



FERTILITY
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Fertility Associates –
Leaders in Fertility



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Everything you wanted to know about fertility/infertility but were too afraid to ask

Dr Freddie Graham

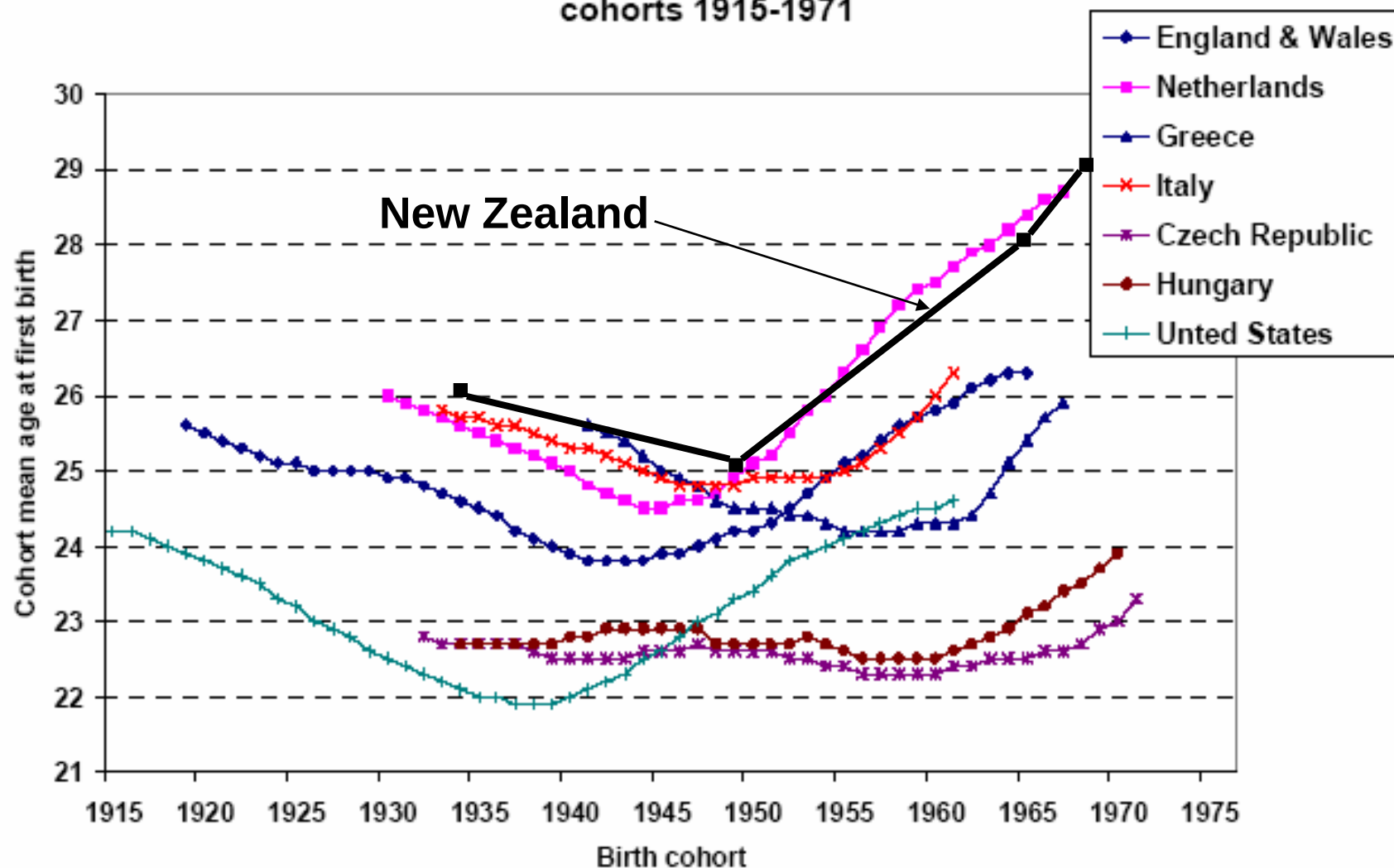
Leaders in Fertility

Outline

- 'Normal' fertility
- Lifestyle factors
- Male problems
- Female problems
- Treatment options
- HART Act.
- Funding



Figure 4 - Cohort mean age at first birth, selected countries, birth cohorts 1915-1971



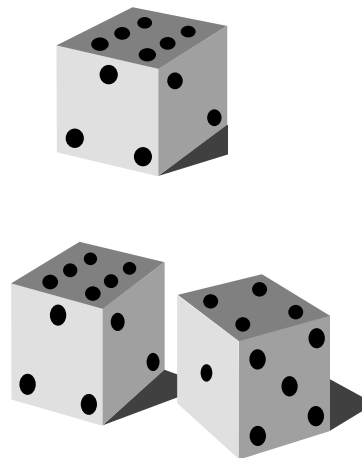
Human Reproduction

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

Getting pregnant is usually a matter of chance

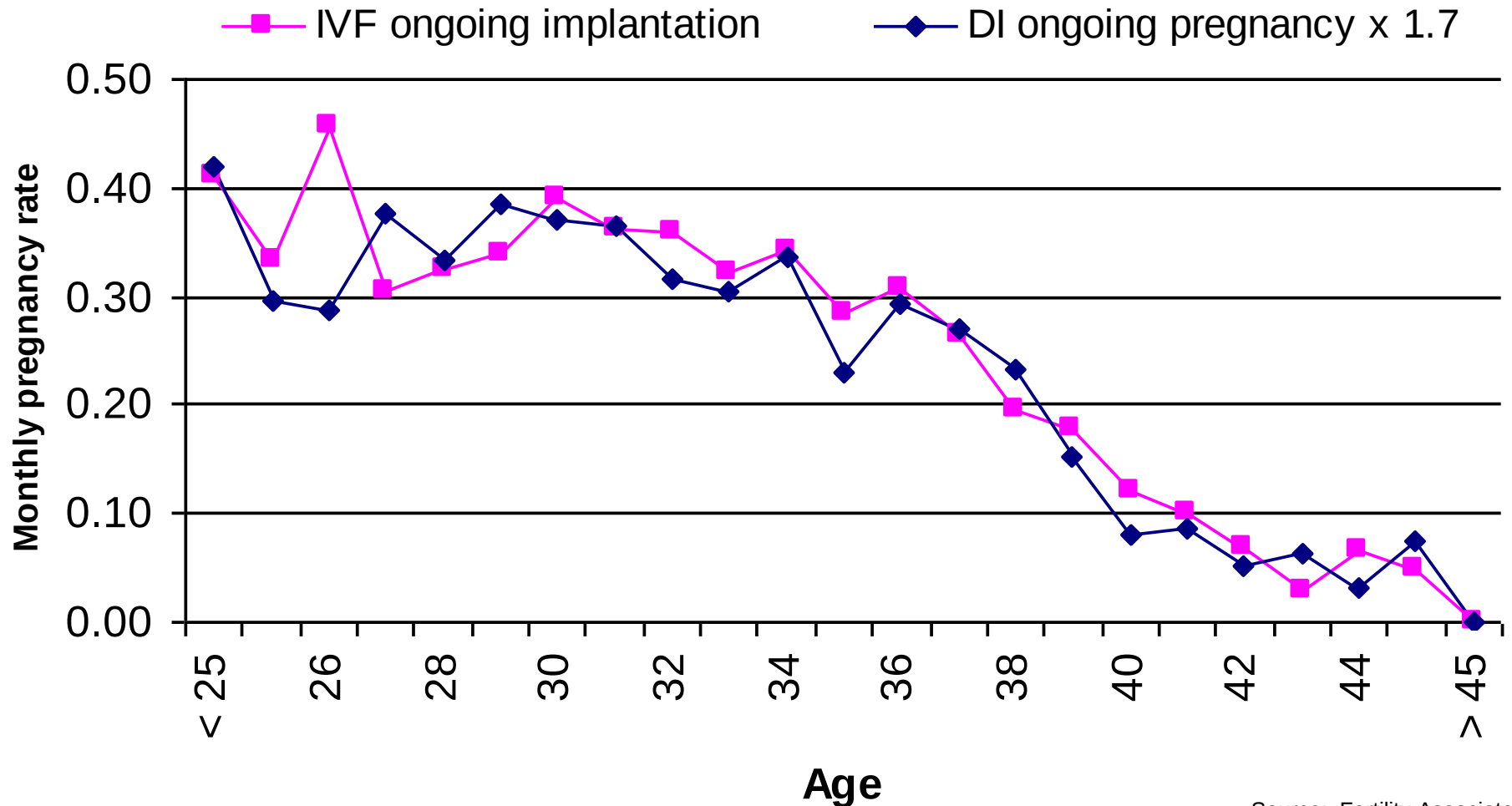
Monthly fecundity by age

Years	%
25	25
30	20
35	16
37	11
40	6
42	4
44	2





Decline in fertility with age



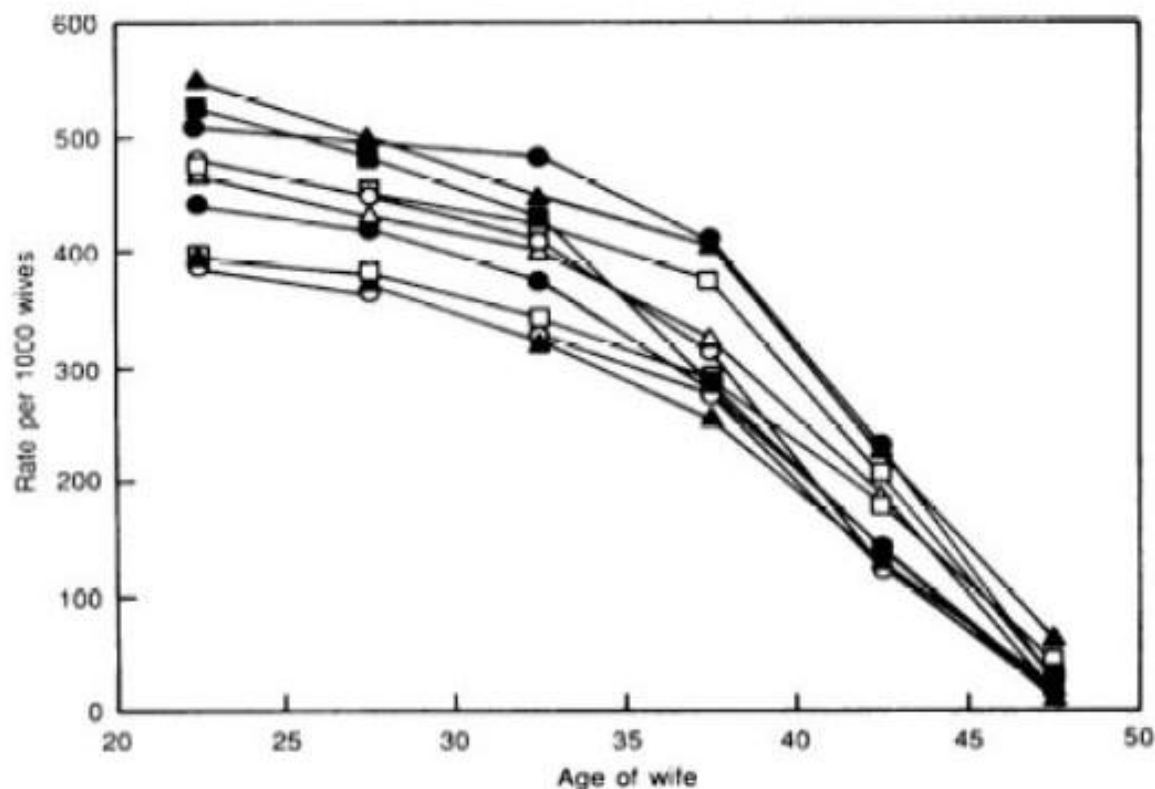
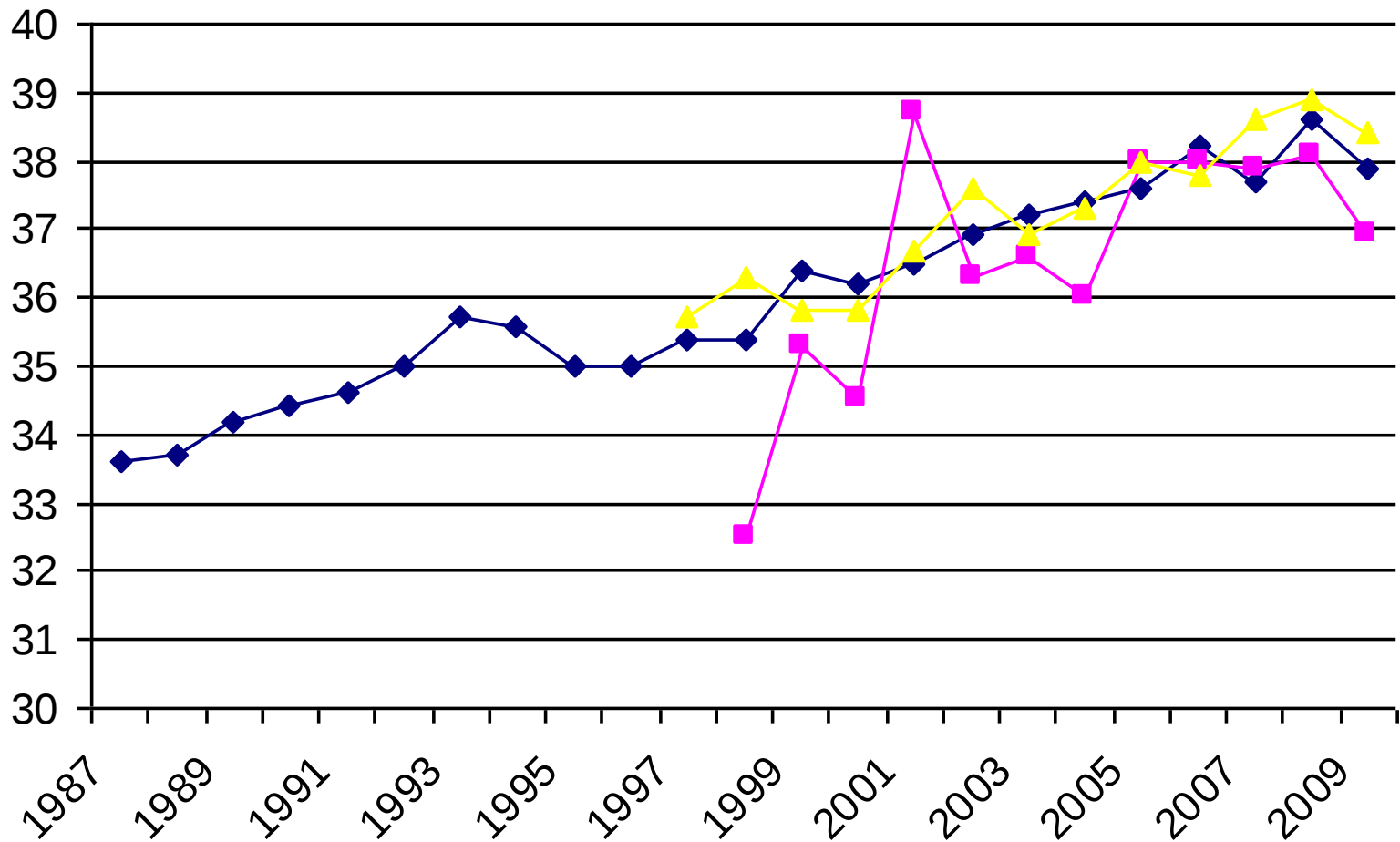


Fig. 1. Marital fertility rates by 5-year age groups (5). The ten populations (in descending order at age 20 to 24) are Hutterites, marriages 1921-30 (▲); Geneva bourgeois, husbands born 1600-49 (■); Canada, marriages 1700-30 (●); Normandy, marriages 1760-90 (○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840-59 (△); Normandy, marriages 1674-1742 (●); Norway, marriages 1874-76 (□); Iran, village marriages, 1940-50 (▲); Geneva bourgeois, husbands born before 1600 (○).



