Saturday, June 11, 2016
16:30 - 17:25  WS #167: Treating the Subfertile Couple
17:35 - 18:30  WS #179: Treating the Subfertile Couple (Repeated)
Managing the Subfertile Patient

Dr Guy Gudex and Dr Karen Buckingham, Repromed Auckland
Rotorua GP CME
June 2016
Overview

• Optimising natural fertility

• Specific fertility treatments:
  • Ovulation induction
  • Intrauterine insemination
  • Lipiodol flushing
  • In vitro fertilisation
  • Pre-implantation genetic diagnosis/screening

• “Third party” reproduction

• Fertility preservation

• Cost and funding of ART in NZ
Optimising Natural Fertility
Optimising Natural Fertility

• Don’t delay childbearing
  • Couples should be informed that delayed childbearing, especially after age 30 years, can decrease the probability of successful conception, and they should take this into account in family and career planning.
Optimising Natural Fertility

- Don’t delay childbearing
  - Couples should be informed that delayed childbearing, especially after age 30 years, can decrease the probability of successful conception, and they should take this into account in family and career planning.

- Encourage couples to bring their BMI into the healthy weight range
Optimising Natural Fertility

• Advise smoking cessation, not only for the overall health benefits but also to:
  • ↓ risk of subfertility
  • ↓ time to pregnancy
  • ↓ miscarriage/ectopic pregnancies
  • ↑ success from IVF
Optimising Natural Fertility

• Advise smoking cessation, not only for the overall health benefits but also to:
  • ↓ risk of subfertility
  • ↓ time to pregnancy
  • ↓ miscarriage/ectopic pregnancies
  • ↑ success from IVF

• Recommend limiting alcohol when trying to conceive:
  • ↓ chance of subfertility
  • ↓ time to pregnancy
  • ↑ success from IVF
  • ↓ risk of harm to fetus
Optimising Natural Fertility

• Reasonable to assume that the general health benefits associated with moderate levels of exercise would also apply to fertility

• Women with BMI <25 kg/m2 who are attempting to conceive should limit vigorous exercise to <5 hours/week
Optimising Natural Fertility

- Reasonable to assume that the general health benefits associated with moderate levels of exercise would also apply to fertility
- Women with BMI <25 kg/m2 who are attempting to conceive should limit vigorous exercise to <5 hours/week
- No evidence that caffeine intake of <200mg/day has an impact on fertility
Optimising Natural Fertility

• Psychological stress
  • Evidence that stress levels may influence the outcome of infertility treatment, as well as contribute to patients' decisions to discontinue treatment.
  • Psychological distress is associated with infertility treatment failure, and interventions to relieve stress are associated with increased pregnancy rates.
  • Couples should be assisted to minimise and cope with psychological stress when attempting pregnancy (support, education, counselling)
Prepregnancy Planning

• Don’t forget Folic Acid/Iodine for women trying to conceive!
Optimising Natural Fertility

• Discuss optimal timing for conception (for suitable couples)
  • Advise sexual intercourse 2-3 times per week from soon after cessation of menses through the day of ovulation to ensure that intercourse falls within the most fertile period and semen quality is optimal.
Ovulation Induction
Ovulation Induction

- Ovulatory disorders can be identified in 18-25% of couples presenting with subfertility
  
  Hull et al, Br Med J 1985

- Majority are a result of PCOS

- Hypogonadotrophic hypogonadism
- PCOS
- Primary Ovarian Insufficiency
- Hyperprolactinaemia
Ovulation Induction in PCOS

• Aim to induce monofollicular development and ovulation (minimize multiple pregnancies/OHSS)

• Generally start with the least invasive/simplest treatment option

• Options:
  • Weight loss, if overweight
  • Oral ovulation induction agents
  • Ovulation induction with gonadotrophins
  • Laparoscopic ovarian drilling
  • IVF
Oral Ovulation Induction Agents
Metformin

• Taken orally 2-3 x daily (500mg tds or 850mg bd)
• Increase menstrual cyclicity and restore spontaneous ovulation
• Associated with modest weight losses, may help acne/hirsuitism
• GI side effects limit use
• Cheaper and more convenient as cycle monitoring is unnecessary
• No increase in multiple pregnancy rates
Clomiphene

• Used for OI for >50 years

• Taken daily (50-150mg) for 5 days during follicular phase

• Side effects → hot flushes, nausea, breast tenderness, mood swings, (headaches/blurred vision rarely)

