Introducing

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GYNAECOLOGY AND REPRODUCTIVE CARE

St Andrew's Hospital

GP Fertility Autumn Series

COMPLEX FERTILITY PATIENTS

Speaker: Dr Victoria Nisenblat
Date: 23/5/2024

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What Fertility Patients are not Complex? Aren’t they all?

OVERVIEW / SPEED DATING

1. Routine Pre-Conception Advice
2. Reproductive Genetic Carrier Screening / PGT
3. Female age and fertility
4. Male Fertility
5. Transgender patients

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ROUTINE PRE-CONCEPTION ADVICE

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ROUTINE PRE-CONCEPTION ADVICE

- Optimise Health
  - History (personal or family) – risks for fertility/ healthy pregnancy?
  - Explore lifestyle habits and occupational exposures
  - Assess mental health
  - Assess iron levels, vitamin D/B12/Folate deficiencies
  - Screen for thyroid disorders, DM, thalassaemia, HTN

- Manage and stabilise chronic conditions
  - HTN, DM, epilepsy, anaemia, anxiety, etc…
  - Consider early referral to an obstetrics physician, high-risk obstetrician, or relevant specialist

ROUTINE PRE-CONCEPTION ADVICE

- Optimise Lifestyle
  - Balanced diet
  - Regular exercise
  - Reduce ETOH consumption (both partners)
  - Reduce caffeine intake
  - Stop smoking
  - Avoid a passive smoking environment
  - Avoid recreational drugs
- Avoid occupational exposures to solvents, pesticides etc
- Identify and manage stress
- Minimize testicular hyperthermia
- **Recommend striving for a healthy normal BMI**

How much alcohol is safe to drink?

Alcohol is never completely safe, it can cause harm to the person who drinks and sometimes to those around them. The Australian guidelines to reduce health risks from drinking alcohol provides evidence-based recommendations on how to keep risk of harm from alcohol low.

Australian Government
Department of Health and Aged Care

Alcohol Guidelines

Australian guidelines to reduce health risks from drinking alcohol

1: HEALTHY ADULTS

Drink no more than
10 standard drinks a week

AND
no more than 4 standard drinks
on any one day

to reduce the risk of harm from alcohol.

The less you drink, the lower your risk of harm.

2: CHILDREN AND PEOPLE UNDER 18 YEARS OF AGE

Should not drink alcohol

to reduce the risk of harm from alcohol.

3: WOMEN WHO ARE PREGNANT OR BREASTFEEDING

Should not drink alcohol

to prevent harm from alcohol to their unborn child or baby.

www.nhmrc.gov.au/alcohol

Recommendations of societies and government bodies on caffeine intake during pregnancy

UpToDate®

Country/region	Society	Recommendation
International	World Health Organization (WHO)	For pregnant women with high daily caffeine intake >300 mg/day, lowering daily caffeine intake during pregnancy is recommended to reduce the risk of pregnancy loss and low birth weight neonates.[1]
	International Federation of Gynecology and Obstetrics (FIGO)	The advice to limit caffeine intake to 200 mg/day during pregnancy continues to be justified. Higher maternal caffeine consumption (>300 mg/day) is associated with an increased risk of fetal growth restriction and is suggested to increase risks of spontaneous abortion and stillbirth.[2]
	March of Dimes	Women who are pregnant or trying to become pregnant consume no more than 200 mg of caffeine/day (1.5 8-ounce cups of coffee). Women who are breastfeeding advised to limit caffeine to no more than two cups of coffee per day.[3]
North America	Health of Canada	Women who are planning to become pregnant, pregnant women, and breast-feeding mothers should limit caffeine intake to 300 mg per day.[4]
	American College of Obstetricians and Gynecologists (ACOG)	Moderate caffeine consumption (<200 mg/day) does not appear to be a major contributing factor to miscarriage or preterm birth. The relationship of caffeine to growth restriction remains undetermined and it remains unclear whether there is a correlation between high caffeine intake and miscarriage.[5]
	US Department of Health and Human Services (HHS)	Strong and consistent evidence shows that moderate coffee consumption up to 400 mg/day of caffeine (three to five 8-oz cups/day) in healthy adults is not associated with an increased risk of major chronic diseases or premature death. Women who are capable of becoming pregnant, who are trying to, or who are pregnant and those who are breastfeeding should consult their health care providers for advice concerning caffeine consumption.[6]
Europe	European Food Safety Authority (EFSA)	Consumption of up to 200 mg per day of caffeine by pregnant individuals in the general population does not give rise to safety concerns for the fetus.[7]
	Royal College of Obstetricians and Gynaecologists (RCOG)	Women before conception and during pregnancy are advised to limit caffeine intake to 200 mg/day.[8]
Australia and New Zealand	National Health and Medical Research Council (NHMRC)	Food Standards Australia and New Zealand (FSANZ) suggests limiting caffeine intake during pregnancy to 200 mg/day.[9]

References:

1. *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience. World Health Organization, Geneva 2016.*
2. *Hanson MA, Bardsley A, De-Regil LM, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". Int J Gynecol Obstet 2015; 131:S4.*
3. *Caffeine in pregnancy. March of Dimes. Available at: https://www.marchofdimes.org/pregnancy/caffeine-in-pregnancy.aspx# (Accessed on November 17, 2021).*
4. *Caffeine and pregnancy. Public Health Agency of Canada. Available at: https://www.canada.ca/en/public-health/services/pregnancy/caffeine.html (Accessed on November 17, 2021).*
5. *American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 462: Moderate caffeine consumption during pregnancy. Obstet Gynecol 2010; 116:467. Reaffirmed 2020.*

SMOKING

- **Smoking is strongly associated with adverse obstetric and neonatal outcomes:** ectopic pregnancy, stillbirth, placenta praevia, preterm birth, low birth weight, congenital anomalies, sudden infant death syndrome, obesity, psychosocial problems and malignancies
- **Passive smoking significantly increased the risk of RPL compared with tobacco-free controls in a dose-dependent manner:**
  - adjusted OR 2.30; 95%CI 1.50-3.52 for exposure of < 1hour/day
  - adjusted OR 4.75; 95%CI 3.23-6.99 for exposure of ≥1 h/day
- In a meta-analysis of 8 studies, **paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of pregnancy loss** after adjustment for maternal smoking status
- **In IVF patients, smoking was associated with a significantly increased risk of pregnancy loss** after adjusting for other factors (OR 2.00; 95%CI 1.27-3.15)

Couples with RPL should be informed that smoking could have a negative impact on their chances of a live birth, and therefore cessation of smoking is recommended.	GPP

Leung and Davies, 2015; Pathak et al., 2010; Zhang et al., 2010; Winter et al., 2002; du Fosse et al., 2021

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

Most studies are small and low quality:

- Women with RPL had higher serum levels of heavy metals (Selenium, Cadmium, Lead) and lower levels of micronutrients (Zink, Copper, vitamin E) compared with controls
- Women with RPL had higher serum levels of organochlorine pesticides compared to controls
- An association was consistently reported by studies evaluating exposure to organic solvents and pregnancy loss
- One study reported an increased risk of pregnancy loss in personnel exposed to anaesthetic gases in operating and recovery rooms (n=8032) as compared to non-exposed hospital staff (n=2525) (OR 1.98; 95%CI 1.53-2.56)
- There is no increased risk of the offspring, nor is there an increased risk of pregnancy loss in parents who have been exposed to Diagnostic Radiological procedures

- Based on small studies, exposure to occupational and environmental factors (heavy metals, pesticide, lack of micronutrients) is associated with an increased risk of RPL.
- Exposure to possible hazardous substances should be avoided during pregnancy.
- There is insufficient data to recommend protection against a certain occupational or environmental factor to prevent RPL.

Ajayi et al., *2012;* ***Pathak et al.,*** *2010;* ***Gold and Tomich,*** *1994;* ***Guirguis et al.,*** *1990*

STRESS

- Studies have suggested that maternal stress during pregnancy is possibly associated with an increased risk of several adverse pregnancy and birth outcomes -> no high-quality studies available

- An association between RPL and stress can be assumed based on the following:
  - Several case-control studies showed that perceived stress scale (PSS) was significantly higher in women with unexplained RPL compared with controls
  - The odds of moderate to severe depression was more than five times higher in women with RPL
  - Higher cortisol levels – proposed mechanism?

Overall, the studies indicate that there is an association between stress and pregnancy loss, but they provide no information on whether the stress is a result or a cause of RPL

Stress is associated with RPL, but couples should be informed that there is no evidence that stress is a direct cause of pregnancy loss.	Strong	⊕■■■

Kolte et al., *2015;* ***Li et al.,*** *2012;* ***Nepomnaschy et al.,*** *2006;* ***Nelson et al.,*** *2003;* ***Plana-Ripoll et al.,*** *2016*

Testicular Hyperthermia

BIOLOGICAL REVIEWS
Cambridge Philosophical Society
Biol. Rev. (2023), **98**, pp. 603–622.
doi: 10.1111/brv.12921

Testicular heat stress, a historical perspective and two postulates for why male germ cells are heat sensitive

Benjamin R. Robinson, Jacob K. Netherton, Rachel A. Ogle and Mark A. Baker*
Faculty of Science and Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, 2308, Australia

Herein, we compare the different experimental regimes used to induce testicular heat stress and summarise their impact on sperm production and male fertility.

Irrespective of the protocol used, scrotal heat stress causes loss of sperm production. This is first seen 1–2 weeks post heat stress, peaking 4–5 weeks thereafter.

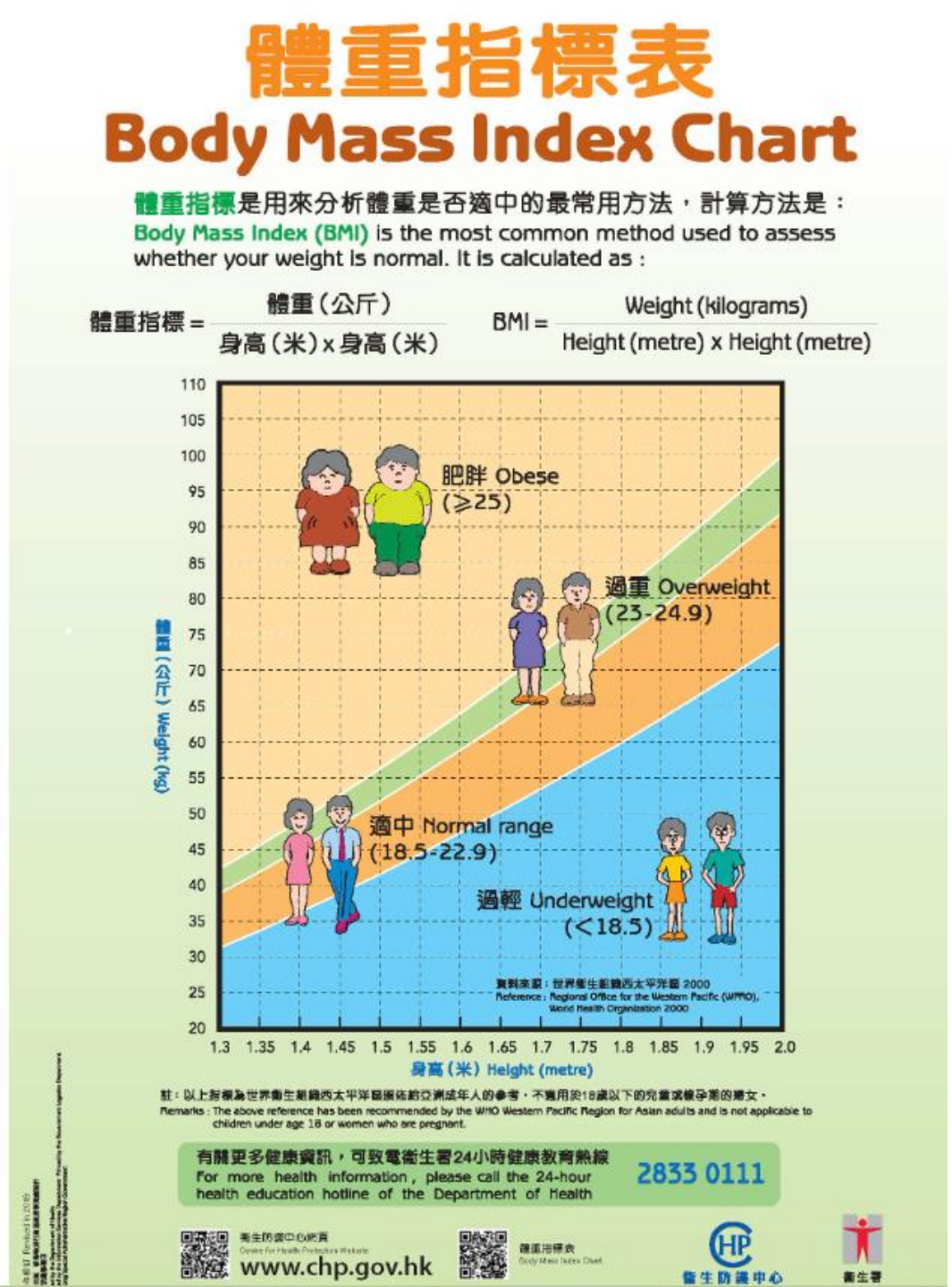
The higher the temperature, or the longer the duration of heat, the more pronounced germ cell loss becomes, within extreme cases this leads to azoospermia.

The second, and often underappreciated impact of testicular hyperthermia is the production of poor-quality spermatozoa. Typically, those cells that survive hyperthermia develop into morphologically abnormal and poorly motile spermatozoa. While both apoptotic and non-apoptotic pathways are known to contribute to hyperthermic germ cell loss, the mechanisms leading to formation of poor-quality sperm remain unclear.