Age at starting private IVF cycle (incl DO)

—◆— FAA —■— FAH —▲— FAW





Loss of primordial follicles with woman's age

Faddy et al, 1992

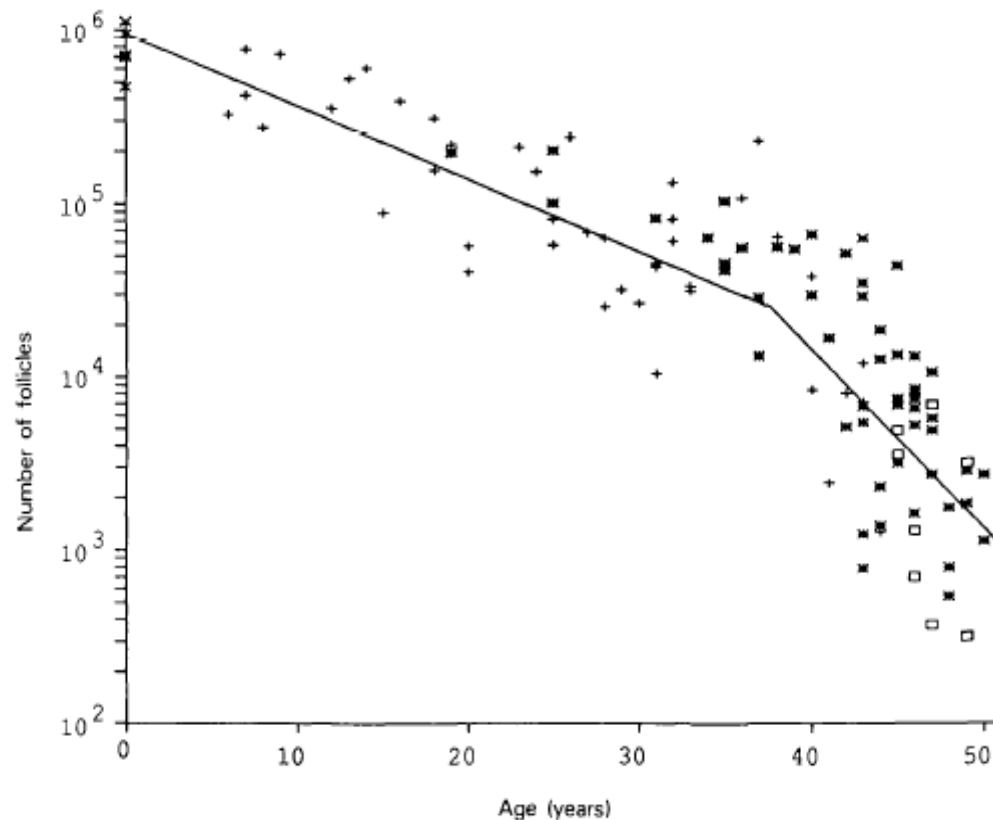


Fig. 1. Bi-exponential model of declining follicle numbers in pairs of human ovaries from neonatal age to 51 years old. Data were obtained from the studies of Block (1952, 1953) ($\times$, $n = 6$; $+$, $n = 43$), Richardson *et al.* (1987) ($\square$, $n = 9$) and Gougeon (unpublished) ($*$, $n = 52$).

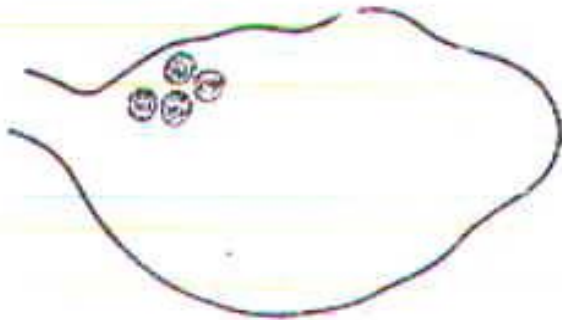


Ovarian Reserve

Oocyte Numbers

Age : minus six months
= 7 million

Age : zero
= 1 million

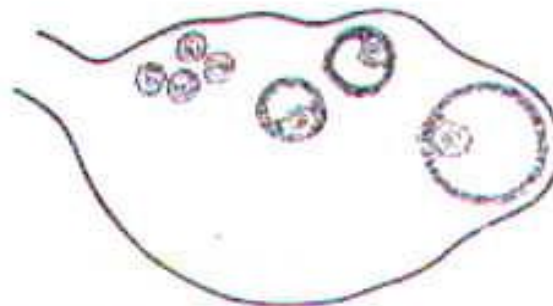


Age : 25
= 100,000

Age : 35
= 25,000

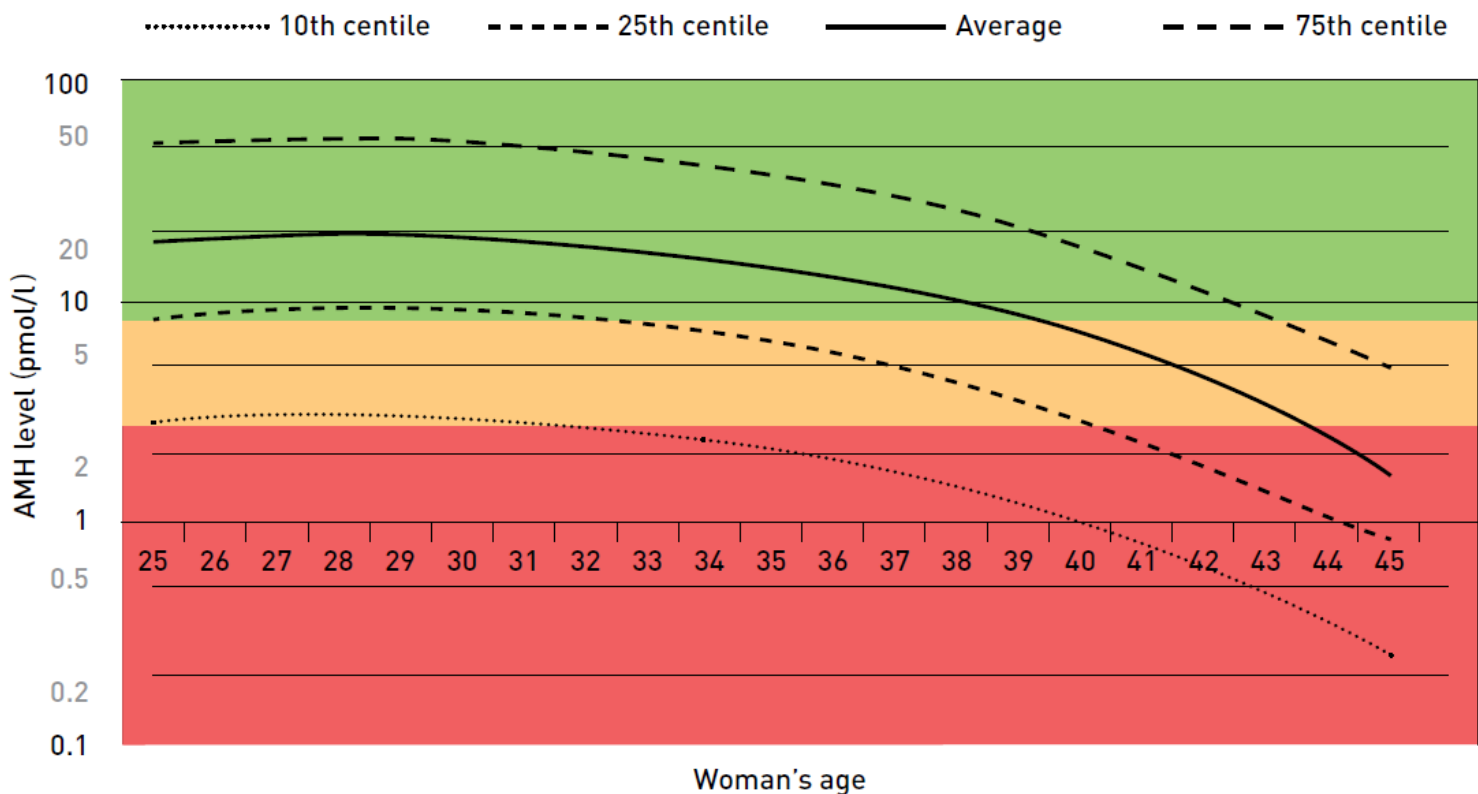
Age : 40
= 20,000

Age : 45
= 2,000



Ovarian reserve

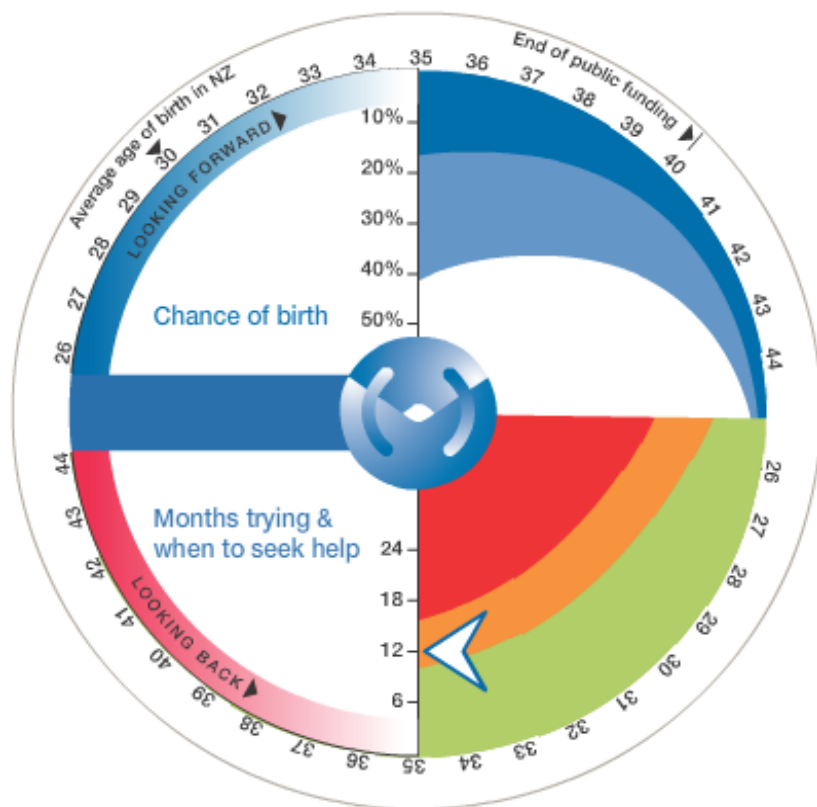
- Predicting earlier/faster egg loss:
 - Follicle stimulating hormone (FSH) levels
 - Antral follicle scans ('Egg check')
 - Anti-Mullerian Hormone (AMH) levels
 - Poor response to ovarian stimulation in IVF
- Predicting later/slower egg loss:
 - No test known
- Nothing can improve the quality of eggs or delay the loss of eggs



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



Biological Clock™



Chance of birth

■ Chance of having a child per month of trying for fertile couples

16%

■ Chance of having a child from one IVF cycle for people experiencing infertility

41%

Months trying & when to seek help

- Time to act
- Time to start thinking about seeing your GP or fertility specialist
- OK to wait, except under circumstances noted [here](#)

Woman's Age

35



Months Trying

12





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ders in Fertility

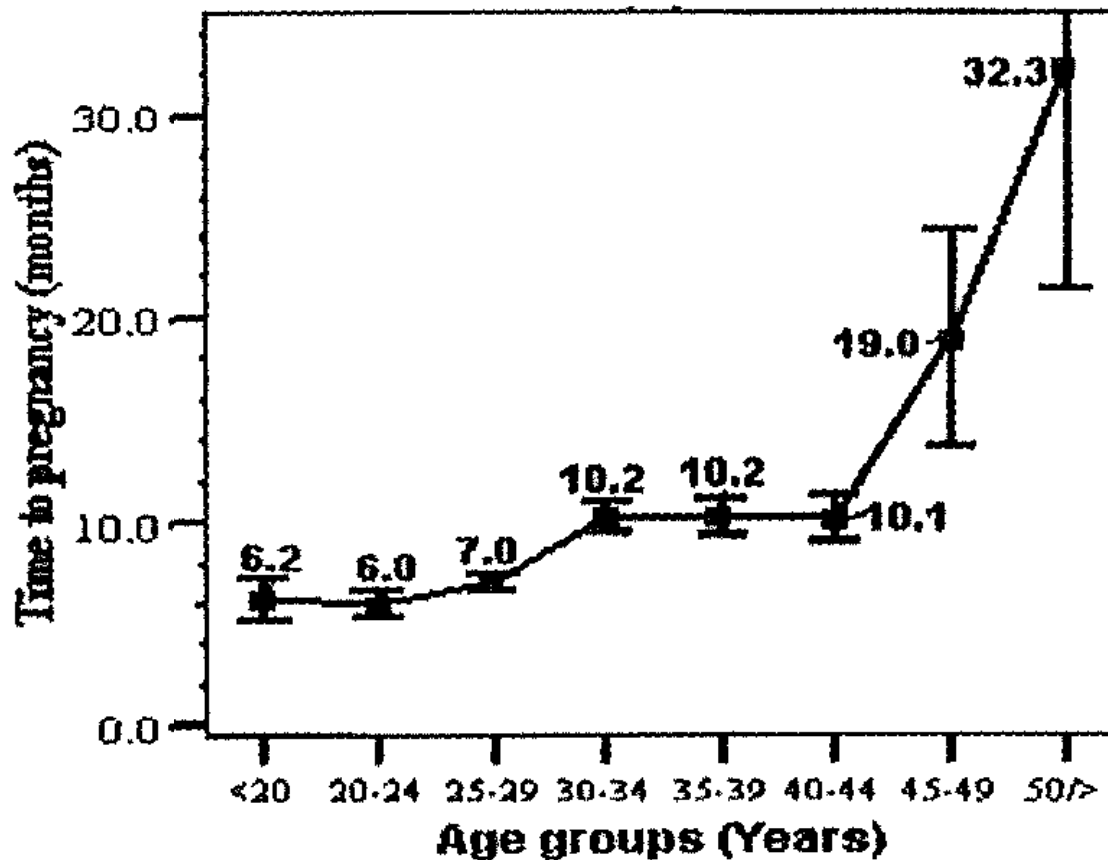
Some Facts about Aging, Men and Sperm

Conception rate adjusted for female age

< 25	1.0
30-34	0.62
35-39	0.50
> 40	0.51

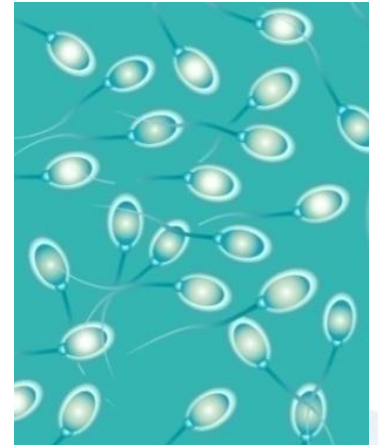


Paternal age effects on time to pregnancy



Some Facts about Ageing, Men and Sperm

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



Some Facts about Older Men and Sperm

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

- ❖ schizophrenia in offspring
 - at 45+ odds ratio 3.0 = 1: 46 chance
 - specific for schizophrenia (Malaspina 2001)
- ❖ increase in autism
 - compared with 30 years
 - > 40 3 x the risk
 - > 50 5 x the risk
- ❖ increase in achondroplasia



