

Chapter 6

Gynecologic and Fertility Issues in Female FA Patients

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Congenital Genital Tract Anomalies

FA patients have not been studied sufficiently to determine if they are at increased risk for congenital genital tract anomalies. In fetal development, the genital tract and renal system are interlinked. Since renal anomalies have been documented in FA patients,¹ those with identified renal or lower gastrointestinal tract anomalies should undergo screening for congenital malformations of the genital tract such as unicornuate or bicornuate uterus or ovarian atresia. In other populations, the rate of renal anomalies in those with genital tract anomalies is 30%.²

Menses and Fertility

Females with Fanconi anemia have a shortened reproductive life and are probably less fertile than the general population. They usually do not begin menstruating until their mid-teens, may have infrequent, irregular menses, and are often menopausal by their thirties.³ These characteristics may be related to the effect of mutations in FA genes, since FA animal models also have hypogonadism and impaired fertility⁴ or they may be related to low body weight or chronic disease.⁵ Endocrine problems, such as thyroid and hypothalamic dysfunction, which may alter the menstrual cycle should be considered (see Chapter 7). Infrequent

menstrual cycles experienced by FA patients could also result from taking androgens to improve hematopoiesis.

Pubertal Delay

Pubertal delay should be considered in patients who do not have breast buds by age 13, or by age 14 if they have low body weight. In the general population, 90% of women begin menses by age 16 or 3 years after breast buds.⁶ While pubertal delay might result from low body mass index or chronic disease, young women with late menarche should be evaluated for hypothalamic dysfunction.^{5,6} If puberty is delayed or does not occur, patients may need hormonal supplementation to optimize their growth and develop secondary sex characteristics (see Chapter 7).

Gynecologic Surveillance

General gynecologic examination

FA patients are at extraordinarily high risk for vulvar cancer, as well as cervical and anal cancers. Therefore, we recommend that all FA patients receive an annual gynecologic exam, beginning at 13, for visual inspection of the external genitalia. These patients should be followed by a gynecologist familiar with FA and with experience in treating patients with lower genital tract neoplasia.

For non-sexually active women, a comprehensive pelvic exam should be considered at age 18, three years earlier than recommended for non-FA patients.

For sexually experienced women, the gynecologic examination should be comprehensive and include cervical cytology testing and careful inspection of the vagina and cervix during a speculum examination. The use of colposcopy in inspecting these areas should be

initiated only after abnormal cytology or squamous intraepithelial lesions have been identified. Any visually abnormal areas should be biopsied to exclude dysplasia or cancer.

FA patients should be counseled on sexually transmitted diseases (STD) and human papillomavirus (HPV) prevention, and be encouraged to receive the HPV vaccination with Gardasil[®].⁷ Gardasil[®] is the only currently available vaccine that helps protect against four types of HPV: two types that cause 70% of cervical cancer, and two more types that cause 90% of genital warts.

Hormonal contraception

Hormonal contraception is not contraindicated in FA patients. The physician should discuss contraception and safe sex practices with these patients and screen for sexually transmitted diseases.⁸ Patients who are prescribed hormonal contraception to regulate their menses or are given androgens to help stimulate the bone marrow may have normal menses.

Possible effects of androgen use

While the regular use of androgens may be contraceptive, if pregnancy does occur, androgens should be discontinued immediately. Androgen use during pregnancy can masculinize a female fetus.

Evaluation and treatment of abnormal uterine bleeding

The evaluation of heavy bleeding in women with FA should include a complete blood count and assessment of hemodynamic status. Pregnancy should be excluded. Heavy or prolonged menstrual bleeding may occur when patients are thrombocytopenic; infrequent ovulation may contribute to prolonged uterine bleeding. Measures to improve the hematologic status should be

instituted, including transfusions of platelets and red cells, as well as the use of hormonal treatments.

Excessive menstrual bleeding, as in other thrombocytopenic and gynecologic conditions, can be treated with hormonal therapy.^{9,10} Options include daily monophasic combined oral contraceptives (estrogen and progestin pills that do not vary in dosage over the cycle) taken continuously, skipping the placebo pills. Oral contraceptive pills containing at least 30 mcg of ethinyl estradiol should be used, as a slightly higher dosage of estrogen minimizes the risk of breakthrough bleeding. During an acute bleeding episode, treatment can begin with two or three tablets of oral contraceptives daily, tapered quickly to one pill a day. Megestrol acetate, medroxyprogesterone acetate or other oral progestins may also be used. Long-acting progestins may be effective. Leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist, given as a 3.75 mg injection monthly (or 11.25 mg every three months), has been used in other thrombocytopenic populations. Use of a GnRH agonist for more than six months increases the risk of bone loss, a particular problem observed in women with Fanconi anemia, regardless of hormone use (see Chapter 7).^{3,11} Therefore, use of GnRH for longer periods may be coupled with additional estrogen and progestin therapy to minimize bone loss.