BMI – The good, bad and ugly

- Obesity has a significant impact on female reproductive health
- Increased BMI
  - Associated with subfertility and poorer outcomes following fertility treatments
  - Is the second most significant factor predicting pregnancy loss (after maternal age) pregnancy loss
  - Is linked with recurrent pregnancy loss
  - Increased risks of complications in pregnancy (GHTN, GDM, IUGR, LGA, intrapartum maternal risks, neonatal morbidity)
  - Is associated with impaired semen parameters and sperm DNA damage
  - Weight loss has a positive impact on fertility and pregnancy outcomes and reduces cardiovascular and diabetic morbidity.
- Aim for the healthier pre-pregnancy BMI possible
- Ethnicity interacts with the health risk posed by obesity
  - For a Caucasian population:
    - BMI of 20-24.9 kg /m^2 –> healthy range
    - BMI of 25-30 kg/m^2 – > overweight (minimal adverse effects on reproduction)
  - **For people of Asian origin BMI of 27 kg /m^2 and above is linked with increased risks**

Metwally et al., *2008,* ***Pandey et al.,*** *2010,* ***Metwally et al.,*** *2010,* ***Misra et al.,*** *2009,* ***Du Plessis et al.,*** *2010,* ***Keszthelyi et al.,*** *2020*



Centre for Health Protection
Department of Health
The Government of the Hong Kong Special Administrative Region

BMI = Weight (kilograms) / Height (metre) ^{2}

- BMI equal or above 25 is obese
- BMI between 23 and 24.9 is overweight
- BMI between 18.5 and 22.9 is normal range
- BMI less than 18.5 is underweight

Reference: Regional Office for the Western Pacific (WPRO), World Health Organization 2000
Revised 2019

Centre for Health Protection
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Planning for Pregnancy

If you are planning to become pregnant, you should aim to give yourself the best chance of a healthy baby.

Because a woman's health and wellbeing before conception can affect her baby's health and development, there are many factors to consider prior to becoming pregnant to give the best chance of a healthy pregnancy and baby.

Steps taken prior to conception to optimise your health can have significant long-lasting benefits for you and your baby.

A healthy lifestyle is of prime importance.

Diet

A balanced diet that includes appropriate portions of a variety of food groups is recommended.

This means eating plenty of vegetables of different types and colours, as well as fruit, grain (cereal) foods, lean meat, poultry, fish, eggs, nuts, and dairy products.

Where possible, fresh unprocessed food is best as processed foods may have unhealthy additives such as sugar and salt.

Vitamin supplements

A healthy, well-balanced diet is recommended before, during and after pregnancy. Some women will need specific supplements.

Folic acid
All women should take at least 0.5mg of folic acid for at least the month before a planned pregnancy, and for the first three months of pregnancy to reduce the risk of neural tube defects and spina bifida (incomplete development of the baby's brain, spine or spinal cord).

Where there is a known increased risk of neural tube defect, a 5mg daily dose of folic acid is recommended. Women who should take 5mg of folic acid are those taking anticonvulsant (epilepsy) medication, women with diabetes, women who are obese, or who have had a previous child or a member of their family affected by a neural tube defect, and those who are at a risk of poor absorption of their food.

Iodine
An iodine supplementation of 150mcg per day is also recommended pre-pregnancy, during pregnancy and while breastfeeding as it is important for your baby's brain development.

Weight

Women who are underweight or overweight have a higher risk of problems in pregnancy. Women who are very underweight may have reduced fertility and may expose their babies to nutritional problems.

A common problem is overweight and obesity. Carrying too much weight can reduce fertility and may increase the risk of miscarriage and other serious problems for the baby. The more overweight a woman is, the greater her risk of problems in pregnancy. These risks include diabetes, pre-eclampsia (high blood pressure), excessive bleeding and developing blood clots. There are also higher anaesthetic risks and greater likelihood of requiring a caesarean section.

Weight is a very sensitive issue for many women. However, because of the great benefit to the mother and her future baby, it is recommended that steps should be taken to lose weight in a healthy manner. These steps include dietary change (help from a dietician can be valuable) and exercise. We recommend that obese women not try for pregnancy until steps have been taken to reduce weight.

Exercise

Moderate exercise improves fertility, particularly for people who are overweight or obese. If you are overweight or obese, you should aim to return your weight to normal with a healthy diet and regular exercise. Exercising together with your partner may be beneficial for both your health and relationship.

Planning for Pregnancy

Medical conditions

Having the best possible control of any medical problems before pregnancy can improve pregnancy outcomes. For example, for women with diabetes, blood sugar control is important prior to pregnancy and during the first three months of pregnancy - better blood sugar control lowers the risk of harm to the baby. It is important to discuss the management of any medical conditions with your doctor prior to conception.

Check your medication

It is important to review all current medications, including over-the-counter preparations, for appropriateness and safety in pregnancy. Some women may need to change medications prior to trying for pregnancy. Avoid stopping long-term medication abruptly without discussing this with your doctor.

Smoking

Cigarette smoking affects the quality of a woman's eggs and the number of healthy eggs she has in reserve. Smoking can also reduce the quality of the man's sperm.

Smoking during pregnancy can harm the placenta, and the placenta is vital for the baby's nourishment and ability to rid the baby's waste products. Smoking may restrict the growth of the baby in the mother's womb. Babies whose growth has been restricted by the placenta not working well, have a higher chance of childhood obesity and adult diseases such as high blood pressure.

Babies of mothers who smoke are at risk of problems both before and after birth. It is important to stop smoking before trying for pregnancy – seek help from your family doctor to quit.

Alcohol and illicit drugs

Alcohol reduces fertility in men and women, and can harm the developing baby. For women who are pregnant or planning a pregnancy, not drinking alcohol at all is the safest option.

Illicit drugs can also adversely affect fertility, the development of the baby and pregnancy. Illicit drug use should cease prior to and during pregnancy – seek help with this if you need to.

Healthy environment

Check and reduce the risk of exposure to toxins, infections or radiation for both you and your partner in the household, workplace, or during recreational activities.

Travel may expose women and their partners to infections which could adversely affect a pregnancy. Specific medical advice may be required depending on the area visited. For example, a woman or her partner returning from a Zika virus affected area should avoid pregnancy until their doctor advises it is safe to conceive.

Pre-pregnancy check-up

Seeing a doctor before trying for pregnancy is important. This allows your doctor to make sure that:

- any existing medical condition is well-controlled
- you are up to date with appropriate vaccinations. For example, checking your immunity for German measles (Rubella) and chickenpox. Each of these infections occurring during pregnancy can cause serious harm to the baby. Vaccines are available for both Rubella and chickenpox. You should vaccinate at least four weeks prior to becoming pregnant. Women should not receive the vaccine if they are pregnant or might become pregnant within four weeks
- you have a blood pressure check and general examination and, where appropriate, breast examination and a pap smear.
- if there is a significant risk of a chromosomal or genetic condition based on your or your partner's family history or ethnic background, then pre-pregnancy genetic testing and counselling may be needed. This includes inherited diseases such as Cystic Fibrosis, Muscular Dystrophy and Thalassemia
- a review of the outcomes of any previous pregnancies (e.g. pregnancy loss, children born with health problems, mother having gestational diabetes) is worthwhile to determine whether there are any measures which could reduce the chance of recurrence

Male partner

Making sure the future father is in good health is important too. Obesity, cigarette smoking, excessive alcohol use, some medications, illicit drug use and a poor diet all may affect a man's fertility and may also affect pregnancy outcomes.

A healthy lifestyle with regular exercise and a healthy diet, as described above, are just as important for men.

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Don’t forget

- Recommend daily folate (0.5 mg/day)
- Update Cervical Screening Test
- Check Rubella and Varicella immunity – vaccinate if non-immune
- Discuss fertile window and timing of intercourse (every 2-3 days)
- **Discuss Reproductive Genetic Carrier Screening**

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Fertile Window

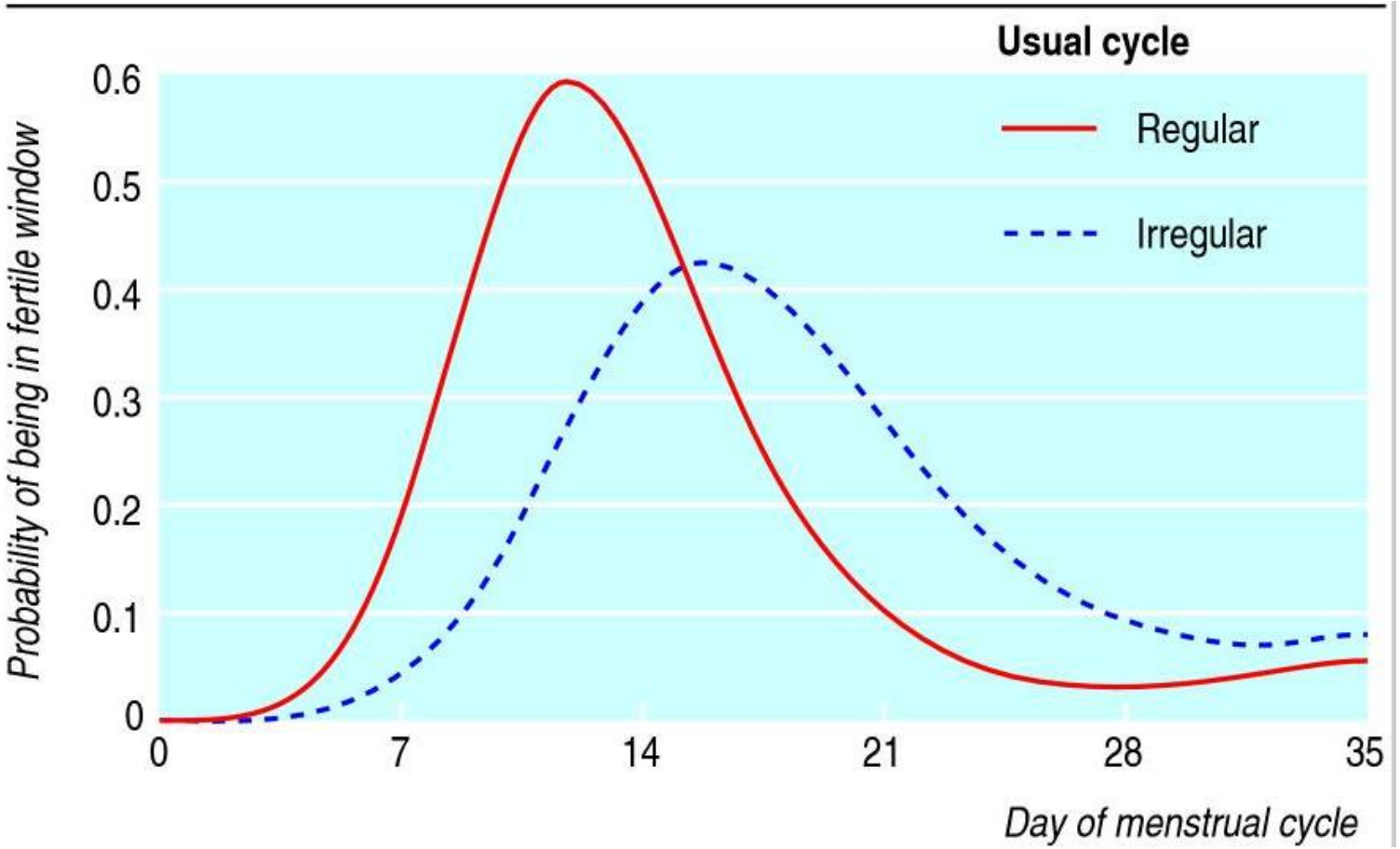
- Fertile “window” comprises the five days before ovulation and the day of ovulation
- As the day of ovulation varies from cycle to cycle, so does the timing of the six fertile days
- Reliable methods to predict ovulation are lacking, and most tools predicting the fertile window are unreliable

- On average, at least 10% of women with regular cycles were in their fertile window on any given day of their cycle between days 6 and 21.
- Only 10% of women ovulated 14 days before the onset of menses

BMJ. 2000 Nov 18; 321(7271): 1259–1262.
doi: 10.1136/bmj.321.7271.1259
PMCID: PMC27529
PMID: 11082086

The timing of the “fertile window” in the menstrual cycle: day specific estimates from a prospective study

Allen J Wilcox, branch chief,[a] David Dunson, investigator,[b] and Donna Day Baird, senior investigator[a]



REPRODUCTIVE GENETIC CARRIER SCREENING

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Carrier Screening

Information about carrier screening should be offered to all women or couples during pre-conception and early in the pregnancy (ie first trimester).

The decision to have screening is a personal choice to be made by the woman or couple

RANZCOG Consensus Statement on Carrier Screening

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Excellence in Women's Health

Genetic carrier screening

This statement has been developed and reviewed by the Genomics Advisory Working Group & Women's Health Committee and approved by the RANZCOG Board and Council.

