Dr Dean Morbeck

Scientific Director

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Dr Michelle Bailey

Fertility Specialist

Fertility Associates, St Georges Hospital, Christchurch

Thursday, August 11, 2016 (Room 4)

14:00 - 16:00 WS #14: Fertility 101

16:30 - 18:30 WS #19: Fertility 101 (Repeated)

Office Gynaecology

Dr Michelle Bailey

Subspecialist in Reproductive Medicine

Obstetrician & Gynaecologist

Fertility Associates Christchurch

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Overview

- Polycystic ovarian syndrome (PCOS)
- Primary Ovarian Insufficiency (POI)
- Miscarriage
- Endometriosis

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Anna

- 30y female G0P0
- Irregular 60-120 day cycles
  - Used to be regular
  - Irregular since getting married
  - gained 20kg
- On Fluoxetine, partner complains about her loud snoring
- Facial acne, she waxes her face and abdomen
- Mother and sister both have had similar problems
- Day 2 FSH 5 LH 15 E2 150 Testosterone **3**
- Day 5 TVUS pelvis: >12 follicles 2-9mm in both ovaries

What's the most likely diagnosis? PCOS

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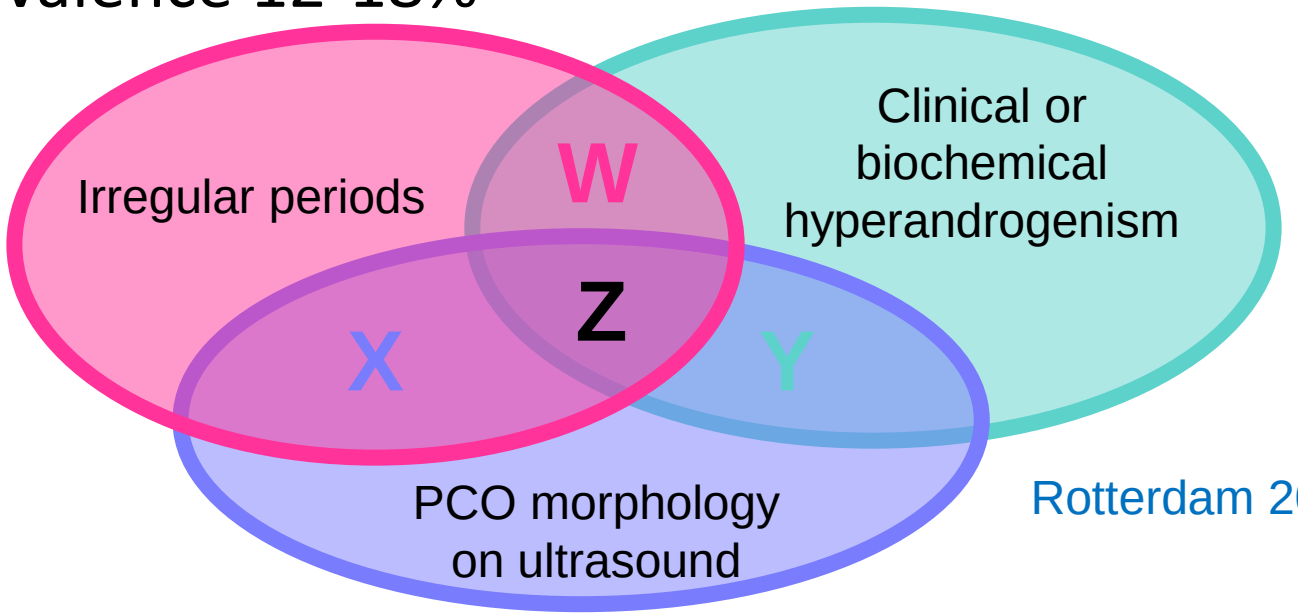
Polycystic Ovarian Syndrome (PCOS)

- Prevalence 12-18%



Rotterdam 2003

Practice point:

PCOS = variety of phenotypes & mx should be individualised

Polycystic Ovarian Morphology (PCOM)

- 20-25% of healthy women
- 68% of adolescents
- Also found in other endocrine conditions assoc with excess androgens or prolactin

Mortenson 2006, Blank 2008, Hickey 2011

Practice point:

PCOM ≠ PCOS and vice versa

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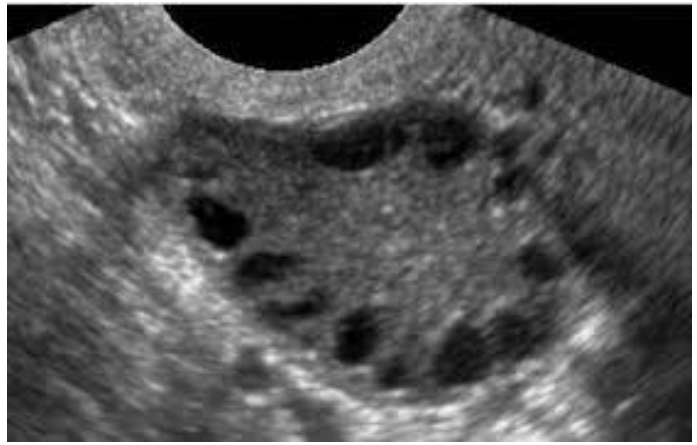

Polycystic ovary syndrome

GP Tool

This resource is informed by the evidence-based guideline for the assessment and management of polycystic ovary syndrome (PCOS), authored by the PCOS Australian Alliance and auspiced by Jean Hailes for Women's Health. We are grateful to the Australian Government for their support and funding of the national PCOS evidence-based guideline project and subsequent translational program.

PCOS and Subfertility

Subfertility

- Oligoanovulatory
- High BMI
- Depression, anxiety, poor body image, psychosexual dysfunction

Management

- Weight loss
- Metformin
- Ovulation induction

When to Prescribe Metformin…

- T2DM / Impaired glucose tolerance
- Obese PCOS
- Oligoanovulatory PCOS – not TTC actively
- Resistance to OI meds

- Increasing regimen as tolerated
  - 500mg OD 1 week
  - 500mg BD 1 week
  - 500mg TDS or 1g BD

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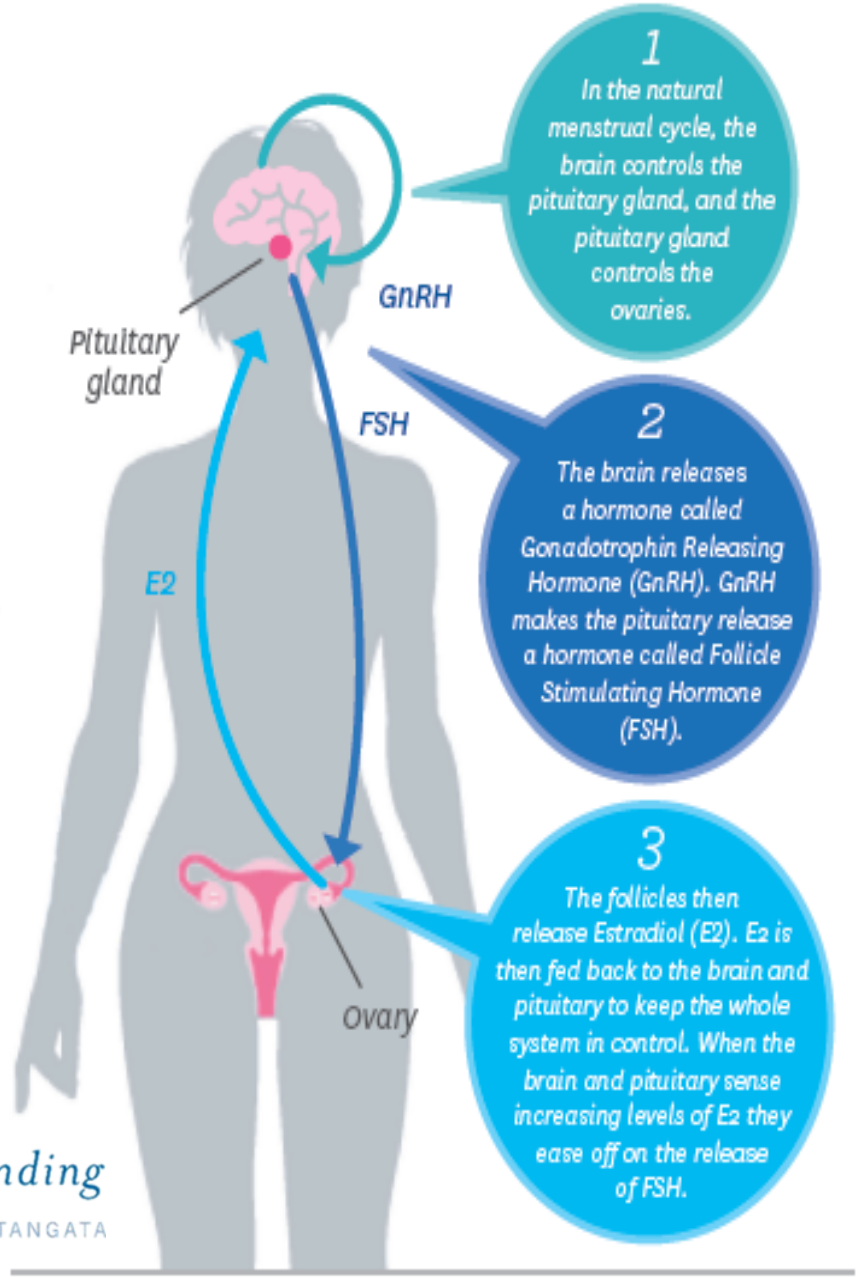
Ovulation Indu

