International Federation of Gynecology and Obstetrics

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WHEN TO REFER FOR ART?

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RCSI

San Jose, December 2016

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OBJECTIVES

- Identify clinical indications for ART
- Understand when should be offered
- Plan for services, data collection and audit

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DETAIL

- Assisted Reproductive Technology
  - IVF/ ICSI
  - Oncology cryopreservation
    - Donor activity
    - Surrogacy
- Referral
- Continuous improvement

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GUIDELINES

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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)

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- Where investigations show there is no chance of spontaneous pregnancy with expectant management and where IVF is the only effective treatment.

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Discretion of the gynaecologist

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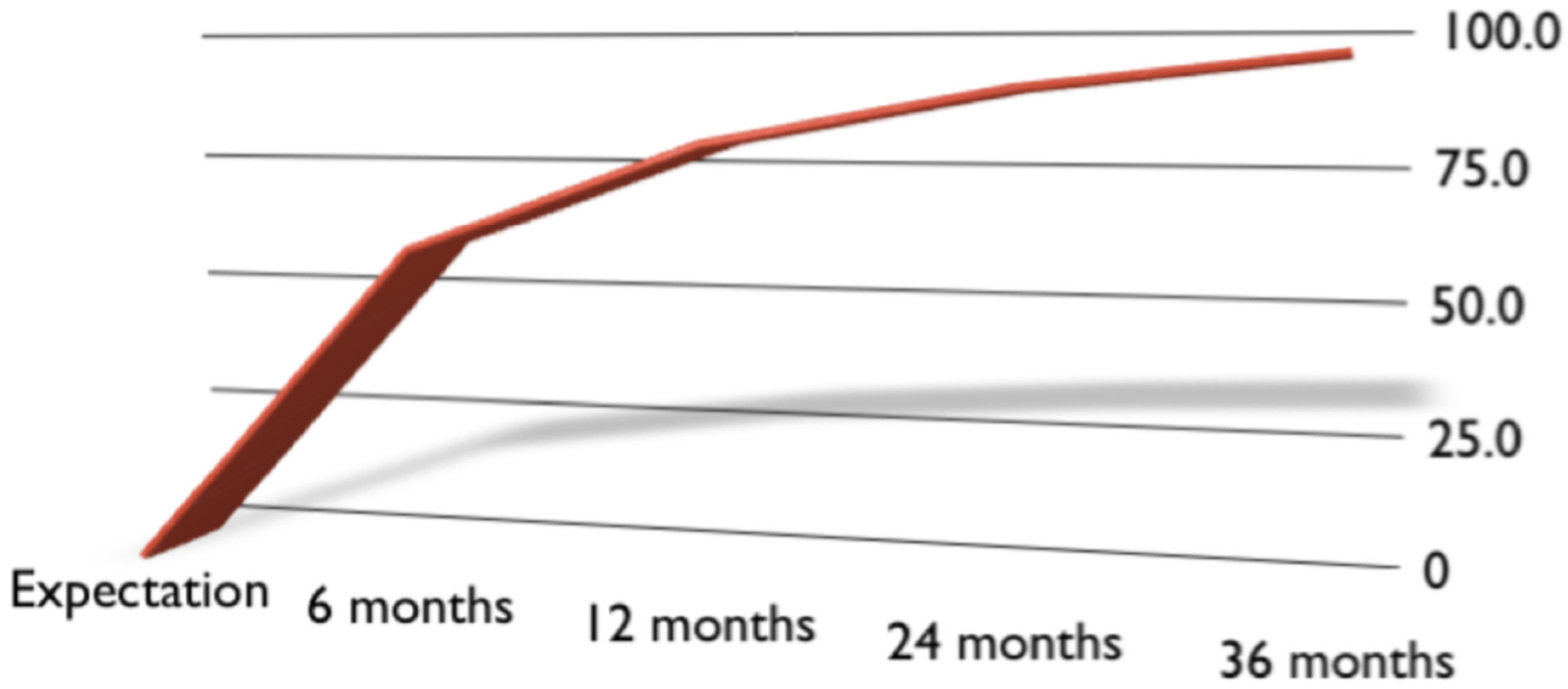
HOW LONG WILL IT TAKE?