A list of Women's Health Committee Members & Genomics Advisory Working Group can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

Disclaimer This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

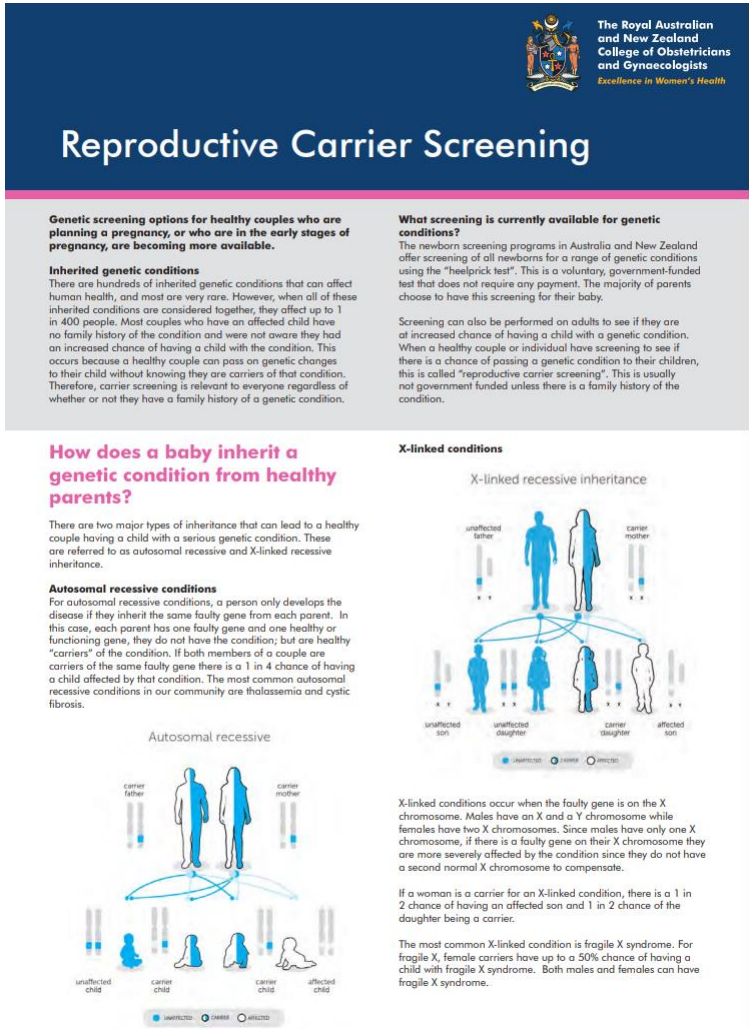
First endorsed by RANZCOG: March 2019
Current: March 2019
Review due: March 2022

Objectives: To provide health professionals with advice on the counselling of women and couples prior to and in the early stages of pregnancy in relation to genetic carrier screening.
Target audience: All health professionals providing care to women and couples prior to and in the early stages of pregnancy.

Values: The evidence was reviewed by the Women's Health Committee (RANZCOG), and applied to local factors relating to Australia and New Zealand.

Background: This statement was first developed by the Genomics Advisory Working Group & Women's Health Committee in March 2019.

Funding: The development and review of this statement was funded by RANZCOG.



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Reproductive Carrier Screening

Genetic screening options for healthy couples who are planning a pregnancy, or who are in the early stages of pregnancy, are becoming more available.

Inherited genetic conditions
There are hundreds of inherited genetic conditions that can affect human health, and most are very rare. However, when all of these inherited conditions are considered together, they affect up to 1 in 400 people. Most couples who have an affected child have no family history of the condition and were not aware they had an increased chance of having a child with the condition. This occurs because a healthy couple can pass on genetic changes to their child without knowing they are carriers of that condition. Therefore, carrier screening is relevant to everyone regardless of whether or not they have a family history of a genetic condition.

What screening is currently available for genetic conditions?
The newborn screening programs in Australia and New Zealand offer screening of all newborns for a range of genetic conditions using the "heelprick test". This is a voluntary, government-funded test that does not require any payment. The majority of parents choose to have this screening for their baby.

Screening can also be performed on adults to see if they are at increased chance of having a child with a genetic condition. When a healthy couple or individual have screening to see if there is a chance of passing a genetic condition to their children, this is called "reproductive carrier screening". This is usually not government funded unless there is a family history of the condition.

How does a baby inherit a genetic condition from healthy parents?

There are two major types of inheritance that can lead to a healthy couple having a child with a serious genetic condition. These are referred to as autosomal recessive and X-linked recessive inheritance.

Autosomal recessive conditions
For autosomal recessive conditions, a person only develops the disease if they inherit the same faulty gene from each parent. In this case, each parent has one faulty gene and one healthy or functioning gene, they do not have the condition; but are healthy "carriers" of the condition. If both members of a couple are carriers of the same faulty gene there is a 1 in 4 chance of having a child affected by that condition. The most common autosomal recessive conditions in our community are thalassemia and cystic fibrosis.

Autosomal recessive

X-linked conditions

X-linked recessive inheritance

X-linked conditions occur when the faulty gene is on the X chromosome. Males have an X and a Y chromosome while females have two X chromosomes. Since males have only one X chromosome, if there is a faulty gene on their X chromosome they are more severely affected by the condition since they do not have a second normal X chromosome to compensate.

If a woman is a carrier for an X-linked condition, there is a 1 in 2 chance of having an affected son and 1 in 2 chance of the daughter being a carrier.

The most common X-linked condition is fragile X syndrome. For fragile X, female carriers have up to a 50% chance of having a child with fragile X syndrome. Both males and females can have fragile X syndrome.

Genetic Panels

The panels that are offered by providers include

- Core – 3 gene panel: CF, SMA, Fragile X – **Covered by Medicare**
- Expanded panel – 250+ genes
- Comprehensive panel – 500+ genes

} **– No reduction in cost**

Can either be a saliva or blood test

Test turnaround 2 – 6 weeks

eugene

Sonic Genetics

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Comparison between the panels

Test Details*	3 Gene Screen Limited Screen	500+ Gene Screen Expanded Carrier Screening
What is tested	3 common genetic conditions • Cystic fibrosis (CF) • Fragile X syndrome (FXS), • Spinal muscular atrophy (SMA)	3 common conditions + 250 - 500 childhood-onset severe genetic conditions
Cost	Bulk Billed – Medicare rebate if eligible	$1200 per couple
Who is tested	Biological female first	Both members of reproductive couple at the same time
When	Pre-conception or ideally before 12 weeks pregnancy	Pre-conception or ideally before 12 of weeks pregnancy
Chance of being a carrier	~ 1 in 20 (5%) of individuals will be reported as a healthy carrier	~ 2 in 3 (~60%) of individuals will be reported as a healthy carrier of at least one of the conditions screened
Chance of high-risk result	~ 1 in 240 (0.4%) reproductive couples tested will be reported as increased risk of having a child affected with one of the 3 conditions screened	~ 1 in 50 (~2%) couples tested will be reported as increased risk of having a child affected with one of the conditions screened

Increased Risk Result

- If the woman was only tested, then important to test the partner

- Couples who are identified as carriers (especially before pregnancy) may be offered options
  - Not to have children as a couple
  - Adoption
  - Take your chances and consider prenatal diagnostic testing with CVS or amniocentesis
  - In-vitro fertilisation (IVF) with pre-implantation genetic testing (PGT)
  - Use of donor gametes (donor without the affected gene)

- Karyotype in both
- Genetic counselling is strongly recommended

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Embryo Testing – PGT Terminology

- The new name for all tests now is Preimplantation Genetic Testing (PGT)

- Under the PGT umbrella, there are three categories:
  - PGT for aneuploidies (PGT-A) – Previously PGS
  - PGT for monogenic/single gene defects (PGT-M) – Previously PGD
  - PGT for chromosomal structural rearrangements (PGT-SR) – Previously PGS translocation

- Sex selection for “family balancing” is not possible in Australia
- But available for a genetic sex-linked condition

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Genetic Conditions Tested

- Any genetic condition that there is an identifiable genetic defect could be tested
- Most common conditions for which PGT-M is performed
  - Cystic Fibrosis
  - Spinal Muscular Atrophy
  - Huntington Disease
  - Beta-Thalassemia
  - Fragile X
  - BRCA
  - Muscular Dystrophies

Preimplantation Genetic Testing

There are 3 types of preimplantation genetic testing (PGT).
All require in vitro fertilization (IVF).

PGT-M
monogenic

formerly known as PGD
for single gene disorders

EXAMPLES: cystic fibrosis, BRCA, Huntington's disease

PGT-A
aneuploidy

formerly known as PGS or CCS

screens for the presence of all 46 chromosomes

PGT-SR
structural rearrangements

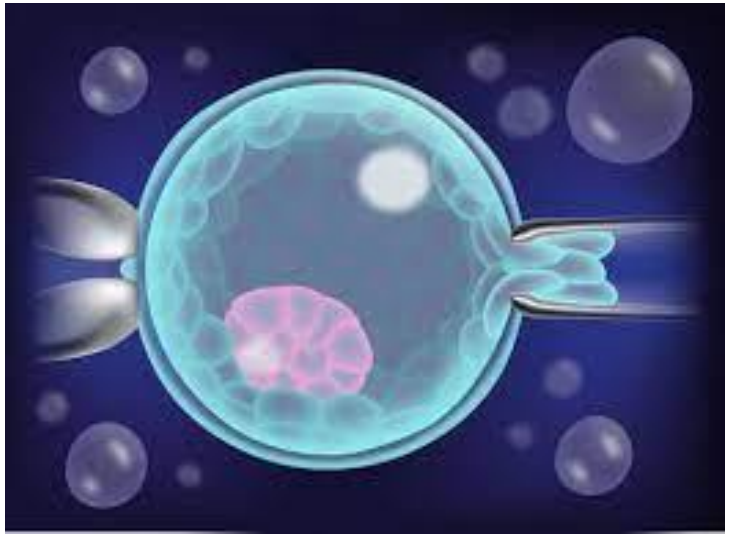
formerly known as PGD
for chromosome rearrangements

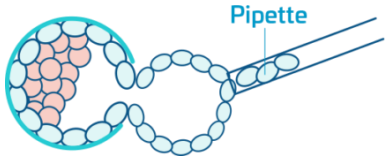
EXAMPLES: chromosome translocations, inversions

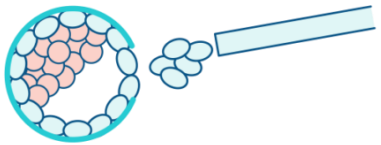
PGT Workflow

Day 5 *(200-300 cells in total)* **biopsy**

2-9 cells from trophectoderm







Embryo Testing Process

- Couple need to undertake an IVF-stimulated cycle
- Eggs collected and fertilised and hopefully embryos develop

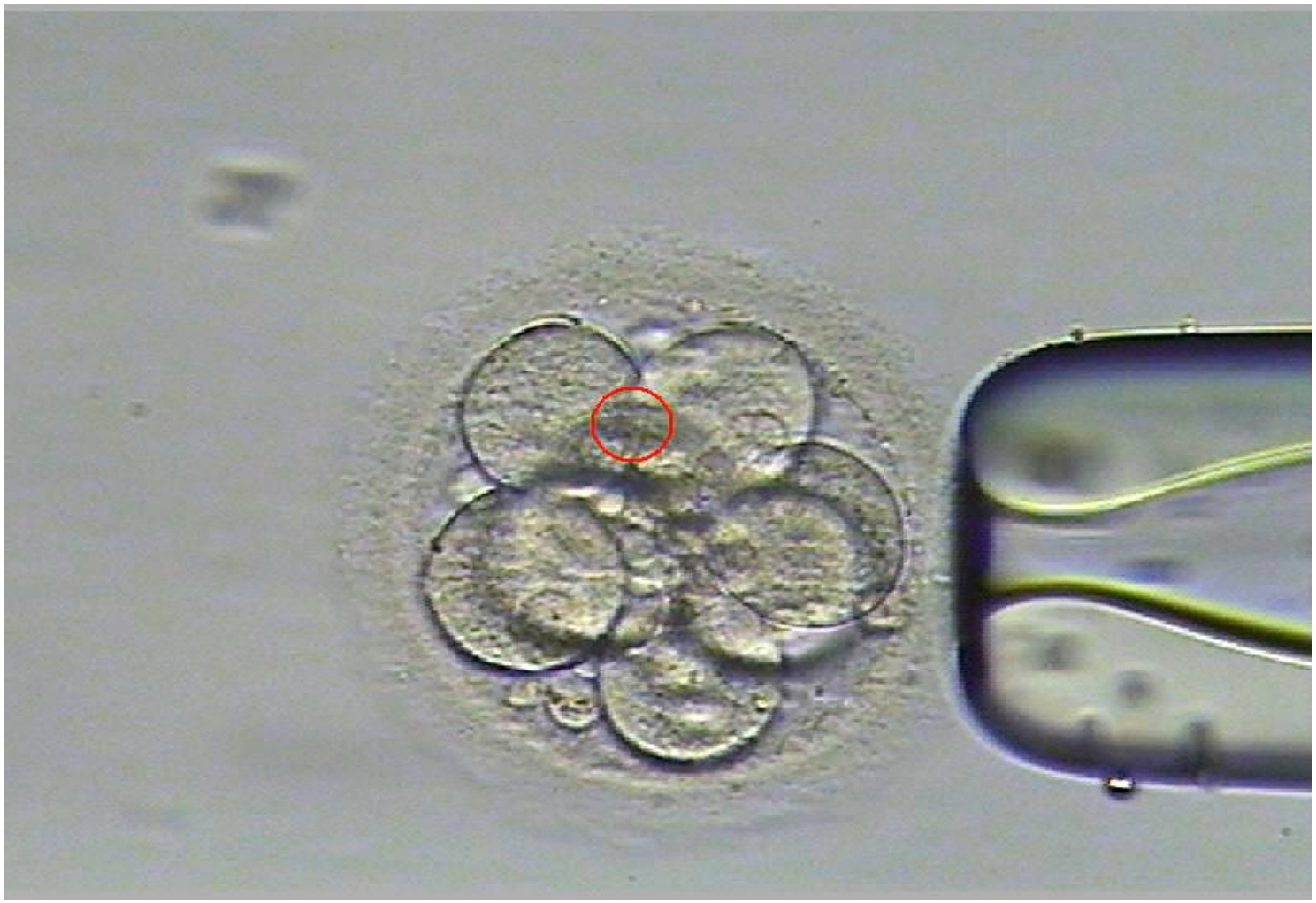
- Assisted hatching is started on day 3
- Embryo biopsy usually occurs on days 5-6
- Usually, 5-10 cells are removed
- The cells that are removed are the trophectoderm cells

- Tested embryos are vitrified and awaiting their results

- Next Generation sequencing (NGS) is performed – takes about 2 weeks

- Suitable embryos (if any) are then transferred on a future appropriate frozen embryo transfer cycle