If these measures fail, non-hematologic reasons for excessive menstrual bleeding should be considered. A transvaginal sonogram is helpful in determining endometrial thickness, the presence of polyps or fibroids in the endometrial cavity, and ovarian activity. The endometrium should be sampled to assess for abnormalities, such as endometrial hyperplasia. Surgical treatment of any endometrial or uterine abnormalities may be indicated.

Cancer Risk

Increased risk of lower genital tract squamous cell carcinoma

A high rate of lower genital tract squamous cell carcinoma, which includes cervical, vaginal, vulvar, and anal cancers, has been reported in women with FA. The median ages of cervical or vulvar cancer in FA women are very young, 25 and 27 respectively, significantly younger than expected in the general population (age 47 for cervical cancer and 72 for vulvar cancer).^{12,13} The young ages for these cancers in FA patients translates into a relative risk of 4,000-fold higher for vulvar cancer and 200-fold higher for cervical cancer compared to the general population.^{12,14}

The high risk for early vulvar cancer provides the rationale for instituting gynecologic care at a young age. Screening for genital tract neoplasia which includes cytology testing and visual inspection of the vulva and vagina should be part of the clinical care for FA patients, as outlined in the earlier section subtitled “General gynecologic examination.” Colposcopy should be done when any abnormal areas are seen on visual inspection or if a cervical cytology test is abnormal. Any suspicious lesions should be biopsied. Any woman with a history of dysplasia or squamous intraepithelial lesions should have twice yearly gynecologic exams to assess for recurrence.

Surgical treatment of dysplastic lesions in FA patients is preferable, as these patients have significant adverse effects from chemotherapy and radiation. They are at increased risk of bone marrow failure with chemotherapy and, as FA is a DNA repair defect, there is a theoretical risk of toxicity with radiation.¹⁵ Because treatment of cancer in FA patients can be complicated,

surgical treatment of lesions should be considered, and consultation with a hematologist experienced with FA should be obtained prior to instituting radiation or chemotherapy.

Human papillomavirus immunization

In two recent studies on a small number of vulvar SCC tumors in FA patients, the tumors tested positive for HPV.^{16,17} Because of the increased risk of genital tract neoplasia in women with FA and head and neck cancer in both men and women with FA, it may be reasonable to consider HPV vaccination for both male and female FA patients at age nine. It is unknown whether FA patients mount the usual immune response to the vaccine. While the vaccine will not treat existing HPV disease, it may prevent the acquisition of some other subtypes. As the HPV vaccine does not prevent all genital tract cancers and the efficacy of this vaccine in FA is not known, vaccinated FA patients should continue regular screening.

Breast cancer surveillance

Breast cancer surveillance should begin by the early 20s and include annual breast exams. Screening mammograms should be initiated if a mass is detected or by age 25. The risk of breast cancer in FA does not appear to be excessive, although a few cases have been reported to date.¹⁸ A few FA patients have acquired breast cancer at a median age of 37 years, compared to a median age of 61 in the non-FA population (see Chapter 2). To avoid radiation, magnetic resonance imaging may be considered. However, breast magnetic resonance imaging, while very sensitive, is non-specific and has a high false positive rate. Thus, it is usually considered to be an adjunct to mammography.¹⁹

Gynecologic Issues Related to Hematopoietic Stem Cell Transplantation

Many FA patients undergo hematopoietic stem cell transplantation during childhood or adolescence and may develop gynecologic problems as a result. Factors that influence post-transplantation fertility and ovarian function include total body irradiation, prescribed drugs, age, and relation of puberty to age at transplant.¹⁸ When patients are transplanted prior to puberty, their ovarian function may be spared. After menarche, transplantation may result in ovarian failure.¹⁸

If the transplant will occur after puberty, patients may wish to preserve their ovarian function. However, there is no definitive way to protect the ovaries during the transplantation process at this time. In other populations, gonadotropin releasing hormone agonists, like leuprolide acetate, have been used to attempt to preserve ovarian function with limited success.^{20,21} Clinical studies using these or other agents called GnRH antagonists are underway.

