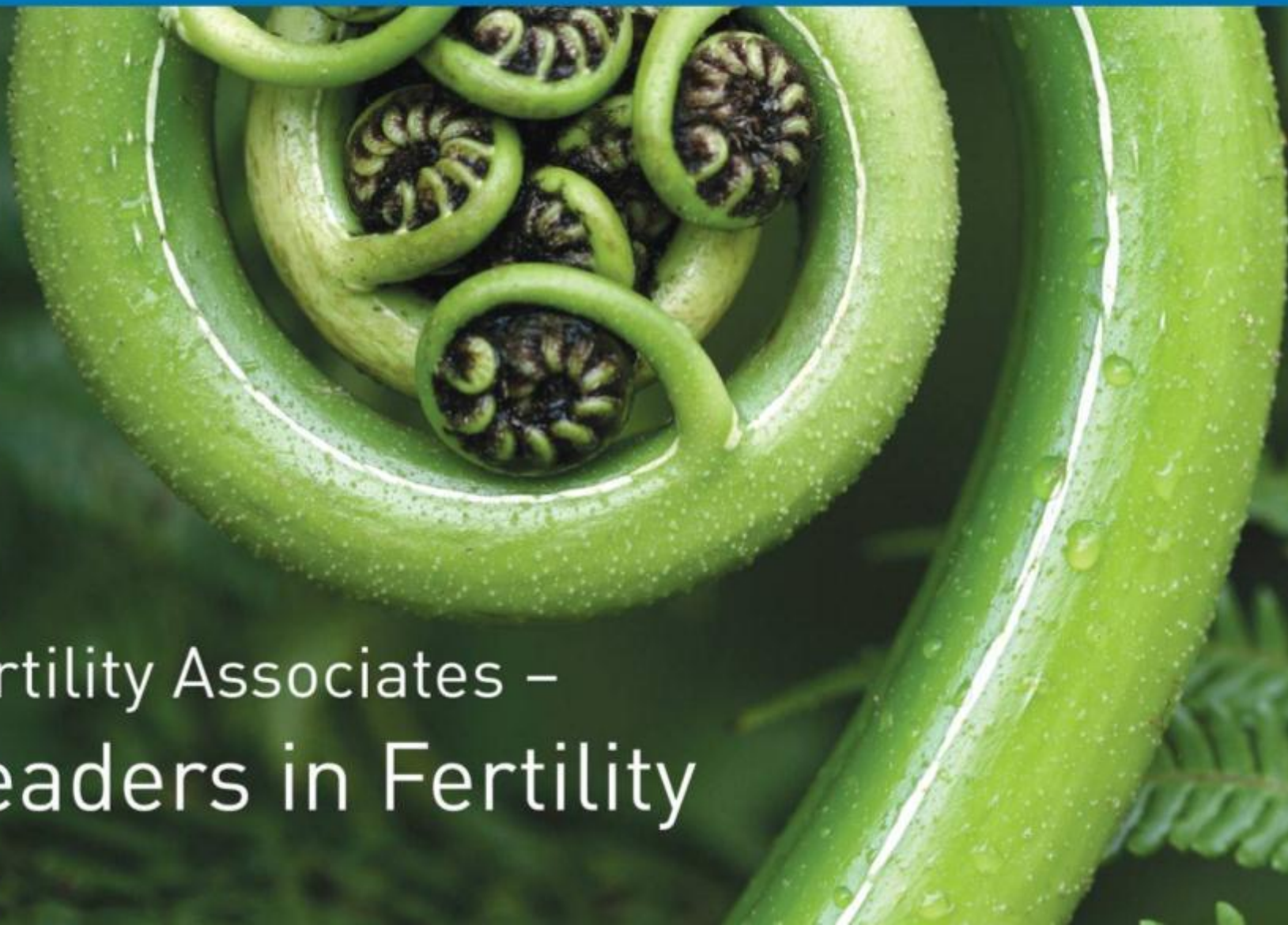




FERTILITY
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Fertility Associates –
Leaders in Fertility

Infertility: 'from whoa to go'

Greg Phillipson
Dunedin 2012



11.05.2012

0:04



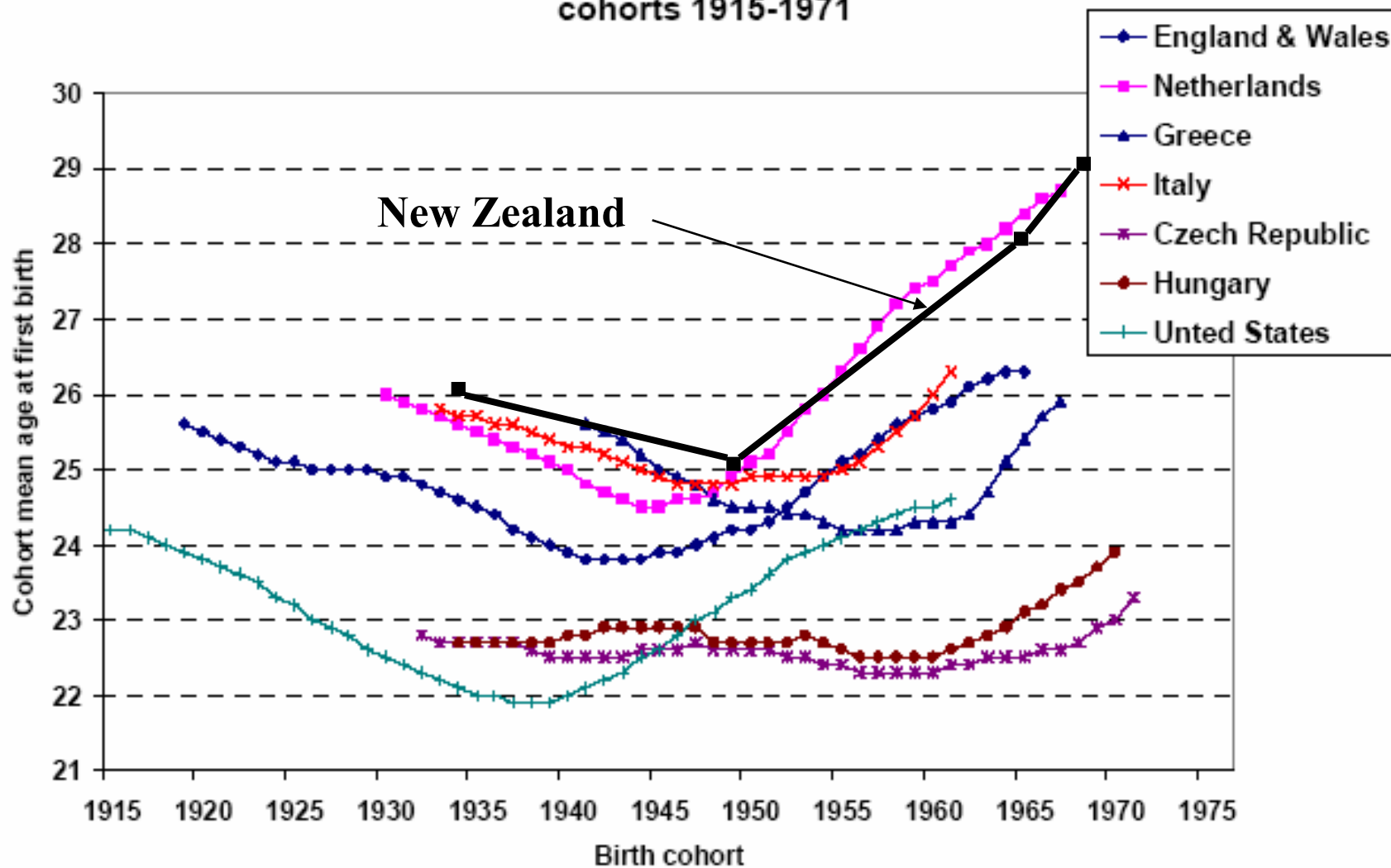
London 2012



- **Lifestyle, environmental and nutritional issues**
- Cost effective and timely investigation
- Recent developments
 - endocrinology, radiology and genetics
- New developments in IVF
- Early pregnancy management, miscarriage and ectopic
- Ethical issues and medical tourism



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

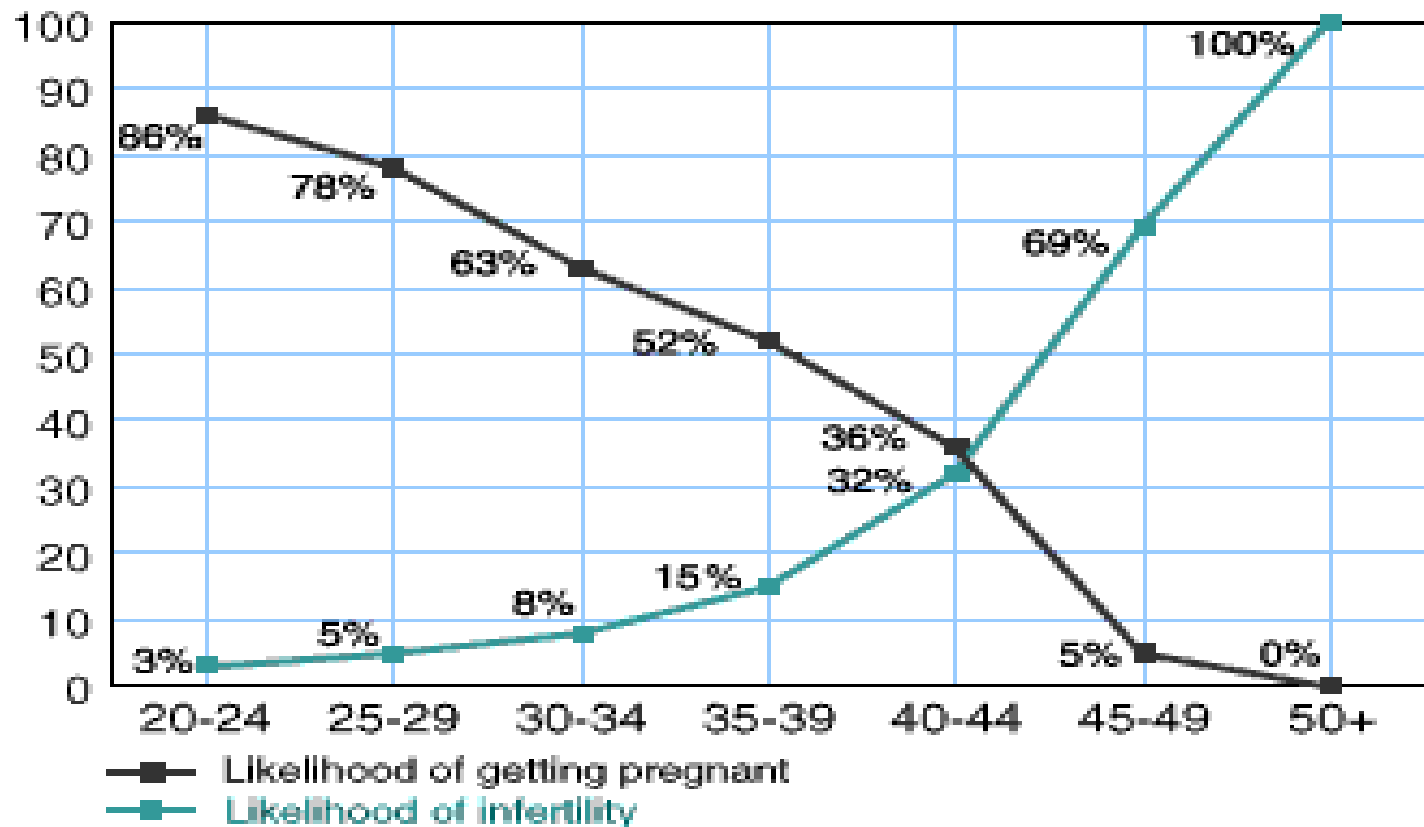


Human Reproduction

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

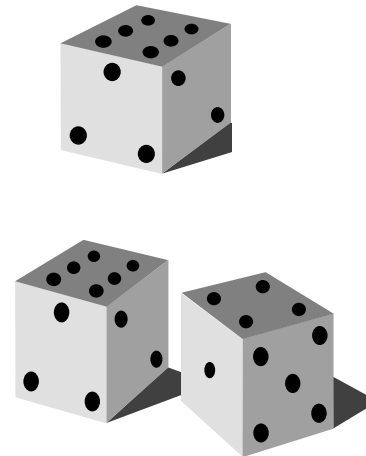
Getting pregnant is usually a matter of chance

Likelihood of pregnancy



Monthly fecundity by age

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



Elevit?