• Risks → twins 7-9%, triplets 0.3%, OHSS <1%

• 15-20% of patients “CC-resistant”
Clomiphene/Letrozole

**Clomiphene**
- Used for OI for >50 years
- Taken daily (50-150mg) for 5 days during follicular phase
- Side effects → hot flushes, nausea, breast tenderness, mood swings, (headaches/blurred vision rarely)
- Risks → twins 7-9%, triplets 0.3%, OHSS <1%
- 15-20% of patients “CC-resistant”

**Letrozole**
- Aromatase inhibitor, used “off license” for ovulation induction
- Taken daily (2.5-7.5mg) for 5 days during follicular phase
- More favourable effects on endometrium
- Side effects → fatigue and dizziness (but less than with CC)
- Risks → twins <5%, 1 case sextuplets
Clomiphene/Letrozole

- Monitor with blood tests/USS
- ~80% of women will ovulate using Clomiphene or Letrozole
- ~20-40% of women <37 years will conceive over 3-4 cycles of OI

- Multiple studies now suggest Letrozole results in higher LBR and ovulation rates compared Clomiphene (especially in obese women with PCOS)
Which Oral Ovulation Induction Agent?

- Opinions vary but....
  - If monitored cycle, use Letrozole first line (↓ side effects/multiple pregnancies/thin endometrium, ↑ LBR’s, especially in obese PCOS women)
  - Consider Metformin for 3 months (cheaper, more convenient, no need for monitoring, may help with weight loss/acne/hirsutism)
  - Worth trying a second agent if the first ineffective in achieving ovulation despite increasing doses
Second Line Ovulation Induction Methods

**Gonadotrophins OI**
- Daily sc injections of recombinant FSH (various regimens)
- Expensive, available in specialist fertility clinics only
- Requires extensive monitoring
- Only 1 ovulatory event achieved
- Risks → multiple pregnancy, OHSS and cycle cancellation

**Laparoscopic Ovarian Drilling**
- 4-10 punctures made in each ovary using an electrocautery needle
- “One-off” treatment, produces multiple ovulatory cycles
- Benefits → minimal monitoring required, ↓ OHSS and multiple pregnancy rates, can combine with tubal patency testing etc
- Risks → may reduce ovarian reserve, risks of GA/surgery
Intrauterine Insemination
Intrauterine Insemination

• Procedure in which washed and concentrated motile sperm is placed directly into the uterine cavity, just prior to ovulation

• Useful for couples with sexual dysfunction, discordance for STI carriage, unexplained infertility, mild endometriosis, mild male factor or for women undergoing treatment with donor sperm

• Minimum requirements:
  • Ovulation in the IUI cycle
  • At least 1 patent tube
  • ≥1 million motile sperm
Intrauterine Insemination

• IUI more effective than timed intercourse (LBR, OR 1.95, 95% CI 1.10-3.44)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>IUI+NC n/N</th>
<th>TI+OH n/N</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Bhattacharya 2008</td>
<td>38/167</td>
<td>23/175</td>
<td></td>
<td>100.0%</td>
<td>1.55 [1.10, 3.44]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>167</td>
<td>175</td>
<td></td>
<td>100.0%</td>
<td>1.55 [1.10, 3.44]</td>
</tr>
</tbody>
</table>

Favours TI+OH 0.1 0.2 0.5 1 2 5 10
Favours IUI+NC

Veltman-Verhulst et al, CL 2016

• Stimulated IUI more effective than natural cycle IUI (LBR, OR 0.48, 95% CI 0.29-0.82)

ANZARD data 2013
Intrauterine Insemination

- 11.1% live birth rate per DI cycle
  - 15.4% 30-34 years
  - 3.4% >40 years
  - Multiple pregnancy rate 4.1%

   ANZARD data 2013

- ~40–50% of women aged <37 years conceive within 4 cycles

HFEA data from 3601 cycles
Lipiodol Flushing
Lipiodol Flushing

- Treatment for mild endometriosis / unexplained infertility
- Mechanism of effect uncertain
- Cochrane review (13 RCT’s, 2914 women)
  - Tubal flushing with oil-soluble media significantly increases the odds of live birth (OR 3.09, 95% CI 1.4-6.9) and ongoing pregnancy (OR 3.59, 95% CI 2.06 – 6.26)
In Vitro Fertilisation
The beginning of IVF

