Fertility Associates – Leaders in Fertility
Infertility: ‘from whoa to go’

Greg Phillipson
Dunedin 2012
• Lifestyle, environmental and nutritional issues
• Cost effective and timely investigation
• Recent developments
  • endocrinology, radiology and genetics
• New developments in IVF
• Early pregnancy management, miscarriage and ectopic
• Ethical issues and medical tourism
Figure 4 - Cohort mean age at first birth, selected countries, birth cohorts 1915-1971

New Zealand

Source: Max Planck Institute
Human Reproduction

- Monthly probability of conception = fecundability
- Monthly probability of live birth = fecundity
- Average human monthly fecundity = 20%

*Getting pregnant is usually a matter of chance*
Likelihood of pregnancy

- **Likelihood of getting pregnant**
  - 20-24: 86%
  - 25-29: 78%
  - 30-34: 63%
  - 35-39: 52%
  - 40-44: 36%
  - 45-49: 32%
  - 50+: 0%

- **Likelihood of infertility**
  - 20-24: 3%
  - 25-29: 5%
  - 30-34: 8%
  - 35-39: 15%
  - 40-44: 5%
  - 45-49: 0%

**Leaders in Fertility**
### Monthly fecundity by age

<table>
<thead>
<tr>
<th>Years</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>44</td>
<td>2</td>
</tr>
</tbody>
</table>
Elevit?

• Multivitamin
• Folate only benefit unless malnourished
• $1 per day
• Folate 800mcg  $1 per week
• High dose folate  5mg day
• phx  Neural tube defect
• Family hx
• Epilepsy
• Iodide from early pregnancy  ?contraindications
Female Lifestyle and pre-pregnancy issues

Age
Smoking
Alcohol
Caffeine

Bmi \( \frac{\text{Height in m}}{\text{(weight in kg)}^2} \)
range 18 to 30

Exercise
The Normal Menstrual Cycle

Pituitary Hormones
- Follicle Stimulating Hormone
- Luteinising Hormone

Ovarian Hormones
- Estrogen
- Progesterone

Follicular Cycle
- Ovulation

Endometrial Cycle
- Menstruation

Body Temperature
- 0.2°-0.5°C

Day
- 2 4 6 8 10 12 14 16 18 20 22 24 26 28
  - Follicular Phase
  - Luteal Phase

Ovulation
Paternal age effects on time to pregnancy

Sartorius & Nieschlag, 2010

Leaders in Fertility
Some Facts about Ageing, Men and Sperm

- As men age the testes get smaller and softer, sperm morphology and motility tend to decline
- DNA fragmentation increases
- IVF pregnancy rate decreases as DNA fragmentation increases
- Paternal age >50 leads to doubling the chance of fetal death
- Paternal age >40 leads to increased rate of miscarriage independent of maternal age
Some Facts about Older Men and Sperm

Paternal age is a robust risk factor for the incidence of:

- schizophrenia in offspring
  - at 45+ odds ratio 3.0 = 1: 46 chance
  - specific for schizophrenia (Malaspina 2001)

- increase in autism
  - compared with 30 years
  - > 40 3 x the risk
  - > 50 5 x the risk

- increase in achondroplasia
Men and overweight – effects on fertility

Risk of overweight for infertility in men adjusted for other factors

Adjusted odds ratio for infertility in farmers in USA increases with increasing BMI with a 10kg increase leading to 10% reduction in fertility

[Graph showing BMI and adjusted odds ratio]

Figure 1. Effect of body mass index class on number of normal motile sperm cells.


[Graph showing sperm count by BMI class]

Figure 2. Effect of body mass index class on sperm chromatin integrity. *Significantly different ($P < .05$).

Kort et al. J Androl 2006
?Over exercising ?Friction in the saddle
Environmental

- Endocrine disrupting chemicals (EDC)
- Dioxin
- Pesticides
- DDT
- Lead
Healthy sperm diet

• Lots of antioxidants
  – fruit and vegetables, nuts, seeds, dark chocolate, green tea, red wine
• Vitamin C and E
• ? Selenium, Zinc
• ? Folic acid
Handy hints for making babies for men

A range of lifestyle factors can help enhance your fertility and chances of conceiving.

