

Gynecological Issues Facing Female Fanconi Anemia Patients

Pamela Stratton, MD

Chief, Gynecology Consult Service

Reproductive Biology and Medicine Branch

Eunice Kennedy Shriver NICHD, NIH



Gynecologic issues in women with Fanconi anemia

- Common obstetric and gynecologic problems
- Screening recommendations
- Treatments



Gynecological Issues

- Genitourinary abnormalities
- Late menarche and premature menopause
- Menstrual abnormalities
- Infertility
- Pregnancy
- Malignancies
- Considerations around HSCT



Genitourinary Abnormalities

- Hypogonadism

- Uterine abnormalities

 - bicornuate uterus

 - Abnormal genitalia

 - Aplasia of uterus and vagina

 - Atresia of uterus, vagina and ovary

- NEED DATA

- If renal abnormality is found, uterine abnormality may exist and ultrasound should be done



Menstrual abnormalities

- Later first menses
- Premature menopause
- Irregular periods and anovulation
 - Directly related to FA or due to low BMI and chronic disease
- Heavy or prolonged menstrual bleeding

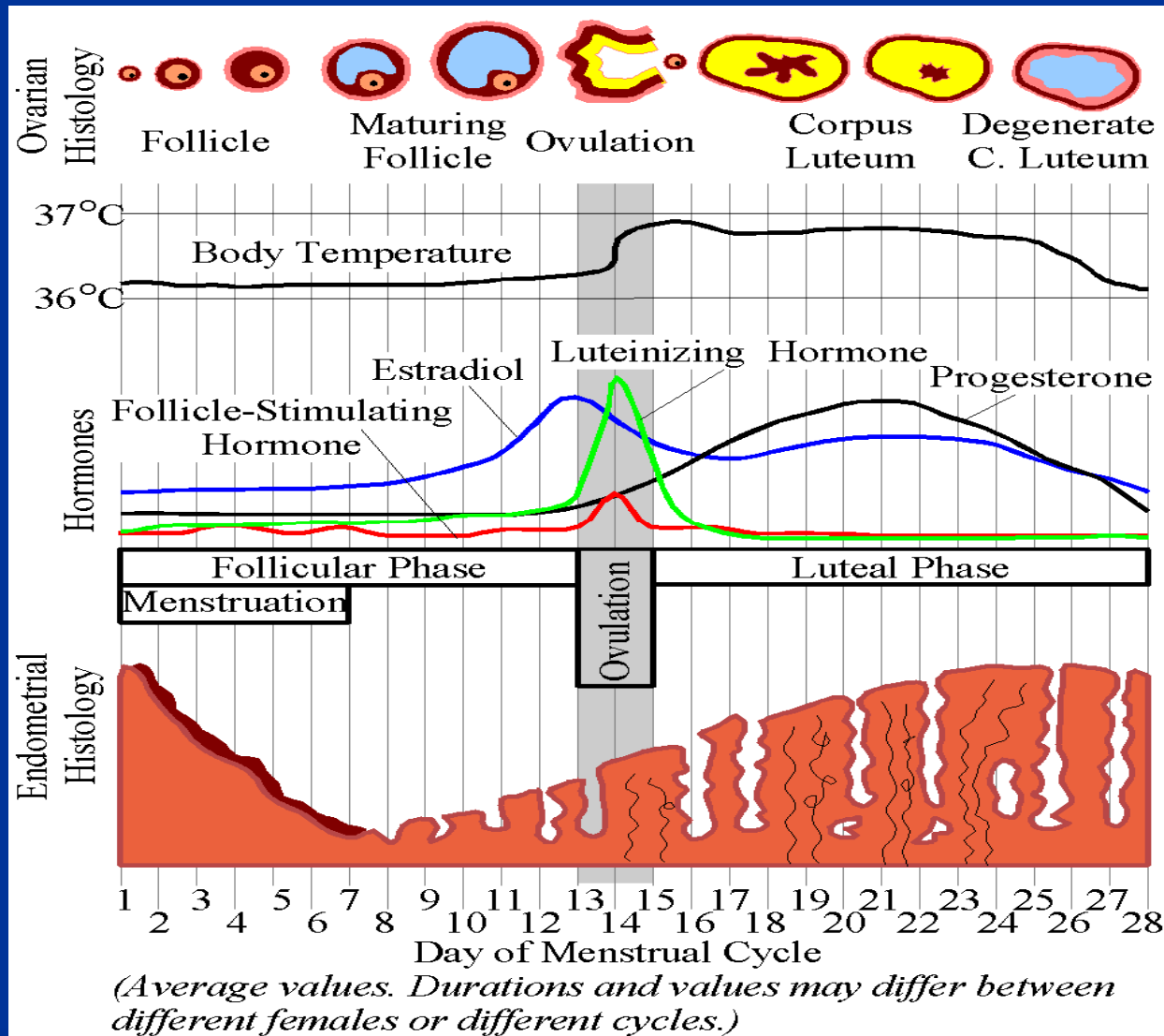


Pubertal delay

- No breast buds by age 13
 - 14 if low body weight
- No menses by 3 years after breast buds or age 16
- Hypothalamic dysfunction
- Low BMI and chronic illness



Normal Menstrual cycle



Infertility in Women with Fanconi Anemia

- Shortened reproductive life
- Decreased fertility but can become pregnant
- Use contraception when pregnancy not desired
- Cryopreservation (preservation by freezing) of embryos possible reproductive option
- Donor oocyte



Infertility in Men with Fanconi Anemia

- Decreased fertility
- Azospermic (have low sperm counts)
- If the sperm counts are not zero, in vitro fertilization or freezing sperm may be options



Excessive menstrual bleeding

Occurs in women with

- Irregular menses
- Low platelets and anemia
- Bone marrow transplant

