Cancer & fertility

Dr.Negin Farshchain

Breast cancer & fertility

- Case :
  - 35 y-old woman with T2 N+ / grade II / I.D.C /ER/PE +
  - SHE TREATED WITH:
  - MRM / + RT
  - CHT
  - TAM

She is seeking medical advice for post-chemotherapy amenorrhea and would like to know :

- 1- if she is menopausal?
- 2-what are the gynecologic consequences of tamoxifen ?
- 3- when can she try to become pregnant ?
- 4- whether she could benefit from medically-assisted reproduction(MAR) ?
- 5- Is it will be necessary to wait ?

MAGNITUDE OF THE PROBLEM:

- BREAST cancer in young women is a more serious cancer
- However is rare before 35 y of age
- 4.7 % in less than 35 y ……> 63.3% in from35 to 39 y
- Age less than 35-33 y is an independent factor of poor prognosis
- More recurrence & poorer survival.

- The risk of recurrence increased by 4% for each year below 34y
- Of note : nulliparity is not a poor factor in these women quite the contrary , nulliparity is then a factor for better prognosis.
- Histologically : larger, more often without hormone receptors and high grade
- The average age of mothers has been increasing & the average age was 30 y in 2000.
- Thus the average age for pregnancy corresponds to the most serious age-linked cancers.

Treatments & Risk of sterility

- Chemotherapy
- Hormone therapy
- Radiotherapy
- Target therapy

Ovarian function after cancer treatment

- Depends on :
- 1-Patients age
- 2-Chemotherapy and type of drugs
- 3-Hormone therapy +/_ GNRH agonists
- 4-Adding radiotherapy

- Age :
  - in general young women will have preserved cycles whereas older will frequently have amenorrhea, indeed an early menopause.
- Drug:
  - risk is more with: 1- alkylating agents(cyclophosphamide),
    2-more cumulative dose(duration/intensity)
    3-age
- in some studies cht-induced amenorrhea is correlated with better prognosis (but age is a confounding factor)

Chemotherapy Drugs :

- CMF regimen
- Newer agents : anthracycline and taxane
- Anthracycline :Improve 4.6% at 10y respect to CMF

- The rate of amenorrhea :
- 66% with CMF
- 50% for : anthracycline alone
- 66% for : : anthracycline + taxane

Tamoxifen:

- reduces the risk of mortality by 24% in young women at the end of 5 y treatment .
- Has not typically been associated with cessation of ovulation.
- At higher doses, tamoxifen can act like the related compound and fertility drug clomiphene, to stimulate ovulation.
- Tamoxifen may cause irregular or absent menses in some patients when given after gonadotoxic chemotherapy or when used alone
- **Tamoxifen-induced amenorrhea is thought to be reversible and temporary**

- **Concomitant treatment with GNRH agonists :**
  - is to be discussed for these young patients ,because chemotherapy dose not necessarily lead to amenorrhea
  - Only 30% with CMF in less than 35 versus 60-80% in >40y
- The risk of sterility is proportional to age at the time of treatment

- Risk of menopause increases with adding treatments and increase in patients age.

- Menopause at age 30: CHT : 5%
  CHT +hormone therapy :15%
  at age 35 CHT : 15%
  CHT+ ht : 33%

- NOTES :
- Post chemotherapy amenorrhea dose not mean menopause
- It is necessary to wait 2 y without periods to speak of menopause after cht.
- Tamoxifen dose not induce menopause so effective contraception is necessary
- IUD without progesterone or high dose progestational agents is 2th line.

Radiotherapy & fertility

- patient age, dose and trajectory of radiation
- The total dose of radiation to the pelvis needed to increase the risk of premature ovarian failure (POF) is estimated at 20 Gy, with failure at lower doses in women 35 years of age and older
- Pelvic radiation also exerts an effect on the uterus, causing changes in both the musculature and blood flow, which can lead to endometrial damage and a higher rate of obstetrical complications

- MORE COMPLICATED:
- when conception occurs **<1 year after** radiation therapy has been completed

- Of the **50 Gy** delivered to the breast during standard whole-breast radiotherapy, only 2.1–7.6 cGy reaches the uterus through internal scatter, which is considerably less than the dose needed to induce POF or cause detrimental effects to the uterus

TARGET AGENTS:

- Trastuzumab (Heceptin)
- Bevacizumab (avastin)

- The effects of trastuzumab and bevacizumab, or newer epothilone agents such as ixabepilone, on fertility have not yet been rigorously evaluated.

Conception after cancer :

- The most important issue:
- **time :**
- **Psychological factors change with time**
- **Return to normal life & Recovering from the disease needs time**
- **Confirmation of cure needs time**
- **Time acts against the fertility**

- In fact the impact of the waiting period for conception on the disease is not very well known.

- For a long time all pregnancy was strictly prohibited after breast cancer. but recently several studies found a protective effect of pregnancy after breast cancer.

- 7% of non-menopausal women will become pregnant after breast cancer
- These women don’t present an increased risk of recurrence.
- Tamoxifen can be delayed to allow for pregnancy after surgery and radiotherapy for breast cancer have been completed, without negatively influencing patient outcomes .

Current strategies for fertility preservation in cancer patient

- **Ovarian suppression during chemotherapy**

- Destruction of follicles engaged in the maturation pathway by chemotherapeutic agents causes an increase in FSH secretion through a loss of negative feedback. This increase in FSH causes additional follicles to enter the maturation pathway, exposing them to the effects of cytotoxic therapy. This cycle can theoretically be interrupted by the administration of a gonadotropin-releasing hormone (GnRH) agonist that achieves reversible arrest of follicle mobilization and maturation preventing an increase in FSH concentration

- OPTION trial
- that 67% of patients recovered normal menses, including 100% of the women <40 years of age

- There is some concern regarding the impact of GnRH agonists on the efficacy of chemotherapy based on evidence that tamoxifen administered simultaneously with chemotherapy may decrease the effect of cytotoxic therapy

- tamoxifen-mediated arrest of cancer cell proliferation
- A similar effect may thus be seen with estrogen suppression via GnRH agonists
- Ultimately, ovarian suppression with GnRH agonists during chemotherapy as a method to preserve fertility remains a highly controversial topic
- clinical trial

Other possibilities?

- In practice no degradation of ovarian function can be repaired at present
- Ovulation inducers have no action on the ovarian reserve.
- So ,the importance of fertility sparing techniques ,before any treatment :
- Cryopreservation of embryos,ovocytes and ovarian tissue

- Medically assisted reproduction (MAR) remains unable to repair this damage but already offers possibilities for **preserving fertility or for a third-party donor** and opens up prospects such as in vitro follicular maturation or freezing of ovarian fragments which have just recently made it possible to become pregnant.
- Breast cancer gives :
- Is hormone-dependent cancer
- So intense hormonal stimulation of MAR is contraindicated.


Thank you all