<table>
<thead>
<tr>
<th>Don’t smoke or do drugs</th>
<th>Smoking and some recreational drugs can reduce sperm quality.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce alcohol</td>
<td>Decrease your alcohol intake to 20 units or less a week. Alcohol has also been shown to affect fertility.</td>
</tr>
<tr>
<td>Have a normal BMI</td>
<td>Keep active and stay slim. Obese men have sperm counts on average 22% lower when compared to their slimmer counterparts. Have a body mass index (BMI) lower than 28.</td>
</tr>
<tr>
<td>Keep testes cool</td>
<td>Wear boxer shorts, not briefs, this helps the testes to keep cool. Men in sedentary jobs can have poorer quality sperm because their testes are more prone to heating up. Keep your laptop off your lap! Don’t have a hot bath, sauna or spa too frequently.</td>
</tr>
<tr>
<td>Have a healthy diet</td>
<td>Eat a diet with lots of healthy antioxidants. Foods rich in antioxidants can reduce the damage that free radicals can have on sperm. Antioxidants are found in fresh vegetables, fruit, nuts, seeds, green tea and dark chocolate. Health supplements containing antioxidants such as Vitamin C and E may help to improve sperm quality.</td>
</tr>
<tr>
<td>Medication</td>
<td>Discuss any medication you are taking with your Doctor.</td>
</tr>
</tbody>
</table>
• Lifestyle, environmental and nutritional issues
• **Cost effective and timely investigation**
  • DHB and private funding explained
• Recent developments
  • endocrine, radiology and genetics
• New developments in IVF
• Early pregnancy management miscarriage and ectopic
• Ethical issues and medical tourism
Internal Sexual & Reproductive Organs (F)
Male Sexual & Reproductive Organs

- Vas deferens
- Bladder
- Seminal vesicle
- Rectum
- Pubic bone
- Cowper's gland
- Corpus spongiosum
- Vas deferens
- Corpus cavernosum
- Epididymis
- Urethra
- Testis
- Glans
- Scrotum
Blastocyst Implantation

1. Sperm surround ovum
2. Fallopian tube
3. Penetration and fertilization
4. Cell division begins
5. Morula
6. Blastocyst
7. Embryo
8. Ovary
9. Uterus
10. Placenta
11. Embryo at 6 weeks

Leaders in Fertility
The Normal Menstrual Cycle

- **Pituitary Hormones**
  - Follicle Stimulating Hormone
  - Luteinising Hormone

- **Ovarian Hormones**
  - Progesterone
  - Oestrogen

- **Follicular Cycle**
  - Ovulation

- **Endometrial Cycle**
  - Menstruation

- **Body Temperature**
  - Day 2 4 6 8 10 12 14 16 18 20 22 24 26 28
  - Follicular Phase
  - Luteal Phase
  - 0.2°C-0.5°C

- **Notes**
  - Hypothalamus
  - Pituitary
  - Ovary
  - Endometrium

- **FSH**
- **LH**

- **Hypothalamus**
- **Gonad**
- **Oestrogen**
- **Luteinising Hormone**
- **FSH**
- **Ovaries**

- **Dot**
- **Solid**
  - Reduces hormone release
  - Stimulates hormone release

Leaders in Fertility
Overall likelihood of pregnancy

60% in 6 months
80% in 1 year
90% in 2 years
Initial investigations that can be done in primary care

Female
- Luteinising hormone, follicle stimulating hormone (FSH), and estradiol concentrations—should be measured in early follicular phase (days 2 to 6)
- Progesterone test—should be done mid-luteal phase (day 21 or seven days before expected menses)
- Thyroid stimulating hormone, prolactin, testosterone test—should be done if woman’s cycle is irregular, shortened, or prolonged or if progesterone indicates anovulation
- Rubella serology test—should be checked even if the woman has been immunised in past
- Cervical smear—should be carried out as normal screening protocol
- Transvaginal ultrasound scan—should be done if there is the possibility of polycystic ovaries or fibroids

Male
- Semen sample for analysis—sample should be taken after two or three days' abstinence and repeated after six weeks if abnormal
<table>
<thead>
<tr>
<th>Primary / Initial Assessment</th>
<th>Secondary</th>
<th>Specialist</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, Blood Group, Rubella, VDRL, Hep B Hep C, HIV</td>
<td>Day 2 FSH and oestradiol, Luteal Phase “day 21” progesterone</td>
<td>Ovarian reserve assessment “Egg timer test” AMH</td>
</tr>
<tr>
<td>Cervical smear, Chlamydia, Vaginal Swabs, PID or IUCD History</td>
<td>PCOS assessment, Testosterone, LH, Prolactin, TSH</td>
<td>Endocrinologist assessment</td>
</tr>
<tr>
<td>Menstrual Calendar</td>
<td>Ultrasound scan</td>
<td>Hysteroscopy Laparoscopy</td>
</tr>
<tr>
<td>Family History of Androgen sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic Assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Female Age issues if over 35

- Pregnancy rates
- Ovarian reserve Day 3 FSH, USS antral follicles
- AMH (egg timer test)
- Miscarriage rates
- Down’s syndrome
- IVF access
- IVF success rates
Assessment FSH
Antral follicle Count

Fig. 3. Photomicrograph of an adult primate ovary. Follicular and luteal units are seen in the cortex and large blood vessels and nerves in the medulla. se, serous or surface epithelium; ta, tunica albuginea; pf, primary follicle; sf, secondary follicle; tf, tertiary follicle; gf, graafian follicle. (From Bloom W, Fawcett DW: A Textbook of Histology. Philadelphia: WB Saunders, 1975.)
Correlation between 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles of antral follicle count (AFC) and age.

