What is Infertility?

• 12 months of trying to conceive
• Incidence 1 in 6
• Increases with age
What is Infertility?

85% within 1 yr, 93% within 2 yrs

% pregnant

Months of trying
# Degrees of Fertility

<table>
<thead>
<tr>
<th>Number of Mild Fertility Factors</th>
<th>Typical Monthly Chance</th>
<th>Estimated Time to Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20%</td>
<td>4 months</td>
</tr>
<tr>
<td>1</td>
<td>5%</td>
<td>2 years</td>
</tr>
<tr>
<td>2</td>
<td>1%</td>
<td>7 years</td>
</tr>
<tr>
<td>3</td>
<td>0.2%</td>
<td>40 years</td>
</tr>
</tbody>
</table>
Degrees of Fertility

**Figure A1.2** Accumulating chance of having gotten pregnant. Modeling the cumulative chance of having gotten pregnant over three years from average first-month fertilities ($f_i$) of 20%, 5%, and 1%. The right-hand figures give the residual average monthly fertility of those still not pregnant after the three years, that is, for month number 37 ($f_{37}$).
The Role of a CREI Specialist

Advice

• Weight loss – diet, exercise
• Smoking advice
• Pre-pregnancy advice

Reproductive surgery

• Female
  • Endometriosis & Fibroids
  • Tubal re-anastomosis & salpingectomy
  • Ovarian pathology/drilling
• Male
  • Surgical sperm collection (PESA, TESA)
  • Vasectomy reversals

Assisted Reproductive Techniques

• OI (ovulation induction)
  • Clomiphene/Letrozole, FSH
• IUI (intra-uterine insemination)
• IVF (in vitro fertilisation)
• ICSI (intra cytoplasmic sperm injection)
• PGD (pre-implantation genetic diagnosis)
• Donor gametes (sperm & eggs)
• Oocyte Vitrification (social egg freezing)
• Oncofertility (fertility preservation)
• Surrogacy
Obesity & Fertility
Female Fertility & BMI

- Overweight & obese women have (Maheshwari et al, Hum Reprod Update 2007; Bellver et al, Fertil Steril 2010)
  - Reduced spontaneous ovulation
  - Increased time to conception
  - Decreased libido and coital frequency (Brewer et al, Reprod 2011)

- BMI >30 significantly associated with
  - Decreased fertilisation rate by up to 45% (Brewer et al, Reprod 2011)
Female Fertility & BMI

- **Increased BMI associated with decreased pregnancy rates in ART** (Bellver et al, Fertil Steril 2007)

- **BMI ≥25 decreased PR with IVF (OR 0.71; 95%CI 0.62-0.81)** (Maheshwari et al, Hum Reprod Update 2007)

Influence of body mass on probability of pregnancy during assisted reproduction treatment. Figures are values (SD) unless stated otherwise.

<table>
<thead>
<tr>
<th>Category</th>
<th>Body mass index</th>
<th>No of women (n=3586)</th>
<th>Age (years)*</th>
<th>No of embryos transferred</th>
<th>No of cycles</th>
<th>% achieving at least one pregnancy†</th>
<th>Odds ratio‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;20</td>
<td>441</td>
<td>31.6 (4.5)</td>
<td>2.4 (0.8)</td>
<td>2.3 (1.5)</td>
<td>45</td>
<td>0.81 (0.65 to 1.01)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20-24.9</td>
<td>1910</td>
<td>32.9 (4.7)</td>
<td>2.4 (0.7)</td>
<td>2.3 (1.7)</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
<td>814</td>
<td>33.0 (4.8)</td>
<td>2.4 (0.8)</td>
<td>2.2 (1.5)</td>
<td>42</td>
<td>0.81 (0.68 to 0.97)</td>
</tr>
<tr>
<td>Obese</td>
<td>30-34.9</td>
<td>304</td>
<td>32.8 (4.7)</td>
<td>2.4 (0.7)</td>
<td>2.1 (1.4)</td>
<td>40</td>
<td>0.73 (0.57 to 0.95)</td>
</tr>
<tr>
<td>Very obese</td>
<td>≥35</td>
<td>117</td>
<td>32.7 (5.1)</td>
<td>2.4 (0.7)</td>
<td>2.0 (1.3)</td>
<td>30</td>
<td>0.50 (0.32 to 0.77)</td>
</tr>
</tbody>
</table>

Wang et al, BMJ 2000
**Mechanisms**

How does Female Obesity Impact Fertility?

