Parenting before conception
- the importance of periconception medicine
Disclosures

• Minor shareholder IVF clinic
• Grant support MSD, Merck and Ferring
• Grant support NHMRC
Big things have small beginnings
The periconception stage

The periconception period

Gametogenesis  Fertilisation  Implantation  Embryogenesis  Placentation

“Parenting before conception”
Why periconception care is important

• Usually simple and inexpensive
  – Few dollars can totally prevent disease at source

• Has the biggest impact on future health
  – Pregnancy programs for health and disease

• Identifies pregnancy risk factors
  – Many diseases of pregnancy have source before conception

• Identifies personal risk factors for disease
  – Reproduction is a window into future health

• Can be built into routine health care
  – Can be done in all age groups

• Provides a rapid fertility solution for some
  – Weight loss, smoking prevention
Preconception care - best investment

“Periconception care is provision of biomedical, behavioural and social interventions to women and couples before and around conception to address health problems and risk factors that contribute to maternal and childhood morbidity or mortality.”

Mustard 2007
Parenting before conception

Before and between pregnancies

Preconception interventions

• Promoting adolescent health
• Promoting reproductive health
• Nutritional status and supplementation
• Preventing and treating infections
• Screening and management of chronic diseases
• Managing substance abuse
• Improving family and mental health
• Optimising the environment
• Targeting health services
Traditional view

![Graph showing the relationship between functional capacity, environment & lifestyle, genes, reproductive disorders, and time with stages of life: infancy, childhood, youth, adulthood, and old age. The graph also highlights disease & disability over time.]
Periconceptional influence affects organisation of the following:

- The DNA
- The epigenome
- Mitochondria
- Metabolism
- Placentation
- Organ development

in the gametes, embryo and fetus
The embryo is vulnerable

Embryo development

- Stress
- Infection
- Smoking and alcohol
- Environmental toxins
- Assisted reproduction
- Poor nutrition
- Weight

Offspring health

Acknowledgement S Robertson
Proven environmental influences on fetus

- Insufficient iodine in mother
- Inadequate folate in mother
- Exogenous drugs and toxins
- Over- and underweight
Environmental effects on embryogenesis

Adapted from M Lane et al. Science 2014;345:756-760
Smoking and reproduction

- Earlier age of menopause
- Higher infertility risk
- Lower pregnancy rate
- Higher miscarriage rate
- Higher ectopic rate
- Worse pregnancy problems
- Reduced eggs and sperm in offspring
- Higher testicular cancer in offspring
Alcohol and pregnancy

The Effects of Alcohol Consumption on a Developing Baby

- Months 1/2/3
  - The major organs develop (heart, lungs, kidneys, etc.).
  - The basic structure of the brain is laid down.

- Months 4/5/6
  - Body grows rapidly.
  - Movement increases.

- Months 7/8/9
  - The brain grows, myelination and organogenesis occur from head to toe.
  - The tongue mature.

- Birth - 18 Months
  - The brain continues to grow rapidly as the baby learns to move.
  - Binge every minute.

Drinking alcohol during the first 3 months can cause a baby to have a smaller growth and cause the baby to have the baby to do the brain develop.

Drinking alcohol during the second 3 months can cause a baby to have a smaller growth and change the way blood is the brain develop.

Drinking alcohol during the third 3 months can cause a baby to have a smaller growth and affect the motor and brain development.

A mother who drinks alcohol while being pregnant and continues to drink is likely to have a child with alcohol-induced fetal alcohol syndrome (FAS).

Stepping: drinking can prevent the most severe effects, but even then, the baby is at risk.

The mother should be made aware of the risks involved and be encouraged to stop drinking alcohol.

