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
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

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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?
## 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>There is inconclusive evidence to suggest that IVF may result in more births than expectant management</td>
<td>37 per 1000 (90 to 879)</td>
<td>OR 22 (2.56 to 189.37)</td>
<td>51 (1 study)</td>
<td>★★★★★ Very low a</td>
</tr>
<tr>
<td>IVF vs expectant management</td>
<td></td>
<td></td>
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<tr>
<td>Pregnancy rate per woman</td>
<td>There is inconclusive evidence to suggest that IVF may result in more clinical pregnancies than 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 a</td>
</tr>
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<td>IVF vs expectant management</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multiple pregnancy rate</td>
<td>Not reported in the included studies</td>
<td></td>
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</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  
  High risk of OHSS
- Vaginismus  
  Pyschosexual therapy first
- Previous major surgery
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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<td></td>
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</tr>
<tr>
<td>Live Birth per couple randomised Follow-up: 3-24 months</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>
</tr>
<tr>
<td>Clinical Pregnancy rate per couple randomised Follow-up: 3-24 months</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>Adverse event: Miscarriage rate per couple randomised Follow-up: 3-18 months</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>
</tr>
</tbody>
</table>

*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).
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

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

- Counselling
  - Cryoadvice
  - Consent discussion and signing
  - 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>
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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

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
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)
DEDICATED UNIT

• Trained staff
  • doctors;
  • nurses;
  • embryologist;
  • counselling

• 365 days availability

• Ideally state supported (responsibility)
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?

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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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