(Brewer et al, Reprod 2011)

**Hormones and chemokines affected by obesity:**
- Oestrogens
- Androgens
- SHBG
- Insulin
- LH
- Leptin
- Adiponectin
- IL6
- PAI1
- TNF

- **Oocyte**
  - ↑ Testosterone
  - ↑ Oestrogen
  - ↓ Progesterone

- **Endometrium**
  - ↓ Fertilisation
  - ↓ Receptivity
  - ↓ Clinical pregnancy rate
  - ↑ Miscarriage
  - ↓ Live birth rate

- **Embryo**

- **Liver**

- **Ovary**

- **Pituitary**
  - ↑ LH

- **Hypothalamus**
  - Altered gonadotrophin secretion

- **Pancreas**
  - ↑ Insulin
  - ↑ IR

- **Adipocytes**
  - ↑ Food intake
  - ↓ Exercise

- **Genetic factors**

- **Liver**

- **Pancreas**
Challenges for Obesity in Pregnancy (RANZCOG 2013)

Antenatal

Fetal
- Miscarriage
- Stillbirth
- Abnormal Fetal Growth

Maternal
- Gestational Diabetes
- Pre-eclampsia
- Thromboembolism

Intrapartum

- Caesarean Section, Instrumental delivery
- Shoulder dystocia, PPH
- Anaesthetic risks

Postpartum

- Wound infection
- Postnatal depression
- Long term Neonatal consequences – eg Obesity
Access to ART based on BMI

“BMI ≥35 is a recognised risk factor in pregnancy and delivery and should be regarded as a contra-indication to assisted fertility”...

“inappropriate to recommend ovarian stimulation (including IVF) as part of first line therapy in the female BMI>35 unless there are exceptional circumstances”...
Male Obesity

Proposed pathways for hormonal alterations associated with male obesity.

Male Obesity leads to:

- Hypo-gonadotrophic, hyper-estrogenic hypo-androgenism
- Accumulation of endocrine disruptors in adipose tissue
- Increased testicular temperature
- Increased sexual dysfunction

Male Obesity


- Sperm concentration
  - J shaped curve

- Decreased motility

- Increased DNA fragmentation
Optimizing BMI Prior to IVF

- Decreases need for IVF – increases spontaneous conception
- Improves IVF success rates
- Decreases pregnancy complications
- Non-reproductive health benefits
The Role of a CREI Specialist

Advice
- Weight loss – diet, exercise
- Smoking advice
- Pre-pregnancy advice

Reproductive surgery
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- Donor gametes (sperm & eggs)
- Oocyte Vitrification (social egg freezing)
- Oncofertility (fertility preservation)
- Surrogacy
Reproductive Surgery
What is Reproductive Surgery?

• Surgery that improves *Spontaneous Conception*
• Surgery that improves *Assisted Conception*
• Surgery that improves *Fertility Preservation*
## What is Reproductive Surgery?

### Objective of Reproductive Surgery

- **Primary treatment of infertility**
  - Tuboplasty: Neosalpingostomy, fimbrioplasty, tubal catheterization, tubal anastomosis
  - Salpingo-oophorectomy

### Enhancement of in Vitro Outcome

- **Surgery to treat hydrosalpinx**
  - Salpingectomy
  - Proximal tubal occlusion
  - Hysteroscopic tubal occlusion

### Fertility Preservation

- Ovarian transposition
- Ovarian tissue removal for cryopreservation
- Ovarian transplantation

### Male Surgery

- Surgical sperm retrieval
- Vas reversals

### Embryo “Surgery”

- Pre-implantation Genetic Diagnosis

---

Fertility Surgery
Endometriosis & Fertility
Endometriosis

Where do you find the latest recommendations?
Endometriosis

• **Incidence**
  • 5-10% in normal population
  • Up to 50% of infertile women

• **Presentation**
  • Pain
  • Infertility
    • *Reduced monthly fecundity* from 15-20% to 2-10%
    • ASRM Stage 1-2 endometriosis *halves spontaneous conception rates*
  • 30% asymptomatic
ASRM Stage 1 Endometriosis
ASRM Stage 2-3 Endometriosis
Pelvic side wall endometriosis excised
Endometrioma resected
Bowel Adhesion dissected free
Endometriosis - Pathophysiology

ASRM Stage 1 & 2

How does this cause infertility?

