Chapter 6: Issues Facing Women with Fanconi Anemia: Improved Survival and New Dilemmas

Introduction

Although the diagnosis and treatment of FA remains challenging, recent advances in the management of FA have enabled patients to survive longer than previously possible, resulting in gender-specific health concerns as they reach reproductive age. The issues that females with FA face during their reproductive lifetime most commonly include:

- *Late onset of puberty and early onset of menopause*
- *Cancer, including gynecologic cancer, breast cancer, or secondary cancers following hematopoietic stem cell transplant (HSCT)*
- *Reduced fertility and reproductive lifespan*
- *Excessive menstrual bleeding*

The clinical care team for females with FA should include a gynecologist and, when needed, an **adolescent gynecologist, reproductive endocrinologist, maternal-fetal medicine specialist, or gynecologic oncologist**. This team should work in close collaboration with other FA care specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

Menarche

Approximately 9 out of every 10 healthy women experience their first menstrual period, known as menarche, about 3 years after breast buds develop, as early as age 11 and before age 16. Most females with FA undergo puberty within this age range, but may not experience menarche until their mid-teens and, once menstruation begins, they may have irregular menstrual periods. In addition, many females with FA reach menopause prematurely [(1)]. As a result, females with FA often have a shorter reproductive lifespan compared with women in

the general population. This reduction in fertility may stem from the genetic changes underlying FA, which are associated with hypogonadism [2], or they may result from chronic disease, low body weight, or treatments for bone marrow failure such as stem cell transplantation. Androgen therapy, which is often used to boost the formation of new blood cells in patients with FA, may suppress menstruation, delay menarche, or contribute to irregular menstrual periods.

Good to Know

Hypothyroidism is a condition caused by low levels of the thyroid hormone. This condition can contribute to reproductive issues, including irregular periods and difficulty becoming pregnant.

As discussed in *Chapter 7*, many females with FA experience other endocrine disorders, including hypothyroidism and hypothalamic dysfunction. Hypothyroidism, if unrecognized and untreated, may contribute to irregular periods and infertility. Hypothalamic hypogonadism is associated with delayed puberty, amenorrhea (absence of menstrual periods), and infertility [3].

Pubertal delay is defined as occurring in any female who has not developed breast buds by age 13, or by age 14 in patients who have low body weight [4, 5]. Although pubertal delay in patients with FA may result from low body mass index, chronic disease, or after stem cell transplantation during childhood, patients who start their periods later in life than their healthy peers (3 years after breast buds develop or age 16) should be evaluated for hypothalamic dysfunction [3-5]. Such patients may need hormonal supplementation to optimize growth and to help develop secondary sexual characteristics.

Sexuality and Contraception

It is important to remember that there is more to a patient with FA than just the disease. Along these lines, contraceptive counseling should be considered a central part of gynecologic care for sexually active patients who do not desire pregnancy. Women of reproductive age should also be counseled about safe sex practices and screening for sexually transmitted infections (STIs) [6]. All patients with FA should be encouraged to undergo vaccination against human papillomavirus (HPV), a STI that can cause genital warts as well as cervical cancer and other types of malignancies.

HPV vaccination

Two HPV vaccines, Gardasil® and Cervarix®, are available and approved for use in females between the ages of 9-26. The vaccines were also recently approved for use in males in the same age range [7]. Gardasil®, approved in 2006, is effective against HPV types 6 and 11, which are associated with 90% of cases of genital warts, and types 16 and 18, which are implicated in about 70% of cases of cervical cancer. Gardasil® has been shown to be effective in preventing cervical cancer [8]. Cervarix® is effective against the two most common types of HPV that cause cancer—types 16 and 18—but does not protect against genital warts [9]. Because women with FA have an increased risk of squamous cell cancers of the lower genital tract, it is reasonable to consider HPV vaccination after age 9, although it remains unclear whether vaccination at such a young age protects against squamous cell cancers that may develop during young adulthood. Three doses of the vaccine are recommended: The second dose is administered 2 months after the first, and the third dose is given 6 months after the first. The long-term effectiveness of HPV vaccination is unknown, but studies have shown that Gardasil® remains effective for at least 5 years and Cervarix® for at least 6.4 years [9]. It is currently unknown whether patients, including those with FA, who receive the vaccination will require subsequent booster vaccinations. Although the HPV vaccines will not cure existing HPV-related disease, they may prevent the acquisition of additional HPV types. Because the HPV vaccines do not prevent all lower genital tract cancers, vaccinated women should still undergo regular gynecologic screening.

