

# Chapter 7

## Gynecologic Care for Female Patients with Fanconi Anemia

### Introduction

Patients with Fanconi anemia (FA) now have a high likelihood of reaching reproductive age due to advancements in clinical care that have increased life expectancy. As patients with FA reach young adulthood, gender-specific health concerns should be monitored and treated. This chapter provides an overview of clinical problems female patients with FA may face during their reproductive lifetime. These issues include pubertal delay, irregular menarche, primary ovarian insufficiency, early onset of menopause, reduced fertility and reproductive lifespan, and gynecologic cancer. Clinical care guidelines for gynecologic complications that can occur during and after hematopoietic cell transplant (HCT) also are discussed.

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### Puberty and Menarche

Approximately 9 out of every 10 healthy women experience menarche within three years after breast buds develop, which typically occurs as early as age 11 and before age 16. Most female patients with FA undergo puberty within a normal age range; however, some may experience pubertal delay or not have menarche until their mid-teens. Pubertal delay is defined as breast bud development that is delayed to age 13, or age 14 for individuals

who have low body weight [1, 2]. Pubertal delay in female patients with FA may result from low body mass index or hematopoietic cell transplant (HCT) performed during childhood. Female patients with FA who have no breast development by age 13 or have not started their periods within three years after breast buds develop (by age 15) should be evaluated for hypothalamic dysfunction [1-3]. As discussed in Chapter 10, many female patients with FA experience other endocrine disorders including hypothyroidism and hypothalamic dysfunction [4]. Hypothyroidism, if unrecognized and untreated, may contribute to irregular periods and infertility. Hypothalamic hypogonadism is associated with delayed puberty, amenorrhea, and infertility [3]. If puberty is delayed or does not occur, patients may need hormonal supplementation to optimize growth [4-6].

## **Menorrhagia**

Female patients with FA may experience menorrhagia, or heavy menstrual bleeding, as a result of thrombocytopenia or anovulatory cycles. Menorrhagia can cause anemia and present the need for a blood transfusion. In addition, for female FA patients with normal menses who also have severe anemia, it may be beneficial to suppress menses to limit any blood loss that may worsen anemia. Female FA patients who experience heavy menstrual bleeding should undergo a complete blood count. An ultrasound can be performed to rule out other potential causes of excessive menstrual bleeding, such as polyps or submucosal fibroids that form in the lining of the uterus.

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# **Gynecologic Issues Associated with Hematopoietic Cell Transplant**

## **Menstrual Suppression**

Hematopoietic cell transplantation (HCT) regimens typically result in severe anemia and thrombocytopenia; therefore, menstrual suppression is typically recommended for female patients with FA during HCT. Ideally, medications that suppress menstrual bleeding should be initiated one to two months prior to HCT to increase the likelihood that menstruation will cease by the time of the HCT. Options for menses suppression in FA patients include reproductive hormones such as estrogen, progesterone, and a class of drugs known as gonadotropin releasing hormone (GnRH) agonists [7]. Estrogen-containing medications increase the risk of venous thromboembolism, and, depending on the patient's diagnosis or treatment regimen, estrogen-containing medication may be contraindicated. Leuprolide acetate, a type of GnRH agonist, has been shown to be effective in inducing ovarian hormone suppression in female patients scheduled for HCT [8-11]. Patients who are being treated with leuprolide acetate to reduce excessive menstrual bleeding also can take additional oral hormone ("add-back" therapy, usually with the progestin norethindrone) to

manage any menopausal symptoms and to prevent osteoporosis, which is associated with long-term (i.e., more than 6 months) exposure to leuprolide acetate and other GnRH agonists [5].

## Genital Graft-Versus-Host Disease

Female patients with FA who have undergone HCT may experience graft-versus-host disease (GvHD) (see Chapter 3) in the anogenital area. The wide range in reported incidence of vulvovaginal GvHD of 3-49% suggests that the true rate is likely unknown [12, 13]. Symptoms include vulvovaginal pain or itching, dysuria, dyspareunia, difficulty with tampon insertion, or postcoital bleeding. Exam findings include vulvar skin erythema and pain on gentle touching, with specific diagnostic mucosal changes (termed lichen planus-like or lichen sclerosis-like features), fissures, erosions, vulvar or vaginal scarring, including loss of the normal vulvar appearance (including vulvar folds). Topical therapies, including steroids and immune modulators, estrogen vaginal rings and dilators, are the mainstays of treatment [14]. Genital exams for female FA patients who have undergone HCT should include examination for the above findings and to distinguish genital GvHD from other conditions, including genital HPV-related disease [12, 15].