Preparation for Embryo Hatching



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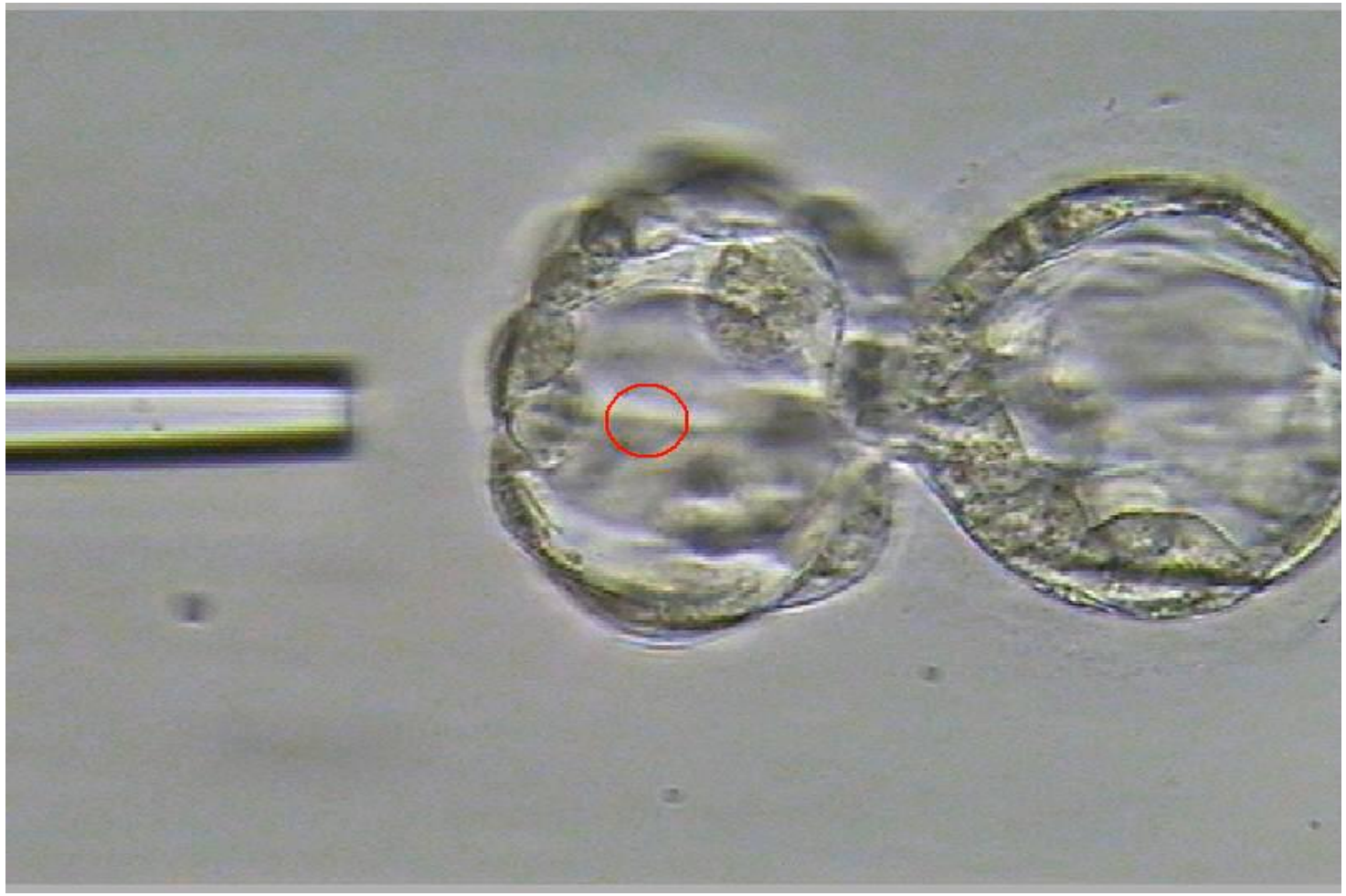
Embryo Biopsy



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Issues

- If the embryo doesn't hatch, then it can't be biopsied

- Reflective of the trophectoderm cells (which make the placenta) and not the inner cell mass (embryo)

- Magnification process fails
- No suitable embryos for transfer
- Embryo does not survive the biopsy (rare) or the thawing process (5%)

- Does not take the place of CVS or Amniocentesis in pregnancy
- Legally, we cannot transfer an embryo that has been tested and regarded as abnormal – they will be discarded

- Costs

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Medicare Rebates for PGT-M / PGT-SR

Medicare Clause 2.7.3A

A patient is eligible for a service described in any of items 73384 to 73387 only if:

(a) the patient or the patient's reproductive partner:

i) has an identified gene variant that places the patient at risk of having a pregnancy affected by a Mendelian or mitochondrial disorder; or

ii) is at risk of an autosomal dominant disorder, which places the patient at risk of having a child who develops

the autosomal dominant disorder, or

iii) has a chromosome re-arrangement or copy number variant, which places the patient at risk of having a pregnancy affected by a chromosome disorder, and

(b) there is no curative treatment for the disorder, and there is a severe limitation of quality of life despite contemporary management of the disorder, and

(c) the patient has previously had a consultation with a specialist or consultant physician practising as a clinical geneticist that included a discussion about the disorder.

No Medicare benefits for PGT-A

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Costs for PGT-M

Description	Prices	Medicare rebate	Out of Pocket Cost	Comments
Clinical Geneticist consultation	$475.00	$249.40	$225	Partner bulk billed for appointment
Work up	$2700.00	$1642.80	$1057.20	
Embryo biopsy	$395.00	$103.45	291.55	
PGT Testing on One embryo	$950.00	$541.80	$408.20	
PGT Testing on two embryos	$1900.00	$1176.80	$723.20	
PGT Testing on Three embryos	$2850.00	$1811.80	$1038.20	
PGT Testing on Four embryos	$3800.00	$1811.80	$1988.20	The fourth embryo does not receive Medicare benefit
PGT Testing on Five or more embryos	$4500.00	$1811.80	$2688.20	Capped Price (5th embryo charged at $700)

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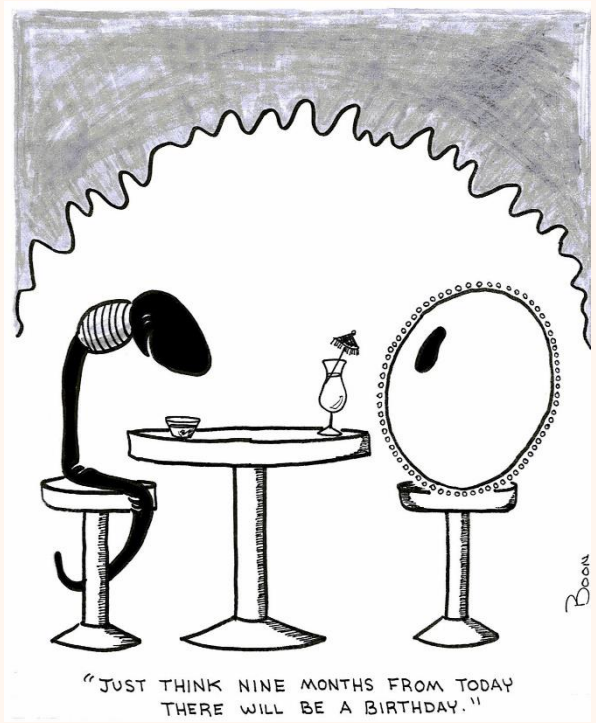
FEMALE AGE AND FERTILITY



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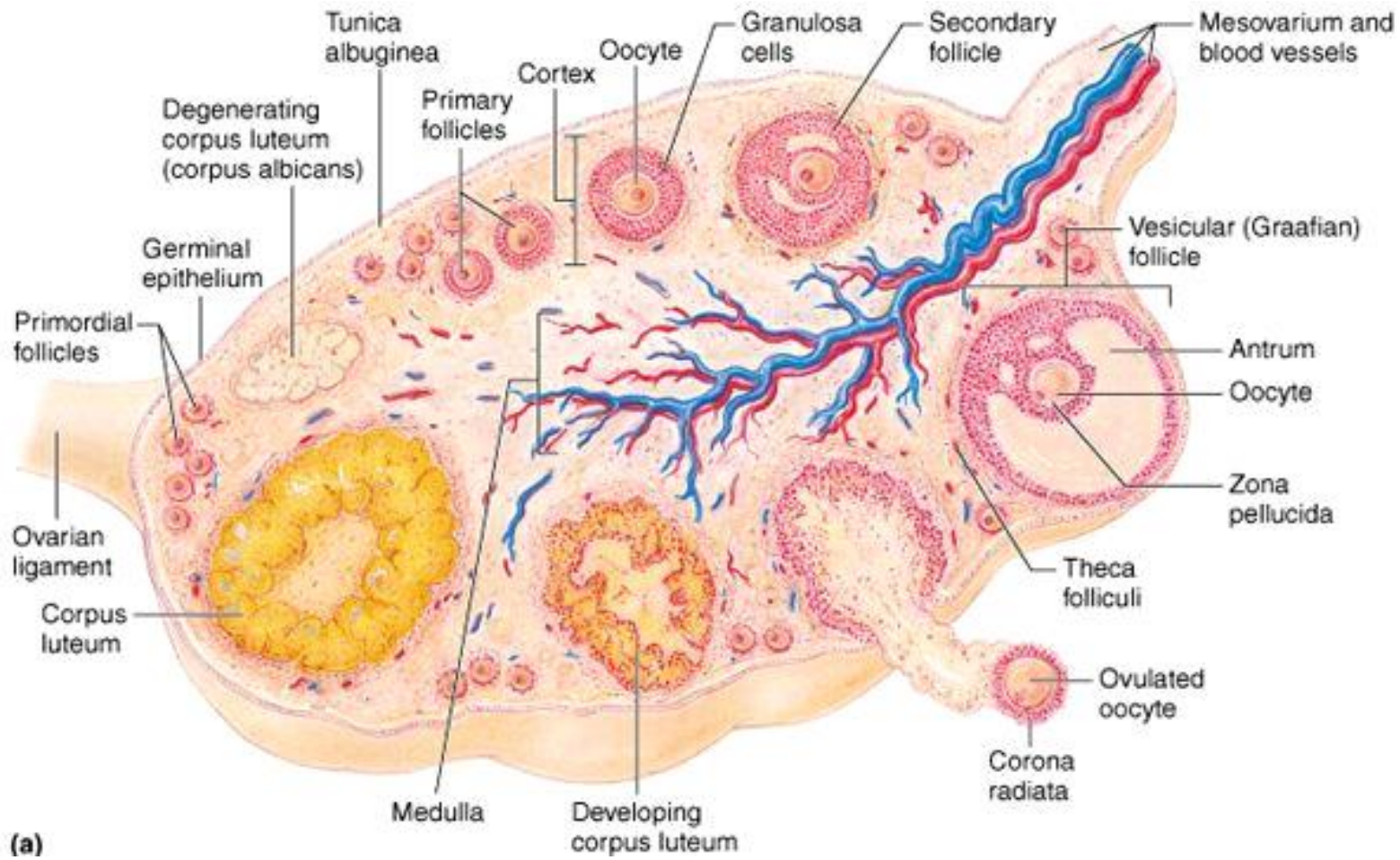
Ovary



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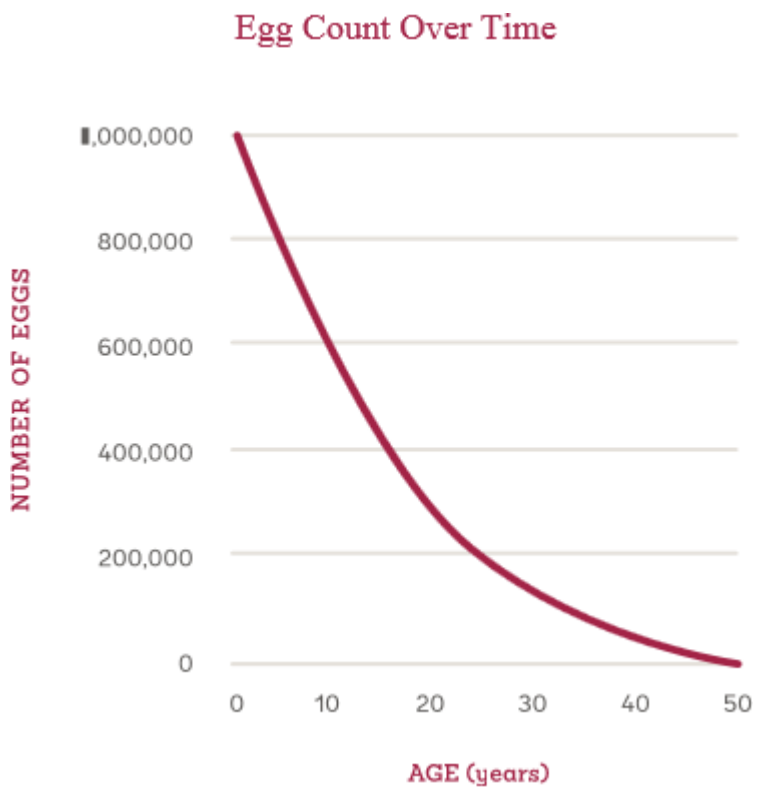
Natural History of Eggs

- Every woman is born with a finite number of eggs
- A woman possibly ovulates approx. 400 times in her life
- But there is a loss of approx. 1000 follicles per month which accelerates as you get older (at least 1 egg / hour)
- Can decline further with an insult to the ovary (e.g surgery, endometriosis or chemotherapy)
- Genetic normality of the eggs also decline over time
- Once ovulated an unfertilized egg can survive for only 12-24 hours

Egg Numbers



Age	Egg supply remaining
Puberty	50%
25	22%
30	12%
35	5%
40	3%
45	1%

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Assessment of Ovarian Reserve

- Day 3 serum follicle-stimulating hormone (FSH)
- Anti-Mullerian Hormone (AMH)
- Antral follicle count and ovarian volume

- Best done around days 2 – 6 of her cycle

- Decreased ovarian reserve (DOR) is associated with
  - lower oocyte quantity and quality, and reproductive potential
  - poor response to gonadotrophins
  - poor embryo quality,
  - increased miscarriage

