Fertility Preservation

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Improved survival of cancer

- 1 in 46 women diagnosed with a malignancy, with ½ of these receive gonadotoxic treatment (1% of female population)
- Breast CA mostly common malignancy under 35; mortality rate for <50 years old decreased by 38%
- Greater attention on improving QOL
- Ability to have children most important aspects of life
- Non-malignant diseases SLE, vasculitis, mosaic Turner's syndrome

Why now?

Improvement in cryopreservation technique

Uptake of fertility preservation services

- Uptake of service >90% in some cases
- Majority consist of young women with cancer undergoing potential gonadotoxic chemo or radiotherapy

Impact of oncology therapy on fertility is age dependent

- The destruction of limited number of follicles can cause premature ovarian insufficiency
- Older women have a lower number of remaining primordial follicles (lower ovarian reserve)
- Gonadotoxic effect on female fertility is age-dependent
- The odds of ovarian failure increased by 24% for each additional year of age

Radiotherapy

- Ovarian damage affected by field of treatment, total dose and fractionation schedule
- Even low dose can have major impact, e.g.
  - Previously thought dosage of 4-18Gy destroy 50% of primordial follicles
  - Recent results showed dosage as low as 2Gy
- Effective sterilising dose
  - 20.3Gy at birth
  - 18.4Gy at 10 years
  - 16.5 Gy at 20 years
  - 14.3 at 30 years

Chemotherapy

Risk level	Chemotherapeutic agents
High risk	Cyclophosphamide; ifosfamide; chlorambucil; melphalan; busulfan; nitrogen mustard; procarbazine; nitrosureas; chlormethine; carmustine; lomustine
Moderate risk	Cisplatin; carboplatin; doxorubicin; adriamycin; actinomycin
Low risk	Vincristine; vinca alkaloids (vinblastine); methotrexate; bleomycin; dactinomycin; mercaptopurines; fluorouracil
Risk exists (but unknown level)	Nitrosources and antimetabolites: cytosine arabinoside
Unknown risk	Taxanes; oxaliplatin; monoclonal antibodies (trastuzumab, bevacizumab, ccetuximab); tyrosine kinase inhibitors (eriotinib, imatinib)

Effects on infertility		
Lesser	**Greater**	
Adjuvant chemotherapy	Radical chemotherapy	Radical chemotherapy generally has a more profound effect on fertility in comparison to adjuvant chemotherapy
Single agent chemotherapy	Combination chemotherapy	Regime involving multiple agents is more likely to have an adverse impact upon fertility than a single agent
Lower dose chemotherapy	Higher dose chemotherapy	Higher dose is likely to have a more profound effect on fertility
Less gonadotoxic agents	More gonadotoxic agents	Among different agents there are marked variations in the impact upon fertility
Younger age	Older age	Advancing age increases the risk of ovarian failure
Lower ovarian reserve	Higher ovarian reserve	Pretreatment AMH, FSH and AFC predicted long-term ovarian activity by univariate analysis. Only AMH was predictive in a multivariate logistic regression

Timing of ovarian stimulation

- Small window of opportunity
- Most patients have one chance before gonadotoxic agents
- Consideration can be made for multiple cycles if not limited by time factor
- One study reported 2 cycles for breast CA patients being safe and feasible
- Post- therapy can be considered as premature ovarian failure possible in the future

Controlled stimulation regimes

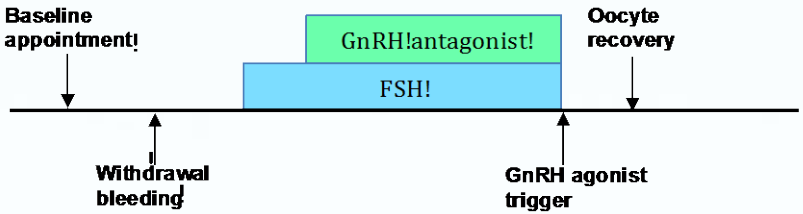
- GnRH antagonist
  - Avoiding extra 10-14 days of down-regulation
  - GnRHa trigger- prevent OHSS