- First baby born from IVF in 1978, followed by 1980 in Australia
- First IVF clinic in NZ opened in 1983; first baby born in 1984
IVF Cycles in Australia/NZ

- 5-6000 IVF cycles/year in NZ (>70,000 IVF cycles/year in Australia/NZ)
- 1272 babies or 2.1% of all live births in NZ were the result of ART in 2012

ANZARD Data 1991-2013
Development to Blastocyst
EmbryoScope Embryo Monitoring System
IVF Success Rates

- Average age of woman undergoing IVF → 35.9 years

- Live Birth Rate/IVF cycle initiated (NZ)
  - <30 years → 29.7%
  - 30-34 years → 32.6%
  - 35-39 years → 24.9%
  - 40-44 years → 11.4%
  - >45 years → 0%

- 1:5 cycles were in woman aged >40 yr

ANZARD data 2012
Success Rates with Cumulative IVF Cycles

- Prospective study of 156,947 women undergoing IVF in UK 2003-2010
  - Women <40 years → LBR 32.3% on 1st cycle and 68.4% after 6 cycles
  - Women 40-42 years → LBR 12.3% on 1st cycle and 31.5% after 6 cycles
  - Women >42 years → LBR/cycle <4%

Smith et al, JAMA 2015
What’s New in IVF?

• “Safer” ↓ OHSS
  • Antagonist cycles
  • Metformin for PCOS patients
  • Agonist trigger
  • More “freeze only” cycles

• ↓ Multiple pregnancy rates
  • Twin rate 5.6% in 2013 vs 17.8% in 2003
  • Single embryo transfer 79.2% in 2013 vs 31% in 2003

ANZARD data 2013
What’s New in IVF?

- “Easier”
  - Shorter regimens
  - Depot FSH preparations - “Elonva”
  - Reduced blood testing
  - Taper tip needles and LA
What’s New in IVF?

- “More successful”
  - IVF success rates continue to increase, despite fewer embryos being transferred

Figure 1 Estimated cumulative probability of a live birth by Kaplan-Meier analysis comparing live birth outcomes for women starting IVF in 2001–2005 with women starting IVF in 2006–2010. Log-rank analysis: $P$ value $< 0.05$. 

Wade et al ANZJOG 2015
What’s New in IVF?
Preimplantation Genetic Testing
Preimplantation Genetic Diagnosis

• Used for detection of embryos with specific single gene defects/translocations
Preimplantation Genetic Diagnosis

- Transport PGD available in NZ since 2006
- Publicly funded PGD may be offered where there is a >25% risk of a pregnancy being affected by a serious inherited disorder e.g. CF, Huntington’s disease etc

**ANZARD Data**

- Number of PGD Cycles Australia/NZ

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3000</td>
</tr>
<tr>
<td>500</td>
<td>1000</td>
<td>1500</td>
<td>2000</td>
<td>2500</td>
<td>3000</td>
<td>3500</td>
<td>4000</td>
</tr>
</tbody>
</table>
Preimplantation Genetic Screening

• Similar process to PGD but screens all the chromosomal pairs instead of looking for a single gene disorder or sex-chromosome linked condition
• ↑ LBR if can replace a euploid embryo (no matter what the maternal age)
• Most appropriate for couples with RIF, RPL, advanced maternal age
Third Party Reproduction

“Modern Families”
HART Act 2004

- Key law that regulates assisted reproductive technology and human reproductive research in NZ

<table>
<thead>
<tr>
<th>Established Procedures</th>
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<tbody>
<tr>
<td>• Artificial insemination</td>
</tr>
<tr>
<td>• Assisted hatching</td>
</tr>
<tr>
<td>• Blastocyst culture</td>
</tr>
<tr>
<td>• Collection of eggs/sperm for purposes of donation</td>
</tr>
<tr>
<td>• Sperm, oocyte, embryo, ovarian tissue cryopreservation</td>
</tr>
<tr>
<td>• GIFT</td>
</tr>
<tr>
<td>• ICSI</td>
</tr>
<tr>
<td>• IVF</td>
</tr>
<tr>
<td>• PGD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Requiring Ethical Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Surrogacy</td>
</tr>
<tr>
<td>• Embryo donation</td>
</tr>
<tr>
<td>• Donation of gametes between certain family members</td>
</tr>
<tr>
<td>• Creation and use of embryos created from donor eggs and donor sperm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prohibited Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Creation or use of cloned or hybrid embryos</td>
</tr>
<tr>
<td>• Obtain or use gametes from a minor (&lt;16 year old)</td>
</tr>
<tr>
<td>• Commercial supply of gametes or embryos</td>
</tr>
<tr>
<td>• Commercial surrogacy</td>
</tr>
<tr>
<td>• Storage of embryos/gametes for &gt;10 years without specific ethical approval</td>
</tr>
<tr>
<td>• Gender selection unless to prevent a genetic disorder/disease</td>
</tr>
</tbody>
</table>
Donor Egg Treatment

