Gynecological Issues Facing Female Fanconi Anemia Patients

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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
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 ≥age 10 were included.
## Inherited Bone Marrow Failure Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Fanconi anemia</th>
<th>Dyskeratosis congenita</th>
<th>Diamond-Blackfan anemia</th>
<th>Shwachman-Diamond syndrome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>15</td>
<td>14</td>
<td>5</td>
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<tr>
<td>Median age at study (range) yrs</td>
<td>25 (10-57)</td>
<td>38 (10-63)</td>
<td>29 (10-59)</td>
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<tr>
<td>Median age menarche (range) yrs</td>
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<td>12 (11-14)</td>
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<tr>
<td>Median age natural menopause (range) yrs</td>
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<td>47,50,50</td>
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<tr>
<td>Irregular menses (anovulatory)</td>
<td>12/18 (67%)*</td>
<td>0</td>
<td>2/7 (29%)</td>
<td>1/5 (30%)</td>
<td>0.004</td>
</tr>
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</tr>
<tr>
<td>Infertility</td>
<td>10/15 (67%)*</td>
<td>1/9 (11%)</td>
<td>2/8 (25%)</td>
<td>-</td>
<td>0.023</td>
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<tr>
<td>Number ever pregnant</td>
<td>5/23 (22%)**</td>
<td>9/12 (75%)</td>
<td>6/10 (60%)</td>
<td>1/3 (33%)**</td>
<td>0.01</td>
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<tr>
<td>Any complication of pregnancy</td>
<td>6/9 (66%)*</td>
<td>20/22 (91%)*</td>
<td>8/22 (36%)</td>
<td>2 (100%)*</td>
<td>&lt;0.001</td>
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<tr>
<td>Miscarriage/number of pregnancies</td>
<td>1/9 (11%)</td>
<td>7/22 (32%)*</td>
<td>2/26 (8%)</td>
<td>2/2 (100%)*</td>
<td>0.016</td>
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<tr>
<td>Median gestation for live births (range)</td>
<td>40 (27-40)</td>
<td>39 (28-40)</td>
<td>40 (32-42)</td>
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<td>0.413</td>
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<tr>
<td>C-section deliveries</td>
<td>3/9 (33%)</td>
<td>9/15 (60%)</td>
<td>5/21 (24%)</td>
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<tr>
<td>Maternal cytopenia/transfusions</td>
<td>3/9 (33%)</td>
<td>5/23 (22%)</td>
<td>2/26 (8%)</td>
<td>-</td>
<td>0.066</td>
</tr>
</tbody>
</table>
# Inherited Bone Marrow Failure Syndrome

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<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Abnormal Pap smears</td>
<td>11/19 (58%)*</td>
<td>4/9 (44%)</td>
<td>0/7</td>
<td>0/2</td>
<td>0.022</td>
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<tr>
<td>Colposcopy</td>
<td>9 (47%)*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.04</td>
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<tr>
<td>CIN (HPV/CIN I, II or III)</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vulvar Cancer/VIN</td>
<td>4/1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number dead</td>
<td>17 (53%)*</td>
<td>4 (27%)</td>
<td>2 (14%)</td>
<td>0</td>
<td>0.016</td>
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<tr>
<td>Median age at death (range) yrs</td>
<td>29 (11-43)**</td>
<td>45,47,62</td>
<td>33,59</td>
<td>-</td>
<td>0.014</td>
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</table>
Results

- Sixty-six women were evaluated at similar median ages.
- All attained menarche at similar ages, but those with FA had:
  - menopause at an earlier age
  - a higher rate of irregular periods
Results

Compared to other IBMFS, women with FA had:
- a higher rate of infertility
- lower rates of pregnancy
- fewer pregnancies/pregnant woman

Pregnancy complications were more common in those with Dyskeratosis Congenita and Schwachman-Diamond Syndrome.
Results

- Women with FA had
  - higher rates of abnormal pap smears
  - underwent more colposcopy
  - had more cases of cervical precancer, vulvar precancer and cancer

- A greater proportion of women with FA
  - had died
  - at a younger median age
Conclusion

- Women with FA have a higher risk of irregular menses, infertility, premature ovarian insufficiency, and lower pregnancy rates than those with other IBMFS.
- 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.
Genitourinary Abnormalities

- Hypogenitalia
- 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
- Irregular periods and anovulation
  - Directly related to FA as FA is associated with hypogonadism
  - OR
  - due to low BMI and chronic disease
  - OR
  - Post transplant
- Premature menopause
- 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 (communication between brain and ovaries)
- Low BMI and chronic illness
Normal Menstrual cycle

