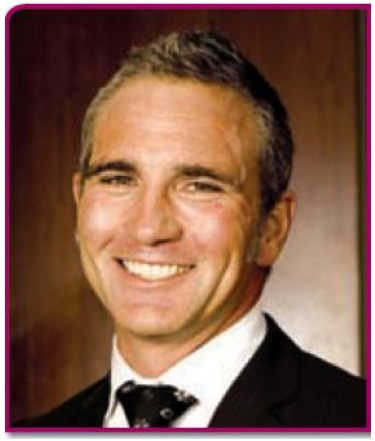


Dr Andrew Murray

Fertility Associates
Wellington

Gynaecology - Womb to Tomb - Pre-Conference Workshop

Thursday, 20 June 2013 Start 4:30pm Duration: 120mins Sigma

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

Fertility Associates –
Leaders in Fertility

From Womb to Tomb

Women's Health through their life stages

Dr Andrew Murray

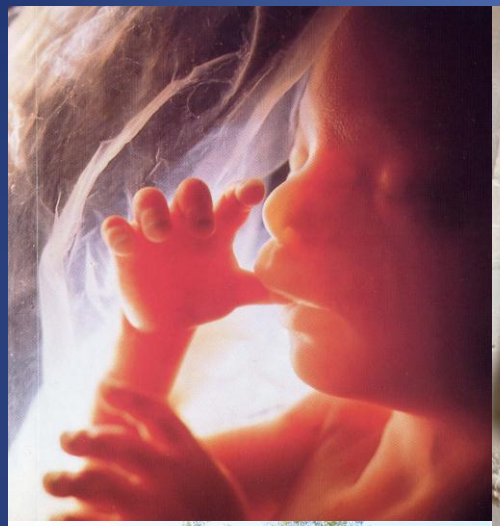
A bit about me….

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

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

Capital & Coast District Health Board
ŪPOKO KI TE URU HAUORA

The Fertility Society of Australia






Workshop Outline

- Pre Conception Care
- Adolescent Gynaecology
- Menstrual Disorders
- Menopause

Part 1

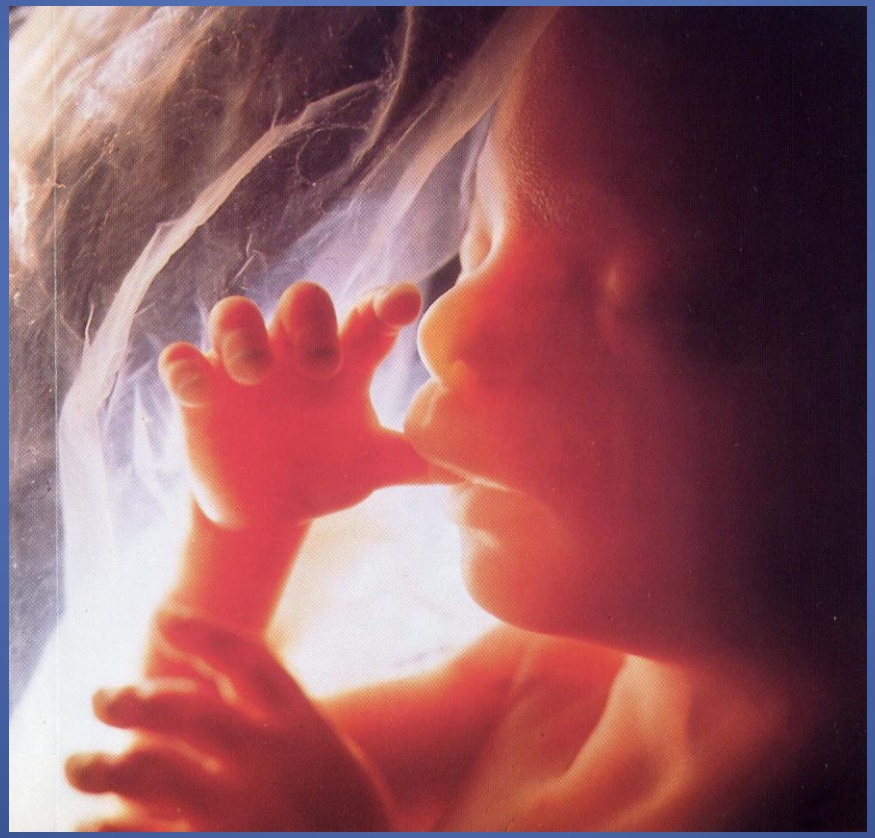
PRE-CONCEPTION CARE

Case 1: Pre Conception Care

Case 1: Pre Conception Care

- Jane is 27
- Seeing you for routine smear
- No past medical problems
- Tom is 33 years old is a builder, enjoys a beer, occasional smoker in weekends
- “Tom and I are thinking we might want kids one day, but we I’m not sure if I’m ready…. Is there anything I should be doing?”

This is really our patient



What are our Goals?

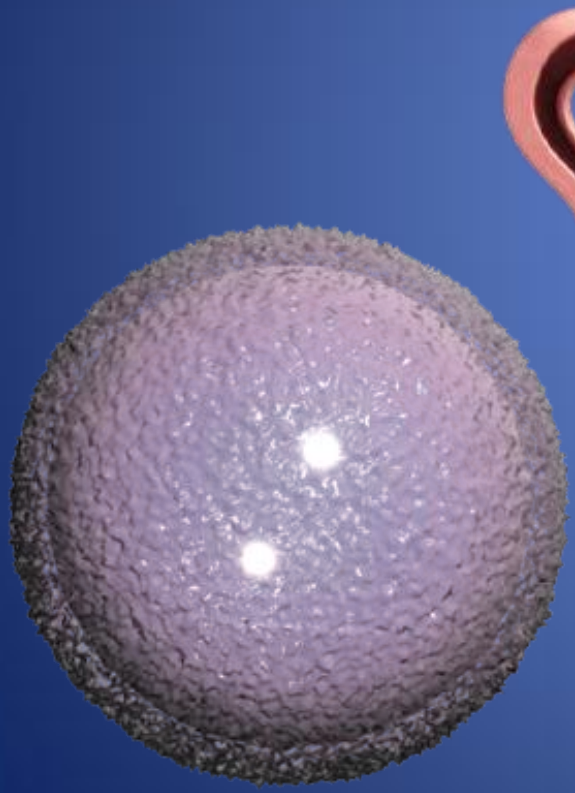
- Maximize chances of conception
- Minimize chances of abnormalities

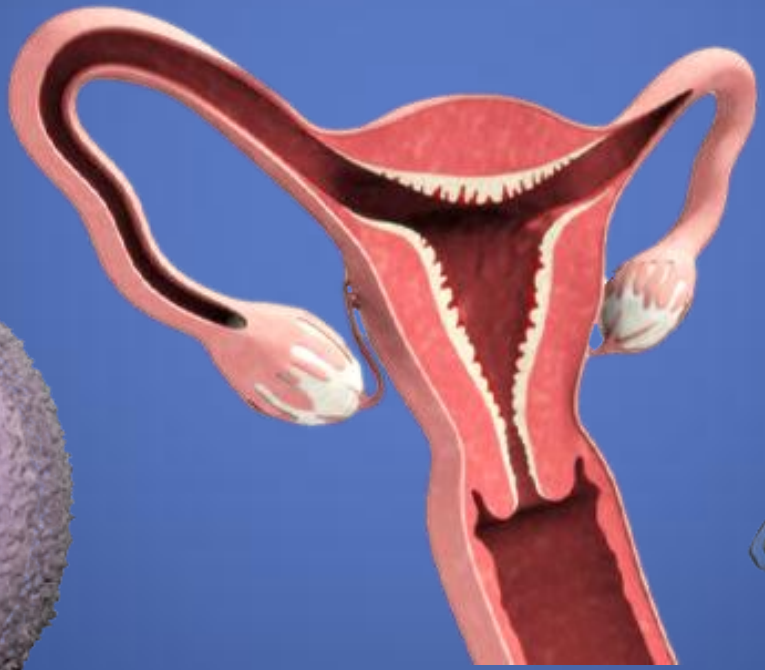
Pre-Conception Care

- Fetal Origins of Adult Disease
- What core ingredients do we need to make a healthy baby?
- What effects the quality of these ingredients?
- Recommendations

3 Core Ingredients to make a baby

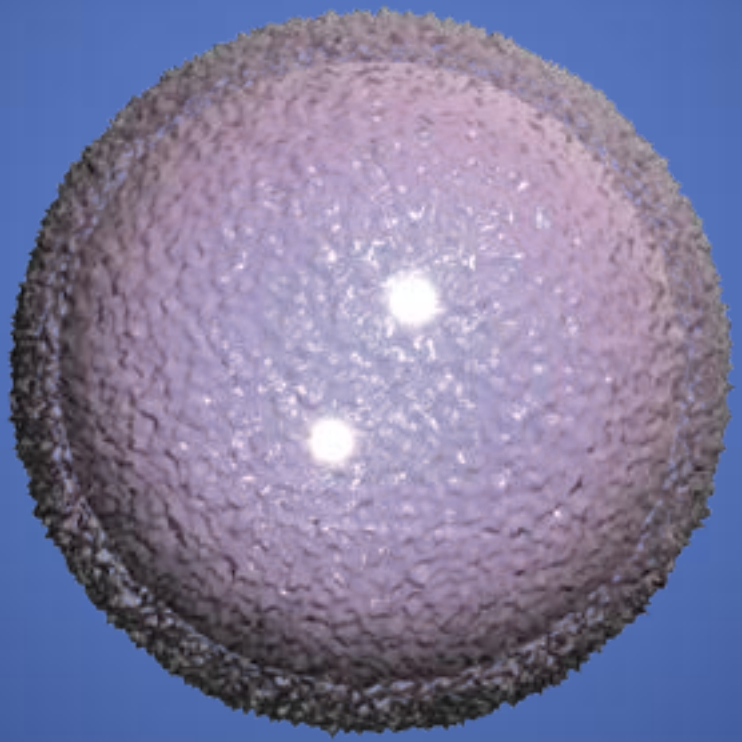
3 Basic Ingredients to get pregnant



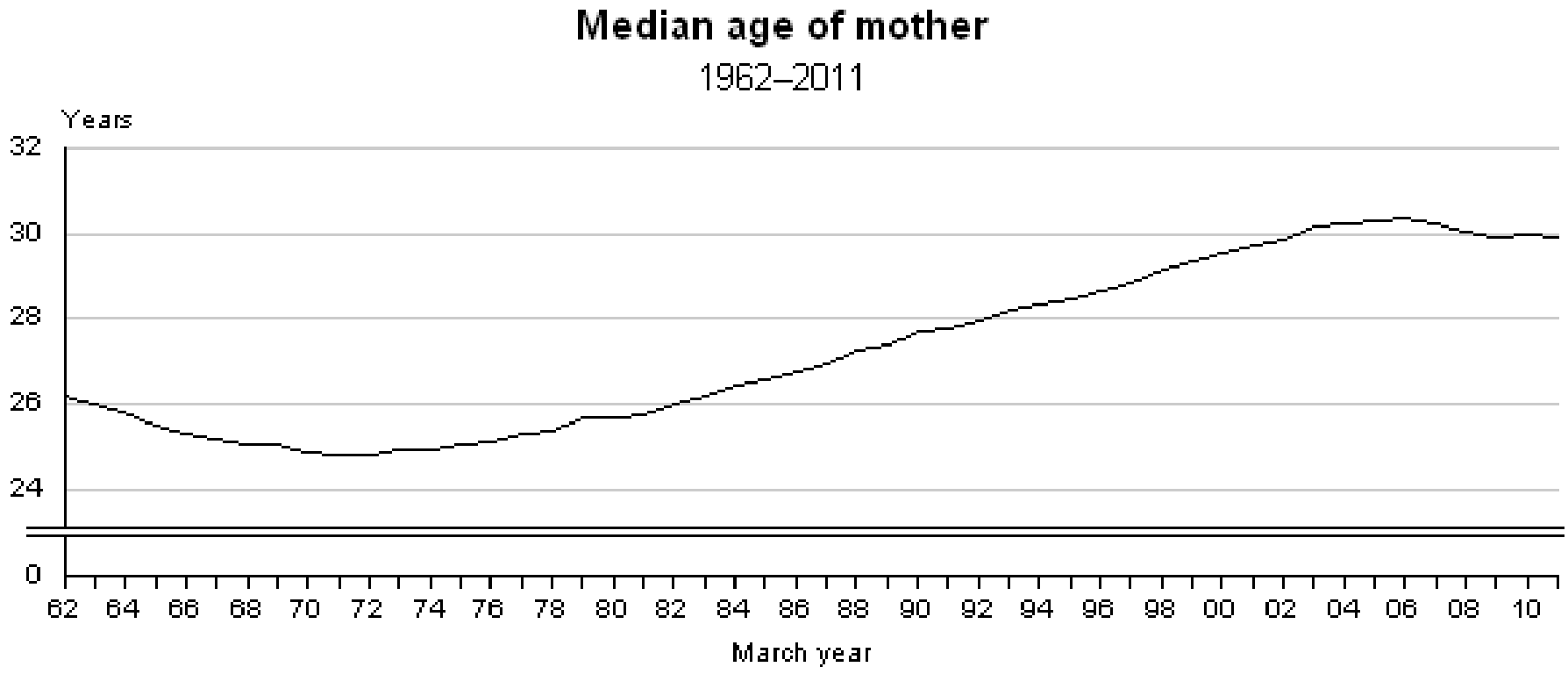


What Effects the Quality?