- Multivitamin
- Folate only benefit unless malnourished
- \$1 per day
- Folate 800mcg \$1 per week
- High dose folate 5mg day
 - phx Neural tube defect
 - Family hx
 - Epilepsy
- Iodide from early pregnancy ?contraindications



Female Lifestyle and pre-pregnancy issues

Age

Smoking

Alcohol

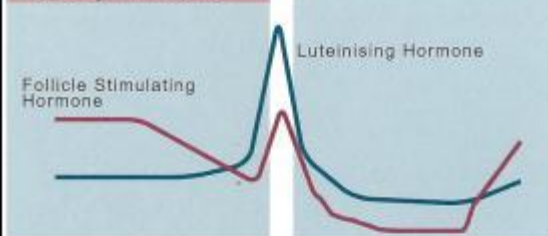
Caffeine

Bmi Height in m / (weight in kg)²
range 18 to 30

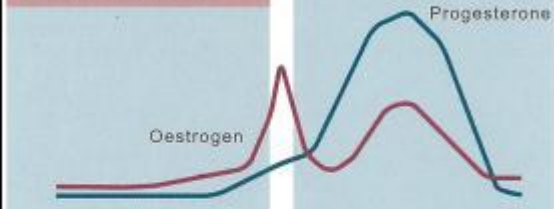
Exercise

The Normal Menstrual Cycle

Pituitary Hormones



Ovarian Hormones



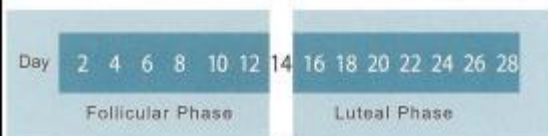
Follicular Cycle



Endometrial Cycle

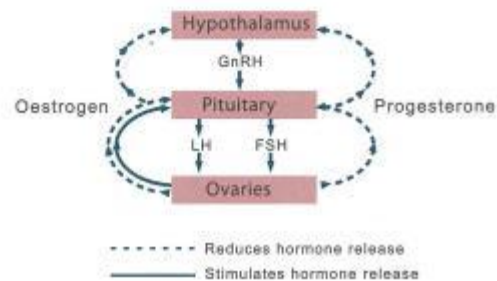
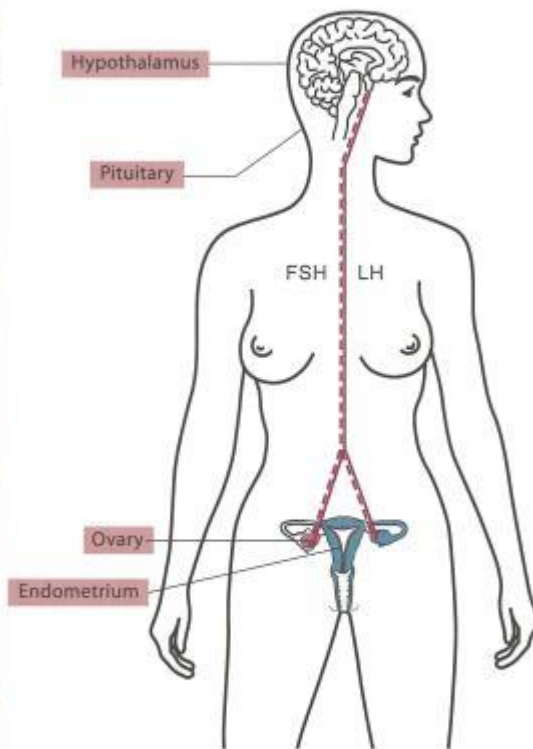


Body Temperature

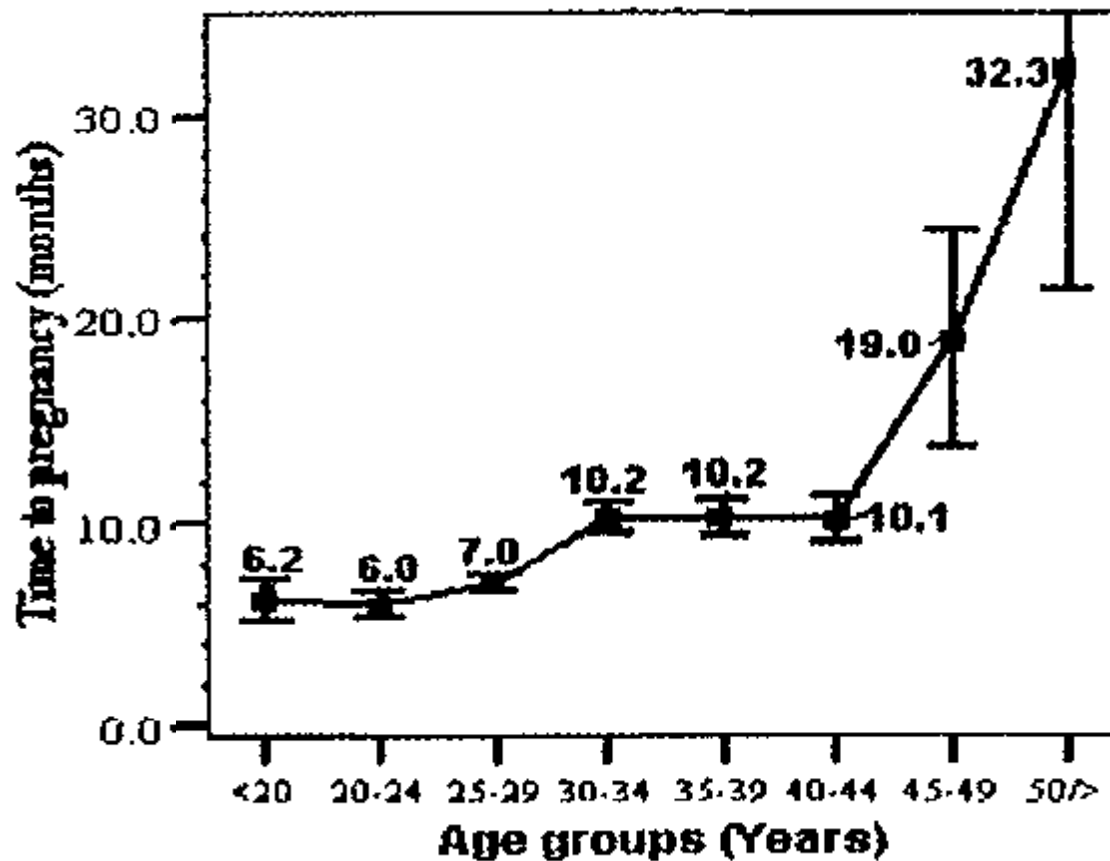


Ovulation

Notes

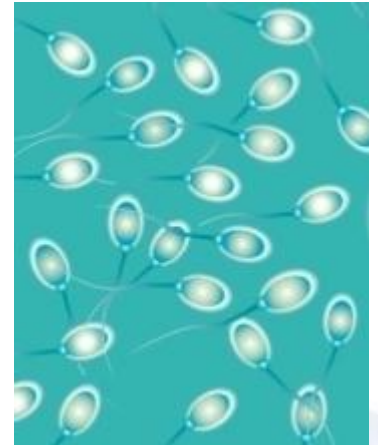


Paternal age effects on time to pregnancy



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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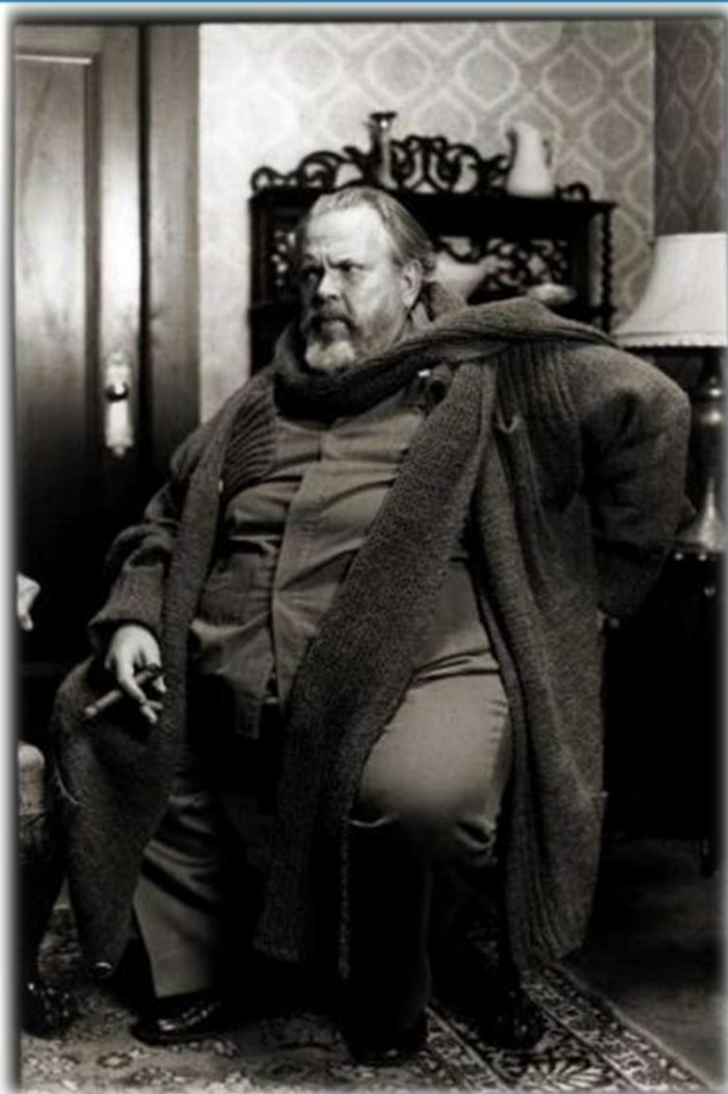
Leaders in Fertility



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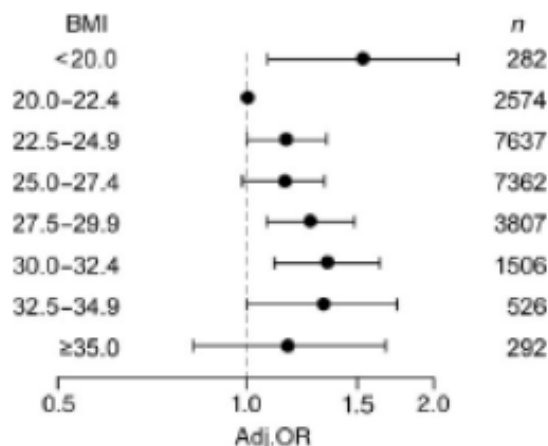


Leaders in Fertility



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

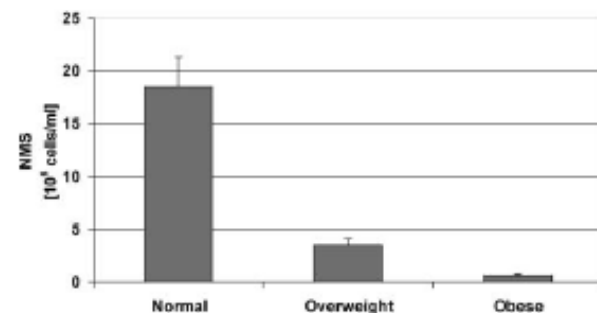


Figure 1. Effect of body mass index class on number of normal-motile sperm cells.

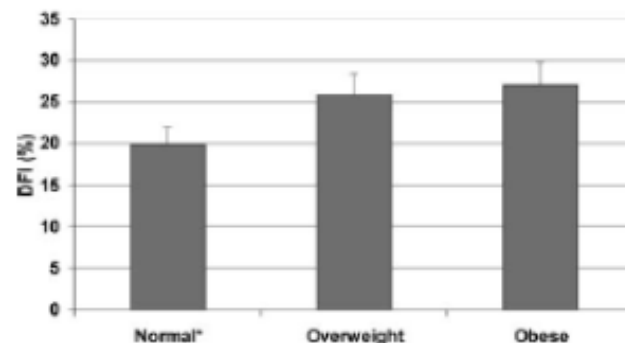


Figure 2. Effect of body mass index class on sperm chromatin integrity. *Significantly different ($P < .05$).

Kort et al J Androl 2006



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?Over exercising ?Friction in the saddle

Leaders in Fertility

Environmental

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



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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





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.

- Lifestyle, environmental and nutritional issues
- **Cost effective and timely investigation**
 - **DHB and private funding explained**
- Recent developments
 - endocrine, radiology and genetics
- New developments in IVF
- Early pregnancy management miscarriage and ectopic
- Ethical issues and medical tourism