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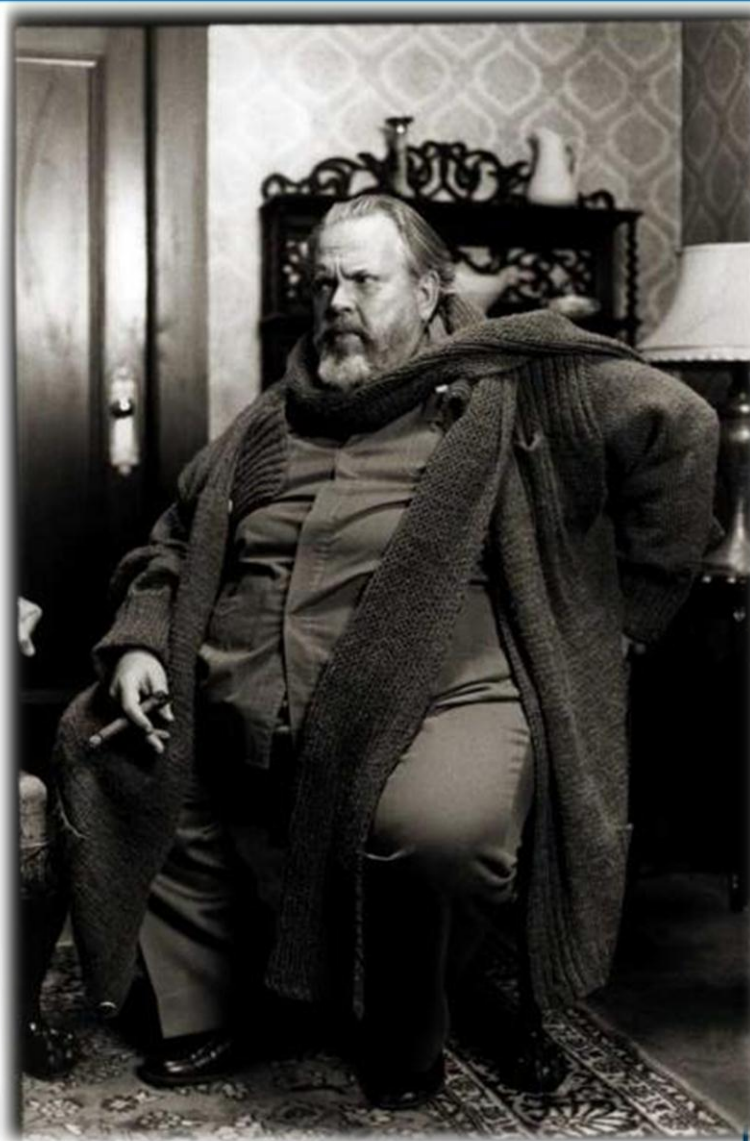
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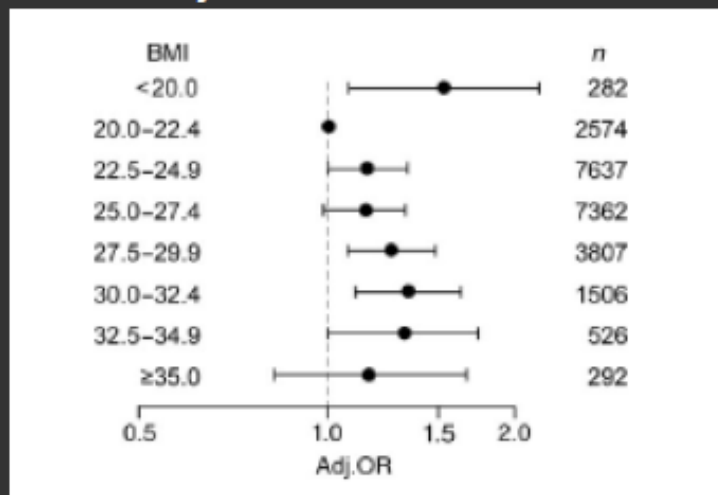


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Men and overweight – effects on fertility

Risk of overweight for infertility in men adjusted for other factors



*Nguyen et al Human
Reproduction 2007*

Adjusted odds ratio for infertility in
farmers in USA increases with
increasing BMI with a 10kg increase
leading to 10% reduction in fertility
Sallmen 2006

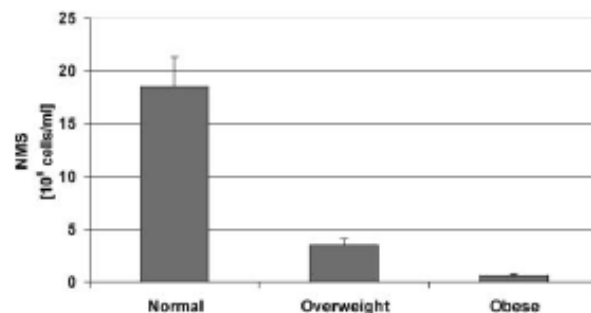


Figure 1. Effect of body mass index class on number of normal-motile sperm cells.

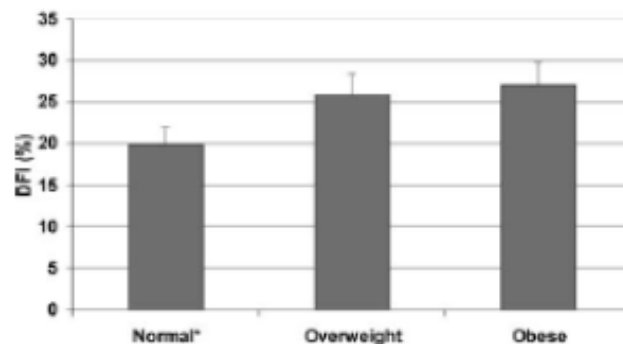


Figure 2. Effect of body mass index class on sperm chromatin integrity. *Significantly different ($P < .05$).

Kort et al J Androl 2006



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Friction in the saddle may be a factor

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Handy hints for making babies for men

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

Don't smoke or do drugs	• Smoking and some recreational drugs can reduce sperm quality.
Reduce alcohol	• Decrease your alcohol intake to 20 units or less a week. Alcohol has also been shown to affect fertility.
Have a normal BMI	• Keep active and stay slim. Obese men have sperm counts on average 22% lower when compared to their slimmer counterparts. • Have a body mass index (BMI) lower than 28.
Keep testes cool	• Wear boxer shorts, not briefs, this helps the testes to keep cool. • Men in sedentary jobs can have poorer quality sperm because their testes are more prone to heating up. Keep your laptop off your lap! • Don't have a hot bath, sauna or spa too frequently.
Have a healthy diet	• Eat a diet with lots of healthy antioxidants. Foods rich in antioxidants can reduce the damage that free radicals can have on sperm. • Antioxidants are found in fresh vegetables, fruit, nuts, seeds, green tea and dark chocolate. • Health supplements containing antioxidants such as Vitamin C and E may help to improve sperm quality.
Medication	• Discuss any medication you are taking with your Doctor.

Healthy sperm diet

- Lots of antioxidants
 - fruit and vegetables, nuts, seeds, dark chocolate, green tea, red wine
- Vitamin C and E
- ? Selenium, Zinc
- ? Folic acid

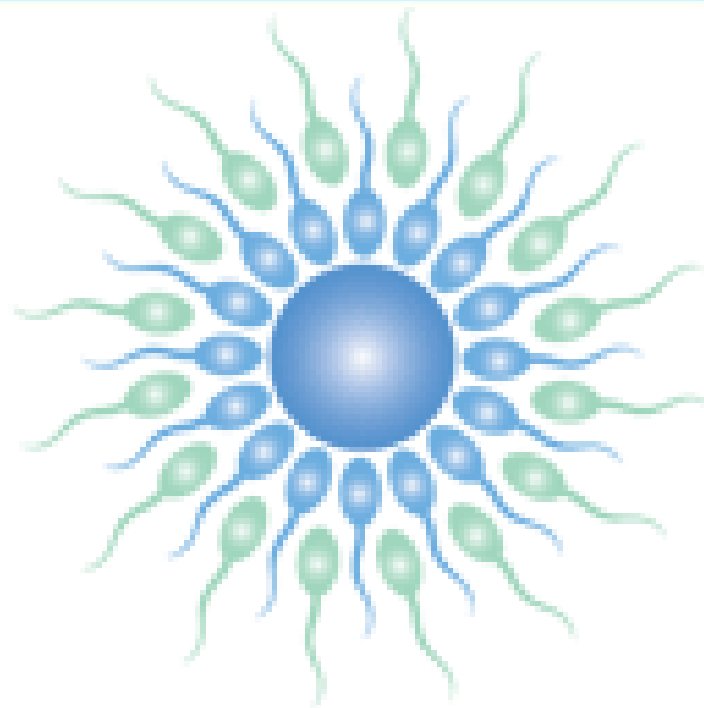




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menevit

DESIGNED FOR MALE FERTILITY

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Handy hints for making babies for women

There are some important changes you can make to your lifestyle that increase your chances of getting pregnant and having a healthy baby.

Have a BMI of 20 – 25	• A healthy body mass index (BMI) is associated with better fertility. • Pregnancy in overweight women is associated with problems such as diabetes and high blood pressure. • Eat healthily and undertake moderate exercise regularly.
Don't smoke or do drugs	• Smoking halves the chances of conceiving each month and can also double the chance of miscarriage.
Take folic acid and multi vitamins	• Take Folic Acid supplements when trying to get pregnant and up to 12 weeks into the pregnancy. • Folic Acid can help reduce the chances of spina bifida by up to 92%. Other minerals and supplements may also be useful. • Use iodised salt, as iodine is necessary for fetal brain development. • Avoid Vitamin A.
Reduce alcohol and caffeine	• Caffeine may reduce your chances of conceiving. • There is no safe limit of alcohol during pregnancy, so it's best avoided.
Medication	• Discuss all your medications with your doctor.
Rubella	• Make sure you have had a rubella immunisation. Rubella can damage unborn babies.

Infertility

- Complete = Sterility
No chance of pregnancy (5%)
- Relative = “Infertility”
Arbitrary distinction between normal fertility and “infertility”

What is Infertility?

An emotional experience often requiring
a physical intervention.

Factors That Decrease Fecundability

- Poor semen quality
- ? Abnormal ovulation
- Tubal disease/dysfunction
- Endometriosis
- Mucus abnormalities
- Antibody problems
- Increased female age (male age)
- Smoking

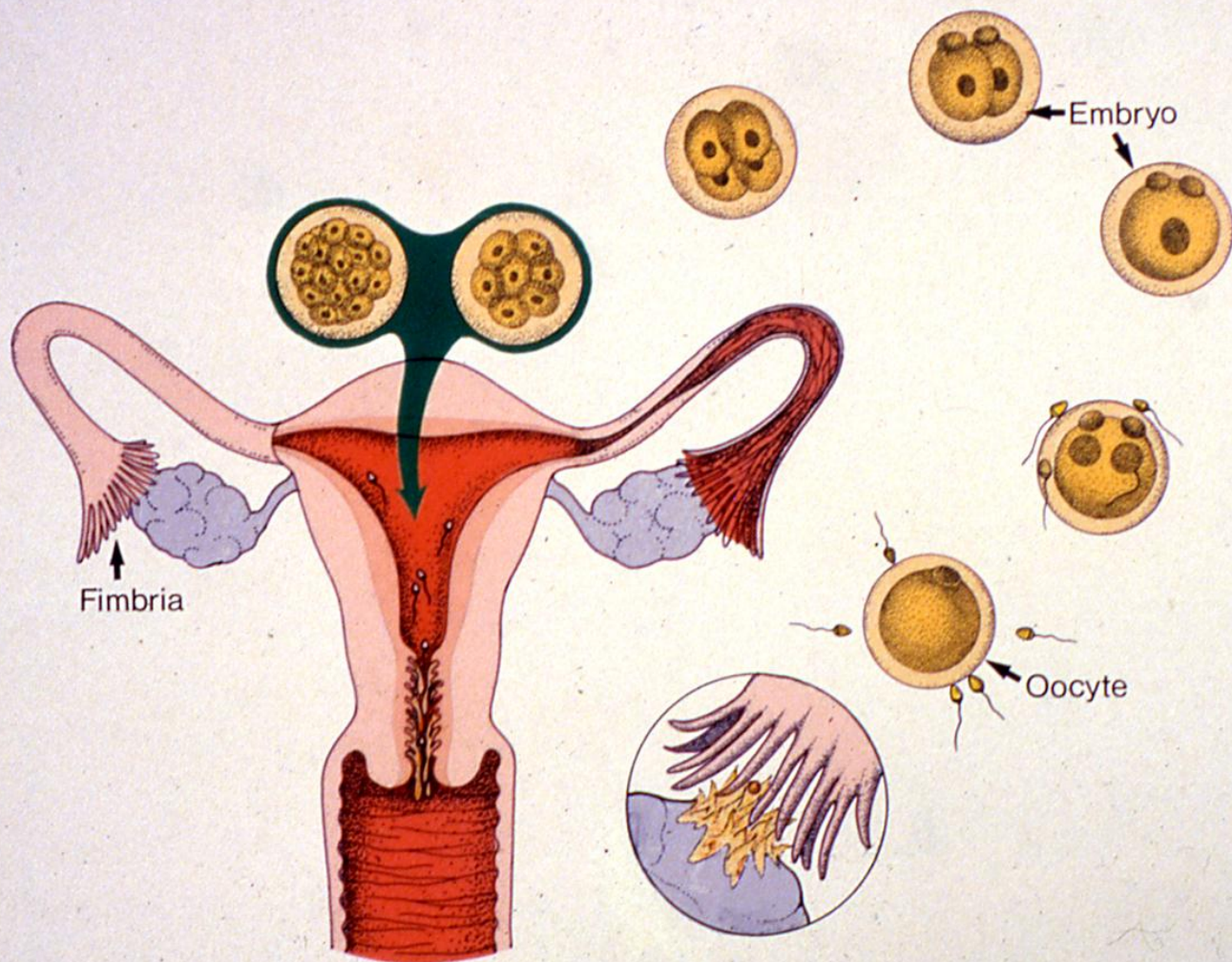


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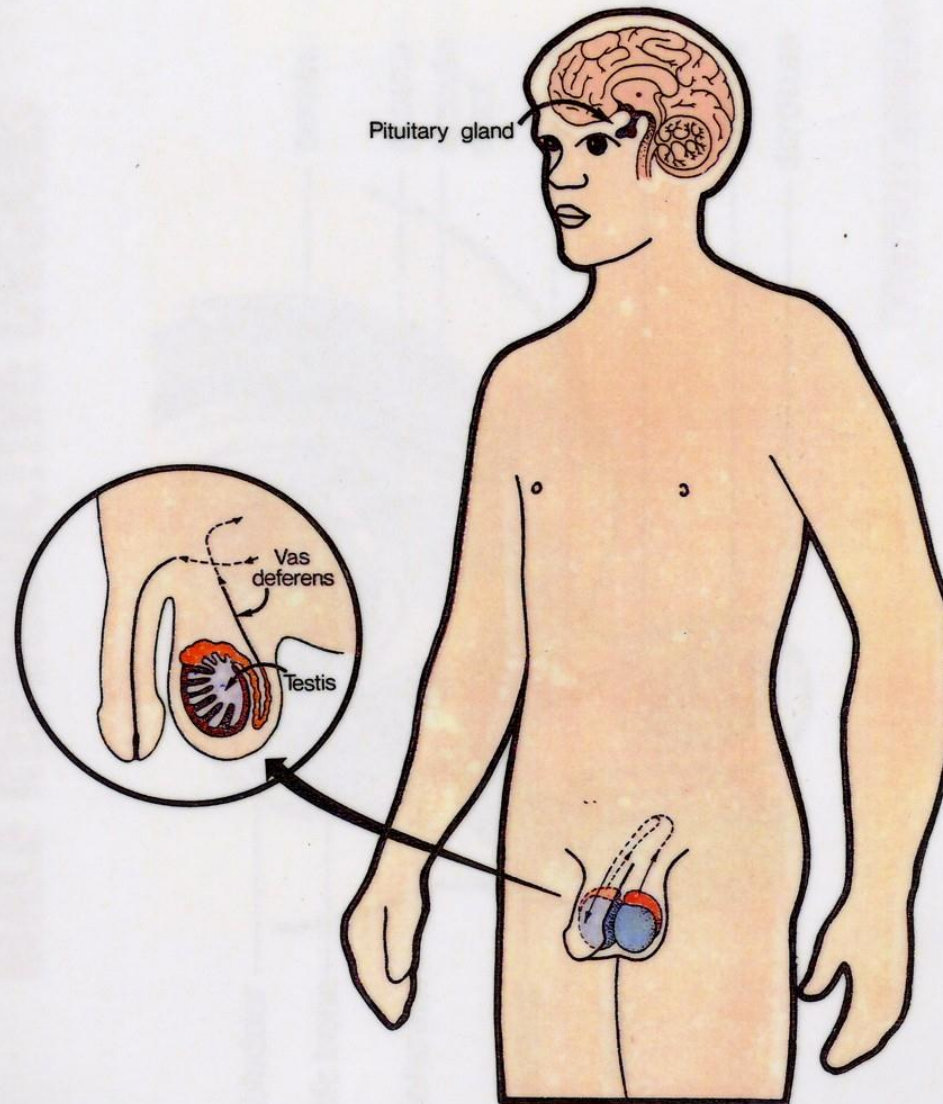
Ovulation, Conception and Embryo Development