Eggs

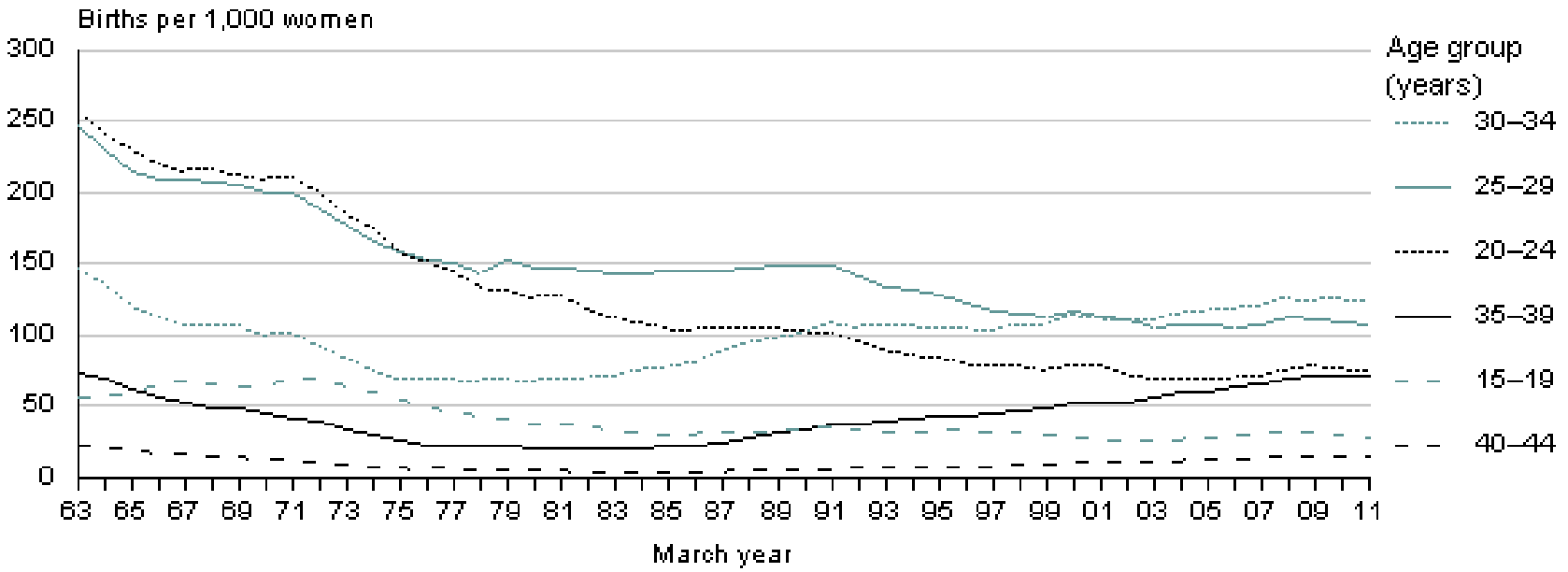


Average Age of Mothers is Increasing



Source: Statistics New Zealand

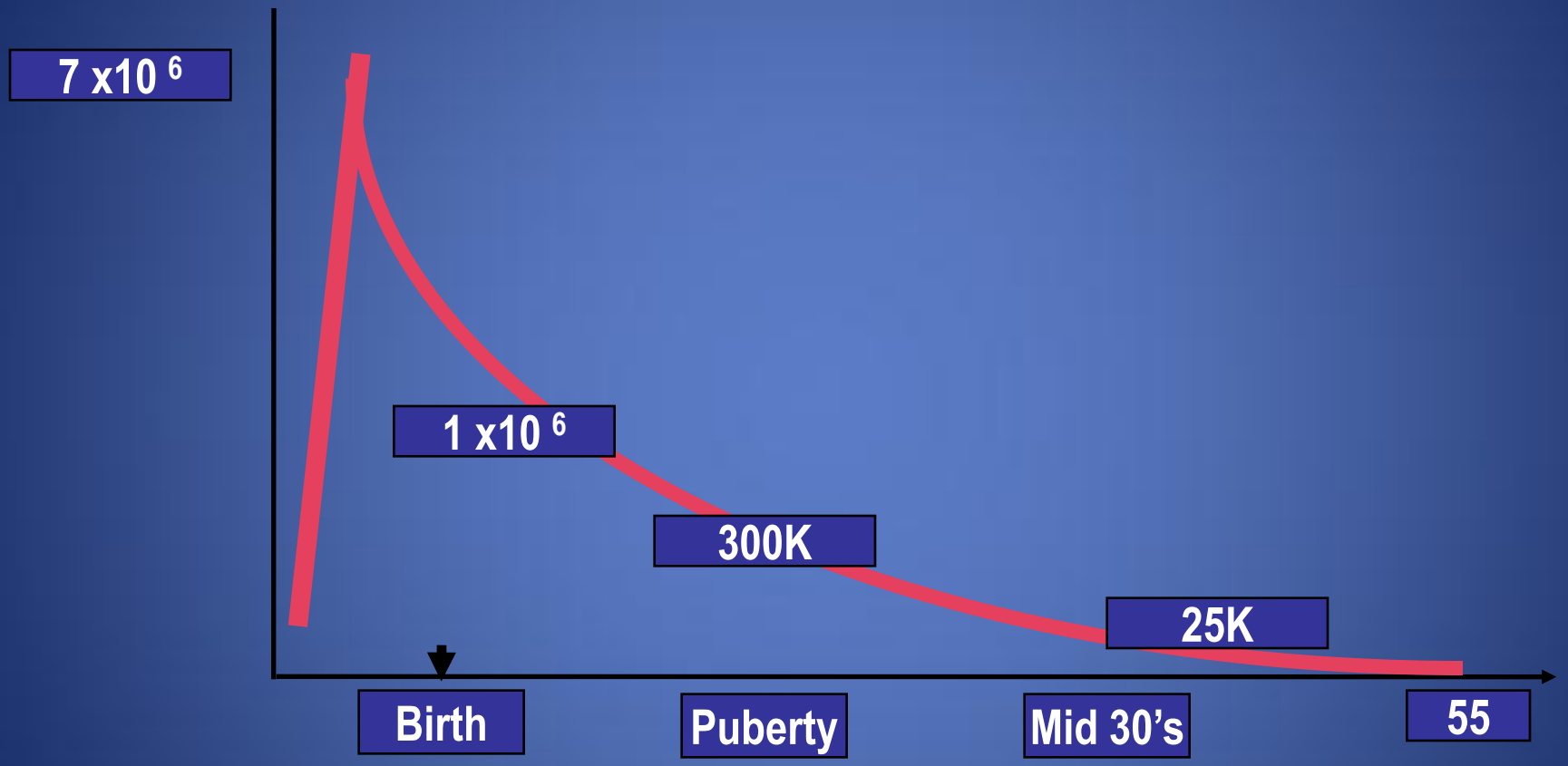
Average Age of Mothers is Increasing



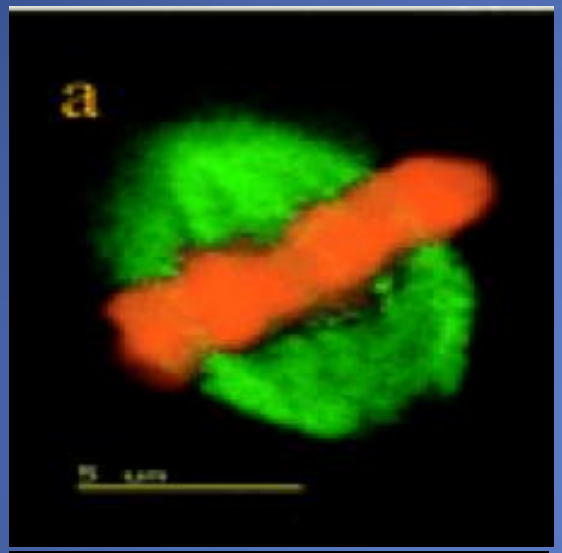
Source: Statistics New Zealand

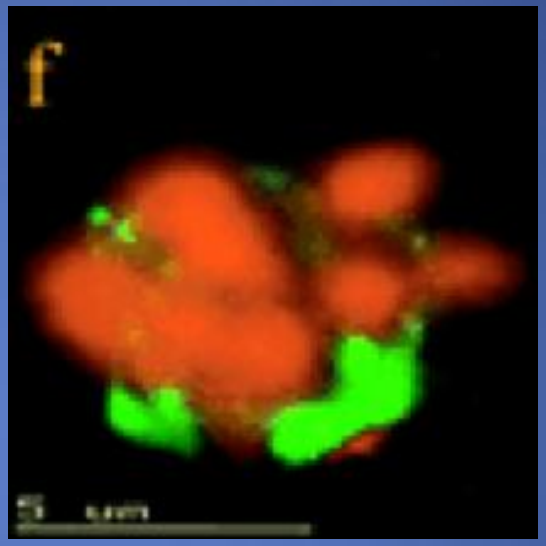
Age has Effects on Egg Quantity

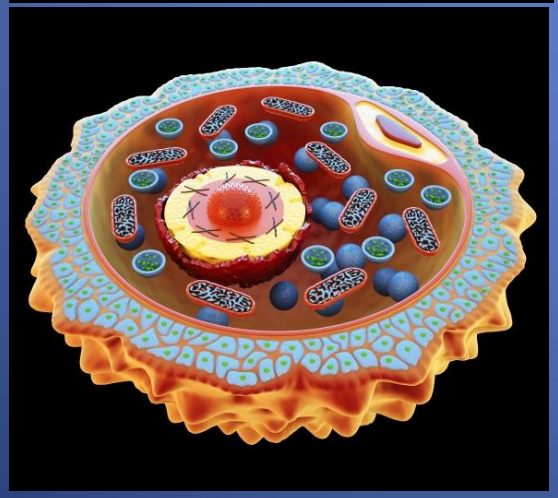
Age has Effects on Egg Quantity

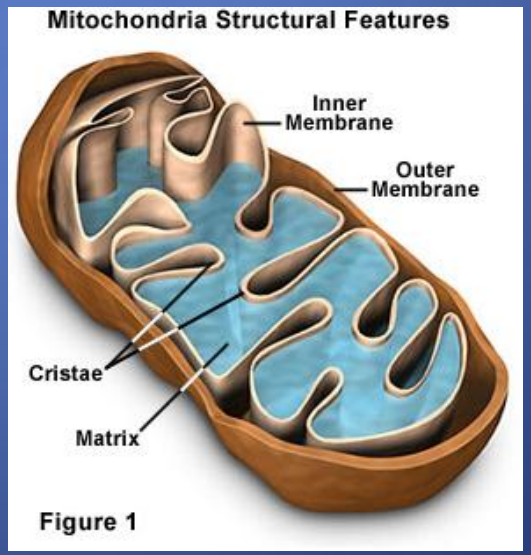


Age Effects Eggs Quality

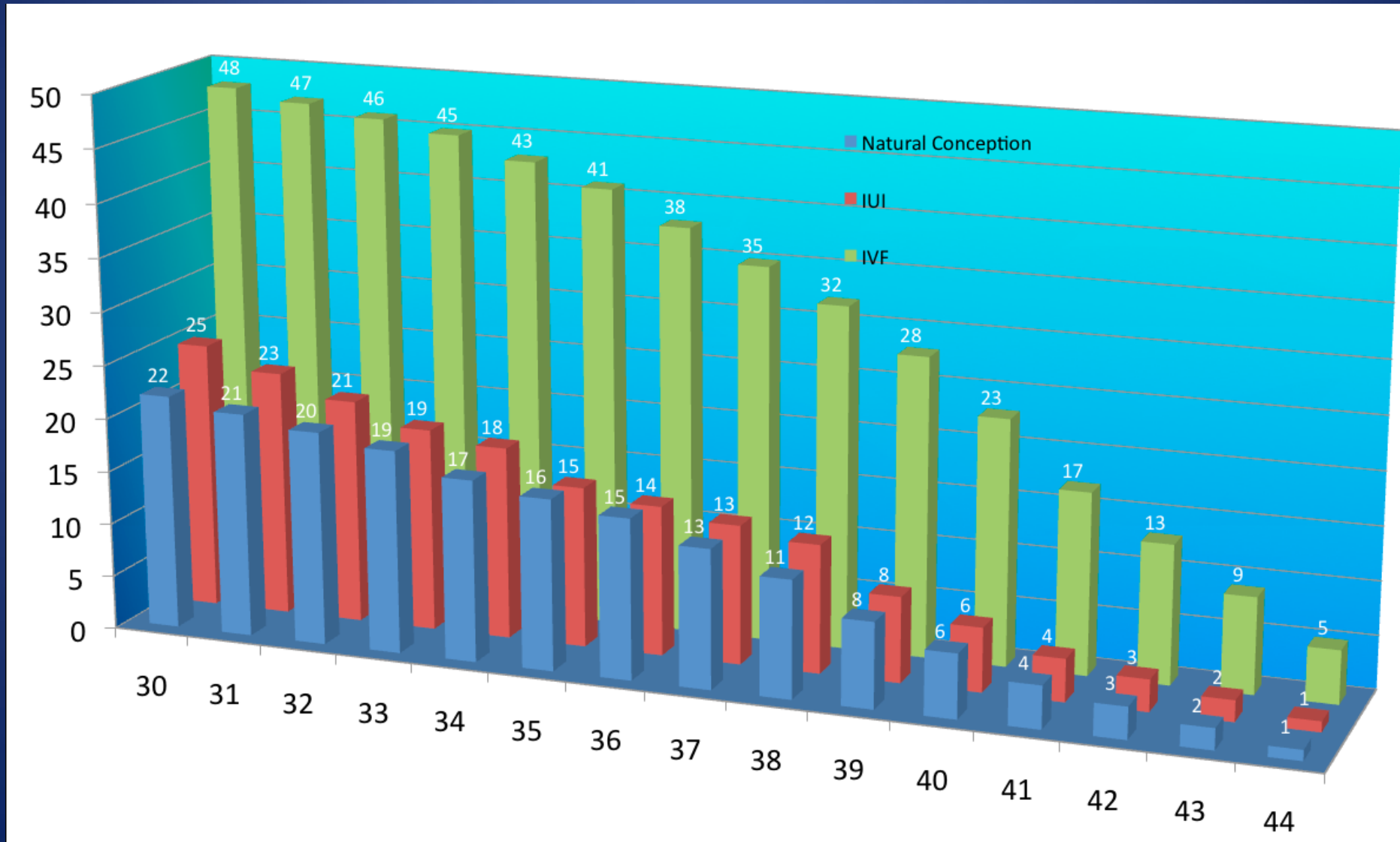








The Biological Clock Waits for No-One

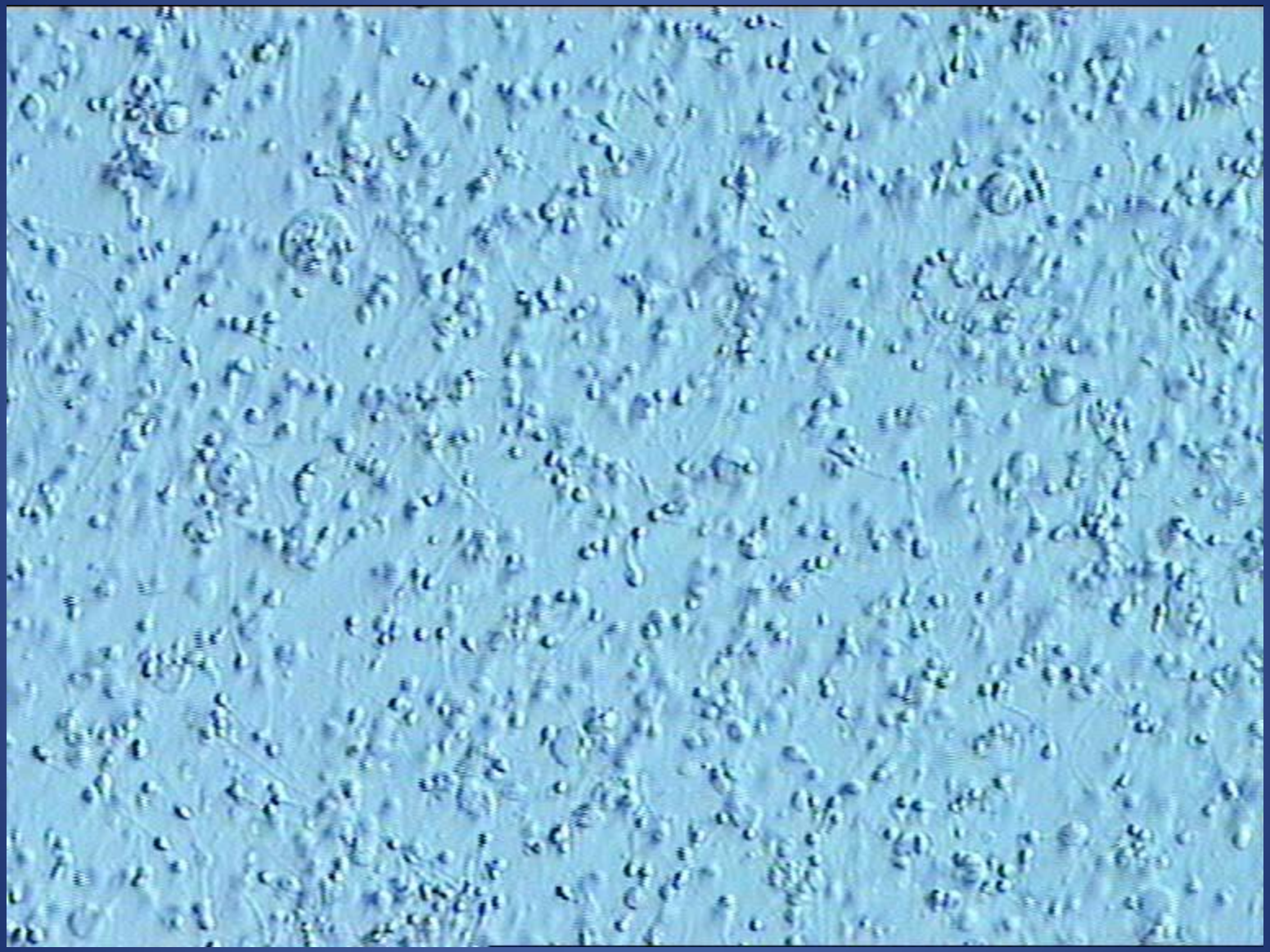


IS 40 REALLY THE NEW 30?