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## Primary Ovarian Insufficiency

On average, menopause typically is diagnosed around age 51 for women in the U.S. Menopause that occurs prior to age 40 is considered premature. By contrast, most female patients with FA experience primary ovarian insufficiency (POI) by their early 30s. The medical diagnosis of POI is sometimes referred to as “premature menopause.” In POI, also described as decreased ovarian reserve, ovarian function can be intermittent. Up to 10% of women with POI experience spontaneous conception. Primary ovarian insufficiency is a spectrum of low ovarian reserve, declining ovarian function, reduced fertility, and estrogen deficiency. Follicle stimulating hormone (FSH) levels measured twice, two months apart, and persistently elevated levels along with irregular menses confirm a POI diagnosis. In girls who underwent gonadotoxic therapy prior to menarche (e.g., in HCT regimens), an absence or arrest of pubertal development together with elevated FSH are indicative of POI. The two main functions of the ovary are to produce the hormones estrogen and progesterone and to release mature oocytes for fertility. In patients with POI, both of these functions are affected.

From a hormone production standpoint, any female FA patient who underwent gonadotoxic therapy prior to or after puberty should be monitored for POI. For pre-pubertal patients, FSH should be measured annually until it is determined whether hormone therapy is indicated to start pubertal development. This monitoring typically is done in consultation with an endocrinologist. Hormone therapy for pubertal development

is comprised of incremental hormone doses during which height (the normal pubertal “growth spurt”) also is monitored. For patients who have not undergone gonadotoxic therapy and who are post-pubertal, clinically monitoring for menstrual pattern and periodic monitoring of FSH is suggested.

## Hormone Therapy

Optimal hormonal treatment of female FA patients diagnosed with POI serves to replace the hormones that would be produced by the ovary before menopause, making treatment distinctly different from hormonal therapy for menopause that focuses on menopausal symptoms. Two types of hormone therapy can be administered to female FA patients who have POI until they reach age 50: oral contraceptive pills (OCs) or postmenopausal hormone therapy (also known as hormone therapy, HT), which consists of low to physiologic doses of estrogen and progestins. Either approach to HT is superior to no therapy regarding the effects on bone and other aspects of health [16, 17]. Many clinicians and the American College of Obstetricians (ACOG) favor recommendations of postmenopausal regimens with enough estrogen (slightly higher doses) to maintain bone health [17, 18]. Large studies comparing various doses and types of HT for hormonal contraception have not been undertaken. Given their young age of onset with POI, female FA patients may benefit from taking oral contraceptives rather than HT to prevent pregnancy. The dose in HT is lower and, thus, may not be effective in preventing pregnancy. This is an opportunity for shared decision-making regarding the use of oral contraceptives versus menopausal hormone therapy for optimal bone health. Furthermore, oral contraceptives given to premenopausal women protect against ovarian cancer and likely have a minimal impact on the risk of breast cancer in the general population as well as in patients with variants in the *FANCS/BRCA1* and *FANCD1/BRCA2* genes [16, 19]. Whether the same protective effect of oral contraceptives occurs in individuals with POI or FA who have variants in the *FANCD1/BRCA2* gene is unknown [20, 21].

Women in the general population who experience POI and do not use HT tend to have higher rates of osteoporosis, cardiovascular disease and stroke, general illness and death compared with those who take hormones [22]. It also is not clear that the risks of HT described in postmenopausal women are the same for women with POI who are replacing and receiving physiologic levels of hormone. Therefore, HT should be recommended for female FA patients who have POI and are not using contraceptives. The goals of HT in POI include levels that maintain bone, cardiovascular, and sexual health [16]. Hormone therapy also remains the most effective treatment for the symptoms of menopause (Tables 1 and 2).

