Gynecological Issues Facing Female Fanconi Anemia Patients

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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
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>
<td></td>
</tr>
<tr>
<td>Median age at study (range) yrs</td>
<td>25 (10-57)</td>
<td>38 (10-63)</td>
<td>29 (10-59)</td>
<td>30 (13-40)</td>
<td>0.369</td>
</tr>
<tr>
<td>Median age menarche (range) yrs</td>
<td>13 (9-16)</td>
<td>12 (11-14)</td>
<td>13 (10-16)</td>
<td>13 (12-14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Median age natural menopause (range) yrs</td>
<td>34 (28-46)**</td>
<td>50</td>
<td>47,50,50</td>
<td>38</td>
<td>0.026</td>
</tr>
<tr>
<td>Irregular menses (anovulatory)</td>
<td>12 of 18 (67%)*</td>
<td>0</td>
<td>2 of 7 (29%)</td>
<td>1 of 5 (30%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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

Stratton, Giri and Alter, SGI, 2010
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<tbody>
<tr>
<td>Infertility</td>
<td>10 of 15 (67%)*</td>
<td>1 of 9 (11%)</td>
<td>2 of 8 (25%)</td>
<td>-</td>
<td>0.023</td>
</tr>
<tr>
<td>Number ever pregnant</td>
<td>5 of 23 (22%)**</td>
<td>9 of 12 (75%)</td>
<td>6 of 10 (60%)</td>
<td>1 of 3 (33%)**</td>
<td>0.01</td>
</tr>
<tr>
<td>Any complication of pregnancy</td>
<td>6 of 9 (66%)*</td>
<td>20 of 22 (91%)*</td>
<td>8 of 22 (36%)</td>
<td>2 (100%)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Miscarriage by number of pregnancies</td>
<td>1 of 9 (11%)</td>
<td>7 of 22 (32%)*</td>
<td>2 of 26 (8%)</td>
<td>2 of 2 (100%)*</td>
<td>0.016</td>
</tr>
<tr>
<td>Median gestation for live births (range)</td>
<td>40 (27-40)</td>
<td>39 (28-40)</td>
<td>40 (32-42)</td>
<td>-</td>
<td>0.413</td>
</tr>
<tr>
<td>C-section deliveries</td>
<td>3 of 9 (33%)</td>
<td>9 of 15 (60%)</td>
<td>5 of 21 (24%)</td>
<td>-</td>
<td>0.073</td>
</tr>
<tr>
<td>Maternal cytopenia or transfusions</td>
<td>3 of 9 (33%)</td>
<td>5 of 23 (22%)</td>
<td>2 of 26 (8%)</td>
<td>-</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Compared to other IBMFS, women with Fanconi anemia 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

Stratton, Giri and Alter, SGI, 2010
### 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 of 19 (58%)*</td>
<td>4 of 9 (44%)</td>
<td>0 of 7</td>
<td>0 of 2</td>
<td>0.022</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>9 (47%)*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>CIN (HPV/CIN I, II or III)</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<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>0</td>
<td>1</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 deceased</td>
<td>17 (53%)*</td>
<td>4 (27%)</td>
<td>2 (14%)</td>
<td>0</td>
<td>0.016</td>
</tr>
<tr>
<td>Median age at death (range)</td>
<td>29 (11-43)**</td>
<td>45,47,62</td>
<td>33,59</td>
<td>-</td>
<td>0.014</td>
</tr>
</tbody>
</table>

**Women with Fanconi Anemia**

higher rates of abnormal pap smears, colposcopy more cervical or vulvar precancer and vulvar cancer cases.

A greater proportion of women with Fanconi Anemia had died; at a younger median age

Stratton, Giri and Alter, SGI, 2010
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 contributes to early mortality.
General Reproductive Health Issues in Fanconi Anemia

- Menstrual cycle abnormalities
- Primary Ovarian Insufficiency
- New marker AMH
Menstrual cycle abnormalities in Fanconi Anemia

- Causes of irregular periods and anovulation
  - Fanconi Anemia associated with hypogonadism
  - Low body weight
  - Chronic illness
- Treatments for bone marrow failure
  - Androgen therapy
  - Post transplant
- Other endocrine disorders
  - Hypothyroidism
  - Hypogonadotropic hypogonadism
- Premature menopause, primary ovarian insufficiency
- Heavy/prolonged menstrual bleeding
  - Low platelets
Normal Menstrual cycle

(Average values. Durations and values may differ between different females or different cycles.)
Primary Ovarian Insufficiency (POI)

- **Definition**
  - Prior to age 40 - Insufficient numbers or faulty function of follicles in the ovary

- **Diagnosis**
  - 2 elevated measures of follicle-stimulating hormone (FSH)
  - amenorrhea for more than 4 months

- **Serum marker**
  - Anti-Müllerian hormone (AMH) may be a better marker of diminished ovarian reserve compared with FSH

Welt CK. *Clin Endocrinol (Oxf)*. 2008
Anti-Müllerian Hormone in Females

AMH
• peptide hormone that circulates in the blood
• produced exclusively in the granulosa cells within the ovaries
• levels do not significantly fluctuate during the menstrual cycle
• demonstrates anti-cancer properties in pre-clinical research

### Clinical Characteristics of AMH study in FA

<table>
<thead>
<tr>
<th>Age and Menarche</th>
<th>FA patients</th>
<th>FA relatives</th>
<th>Unrelated controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>22</td>
<td>20</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>Median age when serum drawn (range)</td>
<td>15 (7-37)</td>
<td>33.5 (3-40)</td>
<td>27 (12-40)</td>
<td>0.004</td>
</tr>
<tr>
<td>Subjects achieving menarche</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>0.37</td>
</tr>
<tr>
<td>Median age at menarche (range)</td>
<td>13.5 (11-17)</td>
<td>12.5 (8-15)</td>
<td>NA</td>
<td>0.09</td>
</tr>
<tr>
<td>Subjects over the age of 10</td>
<td>15</td>
<td>18</td>
<td>21</td>
<td>0.37</td>
</tr>
<tr>
<td>Median age of subjects &gt; age 10 (range)</td>
<td>20 (11-37)</td>
<td>34 (11-40)</td>
<td>27 (12-40)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Clinical details in the 15 females with FA over 10 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>POI</td>
<td>7</td>
</tr>
<tr>
<td>Genes</td>
<td>15</td>
</tr>
<tr>
<td>Cancers</td>
<td>6</td>
</tr>
</tbody>
</table>

Fanconi Anemia patients have significantly lower levels of AMH when compared to unaffected relatives and healthy controls.


*Mann Whitney Test
Significance of low AMH in Fanconi Anemia

- Ovarian defects are a common factor in the otherwise heterogeneous clinical disease
- Most females with FA fail to produce normal levels of AMH at anytime in their lives
- Test AMH levels for earlier knowledge and manage complications of POI
  - infertility
  - osteoporosis
  - menopausal symptoms

Significance of low AMH in Fanconi Anemia

- Different mutations may be associated with infertility and AMH deficiency in patients with FA
- Anti-cancer properties of AMH warrant further research to determine whether AMH deficiency contributes to increased cancer risk in FA

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
Pregnancy and Fanconi Anemia

- Pregnancy course in Fanconi Anemia
- Factors that influence ovarian function and pregnancy after hematopoietic stem cell transplant
- Unique issues in Fanconi Anemia after transplant
- Fertility low but possible after stem cell transplant in Fanconi Anemia
- Ovarian preservation techniques
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