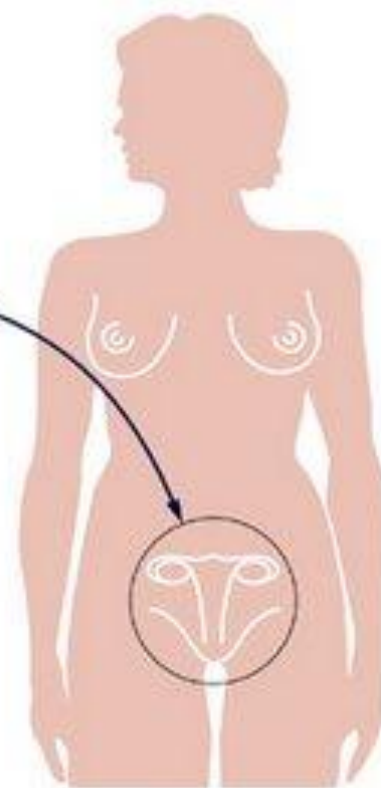
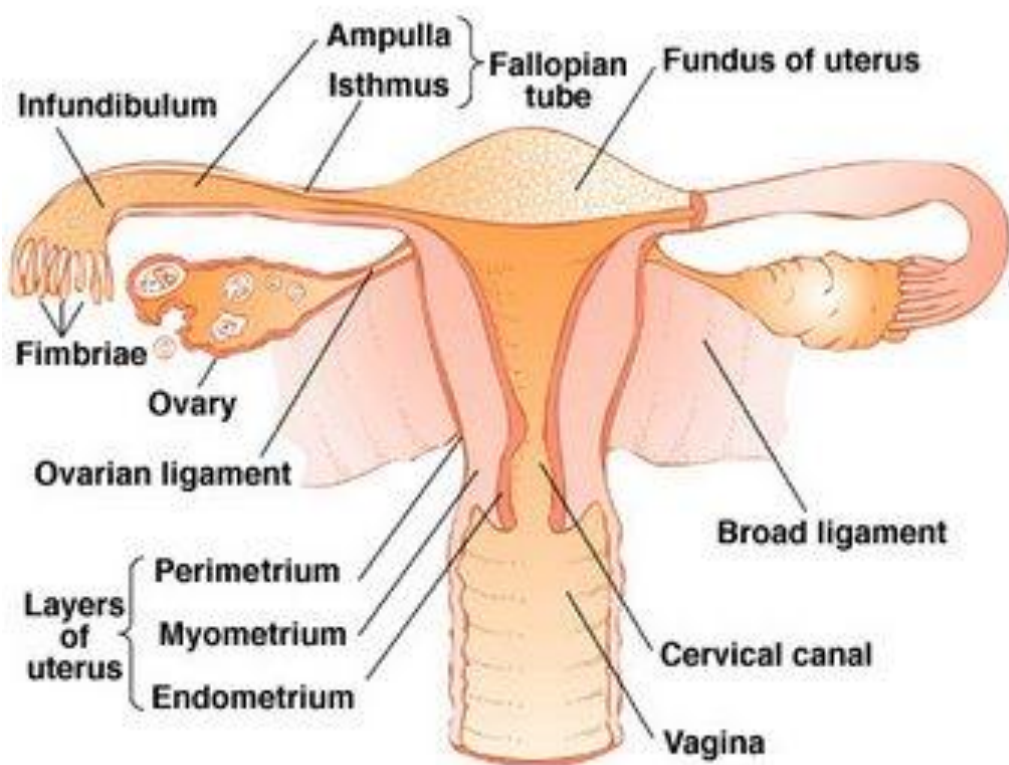
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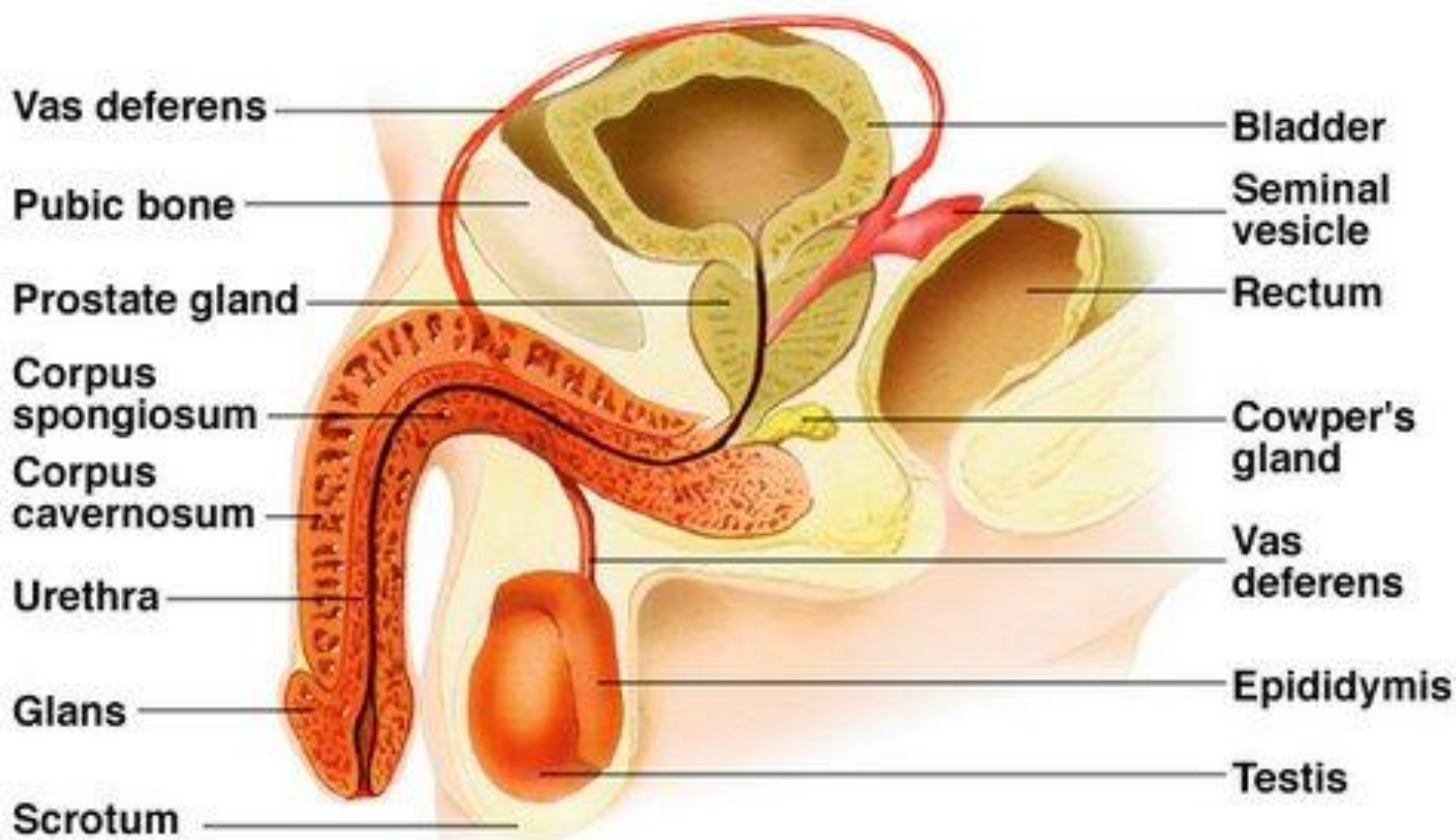
Internal Sexual & Reproductive Organs(F)



Leaders in Fertility

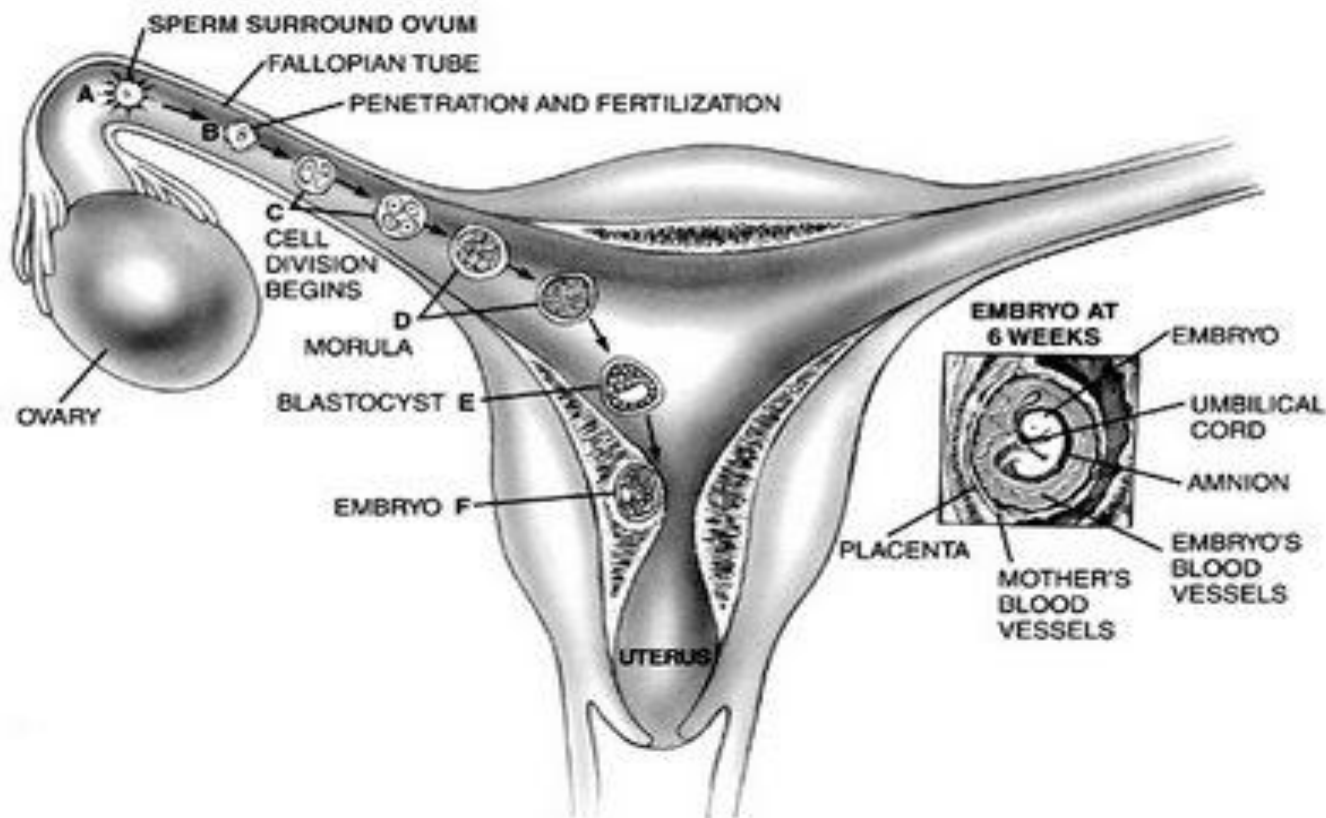


Male Sexual & Reproductive Organs





Blastocyst Implantation



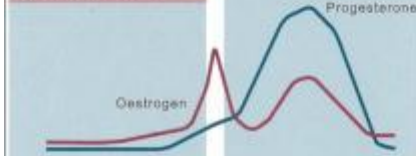


The Normal Menstrual Cycle

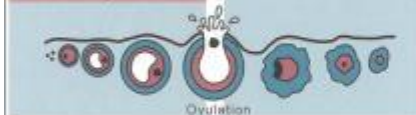
Pituitary Hormones



Ovarian Hormones



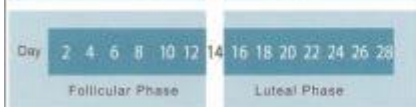
Follicular Cycle



Endometrial Cycle

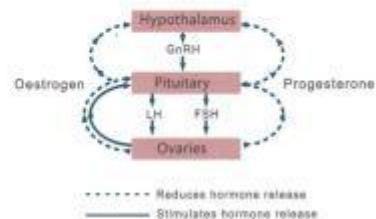
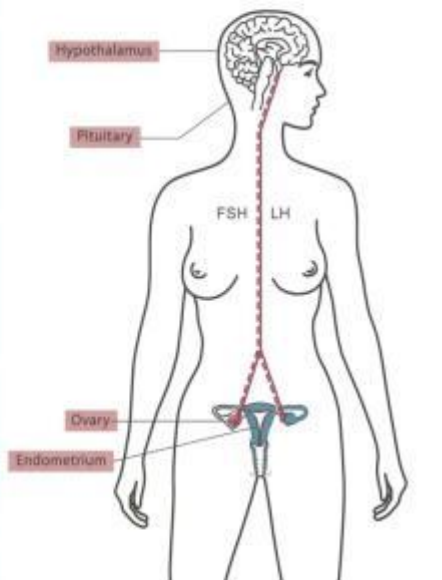


Body Temperature



▲
Ovulation

Notes



Overall likelihood of pregnancy

60% in 6 months

80% in 1 year

90% in 2 years



Initial investigations that can be done in primary care

Female

- Luteinising hormone, follicle stimulating hormone (FSH), and estradiol concentrations—should be measured in early follicular phase (days 2 to 6)
- Progesterone test—should be done mid-luteal phase (day 21 or seven days before expected menses)
- Thyroid stimulating hormone, prolactin, testosterone test—should be done if woman's cycle is irregular, shortened, or prolonged or if progesterone indicates anovulation
- Rubella serology test—should be checked even if the woman has been immunised in past
- Cervical smear—should be carried out as normal screening protocol
- Transvaginal ultrasound scan—should be done if there is the possibility of polycystic ovaries or fibroids

Male

- Semen sample for analysis—sample should be taken after two or three days' abstinence and repeated after six weeks if abnormal



Guide to Fertility Assessment

Primary / Initial Assessment

Secondary

Specialist

CBC, Blood Group, Rubella, VDRL,
Hep B Hep C, HIV

Cervical smear, Chlamydia , Vaginal
Swabs
PID or IUCD History

Menstrual Calendar

Family History of Androgen sensitivity

Pelvic Assessment

Day 2 FSH and oestradiol
Luteal Phase "day 21" progesterone

PCOS assessment
Testosterone, LH, Prolactin, TSH

Ultrasound scan

Ovarian reserve assessment
"Eggtimer test" AMH

Endocrinologist assessment

Hysteroscopy Laparoscopy

Female Age issues if over 35

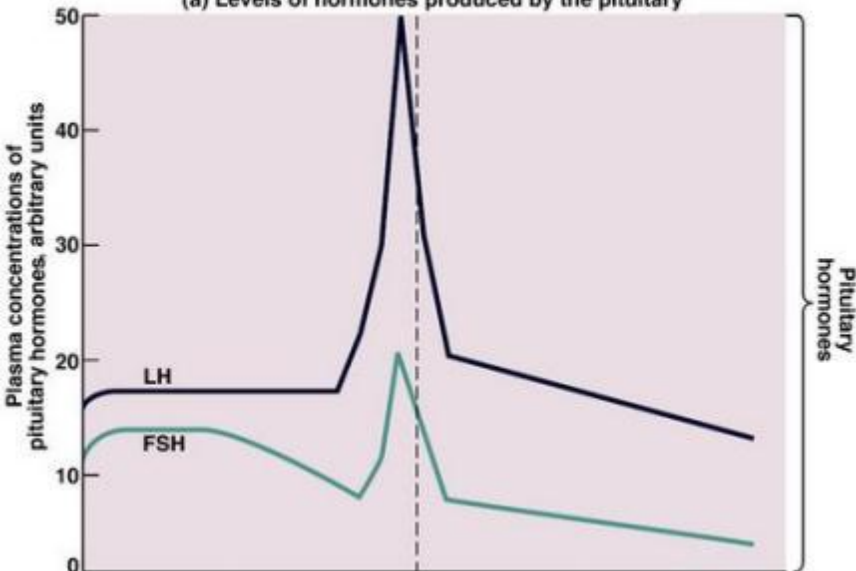
- Pregnancy rates
- Ovarian reserve Day 3 FSH, USS antral follicles
- AMH (egg timer test)
- Miscarriage rates
- Down's syndrome
- IVF access
- IVF success rates

Assessment FSH

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The Biological Events of Menstrual Cycle