Response to ovarian stimulation

- Specific malignancy & multisystemic effect of malnutrition, catabolic state & ↑ stress hormone may adversely affect the hypothalamic-gonadal axis & ovarian reserve
- Research showed conflicting results for ovarian response
- BRCA gene- breast & ovarian CA. Prone to DNA damage impaired ability of DNA repair
  - BRCA1 mutant mice- smaller litter size & ↓ primordial follicles
  - ↓ AMH level, poorer response in patients with BRCA1
- Success rates following oocyte or embryo cryopreservation comparable to non-oncological pts

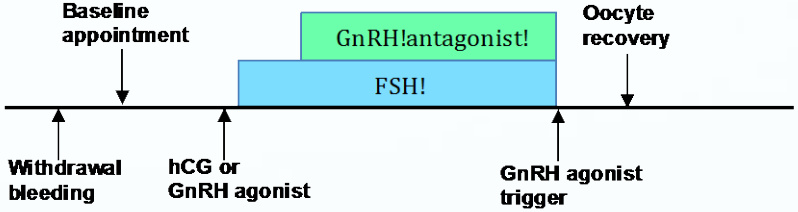
Conventional Start

a)



Random Start/Late Follicular

b)



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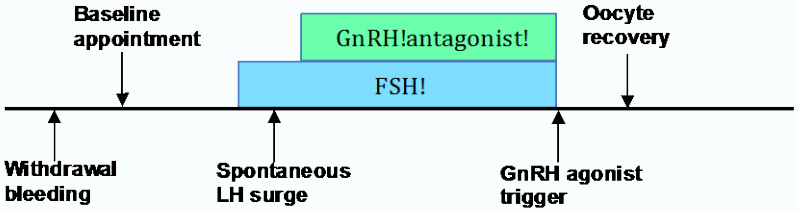

Random Start/Luteal

d)

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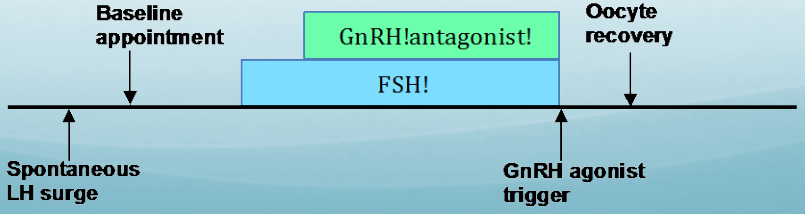


Stimulation for oestrogen sensitive cancers

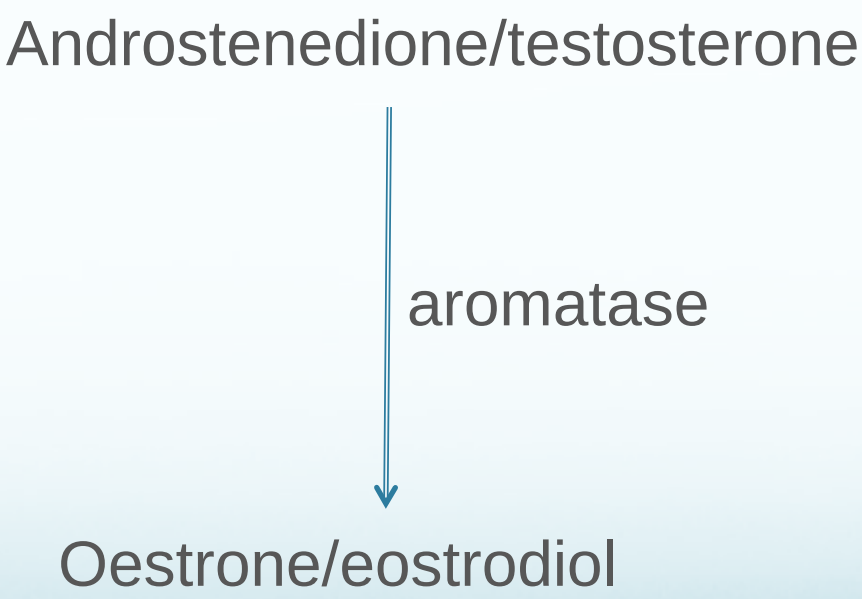
- Endometrial & breast CA
- In the US, >200,000 women/year have breast CA
- Concern of supraphysiological level of E2 promotes growth and metastasis of tumours
- Deleterious effect shown in animal models
- GnRHa trigger → transient surge of FSH & LH → E2 drops more significantly