Causes of Azoospermia

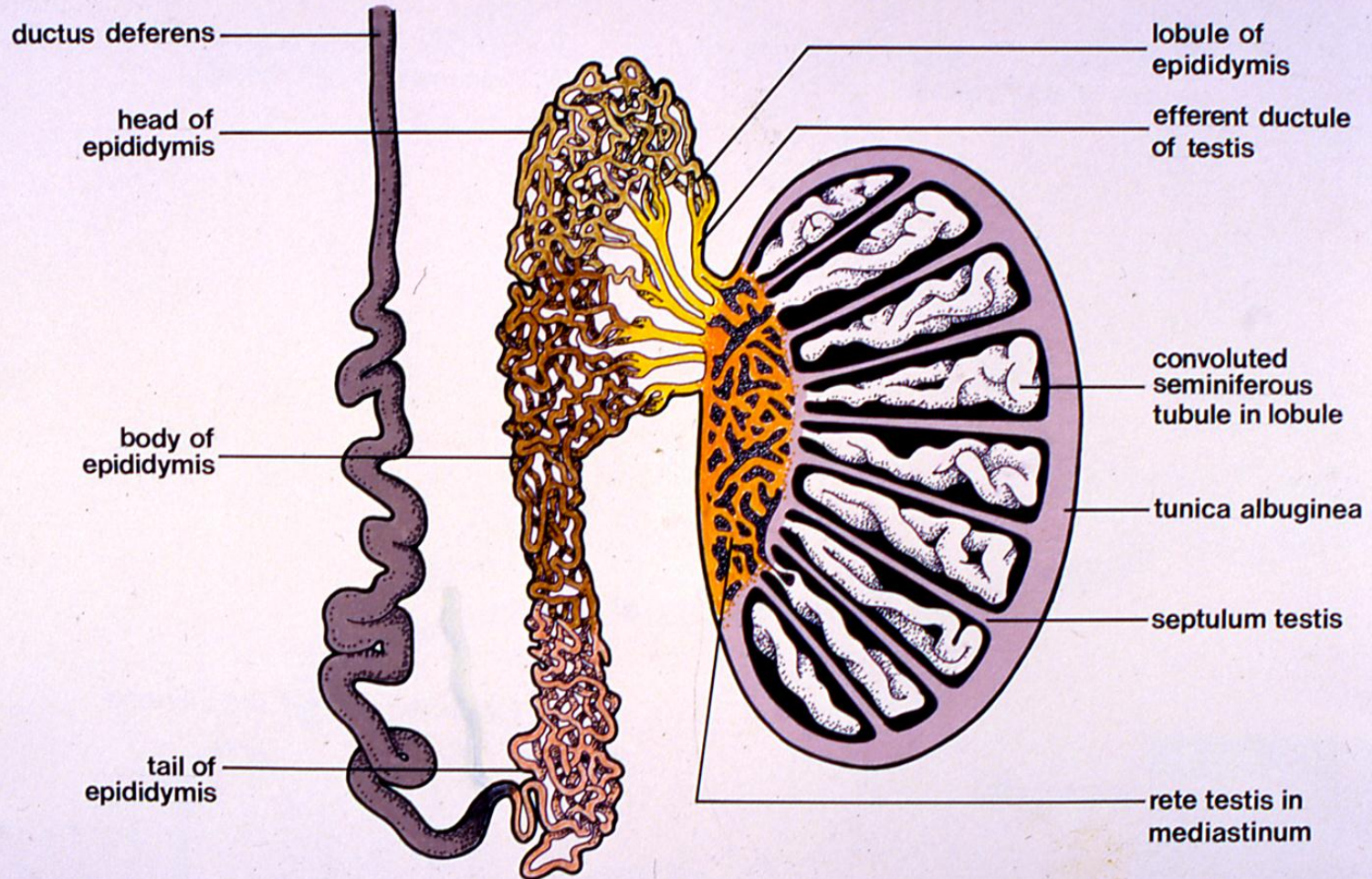
- Obstructive 46.6%
 - 5% trauma
 - 6 % infection
- Non – obstructive 44.2%
 - 27% cryptorchid
 - 1% infection
- Karyotypic abnormality 9.2%

MALE REPRODUCTIVE SYSTEM





STRUCTURE OF TESTIS AND EPIDIDYMIS



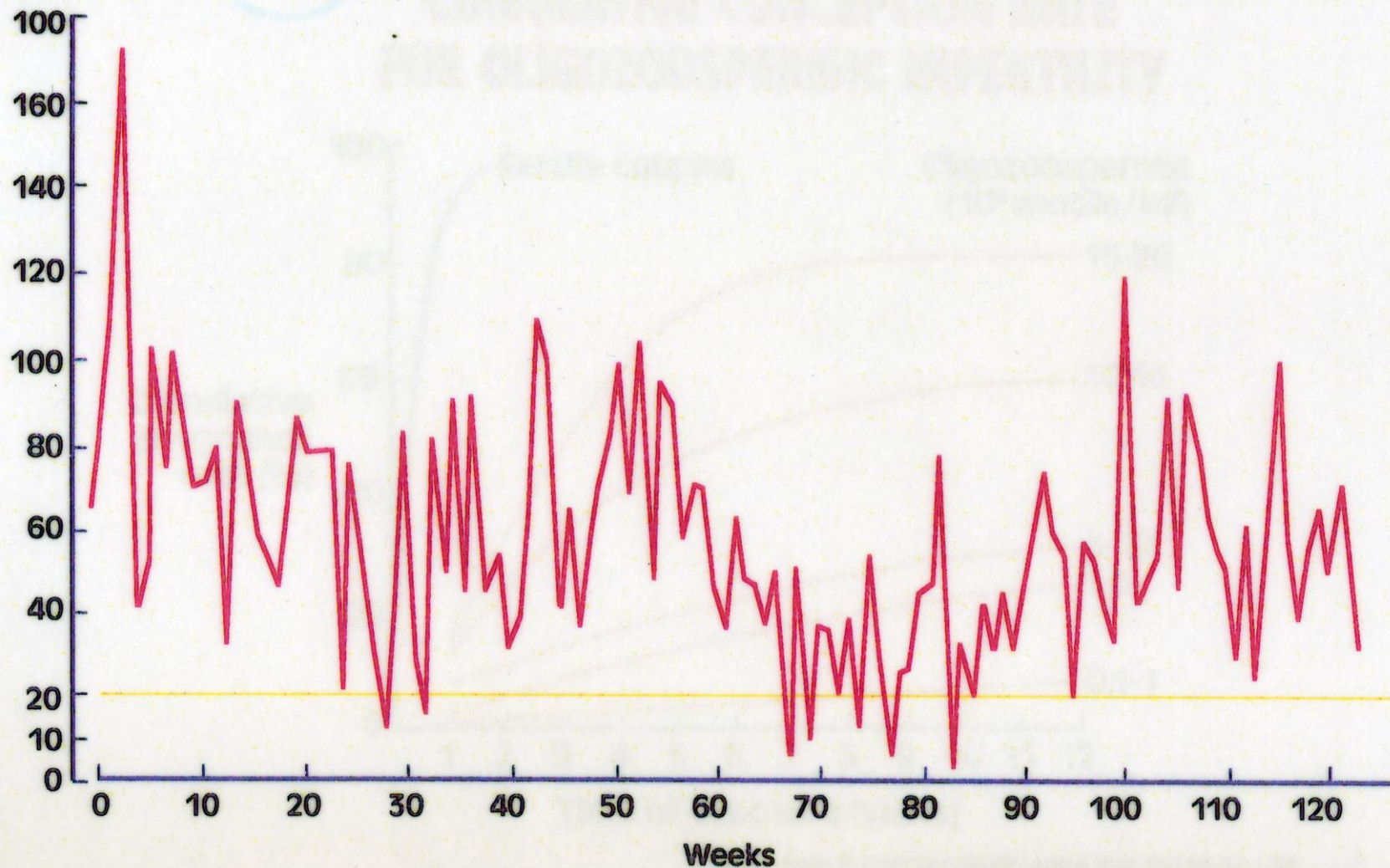


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A FERTILE MAN'S SPERM COUNT OVER 2 YEARS

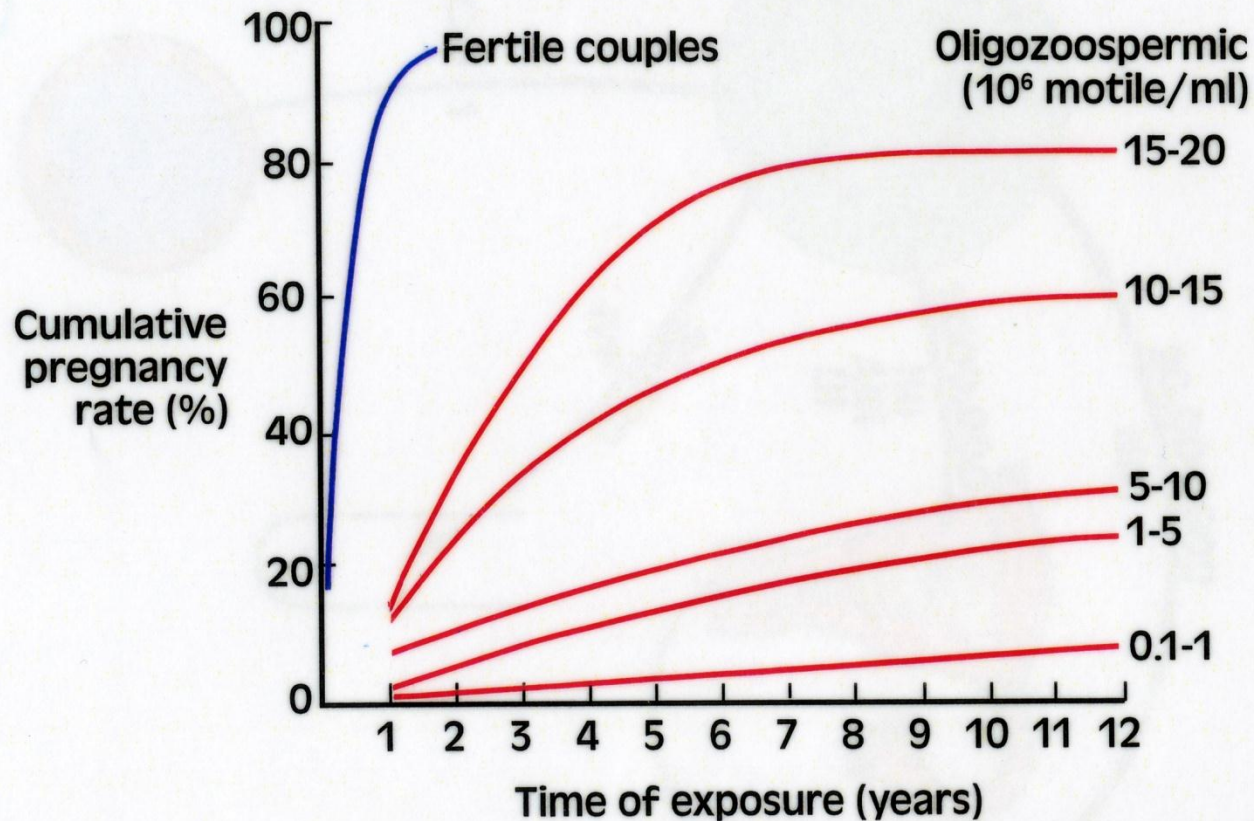
Sperm count
(million/ml)



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CUMULATIVE CONCEPTION RATE FOR OLIGOZOOSPERMIC INFERTILITY



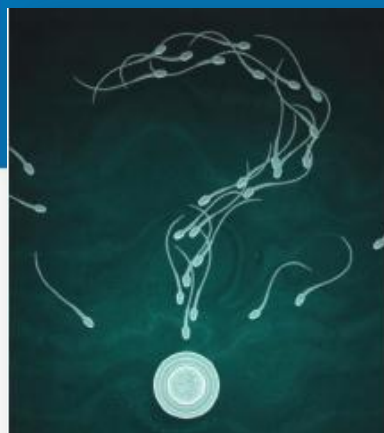
Schoysman & Gerris (1983) Aeta Eur Fertil 14 : 51

Diagnosis

- Semen analysis
- History
- Examine
- FSH
- Testosterone
- Karyotype
- C.F. gene
- Y. microdeletion

Diagnosis

- Tertiary lab semen analysis
- Motility
- Morphology
- Sperm antibodies
- Sperm D.N.A damage



Measuring sperm DNA damage using the SCSA test

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

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

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

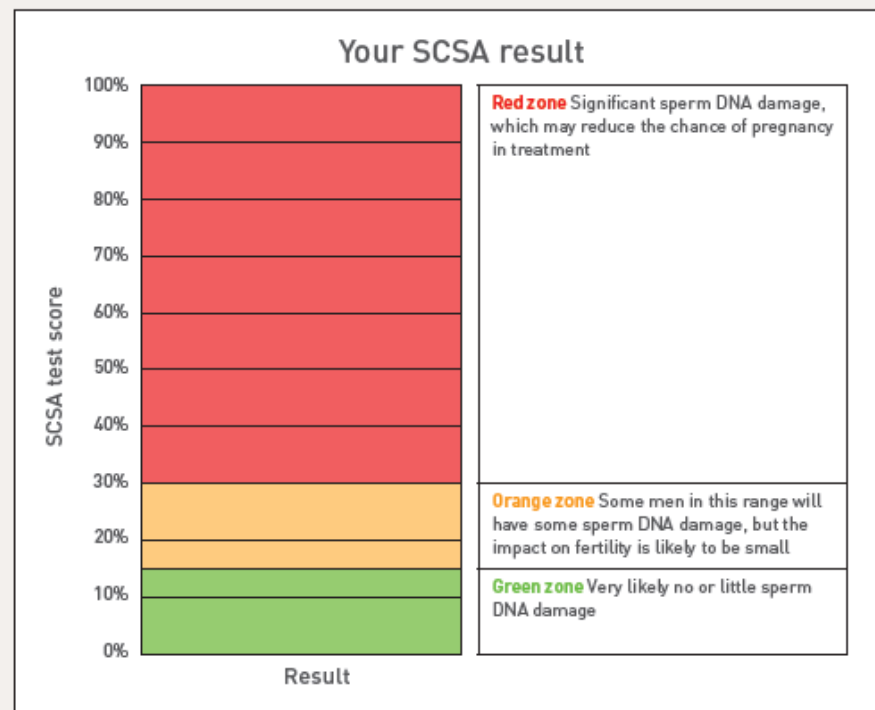
The body's main defence against ROS damage is to maintain an optimal antioxidant environment for sperm maturation and storage before ejaculation. This is one of the reasons why Fertility Associates promotes a healthy lifestyle, healthy eating and considering the use of antioxidant supplements.