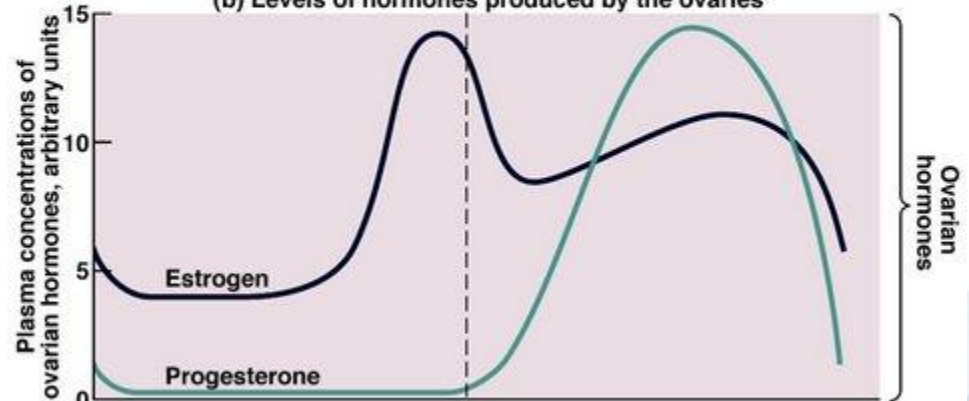
(a) Levels of hormones produced by the pituitary



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The Biological Events of Menstrual Cycle

(b) Levels of hormones produced by the ovaries



Antral follicle Count

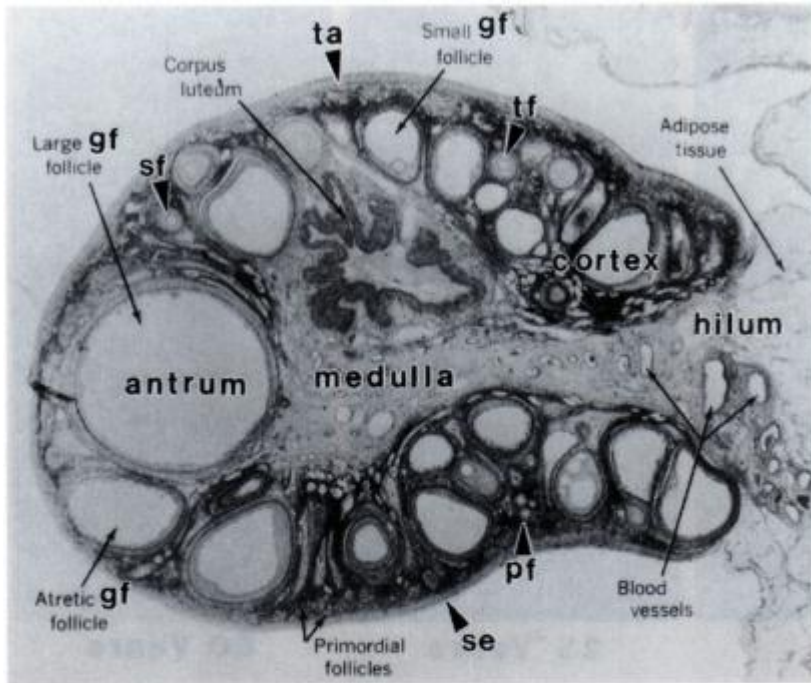


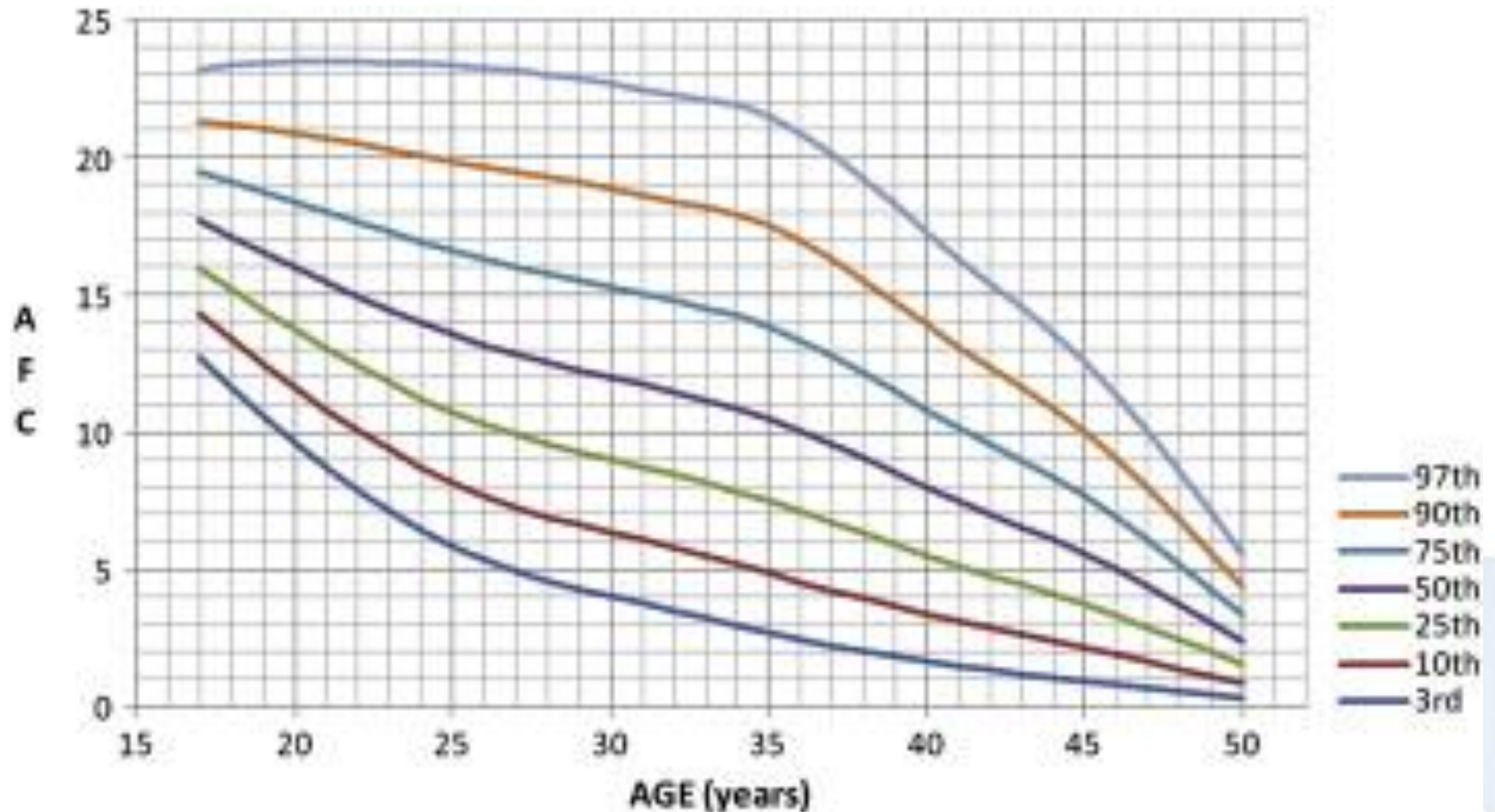
Fig. 3. Photomicrograph of an adult primate ovary. Follicular and luteal units are seen in the cortex and large blood vessels and nerves in the medulla. se, serous or surface epithelium; ta, tunica albuginea; pf, primary follicle; sf, secondary follicle; tf, tertiary follicle; gf, graafian follicle. (From Bloom W, Fawcett DW: *A Textbook of Histology*. Philadelphia: WB Saunders, 1975.)

Abb.: 12 Antrafollikel in der Größe von ca. 4–8 mm



Correlation between 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles of antral follicle count (AFC) and age.

Fertility Sterility , Almog 2011



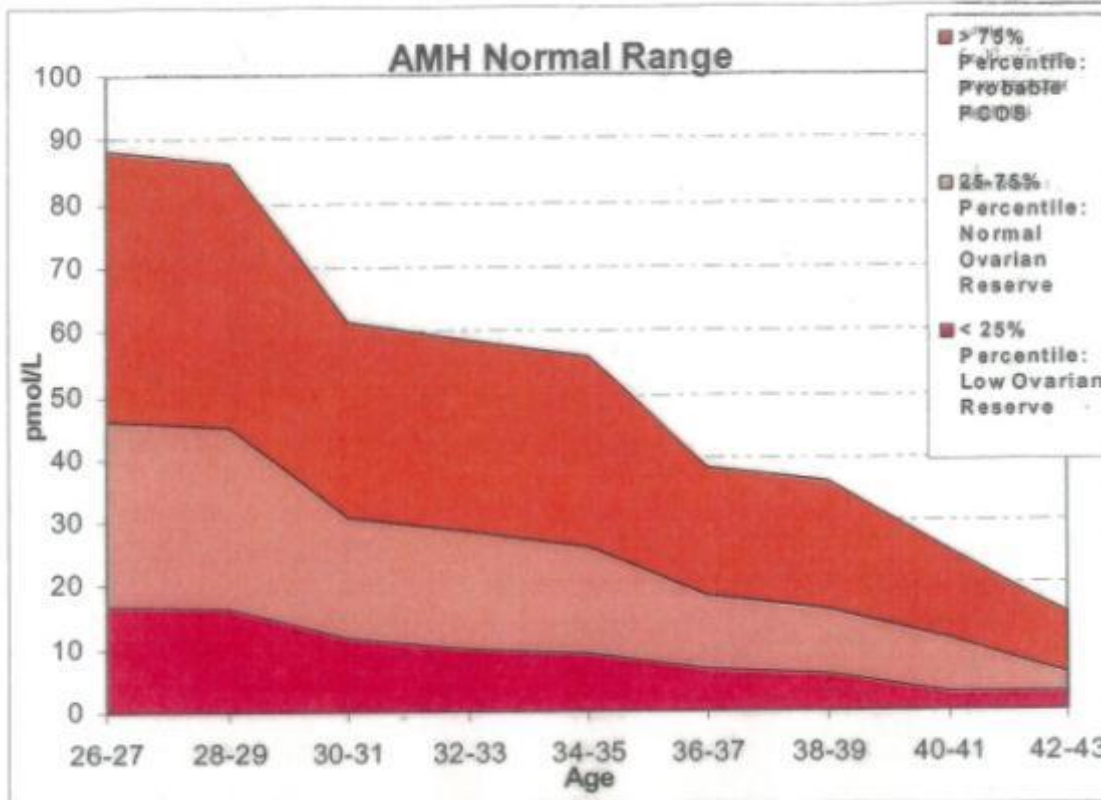


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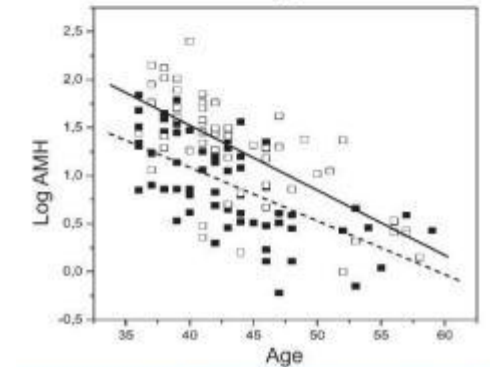
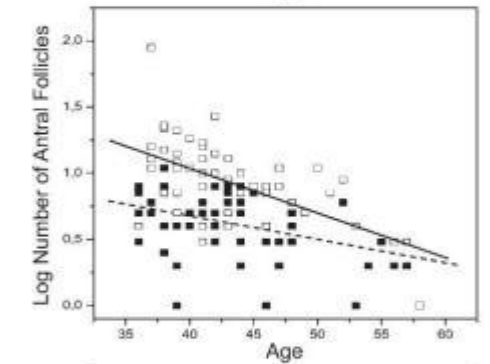
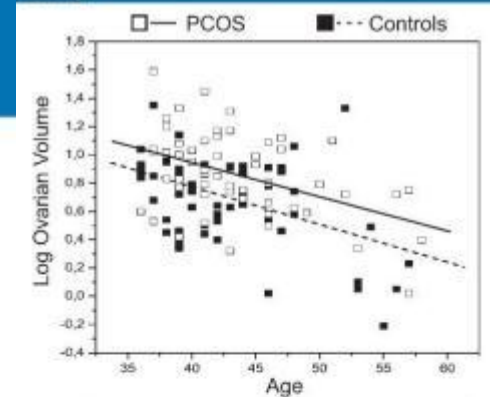
AMH

AMH Profile:



* Research at Ovarian decline IVF treatment has illustrated the connection between a woman's