• Increased E2
• P4 Resistance
• Increased Prostaglandins
• Altered Immune Response
• Aberrant Cytokine Profile
  • VEGF, IL-1β, IL-6, IL-8 & TNFα

Pro-inflammatory products have toxic effects on:

• Oocytes
• Embryo
• Tubal Motility
• Endometrial receptivity
ASRM Stage 4 Endometriosis
Endometriosis – Pathophysiology

ASRM Stage 3 & 4
How does this cause infertility?

In addition to pro-inflammatory effects:

• **Anatomical distortion**
  • Pelvic adhesions & endometriomas
  • Impair oocyte release & tubal transport
• Impairs **ovarian reserve**

• **Poorer outcomes** compared with early stage disease in ART
• Symptoms are not stage specific, but **ART outcomes are stage specific**
Endometriosis - Management

ASRM Stage 1 & 2

What is the evidence?

Spontaneous Conception

- 2 RCT’s
- Marcoux et al (N Eng J Med 1997) – Increased PR (OR 2.06 95%CI 1.28-3.33)
- Gruppo Italiano (Hum Reprod 1999) – no significant difference
- Meta-analysis (Cochrane 2010) – Increased LBR (OR 1.64 95%CI 1.05-2.57)

ART

- No RCT’s
Endometriosis - Management

ASRM Stage 1 & 2

Surgical excision preferred over ablation

- RCT for pain (Healey et al. Fertil Steril 2010) – no significant difference
- No trials studying fertility

- Excision may be superior
  - Histological diagnosis
  - Complete resection of disease
  - Decrease in adhesion formation
  - Lower recurrence rate
Endometriosis - Management

Endometriomas

What is your surgical approach?

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Risks and benefits of observational and surgical management of endometriomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational</strong></td>
<td><strong>Surgery</strong></td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>Avoid surgery</td>
<td>Exclude malignancy</td>
</tr>
<tr>
<td>Lower FSH doses</td>
<td>Relieve symptoms</td>
</tr>
<tr>
<td>Increased E2</td>
<td>Reduce the risk of cyst complications</td>
</tr>
<tr>
<td>Increased follicles</td>
<td>Facilitate transvaginal access to ovarian follicles</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Ovarian failure because of destruction of normal ovarian tissue</td>
</tr>
<tr>
<td>No histological diagnosis</td>
<td>Reduced number of eggs collected</td>
</tr>
<tr>
<td>Pelvic infection following egg collection</td>
<td>Risks of surgery</td>
</tr>
</tbody>
</table>
Endometriosis – Management

ASRM Stage 3 & 4

What is the evidence?

• No RCT’s

• Surgical excision improves pregnancy rates 30-67% (uncontrolled studies)

• Second line surgery reduces pregnancy rates by 50% compared with first line surgery (ACCEPT 2012)
Endometriosis – Management

ASRM Stage 3 & 4

Second line surgery reduces pregnancy rates by 50% compared with first line surgery (ACCEPT 2012)
ASRM Stage 4 Bowel Endometriosis
Bowel nodule due to endometriosis

Bowel Resection & Anastomosis
Endometriosis - Management

Endometriomas

What is the evidence?

Spontaneous Conception

• Excision preferred over drainage – decreased recurrence
• Excision increases spontaneous pregnancy rates (OR 5.21 95%CI 2.04-13.29) (Hart et al. Cochrane 2008)

ART

• Controversial
• No clear evidence for removal of endometriomas for infertility alone
Normal appearing Left Ovary & tube

Bowel & Omental Adhesions

Endometrioma

ASRM Stage 4 Endometriosis

Uterus
Endometriosis - Summary

• **ASRM Stage 1-2**
  - Surgical treatment improves spontaneous conception
  - Excision preferred over ablation

• **ASRM Stage 3-4**
  - Individualize treatment

• **Endometriomas**
  - Individualize treatment
  - Excision preferred over ablation/aspiration
  - Limit electro-surgery for hemostasis – minimize reduction in ovarian reserve
Fibroids & Fertility
Fibroids

Where do you find the latest recommendations?


