

Ovarian function and pregnancy after Hematopoietic Stem Cell Transplant

- 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
- Risk should be discussed before Hematopoietic Stem Cell Transplant

Ovarian function after Hematopoietic Stem Cell Transplant

■ 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

Pregnancy after Hematopoietic Stem Cell Transplant

- 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 in women with FA after Hematopoietic Stem Cell Transplantation

- 285 women with FA
- Only 10 women conceived and delivered
- All prior to age 26
- Pregnancies 4-17 years after HSCT
- Of the 10 women, four had two infants each
- 5 showed signs of gonadal failure before pregnancy, but 2 women recovered spontaneously

Nabhan SK, et al. (2010) Fertility recovery and pregnancy after allogeneic hematopoietic stem cell transplantation in Fanconi anemia patients. *Haematologica* 95(10):1783-1787.

Ovarian preservation: Techniques to preserve ovarian function during chemotherapy and Hematopoietic Stem Cell Transplant

■ 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 included in review

- Outcome: Incidence of premature ovarian failure
- Significant benefit with GnRH agonist
 - OR 0.11, 95% CI 0.03-0.43
- Outcome: Resumption of ovulation
- Significantly better with GnRH agonist
 - 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 time of chemotherapy, large, well-designed prospective randomized trials are 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 small (primordial) follicles which are not actively dividing.

Considerations about Oocyte Cryopreservation for Medical Indications

- Age and health status with FA
- If cancer exist, specific tumor 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

Squamous cell cancer of the genital tract in Fanconi Anemia

- HPV vaccination
- Genital squamous cell cancers occur at young age in FA
- Are genital squamous cell precancer and cancers HPV-associated?
- Screening for genital lesions
- Surgical treatment of genital lesions
- Should medical treatment be added to surgical treatment of precancerous lesions?

HPV vaccine to prevent squamous cell cancer

- Approved vaccine comprised of virus-like-particles for HPV types 6,11,16, and 18
 - HPV types 6 and 11 - 90% genital warts
 - HPV types 16 and 18 - 70% of cervical cancer
- Vaccinate in the teen years or by early adulthood
- Protects against HPV-associated genital and perhaps oral cancers
- NIH trial to examine immune effects of this vaccine after stem cell transplantation
- Revaccinate after transplant

Fanconi anemia

Gynecologic malignancies

- Women with FA tend to develop cervical squamous cell cancer at age 25 and vulvar cancer at age 27
- General population – cervical cancer tends to develop at age 47 and vulvar cancer at age 72
- While number of cases is not high, young women with FA have
 - Several 1000-fold higher risk for vulvar cancer
 - 100-fold higher risk for cervical cancer compared with young women in the general population.

Are squamous cell cancers caused by HPV? Mixed evidence of HPV-association from 3 studies of squamous cell cancer in FA

- 84% of patients with FA who had head and neck squamous cell cancers were infected with HPV.
Kutler DI, et al. (2003)
- HPV present in only 10% of patients with FA who developed anogenital cancers, and none of the patients with FA who had head and neck cancers.
van Zeeburg HJ, et al. (2008)
- Low rates of HPV infection in patients with FA who had genital or head and neck cancers
Alter BP, et al. (2013)

Screen women with FA for cervical and vulvar pre-cancer and cancer

- Early detection of precancerous lesions in patients with FA is imperative to maximize survival
- Begin comprehensive examinations by age 18
 - 3 years younger than general population
 - At least annual
 - Cervical cytology screening
 - Vulvar and vaginal inspection
 - Colposcopy – lesions when identified warrant biopsy

Note: Unlike in general population, HPV testing in women with FA does not lengthen interval between cytology screening.

Treatment of women with FA for cervical and vulvar precancer

■ Optimal treatment –

- surgical excision of moderate or severe dysplasia (precancer)
- Goal: avoid need for cancer treatment

Note: FA individuals do not tolerate chemotherapy and radiation due to the genetic changes underlying FA, which impair cells' ability to repair the DNA damaged by therapies.

- Any woman with FA diagnosed with dysplasia should be examined every 4 to 6 months to identify and treat precancerous lesions

Should medical treatment be combined with surgery for genital tract warts or neoplasia?

- In other immunocompromised populations, squamous precancer recurs.
- In some of these other conditions, improvement has occurred by combining medical and surgical treatments.

Options include:

- Topical Aldara (Imiquimod) – may boost local immune system
- Topical 5 Fluorouracil – chemotherapy that may damage cells
- Injectable Alpha interferon – may boost immune system





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Treatment of Vulvar Intraepithelial Neoplasia with Topical Imiquimod

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)

Principles for using medical therapy for genital neoplasia

- Apply topical medical therapy only to lesions
- Protect adjacent skin with vaseline
- A gynecologist should inspect the genital area periodically to determine
 - If the treatment is working
 - To identify any adverse side effects
- If pain or sores develop during topical treatment, go to the gynecologist

Surgery is the best approach for treatment of gynecologic cancers in Fanconi Anemia

- Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately.
- As chemotherapy and radiation are poorly tolerated, the patient's hematologist should be consulted prior to administering radiation or chemotherapy.

Breast cancer in FA

- Risk of breast cancer
- Screening for breast cancer
- Mammography versus MRI

Breast cancer and Fanconi Anemia

- One of the genes implicated in FA, *FANCD1*, is the breast cancer susceptibility gene, *BRCA2*
- Patients with FA may be at increased risk of breast cancer, although few such cases have been reported

Breast Cancer Cases in FA Literature

| | <u>Age</u> |
|-----------|------------|
| Dosik | 45 |
| Jacobs | 26 |
| Alter | 29 |
| Zatterale | 37 |
| Huck | 37 |
| Holden | 37 |

| | <u>Cohort</u> | |
|--------|---------------|------------|
| German | | 20, 35 |
| Israel | | 39 |
| NCI | | 30 |
| FARF | | 27, 32, 33 |

Age at breast cancer in FA ranges from 20 to 45.
Number of cases of breast cancer in FA is low.