Good to Know

Human papillomavirus (HPV) is the most common sexually transmitted infection.

There are more than 100 different types of HPV. These viruses can cause genital warts, cervical cancer, and several other types of malignancies.

Vaccines against HPV can prevent some of the cancers caused by these viruses.

Cancer Screening and Treatment

Gynecologic cancers

High rates of lower genital tract squamous cell cancers, including cervical, vaginal, vulvar, and anal cancers, have been reported in women with FA. Patients who have undergone hematopoietic stem cell transplantation—

especially those who developed graft-versus-host disease—have a higher risk of squamous cell cancer compared with patients who have not undergone transplantation [10]. On average, women with FA tend to develop cervical and vulvar cancer at ages 25 and 27, respectively, whereas women in the general population tend to develop cervical cancer at age 47 and vulvar cancer at age 72 [11-13]. In other words, although the absolute risk of such a cancer is very low in all younger women, young women with FA have a several thousand-fold higher risk for vulvar cancer and at least a 100-fold higher risk for cervical cancer compared with young women in the general population [11-13]. In fact, FA testing should be considered in any patient who is diagnosed with cervical cancer prior to age 30 or vulvar cancer prior to age 40.

It remains unclear whether the elevated rates of squamous cell cancers of the genital tract in women with FA are HPV-related. One recent study found that 84% of patients with FA who had head and neck squamous cell cancers were infected with HPV [14]. By contrast, another study revealed that HPV was present in only 10% of patients with FA who developed anogenital cancers, and in none of the patients with FA who had head and neck cancers [15]. Similarly, a study published in 2013 reported low rates of HPV infection in patients with FA who had genital or head and neck cancers [16]. These discrepancies in the prevalence of HPV in squamous cell cancers from patients with FA may be due to many factors, including differences in the way that the laboratory testing was performed, the amount of virus in the patients studied, geographic differences in the prevalence of HPV infection, or differences in the mode of squamous cell cancer development among patients with FA.

Early detection of precancerous lesions in patients with FA is imperative to maximize survival. There is ongoing debate regarding the gynecologic cancer-screening schedule for females with FA. While it is important to be vigilant, it is equally important not to overburden patients by subjecting them to extra testing, anxiety while awaiting results, and potentially unnecessary procedures. With that understanding, yet recognizing the high risk for early vulvar cancer and pubertal delay, women with FA should begin receiving gynecologic care at a younger age than is typically recommended for women in the general population. Females with FA should begin having visual examinations of the external genitalia at age 13. Sexually active women with FA should undergo regular, comprehensive gynecologic exams, including a Pap test and a careful inspection of the cervix, vagina, and vulva. Sexually inactive patients should begin having comprehensive gynecologic examinations at age 18, 3 years earlier than recommended for healthy women [17].

Colposcopy should be done when any abnormal areas are seen on visual inspection or if a cervical cytology test is abnormal. Lesions that are identified during colposcopy or routine examination should be biopsied. Any woman with FA who is diagnosed with dysplasia—a precancerous condition that increases the risk of developing cancer—should receive gynecologic exams with biopsy of any identified lesions every 4 to 6 months. HPV testing can be performed at the same time as the Pap test, although it is important to note that the absence of high-risk HPV types in patients with FA does not mean that this screening interval should be extended. Patients with genital tract dysplasia may also need to undergo anal cytology and/or anoscopy to identify anal cancers, which to date have only been reported in women who also have genital tract disease. In addition, women with FA should be encouraged to receive HPV vaccination, and may benefit from counseling about risks related to STIs.

Good to Know

A **Pap test** (cervical cytology testing) is used to detect cervical cancer and precancerous lesions. During the test, cells are scraped from the cervix and examined under a microscope to identify abnormalities.