**Table 1. Medications for management of hot flashes during menopause.**

<b>Agent</b>	<b>Type of Drug</b>	<b>Dose</b>	<b>Comments</b>
Combined hormone therapy (HT) [23]	Hormone (estrogen and progestogen)	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, Paroxetine [24]	Selective serotonin reuptake inhibitor (SSRI)	Fluoxetine: 20 mg per day Paroxetine: 10-25 mg per day	Contraindications include neuroleptic syndrome, serotonin syndrome; drug interactions with tamoxifen
Escitalopram or Citalopram [24]	SSRI	Escitalopram: 10-20 mg per day Citalopram: 10-20 mg per day	Contraindications include neuroleptic syndrome, serotonin syndrome; can be used with tamoxifen
Venlafaxine, Desvenlafaxine [24]	Selective norepinephrine reuptake inhibitor (SNRI)	Venlafaxine: 37.5-150 mg per day Desvenlafaxine: 100-150 mg per day	Contraindications include neuroleptic syndrome, serotonin syndrome; can be used with tamoxifen; side effects, including dry mouth, anorexia, and nausea, are more common at higher doses
Gabapentinoids [24]	Anticonvulsant	300 mg by mouth up to three times per day	Improvement in hot flashes; side effects, including dizziness, unsteadiness, and drowsiness, initially experienced, generally improve over time
Megestrol acetate [23]	Hormone (progestogen)	20-40 mg per day	Patients may experience uterine bleeding upon cessation of therapy; may cause bloating; stimulates appetite
Norethindrone	Hormone (progestogen)	NA: 5-10mg per day	Side effects include bloating, weight gain, stomach upset, diarrhea, gas
Conjugated estrogens and bazedoxifene [23, 25, 26]	Hormone (estrogen and selected estrogen receptor modulator (SERM))	0.625mg/20 mg per day	Side effects include muscle spasms, nausea, vomiting, diarrhea, abdominal pain
Pollen extract [24, 27, 28]	Flower pollen, non-hormonal	2 tablets per day	No contraindication, even if bee allergy; always check with MD before starting any medication
Clonidine hydrochloride [24]	Antihypertensive	0.1 mg by mouth twice per day, or 0.1 mg by transdermal patch weekly	Less frequently used; side effects include hypotension, lightheadedness, dry mouth, dizziness, sedation and constipation

**Table 2. Hormonal medications for management of vaginal dryness and genitourinary symptoms of menopause.**

Agent	Type of Drug	Dose	Comments
Hormone treatments [29]	Hormonal cream (estrogen)	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
Estradiol vaginal ring [30]	Hormonal ring (estrogen)	1 ring 7.5 mcg/24h, inserted into the vagina every 3 months	Minimally absorbed into the general circulation; higher dose rings require progestin use
Estradiol tablets [31, 32]	Hormone (estrogen)	10 mcg tablet 1 tablet inserted into the vagina at bedtime for 14 days; twice per week thereafter for maintenance	Minimal absorption into the general circulation

Findings from the Women’s Health Initiative, an ongoing study of health issues in postmenopausal women, initially reported that HT was associated with a slightly increased risk of breast cancer and increased risks of heart attack, stroke, and thromboembolic disease while it protected against bone loss [33]. However, recent re-evaluation of these study data suggests that continuous estrogen treatment alone either decreases or has no effect on breast cancer risk [34]. These observations may not apply to all estrogen preparations since not all estrogens have been studied and the type of estrogen studied may have protective effects on the breast. Importantly, only those women who have undergone hysterectomy are candidates for estrogen-only therapy, and combination therapy with estrogen and progestins resulted in a slightly increased risk of breast cancer. However, as stated above, these risks were observed in postmenopausal women and are not thought to apply to younger women with POI.

## Bone Density

Most children and adolescents with FA have a normal bone mineral density when the results are adjusted for stature [35]; however, female patients with FA may have low bone density due to the side effects of HCT treatment. Individuals who undergo POI before peak bone mass at age 30 and who do not use hormone therapy are at risk for bone fractures and may develop osteoporosis with further bone loss. There are many osteoporosis treatment options, including drugs known as bisphosphonates including alendronate and risederionate, which prevent bone resorption, and hormones (estrogen and raloxifene), which build bone. Patients who cannot tolerate oral medications or who are resistant to other treatments may benefit from infusions of zoledronic acid or teriparatide. To prevent

bone loss, most postmenopausal FA patients, including those with POI, should take calcium (1200-1500 mg daily) and vitamin D (400-800 IU daily) supplements. Many women are deficient in vitamin D, possibly due in part to the use of sunscreen, which can reduce the amount of vitamin D that the body produces in response to sunlight exposure. Vitamin D levels can be tested to determine whether supplementation is needed.