Stimulation for oestrogen sensitive cancers (tamoxifen)

- Tamoxifen (SERM)- antagonistic effect on E2 receptors in breast CA; stimulates uterine CA
  - 20-60mg/day on day 2-5 of treatment cycle- can be used solely as ovarian stimulation agent
  - Better outcome combined with FSH
- Doubtful effectiveness as fluctuating level of active metabolite endoxifen
- One small study showed no difference in recurrence of CA for patients comparing COH-tamoxifen with no fertility preservation treatment

Stimulation for oestrogen sensitive cancers (letrozole)

- Letrozole- aromatase inhibitor



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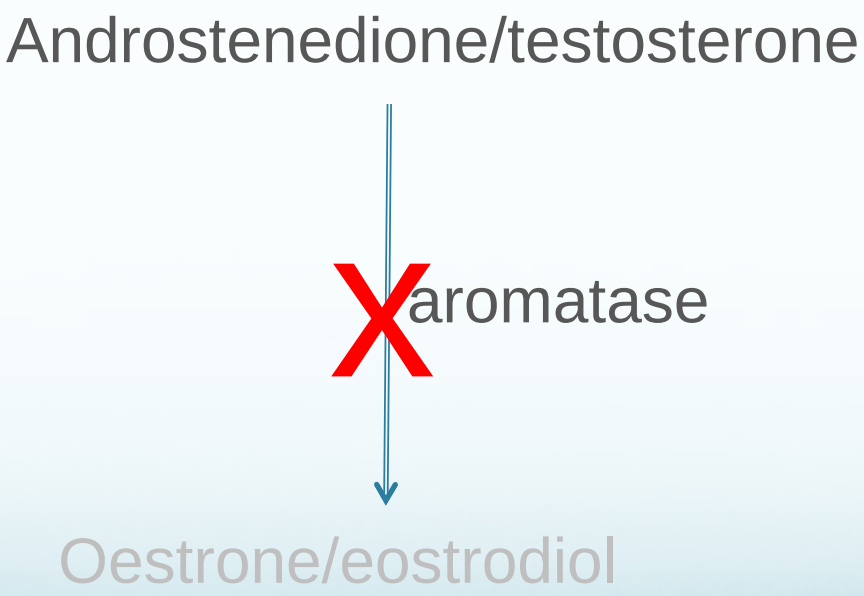

Stimulation for oestrogen sensitive cancers (letrozole)

- Can be used alone or with FSH
- Better numbers of follicles, eggs & embryos vs tamoxifen (used solely as stimulation agents)
- 2.5-10mg/day
- Usually stopped on day of trigger; used to be restarted after OR (not with GnRHa trigger)
- Lower E2 level proven- like natural cycle
- Change of follicular fluid dynamics, ovulation triggered when follicles 19-20mm rather than 17-18mm

Other considerations

- Lab technique to increase success
  - ICSI
  - IVM
- Health state of pts
  - Thrombophilic- anticoagulation
  - Prevent OHSS
  - Coagulopathies for bone marrow disease
  - Neutropaenia- antibiotics & granulocyte colony-stimulating factor
  - Sick patients- multidisciplinary & when to say no
  - Age- case report 13 years old, recommendation 14-40

The future

Ovarian tissue preservation

-insufficient time for stimulation

Teenagers

Aberdeen/Concept

- Email/phone call
- Arrange to see patients within a few days
- Assess suitability- single/ with a partner
- Multiple emails- funding, surgery, adjuvant therapy
- Usually post surgery before chemotherapy- signal by surgeon
- Letrozole for breast CA

KEEP CALM

... THERE'S MORE TO COME


KEEP
CALM
BECAUSE
EVERYONE DESERVES
A CHANCE