For girls or women who are menstruating prior to transplant, menstrual suppression can decrease the risk of anemia, blood loss, and transfusions, and can be accomplished by continuous combined oral contraceptives, depo-medroxyprogesterone acetate or leuprolide.^{9,10}

The gynecologist should discuss childbearing options with adolescents and young adults prior to transplant. This may be especially challenging with an adolescent patient, since it is unlikely that the patient has considered future childbearing. If pregnancy is desired in the future and the young woman is old enough to participate in this discussion, the use of assisted reproductive technologies prior to transplant should

be considered.^{22,23} A higher viability and subsequent success rate has been noted in embryo cryopreservation compared to oocyte cryopreservation. Oocyte or ovarian tissue cryopreservation are both experimental and should occur in the context of a research protocol. For those FA patients who have undergone transplantation prior to considering childbearing, donor oocytes may be an option if they decide to have children. There may be additional concerns regarding the ability of a radiated uterus to carry a pregnancy, as damage to the uterine vasculature from radiation may affect implantation and placental physiology.²⁴⁻²⁶

Some pregnancies have been reported after stem cell transplantation in patients with FA who have not taken any additional hormones or undergone assisted reproductive technologies.²⁷

Fertility

Although young women with FA may be less fertile than the general population, they are able to have children. Because of hypogonadism and menstrual irregularities, FA patients may not ovulate monthly, and the fertile time of the month may be difficult to predict. However, a uterine anomaly or ovarian dysfunction in an FA patient may affect the ability to become pregnant or carry a pregnancy to term. The actual fertility rate in FA is unknown. From case reports of those patients who have given birth, most did so in their 20s, with few pregnancies after age 30. In one reported patient series by Alter et al, 29% of women over age 16 who were not taking androgens conceived, suggesting decreased fertility.²⁸ When those taking androgens were included, the overall pregnancy rate was 15%.

Pregnancy-related complications

Pregnancy for women with FA should be considered high risk and should be co-managed with a maternal/fetal medicine specialist and a hematologist to monitor for pregnancy complications and worsening hematologic status. In the Alter series, FA patients had a higher risk of pregnancy-related complications, such as preeclampsia, eclampsia, and spontaneous abortions, when compared to the general population. The caesarean section rate in this series was 25%, perhaps because the small stature of FA patients may mean they have small pelvises and a higher rate of failure to progress in labor.²⁸

Pregnancy in women with FA does not appear to be life-threatening. Although others report that women with acquired aplastic anemia had pregnancy-related mortality of nearly 50%, no deaths occurred among the FA women in the above series.²⁸ However, the hematologic status of the mother worsened in more than 50% of the FA pregnancies, requiring transfusions for anemia and/or thrombocytopenia.

Menopause

FA patients usually go through premature menopause (age less than 40). Thus, the physician should consider the post-menopausal health risks of osteoporosis, cardiovascular disease, breast cancer, and the management of hot flashes. The results from the Women's Health Initiative Study suggest that post-menopausal hormonal replacement in the general population protects against bone loss, is associated with a slightly increased risk of breast cancer, and an increased risk of heart attack, stroke, and thromboembolic disease.²⁹

For women with FA, there are no data regarding the use of hormone replacement. For those patients who go through menopause at a very early age, the physician can reasonably consider giving hormone replacement of estrogen and progestin (such as monophasic oral contraceptive pills or prempo containing 0.625 premarin and 2.5 mg provera or similar hormonal treatment) until the age of 50. Estrogens are useful in preventing hot flashes and providing a sense of well-being.

Osteoporosis

It is especially important to protect post-menopausal FA women against bone loss, which is common in these patients.³ Osteoporosis treatment options are plentiful, including biphosphonates (Fosamax or Actonel) which prevent bone resorption, and hormones (estrogen or raloxifene) which build bone. Most post-menopausal women with FA would benefit from taking 1,500 mg of calcium a day, vitamin D supplementation, and a biphosphonate like Fosamax (70 mg tablet once weekly) or Actonel (35 mg once weekly). Even if osteoporosis medications are instituted, women with FA should be monitored for osteoporosis with DXA (dual energy X-ray absorptiometry) scans every two years or as clinically indicated (see Chapter 7).

Cardiovascular Risk

The cardiovascular risk for patients with FA may not be high, but the physician should consider an individual patient's family history. Lipids, insulin resistance (see Chapter 7), and blood pressure should be monitored as part of a cardiovascular risk assessment, with special attention paid to the effects of androgens on lipids. In those with documented cardiovascular risk factors, hormone replacement therapy may be contraindicated.

Future Research Directions

1. Defining osteoporosis risk in FA women.
2. Defining the risk of congenital reproductive tract anomalies in FA women.
3. Fertility preservation for patients undergoing stem cell transplantation.
4. The safety and immunogenicity of HPV vaccination in FA men and women.
5. Improving diagnosis and treatment of genital tract dysplasias before cancer arises.

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