بسم الله الرحمن الرحيم

Pregnancy and Fertility in Cancer Patients

An ESMO 2013 CPG-Based Presentation

NOV. 22ND, 2014

BY AHMED NOFAL, MD

LECTURER OF CLINICAL ONCOLOGY

AIN SHAMS UNIVERSITY

Pregnancy and Cancer

Incidence

The most common cancers associated with pregnancy are:

1. Breast cancer
2. Melanoma
3. Cervical cancer
4. Lymphomas
5. Acute leukemias

Natural history

Pregnancy **does not**:

a) Increase incidence of malignancy.
b) Alter biologic behavior or prognosis of cancer *(controversy)*.
c) Reactivate cancer in remission.

Diagnostic and staging studies during pregnancy

- **Ultrasonography:** Safe→ Preferred (no ionizing radiation).
- **Chest radiographs & Mammograms:** both can be safely carried out during pregnancy with proper abdominal shielding. Mammography lacks sensitivity in pregnancy.
- **MRI:** (without gadolinium ?: teratogenic)
  - **1st Trimester:** should be avoided (due to risk of heating/cavitation)
  - **2nd & 3rd Trimesters:** Only done when detailed anatomical info is required e.g. in staging of cervical cancer.
- **CT, BS, &PET:** Should be avoided through out pregnancy.

- **Biopsies:** risk to fetus:
  - **local anesthesia**: No risk.
  - **General anesthesia**: Minimal risk.
- **SLNB:**
  - Technetium-99m: Can be used (Low fetal exposure)
  - Blue dyes: Contraindicated.
- **Spinal tap, BMA & biopsy, & Endoscopies:** Relatively safe.
- **Tumor Markers:** variable during pregnancy; especially **CA 125** & **CA 15.3** → Should not be considered.

Teratogenesis

- **Definition:** include not only any morphologic abnormalities at birth but also other types of malformations, growth retardation, fetal death, and developmental disabilities.
- **Incidence** of major malformation at birth in general population is **3 – 4%**.
- **Chemo teratogenic effect by trimester:**
  - **1st** : Spontaneous abortion and morphologic abnormalities.
  - **2nd & 3rd** : IUGR, microcephaly, developmental delay, mental retardation, and learning problems.

Principles of Cancer Therapy During Pregnancy

- **Gestational age:** must be accurately determined.
- **Surgery:** Not contraindicated, It doesn't appear to increase major birth defects but the risk of miscarriage is increased. Therefore , when possible, surgery should be deferred until the 2nd trimester.
- **RT:** If possible, RT should be administered post-partum.
  - **< 5 - 10 cGy**: Is the limit of fetal exposure to ionizing radiation of any source.
  - **In pelvic fields:**
    - Doses above 100 – 200 cGy: Mental and/or growth retardation and organ malformation can only arise.
    - Doses up to 50 cGy: The situation is less clear.
  - **In non-pelvic fields:** In contrast, RT can be performed if absolutely indicated and in the absence of alternative therapeutic strategies. Fetal doses of <100 cGy should not be a reason for termination of pregnancy. This can only be carried out in **specialized centers** were special devices to shield and protect the fetus are available.

Pregnancy and Cancer

- **CTH:**
  - Can be administered with reasonable safety during 2nd & 3rd trimesters, though with increased risk of stillbirth, GR, and premature delivery.
  - A 3-weeks period should be allowed between the last chemo and the EDD to avoid delivery during the nadir period.
  - Weekly schedules have relatively lower nadir risk and so, warranting consideration in pregnant cancer patients.
    - **Most teratogenic and abortive:** Older-generation alkylators: e.g. **chlorambucil**, and antimetabolites e.g. **methotrexate**.
    - **Least teratogenic:** Anthracyclines, 5-FU, and vinca alkaloids (vinblastine, vincristine).
    - **Relatively safe beyond 1st trimester:** (from emerging evidence) **Taxanes** & **platinum**.
    - **No or scant data:** Pemetrexed, gemcitabine, vinorelbine, and oxaliplatin.

    Note: Breast-feeding is contraindicated during treatment with CTH.
- **HT:** Tamoxifen (TAM) should be deferred until after delivery (due to observed teratogenicity).