DOI: 10.1111/j.1479-828X.2011.01300.x

**Review Article**

Fibroids in infertility – consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence)

Ben KROON,¹,² Neil JOHNSON,³,⁴ Michael CHAPMAN,⁵,⁶ Anusch YAZDANI,¹,² Roger HART⁷,⁸ on behalf of the Australasian CREI Consensus Expert Panel on Trial evidence (ACCEPT) group
Fibroids – Effects on Fertility

- **Anatomical Distortion**
  - Affects gamete transport

- **Decreased endometrial receptivity**
  - Altered myometrial contractility
  - Altered endometrial blood supply
  - Localised endometrial inflammation & abnormal cytokine profile
Fibroids - Classification

How does this help with management?

- Sub-mucosal
  - T0 – pedunculated
  - T1 – <50% intramural extension
  - T2 – >50% intramural extension

- Intra-mural
- Sub-serosal
Fibroids & Fertility

Fibroid Effects on Fertility

Sub-mucosal
- Are associated with reduced fertility and increased miscarriage rates
  - Approx 65-70%

Intra-mural
- May be associated with infertility and increased miscarriage rates
  - Approx 20%

Sub-serosal
- Do not have significant effect on fertility
Fibroids & Fertility

Fibroids – Surgical Management

Sub-mucosal

- Hysteroscopic myomectomy appears likely to improve fertility outcomes

Intra-mural

- Insufficient evidence whether surgical management affects fertility outcomes
# Fibroids - Imaging

## Optimal Imaging for Endometrial Cavity Involvement

<table>
<thead>
<tr>
<th>Cavity assessment</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The optimal imaging techniques for excluding cavity involvement by fibroids are either MRI, sonohysterography or hysteroscopy</td>
<td>Level 3 evidence Consensus grade β. Consensus with caveat. The consensus group felt that cavity assessment with hysteroscopy may at times miss SM lesions because of raised intrauterine pressure causing temporary regression of the fibroid contour</td>
</tr>
</tbody>
</table>
Fibroids & Fertility

Indications for Myomectomy in Infertile Women

• Infertile women with sub-mucosal fibroids
  • Hysteroscopic myomectomy improves fertility outcomes by 2 fold

• Infertile women with symptomatic fibroids

• Infertile women who have multiple failed ART cycles with intramural fibroids
Operative Hysteroscopy – Other Indications

Operative Hysteroscopy can be used to improve fertility outcomes

- Congenital anomalies
  - Uterine Septum

- Acquired anomalies
  - Endometrial Polyps
  - Asherman’s Syndrome
Tubal Disease & Fertility
Hydrosalpinx

Infertility Sequelae due to PID

- 1 infection  – 30%
- 2 infections – 60%
- 3 infections – 90%

- Chlamydia, gonorrhea, anaerobes
- Can be asymptomatic
Hydrosalpinx

What are your options?

• Do nothing
• Salpingectomy
• Other:
  • Tubal Occlusion (Filschie Clip)
  • Essure
  • Tubuloplasty
Hydrosalpinx

Salpingectomy vs Conservative Management (Cochrane 2010)
Hydrosalpinx

Salpingectomy vs Tubal Occlusion (Cochrane 2010)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tubal occlusion</th>
<th>Salpingectomy</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Odds Ratio M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Kontoravdis 2006</td>
<td>23</td>
<td>50</td>
<td>1.65 [0.74, 3.71]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>50</strong></td>
<td><strong>50</strong></td>
<td><strong>1.65 [0.74, 3.71]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.22 (P = 0.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.1.2 Clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tubal occlusion</th>
<th>Salpingectomy</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoravdis 2006</td>
<td>26</td>
<td>50</td>
<td>1.63 [0.74, 3.59]</td>
</tr>
<tr>
<td>Moshin 2006</td>
<td>31</td>
<td>78</td>
<td>1.06 [0.53, 2.12]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>128</strong></td>
<td><strong>110</strong></td>
<td><strong>1.28 [0.76, 2.14]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>57</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.92 (P = 0.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.1.3 Ectopic pregnancy rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tubal occlusion</th>
<th>Salpingectomy</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoravdis 2006</td>
<td>0</td>
<td>50</td>
<td>0.33 [0.01, 8.21]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>50</strong></td>
<td><strong>50</strong></td>
<td><strong>0.33 [0.01, 8.21]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.68 (P = 0.50)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