- Letrozole (Aromatase Inhibitor)
- Clomiphene (SERM)

Practice point:

Letrozole is now first line agent for OI in oligoanovulatory PCOS



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Letrozole for Ovulation Induction

- Safe
- Off-label use – consent required (hcg test prior)
- 3% multiple pregnancy rate
- Overresponse and resistance still occur

Legro 2014, Torres 2016

Practice point:

Letrozole still needs to be monitored

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Anna - followup

- Weight loss – a work in progres
- Metformin for IGT
- High dose folate
- 1st Letrozole cycle - currently pregnant
- Referral made for obstetric care

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Mental Health Issues in PCOS are Common…

- Depression (28-64%)
- Anxiety (34-57%)
- Eating disorders, negative body image, low self-esteem, psychosexual dysfunction

Jean Hailes 2015

Practice point:

Regularly check mental and emotional health

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PCOS – Long term sequelae

- Endometrial hyperplasia and carcinoma

- Metabolic syndrome: hypertension, truncal obesity, DM, hyperlipidaemia
- GDM
- Sleep apnoea

Practice points:

If fertility not desired, needs endometrial protection

Regular assessment of CVS risk

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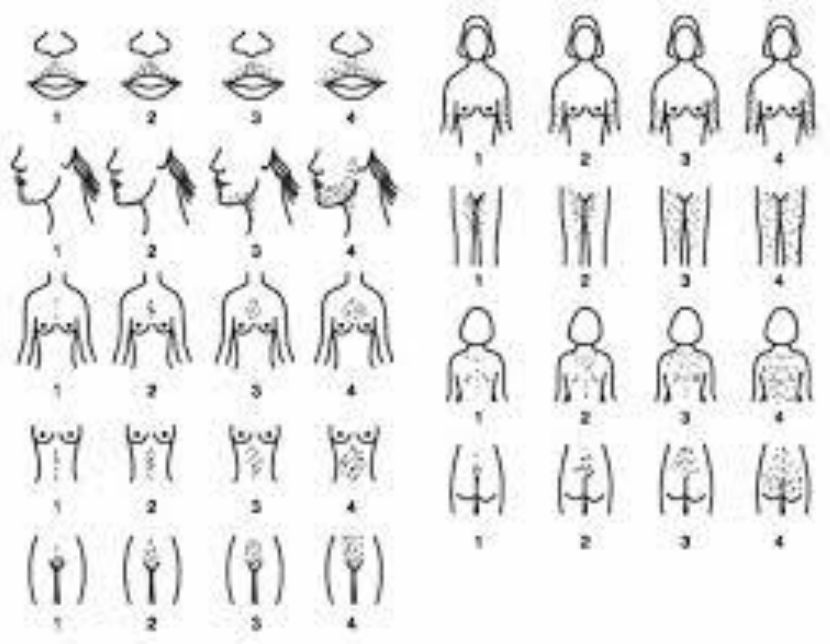
When to refer?

- Fertility desired:
  - < 35y: overweight after 6-12 months intensive lifestyle intervention +/- Metformin + no other fertility factors evident
  - > 35y – earlier referral warranted
  - Other fertility risk factors present , refer earlier
- Adolescents
- Significant clinical hyperandrogenism/virilisation, especially rapid-onset
  - Severe hirustism
  - Male pattern balding
  - Deepening voice
  - Clitoromegaly
- If diagnosis uncertain



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PCOS - Summary

- Heterogeneous group, so individualise management
- Fertility: ovulation induction 1st line
  - assuming tubal patency and no male infertility
  - Monitoring due to risk multiple pregnancy & risk of no response
- Keep in mind long-term sequelae
- Refer when:
  - Fertility desired
  - Adolescents
  - Diagnosis uncertain
  - Virilising features, particularly if rapid-onset

Jane

- 36y G0P0
- No periods since stopping OCP a year ago
- Mother went through menopause at 37yrs, 2x younger sisters
- FSH 59 E2 60 AMH <1.1
- Pelvic scan: normal uterus, thin endometrium, small ovaries and no small follicles seen

What's the likely diagnosis?

Primary Ovarian Insufficiency

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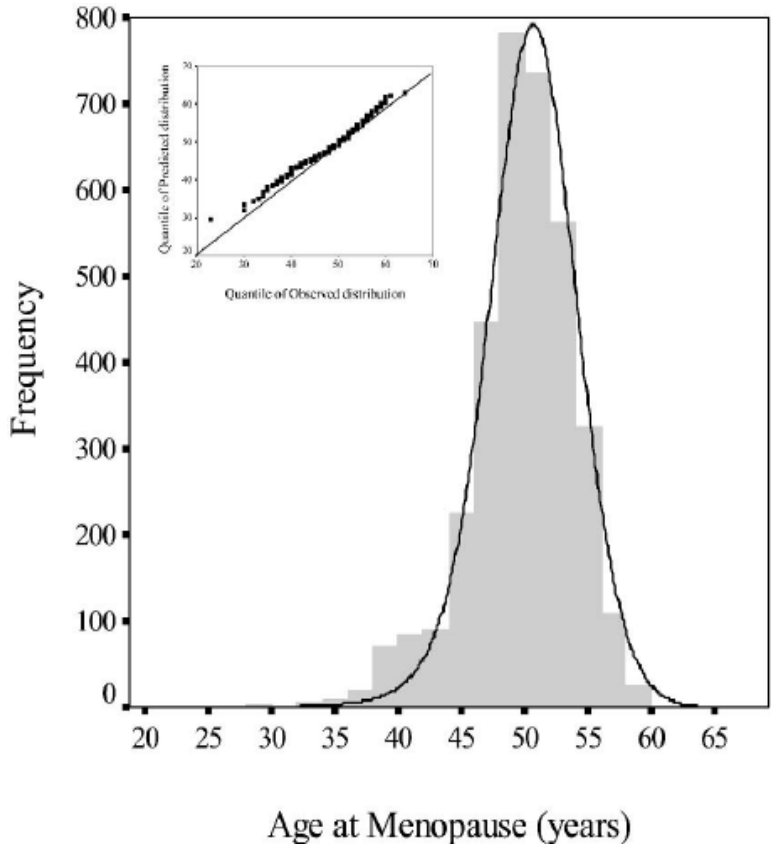
Primary (Premature) Ovarian Insufficiency (POI)

- By definition occurs < 40 yrs
  - 1% of women under the age of 40 yrs
  - 0. 1% women before age 30 yrs
  - 0.01% women before age 20 yrs