Fertility Sterility, Almog 2011
AMH

AMH Profile:

AMH Normal Range

Source: Hum Reprod © 2009 Oxford University Press

Leaders in Fertility
Serum markers of ovarian reserve

Fertility Sterility, Rosen 2012
Decline in fertility with age

Monthly pregnancy rate

IVF ongoing implantation
DI ongoing pregnancy x 1.7

Source: Fertility Associates
Age at starting private IVF cycle (incl DO)

- FAA
- FAH
- FAW

Source: Fertility Associates
Ovarian reserve

• Predicting earlier/faster egg loss:
  - Follicle stimulating hormone (FSH) levels
  - Antral follicle scans (‘Egg check’)
  - Anti-Mullerian Hormone (AMH) levels
  - Poor response to ovarian stimulation in IVF

• Predicting later/slower egg loss:
  - No test known

• Nothing can improving the quality of eggs or delay the loss of eggs
Loss of primordial follicles with woman’s age
Faddy et al, 1992

Fig. 1. Bi-exponential model of declining follicle numbers in pairs of human ovaries from neonatal age to 51 years old. Data were obtained from the studies of Block (1952, 1953) (×, n = 6; +, n = 43), Richardson et al. (1987) (□, n = 9) and Gougeon (unpublished) (*, n = 52).
Ovarian Reserve

Oocyte Numbers

Age: minus six months  
7 million

Age: zero  
1 million

Age: 25  
100,000

Age: 35  
25,000

Age: 40  
20,000

Age: 45  
2,000
The graph shows the AMH level (pmol/L) vs. woman's age. The green zone represents the 10th centile for younger, fertile women and indicates a very likely normal ovarian reserve. The orange zone represents the 25th centile for younger, fertile women and indicates a risk of reduced ovarian reserve. The red zone represents the 75th centile for younger, fertile women and indicates a very likely reduced ovarian reserve.

- **Green zone**: Above the 25th centile for younger, fertile women. Very likely normal ovarian reserve – age is the best predictor of your future fertility. 80% chance of 6 or more eggs in IVF.
- **Orange zone**: Between the 25th and 10th centiles for younger, fertile women. Some women in this range will have reduced ovarian reserve. 50% chance of 6 or more eggs in IVF.
- **Red zone**: Below the 10th centile for younger, fertile women. Very likely reduced ovarian reserve. 20% chance of 6 or more eggs in IVF.
Biological Clock™

 Chance of birth

- Chance of having a child per month of trying for fertile couples: 16%
- Chance of having a child from one IVF cycle for people experiencing infertility: 41%

Woman's Age: 35

Months Trying: 12

Months trying & when to seek help:
- Time to act
- Time to start thinking about seeing your GP or fertility specialist
- OK to wait, except under circumstances noted here

NZ Patent No. 577885. Overseas Patents Pending | © Copyright Fertility Associates Holdings Ltd
Hystrosalpingogram  HSG
Saline Infusion Scan

Contrast (Leovist) flowing through the fallopian tube

Uterus

Cervix

Vagina

HyCoSy catheter

Ovary

Leaders in Fertility
Laparoscopy Dye test
Laparoscopy
“Fitz hugh curtis” chlamydia
Pregnancy rates: other factors
Ovulation disorders
Ovulation Induction

[Diagram showing various conditions and their treatments for ovulation induction.]
Polyps
Fibroids
Fibroids
Tubal ligation reversal

Tubal Obstruction Post Bilateral Tubal Ligation
Male Fertility History

- Past history paternity
- Cryptorchidism
- Torsion
- Infection
- Trauma

- Current
- Varicocele
- Alcohol
- Smoking
- Weight
Male Examination
Male Examination
A FERTILE MAN’S SPERM COUNT OVER 2 YEARS

Sperm count (million/ml)

0 10 20 30 40 50 60 70 80 90 100 110 120

Weeks
Bell curve, the normal distribution
CUMULATIVE CONCEPTION RATE
FOR OLIGOZOOSPERMIC INFERTILITY

Cumulative pregnancy rate (%)

Time of exposure (years)

Fertile couples

Oligozoospermic (10^6 motile/ml)

15-20

10-15

5-10

1-5

0.1-1

Schoysman & Gerris (1983) Aeta Eur Fertil 14: 51
### Table A1.2 Distribution of values for semen parameters from men whose partners became pregnant within 12 months of discontinuing contraceptive use