- Ovarian reserve may be reduced even if ovulatory

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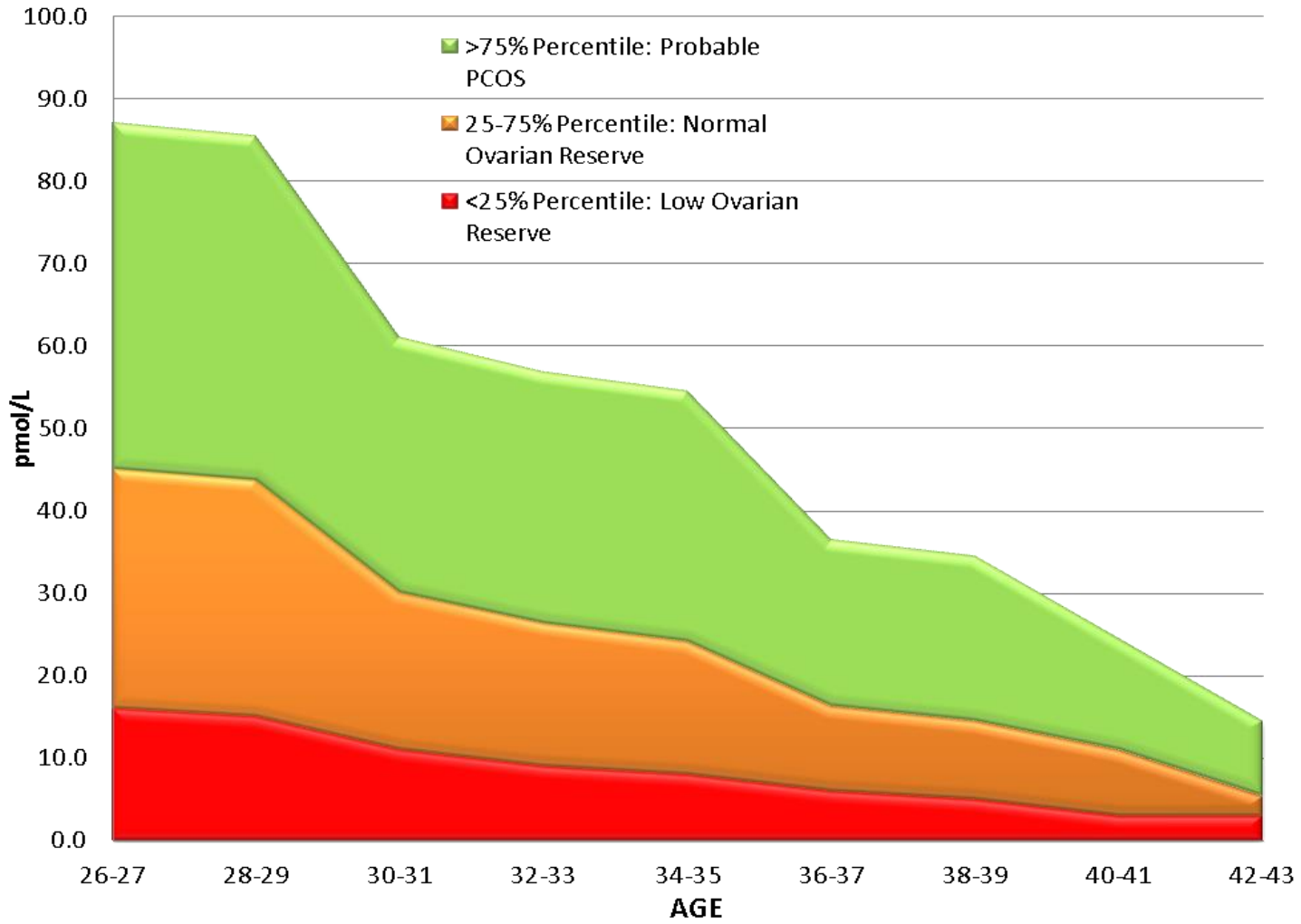
Anti-Mullerian Hormone (AMH)

- Is a glycoprotein
- AMH is produced by the granulosa cells of the small preantral and early antral follicles (<8mm) in the ovary
- Primary function of AMH is to inhibit the transition of primordial follicles into a growing follicle
- AMH levels are elevated 2-3 x in PCOS (surrogate marker)
- AMH declines with increasing age with the declining number of antral follicles
- AMH becomes undetectable about 3-5 years before menopause
- Not covered by Medicare – cost approx. $90-$100

AMH Values with Age



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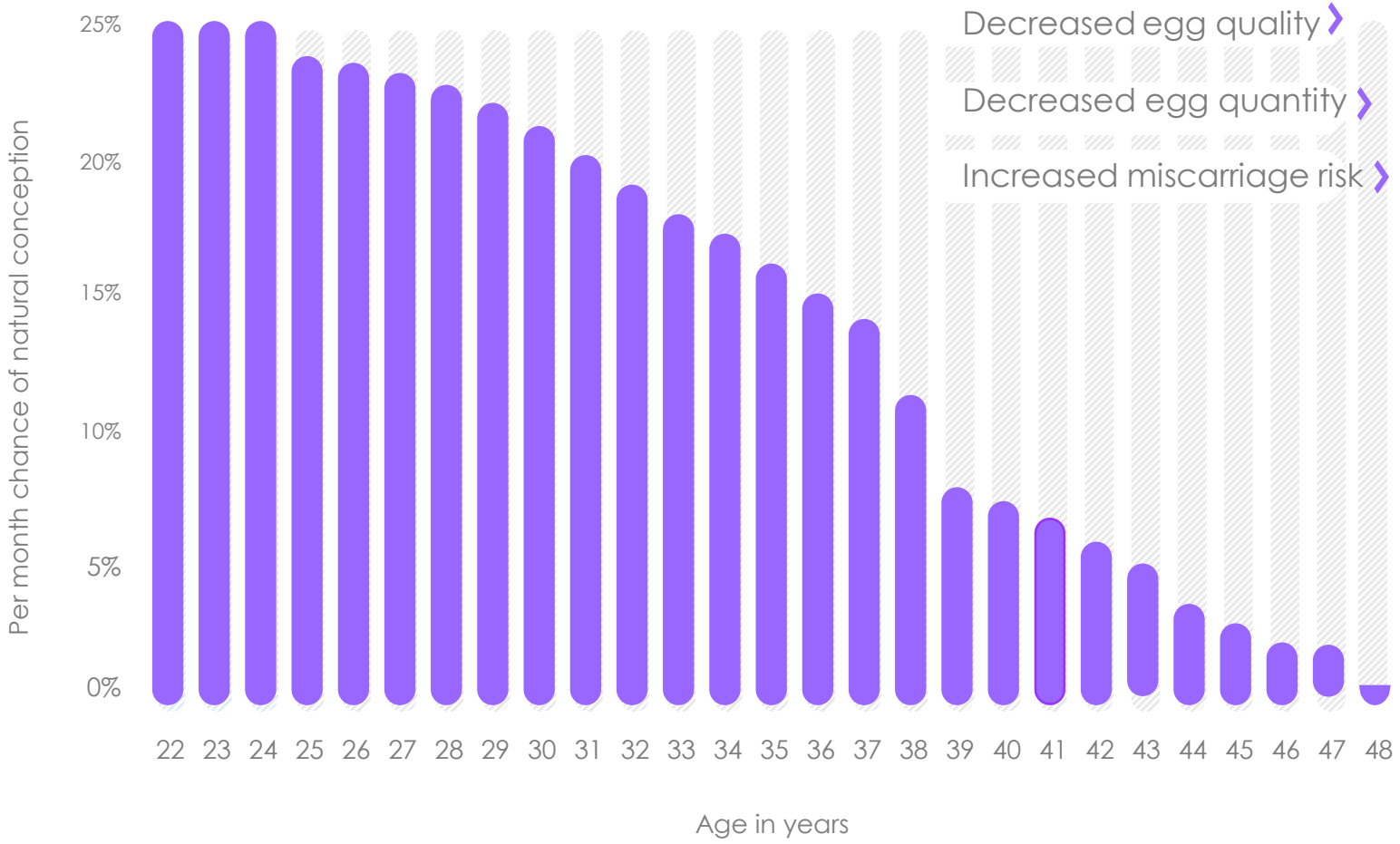
AGE AND FERTILITY



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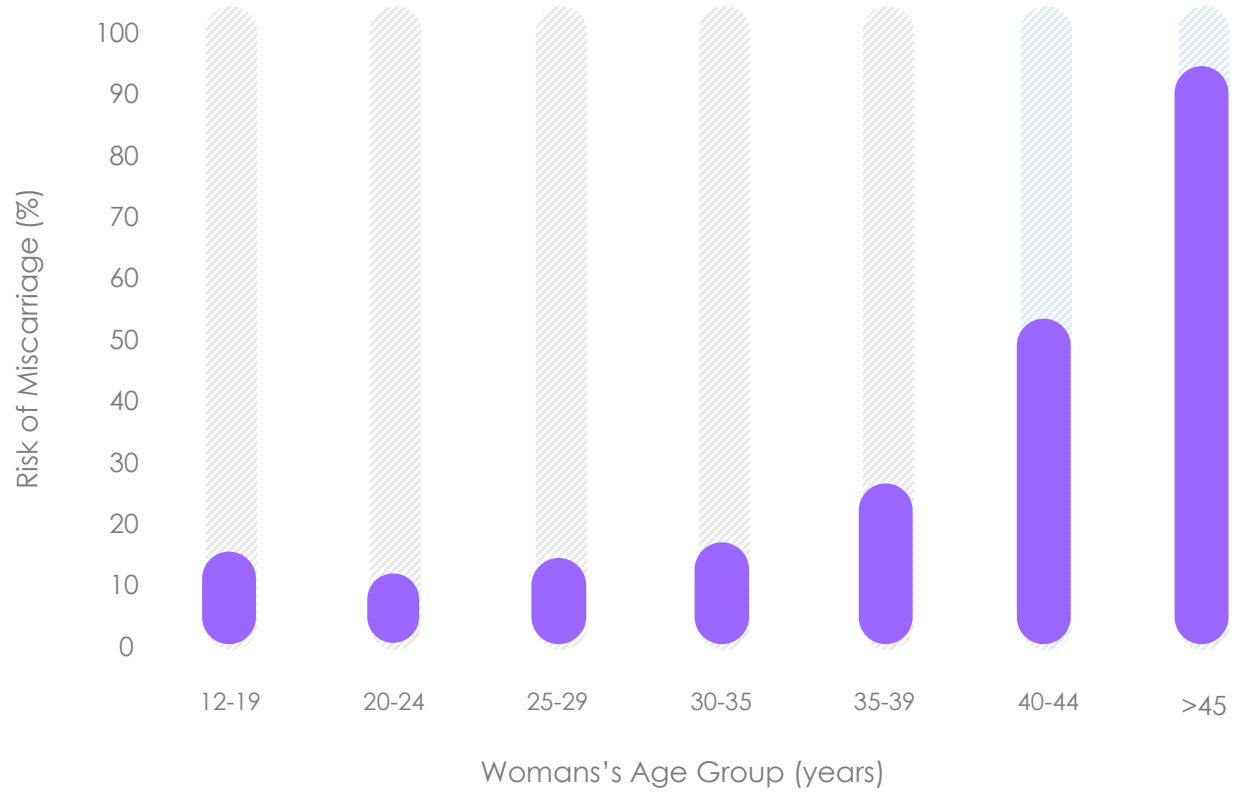
RISK OF MISCARRIAGE BY AGE