Davies 2012

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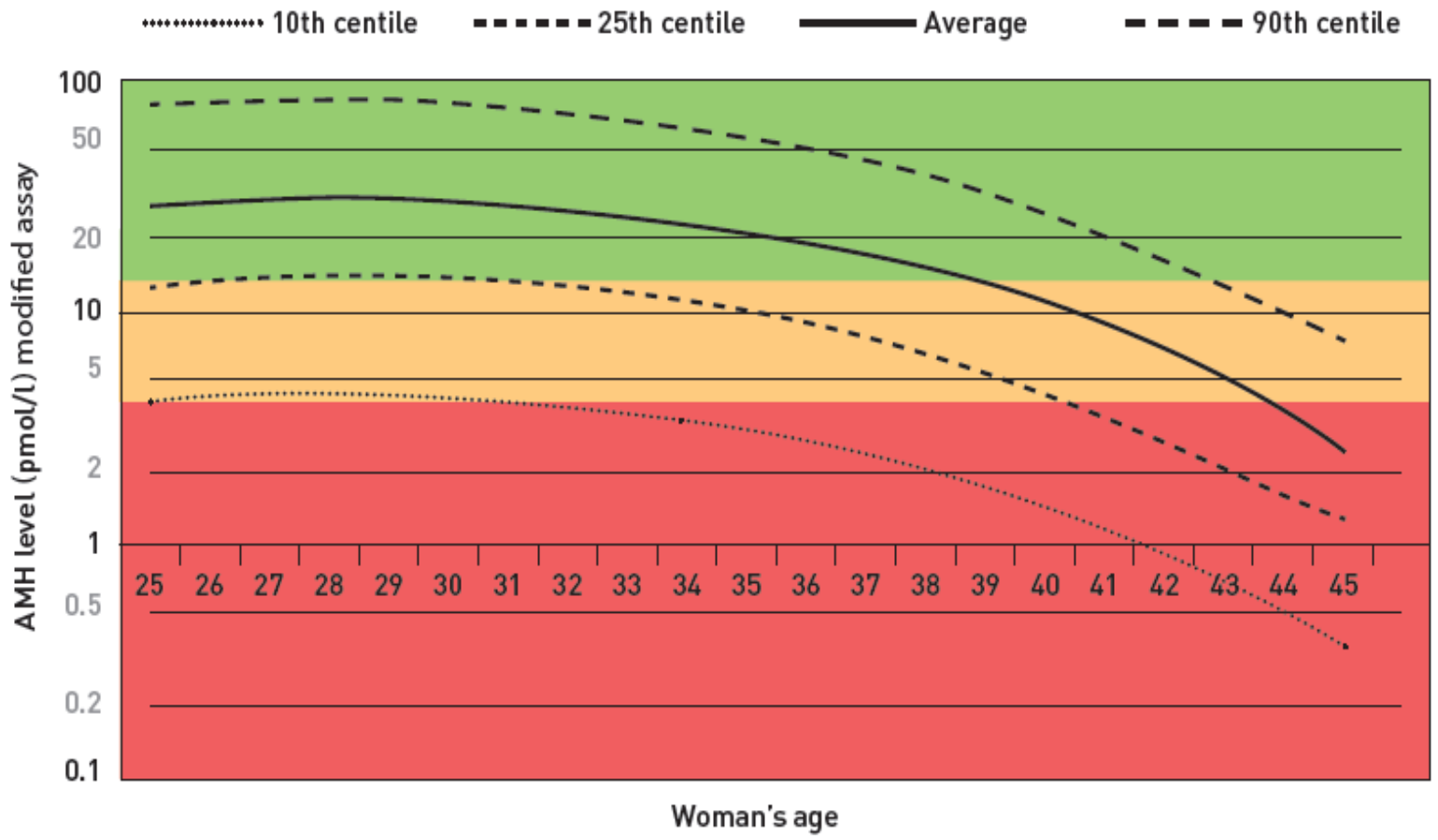
AMH, Ovarian reserve and Maternal age



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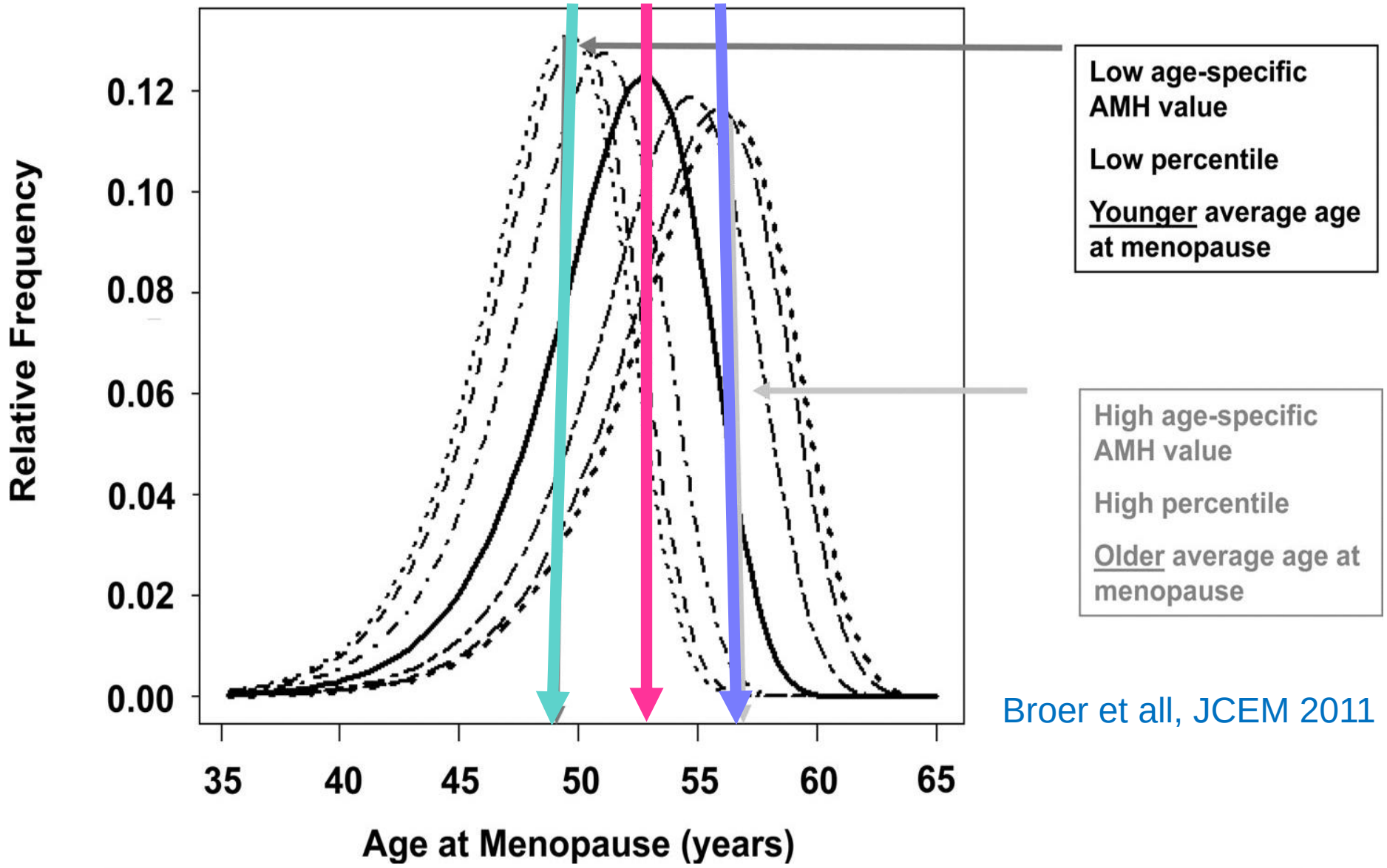
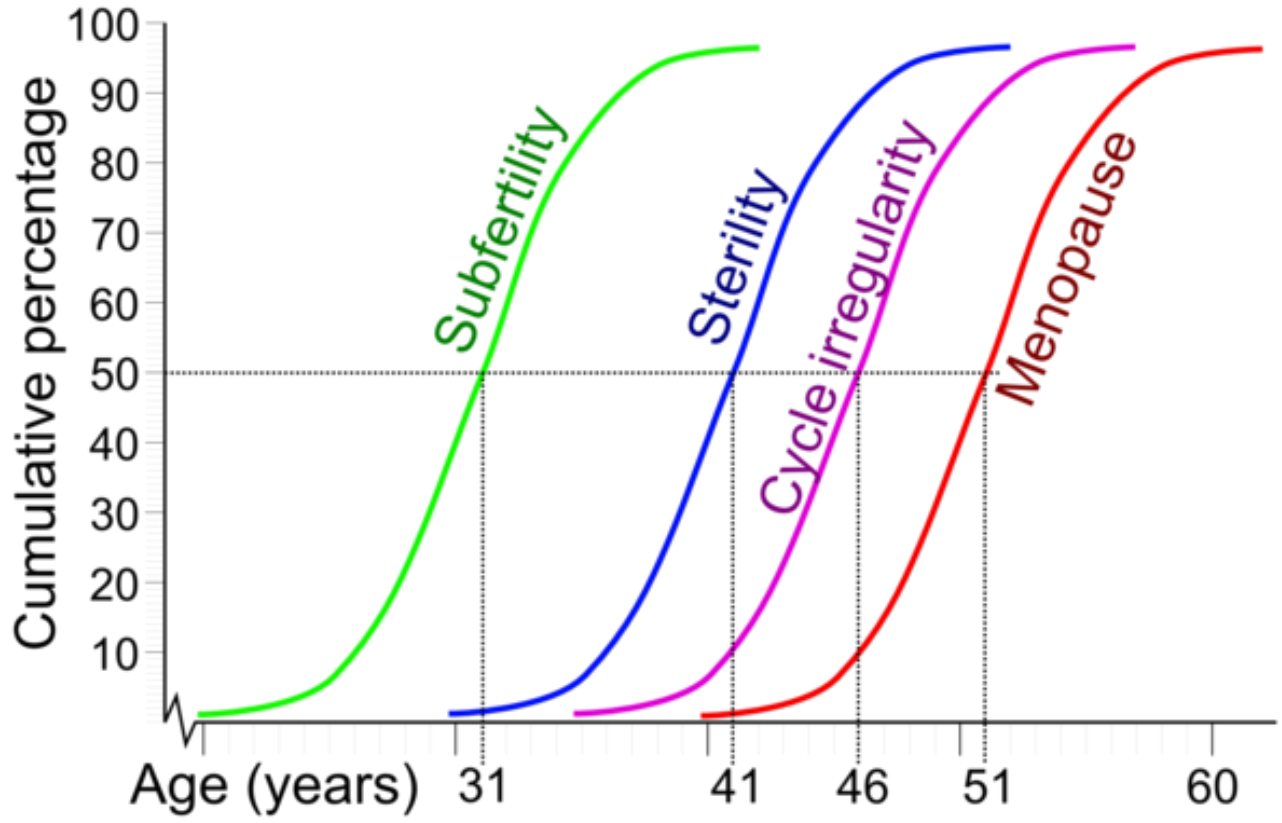


Broer et all, JCEM 2011

Practice point:

Women with a low AMH will have an earlier menopause

Fertility reduces ~13yrs before menopause…



Nikolaou & Tepleton 2003

Practice point:

Women with a low AMH will have a shorter reproductive lifespan

Common Causes of POI….