(Average values. Durations and values may differ between different females or different cycles.)
Infertility in Women with Fanconi Anemia

- Shortened reproductive life
  - Ovaries are small and do not function properly
- Decreased fertility but can become pregnant
- Cryopreservation (preservation by freezing) of embryos possible reproductive option
- Donor oocyte
- Use contraception when pregnancy not desired
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
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
Fertility 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
Ovarian preservation: Techniques to preserve ovarian function during chemotherapy and stem cell transplantation

- Hormones to turn off the ovaries
  - Leuprolide acetate
  - GNRH antagonist

  Both experimental

- Ovary-based options to freeze eggs or embryos
  - Embryo cryopreservation
  - Oocyte cryopreservation - experimental
Metanalysis of GnRH agonist use at time of chemotherapy

Six studies met inclusion criteria for review

- Outcome: Incidence of premature ovarian failure
  - Significant benefit of co-treatment with GnRH agonist
    - OR 0.11, 95% CI 0.03-0.43

- Outcome: Resumption of ovulation
  - Significantly better in the GnRH agonist group
    - OR 4.04, 95% CI 1.04-15.72

- Outcome: Spontaneous conception rates
  - No difference between groups

Suggest a protective role of GnRH agonist cotreatment at the time of chemotherapy, large, well-designed prospective randomized trials are still needed to strengthen the evidence. ASRM annual meeting 2010
Until more definitive evidence exists, many practitioners argue strongly against offering GnRH agonist co-treatment, citing the following concerns:

- False sense of security and failure to consider other potentially more effective methods of fertility preservation such as embryo cryopreservation.

- Mechanism for protective effect is not fully understood since some chemotherapy agents affect primordial follicles which are not actively dividing, and because primordial follicles are not known to have receptors for GnRH or FSH.
Considerations about Oocyte Cryopreservation for Medical Indications

- Age and health status with FA
- If cancer, specific tumor diagnosis
  - Age at diagnosis
  - Prognosis of tumor
- If gynecologic cancer requiring hysterectomy, would need gestational carrier
- Whether person is in relationship conducive to future childbearing

Oocyte cryopreservation is 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
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

Alter Haematol 1991
Pregnancy and Fanconi Anemia

Pregnancy should be managed by maternal fetal medicine specialist
- Perform prenatal diagnosis
- Minimize complications during pregnancy
- Time delivery
Prenatal diagnosis of Fanconi anemia possible

- Using Diepoxylbutane-induced chromosomal breakage studies
- Embryo affected
  - Preimplantation genetic testing
  - amniocentesis
  - chorionic villus sampling
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

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Observed/expected</th>
</tr>
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<tbody>
<tr>
<td>Vulva</td>
<td>3</td>
<td>4317</td>
</tr>
<tr>
<td>Cervix</td>
<td>2</td>
<td>179</td>
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</table>

Rosenberg and Alter, Blood 2003
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 lesions (moderate/severe dysplasia)
- Chemo and radiation not well tolerated by FA patients
Treatments for genital tract warts or neoplasia

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

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.

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).

Conclusions Imiquimod is effective in the treatment of vulvar intraepithelial neoplasia. (Current Controlled Trials number, ISRCTN11290871)
HPV vaccine to prevent squamous cell cancer

- Newly approved vaccine
- Comprised of virus-like-particles for HPV subtypes 6, 11, 16, and 18
  - HPV types 6 and 11 account for 90% genital warts
  - HPV types 16 and 18 seen in 70% of cervical cancer
- NIH trial to examine immune effects of this vaccine after stem cell transplantation
HPV vaccination after stem cell transplant

Background
- After transplant, immunity is altered
- Long-term one third of women post stem cell transplant found to have genital HPV disease

Hypothesis
- Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine is a safe and effective way to reduce the rate of post-transplant HPV-related disease in females who have undergone stem cell transplantation.
Gardasil study visits

24 female stem cell transplant recipients at least 90 days post transplant off all immune suppression

24 female stem cell transplant recipients at least 90 days post transplant on immunosuppression with quiescent GVHD

24 healthy females including 10 donors of study subjects

Gardasil Vaccine schedule

0 months: HPV Titers
HPV DNA Immune Assays

2 months: HPV Titers

6 months: HPV Titers

7 months: HPV Titers
HPV DNA Immune Assays

12 months: HPV Titers
HPV DNA Immune Assays

Follow Up

Off Study
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
  - Unknown risk of breast cancer – a couple of reported cases
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
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