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

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

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

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



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Contact us: www.fertilityassociates.co.nz • Phone 0800 10 28 28

• Auckland Level 3, 7 Ellerslie Racecourse Drive, Remuera	P 09 520 9520	E faa@fertilityassociates.co.nz
• North Shore Level 1, Suite 107, 119 Apollo Drive, Albany	P 09 475 0310	E fas@fertilityassociates.co.nz
• Hamilton Level 2, 62 Tristram Street, Hamilton	P 07 839 2603	E fah@fertilityassociates.co.nz
• Wellington Level 2, 205 Victoria Street, Te Aro	P 04 384 8401	E faw@fertilityassociates.co.nz
• Christchurch Level 1, Hiatt Chambers, 249 Papanui Road	P 03 375 4000	E fac@fertilityassociates.co.nz

We also hold clinics in Whangarei, East Auckland, West Auckland, Tauranga, Gisborne, New Plymouth, Hawke's Bay, Palmerston North, Lower Hutt, Nelson and Queenstown. Please call us or check our website for further details.

Aetiology

- Past history
- Cryptorchidism
- Torsion
- Infection
- Trauma
- Current
- Varicocele
- Alcohol
- Smoking
- Weight

Environmental

- Endocrine disrupting chemicals (EDC)
- Dioxin
- Pesticides
- DDT
- Lead

Genetic

- R. Lilford 1994
- Klinefelters
- Y. Microdeletion
- C.B.A.V.D

Management

- Try to quantitate sperm defect
- Length of infertility
- Time left

Lifestyle modifications

- Timing intercourse
- Vitamins / antioxidants / zinc
- Smoking
- Alcohol
- Weight / exercise
- Heat

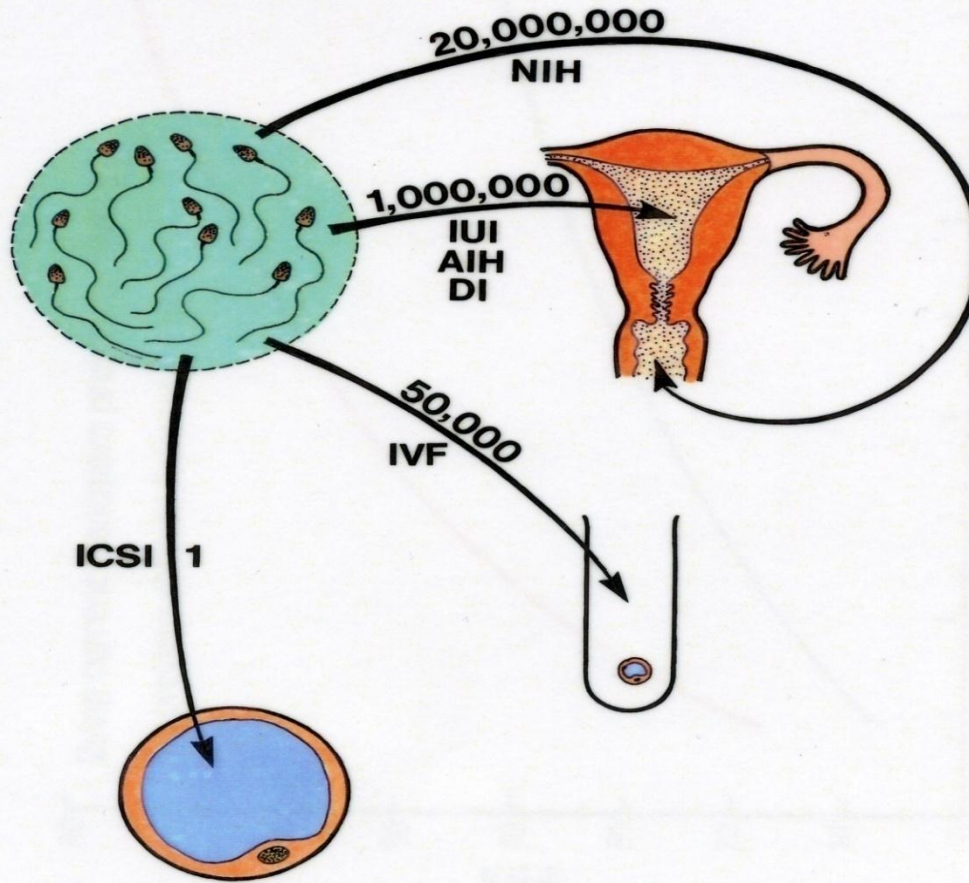
Improve Female Fertility

- Ovulation
- Tubal
- Endometriosis

Treatment - male infertility

- Hyperstimulation / IUI
- IVF / ICSI
- Donor insemination (DI)

NUMBER OF SPERM TO FERTILISE AN EGG





Vasectomy reversal results

	US STUDY		F.G SERIES	
interval	pregnant	patency	pregnant	patency
0-2yrs	76%	97%	80%	100%
3-8yrs	53%	88%	61%	83%
9-14yrs	44%	79%	35%	70%
15 yrs	30%	70%	24%	59%

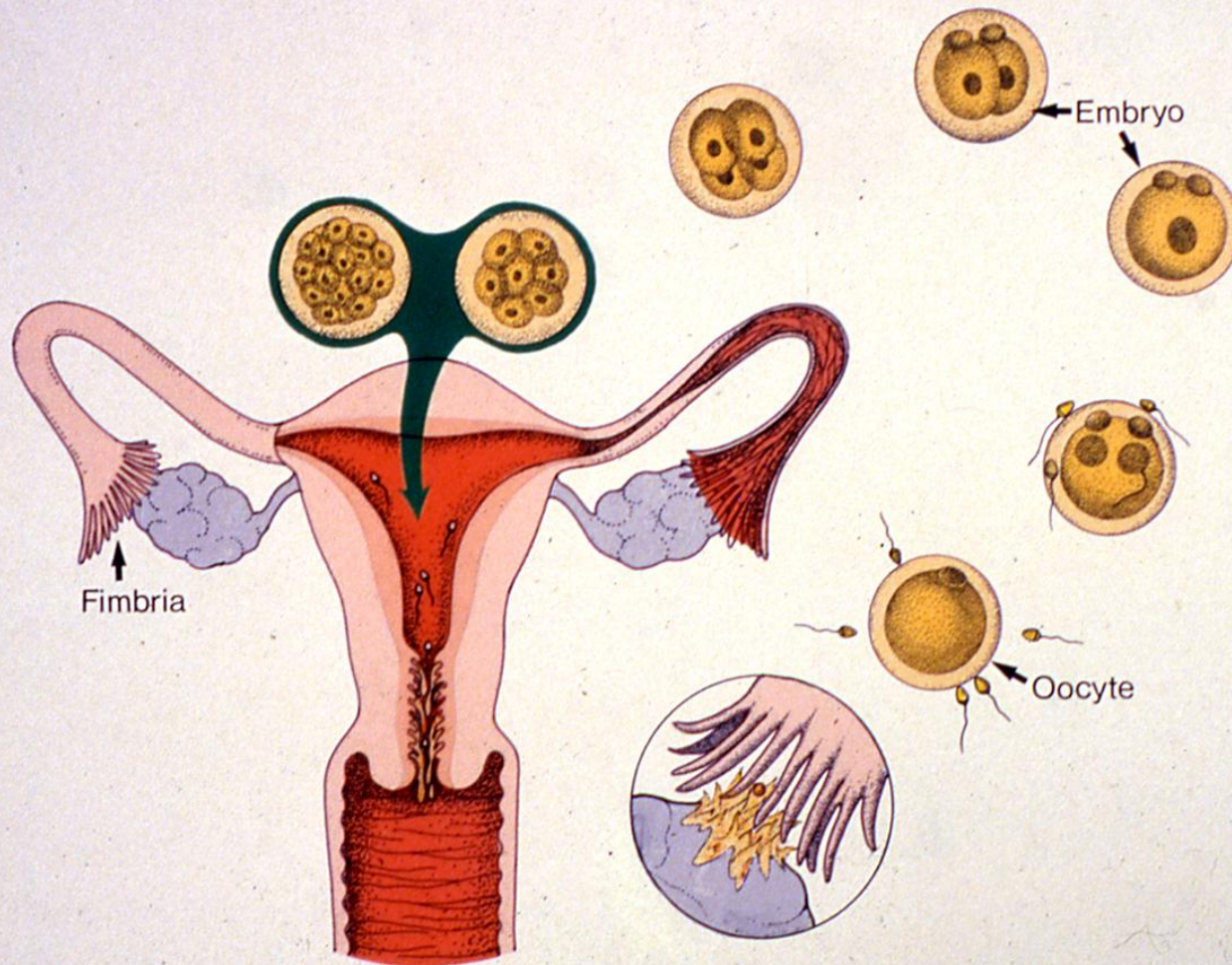
U.S overall 52%

30% > 8yr interval

F.G 43%

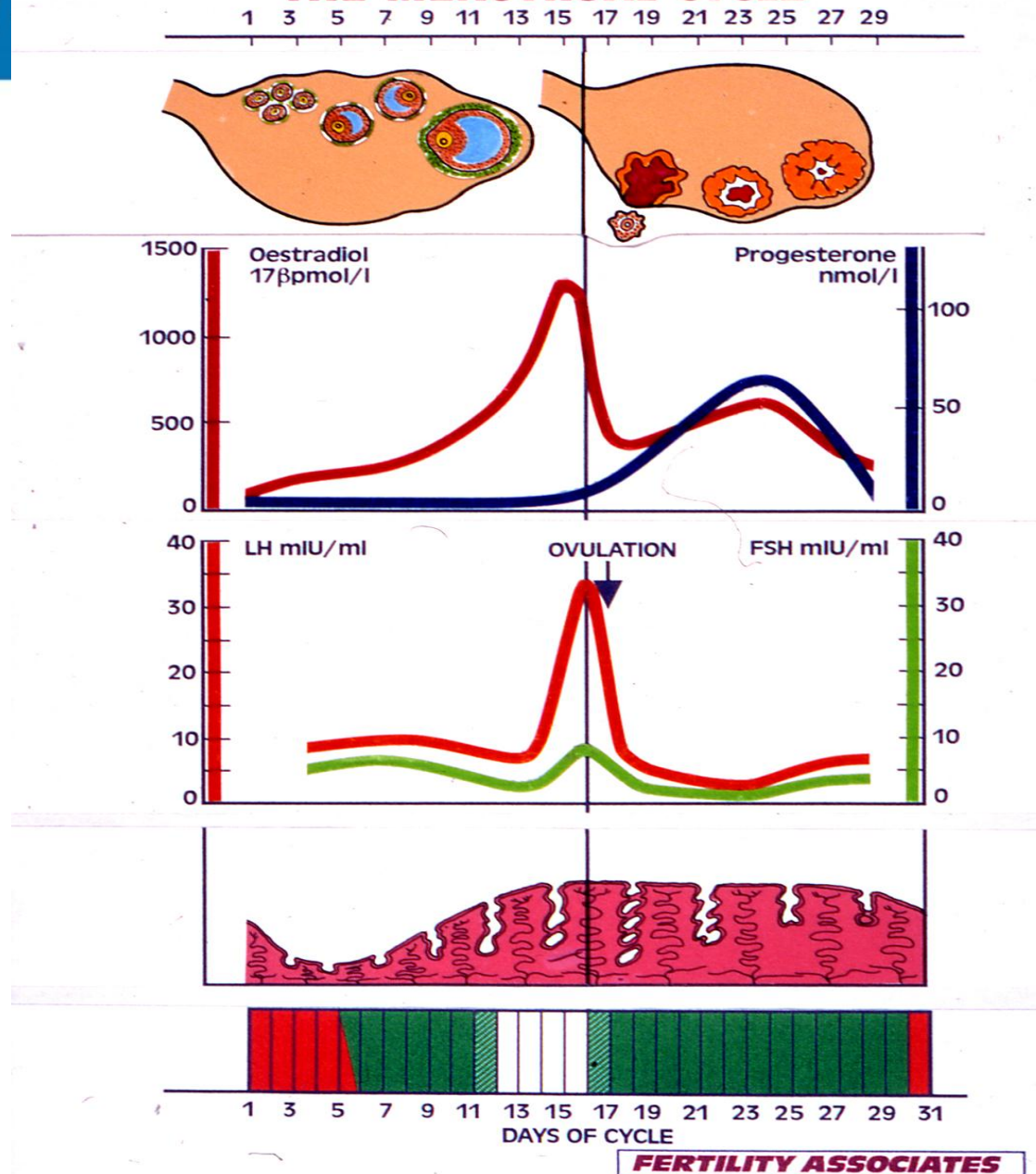
60% > 8yr interval

Ovulation, Conception and Embryo Development





THE MENSTRUAL CYCLE





FOLLICULAR DEVELOPMENT

PRIMORDIAL
FOLLICLE



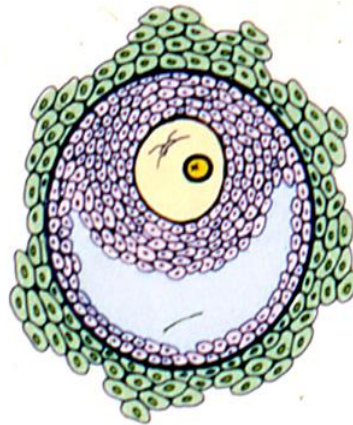
50 μm

PREANTRAL
FOLLICLE



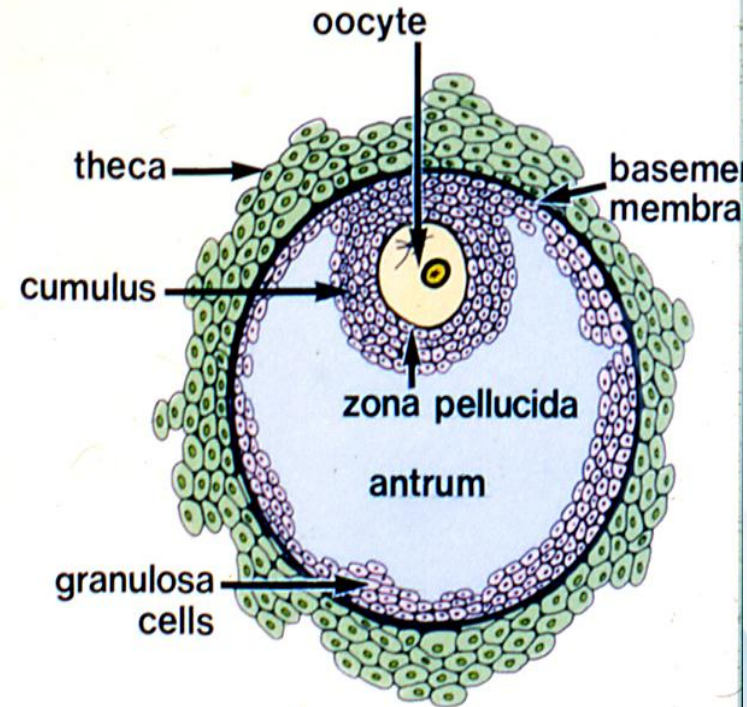
200 μm

ANTRAL
FOLLICLE



500 μm

PREOVULATORY
FOLLICLE



20mm

Treatment Escalator

- Clomiphine
- Hyperstimulation / IUI
- IVF

‘Infertility management is time management’