Medscape

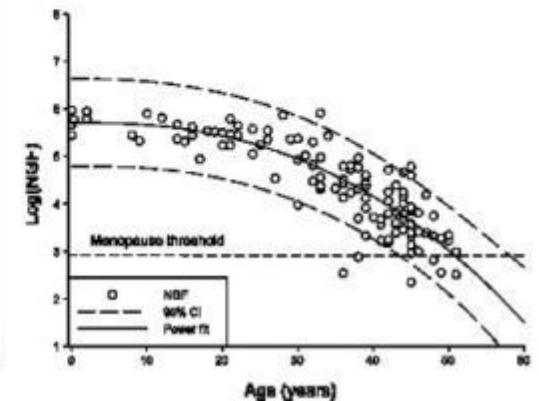
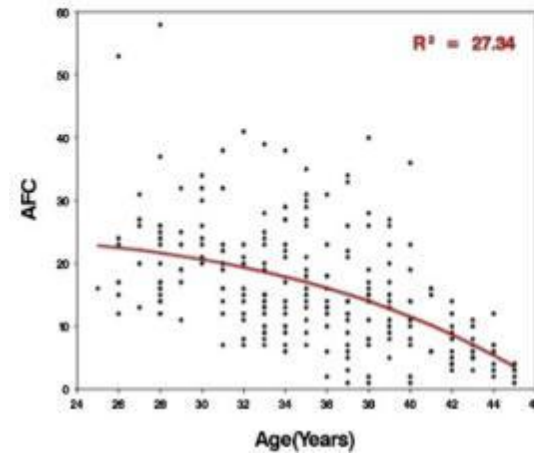
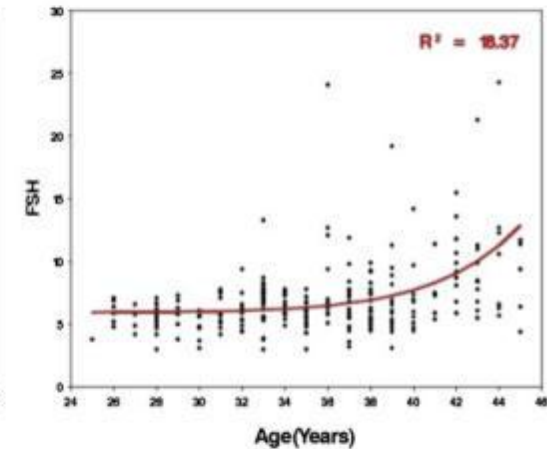
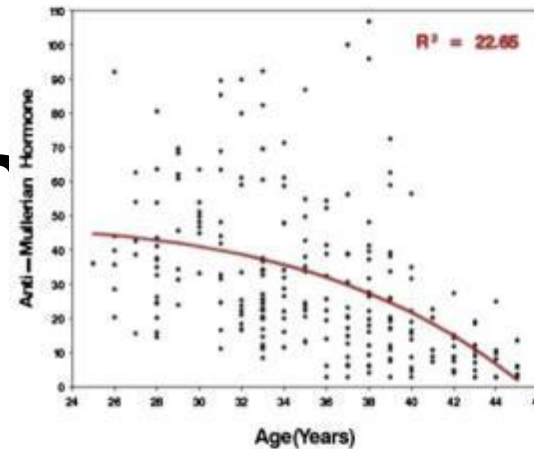
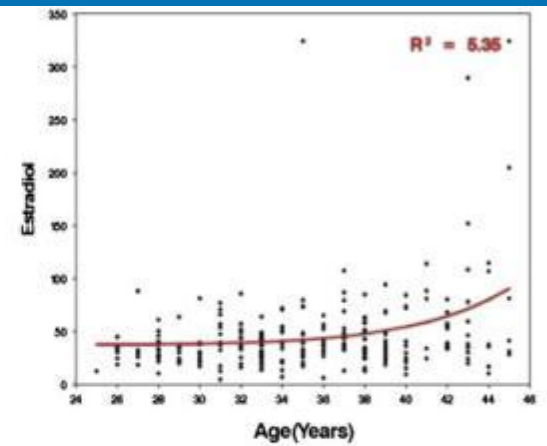
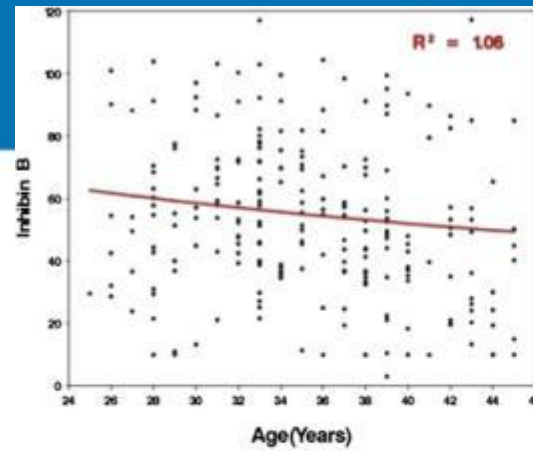


Source: Hum Reprod © 2009 Oxford University Press

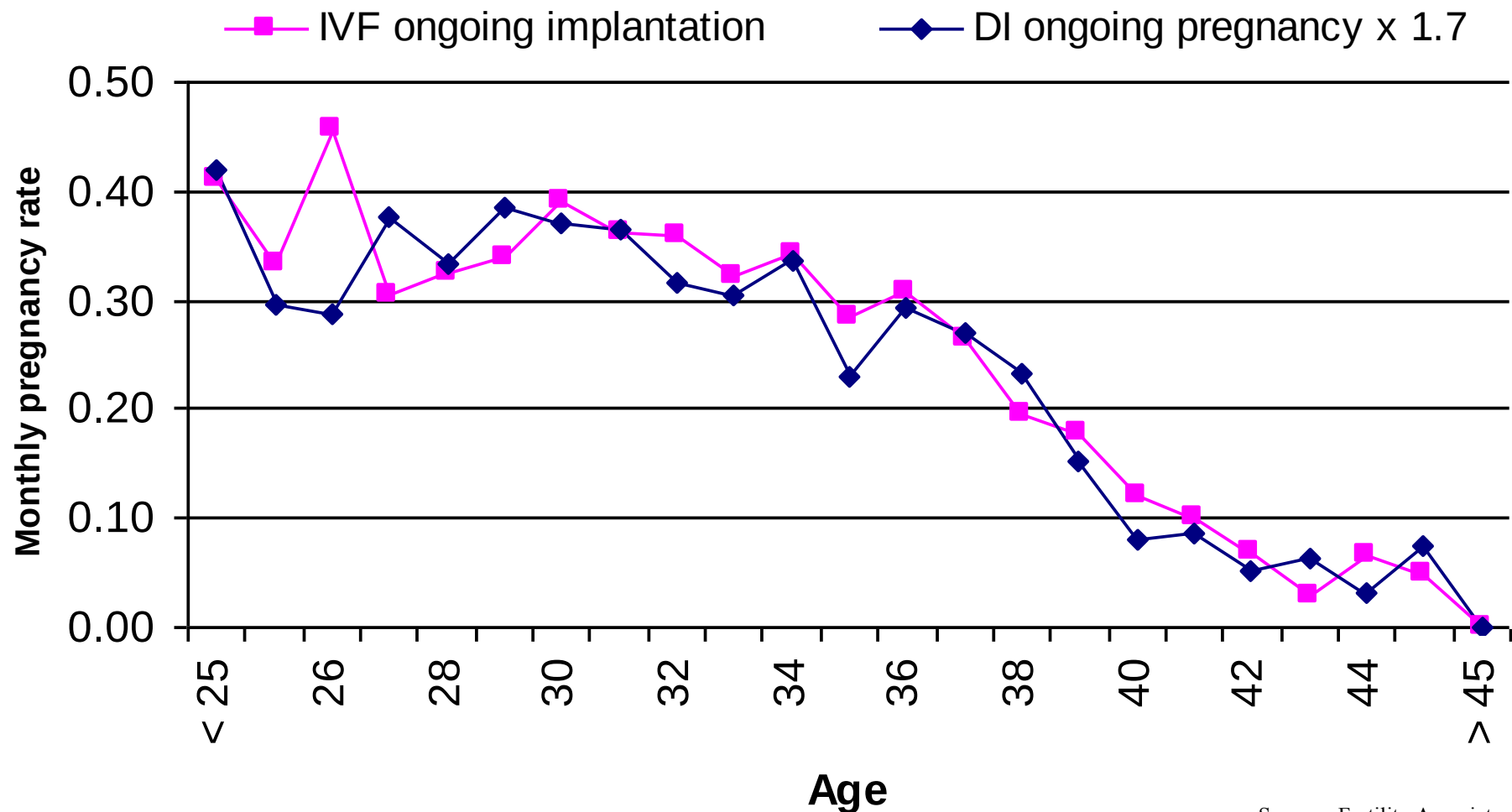
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Serum markers of ovarian reserve

Fertility Sterility ,
Rosen 2012

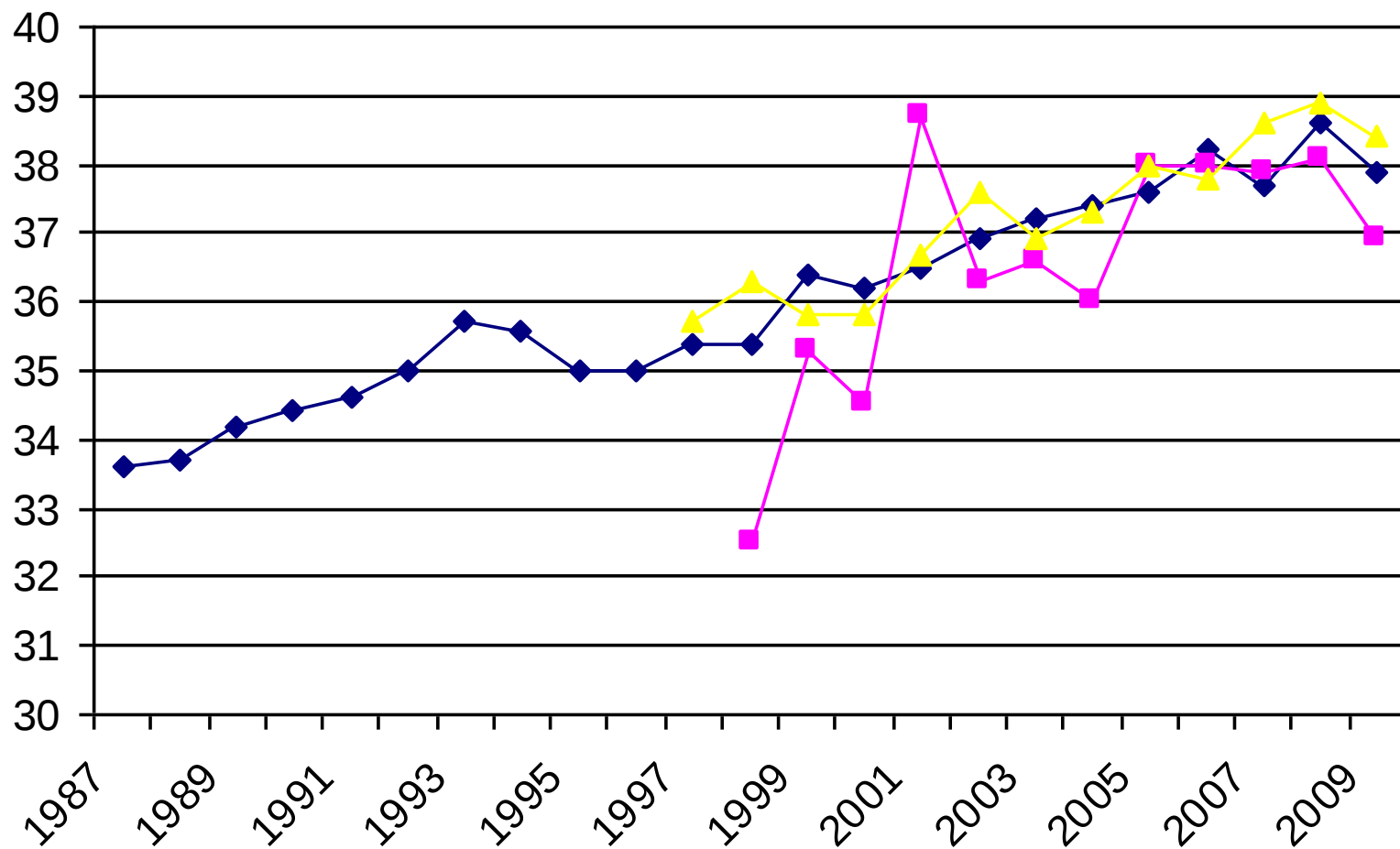


Decline in fertility with age



Age at starting private IVF cycle (incl DO)

—◆— FAA —■— FAH —▲— FAW



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 improving the quality of eggs or delay the loss of eggs

Loss of primordial follicles with woman's age

Faddy et al, 1992

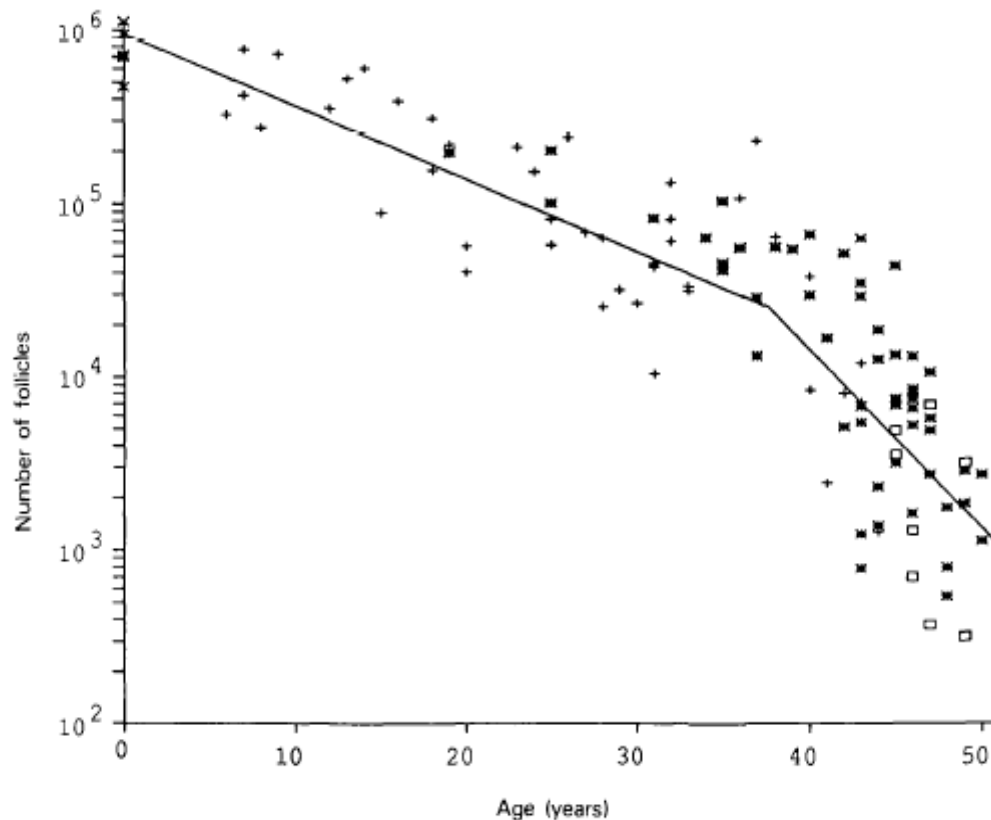


Fig. 1. Bi-exponential model of declining follicle numbers in pairs of human ovaries from neonatal age to 51 years old. Data were obtained from the studies of Block (1952, 1953) ($\times$, $n = 6$; +, $n = 43$), Richardson *et al.* (1987) ($\square$, $n = 9$) and Gougeon (unpublished) (*, $n = 52$).