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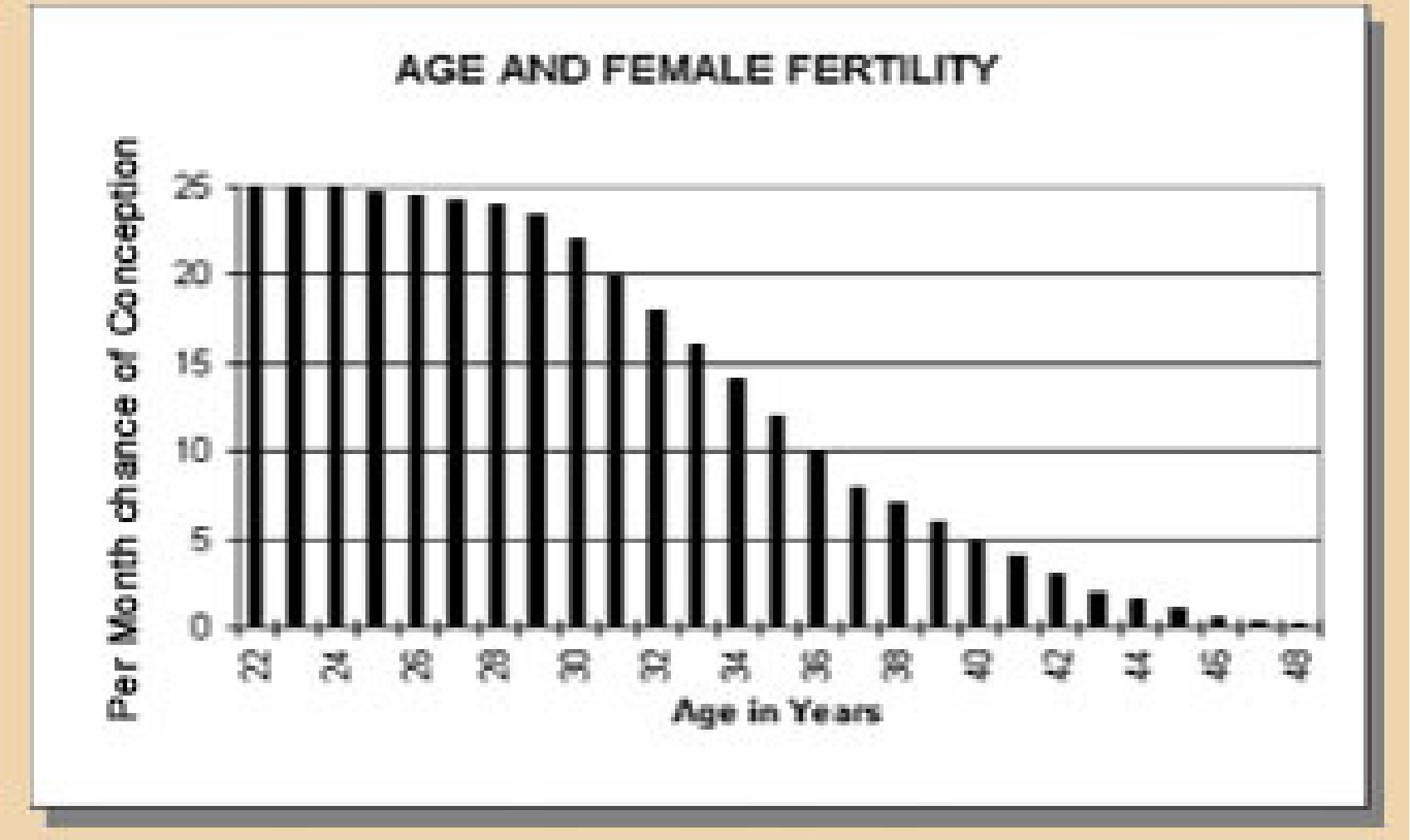
CONCEPTION



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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