- Increasing demand for and utilisation of donor eggs
- Altruistic, non-commercial egg donation allowed in NZ
- Donors may be known or unknown, but not completely “anonymous”; preferably <36 years of age, completed their family, normal ovarian reserve
- ANZARD data:
  - Make up ~5% of all ART cycles
  - Average age of women undertaking donor egg/embryo cycles was 40.7 years
  - Average age of egg donors was 33 years
Donor Egg Treatment

Table 23: Outcomes of oocyte/embryo recipient cycles by donor’s age group, Australia and New Zealand, 2013

<table>
<thead>
<tr>
<th>Stage/outcome of treatment</th>
<th>&lt; 30</th>
<th>30–34</th>
<th>35–39</th>
<th>≥ 40</th>
<th>All(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiated cycles</td>
<td>457</td>
<td>725</td>
<td>738</td>
<td>136</td>
<td>2,305</td>
</tr>
<tr>
<td>Embryo transfer cycles</td>
<td>402</td>
<td>631</td>
<td>629</td>
<td>108</td>
<td>2,017</td>
</tr>
<tr>
<td>Clinical pregnancies</td>
<td>147</td>
<td>204</td>
<td>205</td>
<td>13</td>
<td>636</td>
</tr>
<tr>
<td>Live deliveries</td>
<td>106</td>
<td>157</td>
<td>137</td>
<td>7</td>
<td>462</td>
</tr>
</tbody>
</table>

**Live deliveries per initiated cycle (%)**
- < 30: 23.2
- 30–34: 21.7
- 35–39: 18.6
- ≥ 40: 5.1
- All(b): 20.0

**Live deliveries per embryo transfer cycle (%)**
- < 30: 26.4
- 30–34: 24.9
- 35–39: 21.8
- ≥ 40: 6.5
- All(b): 22.9

**Live deliveries per clinical pregnancy (%)**
- < 30: 72.1
- 30–34: 77.0
- 35–39: 66.8
- ≥ 40: 53.8
- All(b): 72.6

(a) Donor age at start of a treatment cycle.
(b) Includes cycles where donor’s age was not stated.

ANZARD Data 2013
Donor Sperm Treatment

• Altruistic, non-commercial sperm donation allowed in NZ

• Donors may be known or unknown, but not completely “anonymous”; preferably <45 years old with normal SA

• ~12-18 month wait for sperm donor in most clinics; may speed this up by advertising but still at least a 3-6 month “quarantine” period

• ANZARD data:
  - ~2500-3000 DI cycles in Australia/NZ per year
  - Average age of recipient is 35 years
  - Live birth rates ~11.1%/cycle (14.5% <35 years, 3.4% ≥40 years)
  - 4.1% multiple pregnancy rate
Donor Embryo Treatment

- Surplus embryos created as part of a couples own IVF treatment can be on-donated

- Recipients need to have a medical condition affecting their reproductive ability or a medical diagnosis of unexplained infertility that makes embryo donation appropriate.

- Requires ECART approval

- Embryo donation is limited to producing full genetic siblings in no more than two
Surrogacy

• A surrogacy arrangement is where a woman agrees to become pregnant for the purpose of surrendering custody of a child born as a result of the pregnancy

• Legal but not enforceable in NZ; commercial surrogacy not allowed

• Ethically and legally complex and involves risks for the adult parties and resulting children

• Requires ECART approval to be satisfied there is a need for surrogacy and that the proposal is justified in light of the associated risks.
Hired surrogate pregnant with triplets is threatened with financial ruin by the babies' father unless she has one of the fetuses aborted after he paid her $33,000