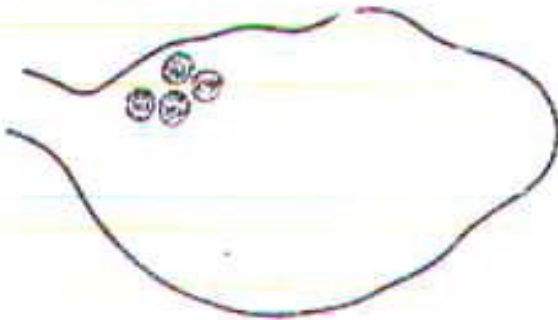


Ovarian Reserve

Oocyte Numbers

Age : minus six months
= 7 million

Age : zero
= 1 million

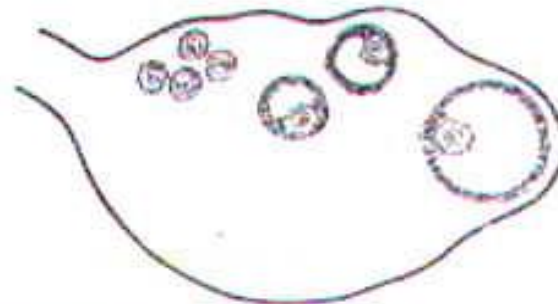


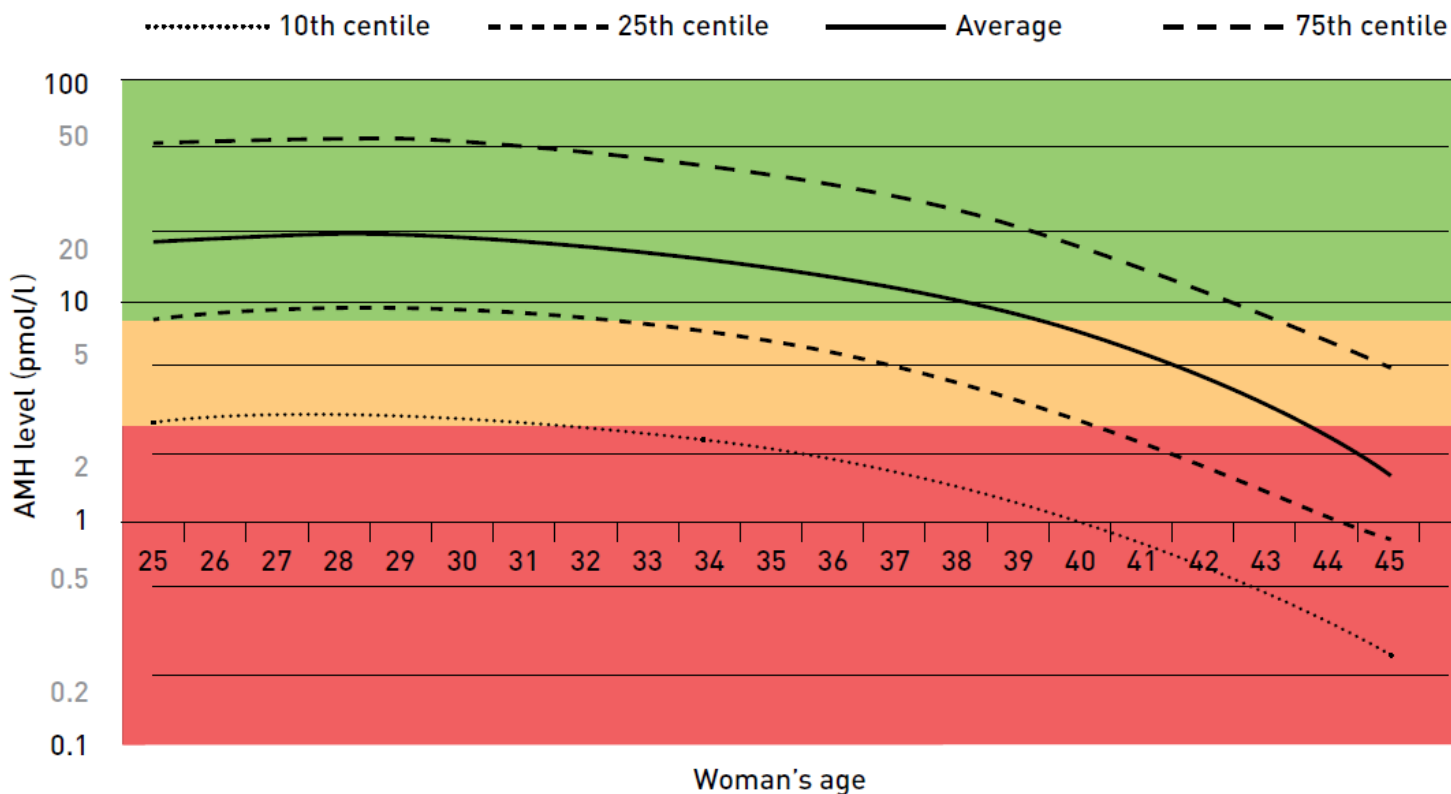
Age : 25
= 100,000

Age : 35
= 25,000

Age : 40
= 20,000

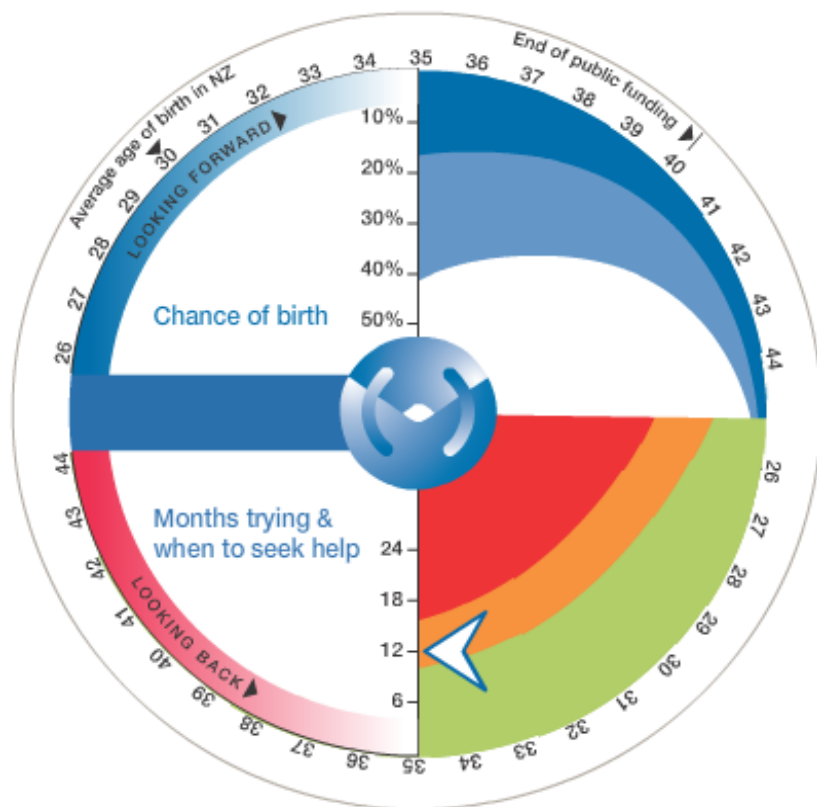
Age : 45
= 2,000





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](#)

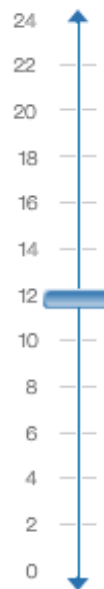
Woman's Age

35



Months Trying

12

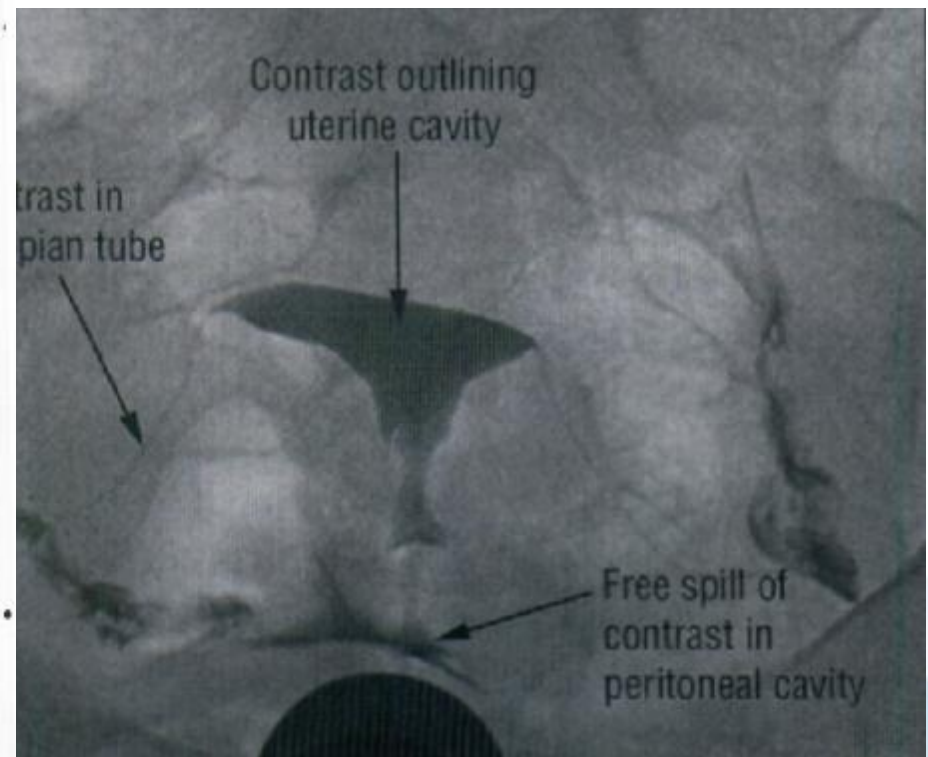
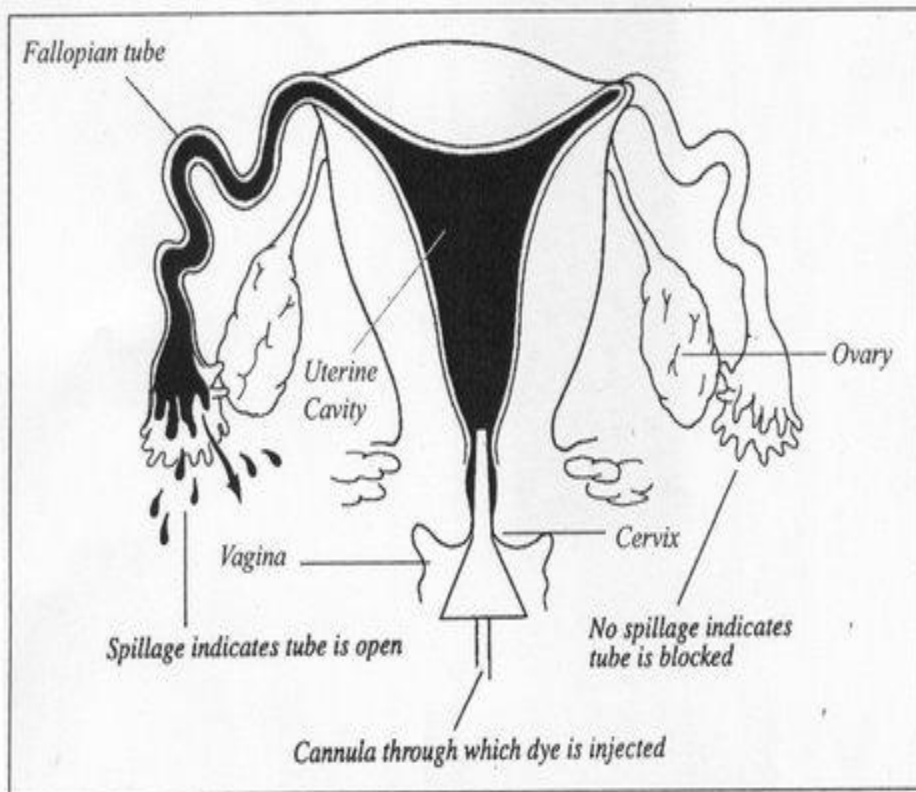