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>N</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>95</th>
<th>97.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume (ml)</td>
<td>1941</td>
<td>1.2</td>
<td>1.5</td>
<td>2.0</td>
<td>2.7</td>
<td>3.7</td>
<td>4.8</td>
<td>6.0</td>
<td>6.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Total sperm number ($10^6$ per ejaculate)</td>
<td>1859</td>
<td>23</td>
<td>39</td>
<td>69</td>
<td>142</td>
<td>255</td>
<td>422</td>
<td>647</td>
<td>802</td>
<td>928</td>
</tr>
<tr>
<td>Sperm concentration ($10^6$ per ml)</td>
<td>1859</td>
<td>9</td>
<td>15</td>
<td>22</td>
<td>41</td>
<td>73</td>
<td>116</td>
<td>169</td>
<td>213</td>
<td>259</td>
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<tr>
<td>Total motility (PR+NP, %)</td>
<td>1781</td>
<td>34</td>
<td>40</td>
<td>45</td>
<td>53</td>
<td>61</td>
<td>69</td>
<td>75</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>Progressive motility (PR, %)</td>
<td>1780</td>
<td>28</td>
<td>32</td>
<td>39</td>
<td>47</td>
<td>55</td>
<td>62</td>
<td>69</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>Non-progressive motility (NP, %)</td>
<td>1778</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>15</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Immotile spermatozoa (IM, %)</td>
<td>1863</td>
<td>19</td>
<td>22</td>
<td>25</td>
<td>31</td>
<td>39</td>
<td>46</td>
<td>54</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Vitality (%)</td>
<td>428</td>
<td>53</td>
<td>58</td>
<td>64</td>
<td>72</td>
<td>79</td>
<td>84</td>
<td>88</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>Normal forms (%)</td>
<td>1851</td>
<td>3</td>
<td>4</td>
<td>5.5</td>
<td>9</td>
<td>15</td>
<td>24.5</td>
<td>36</td>
<td>44</td>
<td>48</td>
</tr>
</tbody>
</table>
Sperm Morphology

A

B

C
**Conservative measures for men with suboptimal semen analyses**

- Stop smoking—Nicotine reduces seminal plasma antioxidants
- Have frequent intercourse—Increases output of non-senile spermatozoa
- Reduce alcohol intake—Alcohol can suppress spermatogenesis
- Wear boxer shorts and avoid hot baths—Heat suppresses spermatogenesis
- Avoid pesticides, herbicides, heat, and radiation at work—All impair spermatogenesis

**What doesn’t work**

- Abstaining from coitus until ovulation does not improve the semen or likelihood of conception. Increasing coital frequency (alternate days) supplies more viable spermatozoa that normally remain motile in the female tract for two to three days
- Treatment with gonadotrophin injections, androgens (mesterolone) or antioestrogens (clomifene or tamoxifen) is not indicated because although they may improve the sperm count, fertility rates are not improved as the spermatozoa remain dysfunctional
Menevit?

- Sperm DNA fragmentation
- TUNEL SCSA
  - Abnm > 15%
- Zn Se Antioxidants
- Farming evidence
- Dietary insufficiency
- No improvement in Semen
- Improved IVF / Miscarriage
Measuring sperm DNA damage using the SCSA test

The SCSA test tends to be more accurate than other sperm tests as it measures thousands of sperm at once.

Traditionally the diagnosis of a male contribution to infertility has been based on the number (‘sperm concentration’), movement (‘motility’) and shape (‘morphology’) of sperm as seen down a microscope.

There is increasing evidence sperm DNA damage may also contribute to male infertility. Most sperm DNA damage is caused in one way or another by ‘Reactive Oxygen Species’ (ROS). It may be associated with increased age, defective DNA packaging inside the sperm head, increased scrotal temperature, having a varicocele, genital tract infection, smoking, a diet with low levels of antioxidants, or exposure to environmental contaminants and toxins.

The body’s main defence against ROS damage is to maintain an optimal antioxidant environment for sperm maturation and storage before ejaculation. This is one of the reasons why Fertility Associates promotes a healthy lifestyle, healthy eating and considering the use of antioxidant supplements.

Sperm DNA damage can be measured by a variety of tests. We now offer the SCSA (Sperm Chromatin Structure Assay) test, which uses computer flow cytometry to measure DNA damage in individual sperm. Because it measures thousands of sperm at once, it tends to be more accurate than other tests.

Your doctor will discuss whether a SCSA test for sperm DNA damage may be useful for you, taking into consideration your medical and fertility history, lifestyle and the outcome of other investigations and treatments.