GOAL: Limit heavy bleeding



Hormonal treatment options

Excessive menstrual bleeding

■ Birth control pills

- Daily monophasic, combined pill without placebo
 - Estrogen may worsen anemia

■ Progestins

- Oral progestins
- Depo provera may worsen bleeding initially
- Levonorgestrel IUD

■ Leuprolide acetate



Evaluation of Excessive menstrual bleeding

Usually done in older patients

- Transvaginal sonogram
 - Endometrial thickness
 - Uterine abnormalities – polyps/fibroids
 - Ovarian activity
- Endometrial biopsy
 - Abnormal lining growth
- Hematocrit and platelet count
- Pregnancy test



Excessive menstrual bleeding

- Surgical treatment options
 - Endometrial ablation
 - Hysterectomy

Both lead to infertility



Prenatal diagnosis of Fanconi anemia

- Prenatal diagnosis possible using Diepoxybutane-induced chromosomal breakage studies
 - 30 fetuses from 24 families
 - 7 FA affected fetuses with anomalies
 - Unaffected fetuses - no Fanconi anemia associated malformations **Auerbach et al. 1985**
- Preimplantation genetic testing, amniocentesis, chorionic villus sampling are all now done to assess whether embryo affected



Fanconi anemia

Pregnancies conceived for early treatment

■ Siblings conceived for treatment

- HLA typing and whether FA affected
- Transplant treatment options include
 - Bone marrow
 - Umbilical cord blood
 - Peripheral blood stem cell transplant

■ Sibling donors may be cheaper and provide better survival than unrelated donor



Pregnancy course in Women with Fanconi anemia

- Fertility – 15 to 29% conceived
- Androgens should be stopped early to avoid masculinization of fetus
- Pregnancy complications
 - Higher risk of preeclampsia or eclampsia, miscarriage, or Caesarean section
 - Lower mortality than acquired aplastic anemia
- Hematologic status often worsened
 - Transfusions for anemia or low platelets