Genetic	45XO - mosaiacs also Other X chromosome abN Fragile X premutation- 2-14% Galactosaemia Familial - 10% several diff genes have been identified	Family History Karyotype FMR1 gene mutations Neonatal screening
Autoimmune	Addison's disease Polyglandular autoimmune failure	Anti-adrenal Anti-21 hydroxylase Anti-thyroid Anti-ovarian Lupus anticoagulant Anti-cardiolipin Beta-2-glycoprotein
Iatrogenic	Chemo/Radiotherapy – 6% Post-ovarian surgery	
Other	Viral, toxins Hypogonadism without follicle depletion	

When to Refer?

- Fertility desired
  - Low AMH
  - FHX early menopause
  - Cluster of autoimmune disease: autoimmune polyglandular syndrome, SLE, myasthenia gravis, vitiligo, hashimoto's, graves

- Patients having/had gonadotoxic treatment or gonadectomy

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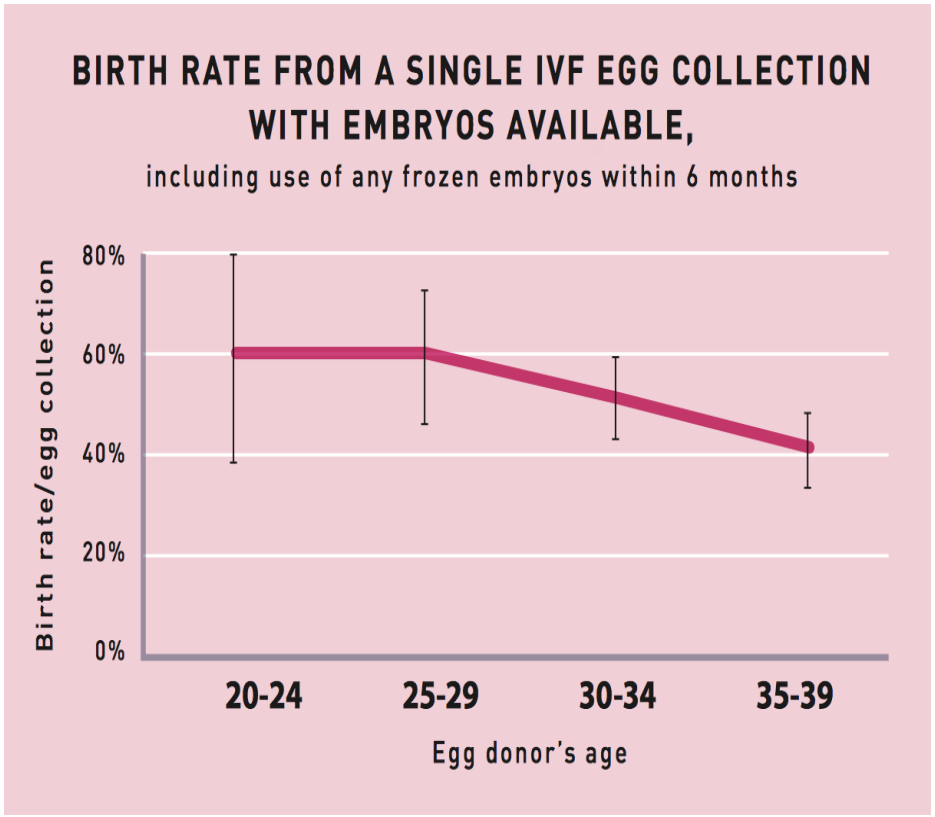
POI – Fertility Options



- </= 5% spontaneous conception
- Donor egg
  - Public funding available
- Future….

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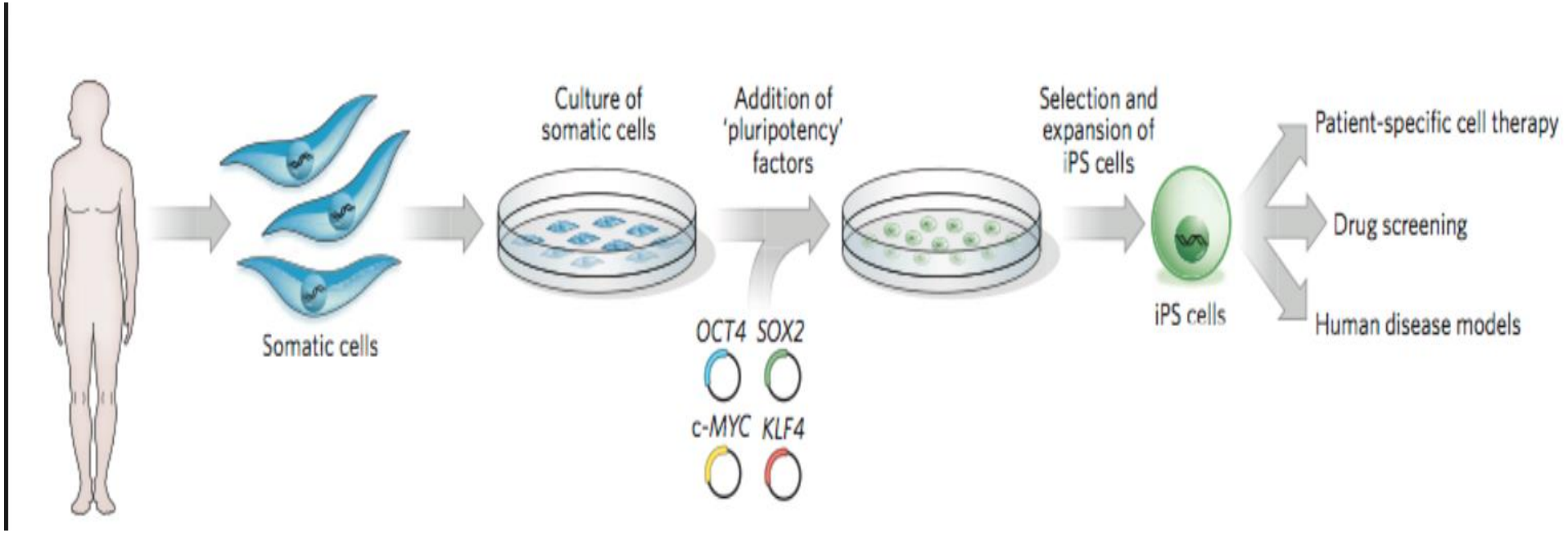
Human induced pluripotent stem cells (HiPSC's)



Jane

- 2x younger sisters both had very low AMH levels
- recruited egg donor, still in contact
- Daughter born Jan 2016
- Both younger sisters have had children since as they had AMH checked and were found to be low so they decided not to delay childbearing

POI – Long-term Health

- General:
  - Healthy, balanced diet, sufficient Calcium + Vitamin D
  - Regular weight-bearing exercise
  - Avoidance smoking
  - Alcohol minimisation
- HRT
  - Until natural age menopause 50y
- Monitoring:
  - Bone marrow density
  - Mammogram
  - Cervical smears

POI - Summary

- Refer: women with low AMH-if fertility is desired, if diagnosis suspected, significant family history, cluster of autoimmune disorders
- Fertility: currently donor eggs publicly funded but future hopefully for own biological children
- Australiasian Menopause Society website has helpful GP resources

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Reeba

- 37y G3P0+2
  - Both conceived <3 months trying
  - Both spont aneous miscarriages < 6wks
- LMP 6wks ago, regular 28d cycles
- No PV bleeding or pain, still has symptoms of pregnancy
- Beta-hCG's rising suboptimally
- Pelvic scan: intrauterine sac with mean sac diameter 29mm, no fetal pole seen

What's the diagnosis?