Live Birth Rate per IVF cycle

BY AGE

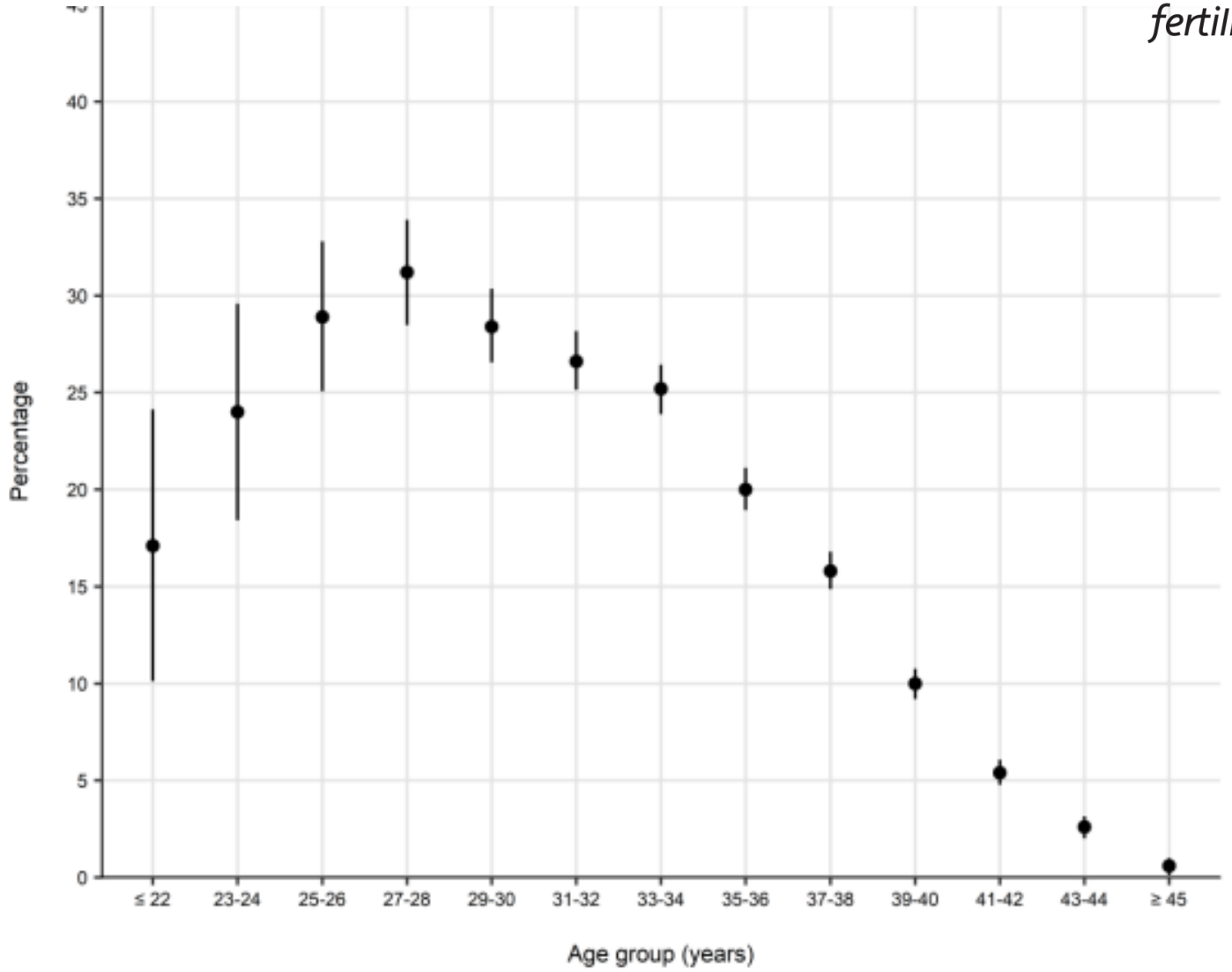
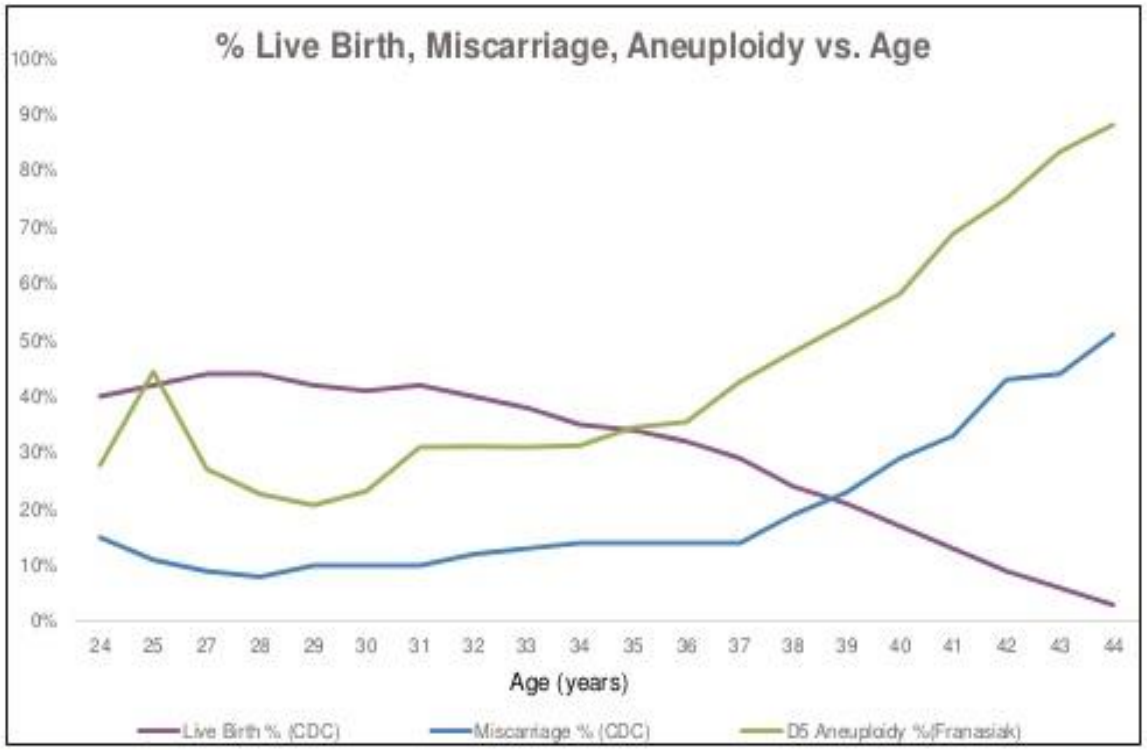


Figure 3: Live birth rate (with 95% confidence intervals) per initiated autologous fresh cycle (excluding freeze-all) by female patient's age at start of a treatment cycle, Australia and New Zealand, 2020

Age Related Decline in Fertility

Maternal Age, Aneuploidy, and Fertility



Aneuploidy is a major cause of the age-related decline in fertility[1,2]

1. CDC. 2013 ART National Summary Presentation, http://www.cdc.gov/art/reports/2013/national-summary.html; Figures 14-16
2. Franasiak JM, Forman EJ, Hong KH, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Steril. 2014;101(3):656-663.e1.

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Advancing Maternal Age

- The decline in live-birth rates with advancing maternal age (primarily due to a decline in oocyte quality) mirrors the drop in serum AMH seen with advancing age
- As AMH is produced by the ovary and is known to play a role in oocyte physiology, AMH may provide a useful non-invasive insight into oocyte quality
- The “bottom of the barrel” hypothesis of oocyte quality suggests the best quality oocytes ovulate first, leaving the poor quality oocytes left at the end
- This doesn’t seem to hold true for the younger woman (<32 yrs old) but does in the older woman
- **Age is still the biggest predictor of oocyte quality**

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Genetically Abnormal Embryos

Table 2
Risk of aneuploidy by maternal age

Maternal Age at EDD (y)	Risk of Trisomy 21	Risk of Other Chromosomal Abnormality
20	1:1480	1:525
25	1:1340	1:475
30	1:940	1:384
35	1:353	1:178
40	1:85	1:62
45	1:35	1:18

Abbreviation: EDD, estimated date of delivery.

Adapted from Practice bulletin no. 163: screening for fetal aneuploidy. Obstet Gynecol 2016;127(5):e124.

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Ages	Number of genetically abnormal embryos
25–30	25%
31–35	35%
35–37	45%
38–40	60%
41–43	80%
≥44	≥80–90%

Australian Bureau of Statistics

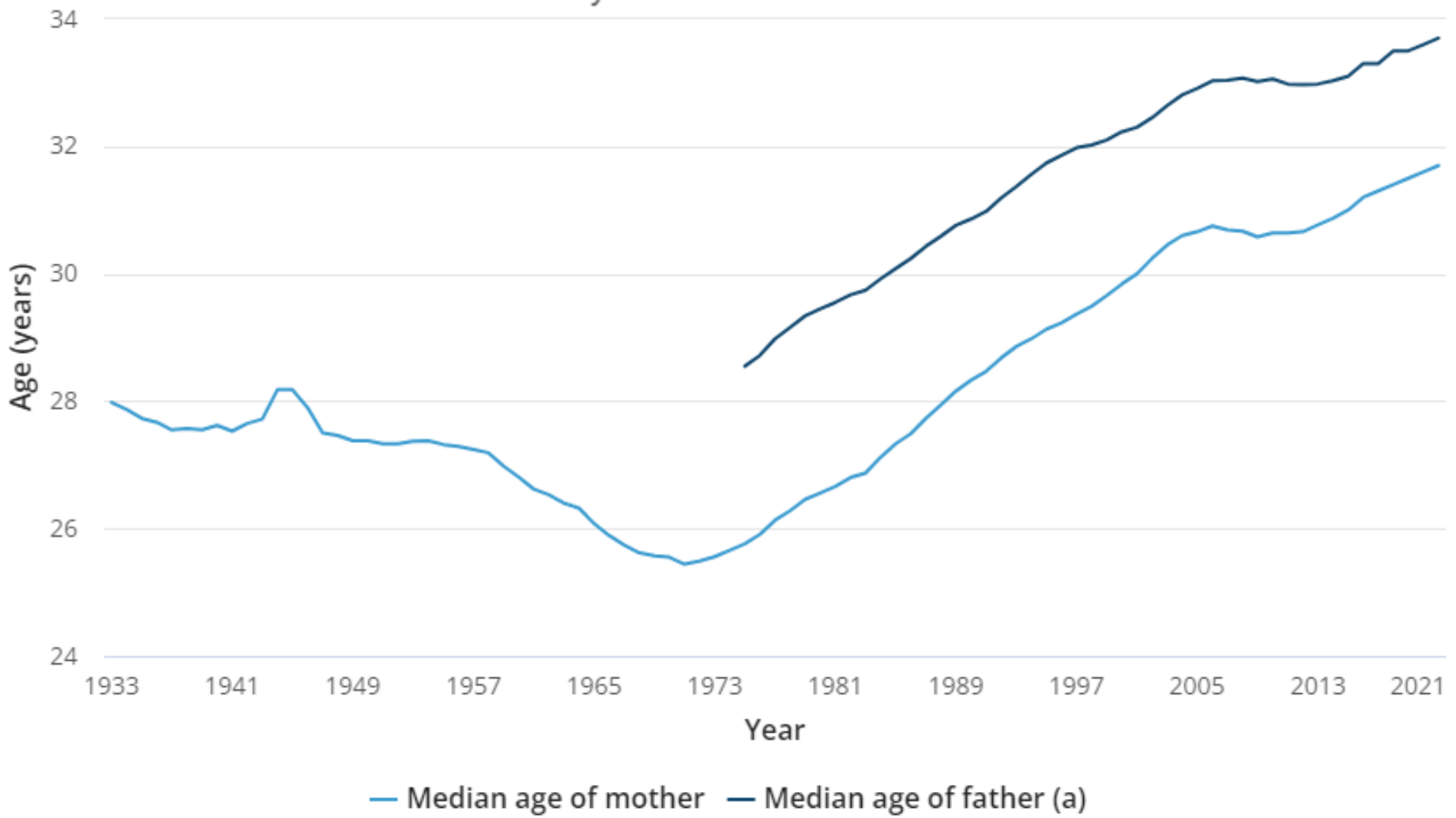
Statistics

Home › Statistics › People › Population › Births, Australia › 2021

Median age of parents 1933 - 2021

For births registered in 2021, the median age of:

- mothers was 31.7 years
- fathers was 33.7 years.



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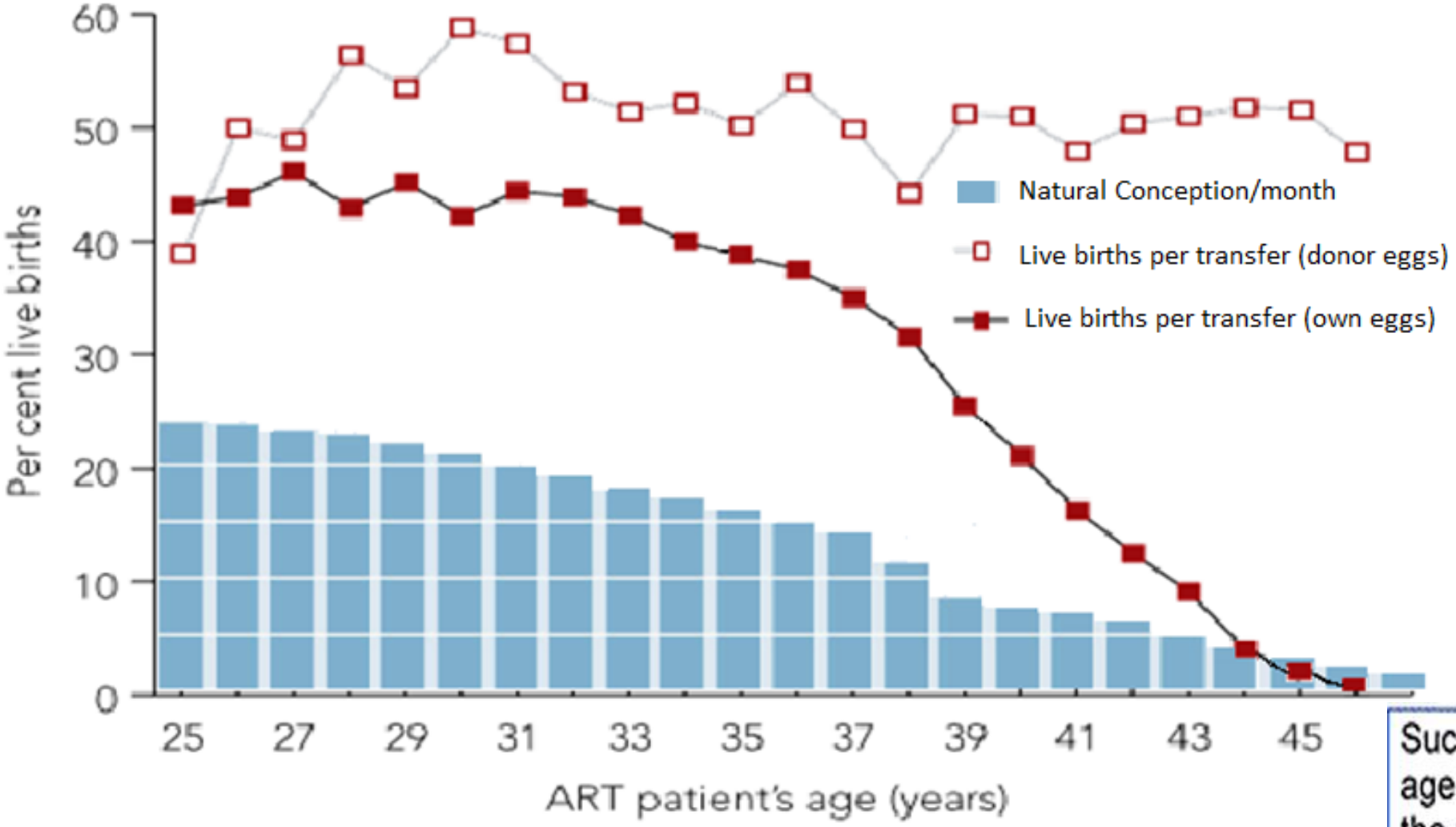
What about the uterus?