During **colposcopy**, the doctor uses an illuminated magnifying device called a colposcope to examine the vulva, vagina, and cervix. The procedure allows the doctor to find abnormal tissues that may be missed by the naked eye.

During a **biopsy**, the doctor removes a small piece of tissue, which is then examined under a microscope to determine whether dysplasia (pre-cancer) or cancer is present.

Anal cytology (sometimes called an anal Pap test) is a screening test used to detect anal cancers and precancerous lesions. During the test, cells are collected from the anus and examined under a microscope to identify abnormalities.

During **anoscopy**, the doctor uses a tube-shaped instrument called an anoscope to search inside the anus and rectum for abnormalities.

The optimal treatment for genital warts or dysplasia is surgical excision or ablation. Vulvar lesions may be treated with immune modulating drugs, such as Aldara, 5-fluorouracil (5-FU), or alpha interferon [18, 19]. The patient's genital area should be inspected periodically during immune modulator treatment to determine whether the treatment is working and to identify any adverse side effects. Patients with FA who have extensive vulvar dysplasia may benefit from a combination of surgical and medical treatment as reported in other patient

populations [20]. Patients with other immune deficiencies typically respond to immune modulators within a few weeks. It is possible that women with FA may benefit from long-term immune modulator treatment due to the likelihood of recurrent or refractory dysplasia. Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately.

Surgery remains the mainstay of treatment for gynecological cancers in patients with FA. These patients tolerate chemotherapy and radiation poorly due to the genetic changes underlying FA, which impair cells' ability to repair the DNA that is damaged by these therapies [21]. Therefore, the patient's hematologist should be consulted prior to administering radiation or chemotherapy.

Breast cancer

One of the genes implicated in FA, *FANCD1*, is the well-known breast cancer susceptibility gene, *BRCA2*; thus, patients with FA may be at increased risk of breast cancer, although few such cases have been reported [22]. Mutations in *BRCA2* also increase the risk of ovarian cancer, but there is no evidence that this risk is enhanced in patients with FA, perhaps because of these patients' shortened lifespan.

Screening for breast cancer in patients carrying *BRCA2* mutations generally begins by age 25-30. Screening is typically performed twice a year, and often includes clinical breast examinations and mammography alternating with MRI [23]. In some instances, both mammography and MRI are performed at the same time, either annually or semi-annually. Ultrasound is often used in conjunction with mammography. These screening guidelines can be extrapolated to patients with FA, regardless of their specific FA gene mutation, because mutations in *BRCA2* or the genes underlying FA disrupt the same DNA repair pathway in cells.

Women with an elevated risk of breast cancer should begin regular breast cancer surveillance, including a clinical breast exam and education about breast self-examination, by the time they reach their early 20s. Mammography may be considered beginning at age 25. Palpable breast lumps should be evaluated immediately. It is unclear whether the mammography screening recommendations apply to patients with FA, as these patients have an elevated sensitivity to radiation exposure due to their underlying genetic defects in DNA repair. The long-term risks of radiation exposure must be weighed against the benefits of early detection [24].

Magnetic resonance imaging (MRI) is very sensitive for detecting breast tumors that may be missed by other screening techniques. However, MRI cannot definitively classify tumors as benign or malignant and has a high false-positive rate; therefore, this technique is usually used in conjunction with mammography [23]. A study that evaluated the use of MRI for breast cancer screening found that scans of premenopausal women had high background enhancement regardless of timing within the menstrual cycle, resulting in a high rate of false-positive cancer diagnoses; however, the diagnostic criteria for suspicious lesions remained the same regardless of the increased false-positive rate [25]. MRI appears to be more sensitive for detecting tumors in patients who have undergone menopause, which causes the breast tissue to become less dense [26]. In the future, MRI may be preferred over mammography in post-menopausal patients with FA as a way to minimize radiation exposure from mammograms [27]; however, this concept has not been studied in this population.

Reproductive Lifespan, Fertility, and Pregnancy

Women with FA may be able to have children, but they often experience reduced fertility and a shortened reproductive lifespan due to delayed menarche and/or early menopause. Very few patients with FA become pregnant after age 30; most reach their maximum childbearing potential by their mid-20s.