Pregnancy and Fanconi Anemia

- Pregnancy should be managed by maternal fetal medicine specialist
 - Perform prenatal diagnosis
 - Minimize complications during pregnancy
 - Time delivery



Ovarian function and pregnancy after HSCT

- Factors that influence post transplantation fertility and ovarian function in women
 - Total body irradiation (TBI)
 - Drugs prescribed
 - Age
 - Relation of puberty to time of transplant



Pregnancy after Hematologic stem cell transplant

- HSCT common in FA patients
- Increased risk of gonadal dysfunction, radiation effects, infertility and ovarian failure after HSCT in FA patients
- Risk should be discussed before HSCT



Ovarian function after HSCT

■ If transplant occurs

- Prior to puberty, ovarian function may be spared
- During teen years, goal to preserve ovarian function
- Early adult, may have ovarian failure



Techniques to preserve ovarian function during chemotherapy

- Leuprolide acetate

- GnRH antagonist

Both experimental

- Other options

- Embryo cryopreservation

- Oocyte cryopreservation - experimental



Pregnancy after HSCT

- Successful pregnancies after HSCT in women with FA reported
- Pregnancy after BMT possible through:
 - Spontaneous conception
 - Ovarian stimulation
 - Assisted reproductive technology (IVF)
 - Donor egg
- Radiation effects on uterus

Dalle et al Bone Marrow Transplant 2004



Fanconi anemia

Secondary cancer after HSCT

- Secondary cancers common after HSCT
- Possibly related to radiation, HPV disease, mosaicism
- Potential role of HPV vaccination



Fanconi anemia

Gynecologic malignancies

- High rate of squamous cell cancer of Cervix, Vagina, Vulva, Anus
 - Very young age, especially for vulvar ca
 - Field effect
 - ?HPV related or not
 - Some studies suggest that it is HPV related but occurs in sexually naïve patients

	Number	Observed/ expected
Vulva	3	4317
Cervix	2	179

Early age cervical and vulvar cancer: indicate need for FA screening

- Individuals with FA may develop bone marrow failure with chemotherapy or have increased risk of cancer with radiation.
- If cervical cancer is diagnosed before age 30 OR
- If vulvar cancer is diagnosed before age 40, CONSIDER
- FA testing



Screen women with FA for cervical and vulvar cancer

- Evaluation – at least annual
 - Cervical cytology screening
 - Vulvar and vaginal inspection
 - Colposcopy/biopsy when indicated
- Treatment – surgical excision of moderate/severe dysplasia when identified as chemo and radiation are not well tolerated by FA patients



Treatments for genital tract warts or neoplasia

- Topical Aldara (Imiquimod: imidazoquinolone amine)
- Topical 5 Fluorouracil
- Injectable Alpha interferon



Aldara (Imiquimod: imidazoquinolone amine)

- Immune response-modifying drug: antiviral and antitumor activity
 - Induces cytokine expression: interferon, interleukin 6, and tumor necrosis factor
 - Enhances cell-mediated cytolytic antiviral activity
- Therapeutic action: probably both local response and stimulation of immune response
- FDA approved in 1997
 - Lower genital tract HPV-induced lesions (genital warts)
 - HPV 16-specific CD4+ T-cell immunity might increase the strong clinical response to imiquimod treatment in women with persistent vulvar intraepithelial neoplasia
 - Topical 5% cream and each gram contains 50 mg





Treatment of Vulvar Intraepithelial Neoplasia with Topical Imiquimod

Manon van Seters, M.D., Marc van Beurden, M.D., Ph.D., Fiebo J.W. ten Kate, M.D., Ph.D., Ilse Beckmann, M.Sc., Ph.D., Patricia C. Ewing, M.D., Marinus J.C. Eijkemans, Ph.D., Marjolein J. Kagie, M.D., Ph.D., Chris J.M. Meijer, M.D., Ph.D., Neil K. Aaronson, Ph.D., Alex KleinJan, Ph.D., Claudia Heijmans-Antonissen, B.Sc., Freek J. Zijlstra, Ph.D., Matthé P.M. Burger, M.D., Ph.D., and Theo J.M. Helmerhorst, M.D., Ph.D.