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

Efficacy of fertility treatment

- Treatment is available for all types of infertility
- IVF will enable > 90% of women (and men) to have children (age permitting)
- Donor Insemination (DI) and Donor Egg (DO) will allow nearly all the rest to have children (availability of donors permitting)

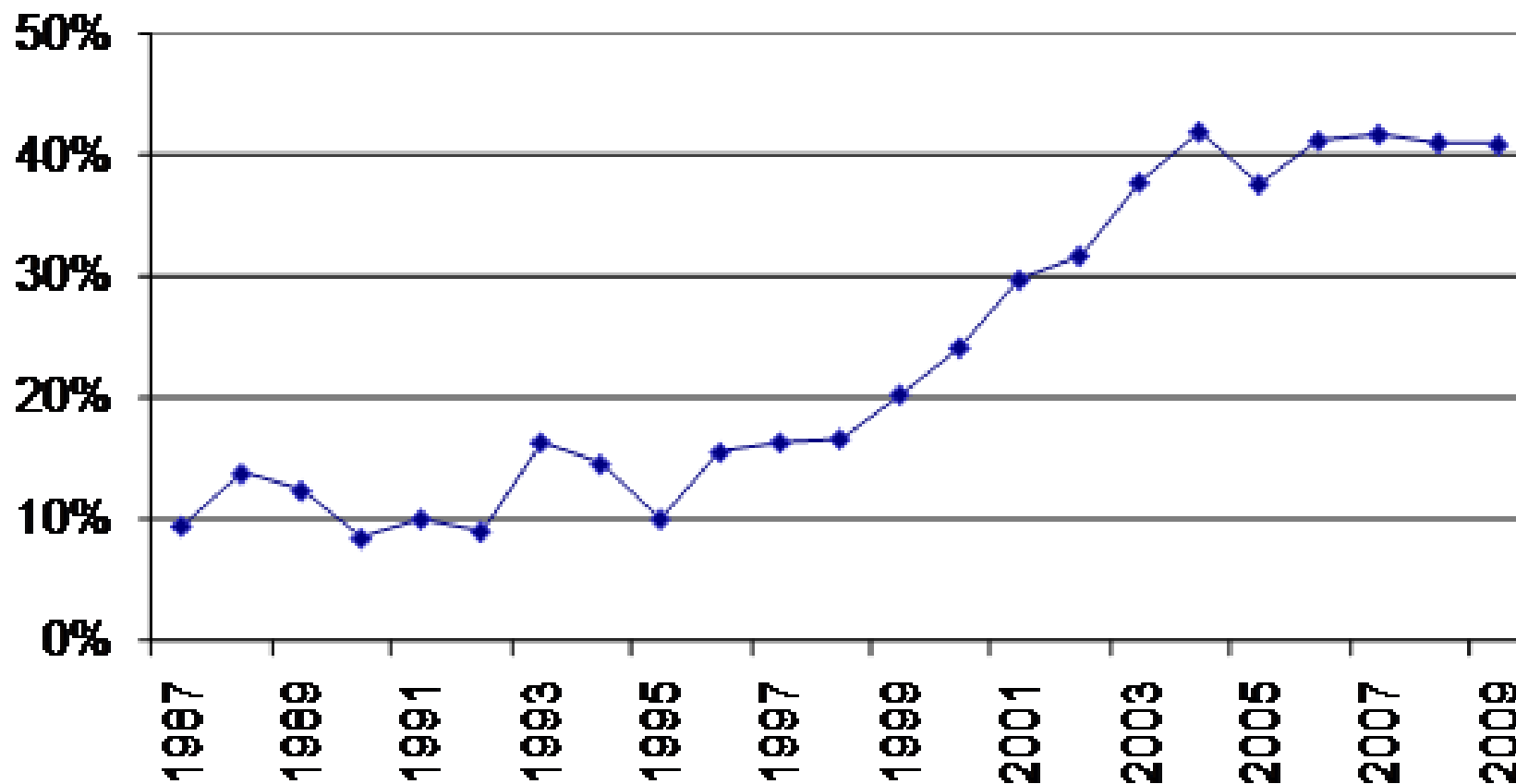


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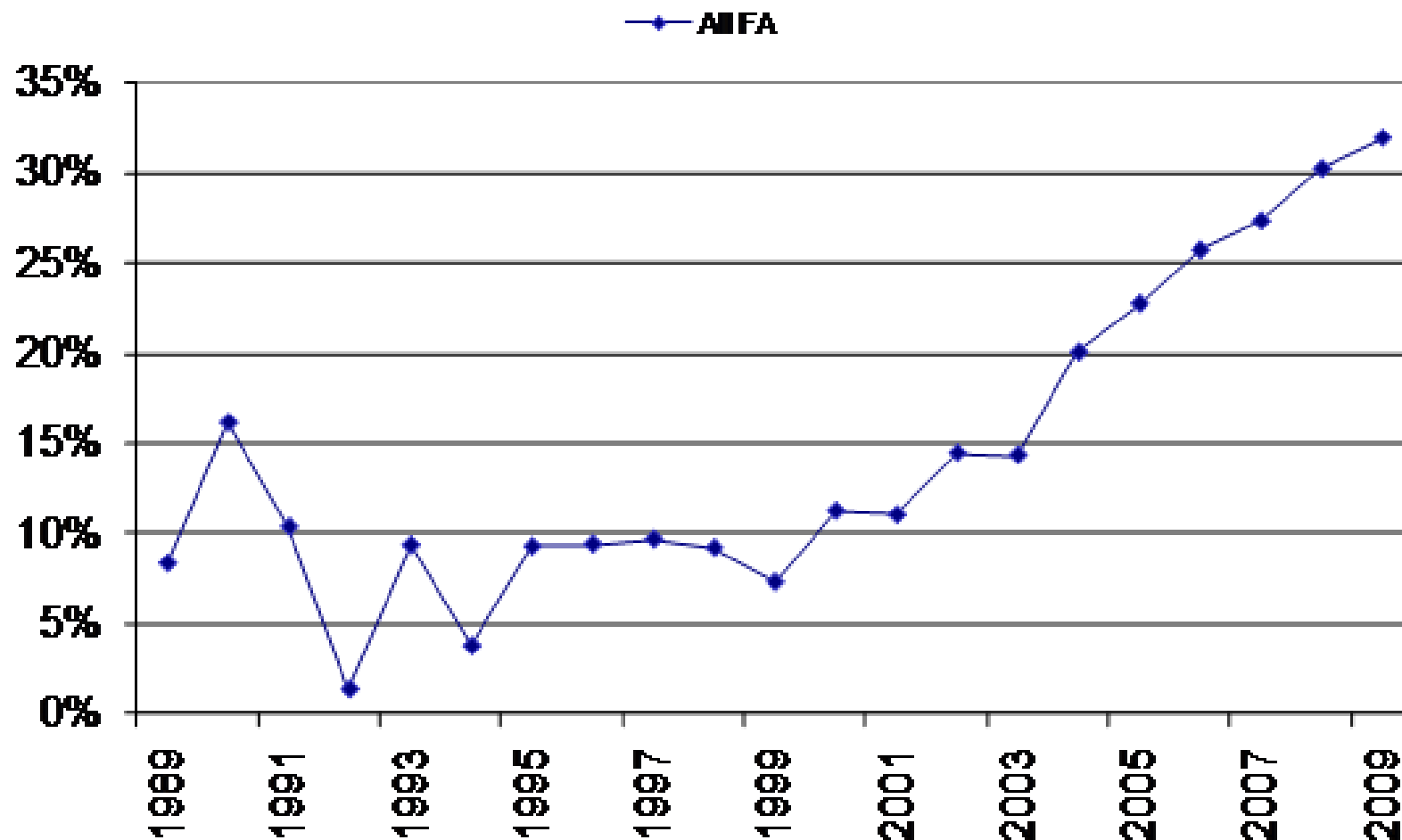
Implantation rates in women ≤ 37 per ET

—♦— All FA



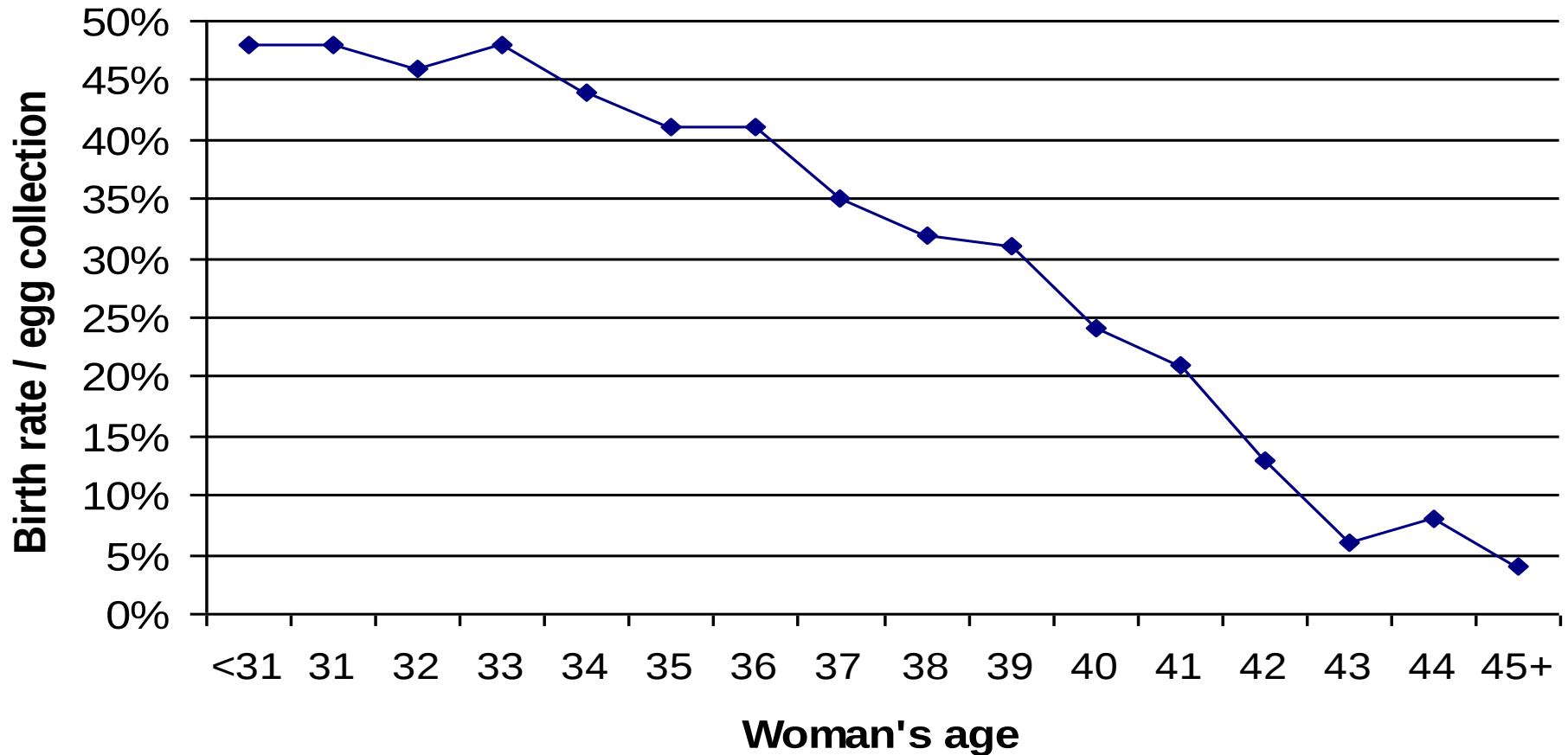


Implantation rates in women ≤ 37 per TER





IVF success rates



Freezing things

- Sperm
- Embryos
- Eggs



Sperm freezing - who might benefit?

- Prior to chemotherapy
- Prior to vasectomy
- In men with family history of declining sperm counts
- 'Social'



Cryopreservation of ovarian tissue

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

Oocyte freezing – who might benefit?

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



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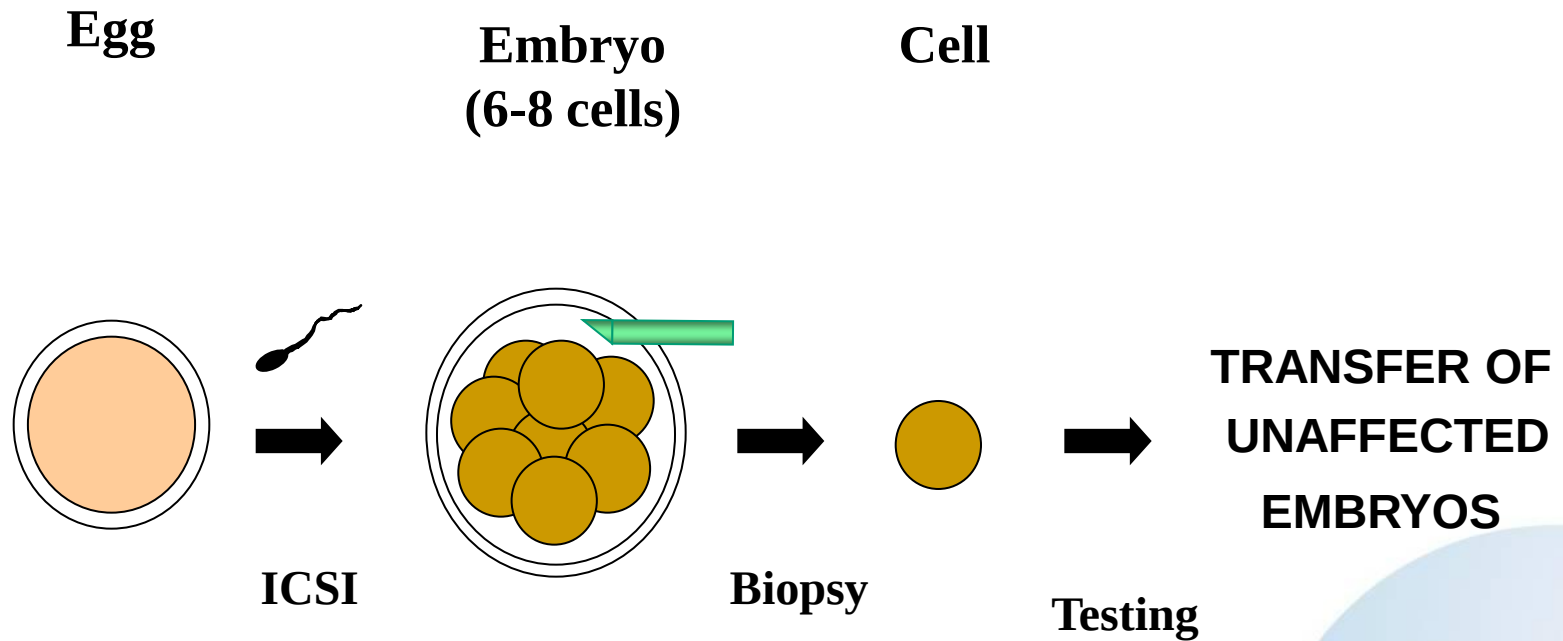
Preimplantation genetic diagnosis