The SCSA test involves booking a semen sample at a Fertility Associates clinic – our semen analysis form covers booking the test, the preferred period of abstinence and other instructions. The tests are done once a week in Wellington, so results are available within two weeks of providing the sample. Your doctor will tell you the result in person, by telephone or by sending you a letter.

Like most fertility tests, a sperm DNA fragmentation test does not give a black and white answer. The higher the test result, the more sperm DNA damage, and the more likely that the damage may affect your chance of pregnancy. We divide the results into green, orange and red zones in the graph to indicate the likely impact of your SCSA test result.

<table>
<thead>
<tr>
<th>SCSA test score</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Red zone Significant sperm DNA damage, which may reduce the chance of pregnancy in treatment</td>
</tr>
<tr>
<td>90%</td>
<td>Orange zone Some men in this range will have some sperm DNA damage, but the impact on fertility is likely to be small</td>
</tr>
<tr>
<td>80%</td>
<td>Green zone Very likely no or little sperm DNA damage</td>
</tr>
<tr>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
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</tbody>
</table>

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- Christchurch Level 1, Hiatt Chambers, 240 Papanui Road
  P 03 375 4000 E fax@fertilityassociates.co.nz

We also hold clinics in Whangarei, East: Auckland, West Auckland, Taunui, Gisborne, New Plymouth, Hawke’s Bay, Palmerston North, Lower Hutt, Nelson and Queenstown. Please call us or check our website for further details.
### Investigating Azoospermia, by Site of Abnormality

<table>
<thead>
<tr>
<th>Obstructive</th>
<th>Non-obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-testicular</td>
<td>Testicular</td>
</tr>
<tr>
<td><strong>Congenital causes</strong></td>
<td>Genetic causes, cryptorchidism, anorchia</td>
</tr>
<tr>
<td>Vasal aplasia, cystic fibrosis, mullerian cysts</td>
<td></td>
</tr>
<tr>
<td><strong>Acquired causes</strong></td>
<td>Radiotherapy, chemotherapy, orchitis, trauma, torsion</td>
</tr>
<tr>
<td>Gonorrhoea, chlamydia, tuberculosis, prostatitis, vasectomy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testicular size</th>
<th>Normal</th>
<th>Small, atrophic</th>
<th>Small, prepubertal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>Normal</td>
<td>Raised</td>
<td>Low</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Azoospermia

- Prevalence 1%
- CBAVD
- Genetic
- Vasectomy

- Donor sperm
- Donor embryo
Vasectomy Reversal

![Graph showing patency and pregnancy rates after vasectomy reversal at different time intervals: <3 yrs, 3-8 yrs, 9-14 yrs, >15 yrs. The graph indicates the percentage of successful patency and pregnancy rates.]

Leaders in Fertility
Management Unexplained delay

- Wait
- Clomiphene 50mg for 5 days
  - Empiric
  - 3-6 months only
  - Multiple pregnancy risk
- IUI
  - Empiric
  - 3-6 months only
  - Multiple pregnancy risk
- IVF
Unexplained Infertility

• One third of couples have no obvious diagnosis
• If young
  – ? Wait
  – ? Clomiphene
  – ? IUI
  – IVF
• If older female partner
  – ? Clomiphene while waiting
  – ? IVF
IUI
IVF
IVF ICSI
Embryo Transfer
The Normal Menstrual Cycle

- **Pituitary Hormones**
  - Follicle Stimulating Hormone
  - Luteinising Hormone

- **Ovarian Hormones**
  - Progesterone
  - Oestrogen

- **Follicular Cycle**
  - Ovulation

- **Endometrial Cycle**
  - Menstruation

- **Body Temperature**
  - 0.2°C - 0.5°C
  - Day 2 4 6 8 10 12 14 16 18 20 22 24 26 28
  - Follicular Phase
  - Luteal Phase

- **Ovulation**
IVF: the current results

• Clinical pregnancy rates
• Natural conception
• Frozen embryos
• Female age and IVF pregnancy rate
Pre implantation Diagnosis
Public Funded Fertility Treatment

- Fertility assessment
- Primary (GP, nurse practitioner)
- Secondary (Hospital)
- Tertiary
  - DHB contracted providers (Fertility Associates, OFS)
  - Specialist first assessment is covered if the criteria are met
  - Two treatment “cycles” (IVF, DI x4, Donor eggs = 1 cycle)
Eligibility for Public Funding

- Eligibility is determined by CPAC (Clinical Priority Access Criteria) specifically defined for fertility services throughout New Zealand.
- Couples require a CPAC score of more than 65 to access treatment.
- The scoring is complex and includes some factors which make patients ineligible for Public Funding:
  - Women who smoke are required to stop and be smoke free for three months to become eligible
  - Women with a BMI greater than 32 or less than 18 are required to lose or gain weight
  - Women aged 40 or older are excluded
  - Patients with two children in their current relationship or two children from previous relationships aged 12 or younger living at home
Eligibility for Public Funding