VIROLOGY

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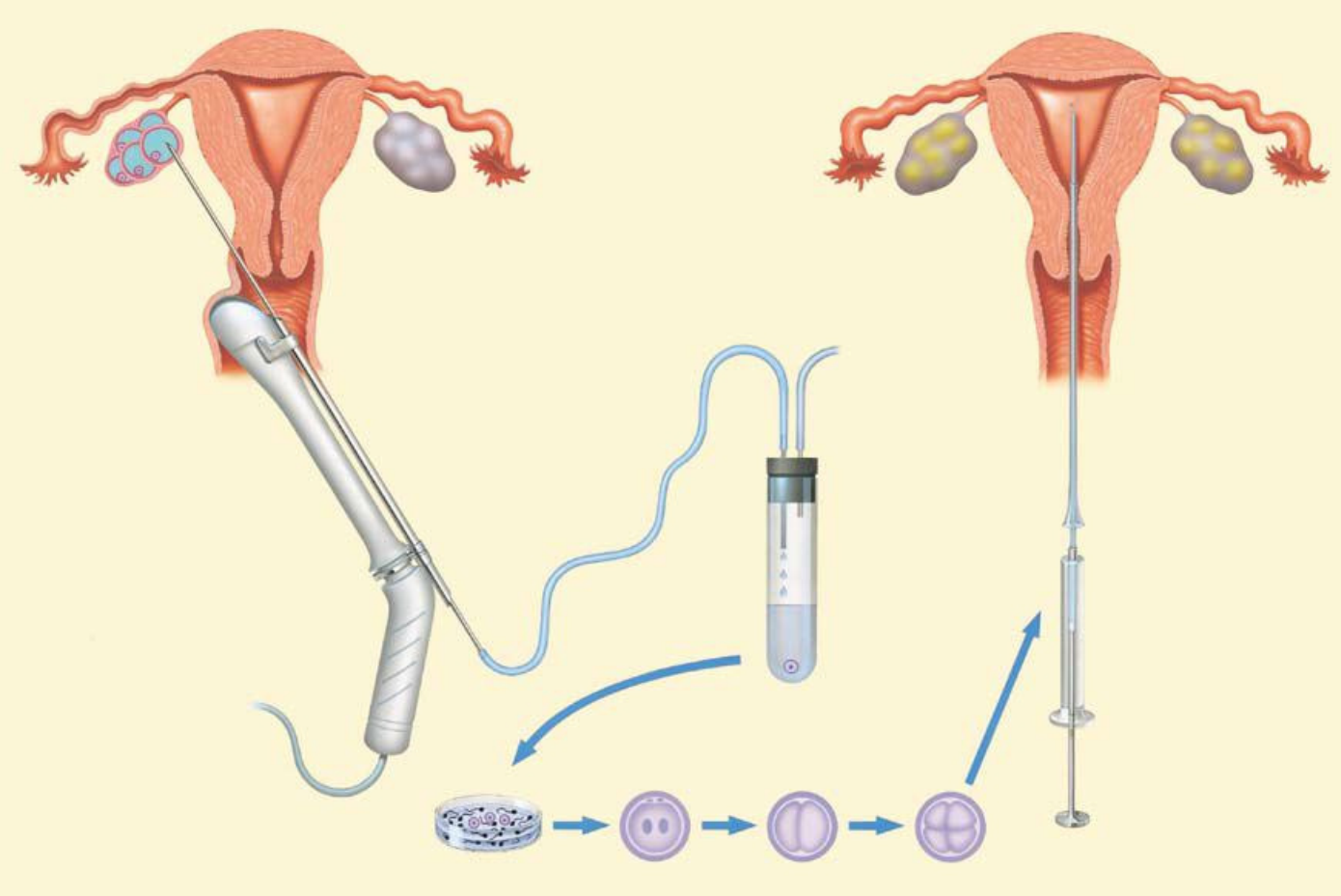
In Vitro Fertilisation (IVF)



INDICATIONS

- **End of the line therapy**

- Absolute
- Wait versus IVF
- Low ovarian reserve
- At request
- CRYOPRESERVATION

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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

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 that expectant management?

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Cochrane 2015

Outcomes	Plain language summary	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
		Assumed risk	Corresponding risk			
		Expectant management	IVF			
Live birth rate per woman IVF vs expectant management	There is inconclusive evidence to suggest that IVF may result in more births than expectant management	**37 per 1000**	**458 per 1000** (90 to 879)	**OR 22** (2.56 to 189.37)	51 (1 study)	⊕⊖⊖⊖ **Very low** [a]
Pregnancy rate per woman IVF vs expectant management	There is inconclusive evidence to suggest that IVF may result in more clinical pregnancies than expectant management	**127 per 1000**	**320 per 1000** (135 to 588)	**OR 3.24** (1.07 to 9.8)	86 (2 studies)	⊕⊖⊖⊖ **Very low** [a]
Multiple pregnancy rate	Not reported in the included studies					