Some factors that affect fertility and reproductive health in women with FA include:

- *Early menopause*
- *Irregular menstrual periods (oligomenorrhea)*
- *Absence of menstrual periods (amenorrhea)*
- *Excessive menstrual bleeding (menorrhagia) arising in women with low platelets (thrombocytopenia) and anovulation (failure to ovulate)*
- *Radiation and chemotherapy prior to stem cell transplant*

Most information about fertility in women with FA is compiled from case reports, which suggest that these women have a low pregnancy rate, ranging from 15% among women on androgen therapy to 29% for women not taking androgens [28]. Women who conceive while taking androgens should discontinue androgen therapy immediately to minimize the risk of masculinizing a female fetus.

A study of 285 women with FA who underwent HSCT during a 30-year period found that only 10 of the women subsequently conceived and delivered infants and all were under age 26 [29]. Of those 10 women, 4 had 2 infants each, and 5 showed signs of gonadal failure prior to pregnancy, although 2 of those women recovered spontaneously. All of the pregnancies included in the study occurred 4-17 years after HSCT [29].

Risk factors during pregnancy and childbirth

When a woman with FA does conceive, the pregnancy is not life-threatening but it is important to have a multi-disciplinary approach to the pregnancy. Therefore, a specialist in maternal-fetal medicine should work closely with the patient's hematologist.

Good to Know

Pre-eclampsia occurs when a woman develops high blood pressure and protein in her urine during the second or third trimester of pregnancy.

If left untreated, pre-eclampsia can lead to a life-threatening condition called **eclampsia**, which includes seizures and the possibility of coma.

One study found that blood cell counts decreased during pregnancy in more than half of women with FA. This was associated with thrombocytopenia and the need for blood transfusions, but did not increase the risk of death [28]. In addition, compared with women in the general population, women with FA had a higher rate of pregnancy complications, such as pre-eclampsia, eclampsia, and spontaneous abortions [28]. This study also reported that women with FA had a higher rate of caesarean section than their healthy peers, which was attributed to the short stature and small pelvises of the women with FA, and a higher rate of failure to progress during labor.

Fertility and cancer treatment

Recent improvements in cancer treatment have increased the lifespan of cancer patients. Unfortunately, cancer treatment often results in reduced fertility. In February 2013, the Ethics Committee of the American Society for Reproductive Medicine issued guidelines for fertility preservation and reproduction in cancer patients [30]. ***The most important take-home message from these guidelines is that physicians should inform patients who are undergoing therapies that are potentially toxic to the gonads about the options for fertility preservation prior to the start of treatment.***

Cryopreservation (freezing) of both embryos and eggs has an excellent success rate and can be considered whenever it is clinically available and does not compromise timely treatment of cancer or other conditions. However, the patient's medical status remains the rate-limiting issue. Some fertility preservation strategies may require a woman to postpone her cancer treatment for a month or more while she undergoes fertility treatment. Some reproductive endocrinologists are attempting to retrieve eggs while the patient is in the luteal phase of her menstrual cycle, which allows two opportunities for egg retrieval in a given month rather than just one opportunity. This approach is not performed by many clinicians and remains less successful than conventional egg retrieval methods. The effectiveness of cryopreservation of embryos and eggs from individuals with FA is unknown.

Other realistic options to achieve motherhood should be discussed with patients, including donor eggs, adoption, and surrogacy. Several experimental options hold great promise, including ovarian tissue cryopreservation and the use of leuprolide acetate, which may protect the ovaries from the gonadotoxic effects of radiation and chemotherapy. However, proven methods of fertility preservation are preferred over experimental options.

Menopause

On average, women in the U.S. naturally undergo menopause around age 51. By contrast, most women with FA experience ovarian failure and menopause by their early 30s. As premature menopause is defined by occurrence prior to age 40, most women with FA have premature menopause. The symptoms and health risks associated with menopause, such as osteoporosis, cardiovascular disease, hot flashes, and vaginal dryness, should be managed in patients with FA to maximize their health. Hormone therapy remains the most effective treatment for the symptoms of menopause. Findings from the Women's Health Initiative, an ongoing study of health issues in postmenopausal women, suggest that while hormone therapy may protect against bone loss, it is associated with a slightly increased risk of breast cancer and increased risks of heart attack, stroke, and thromboembolic disease [31]. Nonetheless, women who experience premature menopause and do not use hormone therapy tend to have higher rates of illness and death compared with those who take hormones [32]. Thus, hormone therapy should be recommended for young women with FA who undergo premature menopause.