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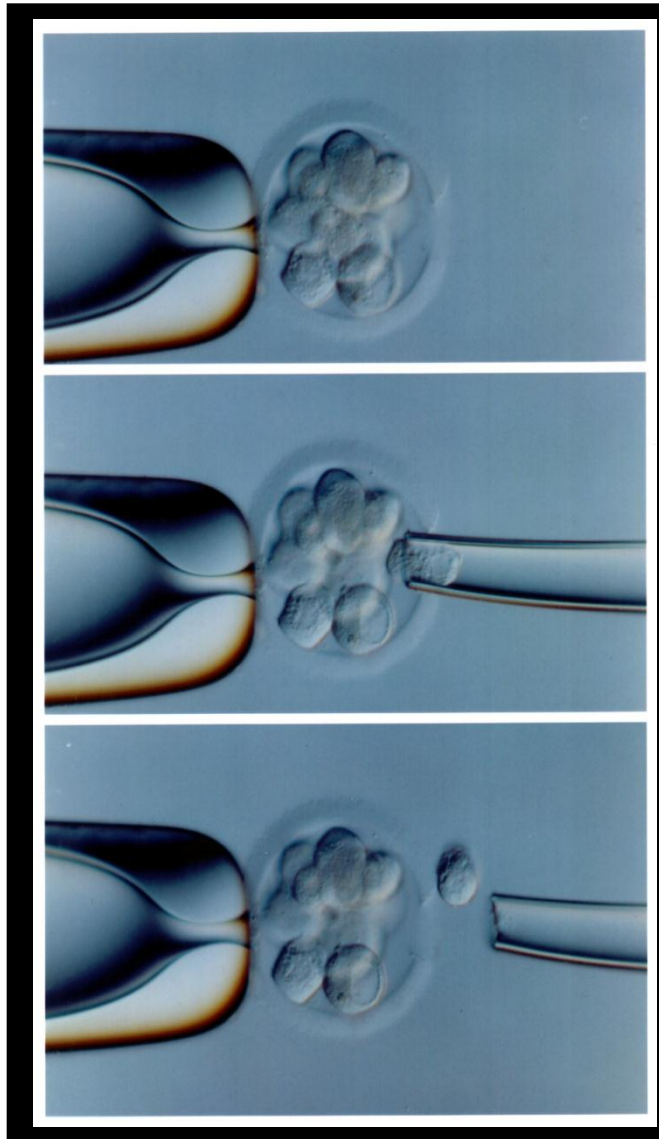
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Day 3 embryo (8 cells)



**Hole in the zona
pellucida by non-
contact laser**

**Insertion of glass
micropipette**

**Removal of a single
blastomere for genetic
analysis**

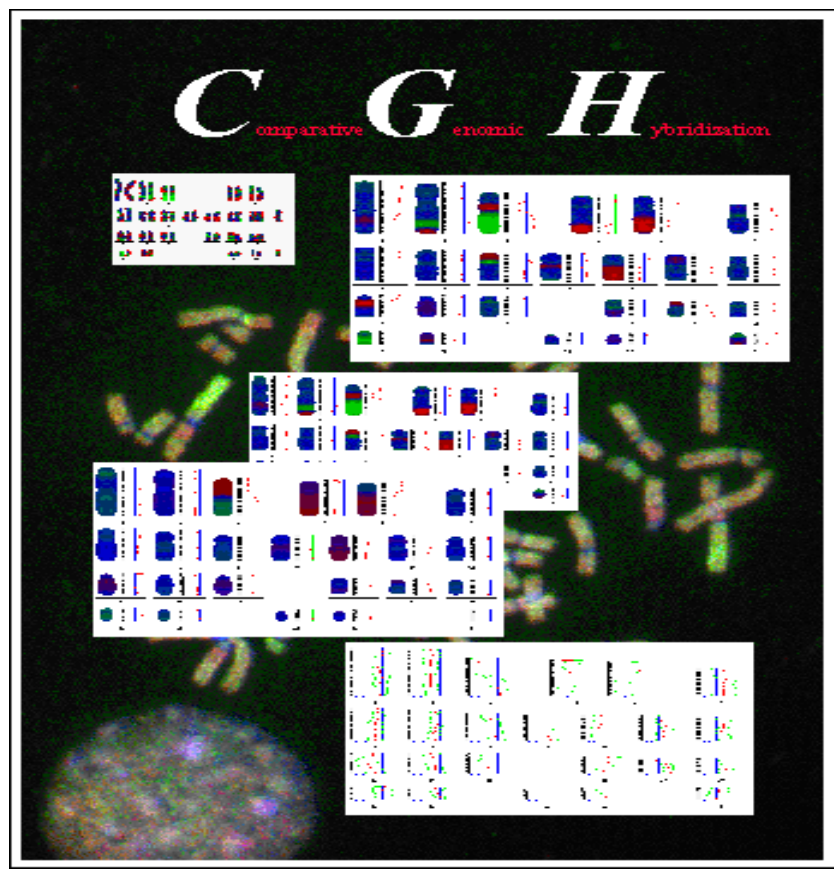
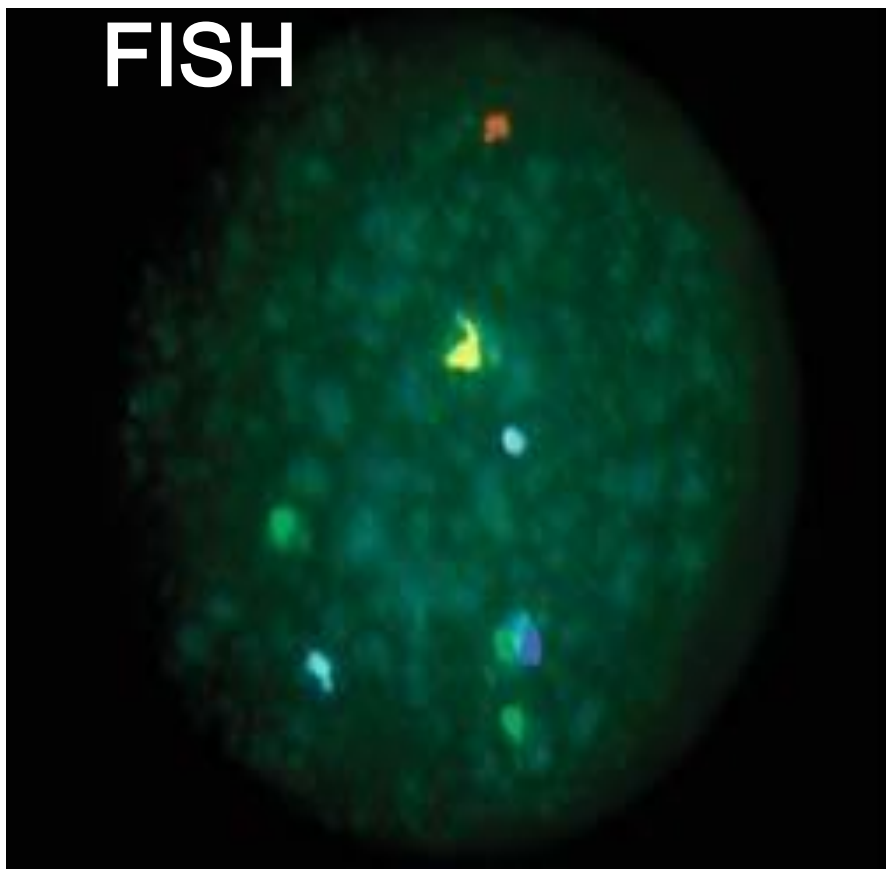
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FISH



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Current Status of PGD

- Public funding now available for 40 cycles annually across the country
- Criteria are broad but must involve serious genetic risk
- Currently under-spent nationally, but severe regional variation
- Wait time at Fertility Associates clinics:
 - Auckland: 2-4 months
 - Hamilton: currently no wait time
 - Wellington: 3-4 months
 - Christchurch: 2-3 years

Principles of the Act

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

HART Act (2004)

Prohibitions (i)

- Cloning for reproductive purposes
- Hybrids
- Human / animal implantation
- Genetic modification
- Derived from embryo or fetus

HART Act (2004)

Prohibitions (ii)

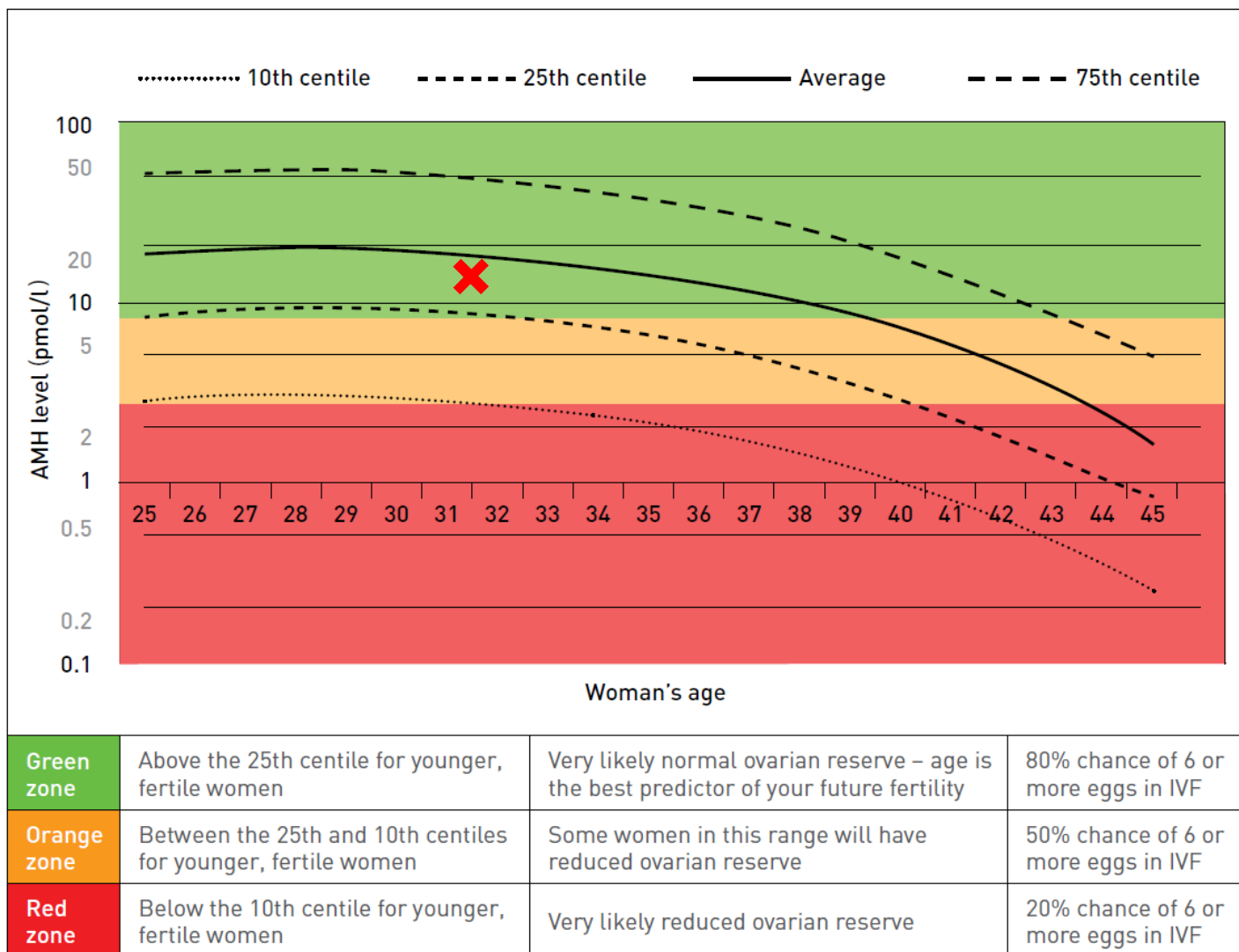
- Embryos beyond 14 days
- Gametes or embryos stored beyond 10 years
- Sex selection (defence)
- Obtaining gametes from minors (defence)
- Commercial supply
- Surrogacy agreement not enforceable

HART Act (2004)

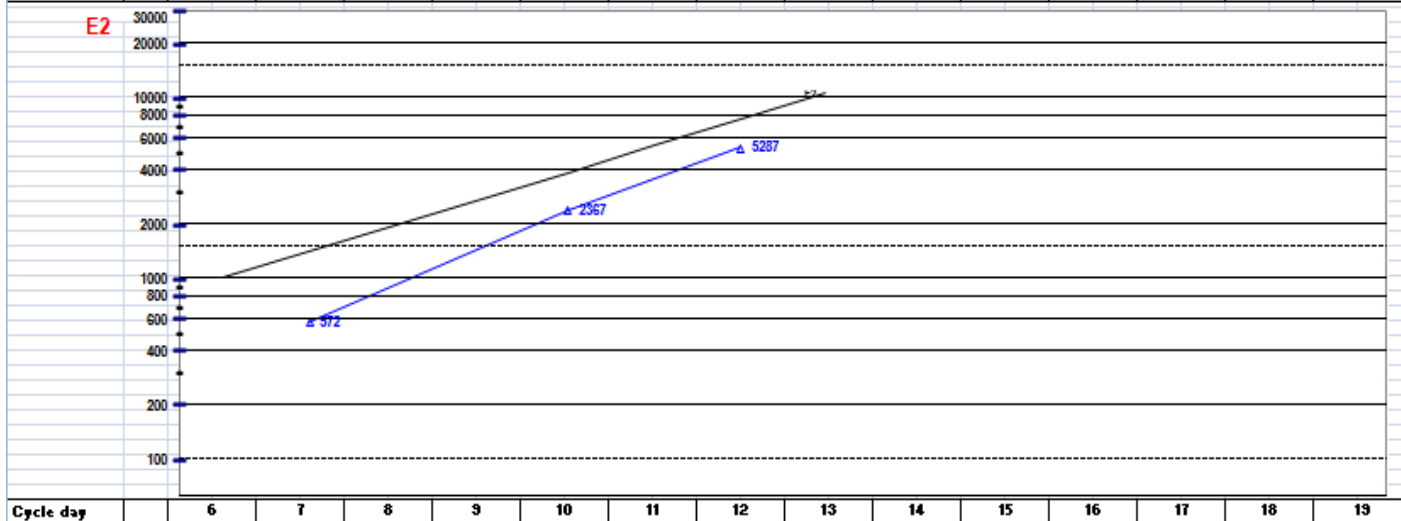
- ACART
- ECART

Case study 1

AMH: 12.5



Case study 1

[illegible]