## Sexual Health

It is important for clinicians to screen for and address sexual health concerns because sexuality is an important aspect of quality of life. Primary ovarian insufficiency can be accompanied by many symptoms that can impair a woman's sexual function, including hot flashes, vaginal dryness, and dyspareunia (suggested hormonal treatments for these symptoms are discussed above and shown in Tables 1 and 2). Conditions related to prior treatments, such as vulvovaginal GvHD, also can impact sexual function.

Treatment for sexual dysfunction is individualized to the patient. Hormone therapy and many non-hormone options exist for managing menopausal symptoms (a sample of available options can be found in Tables 1 and 2). For patients with POI, topical estrogen therapy may be needed in addition to systemic HT for the genitourinary symptoms of menopause. Vaginal dryness and pain during intercourse also can be treated with over-the-counter products including long-acting moisturizers, lubricants, vitamin E capsules and suppositories, and vaginal hyaluronic acid [36-38]. Patients with POI or vulvovaginal GvHD also may need management with vaginal dilators if vaginal stenosis is present. Physical therapy, including pelvic floor physical therapy, also may be appropriate for some patients. In addition, women with chronic medical conditions may be at increased risk of depression, body image concerns, or social isolation, which also can impact sexual function. Mental health and/or relationship concerns relative to sexual dysfunction are best addressed, as appropriate, with a psychologist, psychiatrist, or a sexual health therapist.

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## Reproductive Lifespan, Fertility, and Pregnancy

Female patients with FA may be able to have children, but they often experience reduced fertility and a shortened reproductive lifespan due to delayed menarche, early menopause, and reduced fertility [4, 6, 39, 40].

Some factors that affect fertility and reproductive health in female FA patients include:

- Early menopause
- Infrequent menstrual periods (oligomenorrhea)
- Absence of menstrual periods (amenorrhea)
- Radiation and chemotherapy prior to hematopoietic cell transplantation (HCT)

## Contraception

Contraceptive counseling is a central part of gynecologic care for sexually active FA patients who do not desire pregnancy; this counseling includes patients with a diagnosis of POI, as unpredictable, random ovulation can occur in these patients resulting in a 5-10% chance of spontaneous pregnancy. If female FA patients of reproductive age are sexually active and pregnancy is not desired, use of contraception is advised and missing a menstrual period warrants pregnancy testing [41]. Oral contraceptive pills also can be prescribed to improve menstrual regularity in patients with irregular periods. Contraceptive counseling of patients with FA also provides an opportunity to emphasize the importance of safe sex practices and screening for sexually transmitted infection (STI) [42] and vaccination against human papillomavirus (HPV) (see page 129 of this chapter for more details).

## Fertility and Pregnancy Rates

Pregnancies have been reported in female patients with FA, both those who were treated with HCT and those who were not [39, 40]. In all reports, very few FA patients become pregnant after age 30; most childbearing in FA patients occurs by the mid-20s. Some women with FA whose pregnancies occurred at older ages may have more mild forms of FA and appear unaffected until worsening anemia related to FA is diagnosed during pregnancy [43].

Most information about fertility in female patients with FA who have not undergone HCT 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 [39]. This low fertility rate is supported by animal models of FA [6]. Women who conceive while taking androgens should immediately discontinue androgen therapy to minimize the risk of masculinizing a female fetus.

Regarding pregnancy after HCT, among 101 female patients with FA over age 16 years who underwent HCT during a 30-year period, only 10 patients (10%) conceived and all infants were delivered prior to age 26 [40]. Of those 10 patients, four had two infants each. Five of these patients showed at least transient signs of gonadal failure prior to pregnancy. In this study, the median age at transplant was 12 years and pregnancies occurred 4-17 years after HCT [40]. This pregnancy rate is somewhat higher than pregnancy rates reported after HCT across the transplant population in general. This higher rate may be due to the lower radiation and chemotherapy doses received by female FA patients and their relatively younger age at transplant.

## Monitoring for Primary Ovarian Insufficiency and Infertility

Reproductive endocrinologists and other clinicians currently evaluate anti-mullerian hormone (AMH) as a marker of “ovarian reserve,” or an estimate of the number of

immature follicles that later may be able to become mature oocytes. Anti-mullerian hormone is made by the small, immature follicles in the ovary and does not vary over the menstrual cycle, but slowly declines over a woman's reproductive life. In one study of female patients with FA, the AMH level was extremely low in all patients over age 25, which reflects the known low fertility and primary ovarian insufficiency (POI) in these women [44]. Additionally, chemotherapy treatment has been shown to at least temporarily lower AMH levels [45]. Considering these observations, measuring AMH values over time may allow opportunity for female patients with FA to seek fertility preservation treatments before or when decreasing AMH levels are detected, prior to the onset of POI.