Hormone replacement therapy may be contraindicated for patients who have cardiovascular disease risk factors. The risk of cardiovascular disease in patients with FA is not known, but an individual patient's family history can provide some important clues. Lipid profiles, insulin resistance (see *Chapter 7*), and blood pressure should be monitored as part of a cardiovascular disease risk assessment. Special attention should be paid to the effects of androgen therapy on lipids.

Women with FA may have low bone density due to the side effects of treatments leading to premature ovarian failure. However, a recent study showed that most children and adolescents with FA have a normal bone mineral density when the results are adjusted for stature [33]. Individuals with low bone density may be at risk for bone fractures, and may develop osteoporosis with further bone loss. There are many osteoporosis treatment options discussed in detail in *Chapter 7*.

Two types of hormone therapy can be administered to women with FA until they reach age 50: oral contraceptive pills (OCPs) or postmenopausal hormone therapy (also known as hormone replacement therapy, HRT), which consists of low doses of conjugated estrogen and progesterone. Given their young age at menopause, women with FA may benefit more from oral contraceptives than from post-menopausal hormone therapy. From a psychological standpoint, young women with FA may feel more like their peers when they use oral contraceptives. Furthermore, oral contraceptives protect against ovarian cancer in the general population as well as in patients with mutations in the *BRCA1* and *BRCA2* genes, and may have the same protective effect in patients with FA who have mutations in the *BRCA2/FANCD1* gene [34].

Menopause can be accompanied by many symptoms that can impair a woman's sexual function, including hot flashes, vaginal dryness, and pain during intercourse—a condition called dyspareunia. Many options exist for managing menopausal symptoms (Tables 1-4). It is important for clinicians to address these aspects of menopausal health because such symptoms can negatively impact the quality of life for many patients.

Good to Know

Thrombocytopenia is a condition caused by low levels of platelets. Platelets help the blood clot and form a scab at the site of an injury. People with this condition are prone to excess bleeding.

Management of Excessive Menstrual Bleeding Before and During HSCT

Women with hematological abnormalities frequently have excessive menstrual bleeding as a result of thrombocytopenia or anovulatory cycles. Excessive menstrual bleeding can cause anemia, present the need for a transfusion, and, in women who have low white blood cell counts, increase the risk of infection. Ideally, a plan for managing excessive menstrual bleeding should be defined and enacted prior to HSCT rather than during the transplant period. Suppression of menstrual bleeding can take approximately 1-2 months, independent of the bone marrow suppression induced by immunosuppressive medications prior to HSCT. Regardless of the timing, the options described below have been shown to be effective for treating excessive menstrual bleeding both before and during the transplant period, or in patients who are not planning to undergo HSCT.

Options for treating excessive menstrual bleeding

Women with FA and excessive menstrual bleeding should undergo a complete blood count. Thyroid level testing may also be useful as hypothyroidism can also cause excessive menstrual bleeding. An ultrasound can be performed to rule out other potential causes of excessive menstrual bleeding, such as polyps or submucosal fibroids that form on the lining of the uterus. Treatments may include surgery or medication, depending on the severity of the bleeding and the patient's hematologic status.

Medications for the treatment of excessive menstrual bleeding in patients with FA include reproductive hormones such as estrogen (administered with or without the hormone progesterone) and a class of drugs known as gonadotropin releasing hormone (GnRH) agonists [35]. Leuprolide acetate, a type of GnRH agonist that is administered via intramuscular injection, has been shown to be effective in inducing menopause in women scheduled for bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) [36-39].