ABSTRACT

Background Alternatives to surgery are needed for the treatment of vulvar intraepithelial neoplasia. We investigated the effectiveness of imiquimod 5% cream, a topical immune-response modulator, for the treatment of this condition.

Methods Fifty-two patients with grade 2 or 3 vulvar intraepithelial neoplasia were randomly assigned to receive either imiquimod or placebo, applied twice weekly for 16 weeks. The primary outcome was a reduction of more than 25% in lesion size at 20 weeks. Secondary outcomes were histologic regression, clearance of human papillomavirus (HPV) from the lesion, changes in immune cells in the epidermis and dermis of the vulva, relief of symptoms, improvement of quality of life, and durability of response. Reduction in lesion size was classified as complete response (elimination), strong partial response (76 to 99% reduction), weak partial response (26 to 75% reduction), or no response (25% reduction). The follow-up period was 12 months.

Results Lesion size was reduced by more than 25% at 20 weeks in 21 of the 26 patients (81%) treated with imiquimod and in none of those treated with placebo ($P<0.001$). Histologic regression was significantly greater in the imiquimod group than in the placebo group ($P<0.001$). At baseline, 50 patients (96%) tested positive for HPV DNA. HPV cleared from the lesion in 15 patients in the imiquimod group (58%), as compared with 2 in the placebo group (8%) ($P<0.001$). The number of immune epidermal cells increased significantly and the number of immune dermal cells decreased significantly with imiquimod as compared with placebo. Imiquimod reduced pruritus and pain at 20 weeks ($P=0.008$ and $P=0.004$, respectively) and at 12 months ($P=0.04$ and $P=0.02$, respectively). The lesion progressed to invasion (to a depth of <1 mm) in 3 of 49 patients (6%) followed for 12 months (2 in the placebo group and 1 in the imiquimod group). Nine patients, all treated with imiquimod, had a complete response at 20 weeks and remained free from disease at 12 months.

Conclusions Imiquimod is effective in the treatment of vulvar intraepithelial neoplasia. (Current Controlled Trials number, ISRCTN11290871)



Topical 5 Fluorouracil

- 5-Fluorouracil interferes with the skin cell growth
 - Causes the death of fastest growing cells, like abnormal skin cells
 - Treats scaly skin overgrowths (actinic or solar keratoses)
 - Treats superficial basal cell carcinoma
- Do not use on skin that is irritated, peeling, or infected or on open wounds
- Wait until these have fully healed before using topical fluorouracil
- Not a good option for FA with DNA repair defect



Alpha Interferon

- A protein produced by the body in response to an infection
 - 3 major classes
 - alpha, beta, and gamma
- Used to treat genital warts
- Injection in subcutaneous tissue 2 x a week
- Side effects
 - Flu like symptoms
 - Depression
- Used as a treatment for some types of cancer
 - Kidney cancer, malignant melanoma, and carcinoid tumors
 - Lymphoma and leukemia



HPV vaccine to prevent squamous cell cancer

- Newly approved vaccine
- comprised of virus-like-particles for HPV subtypes 6,11,16, and 18
 - HPV subtypes 6 and 11 account for 90% genital warts
 - HPV subtypes 16 and 18 seen in 70% of cervical cancer
- Possible NIH trial to examine the immunogenicity of this vaccine in FA patients



Management of menopause

- Women's Health Initiative –
Post-menopausal hormone
replacement therapy study
 - Protection against bone loss
 - Increased risk of heart attack, stroke,
and thromboembolic disease
 - Slightly increased risk of breast cancer



Fanconi anemia

Menopause health risks

- Premature menopause
- Post menopausal health risks
 - Osteoporosis
 - Cardiovascular disease
 - Breast cancer
- Consider these risks in FA patients
- Management of hot flashes