Here are the fertility facts you really need to know

Don’t Leave it too late

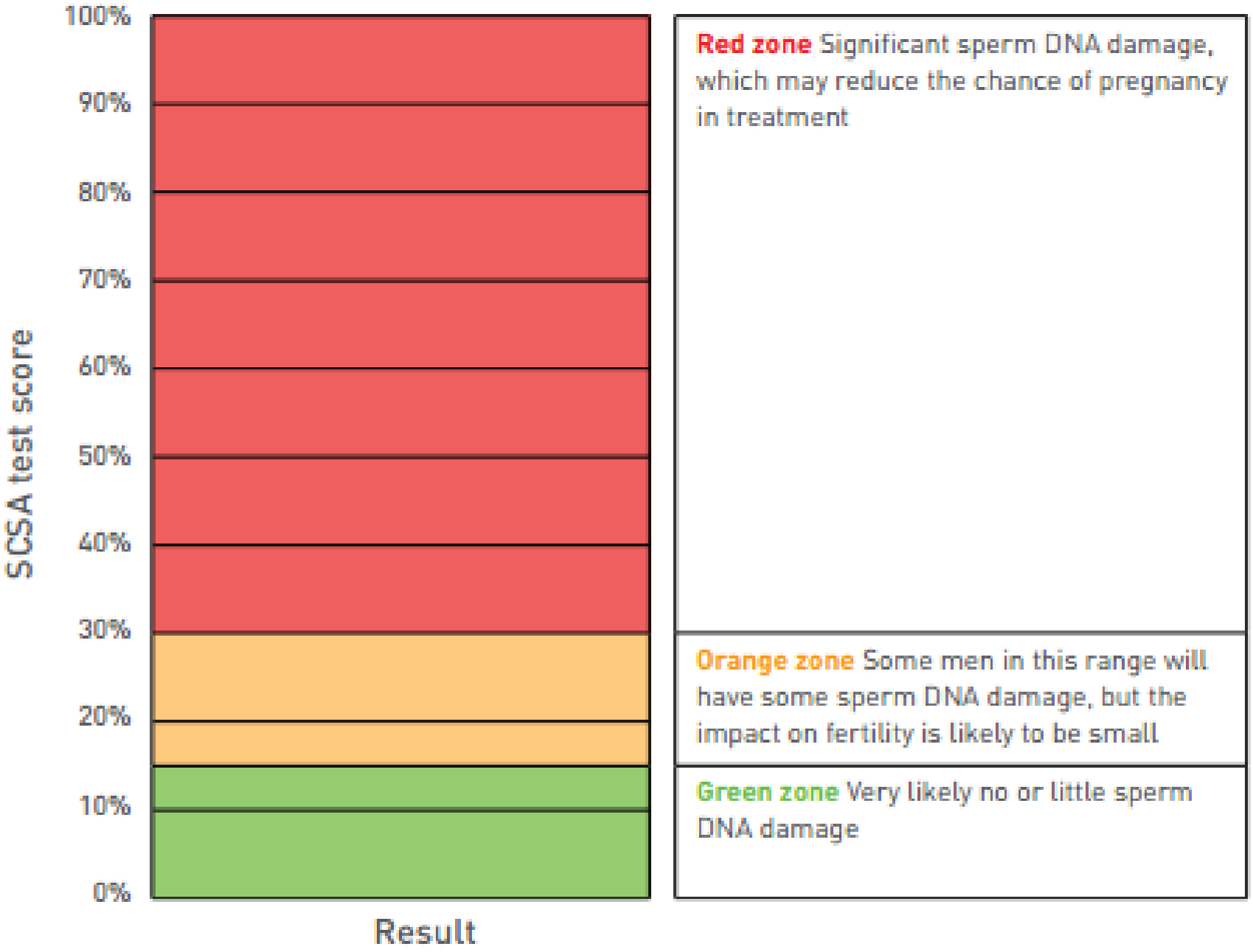
Sperm



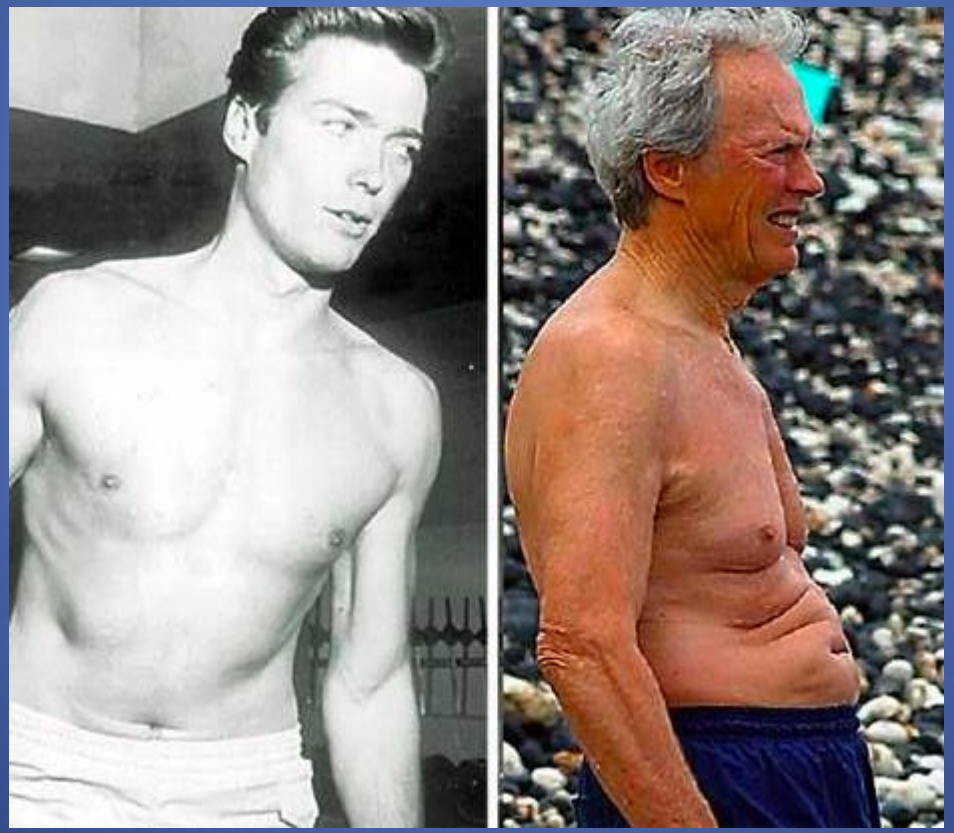
Sperm are like DNA Delivery Vans

…but what if the cargo is damaged

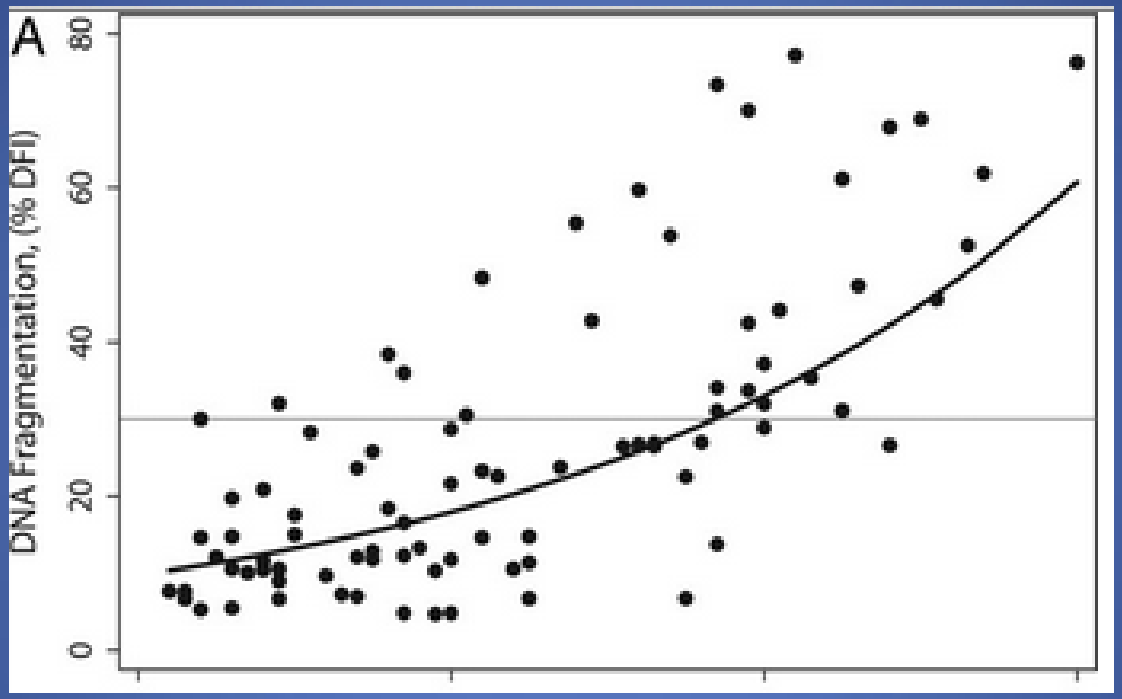
Your SCSA result



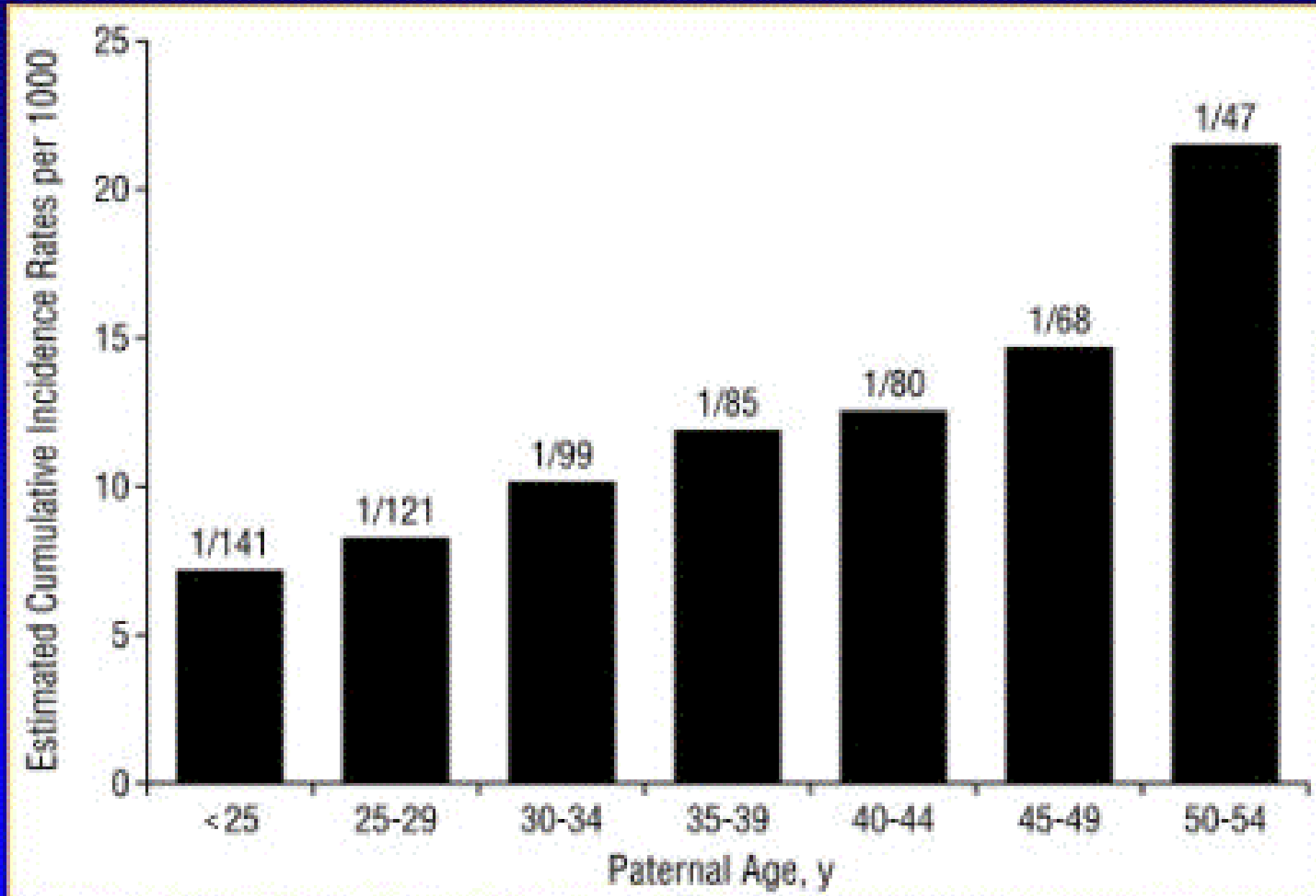
Men Have a Biological Clock Too



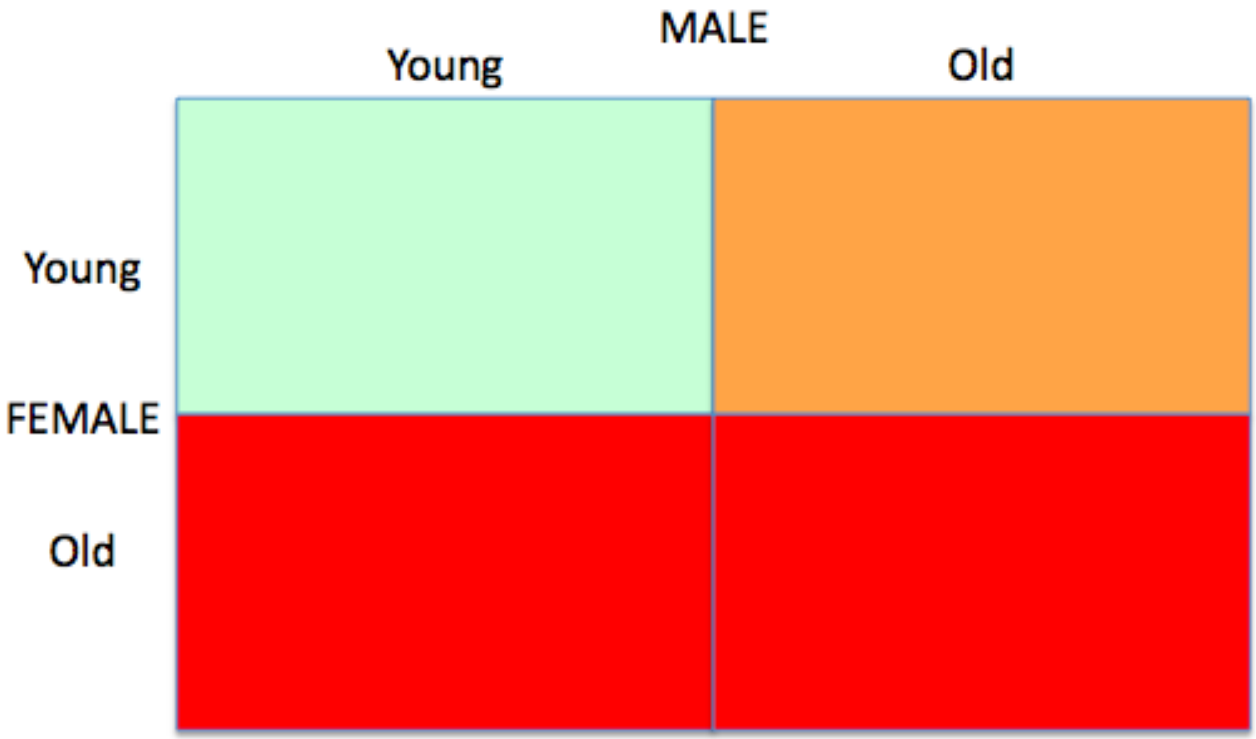
DNA damage increases with Age



Paternal age and schizophrenia risk



MISCARRIAGE RISK AND COUPLES AGE



Don’t Leave it too late for men either!

