International Federation of Gynecology and Obstetrics
WHEN TO REFER FOR ART?

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San Jose, December 2016
OBJECTIVES

- Identify clinical indications for ART
- Understand when should be offered
- Plan for services, data collection and audit
• Assisted Reproductive Technology
  – IVF/ ICSI
  – Oncology cryopreservation
    • Donor activity
    • Surrogacy
• Referral
• Continuous improvement
NICE
National Institute for Clinical Excellence
UK
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• In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse

or

• 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination).

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• In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse

or

• 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination)
• Where investigations show there is no chance of spontaneous pregnancy with expectant management and where IVF is the only effective treatment.
Discretion of the gynaecologist
HOW LONG WILL IT TAKE?

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CONCEPTION

AGE AND FEMALE FERTILITY

Per Month chance of Conception vs Age in Years

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FULLY INVESTIGATED

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- Semen analysis
- Hormonal profile
- Genetic testing
  - Karyotype
  - Y deletions
  - ? CF?
- Urological review

- Hormonal profile
- Rubella
- Smear
- Anatomy assessment
In Vitro Fertilisation (IVF)
INDICATIONS

• End of the line therapy
• Absolute
• Wait versus IVF
• Low ovarian reserve
• At request
• CRYOPRESERVATION
ABSOLUTE
No chance of spontaneous pregnancy

- ED (trauma, performance issues)
- Anejaculation
- Azoospermia

- Obstructive tubal disease
  - Endometriosis
  - PID
  - Previous surgery
  - Bilateral salpingectomies

- Ovarian failure
- Absent vagina/ uterus

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TUBAL DISEASE

- Tubal surgery could offer long lasting restoration of fertility
- Success rates are low, operator dependent
- Type of hydrosalpinx decides subsequent pregnancy rates
- Dealing with the hydrosalpinx beforehand improves pregnancy rates after IVF
- IVF is a temporary solution for a permanent problem
- Better pregnancy rates per cycle/month

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WHY WAIT?

Evidence that intervention is better than expectant management?

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## Cochrane 2015

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Plain language summary</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth rate per woman</td>
<td>IVF vs expectant management</td>
<td>Assumed risk</td>
<td>Corresponding risk IVF</td>
<td>37 per 1000 (90 to 879)</td>
<td>OR 22 (2.56 to 189.37) 51 (1 study)</td>
</tr>
<tr>
<td>Pregnancy rate per woman</td>
<td>IVF vs expectant management</td>
<td>127 per 1000 (135 to 588)</td>
<td>OR 3.24 (1.07 to 9.8)</td>
<td>86 (2 studies)</td>
<td>Very low</td>
</tr>
<tr>
<td>Multiple pregnancy rate</td>
<td>Not reported in the included studies</td>
<td></td>
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</tbody>
</table>
LOW OVARIAN RESERVE

• Young - worth pursuing IVF
• Over 40 – doubtful if reserve is very low
AMH decline
AT REQUEST

• Reasonable as long as fully investigated and no contraindications

• Age

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FLAGS

- Family history of POF
- Previous PID
- Previous abdominal, pelvic, urogenital surgery
CHALLENGES

• CC resistant PCOS
• Vaginismus
• Previous major surgery

High risk of OHSS
Pyschosexual therapy first
## CHALLENGES

- **Severe semen abnormalities**
  - Count = oligozoospermia
  - Motility = asthenozoospermia
  - Morphology = teratozoospermia

- Anti sperm antibodies?

- DNA fragmentation?
# Antioxidants for male subfertility

Marian G Showell, Rebecca Mackenzie-Proctor, Julie Brown, Anusch Yazdani, Marcin T Stankiewicz, Roger J Hart

First published: 15 December 2014

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<th>Illustrative comparative risks* (95% CI)</th>
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<th>No of Participants (studies)</th>
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<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>Antioxidants versus placebo or no treatment</td>
<td></td>
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</tr>
<tr>
<td>Live Birth per couple randomised</td>
<td>50 per 1000 (99 to 309)</td>
<td>OR 4.21 (2.08 to 8.51)</td>
<td>277 (4 studies)</td>
<td>⊗♦♦♦♦ low 1.2</td>
<td></td>
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<tr>
<td>Follow-up: 3 - 24 months</td>
<td></td>
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<tr>
<td>Clinical Pregnancy rate per couple randomised</td>
<td>59 per 1000 (108 to 277)</td>
<td>OR 3.43 (1.92 to 6.11)</td>
<td>522 (7 studies)</td>
<td>⊗♦♦♦♦ low 1.3</td>
<td></td>
</tr>
<tr>
<td>Follow-up: 3-24 months</td>
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<tr>
<td>Adverse event: Miscarriage rate per couple randomised</td>
<td>19 per 1000 (8 to 129)</td>
<td>OR 1.74 (0.40 to 7.60)</td>
<td>247 (3 studies)</td>
<td>⊗♦♦♦♦ very low 1.4</td>
<td></td>
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<tr>
<td>Follow-up: 3-18 months</td>
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*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
ONCOLOGY CRYOPRESERVATION
• Must be considered
• Area of real importance for all cancer patients
• IVF platform developed
WHEN

