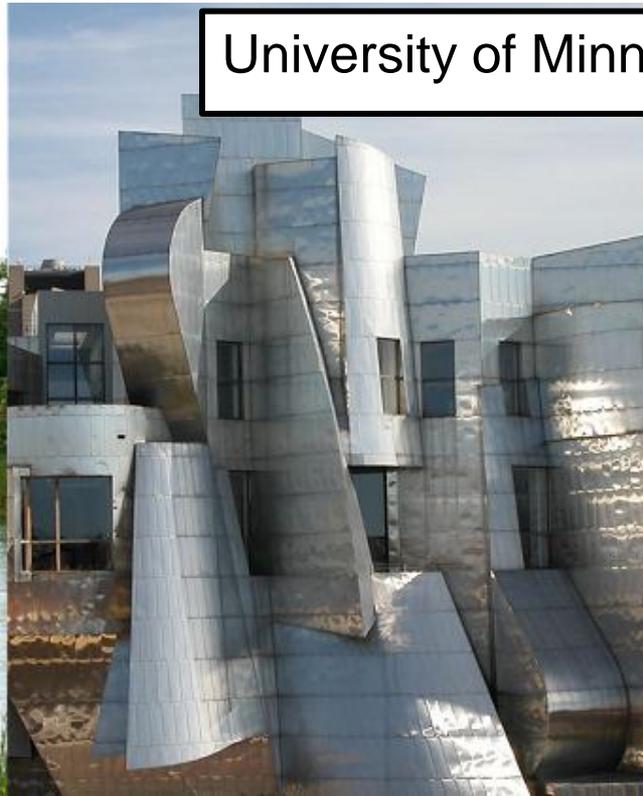


Gynecologic Considerations in Women with FA



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Objectives

- **Recommendation for Gynecologic Care**
 - FA girls starting at age 16 should establish a trusting relationship with a Gynecologist
- **Recommendations for Preventative Care**
 - Health concerns such as contraception, risk of sexually transmitted disease, sexuality, pregnancy and menopause are equally of concern to FA women
- **Common Gynecological Issues**
 - Abnormalities in puberty development and menstrual cycle irregularities are common problems for FA girls and women
- **Considerations for Fertility options**
 - Take the time to discuss fertility options with your family, partner and health care provider
- **Pregnancy outcomes in FA**
 - In selected cases, successful outcomes with pregnancy have been documented in FA women

Recommendations for Preventative Gynecologic Care

- How to establish a trusted Gynecologic care
 - Comprehensive FA care should include gynecologic care for FA girls and women
 - First visit should be to establish trust
 - Find a gynecologist who is aware of FA associated concerns
 - Be prepared to discuss potentially sensitive issues such as
 - Are you sexually active
 - Let's talk about contraception
 - Let's talk about risk for sexually transmitted diseases
 - Physical exam should include an evaluation of the vulva, vagina and cervix

Gynecologic surveillance

- Annual exam
- Beginning at age 16 to 18 or with onset of sexual activity
- Includes cervical cytology (Pap test)
- Careful examination of cervix, vulva skin (and vagina)

Recommendations for Preventative Gynecologic Care

- Sexually transmitted infections
 - Recommendations for annual sexually transmitted infections testing until age of 25
 - Testing for gonorrhea and chlamydia
 - Regular use of condoms to protect against sexually transmitted infections

Recommendations for Preventative Gynecologic Care

- Pregnancy
 - Although fertility is decreased, FA girls/women can become pregnant
 - Use contraception when pregnancy is not desired
- Contraceptive Options
 - Priority is optimizing compliance in young women
 - Achieving menstrual regularity maybe of benefit

Delayed puberty

- No breast buds development by age 13
 - 14 if low body weight
 - Maybe associated with additional growth delay
- No menses by 3 years after breast buds or age 16
- Causes of pubertal delay
 - Hormonal imbalance (Hypothalamic dysfunction)
 - Low body weight and chronic illness

Menstrual abnormalities

- Later first menses
- Abnormalities with cyclical or regular ovulation
 - Irregular periods and or no periods (anovulation)
 - Heavy or prolonged menstrual bleeding
- Multiple factors contribute to menstrual abnormalities
 - FA bone marrow failure (low platelets)
 - Low body weight
 - Chronic disease
 - Medications

Irregular or heavy menstrual cycles

- Heavy vaginal bleeding
 - Limits quality of life
 - Side effects of anemia
 - Occurs in women with irregular menses
 - Pre and post bone marrow transplant- low platelets and anemia
- Irregular vaginal spotting
 - Unpredictable and often annoying to women
 - Associated with hormonal or ovulatory dysfunction

