Reproductive Options for Breast Cancer Patients

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Reproductive Options for Female Cancer Patients

*balancing hope and realistic expectation*

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Overview

• Introduction
• What is currently available?
  – IVF and embryo cryopreservation
  – Donor eggs and surrogacy
  – Oocyte cryopreservation
  – Ovarian cortex collection and IVM/transplantation
• Clinical experience and outcomes
• Special challenges for breast cancer patients
  – Funding
  – Hormone sensitivity and IVF
  – Tamoxifen holiday
  – BRCA PGD screening of embryos
  – Posthumous use
• The patient’s perspective
• What does the future hold?
Introduction

• Fertility preservation is an emerging discipline
  – 1993-1994  3 publications
  – 1999-2000  50 publications
  – 2003-2004  87 publications
  – 2008-2009  184 publications
  – 2011-2012  561 publications
  – 2012-2015  864 publications

• 588 000 hits on Google, Wikipedia

• Trend for extended survival after cancer treatment
  \[\text{Jemal Cancer J Clin 2003}\]

• Quality of life issues have increasing importance
Chemotherapy and reproductive failure

• Gonadal failure is one of the major sequelae of cytotoxic chemotherapy, radiotherapy and surgery
• Irreplaceable number of oocytes
• Oocytes, granulosa and theca cells are very sensitive to cytotoxic drugs
• Bigger effect in older women \textit{Brice Blood 2002}
• Spontaneous recovery may occur: 5-28% chance of pregnancy \textit{Meirow 1996}
• Increased risk of premature menopause
• No increase in non-hereditary cancers or genetic disease \textit{Lobo 2005}
• Don’t delay childbearing once cured!
Breast Cancer and Fertility

• 5-7% of breast cancers occur in women <40
• > 25% of first livebirths occur between 30-40
• Fertility concerns influence treatment decisions in 29% of breast cancer patients
• 51% felt these concerns were adequately addressed by their doctors
• 50% of women <40 who develop invasive breast cancer desire children post diagnosis
• Only 10% go on to have children
What is currently available?

• Depends on
  – presence of partner (or sperm)
  – cancer type
  – time available before sterilising treatment
  – age of the patient
  – available funding
  – Risk of fertility treatment
  – Support of oncologist
What is currently available?

- Elect to do nothing and await events
- Quick cycle of IVF
  - Random start stimulation
  - Egg or embryo freezing, or a combination
- Ovarian cortex cryopreservation
- Subsequent egg donation and or surrogacy
‘Do nothing’: await events

• Ovarian reserve testing pre and post treatment
  – AMH, FSH/E2
  – Ovarian volume, AFC
• Appropriate counselling
• Hope for the best
• Egg donation as fall-back position
IVF and Embryo Cryopreservation

- Patient must have partner or donor and time to go through IVF procedure
- Embryo survival rate per freeze/thaw varies between 35 and 90%
- IVF and FERC pregnancy 41%/ET in < 35, 15% 40-42
Biological principles of IVF and cryopreservation in cancer patients

- Ovarian stimulation
- Block premature LH surge
- Ovulation trigger
- Egg collection
- ICSI
- Embryo cryopreservation
- Frozen embryo replacement cycle
Donor eggs and/or surrogacy

- Performed after cancer treatment completed and patient rendered sterile, not time-sensitive
- Success proportional to age of donor (>50%/cycle)
- Gestational surrogacy if hysterectomy performed, uterine radiation damage or where pregnancy may exacerbate condition
- Appropriate counselling and consent
- Problems
  - Altruistic, identity release= few donors
  - Is it morally acceptable to pay egg donors? What is an egg worth?
  - Fertility tourism
Mature oocyte freezing

• Consider if no partner or donor sperm unacceptable
• Similar process to IVF (still requires controlled ovarian stimulation and transvaginal oocyte recovery) but no fertilisation
• Novel cryopreservation and vitrification procedures
• 51 livebirths in UK
Ovarian cortex cryopreservation

- If no time available for ovarian stimulation in adult patients
- Collection of ovarian cortex laparoscopically and tissue cryopreserved
- Successful pregnancies in animals
- No success at growing mature eggs in-vitro
- Autotransplantation
IVF Hammersmith experience

- New programme established 2003
- Team approach with counselling, gynae-oncology and specialist nurse support
- Agreed referral pathway (FSH, viral screen)
- Funding support from PCT’s (NICE guidelines)
- Treatment only ever offered with oncology support
IVF Hammersmith experience

• Patient pathway
  – Referrals
    • Fax hotline 0208 749 6973
    • Email Kate.Anyanwu@imperial.nhs.uk
  – 10 slots Wednesday mornings at HH
  – Initial screening
    • Ovarian reserve and access
    • Semenanalysis
    • Viral screen
  – Confirmation of funding
IVF Hammersmith experience

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Can potentially start treatment within 48 hours if appropriate
IVF Hammersmith experience

Ovarian cortex cryopreservation

- 105 samples of ovarian cortex in storage since 2003
- GMP preparation since 2006
- Moving from 2x1cm² samples to whole ovarian cortex: primum non nocere
- 3 patients reconsults for use, 1 transferred to Belgium for autotransplantation, 1 to New York
- 46 requests for tissue destruction, 29 patients have died-tissue allowed to thaw and perish
IVF Hammersmith experience

Egg and embryo storage

• Since 2003 208 pre-chemotherapy embryo or egg freezing procedures performed
• Patient characteristics:
  – 73% froze embryos with partners sperm, 24% froze eggs, 3% froze a combination, no donor sperm
  – Distribution of cancer diagnoses
    • 53% were breast
    • 24% haematological
    • 13% gastro-intestinal
IVF Hammersmith Results