What lifestyle factors are important?

- Age
- Smoking
- Weight
- Diet and Exercise
- Psychological stress
- Caffeine consumption
- Alcohol consumption
- Exposure to environmental pollutants

Percentage of adults who smoke in NZ

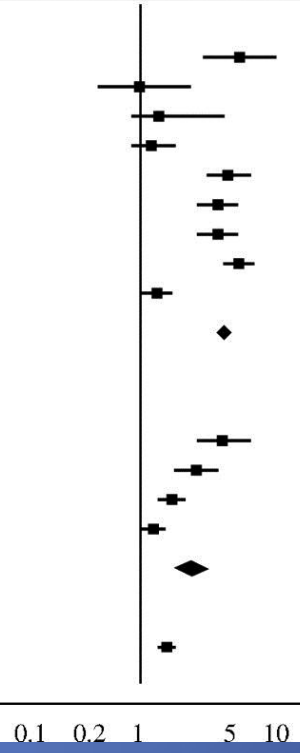
Smoking and male fertility

- In males smoking affects sperm production, motility, morphology and increases DNA damage
- Child born to a father who smokes has 4 X risk of childhood cancer

Smoking and female fertility

- Cotinine and cadmium detectable in follicular fluid
- Menopause occurs 1 to 4 years earlier
- Zona pellucida thicker

Study	Infertility cases (n) in smokers (N) (n/N)	Infertility cases (n) in non-smokers (N) (n/N)	OR (95%CI)	Weight (%)	OR (95%CI)
Cohort studies					
Baird–Wilcox (1985)	11/135	13/543		3.3	3.62 (1.58, 8.26)
de Mouzon (1988)	8/387	31/1500		3.5	1.00 (0.46, 2.19)
Spinelli (1997)	29/203	41/419		5.9	1.54 (0.92, 2.55)
Alderete (1995)	51/554	66/787		7.4	1.11 (0.76, 1.62)
Suonio (1990)	96/521	198/1677		9.0	1.69 (1.29, 2.20)
Laurent (1992)	241/1179	242/1535		9.8	1.37 (1.13, 1.67)
Bolumar (1996a)	298/1341	312/1837		10.1	1.40 (1.17, 1.67)
Bolumar (1996b)	358/1347	592/2642		10.3	1.54 (1.32, 1.90)
Jolle (1994b)	331/1323	452/2129		10.2	1.24 (1.05, 1.46)
Subtotal (95%CI) Chi-square 12.97 (dl = 8), $Z = 6.13$	1423/6990	1857/13069		69.5	1.42 (1.27, 1.58)
Case–control studies					
Tzohou (1993)	24/64	14/188		3.9	4.40 (2.13, 9.07)
Daling (1985)	60/159	25/159		5.6	3.25 (1.90, 5.54)
Joesoef (1993)	509/1815	261/1760		10.2	2.24 (1.89, 2.54)
Cramer (1985)	900/1880	1833/4023		10.7	1.10 (0.98, 1.22)
Subtotal (95%CI) Chi-square 68.50 (df = 3), $Z = 2.82$	1493/3938	2133/6110		30.5	2.27 (1.28, 4.02)
Total (95%CI) Chi-square 81.47 (df = 12), $Z = 516$	2916/10928	3990/19179		100.0	1.60 (1.34, 1.91)



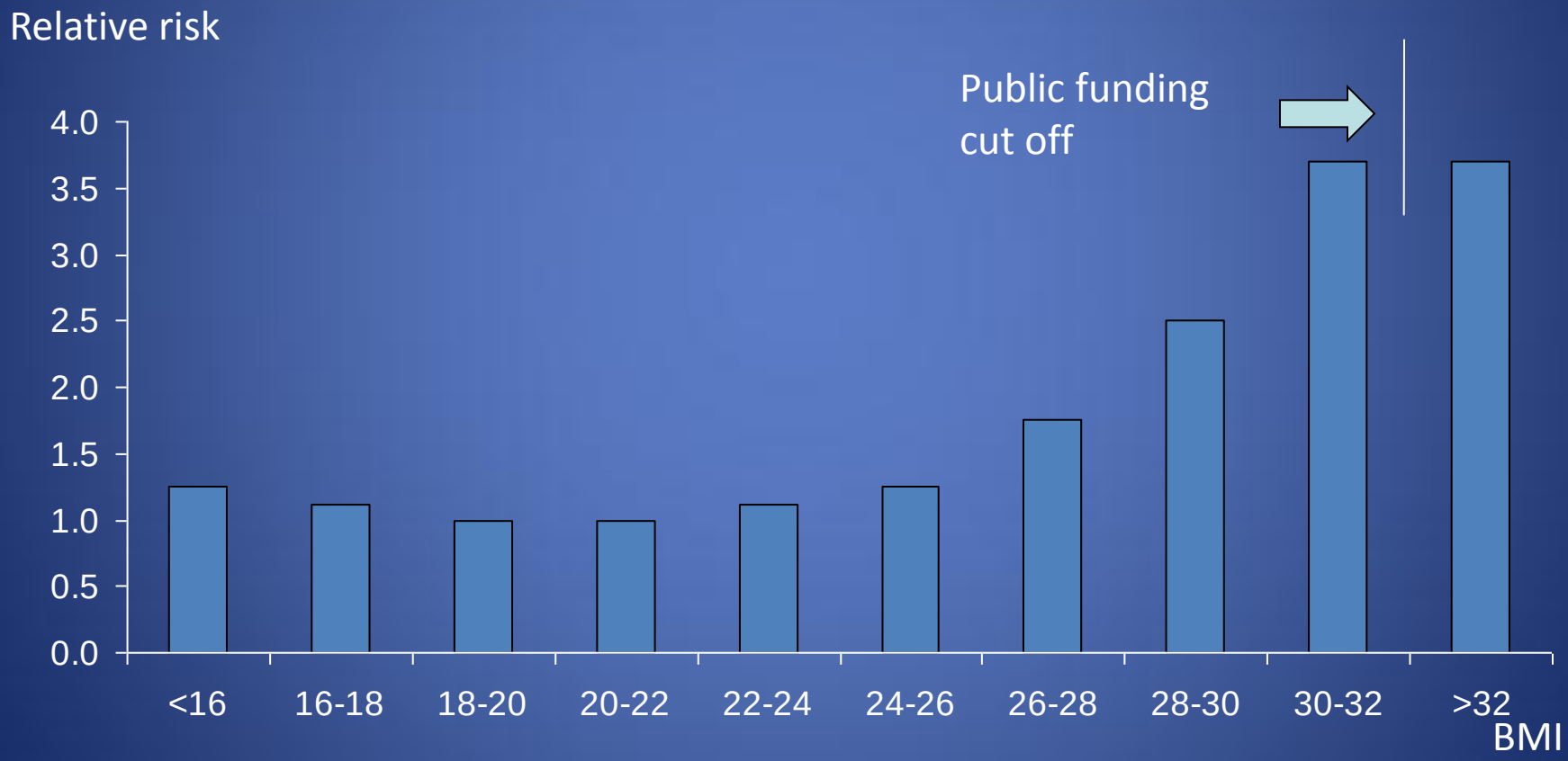
Homan, G.F. et al. Hum Reprod Update 2007 13:209-223; doi:10.1093/humupd/dml056

Human Reproduction Update

Implications of smoking in Fertility Treatment

- 9 studies OR 0.66 (95%CI 0.49-0.88) for pregnancy per number of IVF cycles
- Male smoking significantly reduced ICSI and IVF success rates
- Female smoking doubles risk of early pregnancy loss

Relative risk of infertility vs BMI



Weight…

Overweight men
Body Mass Index
(BMI > 28)
have sperm counts
22% lower

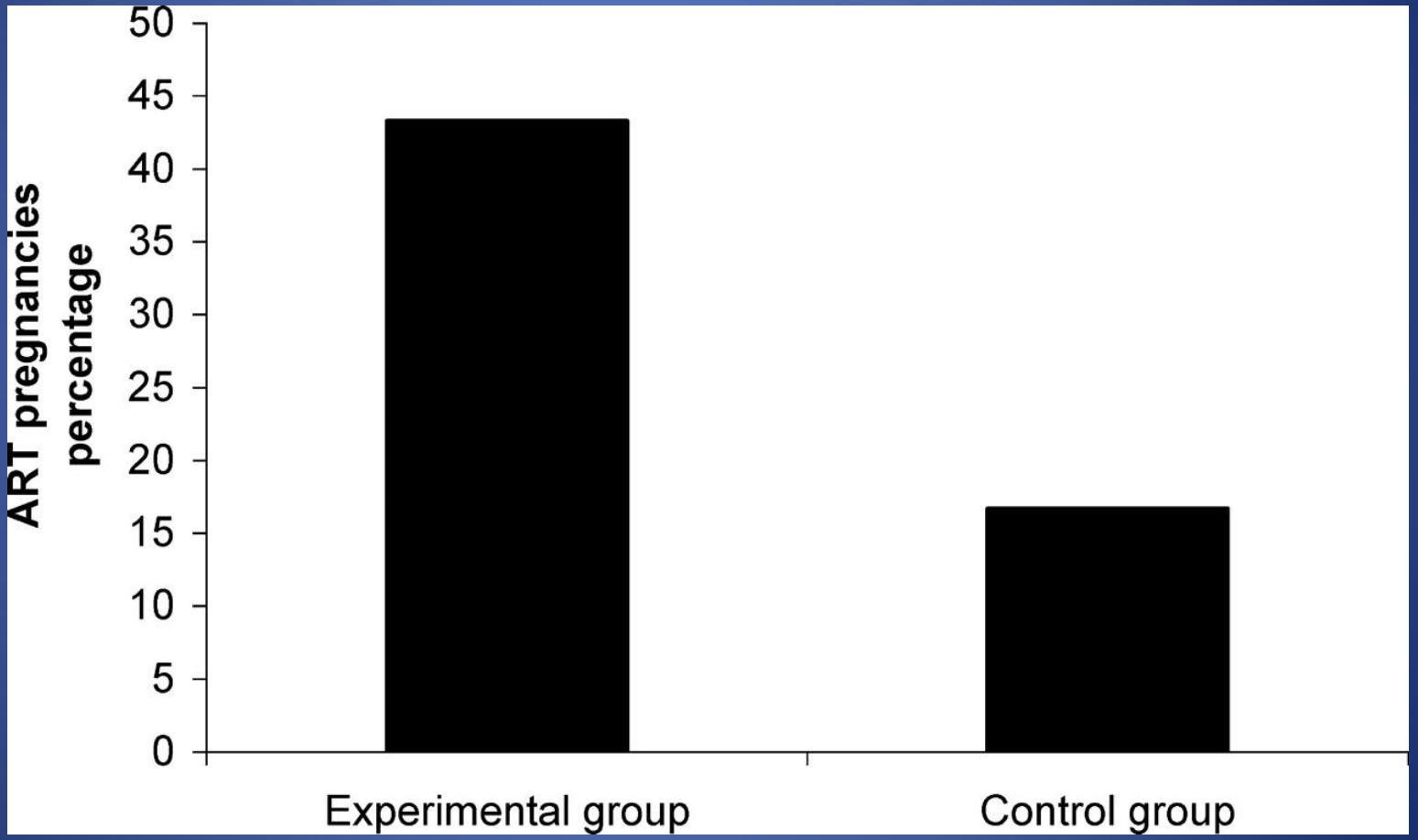
Lifestyle modification programmes

- 87 obese women (BMI>30)
- Weekly programme exercise and diet for 6 months
- Average weight loss 10kg
- 80% women were anovular, 90% ovulating at 6 months
- 78% pregnant 68% live birth

Stress

May reduce female reproductive performance through effects on autonomic, endocrine and immune systems

Effects of counselling and support on ART pregnancy rates



Homan, G.F. et al. Hum Reprod Update 2007 13:209-223; doi:10.1093/humupd/dml056

Caffeine…

Caffeine may impact on treatment

- 221 women (Cohen et al, 2002)
- Caffeine 2-50mg/day compared with nil
  OR 3.1(95%CI 1.0-9.7) for no livebirth
- Caffeine>50mg/day
  OR 3.9 (95%CI 1.3-11.6)
- Starbucks grande latte 150mg caffeine

Alcohol is not good for fertility, or baby

- Known teratogen
  (affects embryo/fetus development)
- Reduces female fertility
- Increases miscarriage risk
- Unknown safe level during pregnancy
- Men >20 standard drinks per week reduced numbers of pregnancies

What about Folic Acid?

- What dose?
- Folic acid alone or Multi vitamins?
- How long for?

What about Folic Acid?

- What dose?
  - If history of Neural Tube defect in first degree relative 5mg daily
  - Otherwise 0.5 to 0.8mg daily

- Folic acid alone or Multi vitamins?
  - Multivitamins with 0.4-0.8 folic acid showed a 92% reduction in NTD
  - Only the Multivitamin preparation showed an additional reduction in other defects eg. Urinary tract, limb deficiencies, pyloric stenosis

(Cziezel 2004)

- How long for?
  - 3 Months pre-conception and 1st Trimester

Take Home Messages

- Maintain a healthy weight

Take Home Messages

- Maintain a healthy weight
- Don’t smoke

Take Home Messages

- Maintain a healthy weight
- Don’t smoke
- Reduce caffeine



Take Home Messages

- Maintain a healthy weight
- Don’t smoke
- Reduce caffeine
- Reduce or avoid alcohol




Take Home Messages

- Maintain a healthy weight
- Don’t smoke
- Reduce caffeine
- Reduce or avoid alcohol
- Folic Acid





Take Home Messages

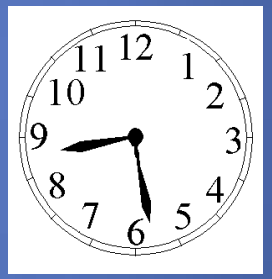
- Maintain a healthy weight
- Don’t smoke
- Reduce caffeine
- Reduce or avoid alcohol
- Folic Acid
- Consider Sperm health





Take Home Messages

- Maintain a healthy weight
- Don’t smoke
- Reduce caffeine
- Reduce or avoid alcohol
- Folic Acid
- Consider Sperm health
- Don’t leave it too late



Part 2

ADOLESCENT GYNAECOLOGY

Case 2: Painful Periods

Case 2: Painful Periods

- Jade is 17
- Menarche at age 13
- Periods have always been painful
- Has had heaps of time off school – is affecting her grades
- Wants to start nursing next year

What are our Goals?