Missed miscarriage –
Blighted ovum

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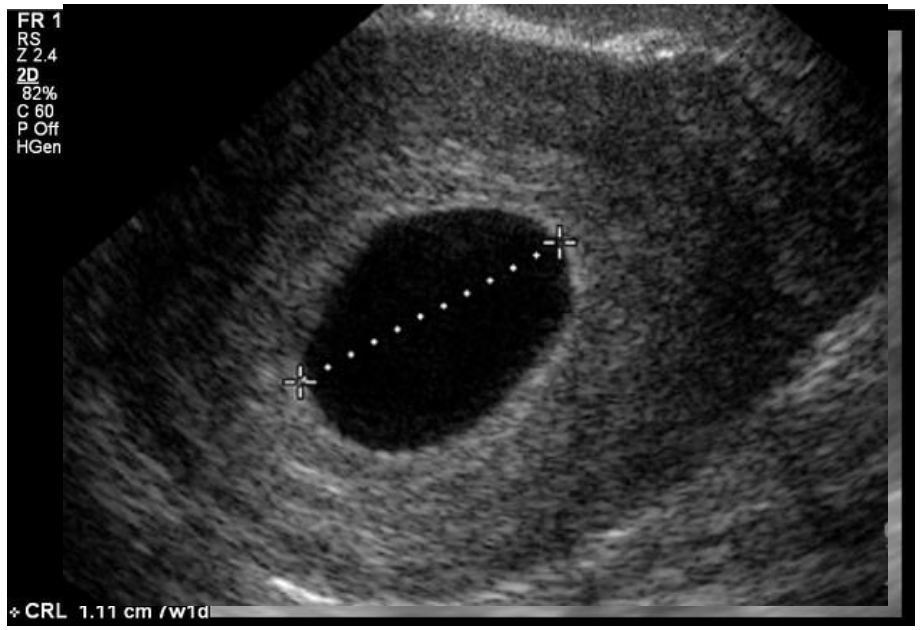
RCOG Green-top guidelines - Diagnosis of Miscarriage



- Transvaginal scan
- Empty intra-uterine sac with mean sac diameter ≥ 25mm
  - no yolk sac or fetal pole
- Fetal pole ≥ 7mm with no fetal heart
- If any doubt, repeat scan ≥ 7 days later

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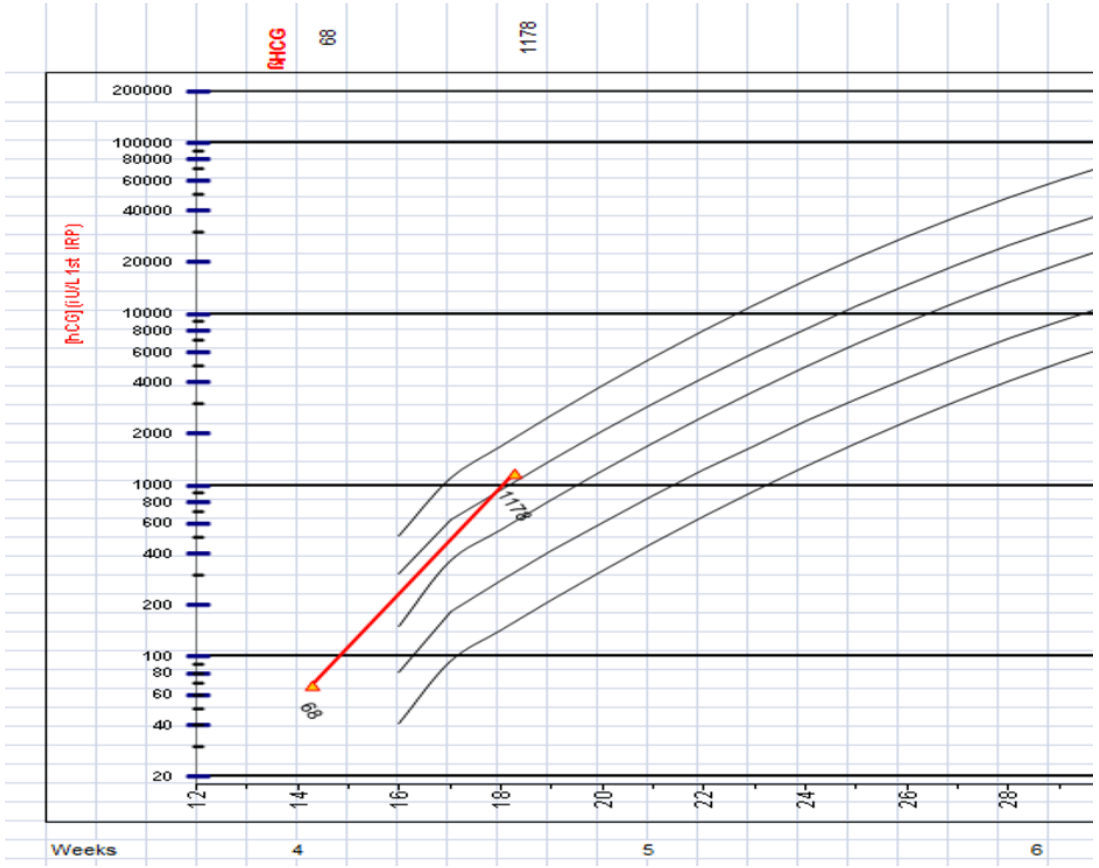
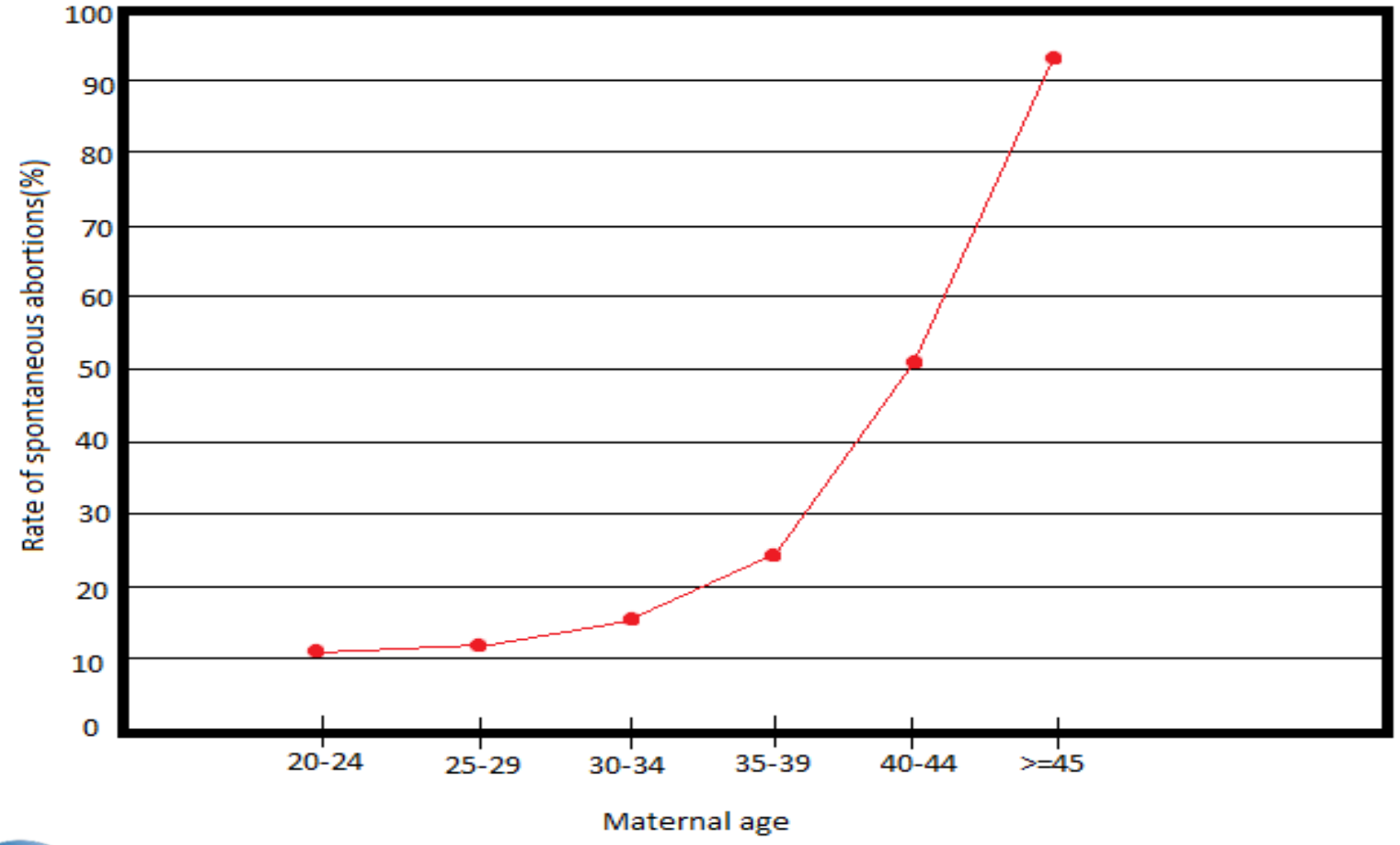
Tracking HCG's