- Age range 14-49 mean 32.5 years
- 208 treatment cycles
- 2271 oocytes collected – median 11.6 per pt (range 0-37)
- Average 5.2 embryos frozen/cycle
- Over last 2 years 50% of patients freezing eggs
- 1 case of OHSS
- 4 cycles non-fertilisation despite routine ICSI
- 4 patients freezing embryos/oocytes have subsequently died (CML, ca bowel, ca cervix, gastric ca)
IVF Hammersmith Results

- 24 embryo transfer cycles
- 1 cycle all embryos perished during thaw
- 13 positive pregnancy tests (56% biochemical pregnancy rate/ET)
- 8 clinical pregnancies (35% clinical pregnancy rate/ET)
- 1 ectopic pregnancy
- 7 livebirths, 1 ongoing pregnancy
- 3 known spontaneous livebirths post chemotherapy (real numbers)
- 3 egg donation cycles, 2 livebirths
- 5 frozen egg thaws 2 pregnancies
Specific challenges for breast cancer patients

• Funding
  – NICE: new guidance 2013
    • Do not apply eligibility criteria for conventional infertility treatment
    • Do not use lower age limit
    • Eligibility criteria do apply when using stored material
    • Store eggs, sperm, embryos
    • Store for 10 years initially (sperm advised beyond this!)
  – Most CCGs use fertility budgets and fertility social criteria- post code lottery
  – Can we transfer to oncology budgets?
  – Unusual to get ovarian cortex funding
  – Problems with ongoing storage costs
  – Liberal use of IFRs

Management of expectation- patient and physician!
Hormone sensitivity and IVF

- Ovarian stimulation traditionally avoided in women with oestrogen sensitive tumours e.g. breast and uterine: primum non nocere
- Natural cycle IVF inefficient
- Prospective RCT 60 women with breast cancer
- Ages 24-43
- Age, stage and receptor status was similar
- 3 arms
  - Tamoxifen 60 mg/day
  - Tamoxifen + FSH
  - Letrozole 5mg + FSH
- 4 year follow up disease free intervals same as control group
# Breast cancer

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<td>5.1</td>
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<td>Embryos</td>
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<td>13</td>
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<tr>
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<tr>
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<td>10.4 (2-17)</td>
<td>10.8 (9-22)</td>
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<tr>
<td>Peak e2</td>
<td>240-2135</td>
<td>5201-10057</td>
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Tamoxifenn Holiday

- 2/3 of women <40 will be HR +ve
- Length of tamoxifen treatment may reduce chance of conception
- Huge pressure from patients
- 3 month wash-out period
- Lack of robust evidence - importance of consent
BRCA and PGD

- High risk patients
- Prophylactic oophorectomy, consider freezing ovary for future IVM?
- IVF and BRCA PGD now routinely licenced in UK- most cases get NHS funding
- Role of embryo sexing?
Posthumous Use

- Routine part of assisted conception counselling and consent
- Even more important with oncology patients
- Example case
  - Bowel cancer, no partner
  - Oocyte cryopreservation, 3 eggs in storage
  - Recurrence 4 years later, patient dies
  - Mother requests
    - Thaw of eggs
    - Fertilisation with donor sperm
    - Transfer into her uterus

High court battle over dead daughter’s frozen eggs

Mother is challenging regulator’s refusal to allow her to take daughter’s eggs to US to become pregnant with her own grandchild

British mum, 59, in bid for world medical first: I’ll give birth to baby of my dead daughter

- Woman is staging legal bid to become pregnant with her own grandchild
- Her daughter’s eggs would be fertilised by donor sperm and implanted
- She and her husband, 58, will claim it was their daughter’s dying wish
- Their only child died of bowel cancer four years ago while still in her 20s
- Potentially large risks to the health of the woman and the unborn child

Judge delays decision on allowing mum to use dead daughter’s frozen eggs to give birth to own grandchild
The patient’s perspective

http://www.myoncofertility.org

- Patient support group USA
- National fertility hotline
- Web resource: video based, FAQ’s, supported by Northwestern University Chicago
- Patient empowerment
- Network for patients, clinicians and researchers
- Engine for fundraising
Future developments

- Ovarian transplantation/grafting techniques
- Can we make new eggs?
  - Haploidisation of adult diploid cells
  - Do egg stem cells exist?
Ovarian transplantation

- Heterotopic transplantation has been associated with embryo generation
  
  Oktay JAMA 2001

- Orthotopic transplantation
  
  - has resulted in spontaneous pregnancy
  
  Donnez Lancet 2004
  
  - 386 patients, 18 transplants in 12 women, 3 births
  
  Rosendahl 2010
  
  - Risk of cancer transmission
  
  - Transplant followed by natural cycle IVF, pregnancy, delivery, ovarian failure
  
  Meirow 2005

- Full vascular transplant in identical twins
Can we make new eggs?

- Hapoidisation
  - Understanding the initiation and control of meiosis to facilitate reduction division of adult diploid somatic nucleus
  - Enucleate donor egg
  - Nuclear transfer of diploid nucleus to enucleated oocyte
  - Reduction division with production of polar body

*Palermo 2002*
Future Developments

• Do egg stem cells exist?
• Egg precursor cells in human ovary have been identified
  – Successfully cultured
  – Follicles identified
  *Nature 2012*

• Ovascience-Private company, proprietary technology, company worth $330 million
  – Augment, Ovaprime, Ovature, Ovaxon

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Oocyte formation by mitotically active germ cells purified from ovaries of reproductive-age women.

White YA¹, Woods DC, Takai Y, Ishihara O, Seki H, Tilly JL.
Conclusion

• Exciting and rapidly expanding field
• Increasing profile and awareness
• Realistic management of expectation
• Physicians, nurses and counselors should discuss fertility preservation in appropriate patients as an integral part of their care at an early stage
• Collaborative approach essential