Pregnancy and Cancer

- **Targeted agents: Not well-studied** as few pregnant women have been exposed to these agents. But current evidence revealed:
  - **Trastuzumab:** can cause oligohydramnios and abnormal implantation, no data on the effect on fetal heart. Recommendation: is to withheld treatment with this agent until after delivery or pregnancy termination.
  - **Rituximab:** Only causes neonatal lymphopenia.
  - **Imatinib:** Safe during the 2nd and 3rd trimesters.
  - **Erlotinib:** No data available, so, its administration is not advised.
  - **Anti-angiogenic agents:** Thalidomide caused fetal malformations in animal experiments. All these agents including: bevacizumab, sunitinib, sorafenib, …) should be avoided during pregnancy.
  - **IFN-a:** Safe even in the 1st trimester.
  - **Ipilumumab & Vermurafenib:** Lacking any safety data, we can use IFN-a instead.

- **Supportive therapy:**
  - **Antiemetics:**
    - These can be safely administered: Ondansetron (Zofran) and metoclopramide (Primpran) with avoiding corticosteroid in the 1st trimester.
    - Discouraged: Tropisetron (Navoban) due to teratogenicity.
    - Rarely used in pregnancy: Granisetron (Kytril, EM-EX, Granitryl).
  - **Analgesics:** Paracetamol, opioids, and anti-inflammatory agents have been administered safely ***beyond the 1st trimester***.
  - **Growth factors:** No fetal adverse effects if given ***beyond the 1st trimester*.**
  - **Bisphosphonates & Somatostatin:** should be ***deferred until after delivery*.**
  - **Anti-infectious agents:** should follow published principles of avoidance of those drugs with teratogenic effects.

- **Therapeutic abortion:**
  - **Not recommended:** If treatment is not going to jeopardize pregnancy (e.g. surgery for breast cancer).
  - **Considered:** when pregnancy is going to delay starting treatment (e.g. a pregnant breast cancer patient presented in the 1st trimester.
  - **Strongly recommended:**
    a) when treatment can not be delayed or accomplished during pregnancy (e.g. most gynecologic cancers).
    b) Treatment is likely to cause abortion or fetal malformations (e.g. MTX and pelvic RT).
- **Delivery guidelines:**
  - **Timing:** when fetal maturity and viability are satisfactory (32nd – 35th week) and at least 3 weeks after last CTH cycle to ensure recovery of maternal/fetal myelosuppression.
  - **Method:** CS is chosen in case of invasive cervical cancer.
  - **Pathology:** Though very rare, placental histopathology is a routine practice to exclude placental metastases.

Treatment outcome

- Is **not significantly inferior** to non-pregnant cancer patient matched for age and cancer stage, though late diagnosis is more frequently seen in pregnant patients. It's still currently not known if this is due to more aggressive tumor biology or patient undertreatment.
- Is not compromised by future pregnancies.
- Long-term effect of in-utero exposure to CTH (beyond 1st trimester) or RTH (< 5 – 10 cGy) on the physical and mental development of children? No data or evidence to support any compromise.
- **In Breast cancer**:
  - Most oncologists would recommend that potentially cured breast cancer patients postpone childbearing for at least **2 years**, to allow resumption of adequate ovarian function and to overcome the time frame associated with a relatively high risk of recurrence.
  - **In patients considered for 5 years of adjuvant TAM**, treatment interruption could have potential detrimental effect on their BC outcome. If the patient is willing to consider this risk, interruption after 2 – 4 years could be considered, then resumption of TAM after delivery is strongly encouraged.

Fertility in Cancer Patients

- **Gonadotoxic effects** of different cancer treatment modalities depend on:
  1. Patient's age.
  2. Nature of insulting agents.
  3. Total dose.
  4. Treatment fields (RT).
- All patients at risk of infertility who did not complete childbearing should discuss **germ-cell storage options** with medical team.
- Women with amenorrhea should be screened for serum levels of estradiol, FSH, and LH in order to better assess their **reproductive potential**.

We're going to discuss:

- **Causes:** either due to
  - Pretreatment hypogonadism in men.
  - Cancer related treatment: RT and CTH in both men and women
- **Fertility preservation options**. In men and women.