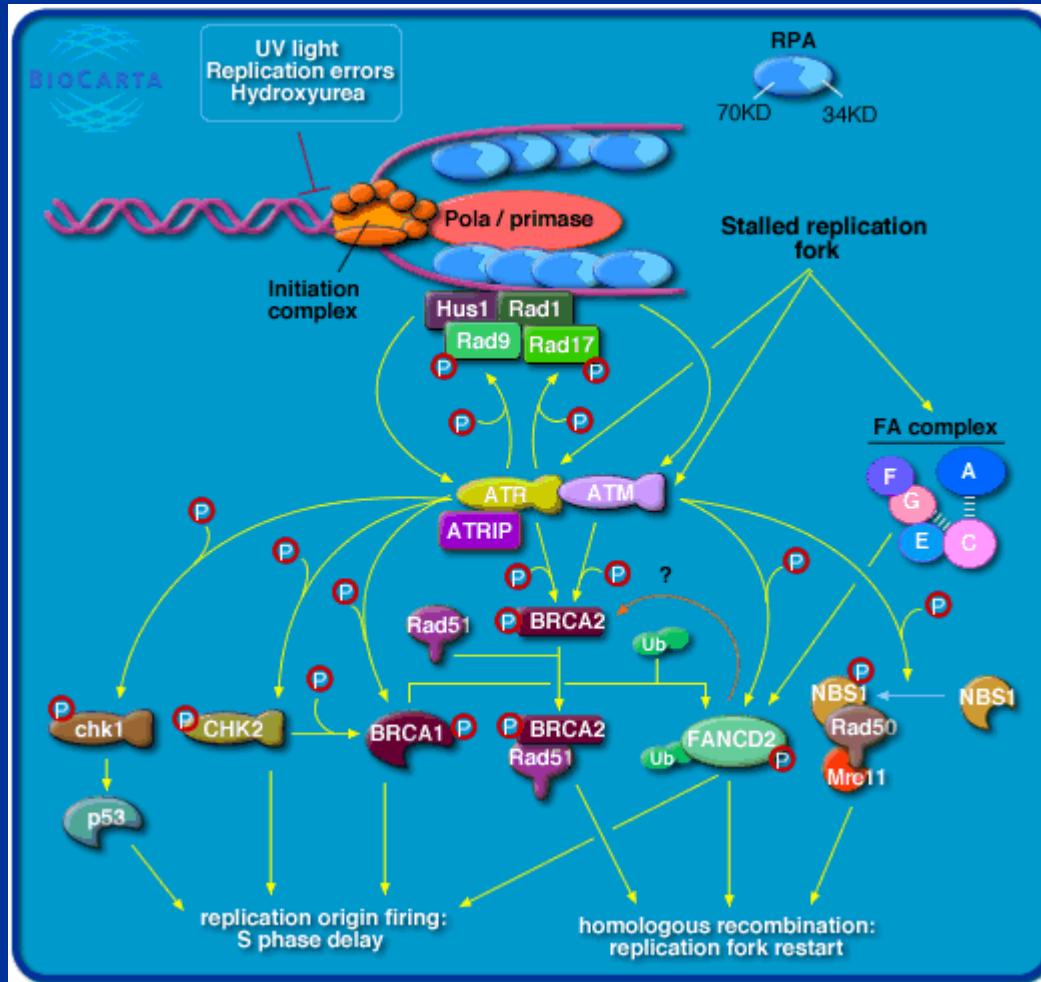
Fanconi anemia

Management of menopause

- Risk or benefit of estrogen and progestin – no data
 - Theoretical bone marrow suppression with estrogen
 - Need protection against bone loss
 - Cardiovascular risk may be higher in face of dyslipidemia and insulin resistance
 - Insulin resistance – need for monitoring per Sue's chapter
 - Unknown risk of breast cancer – a couple of reported cases