Treatment options

- Hormonal management
 - Birth control pills
 - Daily monophasic, combined pill without placebo
 - Estrogen may worsen anemia
 - Progestins
 - Oral progestins
 - Depoprovera may worsen bleeding initially
 - Levonorgestrel IUD
 - Leuprolide acetate (Lupron)
- Surgical options
 - Endometrial ablation
 - Hysterectomy

Risk of gynecologic squamous malignancies

- Higher rate of squamous cell cancer of cervix, vagina and vulva among FA women
- Early onset for cervical, vulvar and vaginal cancer
- HPV vaccine is recommended for boys and girls

Recommendations for Preventative Gynecologic Care

- HPV associated cancers
 - HPV subtypes 6 and 11 account for 90% genital warts
 - HPV subtypes 16 and 18 seen in 70% of cervical cancer
- HPV vaccine (two types)
 - Approved to decrease the risk of HPV associated cancers (cervical, vulvar, vaginal, anal)
 - Comprised of virus-like-particles for HPV subtypes 6,11,16, and 18
 - Recommended for ages 11-12, but can start at ages 9 and above
 - Three doses over 6 months

Screen women with FA for cervical and vulvar cancer

- Evaluation –at least annual
- Cervical cytology screening
 - Pap test
 - Annual HPV testing is not recommended
- Vulva and vaginal inspection for any new lesions
 - Patient should regularly evaluate and report new vulva lesions
- Colposcopy/biopsy when indicated
- Treatment –surgical excision of moderate/severe dysplasia when identified

Ovarian function in FA women

- Early menopause (premature menopause) has been documented in FA women
- Ovarian function can be reduced by Hematopoietic stem cell transplantation (HSCT)
 - Age
 - Relation of puberty to time of transplant
 - Total body irradiation (TBI)
 - Chemotherapy drugs prescribed

Ovarian Failure

- Acute Ovarian Failure (AOF)
 - Loss of ovarian function during cancer therapy or shortly thereafter
- Premature Menopause or Premature Ovarian Failure (POF)
 - Loss of ovarian function before the age of 40 years
 - Increased risk of osteoporosis, impacts sexual function and cardiovascular disease

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
- Discuss the impact of HSCT on ovarian function with patients early

Ovarian failure due to chemotherapy

- Impact on ovarian function is dependent on
 - Age of patient, dose, drug and duration of therapy
- Chemotherapy damage to primordial follicle and the steroid producing cells of ovary (granulosa and theca cells)
- Highest risk with alkylating agents (cyclophosphamide, procarbazine, nitrosoureas, melphalan, chlorambucil)
- Fertility time frame is more narrow, encourage early intervention

Ovarian Failure Radiation

- Associated with dose related reduction in primordial follicle
- Older women are more sensitive to the radiation effect due to decreased ovarian reserve
- Ovarian failure $LD_{50} < 4 \text{ Gy}$
- Permanent ovarian failure occurs at 20 Gy
- Acute ovarian failure in CCSS (Childhood Cancer Survivor Study)
 - 3390 survivors, 6.3% developed AOF
 - 72% of patients treated with dose of 1000 cGy or higher developed AOF
 - AOF increased among Hodgkin's lymphoma survivors, those treated with alkylating agents and abdominal pelvic RT

Menopause health risk for FA women

- Premature menopause
 - Management of hot flashes, consider hormone replacement therapy
 - Osteoporosis
 - due to low estrogen
 - chemotherapy or radiation side effects
 - Monitor bone density
 - Cardiovascular disease
 - Evaluate lipids
 - Androgens may increase cardiovascular risk
- Breast cancer
 - Monitor for breast cancer, increased risk among older FA women

Female fertility

- Female fertility can be compromised by any treatment that:
 - Decreases the number of primordial follicles
 - Affects hormonal balance
 - Interferes with the functioning of the ovaries, fallopian tubes, uterus or cervix.
- Loss of fertility can occur despite maintenance or resumption of cyclic menses.
- Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened by premature ovarian failure.

Post Treatment Fertility

- Infertility
 - Defined as the inability to conceive after one year of intercourse without contraception.
- Multiple factors impact fertility
 - Pre-treatment fertility of the patient
 - Age, gender of the patient
 - Drug or size/location of the radiation field
 - Chemotherapy agents and Bone Marrow Transplant

Post treatment fertility

- Fertility preservation is of great importance to many people diagnosed with cancer.
- Surveys of cancer survivors have identified an increased risk of emotional distress in those who become infertile because of their treatment.
- Long-term quality of life is affected by unresolved grief and depression.