- Melissa Cook was hired to have baby for $33,000 by single Georgia man
- She was implanted with three embryos using eggs of 20-year-old donor
- But when man realized she was expecting triplets, he 'grew concerned'
- He is allegedly now demanding that she abort a fetus in next two weeks
Uterine Transplantation

• First live birth after uterine transplantation occurred in 2014
Fertility Preservation
Fertility Preservation

• Indications include individuals undergoing fertility impairing treatments e.g. surgery on reproductive organs, chemotherapy, radiation therapy + social reasons

• Treatments include:
  • Sperm freezing
  • Surgical sperm retrieval if sperm is not present in ejaculate
  • IVF and embryo freezing
  • Egg freezing
  • Ovarian tissue freezing

• Treatment options are determined by patients age, social circumstances, type of cancer and its hormone sensitivity, prognosis and the time available before the planned treatment should commence
Publicly Funded Fertility Preservation

- Patient is only eligible if they have no biological children and woman <40 at time of referral

- Expedited referrals; referral only requires information on the patient requiring the consultation (partners details do not need to be included unless couple are requesting embryo freezing)

- Note – ovarian tissue freezing is not currently publicly funded
How is fertility treatment funded in NZ?
CPAC Scoring for Publicly Funded Fertility Treatment

• CPAC threshold still 65 points

• Exclusion criteria:
  • Female age >40 years
  • Female BMI >32
  • Current smoker

• Up to two “packages of care” available (1 “package” could be 4 x IUI cycles or 1 x IVF cycle)

• Current wait time ~12 months for IVF treatment
### CPAC Scoring

**Ovulation**
- 6: Ovulation due to hypogonadotrophic hypogonadism
- 5: Ovulation but not pregnant after 12 months
- 4: Ovulation but not pregnant due to resistance to FSH
- 3: Resistance to FSH / LH failure
- 2: < 0 ovulatory cycles/year
- 1: Other
- 0: Other

**Male**
- 6: Any of:
  - Sertoli cell aplasia, azoospermia
  - Sperm concentration < 1 million/mL
  - Sperm motility < 40% positive
  - < 2 years, since vasectomy reversal and not preg.
  - < 1 million motile sperm wash
- 3: Ovulation and male infertility and not pregnant
- 2: < 30% total motile or < 15 million/mL in 2 samples
- 0: Other

**Endo**
- 6: Stage IV
- 5: Stage III
- 4: Stage II
- 3: Stage I
- 2: Stage 0
- 1: None

**Tubal**
- 6: Ovulation / severe adhesions / 12-months surgery
- 5: Moderate adhesions / 6-months surgery
- 4: Mild adhesions / 3-months surgery
- 3: Minimal adhesions / best side
- 2: Minor obstruction / best side
- 1: Other
- 0: Other

**Other**
- 6: Severe
- 5: Moderate
- 4: Mild
- 3: Minimal
- 2: None

**Objective score (OS)**
- OS = (O × D) / Q + 100

**SOCIAL CRITERIA**
- Duration of infertility over time
  - Less than 1 year: 5
  - 1 or 2 years: 20
  - 3 or 4 years: 40
  - 5 years or more: 50

- Children at home
  - None: 30
  - 1 by relationship: 10
  - 1 by previous relationship: 8

- Sterilization
  - Neither partner: 20
  - One or both partners: 10

- Social score (SS)
  - SS = S1 + S2 + S3

**FINAL SCORE (FS)**
- FS = OS × SS

**Please complete all scoring fields (not just summary scores)**

**Diagram**
- Ovulation
- Male
- Endo
- Tubal
- Other

**Reference**
Cost of Private Fertility Treatment

• Ovulation induction with CC/Letrozole $340/cycle
• Intrauterine insemination $1500/cycle
• Lipiodol flushing $500-1000
• In vitro fertilization $10,000-12,000/cycle
• Frozen embryo replacement $1650/cycle
So how to decide which treatment to use......
Choice of treatment depends on:

- Individualised, depending on...
  - Cause(s) of infertility
  - Age of patient
  - Funding and resources available
  - Waiting times for treatments/donor gametes
  - Previous treatments tried
  - Patient preference
Take Home Messages

• Consider optimising lifestyle factors for all couples
• Don’t forget the importance of Folic Acid/Iodine
• Support, education, counselling can improve success rates
• Remember treatment involves the couple
• Individualised management; not “one size fits all”
• Much more than just IVF
• Highly exciting and rapidly changing field!
Questions?