- Treat symptoms effectively
- Maximize quality of life
- Ultimately make a diagnosis if possible

Painful Periods

- Primary Dysmenorrhoea
- Secondary Dysmenorrhoea
  - Endometriosis
  - Adenomyosis
  - Pelvic inflammatory disease
  - Adhesions
  - Outflow Obstruction
  - Ovarian cysts
  - Inflammatory bowel disease

Primary Dysmenorrhoea

- Prevalence as high as 90%
- Under reported
- Rates of absenteeism range from 34 to 50 percent
- US Study 600 million lost work hours and $2 billion in lost productivity annually

Andersch B, Milsom I. An epidemiologic study of young women with dysmenorrhea. Am J Obstet Gynecol. 1982;144:655–60.

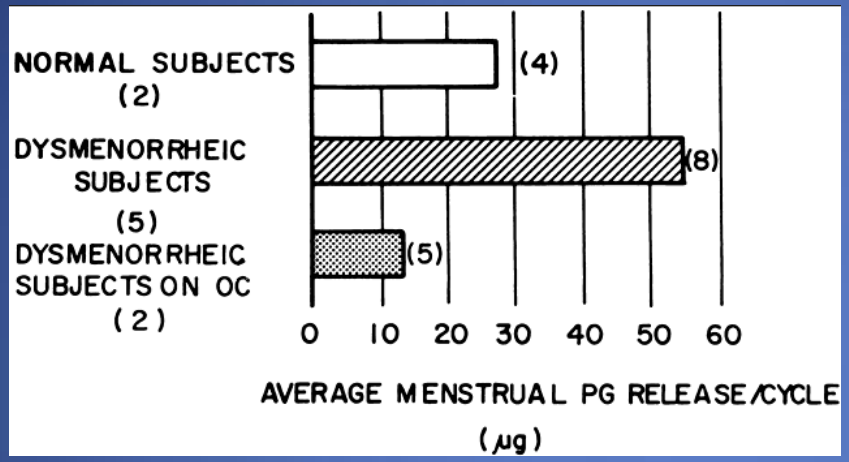
Sundell G, Milson I, Andersch B. Factors influencing the prevalence and severity of dysmenorrhea in young women. Br J Obstet Gynaecol. 1990;97:588–94.

Primary Dysmenorrhoea: Risk Factors

- earlier age at menarche
- long menstrual periods
- smoking
- obesity
- alcohol consumption

Harlow SD, Park M. A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women. Br J Obstet Gynaecol. 1996;103:1134–42

The pathology dictates the treatment



Chan WY, Dawood MY: Prostaglandin levels in menstrual fluid of nondysmenorrheic and dysmenorrheic subjects with and without oral contraceptive or ibuprofen therapy. Adv Prostaglandin Thromboxane Leukotriene Res 8:1443, 1980

- PGF2α released as menstruation begins
- PGF2α stimulates myometrial contractions ischemia and sensitization of nerve endings

Treatment

- NSAIDs
- 73 RCTs in Cochrane review 2010

  Nonsteroidal anti-inflammatory drugs for dysmenorrhoea

  Jane Marjoribanks et al.
- NSAIDs were significantly more effective for pain relief than placebo (OR 4.50, 95% CI: 3.85, 5.27).
- NSAIDs were also significantly more effective for pain relief than paracetamol (OR 1.90, 95% CI:1.05 to 3.44).
- When NSAIDs were compared with each other there was little evidence of the superiority of any individual NSAID for either pain-relief or safety

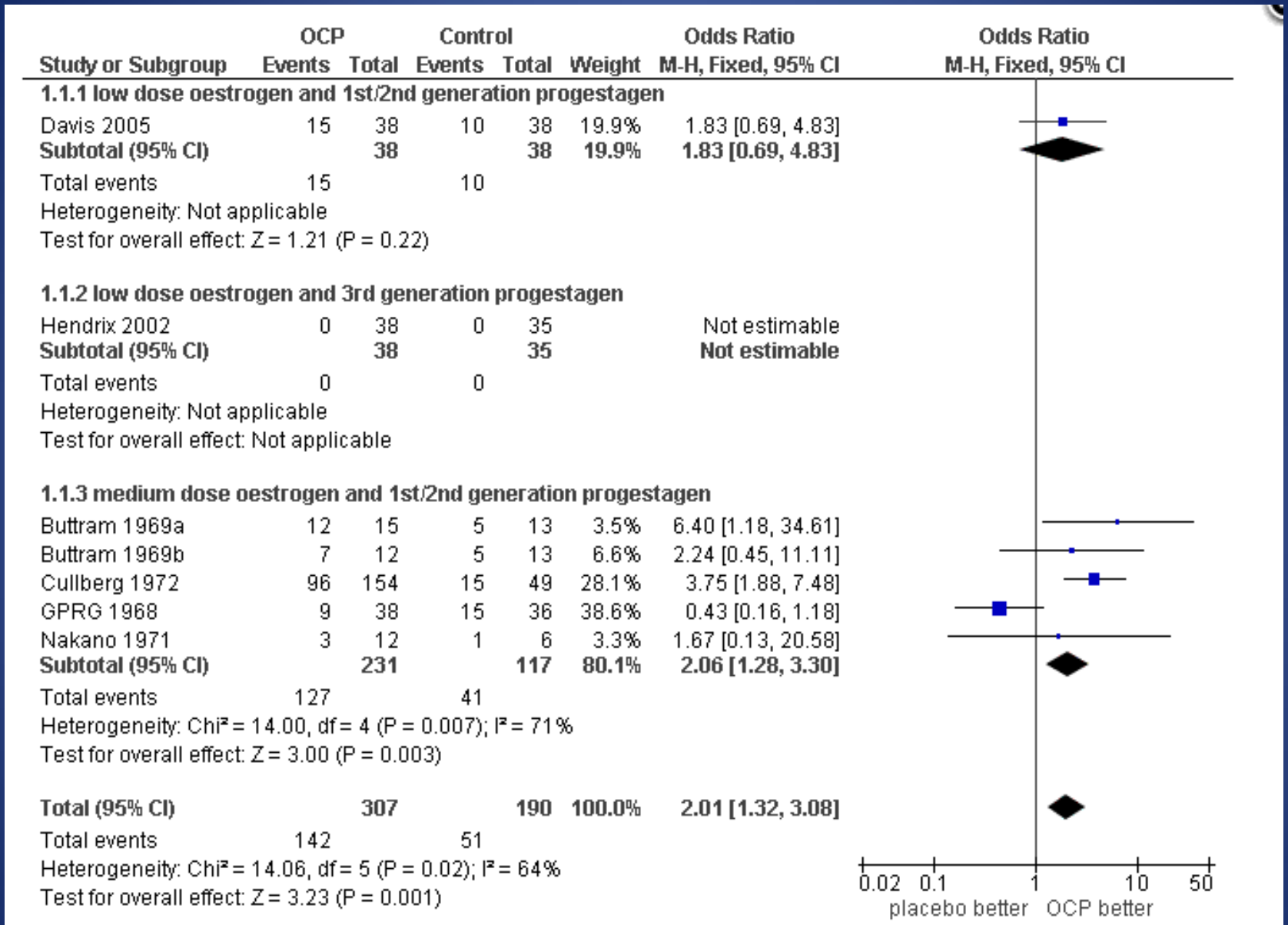


Figure 3. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.1 Pain improvement.

Take Home Messages Primary Dysmenorrhoea

- NSAID are very effective BUT
- Women need to use them effectively

- Combined OCP also very effective

- NSAID/OCP in conjunction will help

What helps distinguish Primary from Secondary Dysmenorrhoea?

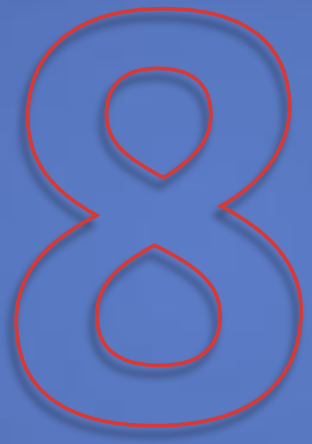
- Dysmenorrhea during the first one or two cycles (congenital outflow obstruction?)
- Dysmenorrhea beginning after 25 years of age
- Pelvic abno
- Coexisting i
  - endomet
  - scarring
- Heavy menstrual flow or irregular cycles
  - adenomyosis, fibroids, polyps
- Dyspareunia
- Little or no response to NSAIDs or OCP

If these are present refer

other causes of

10

9

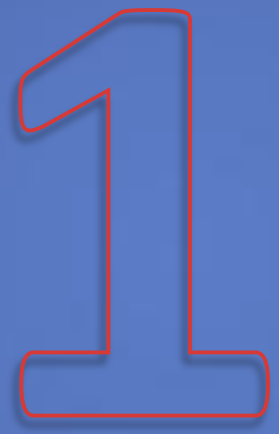


6


5


4

2



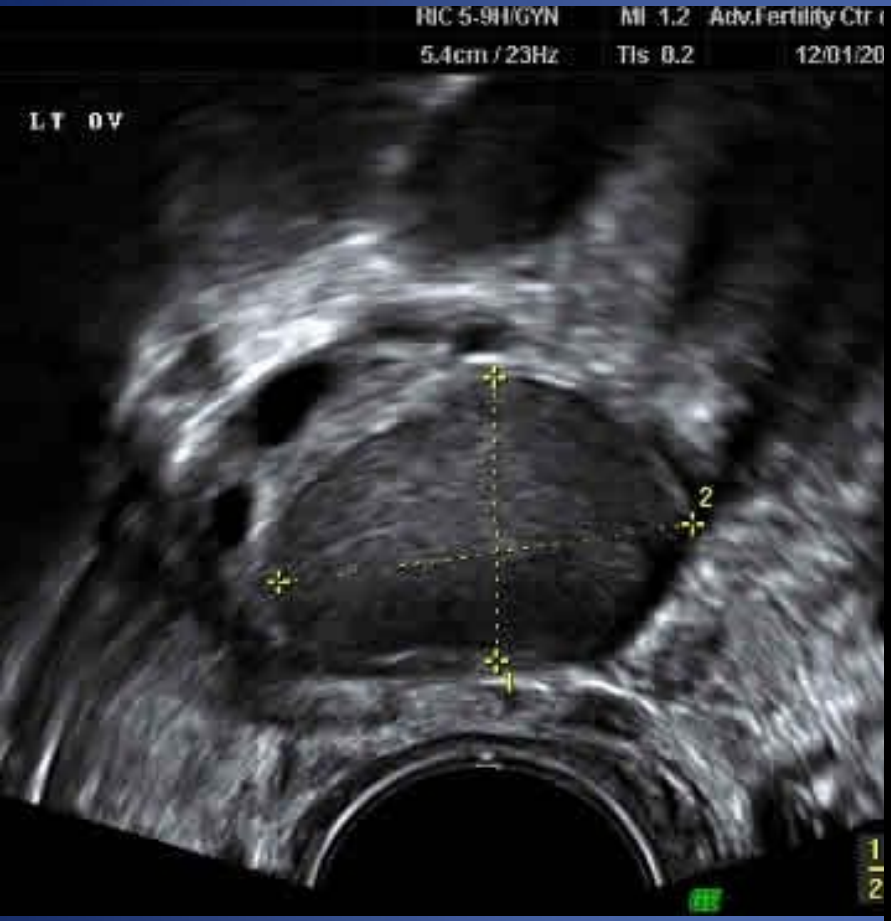
7 Years!

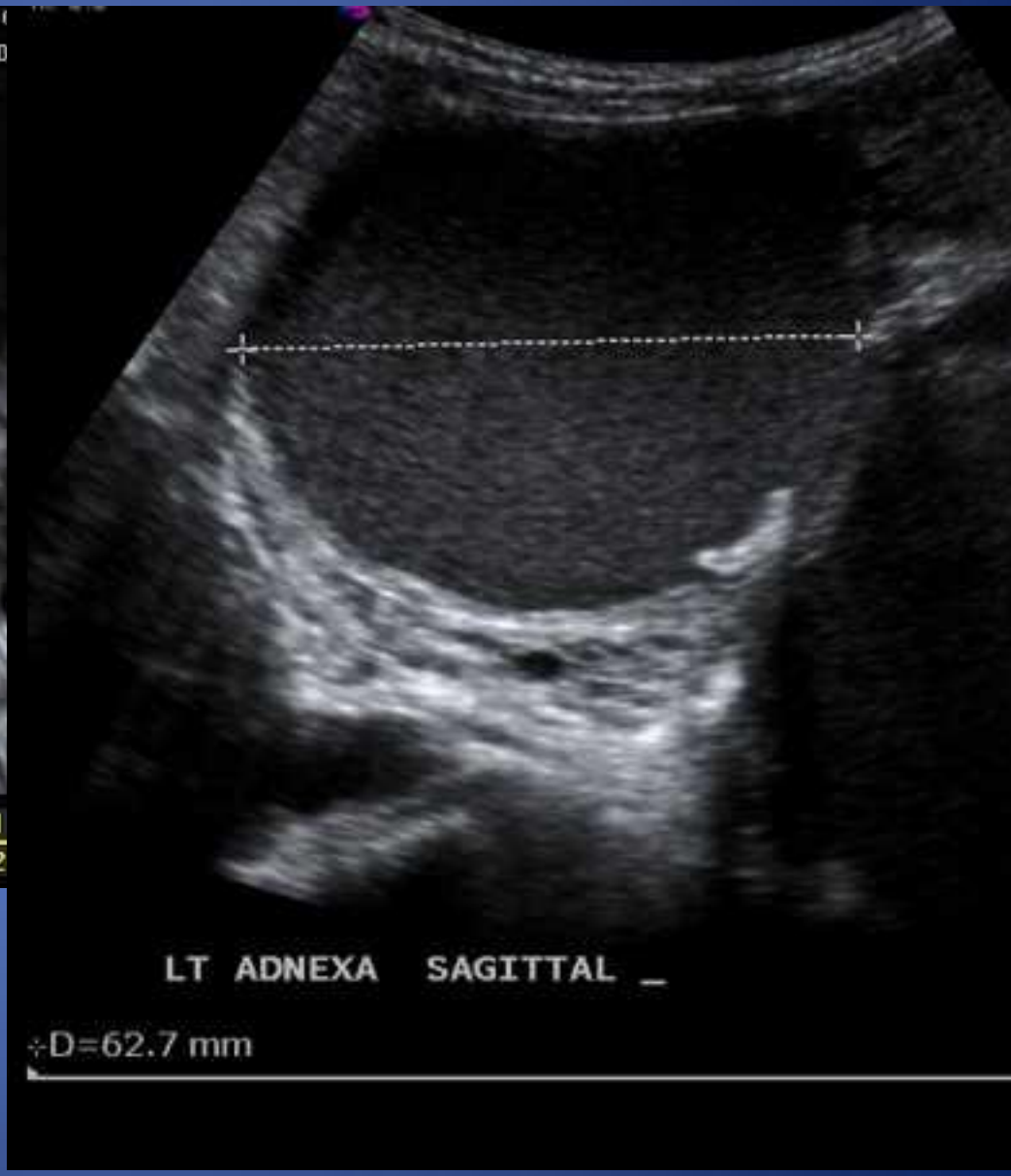
How is it Endometriosis best diagnosed?

- History

How is it best diagnosed?