- 1-3 per 1000 live births
- Up to 9.1 per 1000 in high risk
- Range in Indigenous groups higher
- High rates of binge drinking in young women

Elliott et al 2008; NIDAC 2012
Environment effects on male reproduction

Nutritional impact on seminal fluid
Diet and lifestyle affects seminal fluid constituents which can affect sperm and female reproductive tract

Environment/lifestyle insult
Toxins
Endocrine disruptors
Smoking
Obesity

Insult affects sperm during development in testes or during maturation in epididymis

Changes in histone-bound DNA
Changes in microRNA
Increased DNA fragmentation

Altered gene expression in zygote

Impaired embryo growth and health of offspring

Adapted from M Lane et al. Science 2014;345:756-760
DNA damage: affecting sperm quality

Age/Toxicants/Genetic disposition

DNA damage in the germ line

Cancer Dominant genetic mutations Infertility

DNA mutation in the germ line

Oxidative stress

DNA damage

ICSI

Fertilization IVF or natural

Aberrant DNA repair

Adapted from Aitken
Obesity affects the embryo and fetus

- Maternal obesity metabolic syndrome
- Paternal obesity metabolic syndrome
- Oocyte
  - Cytoplasmic dysfunction
- Sperm
  - Chromatin damage
- Altered offspring phenotype
- Perturbed epigenetic reprogramming in the embryo
  - Methylation, microRNAs
  - Protamine/histone exchange
  - Establishment of epigenetic marks
- Alters transcription and translation profile of the embryo

Lane et al. Trends in Endocrinology and Metabolism 2015 26:84
Weight affects fertility/menstrual cycles

* Significantly different from BMI 22-24

Fat distribution and fertility

N=500 women - 0.1 unit increase in WHR: 30% decrease in probability of conception/cycle

Cumulative pregnancy rates

Number of cycles donor insemination treatment

Zaadstra et al 1993
BMI reflects IVF outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
<th>Numbers</th>
<th>Age</th>
<th>% pregnancy</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;20</td>
<td>441</td>
<td>31.6</td>
<td>45</td>
<td>0.81 (0.65-1.01)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20-24.9</td>
<td>1910</td>
<td>32.9</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
<td>814</td>
<td>33.0</td>
<td>42</td>
<td>0.81 (0.68-0.97)</td>
</tr>
<tr>
<td>Obese</td>
<td>30-34.9</td>
<td>304</td>
<td>32.8</td>
<td>40</td>
<td>0.73 (0.57-0.95)</td>
</tr>
<tr>
<td>Very obese</td>
<td>&gt;35</td>
<td>117</td>
<td>32.7</td>
<td>30</td>
<td>0.50 (0.32-0.72)</td>
</tr>
</tbody>
</table>

33 studies (47,967 treatment cycles) included in meta-analysis
Overweight/obese (BMI ≥ 25) vs normal weight (BMI<25)
↓Clinical pregnancy (RR=0.90, P<0.0001)
↓Live birth rates (RR=0.84, P=0.0002)
↑Miscarriage rate (RR=1.31, P < 0.0001)

Male diet predicts reproductive outcomes

Male diet affects offspring health

• Sweden – grandfather’s food availability related to grandson’s cardiovascular and diabetes related health
• Holland – offspring from undernourished fathers were heavier and more obese than from fathers that were not undernourished
• Paternal obesity related to increased body fat and mass in pre-pubertal children

Male BMI predicts IVF outcomes

350 cycles of IVF
• Male BMI documented
• Female weight controlled
• Decreased pregnancy rates
• Increased pregnancy loss
• Worse embryos

<table>
<thead>
<tr>
<th>Male BMI – results percent pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Live birth</td>
</tr>
<tr>
<td>Loss</td>
</tr>
</tbody>
</table>

Embryo development according to paternal BMI

<table>
<thead>
<tr>
<th>Embryo development</th>
<th>Normal</th>
<th>Over-weight</th>
<th>Obese</th>
<th>Morbid obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5 on time blastocyst</td>
<td>29</td>
<td>28</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>D5 expanded blastocyst</td>
<td>18</td>
<td>15</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