Pregnancy in FA Females

- Fanconi Anemia and Pregnancy (Alter BP, Br. J. Haematol 1991)
 - Report on 110 FA female patients, 16 years or older
 - Age of FA diagnosis 12 to 27 yrs., pregnancy at ages 18-26
 - Total of 26 pregnancies, 19 live births and 18 surviving children
- Fertility recovery and pregnancy after allogeneic hematopoietic stem cell transplantation(HSCT) in FA (Nahan SK, Haematologica 2010)
 - Historical review of 15 transplant centers
 - 285 female patients of which 101 were 16 years or older
 - 10 women with 14 reported pregnancies
- Pregnancy outcome
 - Majority experience a normal delivery with limited maternal and fetal complications
 - Complications reported: Preeclampsia, worsening maternal hematologic status, preterm delivery

Fertility Preservation Options in Females

- **Fertility preservation options in females depend on the patient's:**
 - Age
 - Type of treatment
 - Diagnosis
 - Partner status
 - Time available
 - Overall health status

Options for preservation of fertility in females

- **Options for preserving fertility in females:**
 - Embryo Cryopreservation-harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation
 - Oocyte Cryopreservation-harvesting and freezing of unfertilized eggs
 - Ovarian Tissue Cryopreservation-freezing of ovarian tissue and reimplantation after treatment
 - Ovarian Suppression-use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy
 - Ovarian Transposition-surgical repositioning of ovaries away from the radiation field

Fertility preservation for females

Embryo Cryopreservation

- Well established as part of IVF therapy to store excess embryos
- Need an identified sperm donor
- Survival per thawed embryo is 35-90%, implantation rates 8-30% and cumulative pregnancy at 60%



Fertility Preservation Options in Females

- **Embryo Cryopreservation**

- Requires ~2 weeks of ovarian stimulation w/daily injections of FSH from the onset of menses.
- A delay of 2-6 weeks in chemotherapy initiation may be required if reproductive specialists do not see women early in their menstrual cycle.
- This approach may be associated with high out-of-pocket costs for most women.
- Long-term follow up with a larger number of patients is needed to evaluate the safety and efficacy of this approach.
- For women with hormone-sensitive tumors, alternative hormonal stimulation approaches such as letrozole or tamoxifen have been developed to theoretically reduce the potential risk of estrogen exposure.

Fertility Preservation Options in Females

- **Recommendation (Oocyte Cryopreservation):**
 - Cryopreservation of unfertilized oocytes is another option for fertility preservation particularly in patients for whom:
 - A partner is unavailable, or
 - Religious or ethical objections conflict with embryo freezing.
 - Oocyte cryopreservation should only be performed in centers with the necessary expertise

Female Fertility

Oocyte Cryopreservation

- Oocyte Cryopreservation
 - Ovarian stimulation and harvesting requirements are identical to those of embryo cryopreservation, and thus this technique is associated with similar concerns regarding delays in therapy and potential risks of short-term exposure to high hormonal levels.
 - There have been approximately 120 births with this approach. Further research is needed to delineate the current success rates and safety, as well as to improve the efficiency of this procedure.
- Clinical pregnancy rates are significantly lower
 - Due to the damage during freezing and thawing process
 - Techniques are improving with live birth per thawed oocyte at 4%, pregnancy rates 13-28%

Fertility Preservation Options in Females

- **Ovarian Tissue Cryopreservation**
 - Ovarian tissue is removed laparoscopically and frozen.
 - At a later date, the ovarian tissue is thawed and reimplanted.
 - This is an investigational method of fertility preservation with the advantage of requiring neither a sperm donor nor ovarian stimulation.
 - Because there are too few primordial follicles remaining, the benefit of ovarian cryopreservation for women >40 years of age is very uncertain.

Fertility Preservation Options in Females

- 12 pregnancies reported to date after autologous orthotopic transplantaton of frozen thawed ovarian tissue
 - Contraindicated in certain types of cancers (ovarian, lymphoma)
- Alternative to transplantation
 - Isolation of immature oocyte and maturation in vitro with in vitro fertilization (IVF)
 - No pregnancy reported in human to date

Conclusions

- Gynecologic issues for FA women
 - Best managed by establishing long term gynecologic care
 - Address preventative issues during regular annual exam
 - Manage heavy menstrual bleeding
 - Manage issues of fertility and pregnancy
 - Manage issues related to increased risk of gynecologic squamous cancers
 - Manage symptoms of ovarian failure/premature menopause

Thank You