6.1.4 Miscarriage rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tubal occlusion</th>
<th>Salpingectomy</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoravdis 2006</td>
<td>3</td>
<td>50</td>
<td>1.53 [0.24, 9.59]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>50</strong></td>
<td><strong>50</strong></td>
<td><strong>1.53 [0.24, 9.59]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.46 (P = 0.65)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hydrosalpinx – Summary

- Decreases IVF success rates by 50%
- Doubles miscarriage rates

**Salpingectomy**
- *Laparoscopic salpingectomy increases Live Birth Rate* (OR 2.13, 95%CI 1.24-3.65) prior to IVF (Cochrane 2010)
- Excise close to Fallopian Tube to minimize compromising vascular supply to ovary (minimize possible/theoretical decrease in ovarian reserve)

**Tubal Occlusion**
- Similar results compared with salpingectomy
Hydrosalpinx – Summary

- **Hysteroscopic Tubal Occlusion (Essure)**
  - Case series only – more studies required
  - Use after informed consent for patients not suitable for laparoscopy

- **Fimbrioplasty, Tubuloplasty, Neo-salpingostomy**
  - Consider if “good prognosis” features
    - Hydrosalpinx <3cm diameter, thin tubal wall, preserved mucosal folds
Microsurgery

- Tubal Re-anastomoses
- Vasectomy Reversals
Microsurgical Tubal Re-anastomoses

- 5% request rate
- Up to 40-70% Pregnancy Rates
- Microsurgical vs Laparoscopic
Tubal Reversal – Summary

- Good evidence of its effectiveness
- Compares favourably with IVF (but no RCT’s)
- Microsurgical vs Laparoscopic

- Recommend in:
  - Young women
  - Older women without other fertility factor where IVF success rates are reduced (likely previous proven fertility)
Vasectomy Reversal

1. Inner sutures tied
2. Micro needle through outer muscle layer on both sides of vas
3. Outer sutures tied
4. Completed vasovasostomy
Microsurgical Vasectomy Reversal – Results

• Female Partner

• Duration of vasectomy
  • <3yrs – 97% patency, 71% LBR
  • >15yrs – 76% patency, 30% LBR
  • Overall – 85% patency, 50% LBR

• Best results if no or low levels anti-sperm antibodies
The Future – Robotics Surgery

Robot-assisted laparoscopy procedure.

Interest in robotic assistance in laparoscopy.

<table>
<thead>
<tr>
<th>Conventional laparoscopy</th>
<th>Laparoscopy with robotic assistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D visualization</td>
<td>3D visualization</td>
</tr>
<tr>
<td>Physiologic tremor</td>
<td>Magnification of the operating field</td>
</tr>
<tr>
<td>Instability of the image</td>
<td>Tremor filtration</td>
</tr>
<tr>
<td>Fixed axis of the instruments</td>
<td>Stability of the image</td>
</tr>
<tr>
<td>Discomfort for the surgeon</td>
<td>Micro-motion of the instruments</td>
</tr>
<tr>
<td>Poor quality of the dissection</td>
<td>360° amplitude, 7° freedom</td>
</tr>
<tr>
<td>Hard access for some areas</td>
<td>Ergonomics, comfortable handling of the console</td>
</tr>
<tr>
<td>Difficult intracorporeal stitching</td>
<td>Facilitated dissection</td>
</tr>
<tr>
<td>Long learning curve</td>
<td>Improved accessibility</td>
</tr>
<tr>
<td></td>
<td>Easy suturing</td>
</tr>
<tr>
<td></td>
<td>Short learning curve</td>
</tr>
</tbody>
</table>

Final Remarks
Final Remarks

- Fertility care ≠ IVF

- **Surgical treatments assist** in improving outcomes of both spontaneous conception & IVF

- **Lifestyle modifications are vital** in improving chances of spontaneous conception & IVF success
Final Remarks

• IVF 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

• Overall success rates can be up to 50-60% per cycle