Infertility in Men with Cancer

- **Causes:**
  - **A. Pretreatment hypogonadism:**
    - More than 50% of male patients with disseminated testicular cancer, HL, and metastatic cancer have fertility issues as follows:
      1. Testicular cancer: >80% of patients with disseminated disease are oligo or azospermic, probably due to the disease itself
      2. HL: >50% of patients have low sperm count or poor motility.
      3. Metastatic Cancer: >60% have low testosterone levels believed to be due to malnutrition.

B. Cancer related treatment:

- **RT:** The testes are exquisitely sensitive to radiation (doses as low as 15 cGy can cause transient suppression of spermatogenesis). The duration of azoospermia is proportional to the RT dose delivered as follows:
  - At 200 – 300 cGy: recovery takes 3 years.
  - At 400 – 500 cGy: recovery my take 5 years.
  - A dose > 600 cGy: result in permanent azoospermia.
- **CTH:** Spermatogenesis is highly susceptible to the toxic effect of some CTH agents, depending on: age, total dose per square meter, and whether it's administered in combination or not. *Examples:*
  - Alkylating agents causes germ cell depletion which is dose/age-dependent (e.g. Cyclophosphamide).
  - Combination regimens: e.g. MOPP in HL causes testicular atrophy in 80% of cases, while ABVD regimen results in only 35% of azoospermia with eventual return of spermatogenesis in almost 100% of the cases

- **Fertility preservation options:**

  All available interventions are unlikely to delay cancer treatment, these options include:

  - Semen cryopreservation.
  - Sperm extraction: for azoospermic men.
  - Hormonal manipulation ? No studies to support its effectiveness during chemo or radiotherapy.

Infertility in Women with Cancer

- **Causes:**
  - **RT:** The effects of radiation on fertility are strongly influenced by: patient age, RT (pelvic) field, and total dose. For example:
    - **At doses > 150 cGy:** Temporary cessation of menses for variable periods of time occurs
    - **At dose of 500 – 600 cGy:** (to the ovaries) usually results in permanent ovarian failure.
  - **CTH:** The likelihood of premature ovarian failure after CTH increases with age. Menses rarely return after age 35 – 40 years.
    - **Agents clearly associated** with ovarian failure: Alkylating agents: e.g. cyclophosphamide.
    - **Agents unlikely to cause ovarian dysfunction**: MTX and 5-FU.
    - **Agents with unknown effects** on the ovary: include doxorubicine, bleomycin, vinca alkaloids, cisplatin, paclitaxel.

  Combination regimens: MOPP causes 50% ovarian dysfunction, ABVD is associated with much less incidence of infertility.

- **Female fertility preservation:**

  In contrast to fertility preservation intervention in men, female fertility preservation options have requirements for scheduling and ovarian stimulation resulting in a likely **delay of 2 – 6 weeks of cancer treatment initiation.** The available options are either:

  - **Established options:** this only include:
    - **Embryo/Oocyte cryopreservation (Main method)**: live-birth rates are inferior to fresh embryo procedures. **Short-term ovarian stimulation;** with gonadotrophins and letrozole or TAM, is necessary for oocyte retrieval and may be associated with a theoretical risk of growth of hormone-sensitive tumors.
    - **Ovary transposition**: only about 50% of women resume menstruation (due to ischemia and scatter).

- **Experimental options:**
  - **Unfertilized oocyte cryopreservation:** for women without a partner (also relies on hormonal stimulation for germ-cell harvest). It remains experimental as there is some issues with oocyte damage and DNA integrity.
  - **Laparoscopic removal of one ovary:** and ovarian tissue storage for those who can not undergo ovarian stimulation or are prepubertal. Cryopreserved ovarian tissue can later be transplanted to the patient or subjected to ongoing in-vitro maturation for oocyte extraction.
- **Female gonadal protection**: The concomitant use of GnRH agonists during CTH from to preserve fertility has been studied in several phase III trials with **conflicting results**.

Thank You

Ahmed Nofal, MD
drahmed_nofal@med.asu.edu.eg
ahmedmnofal.synthasite.com