- When sterilising therapy is employed
  - Surgery
  - Adjuvant
  - Female or male
**SERVICE FLOW**

**Diagnosis**
- Surgeon
- Oncologists
- Counsellor
- Fertility specialist

**Advice**
- Successful fertility preservation

**Successful oncology therapy**

**Family desire**
- Spontaneous pregnancy
- Assisted conception
- Own genetic child
- Donor
- Surrogacy
- Adoption
- Acceptance

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Service Provision

Appointment
- Dedicated staff
- Seen within 24 hours
- Bloods
- Information on treatment
- Referral form

Consultation
- Counselling
- Cryoadvice
- Consent discussion and signing
- Cryopreservation

Cryopreservation
- Contact with patient
- Contact with referring services

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# STREAMLINED SERVICE

<table>
<thead>
<tr>
<th>Myth</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in onco-treatment</td>
<td>Immediate start</td>
</tr>
<tr>
<td>Long duration</td>
<td>Average 12-13 days (16)</td>
</tr>
<tr>
<td>Patient heavy</td>
<td>3 injections</td>
</tr>
<tr>
<td></td>
<td>FSH, antagonist, agonist</td>
</tr>
</tbody>
</table>

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STIMULATION

• Short 2 weeks therapy
  – Antagonist
    • Start anytime!
      » Bedoschi et al., J Assist Reprod Genet, 2010
  – 3 injections:
    • FSH
    • GnRH antagonist
    • Agonist

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OOCYTE CRYOPRESERVATION

- Largest body cell

- Freeze techniques
  - Slow freeze - ice formation - spindle damage
  - Vitrification - solidified into a glass like state, no ice

- Following thaw ICSI is required

- First birth reported in ‘97

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EMBRYO CRYOPRESERVATION

- Long standing, safe and successful
- First pregnancy in 1983
  Trounson A et al., Nature 1983; 305: 707-709
- First baby delivered in 1984

Commitment from couple
Responsibility

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OVARIAN TISSUE CRYOPRESERVATION

- removed at laparoscopy
- avoids stimulation, immediate

- Risks of re-implantation
  - reseeding of malignant cells
    - Breast, neuroblastoma, leukemia
      - Sonmezer et al. Hum Reprod Update 2004; 103(3): 251-266
    - Histo/immunochemical analysis of tissue is recommended
  - discussion with gynae-oncologist

- Issues
  - Where to re-implant for optimal results?
  - How much ovarian tissue to remove and store?
  - How long can it survive frozen?

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OVARIAN TISSUE OUTCOMES

- published pregnancies from orthotopic human transplantation
  - *Spontaneous*  Donnez et al., Lancet. 2004; 364(9443):1405-10

- 30 transplantations globally, resulting in six live births and several ongoing pregnancies
REALISM

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ONCOLOGY FREEZE

- If no contraindications present (dialogue)
- Oocytes (2-4% pregnancy rates)
- Embryos (30% pregnancy rates, female age dependant)
- Sperm freezing (pregnancy rates as good as with fresh sperm)

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DEDICATED UNIT

- Trained staff
  - doctors;
  - nurses;
  - embryologist;
  - counselling
- 365 days availability
- Ideally state supported (responsibility)

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Male vs Female

- Minimal intervention
- Multiple opportunities to freeze
- Consult-consent-freeze-inform-store

Full IVF
- Immediate start
- Short protocol
- 2 weeks to return for cancer therapy
- OHSS prevention (antagonist + agonist trigger)

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MEDICAL FERTILITY PRESERVATION

• All that receive medical treatment that could potentially affect reproduction
  – Chemotherapy for arthritis

• Where surgery could severely impair fertility or result in sterility
  – Severe endometriosis
  – Prophylactic oophorectomy

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REFERRAL

• Devise a form (national?)
• Criteria for referral
• Results of investigations
• Final diagnosis

• What was the proposed treatment?
• What was discussed with patient?
FEEDBACK

• Learn from your own experience

• National data a collection
• Therapy outcomes
• eSET and freeze excess embryos

• Obstetrical outcomes

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DISCUSSED

• Indications for IVF referral
• Cryopreservation
• Referral
• Data collection and analysis
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