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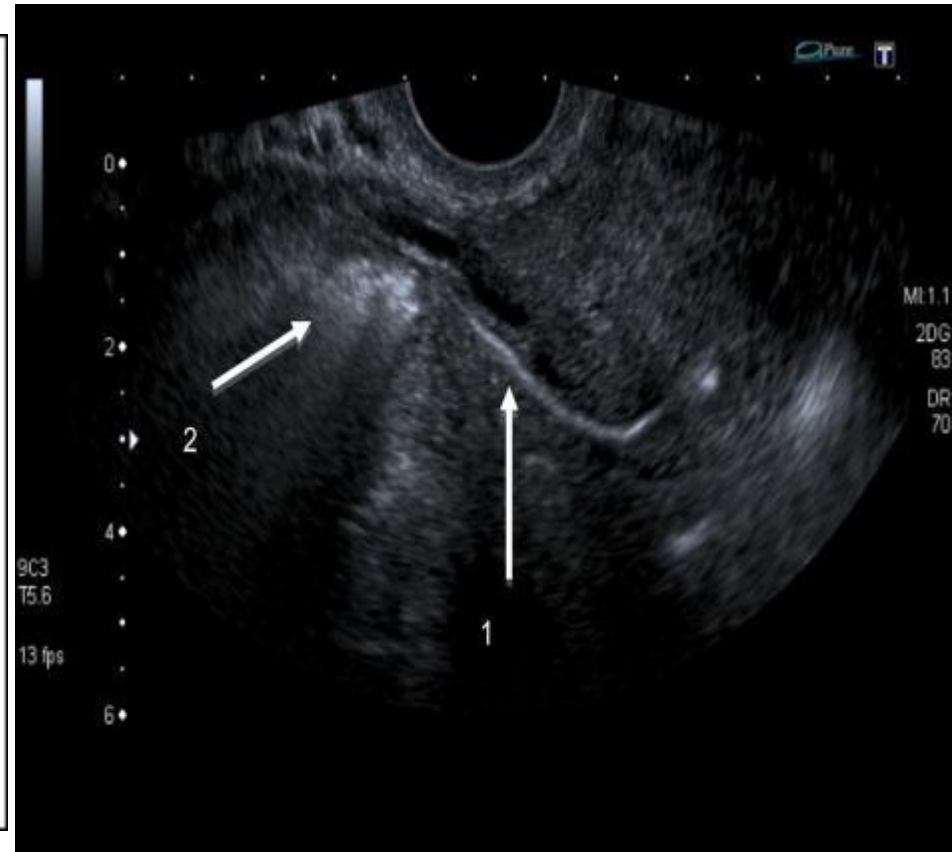
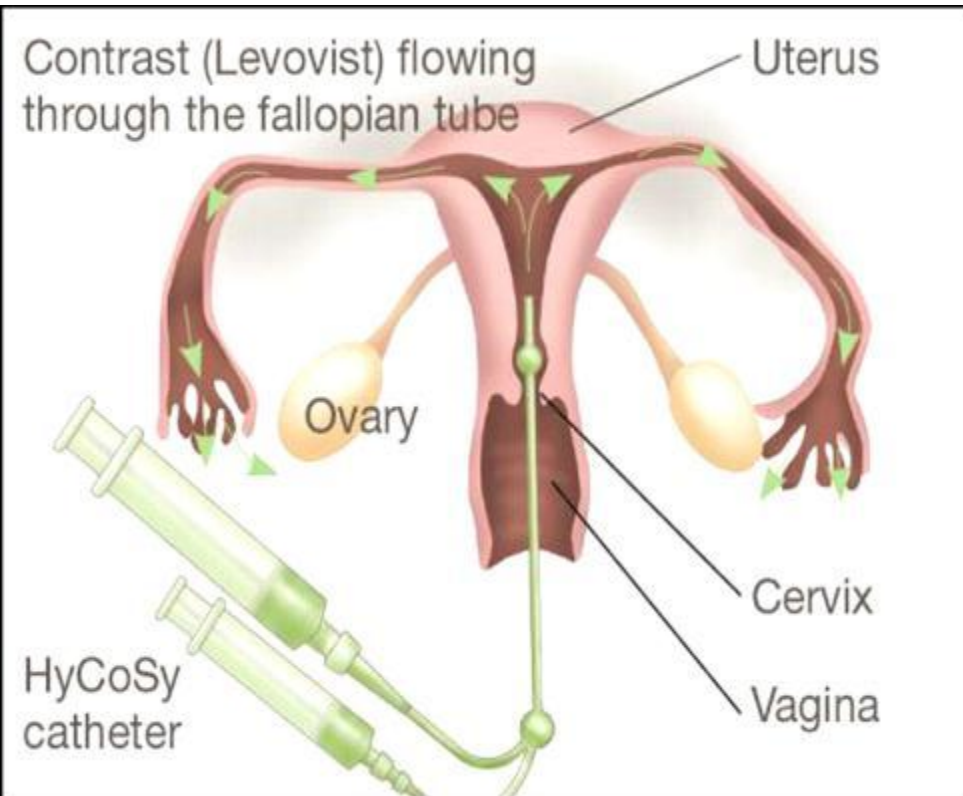
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Hysterosalpingogram HSG