LOW OVARIAN RESERVE

- Young - worth pursuing IVF
- Over 40 – doubtful if reserve is very low

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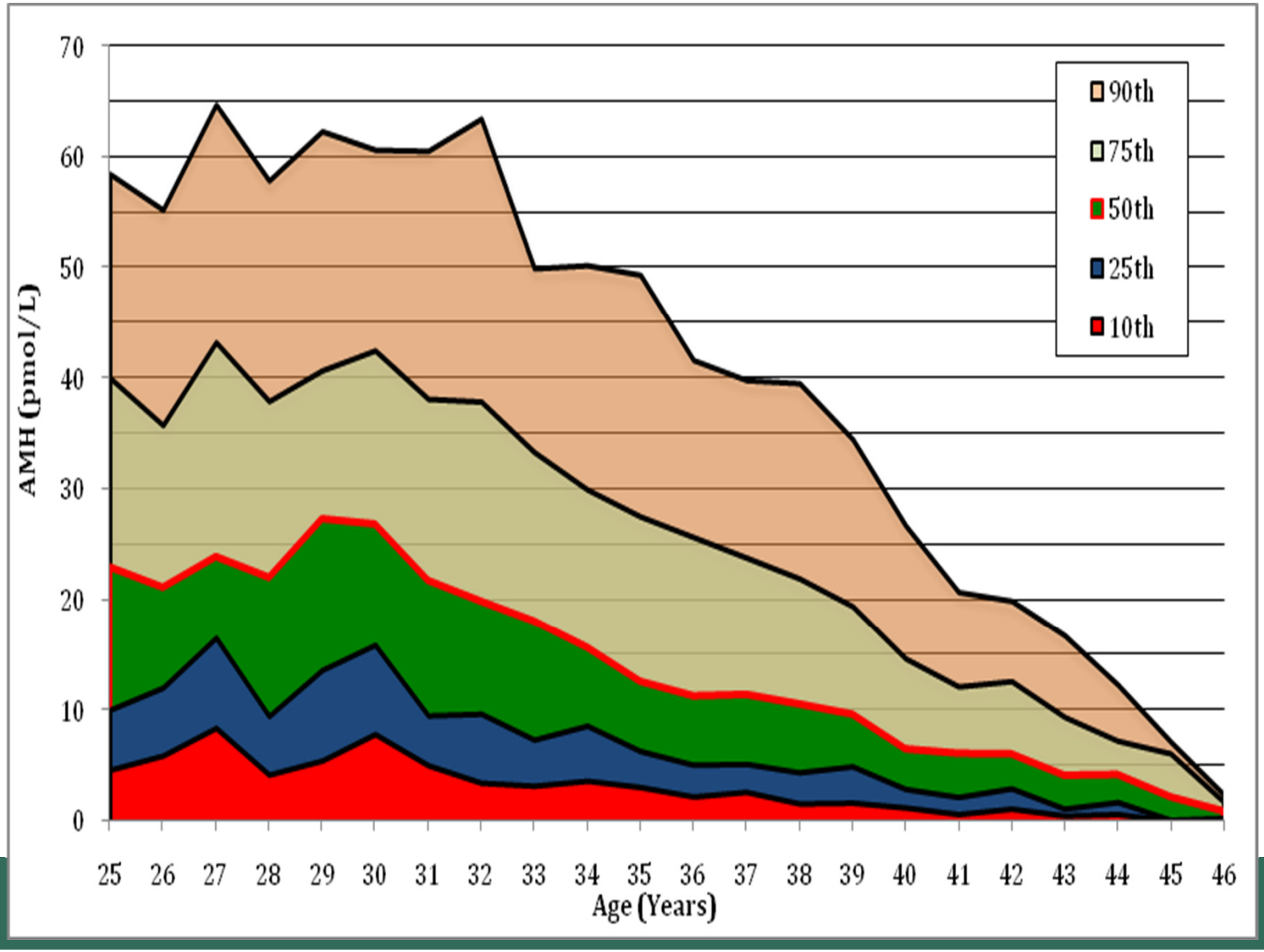
AMH decline



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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

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CHALLENGES

- CC resistant PCOS — High risk of OHSS
- Vaginismus — Pyschosexual therapy first
- Previous major surgery

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CHALLENGES

- Severe semen abnormalities
  - Count = oligozoospermia
  - Motility = asthenozoospermia
  - Morphology = teratozoospermia
- Anti sperm antibodies?
- DNA fragmentation?

