Fertility & Pregnancy in Haematological Malignancies

Jane Apperley
Management of fertility

- Fertility preservation is an emerging discipline
  - 1993-1994: 3 publications
  - 1999-2000: 50 publications
  - 2003-2004: 87 publications
  - 2008-2009: 184 publications

- Trend for extended survival after cancer treatment

- Gonadal failure is one of the major sequelae of cytotoxic chemotherapy, radiotherapy and surgery

- Quality of life issues have increasing importance
Management of fertility

- Begins at diagnosis
- Consider immediate and future treatments
- If possible make provision for maintenance of fertility now
Management of fertility in men

- Men remain fertile throughout life
- Azo- and oligospermia common after chemotherapy but late recovery can occur: age at time of treatment much less impact than in women
- Recovery unusual after myeloablative transplant, occurs in almost 50% after reduced intensity conditioning
- Production of sperm begins 72 days before ejaculation, so chemo effects last at least 10 weeks after last dose
- If possible, cryopreserve sperm prior to any treatment
Management of fertility in women

• Females are born with all oocytes, arrested in meiosis

• Natural attrition from puberty during menstrual cycles

• Menopause when <1000 oocytes remain: at median age of 51 years in Western World

• Chemo- and radiotherapy induce further attrition so even if menses recover after treatment, menopause likely to be premature
Management of fertility in women

Reproductive options

- IVF and embryo cryopreservation
- Donor eggs and surrogacy
- Oocyte cryopreservation
- Ovarian cortex collection and IVM/transplantation
Management of fertility in women

Reproductive options depend on

- presence of partner
- cancer type
- time available before sterilising treatment
- age of the patient
- available funding
Management of fertility in women

Reproductive options

- IVF and embryo cryopreservation
- Donor eggs and/or surrogacy
- Oocyte cryopreservation (‘egg freezing’)
- Ovarian cortex cryopreservation followed by
  - in-vitro maturation
  - transplantation
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%

- Pregnancy rate 41%/ET in < 35, 15% 40-42
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Ovarian hyperstimulation

- Fertility drugs: FSH & HMG
- Superovulation
- Close monitoring with ultrasound
- Minimum of 3 follicles
- Average 12 days
Oocyte retrieval

- Needle passed through vaginal vault and into ovary
- Follicles aspirated by gentle suction from pre-set suction pump into small test tubes
- Tubes passed onto embryologist for identification of oocyte.
- Cumulus/oocyte mass is usually visible with naked eye but microscopy required to confirm presence of oocyte
Fertilisation

- ICSI 40 hours after hCG injection
- 70% will fertilise normally
- Majority of non fertilised oocytes are chromosomally abnormal, other causes are sperm defects and ooplasmic anomalies
- When to freeze, day 1 vs cleavage vs blastocyst
Reimplantation

- HRT cycle (or natural if menses resume)
- Oestrogen and progesterone priming
- 1, 2 or 3 embryo transfer
- Luteal support for 12 weeks with progesterone/oestrogen
Oocyte donation

- Appropriate counselling and consent
- Donor undergoes IVF ovarian stimulation: recipient undergoes endometrial preparation
- Results are favourable (>50%/cycle): increased risk pregnancy induced hypertension (31%), increased risk pre-eclampsia (18%)
- Increased risk of caesarean section (57%)
- Children normal development
Problems with oocyte donation

- Greatest obstacle to treatment is recruitment of suitable donors
- UK altruistic service
- Medico-legal issues
- Stress on relationship
- Desire to be parents influences positive parenting more than genetic link with child
- Support, guidance and advice, implications counseling for recipient and partner
- Is it morally acceptable to pay egg donors?
- If so, what is an egg worth?
- Illegal in Germany, Norway and Sweden
- UK allows covering of expenses, USA no regulation, role of overseas donor clinics
- Egg sharing
- Anonymity controversy
Mature oocyte freezing

- Consider if no partner or donor sperm unacceptable
- Similar process to IVF (still requires ovarian stimulation and transvaginal oocyte recovery) but no fertilisation
- Experimental
- <2% pregnancy per thawed egg, 8% per transfer
- 5 livebirths in UK
- Novel cryopreservation and vitrification procedures
Ovarian tissue cryopreservation

- If no time available for ovarian stimulation in adult patients
- Collection of ovarian cortex laparoscopically and tissue cryopreserved
- Oocytes stored as primordial follicles arrested in meiosis, tissue thawed and oocytes matured
- Mature eggs fertilised with sperm and embryos transferred
Ovarian cryopreservation and in-vitro maturation (IVM)

- Successful pregnancies in animals
- No success at growing mature eggs in vitro
- Long-term research aim, suitable for children
- Problems with long-term storage, now need GMP facilities
Hammersmith Results: eggs & embryos

• Since 2003 68 pre-chemotherapy embryo or egg freezing procedures

• Patient characteristics: 45% breast, 36% haematological, 3% gynaecological cancer

• Mean age 32 (range 16-49)
• Mean FSH 6 (range 3-10.5)

• Mean eggs collected 12.7 (range 1-37)

• 73% froze embryos with partners sperm, 24% froze eggs, 3% froze a combination, no donor sperm
Hammersmith Results: eggs & embryos