- Severe causes of infertility (anovulation, bilateral tubal damage, poor sperm) score a higher CPAC score.
- Previous vasectomy or tubal ligation, duration of infertility and history of unsuccessful other treatments are taken into account.
- Lesbian couples and single women may be eligible for Public Funded treatment if they have a biological reason for fertility delay or have not achieved pregnancy after 12 cycles of donor insemination.
- Funding covers the most appropriate treatment for that patient and may include ovulation induction, insemination of sperm, donor insemination, IVF, egg donation or surrogacy.
Public Funded Fertility Treatment

• Specialist assessment
• Scoring
• Waiting time until treatment starts
• Second scoring and treatments
• Other options
Private treatment costs

- Private specialist assessment vs FSA
- Clomiphene ...
  - Cycle monitoring, blood tests, Ultrasound scanning
- IUI (prev AIHusband)
- IUDI (donor sperm)
- IVF...ICSI
- Oocyte freezing (oncology....social)
• Lifestyle, environmental and nutritional issues
• Cost effective and timely investigation
• **Recent developments**
  • endocrine, radiology and genetics
• New developments in IVF
• Early pregnancy management miscarriage and ectopic
• Ethical issues and medical tourism
• Radiology
  – Saline scanning
  – 3 d ultrasound
  – MRI for uterine anomalies
• Endocrinology
  – AMH
• Genetics
  – Sperm DNA
  – Endometrial and implantation factors
• Lifestyle, environmental and nutritional issues
• Cost effective and timely investigation
• Recent developments
  • endocrine, radiology and genetics
• New developments in IVF
• Early pregnancy management miscarriage and ectopic
• Ethical issues and medical tourism
IVF in 2012

- All causes, both male and female
- Blood tests
- Drugs to block ovulation
- Ultrasound egg retrieval & embryo replacement
- Common to be in 40’s
- Single women and lesbian couples increasingly represented
- Fertility preservation now an option
Fresh implantation rates, women aged <= 37

- Gradual move to blastocyst ET
- Move to day 3 ET
- Culture under oil,
- New culture media
- SET
‘Infertility management is time management’

- Chance of conception naturally

- Time available to try conception naturally
  - Woman’s age
  - Estimate of ovarian reserve
  - Desired family size

- Chance of conception with treatment
Efficacy of fertility treatment

• Treatment is available for all types of infertility

• IVF will enable > 90% of women (and men) to have children (age permitting)

• Donor Insemination (DI) and Donor Egg (DO) will allow nearly all the rest to have children (availability of donors permitting)
Multiple IVF birth rate fresh IVF
IVF success rates

Source: Fertility Associates
Freezing things

• Sperm
• Ovarian Tissue
• Eggs
Sperm freezing - who might benefit?

- Prior to chemotherapy
- Prior to vasectomy
- In men with family history of declining sperm counts
- ‘Social’
Cryopreservation of ovarian tissue

- Ovarian tissue is removed laparoscopically
- Ovarian tissue finely sliced (200 slices)
- Fertility Associates has approval to store ovarian tissue in women aged 16 to 36
- Ideal for children but not available as yet
- How to use this tissue?
Oocyte freezing – who might benefit?

- Prior to chemotherapy (not the only option)
- Prior to surgical management of endometriosis
- Mosaic Turners Syndrome
- Family history of early menopause (with early evidence)
- ‘Social’
Day 3 embryo (8 cells)

Hole in the zona pellucida by non-contact laser

Insertion of glass micropipette

Removal of a single blastomere for genetic analysis
FISH

Comparative genomic hybridization

Leaders in Fertility
Current Status of PGD

• Public funding now available for 40 cycles annually across the country
• Criteria are broad but must involve serious genetic risk
• Currently under-spent nationally, but severe regional variation
• Wait time at Fertility Associates clinics:
  – Auckland: 2-4 months
  – Hamilton: currently no wait time
  – Wellington: 3-4 months
  – Christchurch: 2-3 years
• Lifestyle, environmental and nutritional issues
• Cost effective and timely investigation
• Recent developments
  • endocrine, radiology and genetics
• New developments in IVF
• Early pregnancy management miscarriage and ectopic
• Ethical issues and medical tourism
Early Pregnancy

• Normal
• Ectopic
• Miscarriage
• Recurrent Miscarriage
  – Immune disorders
  – Thrombophilias
  – Genetics
  – PGD
Early Pregnancy hCG

Fig. 9.1. Different hCG patterns in early pregnancy. A, normal increase of hCG; two consecutive samples will show the rate of hCG production (iu/l × day). B, subnormal increase, where the ‘hCG score’ can give diagnostic information. C, initial normal increase followed by decline.
Early pregnancy scanning