## **Risks to Fertility and Methods of Fertility Preservation**

Female patients with FA have low fertility in general and some treatments involving chemotherapy or pelvic radiation may further impair future fertility. In particular, HCT regimens typically require pre-transplant chemotherapy and radiation that pose a significant risk of infertility. In February 2013, the Ethics Committee of the American Society for Reproductive Medicine issued guidelines for fertility preservation and reproduction in cancer patients [46]. The most important take-home message from these guidelines is that physicians should inform patients about the options for fertility preservation prior to the start of therapies that are gonadotoxic. The known risks of infertility and of POI in female FA patients has led to consideration of elective oocyte or embryo cryopreservation before primary ovarian insufficiency occurs.

Cryopreservation of both embryos and eggs has an excellent success rate and may be considered whenever it is clinically available and medically feasible. The process of embryo or egg cryopreservation requires a month or longer. In cancer treatment settings, it does not appear to compromise timely cancer treatment or increase the risk of mortality [47, 48]. However, the patient's medical status and the urgency to complete the next steps in treatment (for example, initiating urgent therapy for a cancer diagnosis) remain the rate-limiting issues. New assisted reproduction protocols are enabling a shorter time to oocyte retrieval.

Other realistic options to achieve motherhood should be discussed with patients, including donor eggs, adoption, and surrogacy. Several options are being actively pursued, including gonadotropin releasing hormone agonists [9], which currently are used to suppress menses and additionally may protect the ovaries from the gonadotoxic effects of radiation and chemotherapy, and ovarian tissue cryopreservation [22]. However, proven methods of fertility preservation are preferred over experimental options.

Some parents of children with FA explore the use of assisted reproductive technologies such as in vitro fertilization with embryo selection and tissue matching to conceive additional children who do not have FA. These children may be able to provide stem cells to assist with the early treatment of their sibling with FA (see Chapter 3). As part of assisted

reproductive technologies, preimplantation genetic diagnosis (PGD) can be performed to identify the FA status of the embryos and implant only those that are FA-negative (see Chapter 2). If PGD is not available, amniocentesis or chorionic villus sampling (CVS) can be used to determine the FA status of a fetus during pregnancy.

## Risks During Pregnancy and Childbirth

When a female patient with FA does conceive regardless of whether she has undergone HCT, a specialist in maternal-fetal medicine should work closely with the patient's hematologist. Pregnancy risks vary based on a woman's current health status, prior diagnoses, and prior treatments; however, some risks may be common to all female FA patients.

In women who have not undergone HCT, the largest case series found that blood cell counts significantly decreased during pregnancy in more than half of the female patients with FA; this decrease was associated with thrombocytopenia and the need for blood transfusions, but did not increase the mother's risk of death [39]. In contrast, similar rates of transfusion and an increased mortality risk were seen in female patients with other types of aplastic anemia, a condition that occurs when the bone marrow does not produce enough blood cells [39]. Compared with female patients in the general population, patients with FA who had not undergone HCT had a higher rate of pregnancy complications, such as pre-eclampsia, eclampsia, and spontaneous abortions [39]. In this same study, female patients 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 FA patients; the patients with FA also had a higher rate of failure to progress during labor [39].

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## Gynecologic Cancers

High rates of lower genital tract squamous cell cancers (SCC), including cervical, vaginal, vulvar, and anal cancers, have been reported in female patients with FA. Patients who have undergone HCT—especially those who developed graft-versus-host disease (GvHD) (see Chapter 3)—have a higher risk of SCC compared with patients who have not undergone HCT [49, 50]. On average, female patients 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 [51-53]. This age difference means that young female patients 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 [51-53]. Because of this, 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.