Ideally, medications that suppress menstrual bleeding should be initiated 1 to 2 months prior to HSCT to increase the likelihood that menstruation will cease by the time of transplant. However, many patients are too ill and cannot delay HSCT for such a long time. In those women, high-dose oral contraceptives (containing 50 micrograms or more of ethinyl estradiol) are an effective alternative. These contraceptives avoid the potential complications

associated with intramuscular injections in patients who are prone to excessive bleeding elsewhere in the body due to low platelet levels [36]. However, oral contraceptives may not be an option for patients who have already undergone HSCT. These individuals often cannot tolerate oral medications (due to inflammation of the gastrointestinal tract, nausea, and vomiting) and often have abnormalities in their liver function tests due to hemolysis (the destruction of red blood cells), the toxic side effects of medications, or graft-versus-host disease.

Previously, high-dose oral contraceptives have been used for managing mild to moderate excessive menstrual bleeding. However, studies have shown that low-dose oral contraceptives (containing 35 micrograms or less of ethinyl estradiol) can be as effective as high-dose oral contraceptives for the management of excessive menstrual bleeding and can minimize the risk of endometrial atrophy (thinning of the uterine lining), which is associated with continuous or long-term oral contraceptive use and can eventually lead to excessive bleeding [35, 36]. The treatment regimen has conventionally been 2 tablets per day for 5 days, followed by 1 tablet daily (with no placebo break) until the patient is deemed stable enough to resume menstrual cycles or is considered menopausal [40]. A retrospective review of 33 females who had undergone HSCT and were referred to gynecologists for excessive menstrual bleeding during the transplant period revealed that hormone therapy eliminated symptoms in 97% of the women, and that 79% of the women required only one oral contraceptive regimen [36]. The study found no differences in the response rates among women using low-dose versus high-dose oral contraceptives, monophasic versus multiphasic oral contraceptives, or ethinyl estradiol delivered in the form of pills versus transdermal patches. Patients who have severe excessive menstrual bleeding or are unresponsive to low-dose oral contraceptives may be prescribed high-dose oral contraceptives or injections of conjugated estrogens (25 micrograms every 6 hours for 24 hours). These patients should be switched to some other form of continuous hormonal treatment, such as low-dose oral contraceptives or leuprolide, once their excess bleeding has stopped.

If a patient's excessive menstrual bleeding cannot be managed using medication, additional treatment options are available for individuals who are considered suitable for surgery:

- ***Dilation and curettage***, a procedure in which the doctor dilates the cervix (the narrow passageway between the vagina and the uterus) and inserts a tool called a curette, which is used to gently scrape off some of the tissue

lining the uterus. This tissue is known as the endometrium, which is responsible for menstrual bleeding.

- ***Endometrial ablation***, a procedure that permanently destroys the endometrium. This procedure results in infertility.
- ***Hysterectomy***, a procedure in which the entire uterus is removed.
- Patients who are being treated with leuprolide acetate to reduce excessive menstrual bleeding can also take oral contraceptives to manage any menopausal symptoms and to prevent osteoporosis, which is associated with long-term (more than 6 months) exposure to leuprolide acetate and other GnRH agonists [1].

Future Research Directions

Though FA research has been transformed by a number of remarkable discoveries in recent years, much work remains. Premature ovarian insufficiency and early menopause in women with FA remains poorly understood, and women in their reproductive years need access to better methods of fertility and ovarian preservation before they undergo stem cell transplantation. Future research should also aim to define the risk of breast cancer, delineate the optimal methods for breast cancer screening, and quantify the frequency of successful pregnancies in women with FA. Finally, further studies are needed to improve the diagnosis and treatment of genital tract dysplasia before cancer arises.