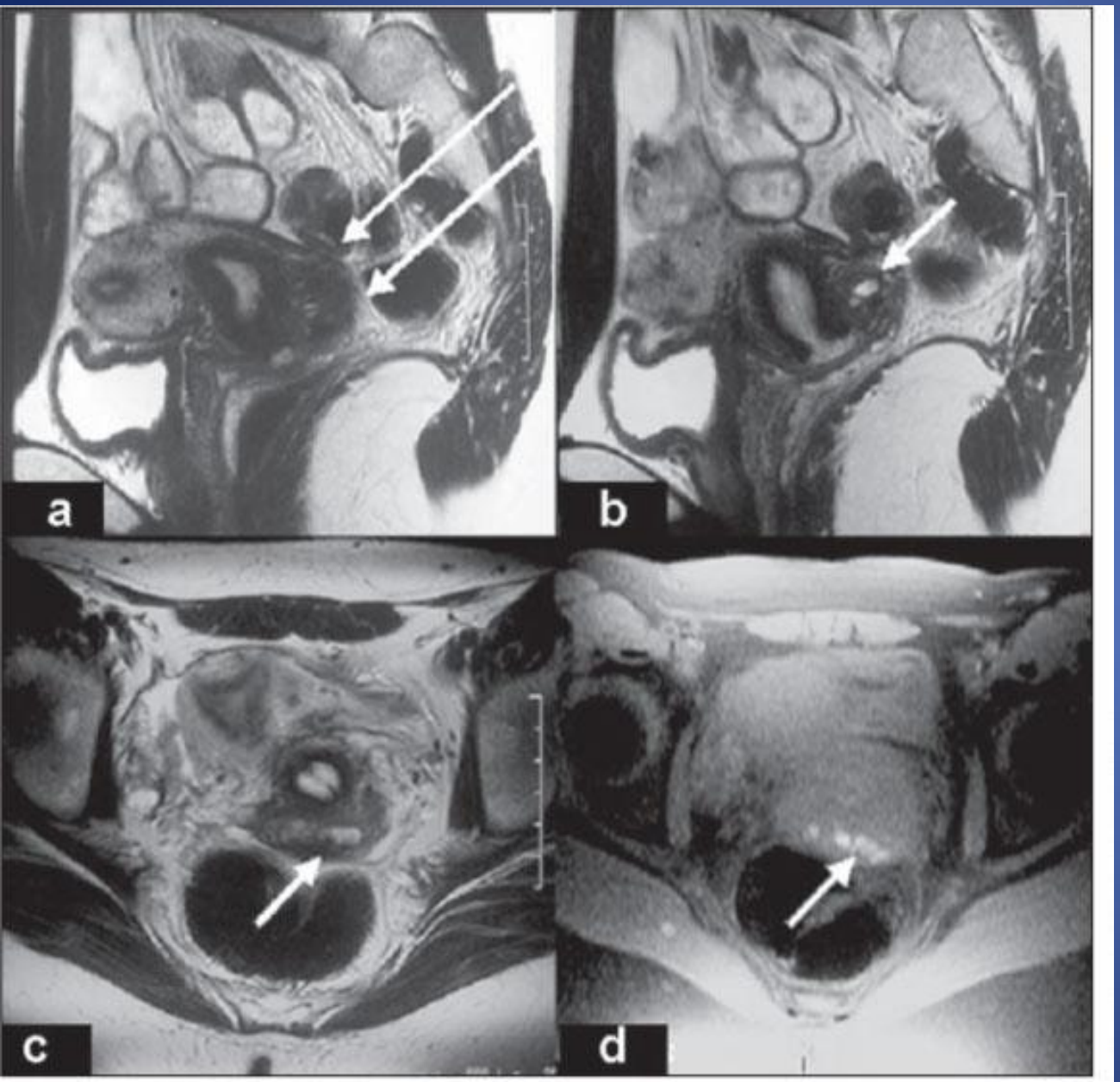
- History
- Ultrasound


RIC 5-9H/GYN
MI 1.2
Adv.Fertility Ctr
5.4cm / 23Hz
TIs 0.2
12/01/20
LT OV
2


LT ADNEXA SAGITTAL _
D=62.7 mm

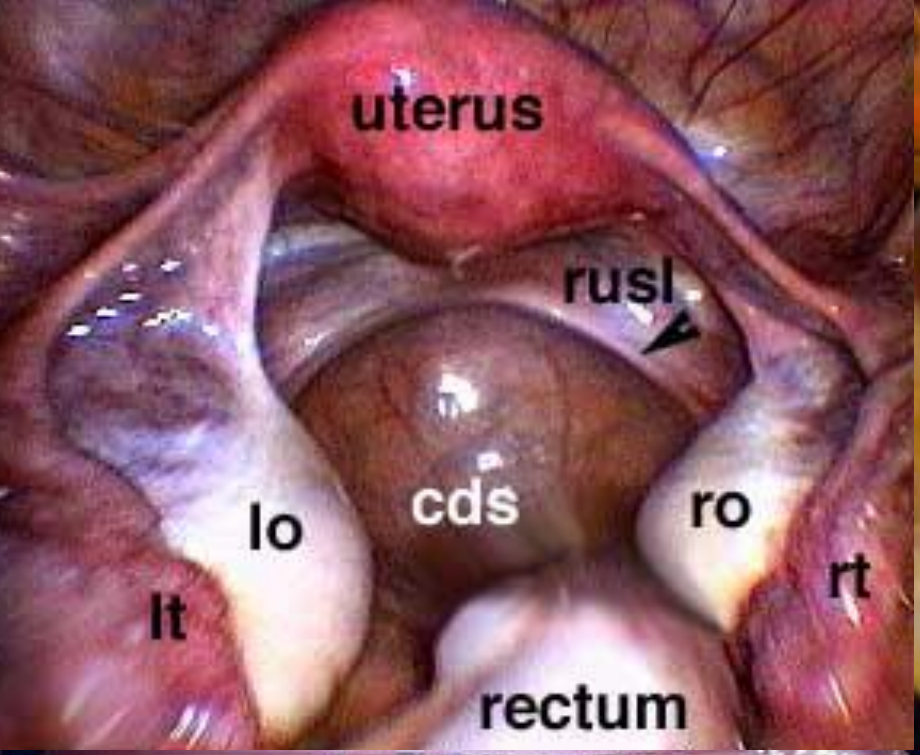
How is it best diagnosed?

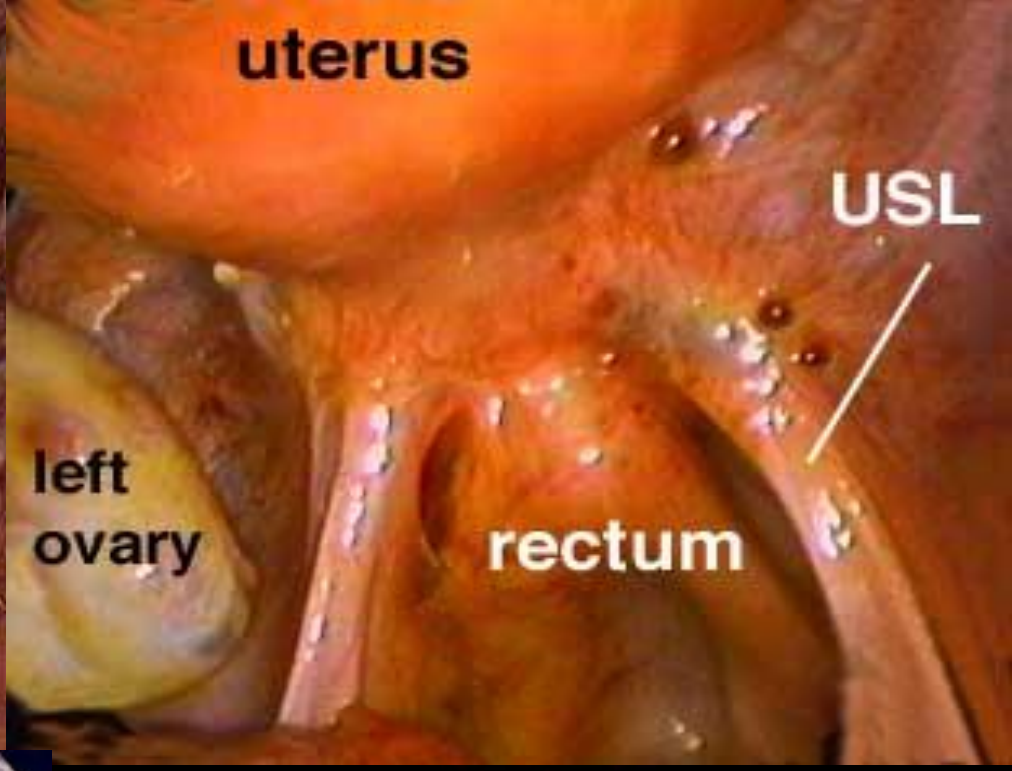
- History
- Ultrasound
- MRI?

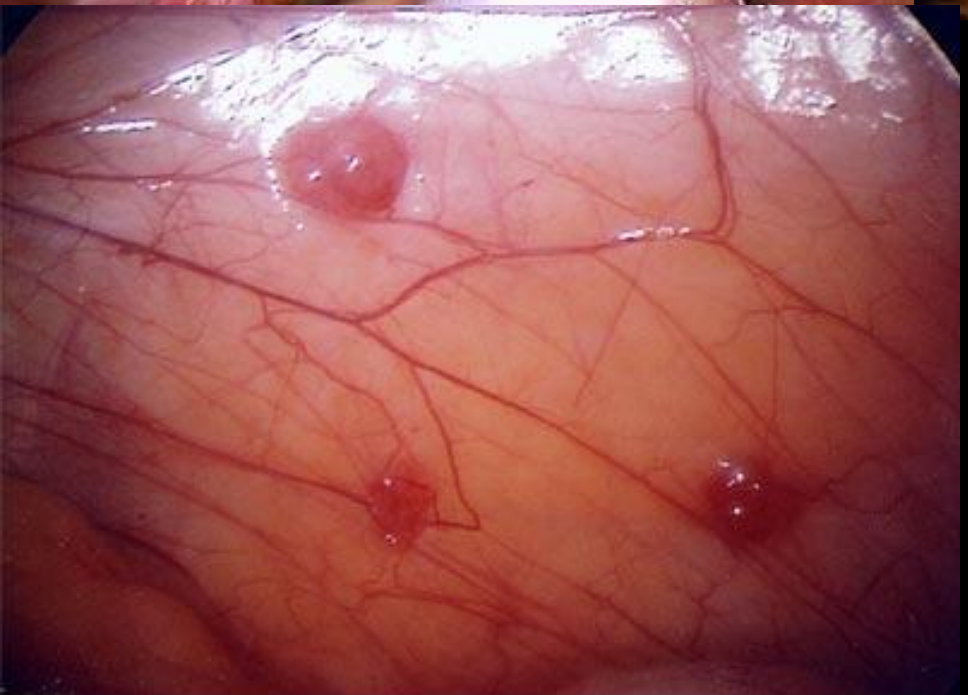

a
b
c
d

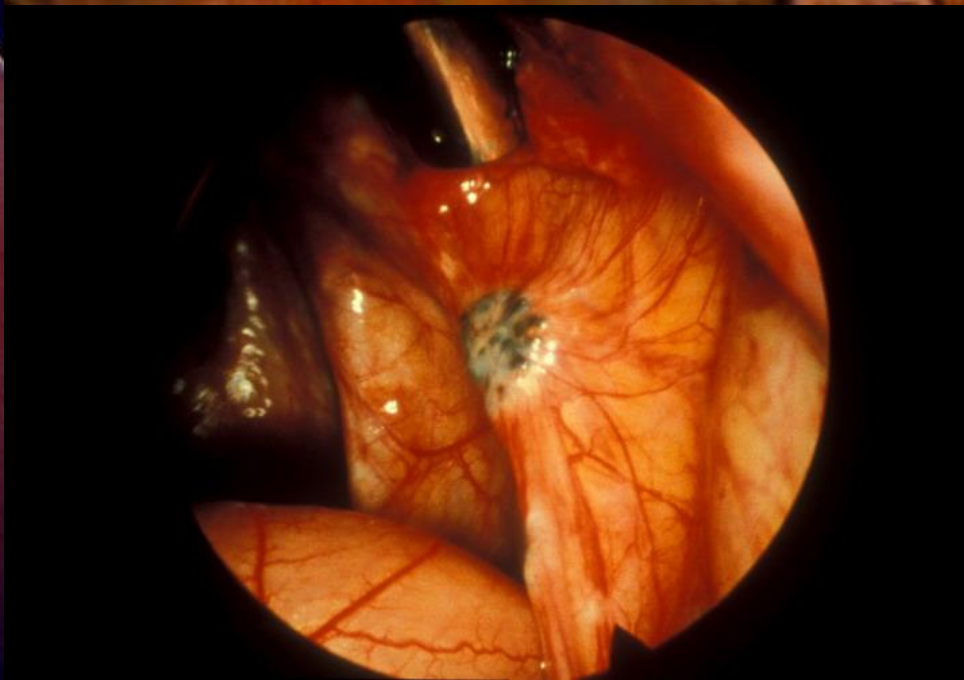
How is it best diagnosed?

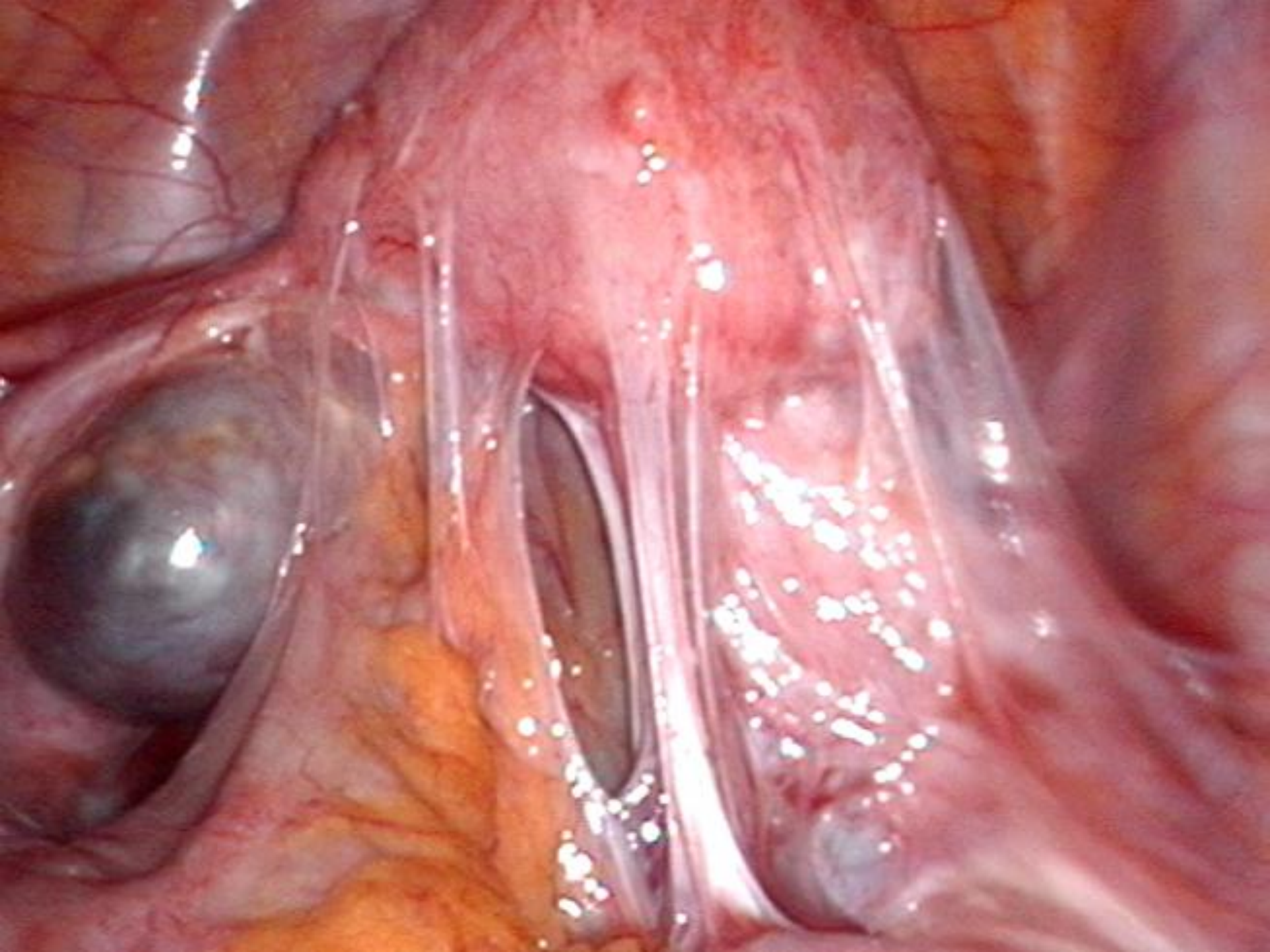
- History
- Ultrasound
- MRI?
- Laparoscopy


uterus
rusl
lo
cds
ro
rt
lt
rectum


uterus
USL
left
ovary
rectum







Take Home Points

- Dysmenorrhoea is under-estimated
- Huge Social Cost
- Don’t Assume Patient is treating symptoms with OTC meds
- NSAIDs and OCP good first line (90% efficacy)
- Lack of response ? Endo
  - Arrange scan and refer

Case 3: Absent Periods

Case 3: Absent Periods

- Jacinta 16
- No period yet
- Keen runner (>50km/week)

"My girlfriends have all had there period for years, I'm not bothered, but Mum said I have to get this checked out"

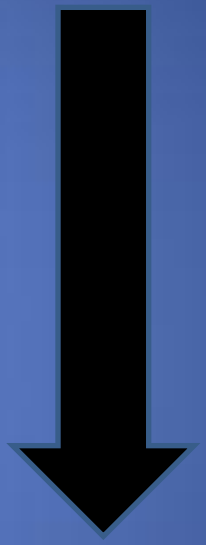
Primary Amenorrhea

Definition

- Failure of menses to occur by age 16 years.
- Failure of menses to occur within 5 years of first secondary sexual characteristics.

