YOUNG PATIENTS, OFS AND PREGNANCY

INTRODUCTION

These patients pose very specific problems in regard to their breast cancer treatment. This section will highlight those issues and what evidence there is to support the management.

YOUNG PATIENTS WITH BREAST CANCER

- 15% of cases of breast cancer occur in under 45s.
- ~5-10% of all breast cancer cases are due to BRCA1/2 and these tend to present in the younger population.
- Young women are more likely to have tumours with higher incidence of negative clinicopathologic features (higher histological grade, more lymph node positivity, lower oestrogen receptor (ER) positivity, higher rates of Her2/neu overexpression)
- **TEXT/SOFT** trials found in subgroup analysis that younger <35 yrs, high risk patients, who remained pre-menopausal post chemo, had a significant benefit from adding ovarian function suppression (OFS) to either Tamoxifen or Exemestane. Exemestane is superior to Tamoxifen + OFS but has worse SE profile.
- Meta-analysis by Pagani et al. 2014 NEJM of TEXT and SOFT combined shows DFS:
    - Tamox alone = 67.7%
    - Tamox + OFS = 78.7%
    - Exemet + OFS = 83.4% hence guidance that if <35 this should be discussed.
    - So 68% →79% → 83%. If discussing these papers, be aware that the chemo regimens are out of date and we know that OF is suppressed by chemotherapy so difficult to interpret.
- Options for ovarian suppression:
    - GnRH agonists – Goserelin (Zoladex)/ Triptorelin (Triptodur), SC once monthly X
    - LHRH agonists – Leuprorelin (Prostap), SC/IM once monthly or 3 monthly
    - Oopherectomy
- **SOFT-TEXT update (Pagani et al, Journal of Clinical Oncology 2022):** Median follow-up of 13 years, showing sustained reductions of risk of recurrence with adjuvant exemestane + OFS vs tamoxifen + OFS, with estimated DFS and DRFI benefits strongest during years 0-5 and attenuated during years 5-10 and ≥ 10 years
    - Exemestane + OFS vs Tamoxifen + OFS
        - 12-year DFS - 4.6% absolute improvement
        - Distant recurrence-free interval - 1.8% absolute improvement
        - No overall survival improvement 90.1% v 89.1%
    - HER 2-negative tumors
        - Absolute improvement in 12-year OS
            - with exemestane + OFS - 2.0%
            - with exemestane + OFS + chemo - 3.3%
    - High risk patients OS benefit - clinically significant
        - age <35 years - 4.0%
        - >2 cm - 4.5%
        - Grade 3 tumors - 5.5%
- Recommend easy video on physiology if preparing for exam How do GnRH analogues work? Zoladex, Prostap and other GnRH analogues

Breast Cancer in Pregnancy

Background

For all pregnant Women there are the "Green Top Guideline 12" produced by the Royal college of Obstetrics and Gynaecology and Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015;1(8):1145–1153. doi:10.1001/jamaoncol.2015.2413

- When breast cancer is diagnosed in women aged 30 years or less, 10–20% of cases may be associated with pregnancy or occur within 1 year postpartum. 2 cases per 10k live births quoted by RCOG.
- Incidence of breast cancer is 1 in every 3000 pregnancies.
- Pregnancy itself does not appear to worsen the prognosis for women diagnosed in pregnancy compared with non-pregnant controls matched for age and stage, however as pregnancy-associated breast cancer occurs in a younger population who may have features that carry a higher risk of metastases such as high-grade tumours and oestrogen receptor negative tumours, these younger women may be expected to have an inferior prognosis.

Investigation and staging considerations

- Pregnant women presenting with a lump should go through standard triple assessment. Core biopsy is preferable to cytology as proliferative change during pregnancy renders cytology inconclusive in many women. If mammography is indicated then foetal shielding is offered.
- Staging for metastases is conducted only if there is high clinical suspicion and should comprise chest x-ray and liver ultrasound, if possible, rather than CT.
- Gadolinium enhanced MRI is not recommended unless there is a specific need for it.
- Bone scanning and pelvic x-ray computed tomography are not recommended because of the possible effect of irradiation on the foetus. If there is a concern regarding bony metastasis a plain x-ray of the area is preferred.

- https://ijgc.bmj.com/content/31/3/423 is a good paper on imaging in breast cancer and quotes the following rx to the foetus:

Foetal radiation dose for the different ionizing radiation techniques

Imaging technique	***Foetal radiation dose (mGy)***
Chest X-Ray	<0.01
Mammography (two planes, bilateral)	<0.01
CT head	<0.005–0.5
CT chest	0.001–0.66
CT abdomen/pelvis	8–25
99mTc bone scintigraphy	3.3
18F-FDG PET/CT	10–50

Surgical management

- Surgical treatment can be undertaken in all trimesters.
- If the patient presents in the 1st trimester then mastectomy is often preferred to WLE as radiotherapy cannot be given until after delivery.
- Reconstruction should be delayed to avoid prolonged anaesthesia and to allow optimal symmetrisation of the breasts after delivery.
- Sentinel node assessment using radioisotope does not cause significant uterine radiation, but blue dye is not recommended as the effect upon the foetus is unknown.