Successful live birth is dependent on the age of the eggs used, not on the age of the mother. Women in their 40s can achieve the same pregnancy success as 25-year-olds if they use donor eggs that are provided by younger women — or their own younger, preserved eggs

2003 Assisted reproductive technology success rates: national summary and fertility clinic reports.

Advanced Maternal Age

Women planning pregnancy at advancing reproductive age should know:

- It may take longer to become pregnant
- Higher chance of conceiving a multiple dizygotic pregnancy
- Have a higher risk of miscarriage
- Higher risk for offspring with chromosomal abnormalities
- Worsening of any existing medical conditions

- They may have more complications with the pregnancy
    - Pre-eclampsia / gestational hypertension
    - Gestational diabetes
    - Preterm delivery / fetal growth restriction
    - LSCS for delivery

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Advanced Maternal Age

- Advanced female age is a well-established risk factor for female subfertility, fetal anomalies, stillbirth, and obstetric complications ***Nybo Andersen et al.,*** *2000;* ***Sauer,*** *2015*

- Women should be sensitively informed of the risk of pregnancy loss:
  - Lowest in women aged 20 to 35 years
  - Rapidly increases after the age of 40 years

Computer Simulation Fertility Model ***Habbema et al.,*** *2015*

- To achieve a two-children family -> couples should start trying to conceive when the female partner **≤ 31 years** or **no later than 27 years if IVF is not an option** (at least 90% chance)

- To achieve a one-child family -> couples should start trying to conceive when the female partner **≤ 35 years** or **no later than 32 years if IVF is not an option**

Increasing male age is significantly associated with the incidence of miscarriage/ infertility/ ASD (40+)

Outdated terms

- Elderly primigravidae (Elderly primip)
- Geriatric pregnancy

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Identified as Decreased Ovarian Reserve (DOR)

- Bring forward plans to start a family
- Earlier referral to fertility unit
- Annual serum AMH checks to monitor rate of decline in ovarian reserve
- Early consideration of oocyte freezing if the decline is rapid and the woman is not in a social position to start a family
- Donor sperm – if single

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Ovarian Failure

- High FSH, LH and low E2, undetectable AMH
- Normal prolactin and thyroid function

- In premature ovarian failure or DOR further investigations
  - Karyotype
  - Fragile X
  - autoantibody screen

- Treatment options
  - counselling
  - donor oocyte / embryo programme
  - estrogen replacement therapy

MALE FERTILITY

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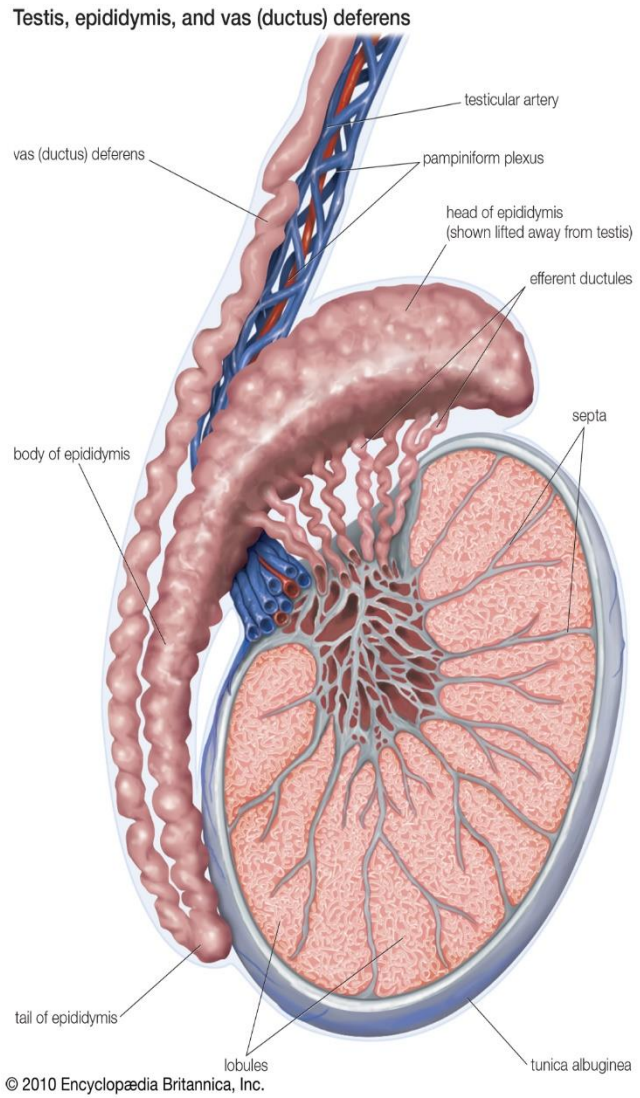
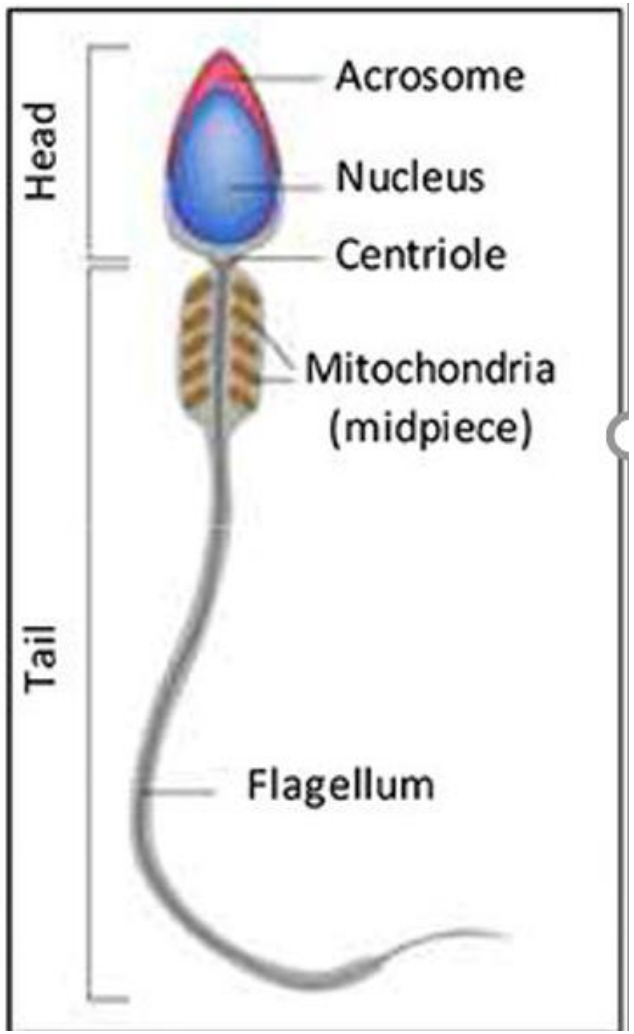
Sperm





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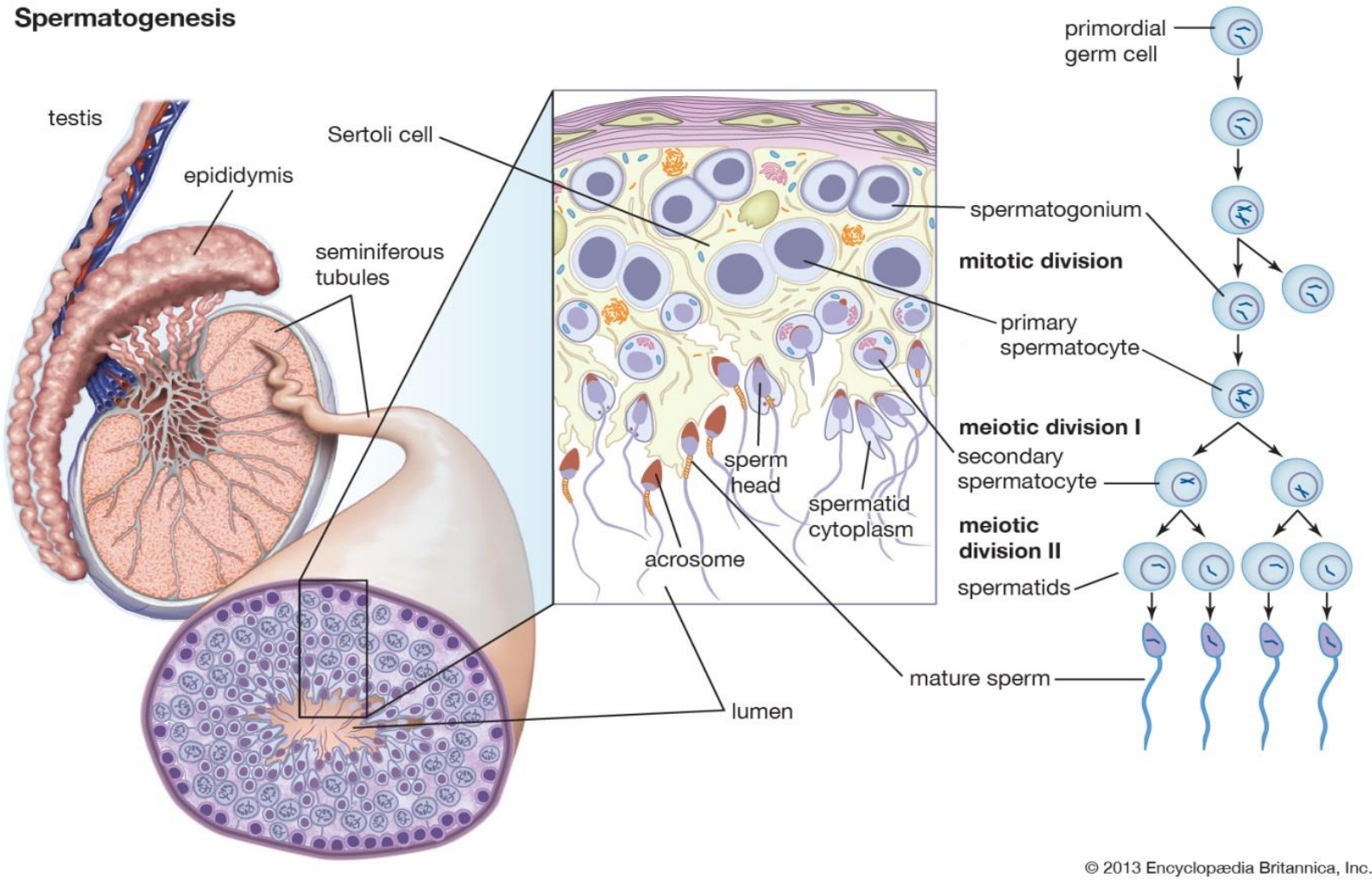
Life Span of Spermatozoa

- Potentially sperm production occurs from puberty to death
- Produced in the testis (plural testes) or testicle
- Human sperm are about 70 µm long
- Testes are found in the scrotum outside the body as spermatogenesis works best at 2-8 degrees C below core body temperature
- 60 – 75 days for sperm production
- 10 -14 days in the epididymus (maturation and storage)
- Makes up only 2-5% of the total semen volume
- 60% from the seminal vesicles and 30% from the prostate
- Sperm can still be viable in the female reproductive tract on average up to 3 days; Rarely up to 5 days

Spermatogenesis



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Semen Analysis

- Cornerstone of the assessment of the male partner
- It Can be difficult to convince a partner to have a test
- “Its not me”, “I got my previous girlfriend pregnant”
- There may be religious or psychological reasons as well
- Collection of semen sample
  - Abstain for 3 days prior
  - Ideally produced by masturbation
  - Keep sample at body temperature
  - Deliver to lab within 1 hour of collection
- Other Methods;
  - Withdrawal method – requires good control
  - Condom – non latex and no spermicidal, cost $40

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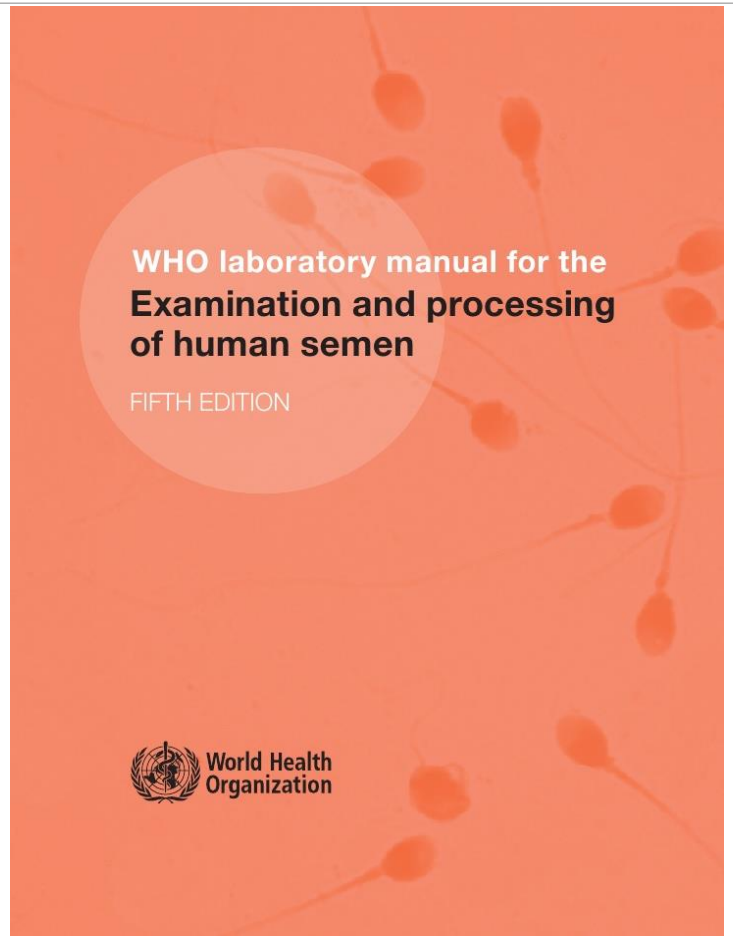
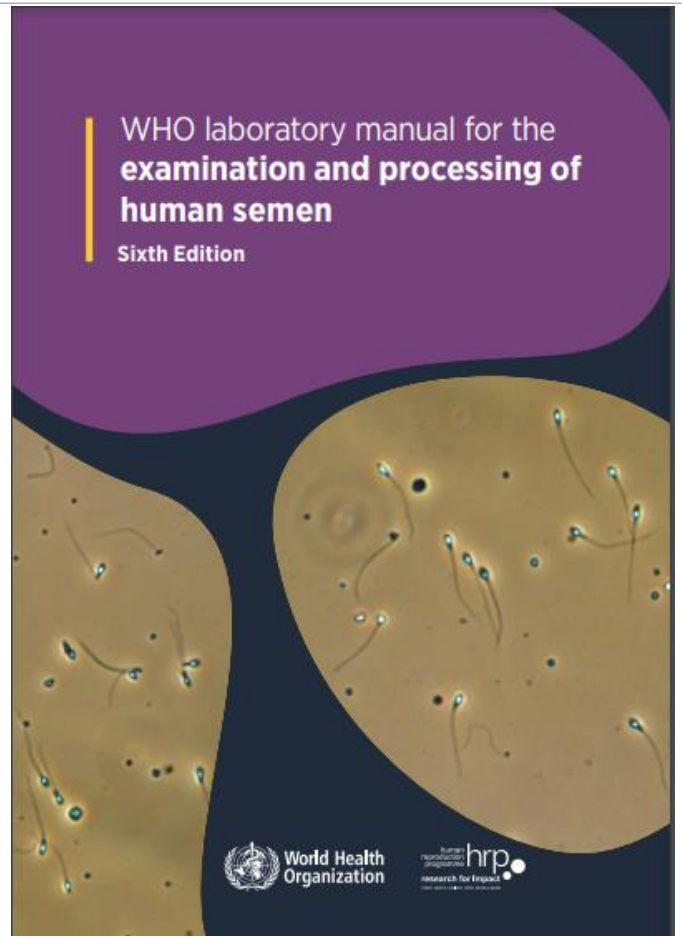
WHO Manuals