## **Human Papillomavirus and Gynecologic Cancer in Patients with Fanconi Anemia**

In individuals with FA, detection of HPV in primary anogenital or head and neck squamous cell cancers was high in one study [54], and low in vulvar or absent in the head and neck cancers in two other studies [55, 56]. Importantly, others reported high rates of HPV detected in oral rinses in adults and children [57, 58] and laboratory studies have shown that the loss of FA pathway components in mucosal and skin cells stimulates proliferation of HPV lesions (via HPV genome amplification). These studies provide some evidence that an intact FA pathway functions to limit the HPV life cycle [59]. The variable prevalence of HPV in squamous cell cancers, high rates of HPV in oral rinses from a wide age range of individuals with FA, and insights into the important role the FA pathway serves in controlling HPV together illustrate that our current understanding of the role of HPV in FA-related tumors is incomplete and indicate that further research is needed. The discrepancies in the role of HPV may be due to many factors, including differences in the amount of virus in the individuals studied, geographic differences in the prevalence of HPV infection, or differences in the mode of squamous cell cancer development among individuals with FA. Testing for HPV in female FA patients can be performed at the same time as the Pap test, although the absence of high-risk HPV types in patients with FA should not change the screening interval. Individuals with genital tract squamous intraepithelial lesion (SIL) also may require anal cytology, anoscopy, and lesion biopsy to identify anal SIL and cancers.

## **Recommendations for Vaccination Against Human Papillomavirus**

Current guidelines from the U.S. Centers for Disease Control and Prevention (CDC) recommend routine HPV vaccination of both females and males [60]. There are many different types of HPV; the current vaccine protects against acquiring the nine HPV types that are most commonly associated with cervical, vaginal, and vulvar cancers, and genital warts. The vaccine is available for ages 9-45 years [61]; ideally, the vaccine should be given before the patient has ever been exposed to HPV through sexual intercourse. Three doses of the vaccine are recommended for healthy individuals age 15 years and older. For healthy individuals age 9-14 years old, only two doses of the vaccine are recommended to achieve the same immune response [62]. The long-term effectiveness of HPV vaccination is unknown, but studies have shown that the vaccine immunity continues for at least 10 years in healthy individuals [62]. Because female patients with FA have an increased risk of squamous cell cancers of the lower genital tract, it is strongly recommended that they receive HPV vaccination starting at age 9. Recent small, cross-sectional studies of individuals with FA after HPV vaccination showed a similar, durable response compared to studies in healthy volunteers, suggesting that female FA patients will respond to vaccination [63, 64]. It currently is unknown whether patients with FA who receive the vaccination will require all three doses of vaccine in the series or booster vaccinations

later in life. Although the HPV vaccines will not treat or cure existing HPV-related disease, they may prevent the acquisition of HPV types not currently present. Because the HPV vaccines do not prevent all lower genital tract cancers observed in female FA patients, vaccinated women should undergo regular gynecologic screening, including Pap test. Re-vaccination (or vaccination) against HPV after transplantation is advised, as this will decrease the risk of acquiring HPV after HCT and may reduce the occurrence of HPV-related disease, which, in turn, may help to minimize the risk of secondary cancers [65]. Female FA patients vaccinated after HCT have similar immune responses to those who have not undergone HCT and healthy women [63, 64].

## **Gynecologic Cancer Surveillance**

Early detection of precancerous lesions in individuals with FA is imperative to maximize survival. There is ongoing debate regarding the gynecologic cancer-screening schedule for female patients 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, and because these patients have a high risk for early vulvar cancer and pubertal delay, female FA patients should begin receiving gynecologic cancer screening at a younger age than is typically recommended for women in the general population. Female FA patients should begin having visual examinations of the external genitalia at age 13. Sexually active FA patients, and all women with FA who are 18 years or older, should undergo regular, comprehensive gynecologic exams, including a Pap test and a careful inspection of the cervix, vagina, and vulva. As a comparison, current guidelines for women without FA recommend beginning Pap testing at age 21 years [66].

## **Recommendations for Colposcopy and Biopsy**

Colposcopy of the vulva, vagina, or cervix should be performed 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 promptly. Clinicians should biopsy even those lesions with a benign appearance, as malignant lesions may have an atypical appearance and biopsy is the only way to exclude precancerous disease needing treatment or cancer. Any female patient with FA who is diagnosed with squamous intraepithelial lesion (SIL, a precancerous condition that increases the risk of developing cancer) should undergo gynecologic exams with biopsy of any identified lesions every four to six months.