Normal Sequence of Development

- breast budding
- development of pubic hair
- accelerated growth
- finally menarche



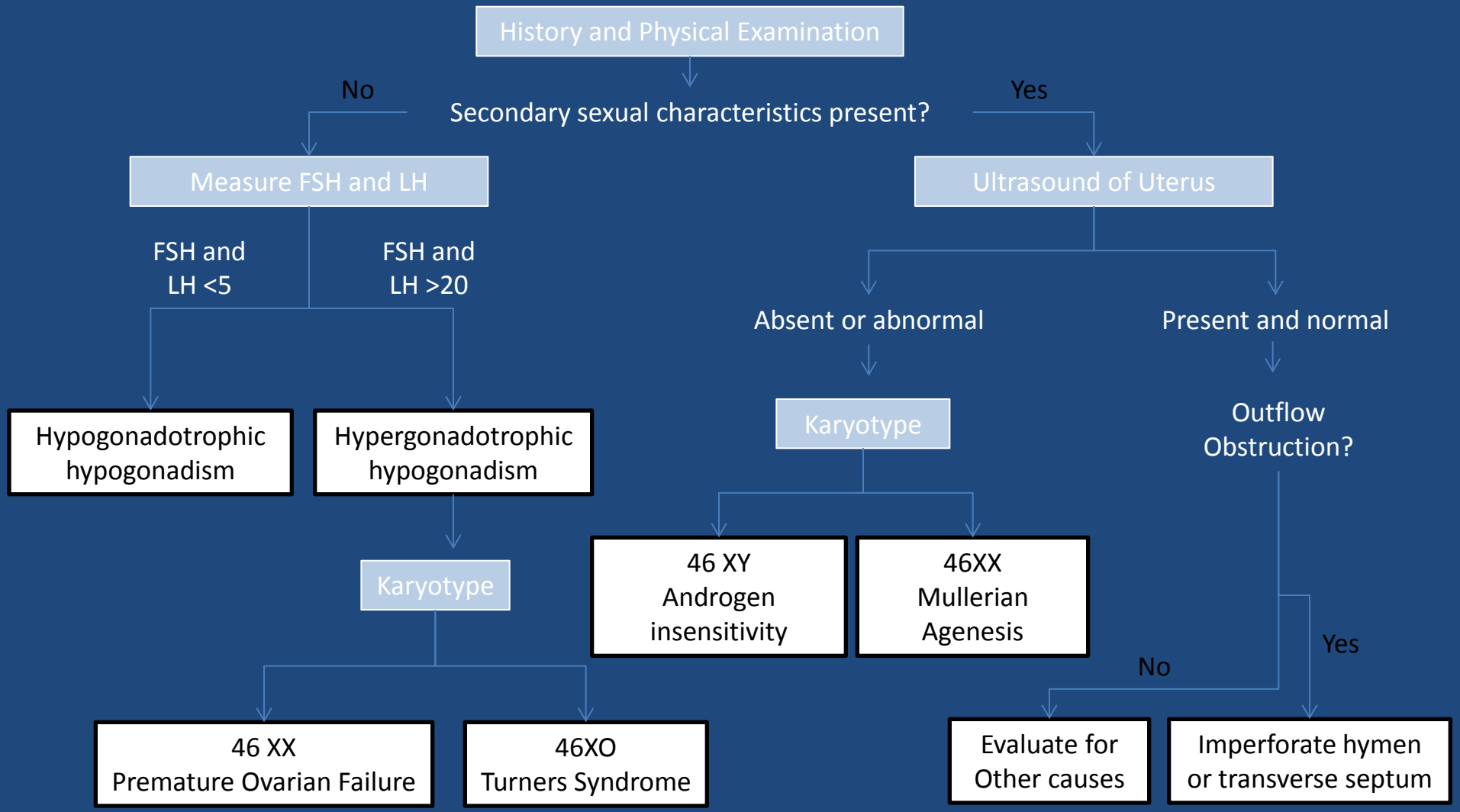
Question to Ask?

- Is there otherwise normal sexual development?
- If No, constitutional/idiopathic is most likely diagnosis
- If Yes, next thing to establish – Is there a Uterus?

Basic Investigations

- Karyotype
- FSH
- Abdomino-pelvic ultrasound.

Evaluation of Primary Ammenorrhoea



Important to rule out

Pregnancy

Thyroid Disease

Prolactinoma

Referral

Treatment

- Treat Underlying cause
- Prevention of osteoporosis,
- Progression of normal pubertal development

In our case?

- Wasn’t pregnant
- Normal TSH, Prol, Karyotype
- Had uterus on scan
- BMI 17

- Counseled to reduce exercise intensity
- Dietician re Increasing BMI
- OCP to induce bleeds, protect bones until BMI healthier

Part 3

MENSTRUAL DISORDERS

Case 4: Irregular Periods

- Judy is 32
- She stopped the pill bout 9 months ago
- Only 2 periods since
- Skin is now “terrible”
- Last period was really heavy

“What is wrong with me? My cycle is everywhere and I’d like to have better skin again … its really getting me down.”

What are our Goals?

- Make the right diagnosis
- Target therapy to the symptoms
- Manage long term health implications

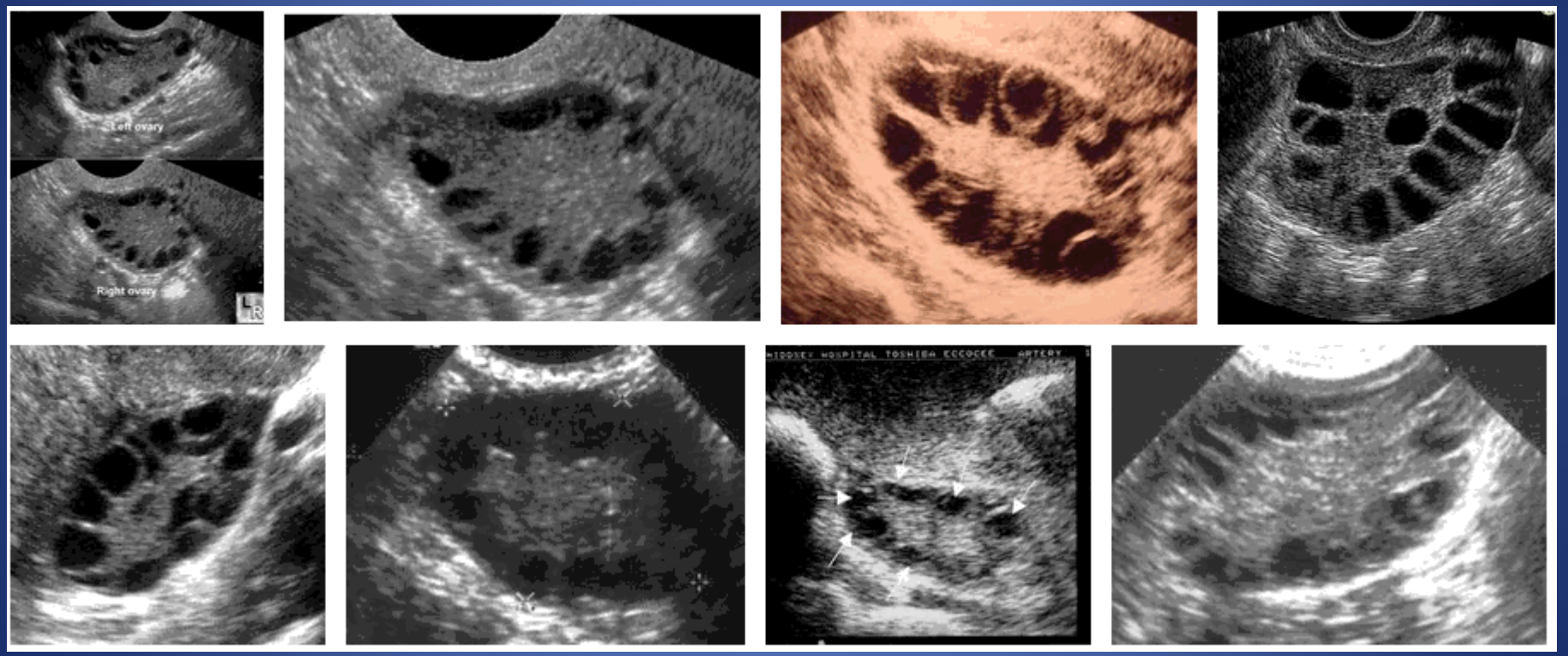
Polycystic Ovary Syndrome

2 out of the following 3 features:

- Irregular or Absent periods
- Clinical (acne or hirsutism)
  Biochemical (raised LH or T)
  evidence of raised androgens
- Polycystic Ovaries on Scan

Exclude other causes……. Check Prolactin and TSH

POLYCYSTIC OVARIES



Prevalence

- Polycystic Ovaries (PCO)
  - increased ovarian stroma
  - 12+ follicles 2-9mm
  - increased ovarian volume (>10ml)

25%

- Polycystic Ovarian Syndrome (PCOS)

  above + signs of excess androgens

  - oligomenorrhoea
  - obesity
  - acne and hirsutism

5%

Clinical Presentation

- Menstrual Dysfunction
  - periods often <6/yr
  - unopposed E_2
  - Not all PCOS women are anovulatory

    (CL seen in 16% of PCO at laparoscopy)
- Androgen Excess
  - hirsutism
  - acne
- Infertility
  - anovulation
  - ?increased m/c
  - preg rate not equal to ovulation rate even with Rx
- Obesity
  - approx 50%
  - android pattern
  - long term implications

Genetics and PCOS

- >70 genes identified
- Gonadotrophins
- Androgens
- Insulin Signalling
- Obesity

PCO and Insulin Resistance

- Hyperinsulinaemia and insulin resistance.
- 20-40% PCO women go on to develop NIDDM (especially obese).
- In PCO there is probably a post-receptor defect.

PCO and Insulin Resistance

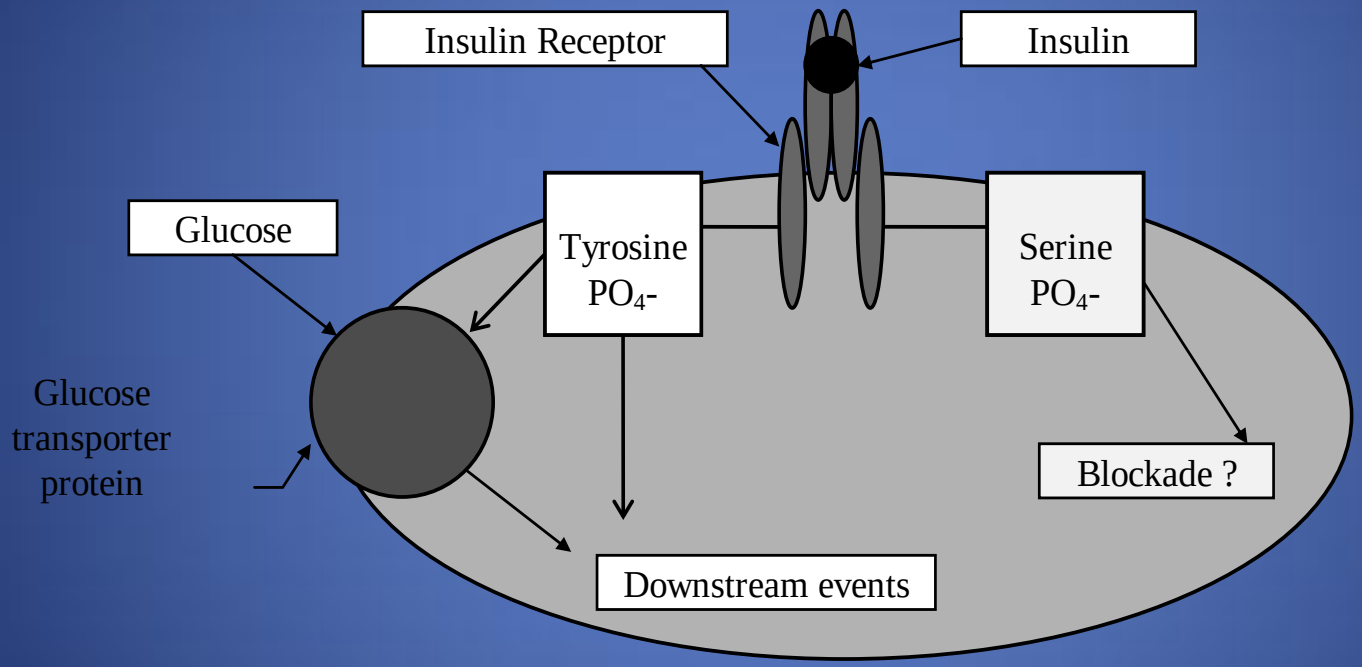


Fig. 1: Possible intracellular events after activation of the insulin receptor by insulin binding in women with polycystic ovary syndrome

PCO and Long term disease risks

Table 1. Long term Disease Risks in Polycystic Ovary Syndrome (independent of obesity)

Increased risk definite or very likely	
	Type 2 Diabetes Mellitus
	Dyslipidaemia
	Endometrial Cancer
Increased risk possible	
	Hypertension
	Cardiovascular disease
	Gestational diabetes mellitus
	Pregnancy-induced hypertension
	Ovarian Cancer
Increased risk unlikely	
	Breast cancer

from Solomon CG: The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks. Endocrin Metab Clin N America 28(2):247-263, 1999

Treat the Presenting Symptom

- Cycle Control
  - OCP
    - Increases SHBG (reduces free T)
    - Protects against Endometrial Hyperplasia
    - Cypreterone containing OCP eg Diane, Estelle
- Hirsutism
  - OCP
  - Spirinolactone
- Metabolic Protection
  - Understanding CHO Metabolism –> low carbs
  - Metformin
  - Exercise
- Fertility
  - Weight control
  - Clomiphene
  - Advanced Treatment (gonadotrophins, ovarian diathermy, IVF)

Case 5: Heavy Periods

- Anna is 44
- 3 children (14, 11 and 7)
- Last 24 months increasingly heavy periods
- Knows where every loo in the shopping mall is
- Has had a couple of “accidents” with bleeding
- Is very tired all the time

“I’m fed up with this … its doing my head in!”