Updated in 2010



Updated in 2021

Available free online to download from the WHO website

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Comparison over the years

Cut-off reference values for semen characteristics as published in consecutive WHO manuals

Semen characteristics	WHO 1980	WHO 1987	WHO 1992	WHO 1999	WHO 2010
Volume (mL)	ND	≥ 2	≥ 2	≥ 2	≥ 1.5
Sperm count (10^6/mL)	20-200	≥ 20	≥ 20	≥ 20	≥ 15
Total sperm count (10^6)	ND	≥ 40	≥ 40	≥ 40	≥ 39
Total motility (%)	≥ 60	≥ 50	≥ 50	≥ 50	≥ 40
Progressive motility	≥ 2	≥ 25%	≥ 25% (a)	≥ 25% (a)	≥ 32% (a+b)
Vitality (%)	ND	≥ 50	≥ 75	≥ 75	≥ 58
Morphology (%)	80.5	≥ 50	≥ 30	(14)*	≥ 4*
Leukocyte count (10^6/mL)	< 4.7	< 1.0	< 1.0	< 1.0	< 1.0

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References

How the references were obtained

	Percentile		
	5%	50%*	95%
Volume (mL)	1.5	3.7	6.8
Count (x10^6/mL)	15.0	73.0	213.0
Total count (x10^6)	39.0	255.0	802.0
% Motile	40	61	78
% Progressive motility	32	55	72
% Normal (Kruger)	4	15	44
% Alive	58	79	91

Cooper et al: World Health Organization reference values for human semen characteristics. *Hum Reprod Update* 16: 231-245, 2010

References were obtained from 1953 semen specimens from recent fathers with time to pregnancy <12 months.

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Terminology in Semen Analysis

- Normospermia – normal semen volume
- Aspermia – no semen volume (dry orgasm)
- Oligospermia – sperm conc <15 mil/ml
- Azoospermia – no spermatozoa seen
- Asthenozoospermia - <32% progressive motility
- Teratozoospermia - <4% normal morphology
- Necrozoospermia – all “dead” sperm
- Oligo-atheno-teratozoospermia (OAT) – across the board

Abnormal Semen Analysis

- If semen analysis abnormal - repeat semen analysis after 3 months
- Address all lifestyle issues
- If mild/ moderate oligozoospermic (majority) – refer to Fertility unit for consideration of IUI/IVF/ICSI
- If azoospermic / severe oligozoospermia – requires further investigations

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Investigation of Severe Semen Defect

- Hormonal
  - FSH / LH
  - testosterone
  - Prolactin
  - TSH
- Karyotype / CF mutations / Y chromosome deletions
- USS testes
- Testicular biopsy (azoospermia)

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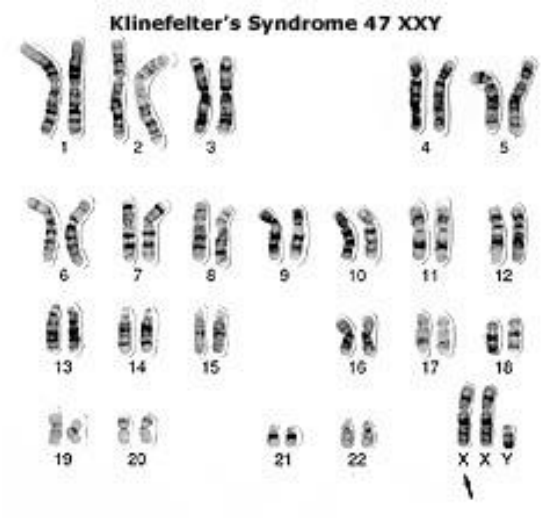
Implications

- Infertile man with abnormal semen analysis have a 20 fold greater incidence of testicular cancer when compared to the general population
- Important to do testicular self examination and report any changes

- In severe oligospermia / azoospermia
  - Chromosomal translocation – up to 15%
  - Y microdeletion up to 10-18%
  - Klinefelter Syndrome (XXY) – up to 15% of infertile male with azoospermia
  - Most commonest sex chromosome abnormality 1 in 500 males



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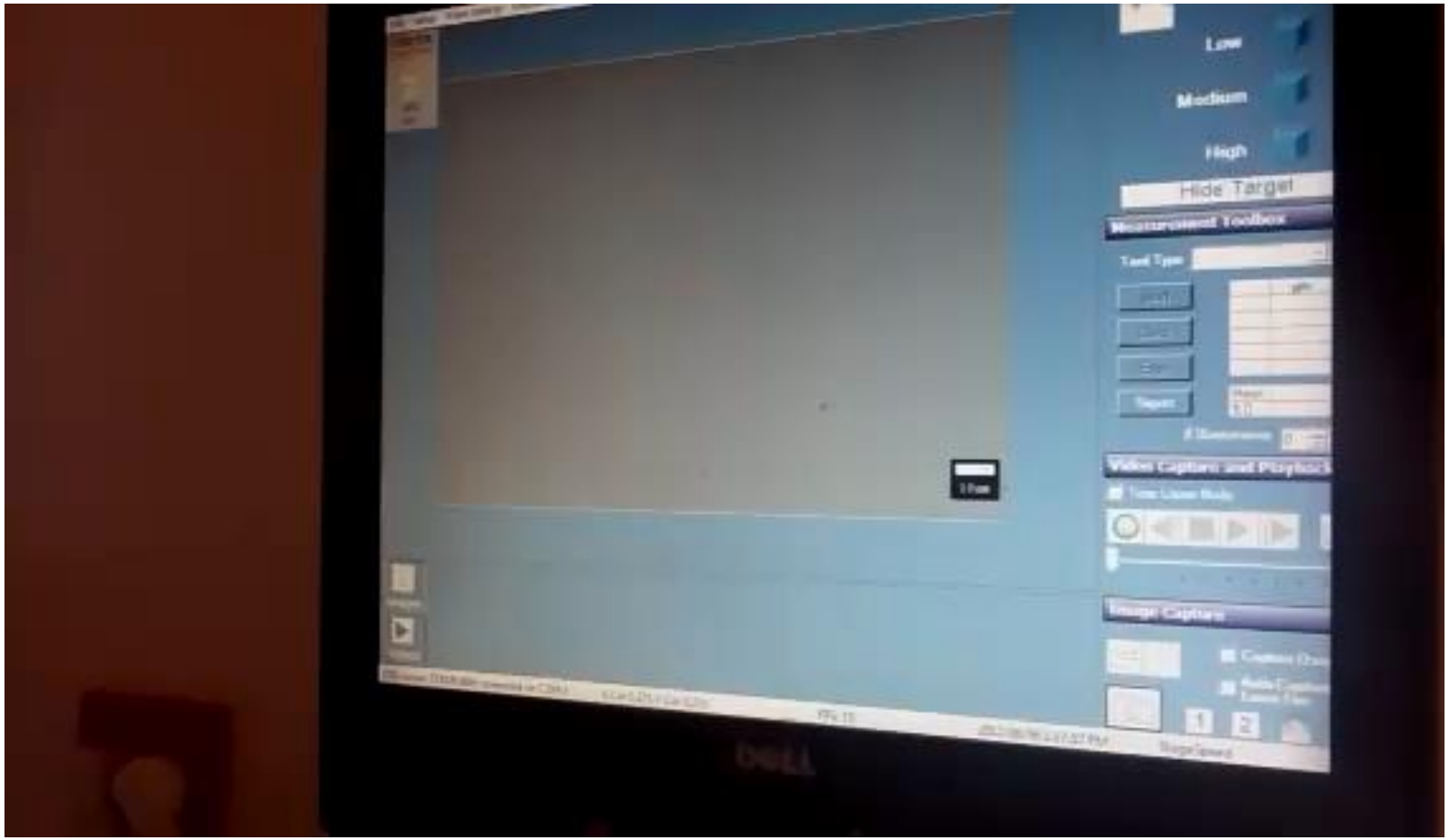
ICSI Procedure



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Effects of Age

- Male fertility decline is more subtle, but a man's age affects the chances of his (female) partner conceiving and increased miscarriage rates
- Although still low, children of older fathers have an increased risk of developing schizophrenia and other mental health disorders later in life.
- Children of fathers aged 40 or over are 5 times more likely to develop an autism spectrum disorder than children of fathers aged 30 or less.
- Accumulation of chromosomal aberrations and mutations during the maturation of male germ cells are thought to be responsible for the increased risk.

TRANSGENDER

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Incidence

In the U.S., 0.3%–2% of the population identify as transgender, although this may be grossly underestimated

The World Professional Association of Transgender Health (WPATH) estimates that worldwide, the prevalence for male-to-female individuals is 1:45,000 to 1:12,000, and for female-to-male individuals is 1:200,000 to 1:30,400; however, most of the studies used to derive these numbers are from European countries.

Several recent studies have demonstrated that transgender people do desire parenthood, or at the least wish to preserve that possibility

The first and key intervention is to preserve fertility through the cryopreservation of gametes before medical or surgical transition. In transgender men, this can be done via oocyte, embryo, or ovarian tissue cryopreservation. In transgender women, sperm freezing.

Transgender Women

- Limited studies and experience has shown that unfortunately universally the semen samples produced have been of poor quality
- This highlights the importance of discussing options with patients about parenthood options and sperm freezing preferably before starting any hormonal treatment
- Counselling needed in regards to this and that possible multiple semen samples may be required

- Gender affirming hormonal treatment (GAHT) in this setting have significant effects on fertility.
- The GAHT for transgender women most often consists of estrogen combined with continued suppression of testicular activity with or without peripheral androgen receptor blockade. With this treatment the testicles usually atrophy with a significant drop of testosterone secretion, causing sperm production to stop.

- Gender affirming surgery for transgender women includes orchidectomy, which causes irreversible sterility.

Sperm Quality

Sperm quality in transgender women before or after gender affirming hormone therapy— A prospective cohort study

Kenny A. Rodriguez-W allberg, Jakob Häljestig, Stefan Arver, Anna L. V. Johansson, Frida E. Lundberg

TABLE 3 Frequency of sperm abnormalities compared to the WHO reference population[24]

Sperm abnormality	Reference population (n = 930)	Patients without previous GAHT (n = 161)	p- value*	Patients with previous GAHT (n = 16)	p-value*
Low semen volume (<1.2 ml)	46/929 (5.0%)	7/161 (4.4%)	0.845	1/16 (6.3%)	0.561
Low sperm concentration (<9 × 10^6/ml)	47/930 (5.0%)	39/161 (24.2%)	<0.001	10/16 (62.5%)	<0.001
Low total sperm count (<20 × 10^6)	46/928 (5.0%)	35/161 (21.7%)	<0.001	8/16 (50.0%)	<0.001
Low sperm motility** (<36%)	46/928 (5.0%)	24/150 (16.0%)	<0.001	5/10 (50.0%)	<0.001

Reasons?

Although the reasons for this are unclear, hypotheses include

- Self medicating without disclosing due to fear of judgement
- Avoiding ejaculations due to risk of triggering dysphoria
- Transgender specific practices such as tucking (intentional retraction of the testes into the groin), very tight underwear to conceal the genitalia
- ??possible underlying androgen receptor polymorphism / other genetic disorders that may predispose to a gender diverse identity

Transgender Male

- Emerging field of research – but still more evidence is needed as there is a knowledge gap about how these patients respond to treatment and their experiences and outcomes with fertility preservation or IVF.

- In this cohort of patients, it is encouraging that despite the prolonged use of androgens, it does not seem to affect the overall outcomes for egg retrieval especially after stopping testosterone.

- Likely need to be off testosterone for 4 months to achieve the predicted result. But for many transgender patients, stopping androgen therapy can be both physically and psychologically distressing, especially because many experience the resumption of menses.

- Despite high androgens it does not appear to be reflected in the AMH and AFC levels. Also the ovaries do not develop a PCO appearance.

Unknowns

Impact of testosterone is still unknown but the concerns are

- Ability of ovary to respond to gonadotrophins
- Oocyte quality
- Fertilization and live birth rates
- Epigenetic impacts on the offspring

Thank you

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Questions?

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