Figure 8-2. Early intrauterine pregnancy and its relationship with the transvaginal probe. Note that the embryonic disk (E) lies between the developing amnion (A) and yolk sac (YS).
Early pregnancy scanning
Early pregnancy, hCG and scans
Pregnancy Hormones

Fig. 11.9 Hormone levels during pregnancy
First trimester $\beta$ hCG centiles

- mRNA from embryo day 4
- Serum HCG from day 6 (immuno radiometric assay)
- Wilcox 1988: 30 % pre-clinical loss
- Luteal phase
  - doubles over 16 hrs
- from 4w to 7w (ELISA)
  - doubles over ~48 hrs
- Peak ~7-8w 100,000iu+
Patterns of β hCG rise 1\textsuperscript{st} trimester.

Fig. 9.1. Different hCG patterns in early pregnancy. A, normal increase of hCG; two consecutive samples will show the rate of hCG production (iu/l x day). B, subnormal increase, where the ‘hCG score’ can give diagnostic information. C, initial normal increase followed by decline.
Figure 8-2. Early intrauterine pregnancy and its relationship with the transvaginal probe. Note that the embryonic disk (E) lies between the developing amnion (A) and yolk sac (YS).
### Early Pregnancy Ultrasound Dates

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<td>Yolk Sac</td>
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</table>

- ○ = earliest detection
- ○○ = usually detected
- ●● = always detected
Early pregnancy ultrasound

• Mean Gestational Sac diameter
  – If >20mm with no Yolk Sac, no embryo = EPL

• Crown Rump Length
  – If >6mm without fetal cardiac activity = EPL
  – But if CRL <6mm, repeat in 7 days
    • Expect CRL increase ~ 1mm/day and +FH

• Heterotopic pregnancy (1% IVF…1/3000)
Pregnancy of unknown location

- (PUL) ? 8-31% of presentations
- += + HCG with no sign of intra or extra uterine pregnancy with no evidence retained POC
- 4 possible reasons
  - Failing pregnancy
  - Early viable pregnancy
  - Early ectopic
  - Persistant PUL
Serum progesterone in pregnancy

Fig. 9.2. Initial serum level of progesterone in viable intrauterine pregnancy (IUP) \((n = 24)\), in miscarriage (M) (SPAB) \((n = 37)\) and in ectopic pregnancy (EP) \((n = 97)\). Values are given as means ± standard deviation. The values for M and EP are significantly different from IUP \((P<0.001)\). The dotted line is the discriminatory level of progesterone (30 nm) below which no viable intrauterine pregnancies were found. Reproduced, with permission, from Hahlin et al. (1990).
Discriminatory zone

• Correlation of HCG with GSD (but note centiles)
• Limitations:
  – Twin gestation (higher than expected HCG)
  – USS hardware (TV USS 1000-1500iu cf Abdo USS 5000iu)
  – USS operator experience
• HCG doubling over 48 hrs in ongoing pregnancy
  – cf Complete EPL HCG should fall to <20% in 48hrs
  – cf after ERPOC HCG should fall by ~15% in first 12 hrs
• ?serum progesterone
  – <15 nmol implies non-viable pregnancy
  – >80 nmol 97% sensitivity to exclude ectopic
  – BUT many patients between 15 to 80 nmol
Ectopic Pregnancy:

? Expectant management

- If stable + no haemato peritoneum or signs of tubal rupture
- HCG <200iu (?<1000iu)
- ??60% resolve.
- Careful followup USS and HCG
Ectopic Pregnancy:

? Medical management

• If stable + no haemato peritoneum
• HCG <5000 iu
• EP diameter <30mm
• No fetal cardiac activity
• No contraindication to Methotrexate
  – (Viable pregnancy, liver, renal, bone abnm.)
• Follow up USS and HCG. ?80% resolve
• But 10% persist or rupture even if HCG falls
  – (possible even if HCG falls to non-pregnant levels)
Summary

- Understanding of physiology
- Correlation of history, dates, HCG and USS
- Careful follow-up @ 48 hours
- HCG doubling expected 4-7 weeks
  - if plateau or failure to fall after presumed intrauterine loss / ERPOC ? ectopic
- Limitations of single HCG, P, USS <6/40
• Lifestyle, environmental and nutritional issues
• Cost effective and timely investigation
• Recent developments
  • endocrine, radiology and genetics
• New developments in IVF
• Early pregnancy management miscarriage and ectopic
• Ethical issues and medical tourism
Principles of the Act