Miscarriage increases with maternal age



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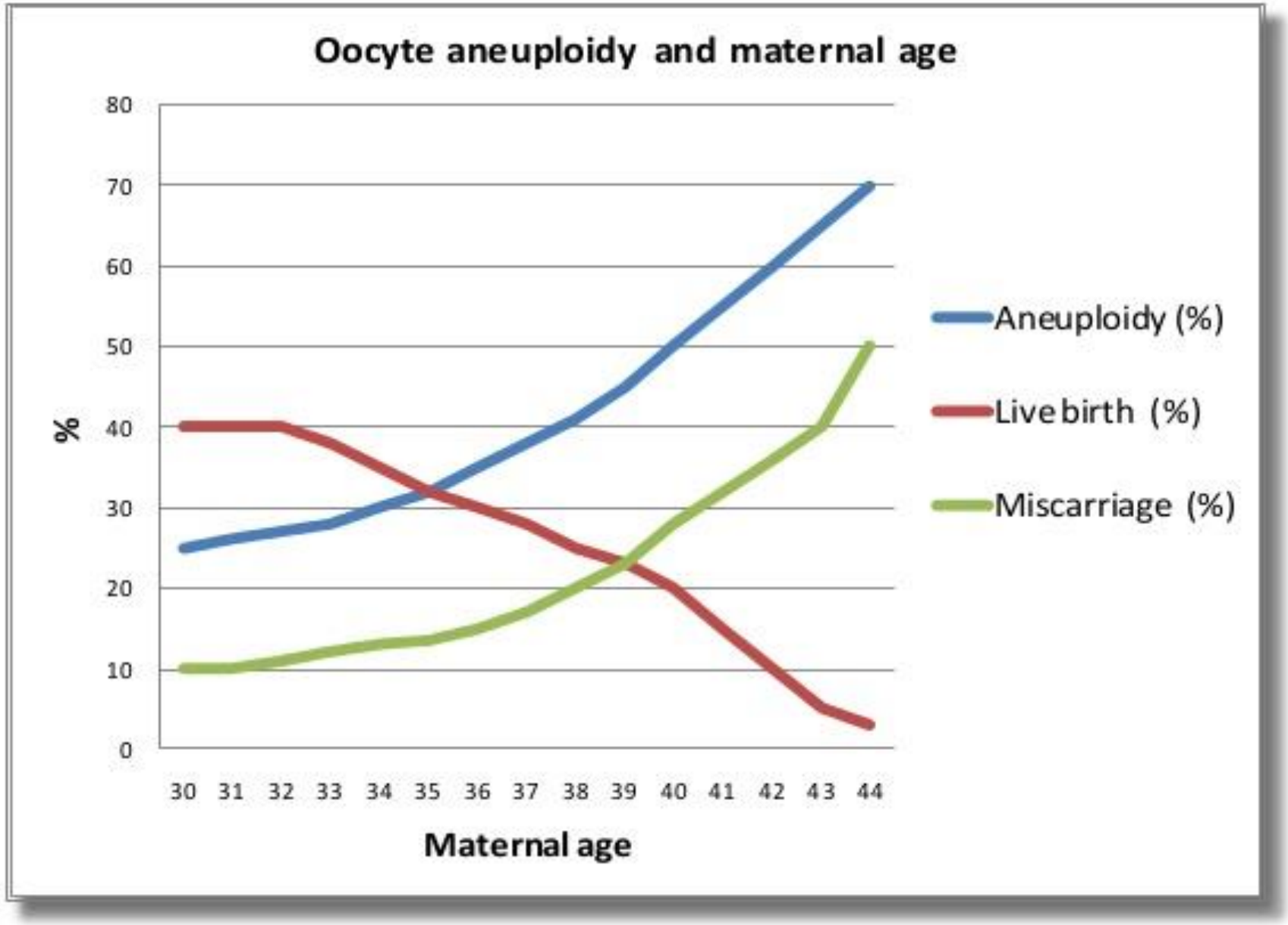
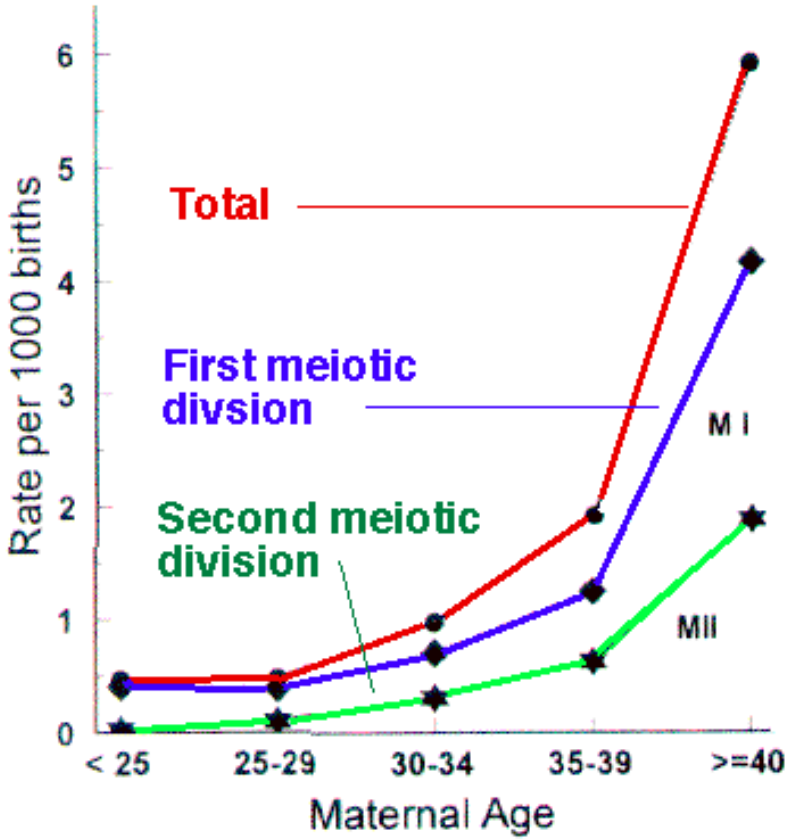
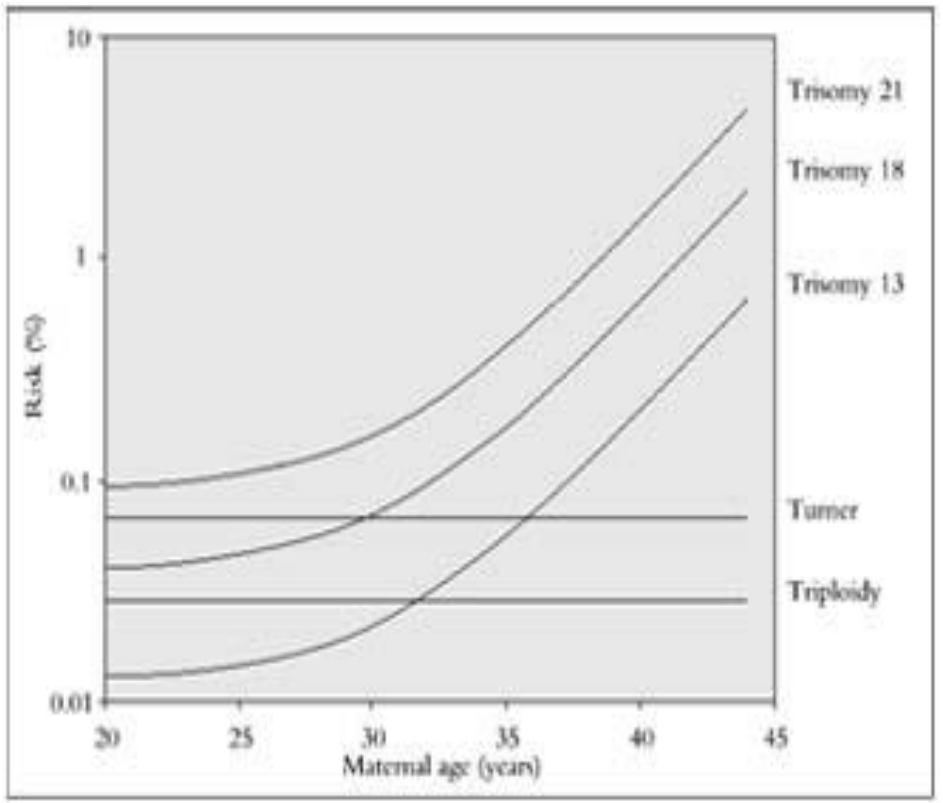