Antioxidants for male subfertility

New search | Conclusions changed | Review | Intervention

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

First published: 15 December 2014

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antioxidants versus placebo or no treatment				
Live Birth per couple randomised Follow-up: 3 - 24 months	50 per 1000	181 per 1000 (99 to 309)	OR 4.21 (2.08 to 8.51)	277 (4 studies)	⊕⊕⊖⊖ **low** [1,2]	
Clinical Pregnancy rate per couple randomised Follow-up: 3-24 months	59 per 1000	177 per 1000 (108 to 277)	OR 3.43 (1.92 to 6.11)	522 (7 studies)	⊕⊕⊖⊖ **low** [1,3]	
Adverse event: Miscarriage rate per couple randomised Follow-up: 3-18 months	19 per 1000	33 per 1000 (8 to 129)	OR 1.74 (0.40 to 7.60)	247 (3 studies)	⊕⊖⊖⊖ **very low** [1,4]	

*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).

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ONCOLOGY CRYOPRESERVATION

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- Must be considered
- Area of real importance for all cancer patients
- IVF platform developed

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WHEN

- When sterilising therapy is employed
  - Surgery
  - Adjuvant
  - Female or male

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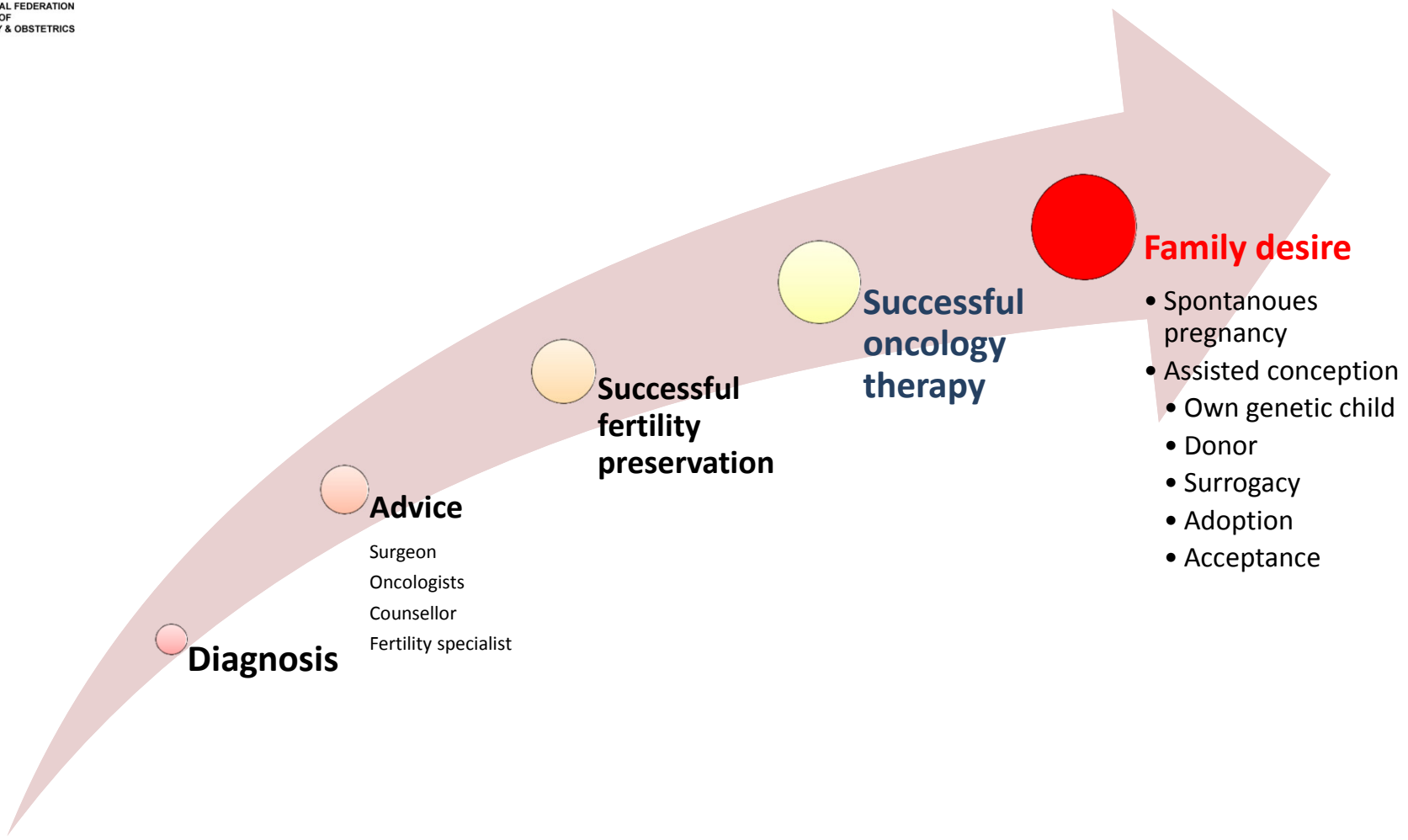
SERVICE FLOW



