Infertility: Investigations and Treatment Options

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The problem of infertility

- 15% of couples actively trying to conceive will have difficulty attaining pregnancy
- Simple investigations will usually identify a cause for the majority of couples
- A range of therapeutic options are available, particularly if an identifiable cause is found
- IVF is commonly undertaken, either because it is a first line indication; a treatment where simple measures have failed or a treatment for combined fertility factors

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Female age and fecundity

The graph illustrates the decline in follicle units over time. At birth, the follicle units are at peak levels of 6 to 7 million. Over time, the number of follicle units decreases rapidly, reaching a lower number as time progresses. The x-axis represents time in years, starting from birth and extending to 70 years.
Two sides of the story – male and female fertility

- Female fertility can be compromised by:
  - Irregular ovulation
  - Damage / obstruction of the fallopian tubes
  - Endometriosis
  - Age

- Male fertility can be compromised by:
  - Low sperm parameters (eg. number, motility)
  - Obstruction
  - Anti-sperm antibodies
Useful basic investigations

- Semen analysis and IBT
- Ultrasound / HyCoSy
- Hormonal assessment of ovulation
- Other serology – antenatal screening
Anti-Mullerian hormone (AMH)

- Originally described in human fetal sexual differentiation
- Produced by granulosa cells of primary follicles / small follicles (not visible on ultrasound)
- A reflection of total oocyte pool
- Cycle independent
- Does not necessarily relate to egg quality
Treatment of infertility

• Significant problem – assisted conception (= IVF or related technology)

• Options outside of assisted conception
  – More time / lifestyle alterations
  – Laparoscopic surgery for endometriosis
  – Surgery to repair obstructions
  – Tablets to correct ovulation (clomiphene – Clomid)
  – Sperm donation – medical problem / social problem

• Unexplained infertility / time lapsed / no time left – assisted conception
Unexplained infertility

- Normal detailed semen analysis
- Regular ovulation
- No anatomical factors seen at HyCoSy
- No obvious immunological issues (no antisperm antibodies)
- No detectable endometriosis
- 25 – 30% of our patient group

*Note: the explanation may simply be “older eggs”*  
*ie women beyond the late 30s*
Management of options for unexplained infertility

*Eg. 18 months trying, 34 years old, prognosis of next 6 months*

- **Fate?**
  - 2-3% chance / month
- **Clomiphene?**
  - little / no difference
- **Intrauterine insemination (IUI) natural cycle:**
  - 4-5% per cycle
- **IUI with ovarian stimulation:**
  - 15-20% per cycle, but with multiple pregnancy risk
- **IVF and single embryo transfer:**
  - 50% per oocyte collection (fresh and frozen combined)
IVF

- Ovarian stimulation
- Oocyte collection
- Embryo transfer
IVF patient journey

Initial consultation and tests
Nurse interview and trial wash

Ovarian stimulation
- *self administered*
Intermittent monitoring

2 weeks

Oocyte collection and embryo transfer

5 days

[Images of medical processes and patients]
Oocyte collection
“Routine” IVF insemination
ICSI (intra cytoplasmic sperm injection)

Ovarian stimulation

Egg pick-up

Sperm

Incubator

Embryo transfer

Cryostore

Excess embryos
Embryo development

Day 1

Day 3

Day 5 = blastocyst

Day 4
Cumulative success rate

- Per one round of ovarian stimulation, there are potentially multiple opportunities to conceive
- The average stimulation cycle yields 2 – 4 blastocysts
- Frozen transfers are usually undertaken in a natural ovulation cycle
- Some couples have more than one successful pregnancy for one oocyte collection
Vitrification of embryos

- Vitrification of embryos at day 5 does not reduce the chance of implantation.
- Compared to traditional “fresh” transfer, transferring a vitrified-warmed embryo into a natural ovulation cycle:
  - Is at least equivalent in terms of implantation chance.
  - May lead to less placentation anomalies and blastogenesis abnormalities.

*Healy 2011*
Cumulative live birth / OPU

First OPU at Genea 1 July 2009 - 31 December 2009
Assessed at late 2011
Final cumulative live birth rate / OPU – 1 or 2 to transfer?

<table>
<thead>
<tr>
<th></th>
<th>Initial single ET</th>
<th>Initial double ET</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>121</td>
<td>285</td>
</tr>
<tr>
<td>Total live birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pregnancies</td>
<td>79 (65.2%)</td>
<td>185 (64.9%)</td>
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<tr>
<td>Total live birth</td>
<td></td>
<td></td>
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<tr>
<td>multiple pregnancies</td>
<td>7 (8.8%)</td>
<td>78 (42%)</td>
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</table>
Single embryo transfer and success rates, Australia

Perinatal mortality (PMR) is reduced through SET:

- PMR for DET: 19.1 / 1000
- PMR for SET: 13.1 / 1000
- PMR for twins: 27.8 / 1000
- PMR for singletons: 12.4 / 1000

Sullivan and Wang ESHRE 2012
Modern IVF with blastocyst transfer & vitrification

- Will help the large majority of women under 38 years of age
- If success is to be attained, it will usually be so within three stimulation cycles
- If success is not to be attained, it is usually evident within three stimulation cycles
- Aids resolution, for better or worse
IVF will not be successful:

- In women with persistently elevated FSH, irrespective of age
- In women 45 years of age or older, irrespective of cycles
- Both groups will likely only conceive through oocyte donation
Variants of assisted conception

- **Donor gametes**
  - Sperm – very little needed in heterosexual couples
  - Eggs – commonly used esp for older women
  - Now non-anonymous & altruistic

- **Embryo donation**
  - Not common

- **Surrogacy**
  - True medical indications are narrow – no uterus, serious maternal medical disease or *true* implantation disorder
Blastocyst biopsy–preimplantation genetic diagnosis (PGD)
Embryo development in PGD cycle

- **Oocyte**
- **Day 2 stage**
- **Day 3 stage**
  - Assisted hatching
- **Day 4 stage**
- **Embryo biopsy**
Applications of PGD

- Prevention of genetic disease
  - DNA mutational screening (PCR), whole chromosome assessment
- Miscarriage prevention in cases of balanced translocation
- Aneuploidy screening
  - Recurrent IVF failure
  - First line IVF?
- Miscarriage management
  - Exclusion of random aneuploidy
Cell

- Nucleus
- Mitochondrion

Pairs of Chromosomes in a Human Cell

DNA Double Helix

- Strands
- Phosphate
- Hydrogen bonds
- Base pairs:
  - Cytosine
  - Guanine
- Sugar
- Base pairs:
  - Thymine
  - Adenine

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Polymerase Chain Reaction (PCR)

- Basic technique of DNA amplification
- Whole genome amplification for array CGH, or
- Locus-specific DNA for single gene analyses
Micro array analysis

- 60,000 points on chromosomes measured (oligonucleotides)
- 8 sub arrays = 8 embryos per slide
- embryo karyotypes
Frozen embryos - CGH

Frozen - CGH Only - 2011, 2012

- <30 [23]: 65.2%
- 30-34 [29]: 51.7%
- 35-37 [63]: 55.6%
- 38-39 [48]: 39.6%
- 40-42 [39]: 53.8%
- 43+ [6]: 66.7%
Summary

• Infertility is a common and distressing problem.
• Whilst specific treatments are applicable in some circumstances, IVF is commonly undertaken given its higher return.
• Cumulative outcomes from IVF are improved through the use of frozen (vitrified) embryos.
• Genetic testing of embryos (PGD) gives the opportunity to help both specific problems within fertility treatment and to aid in prevention of the passage of genetic disease.