What are our Goals?

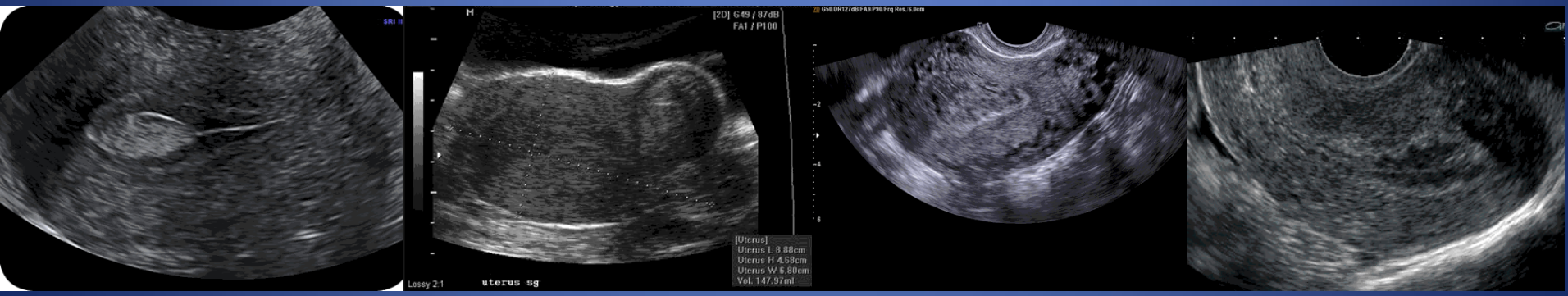
- Make the right diagnosis
- Improve quality of life
- Have a definitive plan in place

HMB: Differential Diagnosis

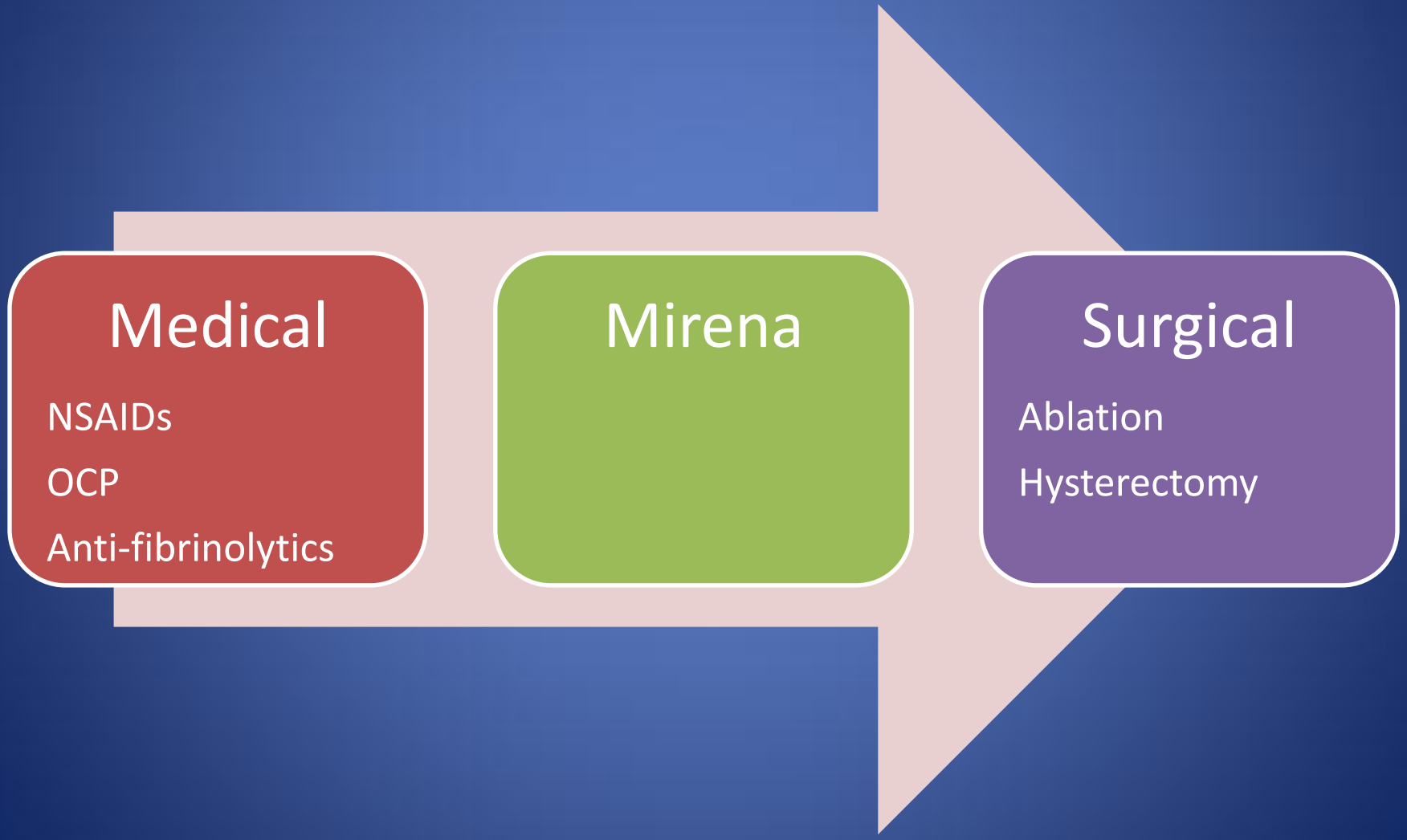
- Fibroids
- PCOS
- Polyps
- Endometriosis
- Endometrial Hyperplasia
- Dysfunctional uterine bleeding

HMB: Standard Work Up

- History and Exam
- FBC, Iron Studies, TSH
- Ultrasound



HMB Treatment Options:

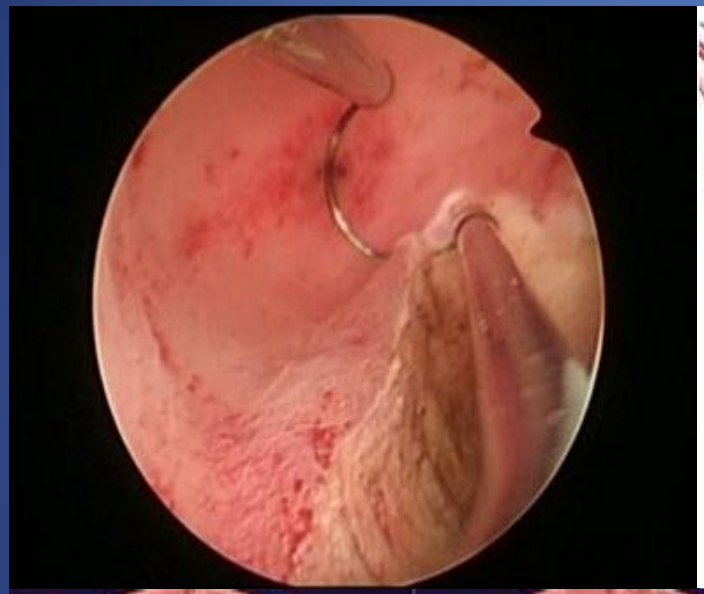


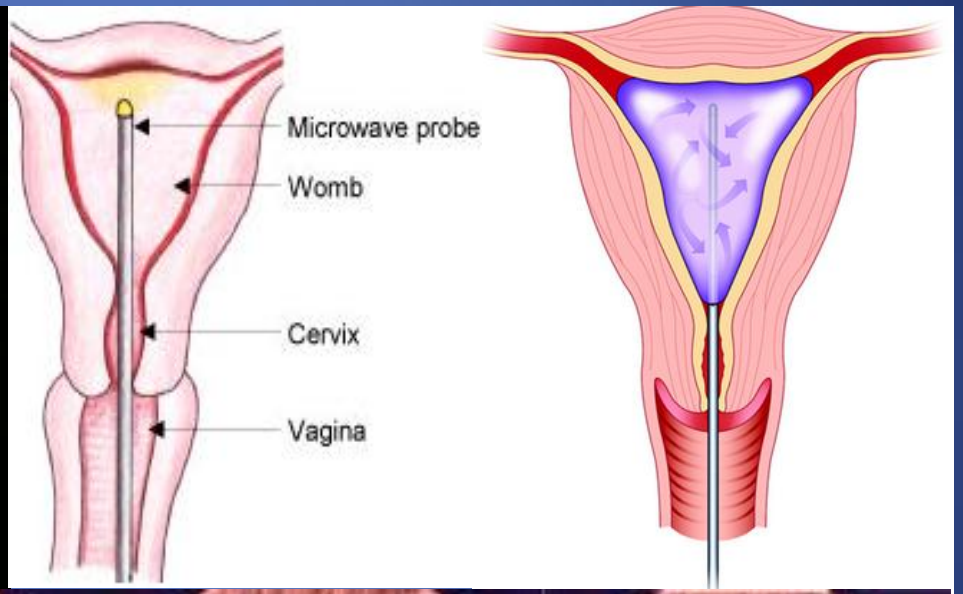
Treatment Options: Medical and Reversible

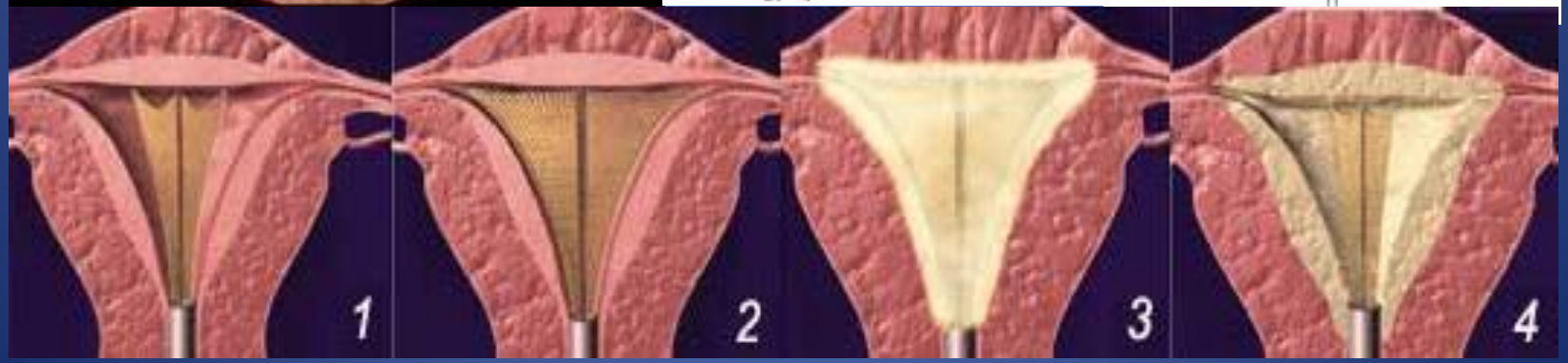
- NSAIDs — reduce PGs
- OCP — most women are "over the OCP"
- Danazol — bad side effects
- Tranexamic Acid — the most effective oral therapy
- Mirena — very effective 90% experience less or no bleeding

» Hb <110 or Ferritin <15 > Pharmac will subsidise

Treatment Options: Surgical and Irreversible







Hysterectomy

- Abdominal
- Vaginal
- Laparoscopic

- “I wish I had done this years ago..”

Part 4

MENOPAUSE

Case 6: Menopause

- Martha is 52
- Last period was 12 months ago
- Distressing hot flushes (soaks bed at night)
- Not interested in sex, it has become uncomfortable

“I’m just not myself, I don’t seem to be able to think straight!”

What are our Goals?

- Alleviate Symptoms
- Improve quality of life
- Minimize/Counsel regarding Risks/Benefits

HRT

- Who Can
- Who Cant
- Pros
- Cons
- How Long
- Other Options

HRT: Who?

- Women with symptoms interfering quality of life
- Exclude other possible causes:
  - Thyroid
  - Depression
  - Diabetes
  - Iron deficiency
  - Drug effects

Review after 6 months then annually

Are needs being met?
Any new contraindications?

HRT

urogenital symptoms alone → vaginal oestrogen

hysterectomy → continuous oestrogen

Intact Uterus

Premature Menopause

<40 Years
Continue HRT until 50 years unless contraindicated

Low dose OCP

Or

Continuous Oestrogen
+
Cyclic/continuous Progestin

Menopausal Transition

Low dose COC if Cardiovascualr Risk Profile Low

Or

Continuous Oestrogen
+
Cyclic Progestin
14 days

Or

Continuous Oestrogen
+
LNG IUD

Post Menopausal

Continiuous Oestrogen
+
Continuous Progestin if menopause >1 year ago

Or

Continuous Oestrogen
+
Cyclic Progestin
Or
LNG IUD

Non HRT Options for Hot Flushes

- Venlafaxine
- Paroxetine
- Clonidine
- Gabapentin

HRT Contraindicated

- history of breast cancer
- endometrial cancer
- unexplained vaginal bleeding
- history of DVT
- history of, or increased risk of, heart disease or stroke

Possibly Contraindicated

- liver disease
- migraines
- epilepsy
- diabetes
- gall bladder disease
- fibroids
- endometriosis
- hypertension

Consider Route of Administartion

Weigh Up Risks vs Benefits

HRT Benefits

Treatment of menopause symptoms

- hot flushes and vaginal dryness
- lowered mood
- anxiety
- insomnia
- headaches,
- muscle and joint pain
- decreased sex drive

HRT Benefits

Osteoporosis

- Prevention of bone loss.
- Decreases fractures of the verterbrae by up to 40 per cent
- Reduces hip fractures

Heart disease

- Original studies indicated that oestrogen replacement therapy may protect post-menopausal women against coronary heart disease.
- Confirmed in women <60 years
- May increase risk starting therapy with oral hormones >60 and especially over 70 years of age
- Standard oral therapy should be avoided in women who already have established coronary heart disease.

HRT Benefits

Short-term memory and Alzheimer's disease

May prevent or delay the onset of Alzheimer's disease.

Colorectal cancer

HRT reduces the risk of colorectal cancer.

HRT Risks

Breast cancer

- Long-term HRT (oestrogen with progestin) is associated with a slight increase in the risk of developing breast cancer. (WHI) (July 2002
- For women who have had a hysterectomy and take oestrogen only the WHI study of 11,000 women has shown no increase (rather a trend to decrease) in breast cancer risk.

Thrombosis

- There is an increased risk of venous thrombosis in women using HRT, however the incidence is very low and more likely in the first year of therapy.

For every 10,000 women followed up over 1 year	Number of events in the HT/HRT group	Number of events in the placebo group (not taking HT/HRT)	Change in number of events attributable to HT/HRT
Risks			
Heart attacks	37	30	7 extra
Strokes	29	21	8 extra
Breast cancer	38	30	8 extra
Clots in deep veins (DVT)	15	7	8 extra
Benefits			
Hip fracture	10	15	*5 fewer*
Bowel cancer	*10*	*16*	*6 fewer*

Take Home Messages

- Short Term (<5 years) use of HRT can significantly improve quality of life
- There are (small) risks women need to be informed of

From Womb to Tomb:

- Care of women starts before they are born
- We need to do better at diagnosing and treating pelvic pain
- PCO has immediate and long term issues
- HMB has logical treatment options
- HRT is not the bad guy – can make a huge difference to quality of life

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

Fertility Associates –
Leaders in Fertility