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Service Provision

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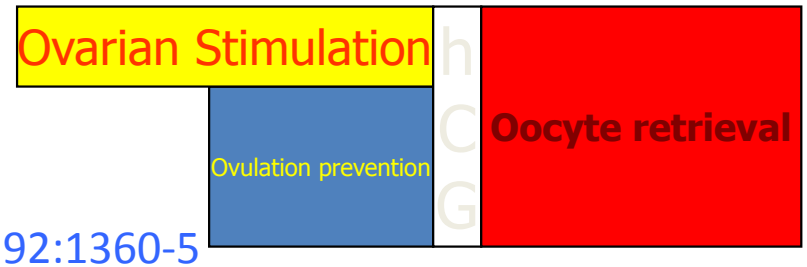
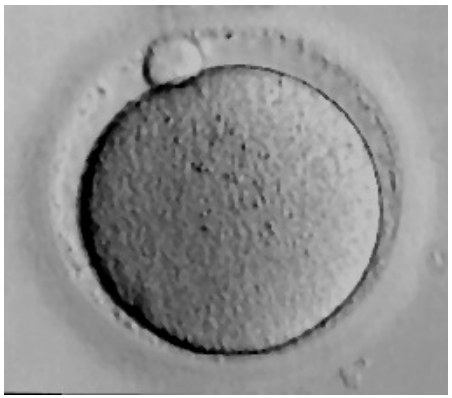
STREAMLINED SERVICE

Myth	Reality
Delay in onco-treatment	Immediate start
Long duration	Average 12-13 days (16)
Patient heavy	3 injections
	FSH, antagonist, agonist

STIMULATION

- Short 2 weeks therapy
  - Antagonist
    - Start anytime!
      - » von Wolf, Fertil Steril 2009;92:1360-5
      - » Bedoschi et al., J Assist Reprod Genet, 2010
  - 3 injections:
    - FSH
    - GnRH antagonist
    - Agonist





OOCYTE CRYOPRESERVATION

- Largest body cell
- Freeze techniques
  - Slow freeze - ice formation - spindle damage
  - **Vitrification - solidified into a glass like state, no ic**e
- Following thaw ICSI is required
- First birth reported in ‘97
  - » Porcu et al, 1997; Fertil. Steril, 68:724-726.

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

  Zeilmaker GH, et al., Fertil. Steril. 1984; 42: 293-296

Commitment from couple
Responsibility

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

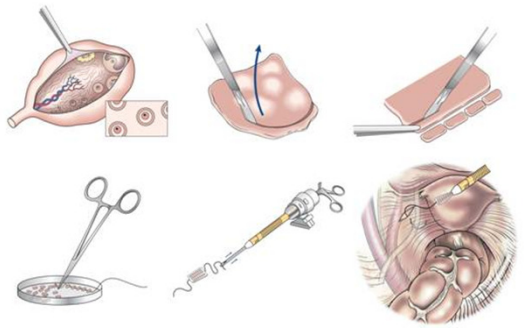
Issues

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

OVARIAN TISSUE OUTCOMES

- published pregnancies from orthotopic human transplantation
  - *Spontaneous* Donnez et al., Lancet. 2004; 364(9443):1405-10
  - *IVF* Meirow et al., N Engl J Med 2005; 353: 318-321

- 30 transplantations globally, resulting in six live births and several ongoing pregnancies
  - von Wolff M, Eur J Cancer. 2009 Jun;45(9):1547-53.



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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)

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)

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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