IVF PLAN

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

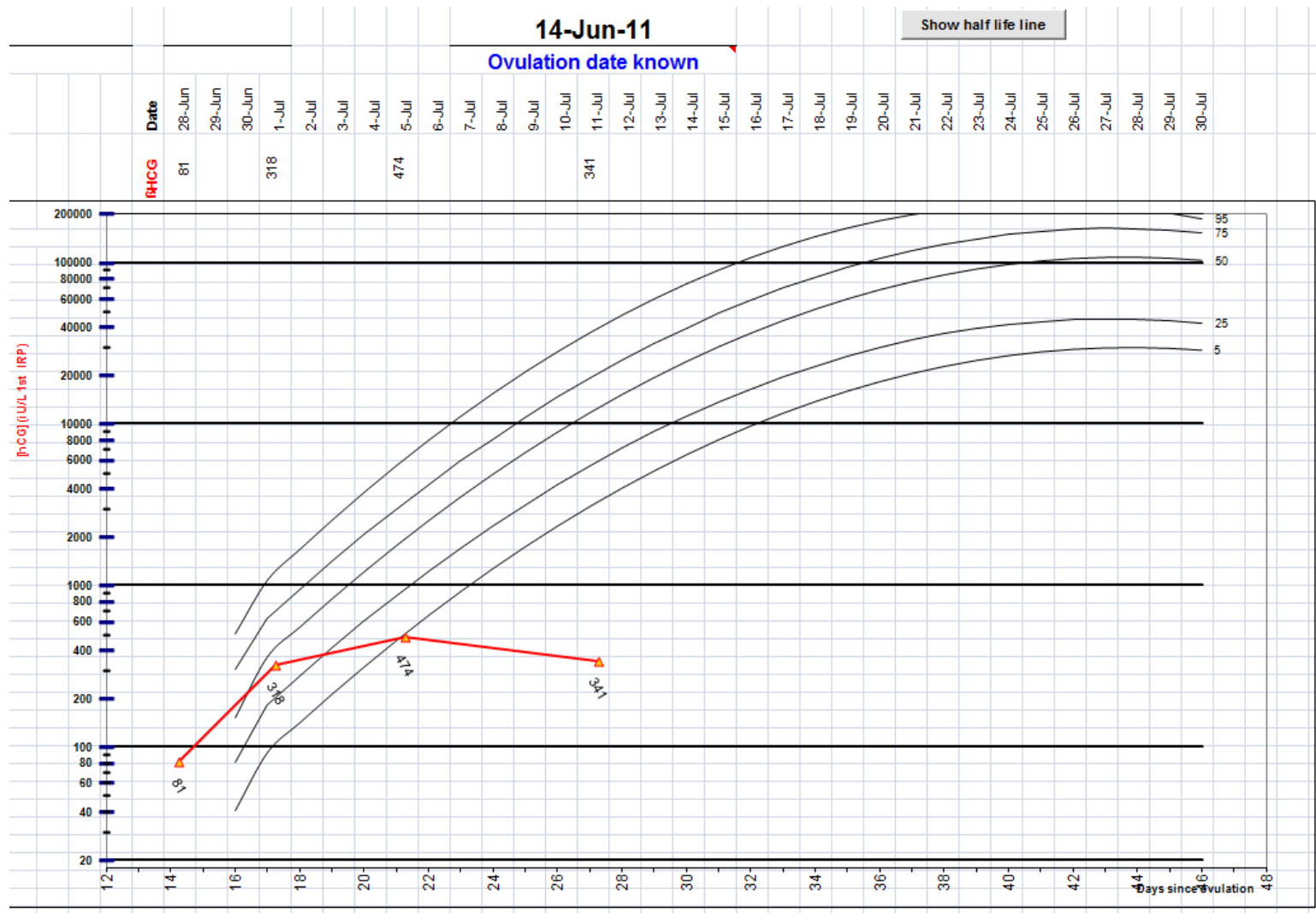
*** SIGNED OFF BY FREDDIE
GRAHAM

Case study 1



Leaders in Fertility

Case study 1



Case study 2 - Feb 2011

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

Case study 2

Paste Dr plan here

IUI CYCLE PLAN

(Unstim)

Cycle #

1

Protocol #

*

Monitoring (CP/BI/Sc)

*blood

Trigger (Y/N/AugLH)

no

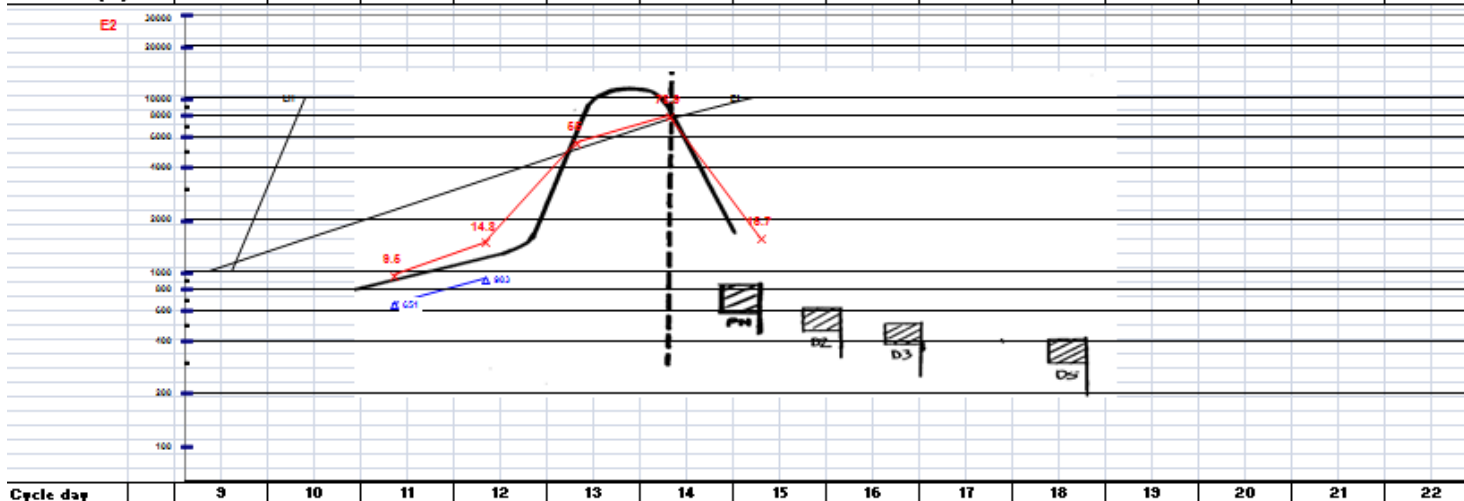
Sperm (Ejac/Fz)

DI

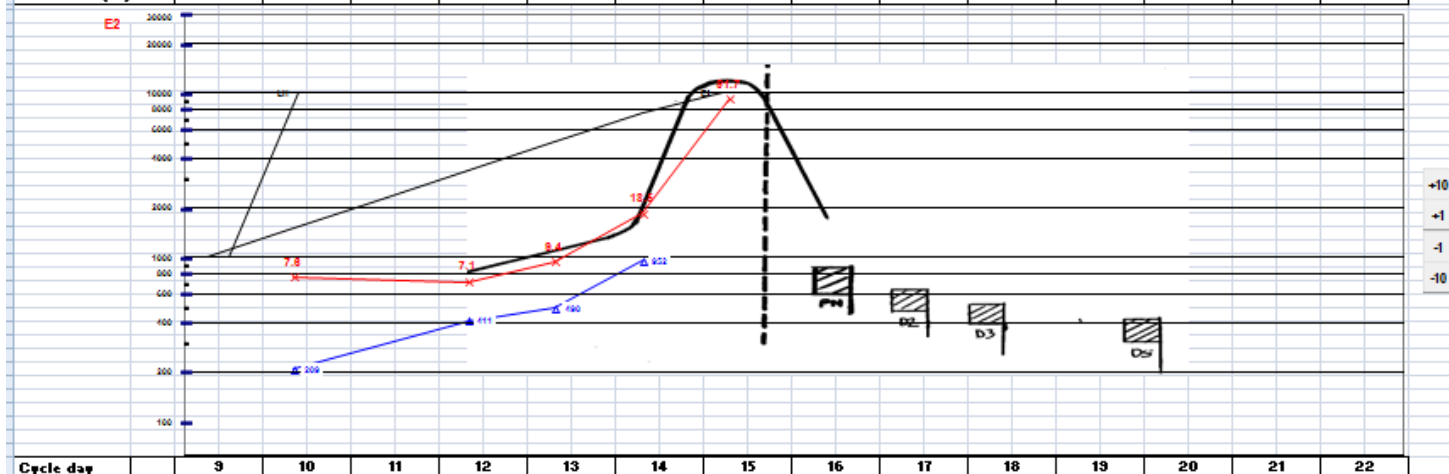
Comments

*

Scan doctor		Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	Size	x	
L Ovary																												
R Ovary																												
Cycle day		9		10		11		12		13		14		15		16		17		18		19		20		21		22
Date		9-Jul		10-Jul		11-Jul		12-Jul		13-Jul		14-Jul		15-Jul		16-Jul		17-Jul		18-Jul		19-Jul		20-Jul		21-Jul		22-Jul
Weekday		Sat		Sun		Mon		Tue		Wed		Thu		Fri		Sat		Sun		Mon		Tue		Wed		Thu		Fri
E2 (pM)						651		903																				
LH (iu/l)						9.5		14.8		55		78.9		15.7														
CC (mg)																												
FSH (iu)										insem		insem																



Case study 2

[illegible]

(Unstim)

Cycle #

Protocol #

Monitoring (CP/BI/Sc)

Trigger (Y/N/AugLH)

Comments

*2

 $\ast d_i$

*bl

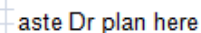
 γ

*day 10 8/7an here

Case study 3 – June 2008

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

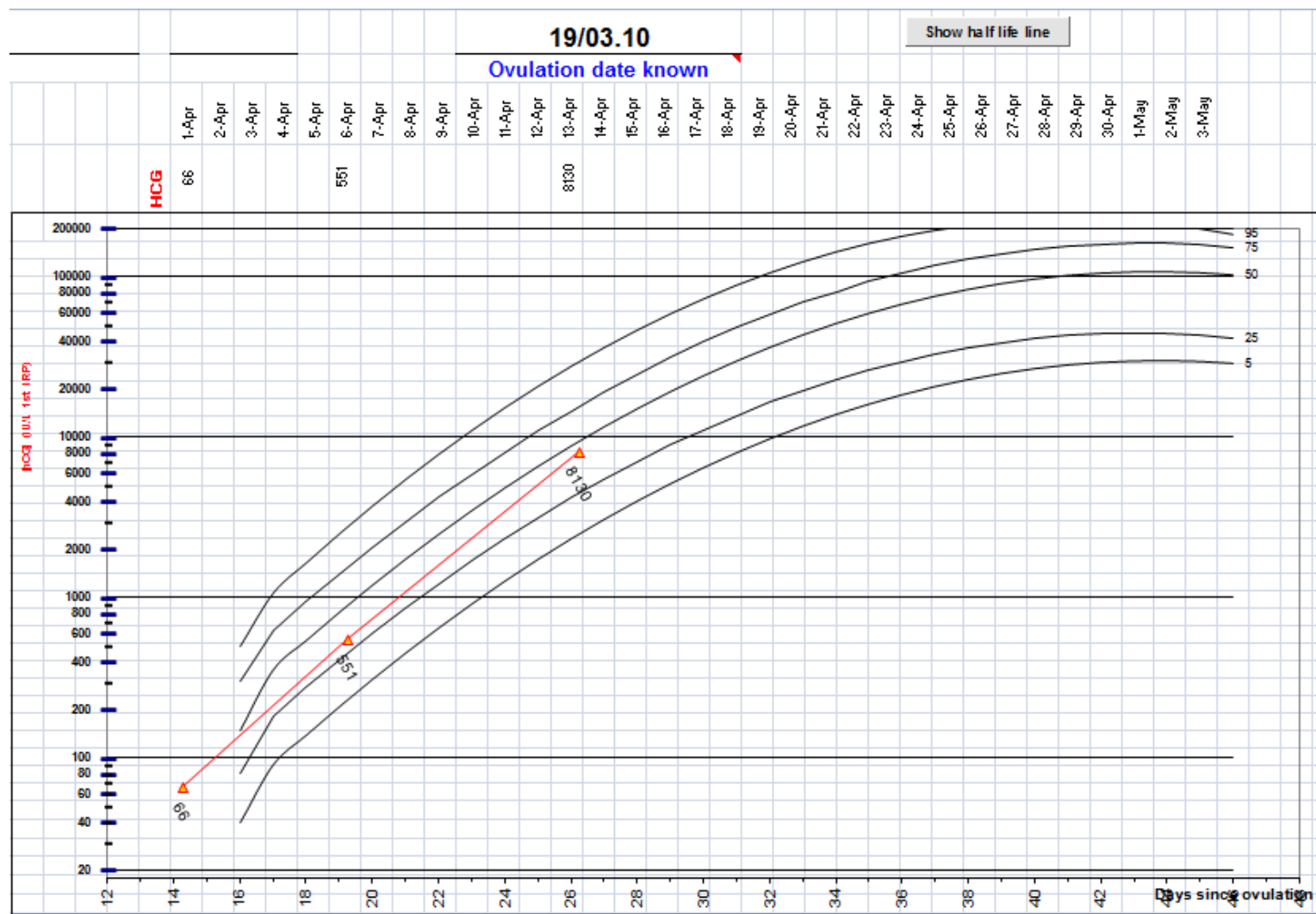
PIVF PLAN
Cycle# *2
Protocol# *5.86
GnRHA(Bus/Cet/etc) *bus
FSH (GF/Pur) *GF
FSH dose *150
Trigger (type, time) *ov
OPU (Narc/MAC/etc) *narc
Sperm (Ejac/Don/Fz) *ejac
IVF/ICSI *ivf
LPS (P4/P4+E2V) *p4
Transfer (D2/D3/B) *d3 or 5
ET# *2 or 3
Com(AH, Col) *coasted last time.



Case study 3



Case study 3



Funding

Tertiary Consultation

- 1) Complete sterility
- 2) Fully investigated couple

To Access Treatment

- MUST SCORE 65 POINTS

Treatment

- 4 Ovulation Induction
- 4 IUI / hyperstimulation
- 1 IVF + ICSI
- 4 Donor Insemination

Ovulation	6 3 2 1 0	Amenorrhea Oligomenorrhea/ luteal defects Normal cycles but no ovulation Irregular ovulation No ovulation defect	Consultation type: private / public Date scored:		
Male	6 3 2 1 0	< 1 M motile/ml/ severe ABs/ severe ejaculatory 1-5 M motile/ml/ mod ABs/ sperm function abn 5-10 M motile/ml Any other sperm defect No sperm defect	Month & year started trying: W/H² = / BMI =		
Endo	6 3 2 1 0	Stage IV Stage III Stage II Stage I None	Planned Treatment: IVF ICSI DI AIH AIH/S OI		
Tubal	6 3 2 1 0	Occlusion/ severe adhesions/ 12 months surgery Mod adhesions/ 6 months surgery Polyps/ mild adhesions/ normal tube one side Minimal adhesions best side No tubo-peritoneal pathology	☐ Ineligible within next 2 years ☐ >= 65, enrol from date		
Other	6 3 2 1 0	Severe Moderate Mild Minimal None	☐ < 65 points / smoker / BMI / other so review in months		
Duration of infertility	>= 5 years >= 4 and < 5 years >= 3 and < 4 years < 3 years		Now 6 3 2 1	At: 6 3 2 1	At: 6 3 2 1
Total Diagnostic score					
OBJECTIVE CRITERIA			Points		
Diagnostic (O1)	Total diagnostic score >= 6 3 – 5 2 0 – 1		10 7 4 2		
Woman's age (O2)	=< 39 y 40, 41 >= 42		10 5 1		
Basal FSH (O3)	Always in reference range Sometimes, or always just above Mostly well above		10 8 2		
Smoking (O4)	Non-smoker Smoked in past 3 months		10 6		
Objective score	OS=O1xO2xO3xO4/10000				
SOCIAL CRITERIA					
Duration of infertility over time (S1)	Less than 1 year 1 or 2 years 3 or 4 years 5 years or more		5 20 40 50		
Children at home (S2)	None 1 by relationship >1 by relationship By previous relationship		30 10 5 8		
Sterilisation (S3)	Neither partner Yes, but death of child Yes		20 20 10		
Social score	SS=S1+S2+S3				
FINAL SCORE	=OSxSS				

For more info, please visit our website:
www.fertilityassociates.co.nz/GP