- Health and wellbeing of children...important consideration
- Health, safety, and dignity of future generations ...protected
- ...Health and wellbeing of women protected
- Informed choice and informed consent
- Donor offspring...access to genetic origins
- Needs and values of Maori
- Different ethical, spiritual, cultural perspectives...respect
HART Act (2004)

Prohibitions (i)
- Cloning for reproductive purposes
- Hybrids
- Human / animal implantation
- Genetic modification
- Derived from embryo or fetus
HART Act (2004)

Prohibitions (ii)

- Embryos beyond 14 days
- Gametes or embryos stored beyond 10 years
- Sex selection (defence)
- Obtaining gametes from minors (defence)
- Commercial supply
- Surrogacy agreement not enforceable
HART Act (2004)

- ACART
- ECART
Estimate cumulative birth rate, women 42y using donor eggs

Cycle of treatment

IVF, own egg  25 y donor  35 y donor
Donor egg cycles

- FAA
- FAH
- FAW
- San Diego
Cross border reproductive care

Oct 2010 to Sept 2011 AUCKLAND

- 28 Patients to San Diego Fertility Clinic alone
- Average age of egg donors around 23
- Clinical pregnancy rate of around 65%
- Returned for thawed embryo replacement 6
- Transport of frozen embryos
Dilemmas

• Age
• Weight
• Marital status
• Cancer care
• Fertility preservation
• Cross border reproductive care
• Embryo disposal
• Embryo research
NZ Census 2006

9% more women than men in 30 – 34 year group
### Indication for Donor Insemination at FA

#### Social indicators

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<th>Year</th>
<th>Total</th>
<th>FAA</th>
<th>FAH</th>
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<td>2011 to date</td>
<td>62%</td>
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**Average age of women at the time of DI treatment**

- Social causes: 38.3
- Other causes: 34.5
Families in NZ

• Couples with child(ren) 447,894
• One parent with child(ren) 193,635
• 30% of children are from one parent families

Statistic NZ 2006 Census
Oocyte freezing

- Prior to chemo/radiotherapy
- Religious reasons
- Legislative restriction
- Strategy for cumulative outcomes
- “Social”
Oocyte freezing

A. Cobo - Vitrification

- 486 cycles
- 2721 oocytes
- 84% survived thawing
- 128 deliveries, 29% / transfer

If >8 oocytes then pregnancy rate (46.4%)
The future
For more info, please visit our website:
www.fertilityassociates.co.nz/GP

www.nice.org.co.uk
The future?

• Sperm Transport
  – Sperm selection IIMSI
• Endometrial factors
• Embryo factors
  – Time lapse assessment
  – Genetics
Fertility Associates –
Leaders in Fertility
### Case study 1

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<td>225</td>
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**IVF PLAN**
- Cycle# *1
- Prot# *5.86
- GnRHA(Bus/Cet/etc) *bus
- FSH (GF/Pur) *GF
- FSH dose 225 *
- Trig (type, time) *ov
- OPU (Narc/MAC/etc) *narc
- Sperm (Ejac/Don/Fz) *ejac
- IVF/ICSI icsi *
- LPS (P4/P4+E2V) p4 *
- Transfer (D2/D3/B) *try blast
- ET# 1
- Com (AH, Col) *lives Whangarei

*** *** SIGNED OFF BY FREDDIE
GRAHAM
Case study 1
Case study 1
Case study 2 - Feb 2011

- 5 yrs infertility
- Male aged 33
- Right orchidoplexy aged 8
- 3 brothers, all children
- On examination: 20ml testes, “soft”
- Semen analysis, azoospermia
- Testosterone 10, FSH 26
- Karyotype – mosaic cell line
- Female aged 29
- Regular periods
- FSH 7.2, E2 137
Case study 2

|       | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size | Size |
|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| L Ovary |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| R Ovary |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |

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Leaders in Fertility
Case study 2
Case study 3 – June 2008

- 4 yrs infertility
- Male aged 41
- Female aged 41
- Past history of chlamydia so referred laparoscopy – normal
- FSH 6.1, E2 <150
- IVF requested
Case study 3
Case study 3
Case study 3
Case history

6/12 trying
Age 35
Irregular cycles, 35-56 days
BMI 25

• What differential diagnosis?
• What tests to confirm?
• What treatment likely?
Case history

Age 32
3 miscarriages in 1st trimester

- What history matters?
- What tests?
- What treatment?
Case history

8/12 trying
Age 25
Regular cycles

• What history?
• What tests?
• What treatment?
Case history

9/12 trying
Age 39
Partner had vas reversal, normal semen analysis
Regular cycles
Previous pregnancy terminated in prior relationship

• What history?
• What tests?
• What treatment?
Fertility Associates – Leaders in Fertility
Fertility Associates – Leaders in Fertility
Fertility Associates – Leaders in Fertility
Case study 1

AMH: 12.5