Fanconi anemia and Breast cancer pathways



Fanconi anemia

Management of menopause

- Consider hormone replacement therapy – estrogen and progestin to women under age 50 with premature menopause
- Monitor for breast cancer
 - Mammogram with MRI rather than x-ray mammography
- Monitor lipids, cardiovascular risk
 - Androgens may increase cardiovascular risk
- Monitor for osteoporosis



NIH Natural history study of Inherited bone marrow failure syndromes:

- Pregnancies in women with inherited bone marrow failure syndromes may be associated with anemia and obstetric complications.
- Women with FA may be at higher risk of late menarche, premature menopause, subfertility, and gynecologic neoplasms than those with other IBMFS.



Fanconi Anemia has Different Gynecologic Natural History than other Inherited Bone Marrow Failure Syndromes

- To compare the gynecologic natural history in women with FA to those with other IBMFS.
- Women with FA were compared with those with DC, DBA and SDS in the NCI natural history study of IBMFS.
- All women \geq age 10 were included.



Results

- Sixty-six women: 32 with FA, 15 with DC, 14 with DBA, and 5 with SDS, evaluated at similar median ages
- All attained menarche at similar ages, but those with FA had
 - menopause at an earlier age (FA 34, DC 50, DBA 50, SDS 38 years; $p=0.03$)
 - a higher rate of irregular periods (FA 67%, DC 0%, DBA 11%, SDS 25%; $p=0.004$)

Results

- Compared to other IBMFS, women with FA had
 - a higher rate of infertility
(FA 67%, DC 11%, DBA 25%, SDS 0%; $p=0.02$)
 - lower rates of pregnancy
(FA 22%, DC 75%, DBA 60%, SDS 33%; $p=0.01$)
 - fewer pregnancies/pregnant woman
(FA 1.8, DC 2.4, DBA 4.3, SDS 2; $p=0.04$)
- Pregnancy complications were more common in those with DC and SDS
(FA 66%, DC 91%, DBA 36%, SDS 100%; $p=0.001$)

Results

- Women with FA had
 - higher rates of abnormal pap smears ($p=0.02$)
 - underwent more colposcopy ($p=0.04$)
 - had more cases of CIN
(FA 7, DC 1, DBA 0, SDS 0 cases)
 - VIN/vulvar cancer
(FA 5, DC 0, DBA 0, SDS 0 cases).
- A greater proportion of women with FA
 - had died
(FA 53%, DC 27%, DBA 14%, SDS 0; $p=0.02$)
 - at a younger median age
(FA 29, DC 47, DBA 46 years; $p=0.01$).



Conclusion

- Women with FA have a higher risk of irregular menses, infertility, premature ovarian insufficiency, and lower pregnancy rates than those with other IBMFS.
- Those with DC have a higher rate of pregnancy complications.
- Pregnancy in IBMFS patients should be considered high risk and monitored accordingly.
- Genital tract neoplasia, including invasive cancer, is more common in FA than in the other IBMFS, and clearly contributes to early mortality.



Gynecologic surveillance

■ Annual exam

- Beginning at age 16 or menarche
- Includes cervical cytology
- Careful examination of vulvar skin (and vagina)
- Any lesions should be treated aggressively with surgery, since FA patients respond poorly to standard radiation and chemotherapy



Gynecologic surveillance

- Endocrine and pubertal evaluation
 - Attention paid to puberty, fertility, pregnancy, contraception, and early menopause
- Risk of breast cancer
 - Complement group related to BRCA1/2 pathways
 - MRI breast



Fanconi anemia

Gynecologic, fertility issues

- May be less fertile
- Pregnancy well tolerated
- Increased risk of gynecologic squamous cancer
 - warrants at least annual cytology screening/exam
 - HPV vaccination?
- Manage heavy menstrual bleeding
- Optimal management of premature menopause unknown – consider HRT