Female patients with FA and clinicians may find increased challenges with Pap tests and colposcopy. There may be a higher rate of “Unsatisfactory for evaluation” Pap test results due to insufficient cells, likely related to hypoestrogenism from primary ovarian insufficiency. Hypoestrogenism-associated vaginal atrophy also may cause increased discomfort with speculum exams in these patients. This discomfort can be minimized if

clinicians undertake examinations using either pediatric-sized or very narrow speculums, even in adult patients, and additionally lubricate the speculum with warm water or a thin coating of gel-based lubricant. Procedures under anesthesia may be appropriate for select patients.

With these challenges in mind, clinicians need to weigh the risks and benefits of strict adherence to the above Pap test and colposcopy guidelines, which are based on expert opinion and, at times, develop an individualized follow-up schedule that accomplishes long-term screening goals. For example, for patients whose Pap test results are “Unsatisfactory,” current American Society for Colposcopy and Cervical Pathology guidelines recommend a repeat Pap test in 2-4 months; however, for a female FA patient with otherwise normal-appearing external genitalia and speculum exam, a slightly longer interval may be desirable, particularly if an intervention such as vaginal estrogen is initiated to treat hypoestrogenism or if sedation is required to obtain the Pap test. The risks and benefits of colposcopy for a patient with a visually normal cervix and genital tract and a Pap test result of atypical squamous cells of undetermined significance (ASCUS) that is HPV negative, is an opportunity for shared decision-making regarding the options of colposcopic evaluation versus increased frequency of Pap tests for surveillance.

## **Surgical Treatment of Gynecologic Cancer**

The optimal treatment for genital warts or SIL is surgical excision or ablation. Vulvar lesions also may be treated with immune modulating drugs, such as imiquimod, 5-fluorouracil (5-FU), or alpha interferon [67, 68]. 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 SIL may benefit from a combination of surgical and medical treatment as reported in other patient populations [69]. Patients with other immune deficiencies typically respond to immune modulators within a few weeks, and thus female FA patients may benefit from long-term immune modulator treatment due to the likelihood of recurrent or refractory SIL. Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately.

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## **Breast Cancer Screening in Patients with Fanconi Anemia**

Five of the genes implicated in Fanconi anemia (FA) are breast cancer susceptibility genes (see Chapter 2): *FANCD1/BRCA2*, *FANCI/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, and *FANCS/BRCA1*. Breast cancer risk for individuals with FA who harbor variants in these genes or other FA genes has not been established; therefore, more research is needed to

develop guidelines for breast cancer screening for female patients with FA (regardless of their specific FA variant).

Screening for women in the general population who are carriers of variants in the *FANCD1/BRCA2* and *FANCS/BRCA1* genes starts with annual breast exams and annual breast magnetic resonance imaging (MRI) examination starting at age 25 years. Imaging is increased in frequency at age 30 years to twice a year and includes clinical breast examinations and mammography alternating with MRI [70]. In some instances, both mammography and MRI are performed at the same time, either annually or semi-annually. Ultrasound is recommended by the U.S. Food and Drug Administration in conjunction with mammography, particularly for women with dense breasts [71-73].

It is unclear whether the mammography screening recommendations apply to individuals with FA, as they 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 [74]. Magnetic resonance imaging can reduce radiation exposure for patients with FA and 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 [70]. 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 [75]. Magnetic resonance imaging appears to be more sensitive for detecting tumors in patients who have undergone menopause, even in those on hormone therapy, which causes the breast tissue to become less dense [76, 77]. In the future, MRI may be preferred over mammography in post-menopausal patients with FA as a way to minimize radiation exposure from mammograms [78]; however, this approach has not been studied in the FA population.



## Summary

Female patients with FA face gynecologic issues including late onset of puberty, abnormal menstrual bleeding, primary ovarian insufficiency, cancer, and reduced fertility. Gynecologic care for female patients with FA should cover the spectrum of these complications and focus heavily on cancer screening. Gynecologic assessment for pubertal delay and genital lesions for female FA patients should begin at age 13 with complete vulvovaginal examinations and Pap testing once the patient becomes sexually active or by age 18. Screening for gynecologic cancer should be performed every 6–12 months with immediate referral to a gynecologic oncologist when gynecologic cancerous lesions are confirmed by biopsy. Surgical resection is currently the best curative option for gynecologic cancers in FA patients; therefore, early detection is imperative. There are currently no consensus guidelines for breast cancer screening in patients with FA; more research is needed to define the risk for breast cancer in patients with FA.

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