Recommendations for Women with FA

- Clinical experts recommend screening for gynecological cancer every 6-12 months. Biopsies should be performed on any visible lesions, because dysplasia can rapidly progress to cancer.
- Gynecologic assessment for pubertal delay and genital lesions in women with FA should begin at age 13. Thorough vulvovaginal examinations and Pap testing can begin when women become sexually active or by age 18, whichever is earlier. Anal pap smears and anoscopy may be considered in those women who have vulvar disease.
- As with the general population, colposcopy is appropriate in the setting of abnormal cytology or suspicious lesions noted on examination.
- Current consensus guidelines for cervical cancer screening, which are published by the American Society for Colposcopy and Cervical Pathology (ASCCP) and call for longer screening intervals than previous guidelines, do not apply to patients with FA.
- To help prevent against HPV infection, females between the ages of 9-26 should get vaccinated with either Gardasil® or Cervarix®.
- Suspicious genital tract lesions should be biopsied. If dysplasia is found, surgical resection or ablation is the preferred method of treatment. Medical therapy with immune modulators or a combination of medical and surgical therapy can also be used, but the patient must be closely monitored for treatment success and adverse effects.
- Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately. Early referral may enable surgical treatment of the cancer, thereby avoiding the risks associated with chemotherapy or radiation in patients with FA.
- Patients with FA should begin breast cancer screening at a younger age than women in the general population. The screening recommendations for patients with FA are similar to the recommendations for other populations at high risk for breast cancer, such as individuals with mutations in the *BRCA1* and/or *FANCD1/BRCA2* genes, and those who have undergone mantle field radiation (a type of treatment that delivers radiation to a large portion of the upper body).
- Breast cancer screening modalities include mammography and MRI. Please see detailed discussion earlier in the chapter under the *Breast Cancer* section.
- Women who are diagnosed with cervical cancer before age 30 and vulvar cancer prior to age 40 may benefit from screening for FA.
- Women with FA who experience premature ovarian failure as a result of FA or HSCT may benefit from oral contraceptive pills or traditional hormone replacement therapy until age 50, at which time other options for managing menopausal symptoms can be discussed with symptomatic patients.

Table 1. Medications for the management of hot flashes.

Agent	Type of drug	Dose	Comments
Traditional hormone replacement therapy (HRT) (31)	Hormone (estrogen is a key component)	Several oral and transdermal (skin patch) options are available	Generally contraindicated for breast cancer survivors Combination therapy recommended for patients who have a uterus Patients may experience uterine bleeding upon cessation of therapy
Fluoxetine (41)	Selective serotonin reuptake inhibitor (SSRI)	20 mg by mouth daily	Significant improvement in the frequency and intensity of hot flashes
Paroxetine (41)	SSRI	10-20 mg by mouth daily	67% reduction in the number of hot flashes 75% reduction in the intensity of hot flashes
Megestrol acetate (42, 43)	Hormone (progestin)	20-40 mg daily	Improvement in hot flashes in up to 70% of women Patients may experience uterine bleeding upon cessation of therapy May cause bloating Stimulates appetite
Clonidine hydrochloride (44)	Antihypertensive	0.1 mg by mouth twice per day, or 0.1 mg by transdermal patch weekly	10-20% reduction in hot flashes Side effects include lethargy, irritability, hypotension, and vomiting
Venlafaxine (45, 46)	SSRI	25-75 mg daily	Improvement in hot flashes Side effects including dry mouth, anorexia, and nausea are more common at doses of 75 mg per day
Gabapentin (47)	Anticonvulsant	300 mg by mouth 3 times per day	

Table 2. Medications for the management of vaginal dryness.

Agent	Type of drug	Dose	Comments
HRT (48)	Hormone (estrogen-based vaginal creams available)	½-1 applicator full, inserted into the vagina at bedtime for 10 days; twice per week thereafter for maintenance	Messy Absorbed into the general circulation Improves vaginal symptoms
Estradiol vaginal ring (49)	Hormone (estrogen)	1 ring, inserted into the vagina every 3 months	Minimally absorbed into the general circulation (7.5 mcg/24h) Improves vaginal symptoms
Estradiol tablets (48, 50, 51)	Hormone (estrogen)	10 microgram tablets 1 tablet inserted into the vagina at bedtime for 14 days; twice per week thereafter for maintenance	Minimal absorption into the general circulation Improves vaginal symptoms

Table 3. Behavioral therapy for the management of hot flashes.

Agent	Type of Drug	Dose	Comments
Paced respirations (52)		6-8 slow, deep breaths per minute, for 15 minutes at least twice a day May do at outset of a hot flash	40-50% reduction in hot flashes (measured objectively)

Table 4. Over-the-counter options for the management of vaginal dryness and painful intercourse [53-55].

Replens®
Astroglide®
Lubrin®; K-Y Jelly®
Vitamin E (capsules/suppositories)
Hyalo GYN®
Bodyglide®

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