Radiotherapy

- Radiotherapy is contraindicated until delivery unless it is lifesaving or to preserve organ function (e.g. spinal cord compression).
- If necessary, radiotherapy can be considered with foetal shielding or, depending on gestational age, early elective delivery could be discussed. Routine breast/chest wall radiotherapy can be deferred until after delivery.

Chemotherapy and hormone therapy

- Systemic chemotherapy is contraindicated in the first trimester because of a high rate of foetal abnormality, but is safe from the second trimester.
- Anthracyline regimens are safe; there are fewer data on taxanes, which should be reserved for high-risk (node-positive) or metastatic disease.
- There is no evidence for an increased rate of second-trimester miscarriage or foetal growth restriction, organ dysfunction or long-term adverse outcome with the use of chemotherapy.
- Haemopoietic growth factors (granulocyte colony stimulating factor) may be used to reduce chemotherapy-induced neutropenia.
- Tamoxifen and trastuzumab are contraindicated in pregnancy and should not be used.

Pregnancy and delivery

- Most women can go to full term of pregnancy and have a normal or induced delivery. Birth should be more than 2–3 weeks after the last chemotherapy session to allow maternal bone marrow recovery and to minimise problems with neutropenia.

Breastfeeding

- Breastfeeding while on chemotherapy is not advised, as the drugs cross into breast milk and may cause neonatal leucopoenia with a risk of infection. There should be a time interval of 14 days or more from the last chemotherapy session to start of breastfeeding to allow drug clearance from breast milk.
- Women should not breastfeed when taking trastuzumab or tamoxifen, as it is unknown whether these drugs are transmitted in breast milk.
- There is no evidence that breastfeeding increases the risk of recurrence in women who have completed treatment for breast cancer.

Prognosis

- The prognosis is good for women with a subsequent pregnancy after early-stage breast cancer.
- Long-term survival after breast cancer is not adversely affected by pregnancy.

Adjuvant therapies and Fertility

Chemotherapy and hormone therapy

- Chemotherapy may cause permanent amenorrhoea with complete loss of germ cells, transient amenorrhoea, menstrual irregularity and subfertility.
- The classic CMF regimen (cyclophosphamide, methotrexate, 5-fluorouracil) caused a higher incidence of amenorrhoea than anthracycline-based regimens such as FEC (5-fluorouracil, epirubicin, cyclophosphamide).
- The agents used for adjuvant hormonal therapy do not in themselves cause long-term effects on fertility.
- Tamoxifen causes menstrual irregularity and there is an increased risk of endometrial pathology; conception during tamoxifen therapy should be avoided because of potential teratogenicity, and a ‘washout period’ of 2–3 months is advised before trying to conceive.
- GnRH analogues cause amenorrhoea and profound oestrogen deficiency but the effect is entirely reversible.
- Herceptin - there is no evidence that it impairs fertility, but pregnancy is not advised during treatment.

Additional fertility considerations

- Most women should wait at least 2 years after treatment before trying to conceive, which is when the risk of cancer recurrence is highest. They may delay to 5 years however to complete adjuvant tamoxifen.
- Women with a history of breast cancer should seek specialist contraceptive advice. Hormonal contraception is contraindicated in women with current or recent breast cancer.

- Women on tamoxifen are advised to stop this treatment 3 months before trying to conceive because of the long half-life of the drug, and to have any routine imaging before trying to conceive to avoid the need for imaging during pregnancy.
- Women with metastatic disease should be advised against a further pregnancy as life expectancy is limited and treatment of metastatic disease would be compromised.
- Ovarian stimulation for egg or embryo freezing requires careful discussion in light of unknown long-term risks. Modified stimulation regimes should be considered for women with oestrogen-sensitive breast cancer.
- Women who are known to be breast cancer gene (BRCA) carriers may wish to consider preimplantation genetic diagnosis, which is now available in the UK.
- Royal college of Gynaecology has strict criteria for determining chemotherapy induced menopause; MUST WAIT 2 YEARS to establish as may resolve. Stop Tamoxifen 8/52 then 2x blood samples 6/52apart showing FSH>30 are confirmatory.
- **The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial (Partridge et al, NEJM 2023)** looked at risk of recurrence among women with hormone receptor–positive early breast cancer who temporarily discontinue endocrine therapy to attempt pregnancy.
    - Prospective study, across 4 continents
    - <42 year old, Stage 1-3 disease, had adjuvant endocrine for minimum 18 months
    - The 3-year incidence of breast cancer events was 8.9% in the treatment-interruption group and 9.2% in the control cohort
    - In select women, temporary interruption of endocrine treatment after 18 months did not increase short term risk of breast cancer
    - Will need long term follow-up (10yr) data