US CDC/SART data

Non-disjunction errors increase with maternal age





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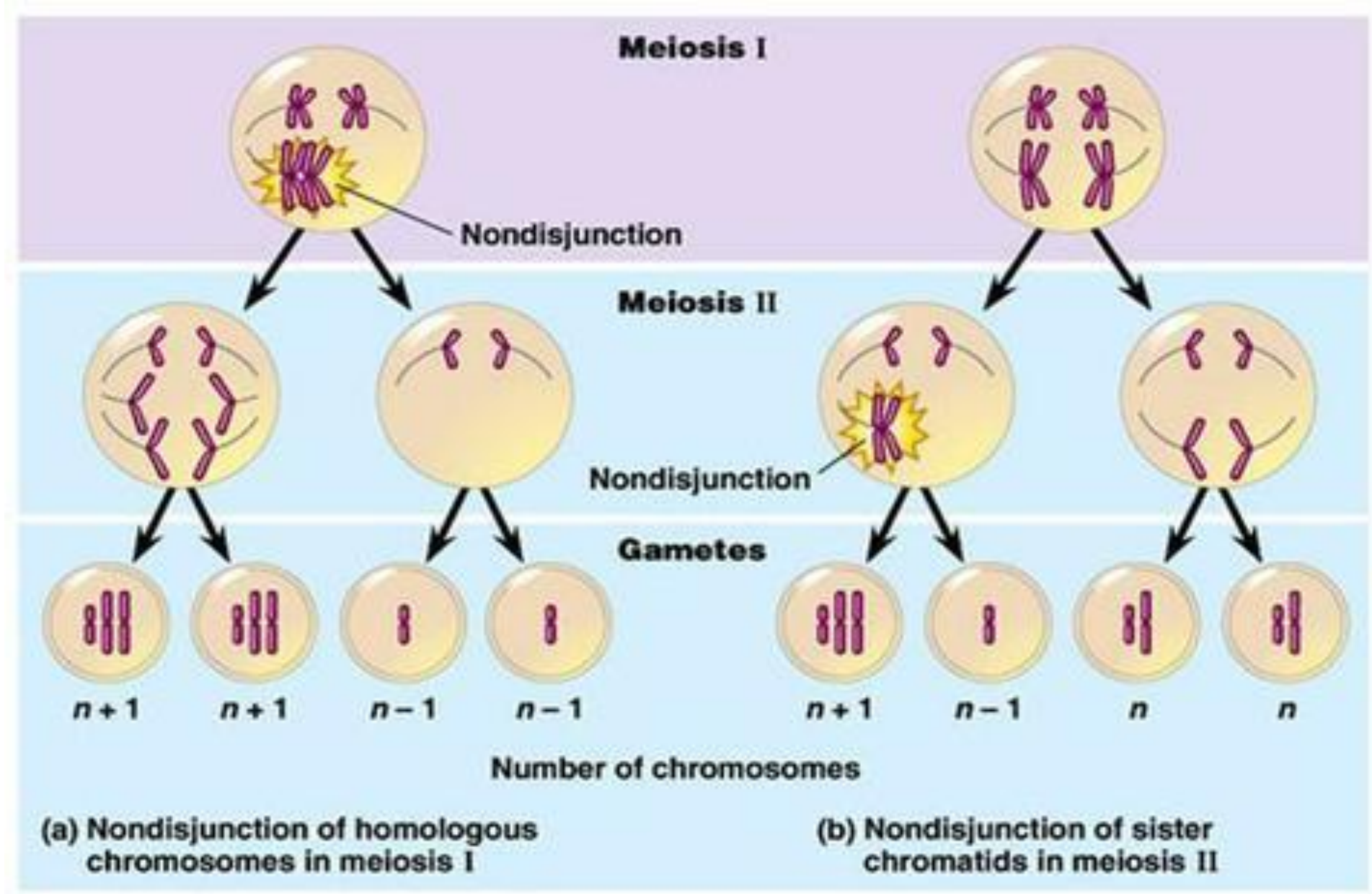
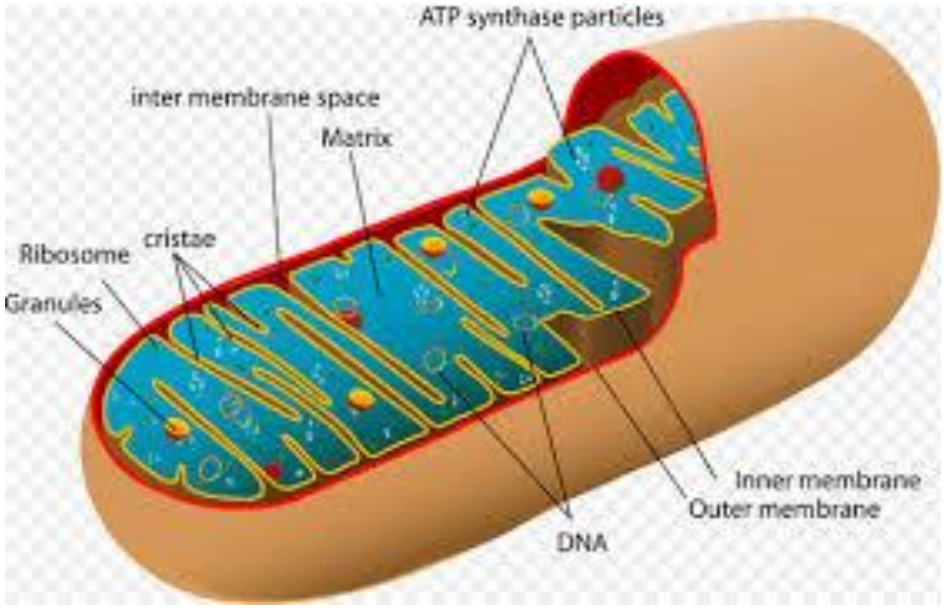
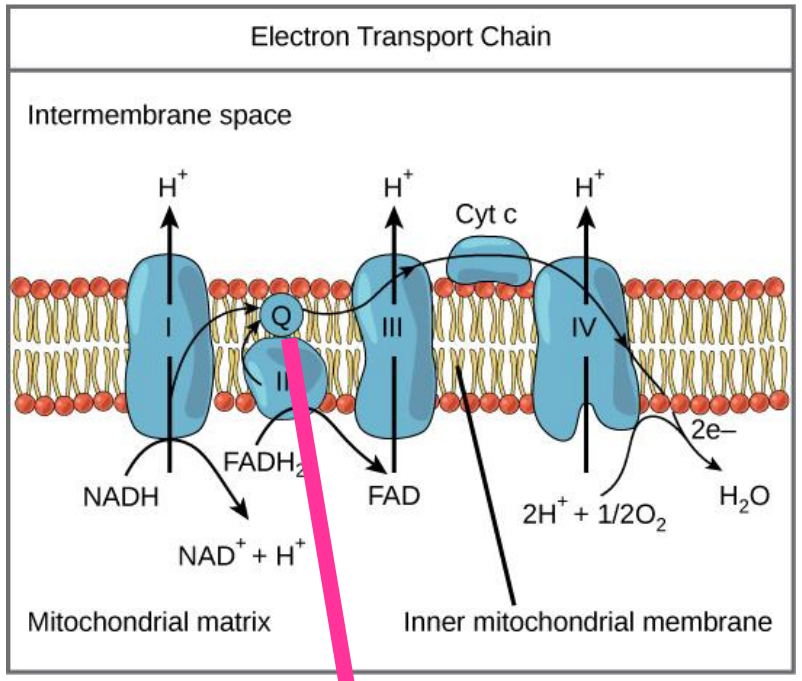
Mechanism of Non-Disjunction….







Coenzyme Q10

Practice point:

CoQ10 may be the new 30!

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Ways to prevent miscarriage??

- Progesterone may reduce the risk of miscarriage with a threatened MC , but not useful for recurrent MC

