemotherapy on fertility is an important concern, and may play an important role in a woman's decision about timing and type of treatment for cancer [19]. In a study of women diagnosed with breast cancer, 29% stated that fertility concerns affected their treatment decisions [20]. Fertility concerns may influence a women to forgo or delay chemotherapy or endocrine therapy, as well as opt for one chemotherapy regimen over another [19]. These decisions may affect the survival rate of women with breast cancer.

Current treatment strategies to preserve fertility in women undergoing chemotherapy include embryo and oocyte cryopreservation and gonadotropin-releasing hormone agonists (GnRHa) [21]. GnRHa are proposed to preserve ovarian function; however, results are conflicting about the efficacy of GnRHa [22–24]. Therefore, alternative treatments to preserve or regain ovarian function are of value. Exercise presents as a potential non-pharmacological treatment for women with breast cancer to prevent CIA. Aerobic exercise has systemic effects in vasculature in non-exercising tissues and may improve ovarian blood flow through antiatherogenic effects and a reduction in vascular remodeling [25–27]. Aerobic exercise at moderate intensity upregulates antioxidant production in humans and has been shown to decrease ovarian oxidative stress in a murine model [28–31]. The purpose of this paper is to formulate a mechanistic hypothesis on how exercise may attenuate the effects of chemotherapy on ovarian function, possibly reducing the prevalence of CIA in premenopausal women undergoing chemotherapeutic treatment for cancer.

Chemotherapy induced amenorrhea

Clinical characteristics of advanced ovarian aging, including changes such as decreased follicular count, increased follicular apoptosis, and ovarian blood vessel damage, accompany CIA, suggesting CIA results from or mimics advanced ovarian aging [32–35]. Proposed mechanisms by which chemotherapy treatment induces CIA include vascular endothelial wall damage leading to decreased ovarian blood flow and increased oxidative stress (OS) in the ovaries [2,36–39]. We will first describe how chemotherapy may induce increased ovarian OS and decreased ovarian blood flow. Then we will explore how exercise may ameliorate the effect of chemotherapy on ovarian blood flow and OS levels.

Chemotherapy and ovarian oxidative stress

Alkylating antineoplastic agents and anthracycline based drugs are known to induce CIA in premenopausal women by reducing the number of follicles [5,35,40]. One mechanism through which depletion of the follicular pool occurs is increased induction of follicle apoptosis in the ovaries secondary to granulosa cell apoptosis, which is mediated by increased oxidative stress [5,35]. In vitro, cyclophosphamide, an alkylating agent, induces granulosa cell, and thus ovarian follicle, apoptosis [41,42]. Cyclophosphamide-induced granulosa cell and ovarian follicle apoptosis was found to be mediated by a reduction in the antioxidant glutathione (GSH) and increased intracellular oxidative stress [41,42]. Granulosa cell apoptosis induced by cyclophosphamide was increased in granulosa cells with pretreatment of a GSH-inhibitor (buthionine sulfoximine) and attenuated by treatment with GSH or another antioxidant [41]. Cisplatin, another alkylating agent, has also been shown to induce in vitro oocyte apoptosis preceded by an increase in intracellular oxidative stress and augmented by an inhibition of GSH [42].

In vitro, doxorubicin (DXR) was observed to cross the blood barrier surrounding the oocyte and enter the cell, specifically targeting the mitochondria, suggesting that DXR can enter and have direct cytotoxic effects on the oocyte in vivo [43]. Once inside the oocyte, DXR targets the mitochondria and leads to the generation of mitochondrial superoxides and intracellular oxidative stress [43,44]. DXR-induced toxicity has been shown to be result in GSH depletion in vitro [45,46]. DXR toxicity, in vitro and in murine studies, has been significantly modulated by the addition of a variety of antioxidant compounds, suggesting a protective effect of antioxidants against DXR-induced oxidative stress [46–48]. These findings suggest that follicle damage due to chemotherapy is mediated by an increase in oxidative stress and may be able to be prevented or reduced with sufficient antioxidant protection in the ovary.

Chemotherapy and ovarian blood flow

Chemotherapy has been shown to significantly decrease blood flow to the ovaries [37,47] both in animal models and in humans. In mice administered a therapeutic dose of doxorubicin (DXR), ovarian blood volume was reduced by 33% within 3 min of receiving chemotherapy, which was not significantly improved during a 20 min observation period; however, blood flow was not monitored beyond this period [49]. In the same study, small blood vessels demonstrated significant narrowing within 2–5 min of DXR administration [49]. In humans, ovarian blood flow has been found to decline as early as after the first cycle of chemotherapy, as measured by transvaginal ultrasound which showed a significant decline in vessel resistance and blood velocity [36]. Decreased ovarian blood flow was accompanied by significant increases in follicle stimulating hormone and decreases in anti-Müllerian hormone and ovarian volume, suggesting that the decrease in ovarian blood flow accompanies ovarian dysfunction in women undergoing various regimens of chemotherapy [36]. Ovarian blood flow in humans remains low at 6 months following completion of chemotherapy treatment, with partial recovery observed at 1 year following completion of chemotherapy treatment in women < 35 years of age [35].

It is currently unknown if reduced ovarian blood flow is the cause or consequence of CIA and follicular apoptosis. Ovarian blood flow changes throughout the menstrual cycle [50]. Ovarian blood flow peaks during the preovulatory phase and plateaus during the luteal phase [48–50]. Ovaries of ovulating women were significantly more vascularized compared to the ovaries of non-ovulating women, suggesting a direct relationship between follicle development and ovary vascularization [50]. This is likely due to the increased metabolism of developing follicles [51]. This suggests the possibility that a decline in follicle count as a consequence of chemotherapy-induced follicle apoptosis may result in the decreased ovarian blood flow seen in women diagnosed with CIA. The following section will discuss the direct effects of chemotherapy on ovarian blood vessels that may directly result in decreased ovarian blood flow and ovarian dysfunction.

Vascular endothelial dysfunction

Chronic decreased ovarian blood flow in women treated with chemotherapy is likely secondary to vascular endothelial injury and vascular remodeling as a direct result of chemotherapy. Several chemotherapeutic agents have known vascular endothelial toxicities [52]. While the exact mechanism of vascular endothelial cell damage is still being determined, the downstream effects of endothelial wall damage have been well documented for various classes of chemotherapeutic drugs, including anthracyclines, such as DXR, and alkylating agents, such as cisplatin and cyclophosphamide [52]. Effects of these chemotherapeutic drugs include vascular remodeling by activating cell signaling pathways that promote endothelial remodeling resulting in narrowing of blood vessels, induction of atherosclerotic or prothrombic changes, and changes in vasoconstriction and vasodilation