Bakos et al Fertility and Sterility 2011
Health responses to periconception

**Individual advice**
- eg GP, midwife, other health professionals

**Collective action**
- ie folate, immunisation, iodine, iron supplements, radiation prevention

**Genetic and other complications**
- eg diabetes mellitus, hyperlipidaemia, hypertension

**Social and working conditions**
- eg exercise, food, bicycle friendly cities, appropriate education

**Illness and medications, blood sugar, lipids, stopping statins, reviewing blood pressure medications**

**Reducing environmental disruptors, health education, regulation of food sales, healthy school foods etc**

Reproductive risk identification
Reproductive life plan
Preconception intervention programmes

Based on evidence based recommendations by Netherlands Health Council
What patients can do

- Nutritional supplements eg folate, iron, iodine
- Vaccinations for rubella, varicella etc
- Control of known toxins and medical drugs
- Avoid pesticides, heavy metals, environmental disrupters
- Reduce risks including alcohol, recreational drugs, anabolic steroids
- Creation of environment for exercise, rest, prevention of exposure to risk at work, child labour
- Approaches to allowing earlier parenting and maternity leave and economic relief
What we can do

• Adequate family, personal and genetic history
• Discuss medical, lifestyle and environmental risks
• Discuss testing for genetics, immunity, endocrine
• Ensure male partner is treated equally as above
• Give advice on optimal time for intercourse
• Give realistic chances of pregnancy based on age etc
Australian Your Fertility project

40 is the new 30. Unless you want to have children.

We live longer, healthier lives these days, so we can falsely believe that good health inevitably means good fertility. The truth is, the longer we leave it, the harder it can be to get pregnant.

Find out more about the fertility factors

http://www.yourfertility.org.au
1. Seize the opportunities

- Assess individuals and couples systematically for
  - Lifestyle, weight, smoking, stress
  - Medical, drugs and genetic factors
  - Environmental risks
- Provide advice and opportunity to correct these
  - Lifestyle intervention programs
  - Stress reduction
  - Controlling blood sugar, medication, diet
- Offer program to reduce risks to offspring
  - Natural fertility, frozen embryo cycles, PGS
  - Single embryo transfer
2. Pre-pregnancy checkup

Planned pregnancy
• Review of risks
• Preventative factors such as folate
• Health promotion
• Mental and family health
• Nutrition screening and supplemental food
• Iron, iodine, folate supplementation
• Screening for HIV, STD, genetic diseases
• Vaccinations
• Workplace safety
• Maternity leave and spacing
3. Action for identified risk

Focus on men and women with risk factors that can be addressed before pregnancy

- Medications with known teratogens
- Diabetes and hypertension
- Heart disease, thrombophilias
- Dental disease
- Obesity
- HIV/AIDS
- Thyroid disease
- Smoking and alcohol
- Illicit drug use
- Genetic conditions
  - Known
  - Family history
4. Lifestyle intervention programs

Fertility Fitness for Women
- 50% increase in pregnancy rates
- Reduction in IGT
- Better pregnancies
- Fertility Fitness

Fertility Assessment Project
- Individualised program for couples
- Nurse-initiated, physician informed
- Personalised followup
- Health and well-being program
  - Many pregnancies without medical treatment
  - Improved metabolism before pregnancy
5. Change our IVF practices

Perinatal mortality rate per 1000 births – effect of time

One, two or more embryos transferred – effect of time

Source: Assisted reproductive technology in Australia and New Zealand 2002 to 2011
6. Promote research collaboration

Cross generational health

Developmental origins of health and disease across generations

- Pregnancy
- Childhood
- Adulthood
- Later life

Translational research pathways

Laboratory and clinical investigators in team-based translation

- Basic biology
- Clinical investigation
- Community translation
7. Research across translational barriers

Science

- University based across faculties
- State health policies
- National health priorities
- International guidelines

Clinical medicine

- 4 state hospitals
- 2 private fertility clinics
- Private facilities
- Integrated cohort management
- State data linkage
- National clinical registries

Translational medicine

Public health/epidemiology
“We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time”

TS Eliot *Four Quartets*