- Fertility treatments may reduce risk of MC

- Expectant Management – 63-65% will have a baby within 1y

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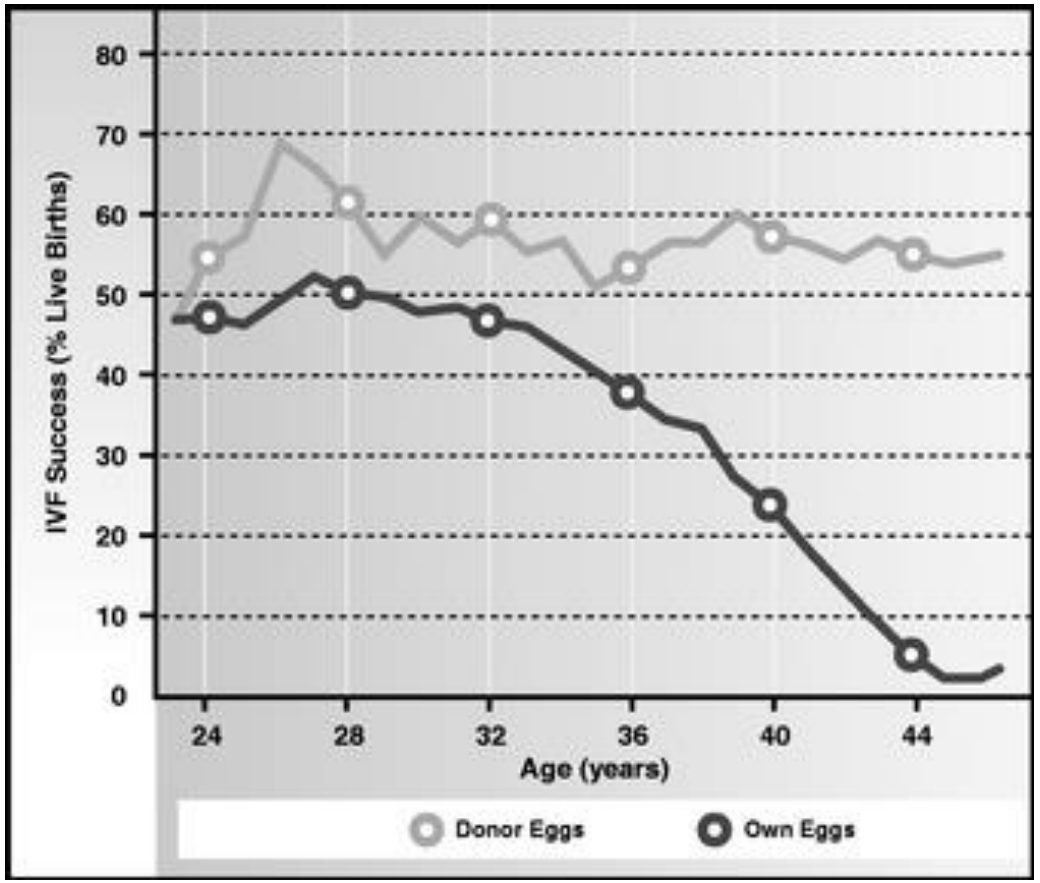
Own or donor eggs??



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Pre-implantation genetic screening (PGS)

- Reduces time to pregnancy

Reeba

- 6th spontaneous miscarriage <7 weeks
- IVF + PGS: 3/5 embryos euploid, 1/5 no result

Indication:
Recurrent pregnancy loss

Embryo	PGS Result	Suitable for transfer?	Data Quality (A/B)*
2	Aneuploidy NOT detected	Yes	A
3	NO RESULT		
6	Aneuploidy NOT detected	Yes	B
8	Abnormality detected:triploid	No	B
9	Aneuploidy NOT detected	Yes	A

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Miscarriage - Summary

- Diagnosis guidelines have become more lenient – if in doubt, rescan in > 7-14 days later
- Can trial UG if threatened MC
- Follow-up and support is important
- RANZCOG guideline is to offer anti-D 250u if MC, but not necessarily with threatened MC
- Look for treatable causes with recurrent miscarriage
- PGS is promising for couples with recurrent miscarriage

Kate

- 36y G0P0
- Primary infertility – 5yrs
- Increasing painful periods
- Mother – TAH for endometriosis
- Bimanual: Fixed retroverted uterus
- Pelvic scan: thickened anterior uterine wall > posterior with ?adenomyosis, non-mobile uterus, kissing ovaries with low level – echo cysts bilaterally ?endometriomas
- Ca125 45**

What's the diagnosis?

Endometriosis

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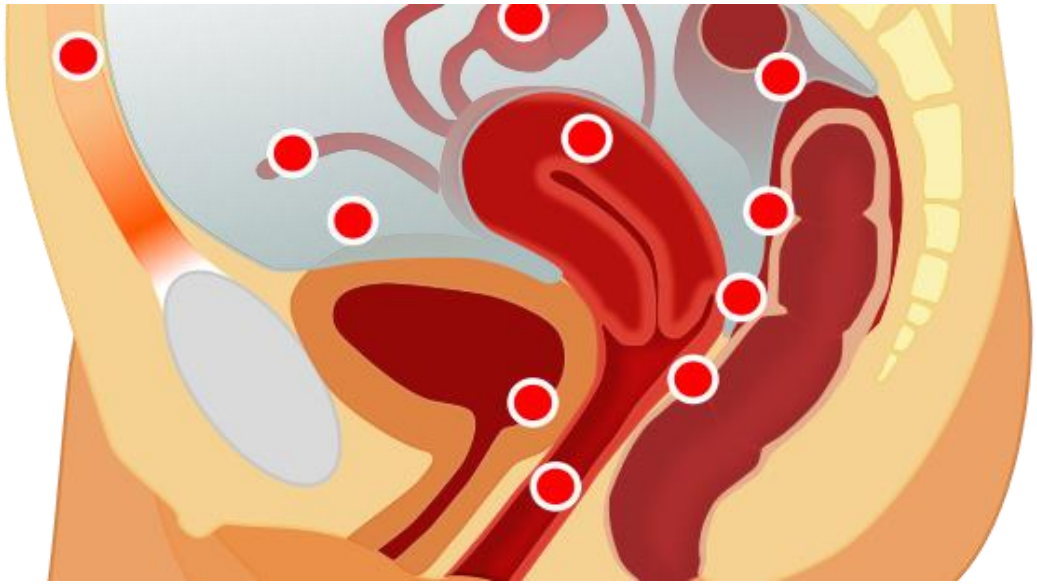
Sites of Endometriosis and Symptoms



- Painful periods 80%
- Pelvic pain 70%
- Painful intercourse 45%
- Painful defecation
- Infertility 26%
- Bladder symptoms 10%
- Incidental finding

Practice point:

Symptoms can indicate site of endometriosis

Extent of symptoms does not correlate to extent of disease

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Symptoms Predictive of Endometriosis

Symptom	Predictive for endometriosis OR (95% CI)
Abdominopelvic pain	5.2 (4.7 – 5.7)
dysmenorrhoea	8.1 (7.2 – 9.3)
menorrhagia	4.0 (3.5 – 4.5)
Dyspareunia/ post-coital bleeding	6.8 (5.7 – 8.2)
Urinary tract symptoms	1.2 (1.0 – 1.3)
Infertility	8.2 (6.9 – 9.9)
Hx ovarian cyst	7.3 (5.7 – 9.4)
Irritable bowel syndrome	1.6 (1.3 – 1.8)
PID	3.0 (2.5 – 3.6)
Hx fibrocystic disease	1.4 (1.2 – 1.7)

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Ballard 2008

Endometriosis & Infertility - ACCEPT Guidelines

Australian and New Zealand Journal of Obstetrics and Gynaecology 2012; **52:** 513–522 DOI: 10.1111/j.1479-828X.2012.01480.x

Original Article

Endometriosis and Infertility – a consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence)

Juliette KOCH,[1] Katrina ROWAN,[2] Luk ROMBAUTS,[3] Anusch YAZDANI,[4] Michael CHAPMAN[5] and Neil JOHNSON[6]

[1]*IVF Australia, Bondi Junction, New South Wales, Australia,* [2]*Genea, Sydney, New South Wales, Australia,* [3]*Department of O&G, Monash University, Clayton, Victoria, Australia,* [4]*QFG Research Foundation, University of Queensland, St Lucia, Queensland, Australia,* [5]*Department of O&G, University of New South Wales, Randwick, New South Wales, Australia, and* [6]*University of Auckland, Auckland, New Zealand*

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IVF or Surgery ???

IVF

Pros

- Faster time to conception
- Avoids risks of surgery

Cons

- Poor response to stimulation
- Anatomical distortion + Endometriomata increase IVF procedural risks

Surgery

Pros

- Can relieve pain
- Can CPAC code for publicly-funded IVF (surgical staging)
- Histological diagnosis

Cons

- Delays time to conception
- Ovarian reserve/ AMH lowered further by ovarian excisional surgery

Kate

- Stage 4 endometriosis excised
- Downregulation with GnRHa (Lucrin)
- Starts publicly funded IVF cycle in August now 38y
  - Waited 16 months on waitlist
  - Wasn't referred for surgery
  - Started public cycle + was found to have bilateral large endometriomas
  - Referred for surgery < 1month using private insurance
  - 3months post-operative downregulation before starting Lucrin

Practice point:

Refer early if suspected otherwise advanced maternal age can reduce chances of a baby further

When to Refer?

- History of or clinically suspected endometriosis
  - Irrespective of time trying to conceive
  - Refer women >35 early
  - 1st degree relatives with endometriosis

- Chronic pelvic pain (resistant to medical therapy)
  - Refer to gynae if fertility not desired

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Endometriosis – long-term

- HRT – concern for reactivation of endometriosis + malignant transformation with unopposed E2

ESHRE 2013

Practice point:

If needing HRT, use combined HRT in a woman with previously diagnosed endometriosis

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Endometriosis - Summary

- Symptoms can correlate to site but extent of symptoms does not relate to extent of disease
- Refer early especially if clinically suspected or a family history
- Possibly lower chances of having a baby compared to other causes of infertility
- IVF can be more difficult, has more risks in these women

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Thank - you

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