- Age range 16-49 mean 32.5
- 99 treatment cycles in 96 patients
- 768 oocytes collected – average 11.6 per pt (range 0-37)
- 382 embryos frozen (average 5.2 embryos)
- 180 oocytes frozen
- 4 cycles non-fertilisation despite routine ICSI
- 4 patients freezing embryos/oocytes have subsequently died (CML, ca bowel, ca cervix, gastric ca)
Hammersmith Results: eggs & embryos

- 27 embryo transfer cycles
- 1 cycle all embryos perished during thaw
- 11 positive pregnancy tests (41% biochemical pregnancy rate)
- 7 clinical pregnancies (26% clinical pregnancy rate/ET): 1 ectopic pregnancy, 5 livebirths, 1 ongoing pregnancy
- 3 known spontaneous livebirths post chemotherapy (real numbers)
- 3 egg donation cycles, 2 livebirths
Normal male and female mice fed with imatinib 150mg/kg per day for 12 months or placebo

- No differences in follicular numbers and development
- No differences in spermatogenesis or size of seminiferous tubules
- No evidence for a direct effect of imatinib on fertility (ovarian & testicular function)

* Courtesy of Dr. Schultheis
Imatinib, men and offspring

- Approximately 60 pregnancies reported in partners of men on imatinib
- No suggestion of any problems in conception, pregnancy, delivery or of any increase in congenital abnormalities
Pheresis in pregnancy

- Aim to keep WCC < 100 and platelets < 500
- Frequency varies between patients and at different times in the pregnancy: alternate days, weekly, fortnightly
- Frequency reduces in third trimester
- Does it work?
CML diagnosed in pregnancy

20 patients (2 miscarriages)
3 did not require treatment
1 received HU from week 16: normal delivery of a son at 36 weeks
14 managed by pheresis
• 14 live births
• 13 normal, 1 with talipes

Courtesy of J. Apperley
180 pregnancies reported on imatinib

- We know the outcome of 125
- >70% received imatinib in first trimester only
- 26% received imatinib throughout pregnancy

# Imatinib in Pregnancy

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Total number</th>
<th>Percentage of those with known outcome (n=125)</th>
<th>Percentage of total (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Live Infant</td>
<td>63</td>
<td>50 %</td>
<td>35 %</td>
</tr>
<tr>
<td>Elective Termination</td>
<td>35</td>
<td>28 %</td>
<td>19.5 %</td>
</tr>
<tr>
<td>Fetal Abnormality</td>
<td>12</td>
<td>9.6 %</td>
<td>6.7 %</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>18</td>
<td>14.4 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>

Fetal abnormalities (n=12)

Case 1: Premature closure of skull sutures

Case 2: Hypoplastic lungs, exomphalos (omphalocele), left duplex kidney, right absent kidney, hemivertebrae and right shoulder anomaly.

Case 3: Exomphalos, right renal agenesis and hemivertebrae.

Case 4: Small exomphalos, scoliosis

The expected incidence of exomphalos in the general population is approximately 1 in 4,000

## Advice for women who wish to become pregnant

<table>
<thead>
<tr>
<th>Pre-conception</th>
<th>At least 24 months in MMR</th>
</tr>
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<tbody>
<tr>
<td>Imatinib wash-out prior to conception</td>
<td>Not really necessary, perhaps stop at end of menstrual cycle</td>
</tr>
<tr>
<td>Disease monitoring</td>
<td>Frequency of RQ-PCR No treatment in remains in MMR/CMR Interferon in 2nd trimester if RQ-PCR starts to rise</td>
</tr>
<tr>
<td>After delivery</td>
<td>Breast feeding contra-indicated</td>
</tr>
</tbody>
</table>
Poor outcome after reintroduction of imatinib in patients who interrupt therapy for pregnancy without having achieved an optimal response

<table>
<thead>
<tr>
<th>N</th>
<th>Sokal risk group</th>
<th>Months on imatinib prior to discontinuation</th>
<th>Clinical response at time of discontinuation</th>
<th>Clinical response at time of discontinuation according to ELN</th>
<th>Months without imatinib</th>
<th>Months of imatinib therapy after reintroduction</th>
<th>Clinical response after restarting imatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>9</td>
<td>MMR</td>
<td>optimal</td>
<td>9</td>
<td>30</td>
<td>CMR</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>42</td>
<td>CCyR</td>
<td>suboptimal</td>
<td>9</td>
<td>18</td>
<td>No MCyR, subsequent loss of CHR</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>21</td>
<td>CCyR</td>
<td>suboptimal</td>
<td>13</td>
<td>26</td>
<td>CCyR</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>19</td>
<td>CCyR</td>
<td>suboptimal</td>
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<td>Low</td>
<td>14</td>
<td>MMR</td>
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<td>6</td>
<td>90</td>
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<td>High</td>
<td>7</td>
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<td>suboptimal</td>
<td>8</td>
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Kuwabara et al, Blood 2010
What about 2G-TKI?

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<thead>
<tr>
<th>Pregnancy Outcome after 2G-TKI (women)</th>
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* One pregnancy after nilotinib

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<tr>
<th>Pregnancy Outcome after 2G-TKI (men)</th>
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<td>8</td>
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<tr>
<td>Ongoing</td>
<td>1</td>
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</table>

Stuart Lavery, Nivy Reddy & the IVF Team
HSCT and CML Teams at Hammersmith Hospital
Patients and children
Colleagues at Novartis and Bristol-Myers-Squibb