Leaders in Fertility

Saline Infusion Scan

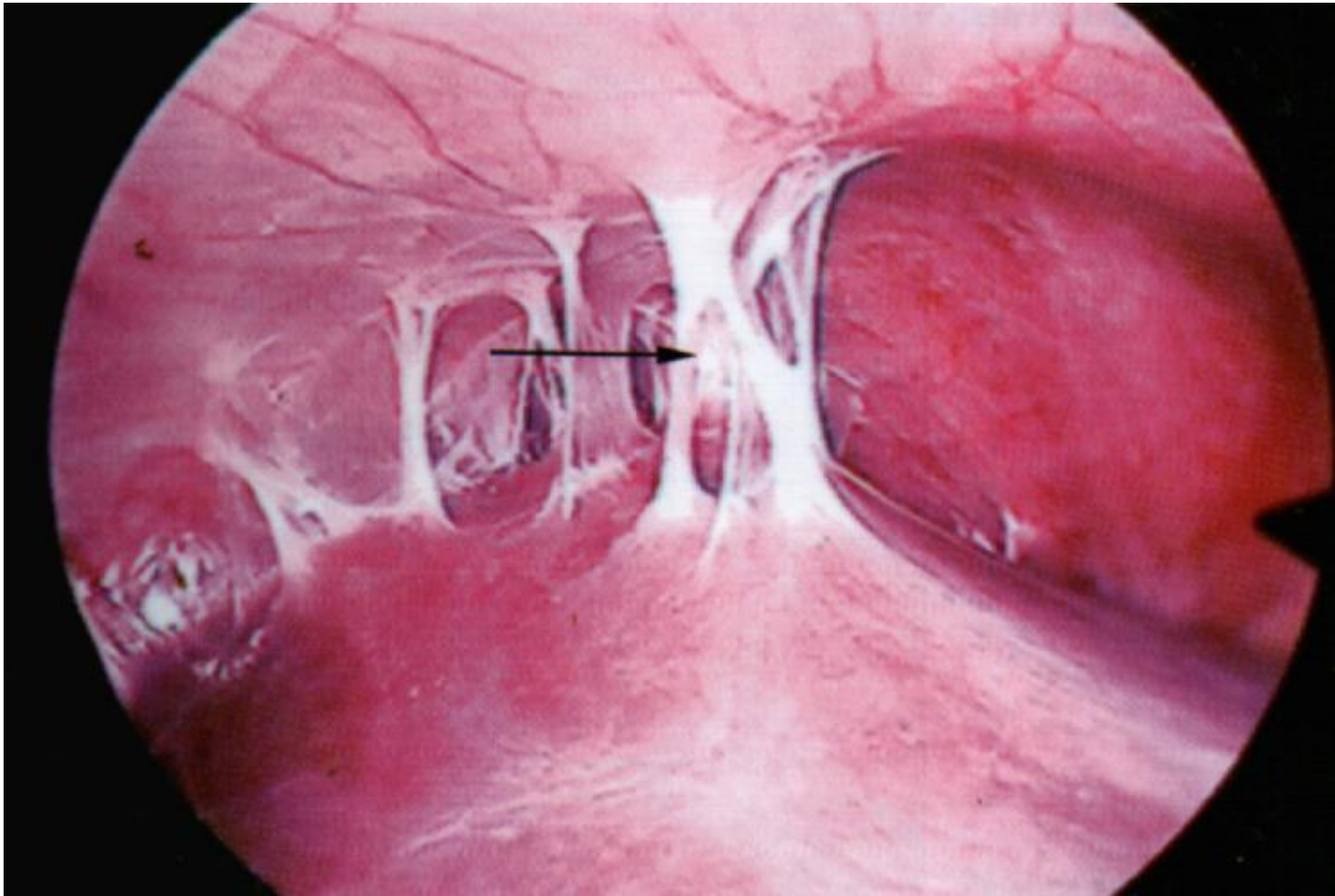


Laparoscopy Dye test

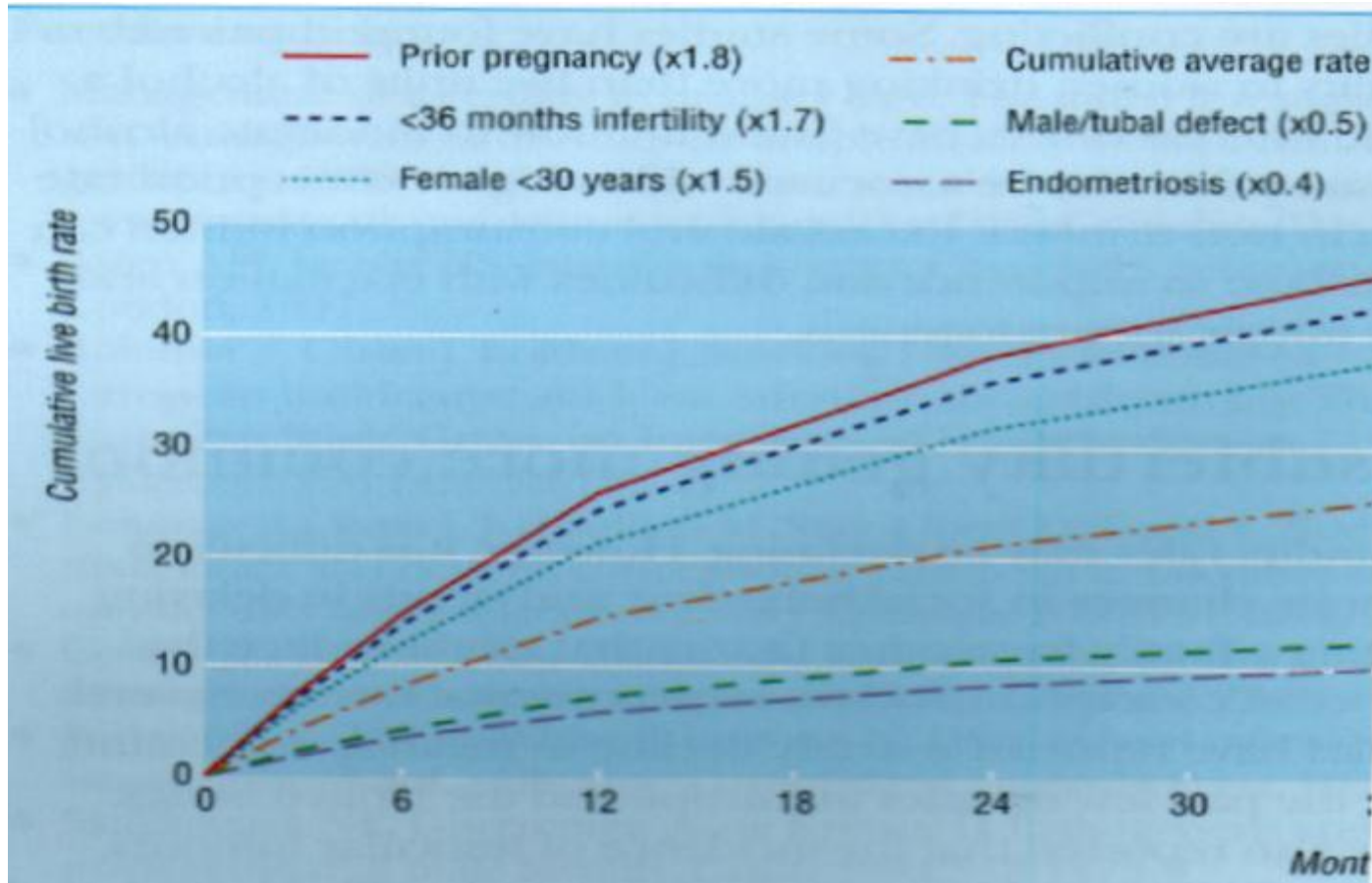


Laparoscopy

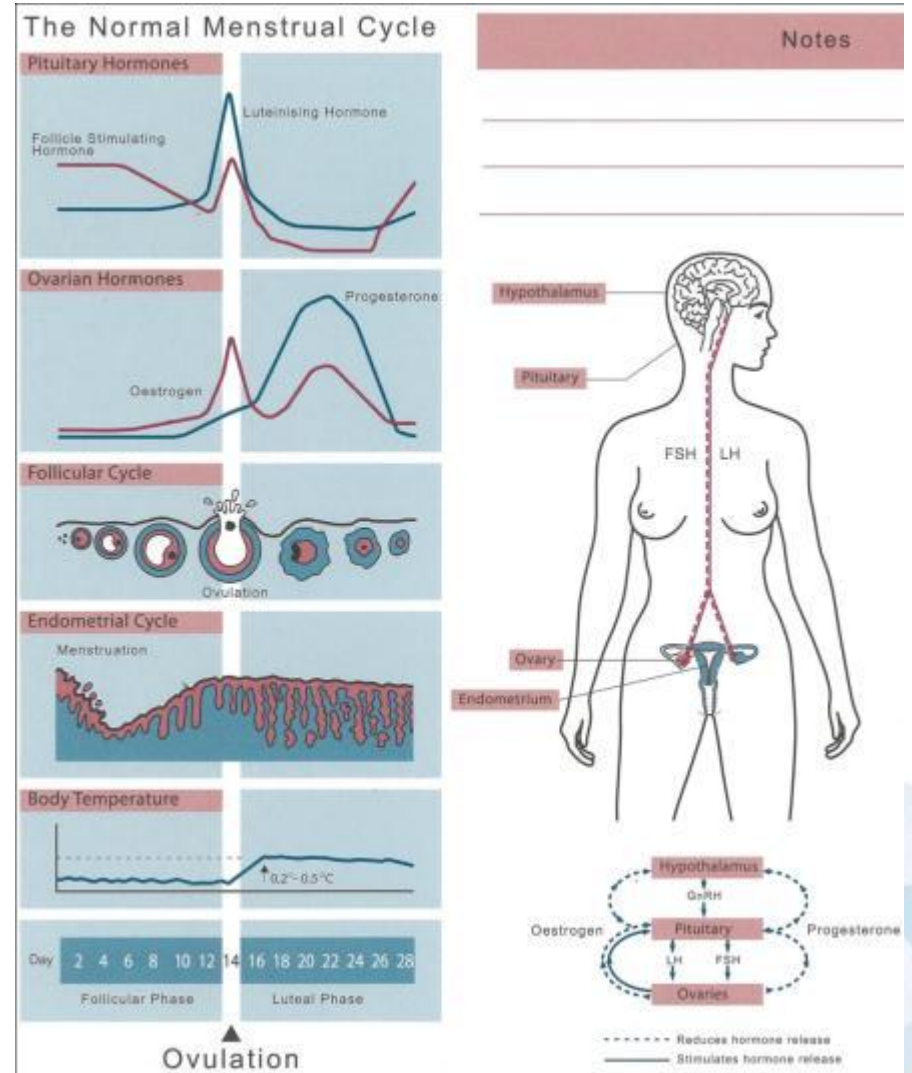
“Fitz hugh curtis” chlamydia



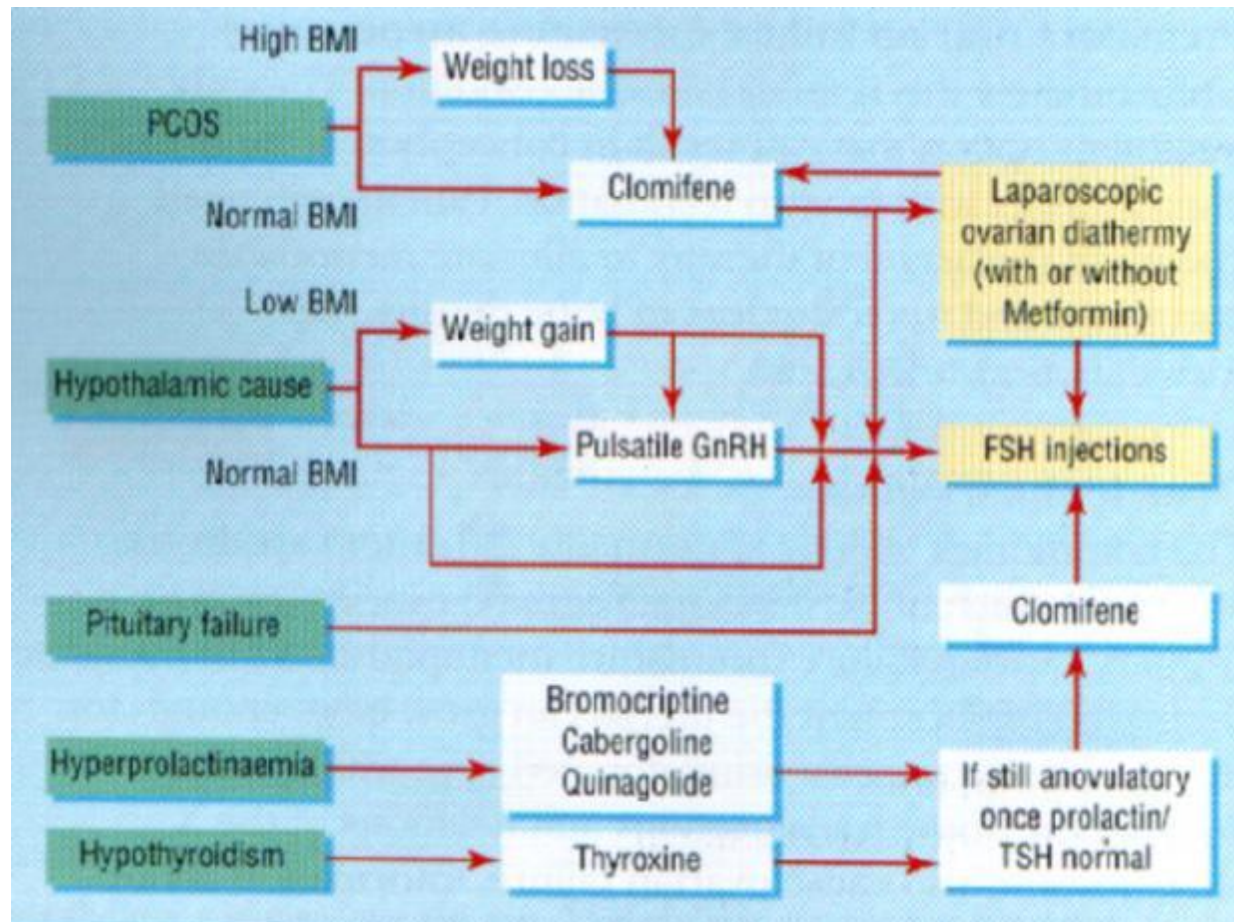
Pregnancy rates: other factors



Ovulation disorders

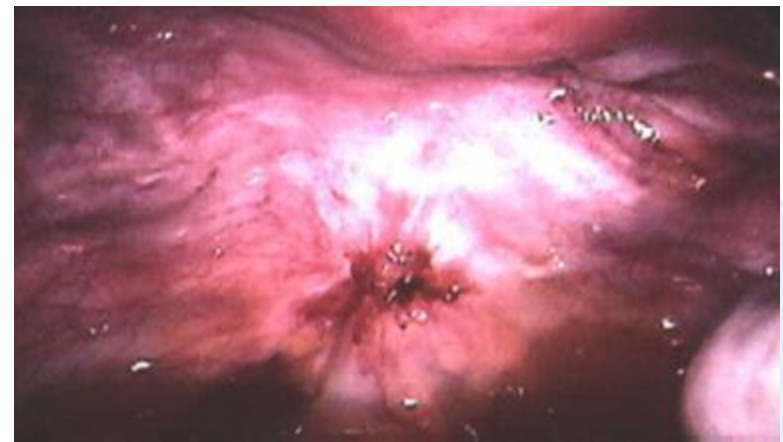
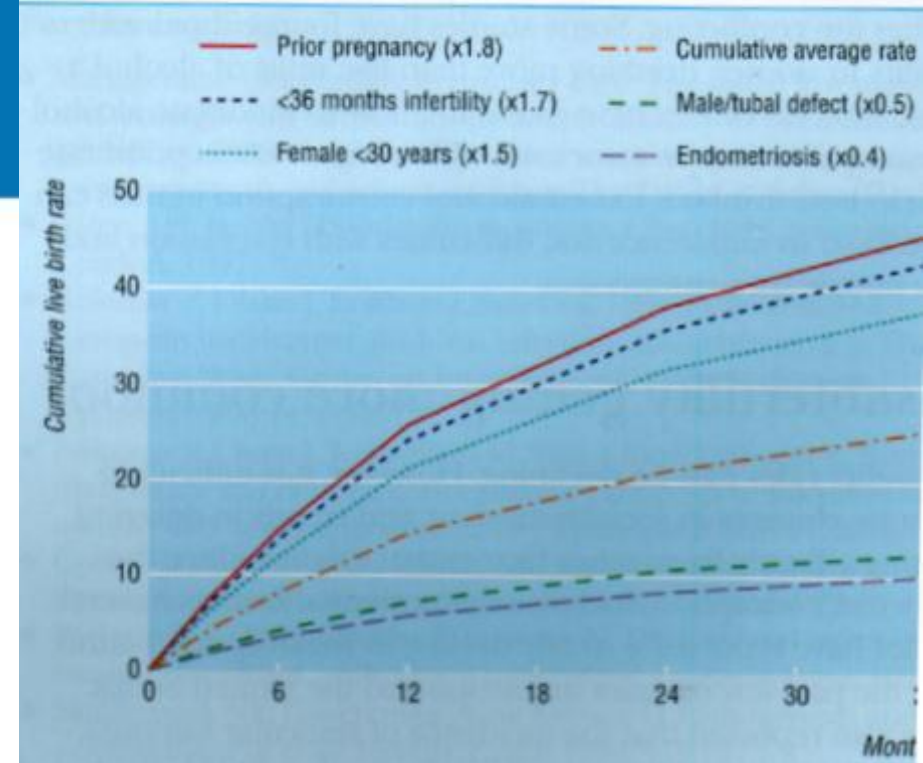


Ovulation Induction

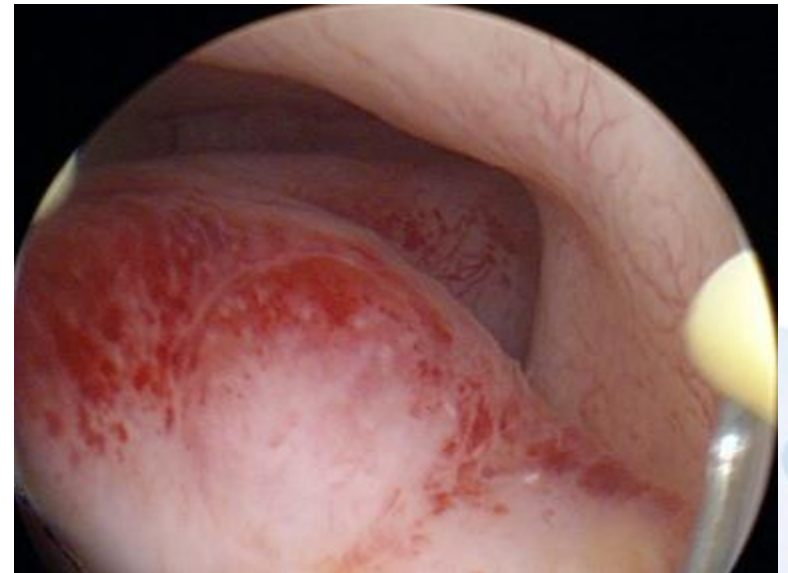
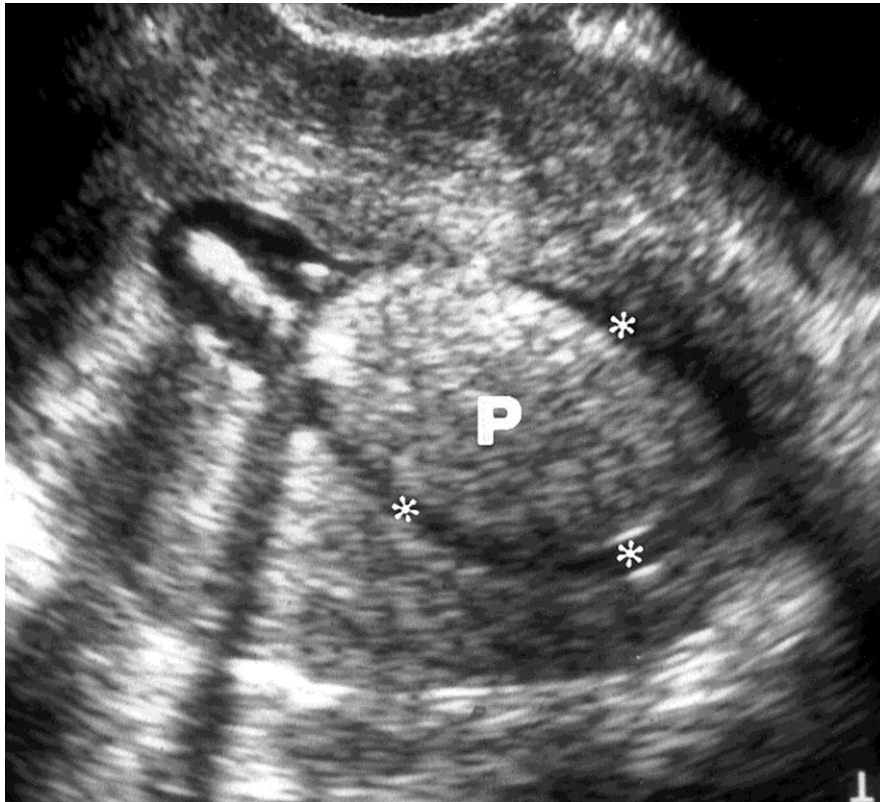
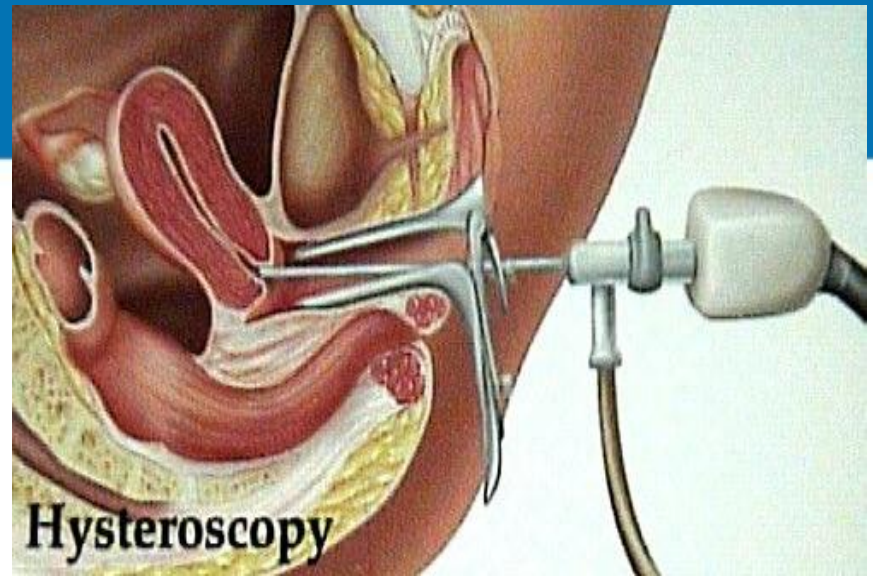




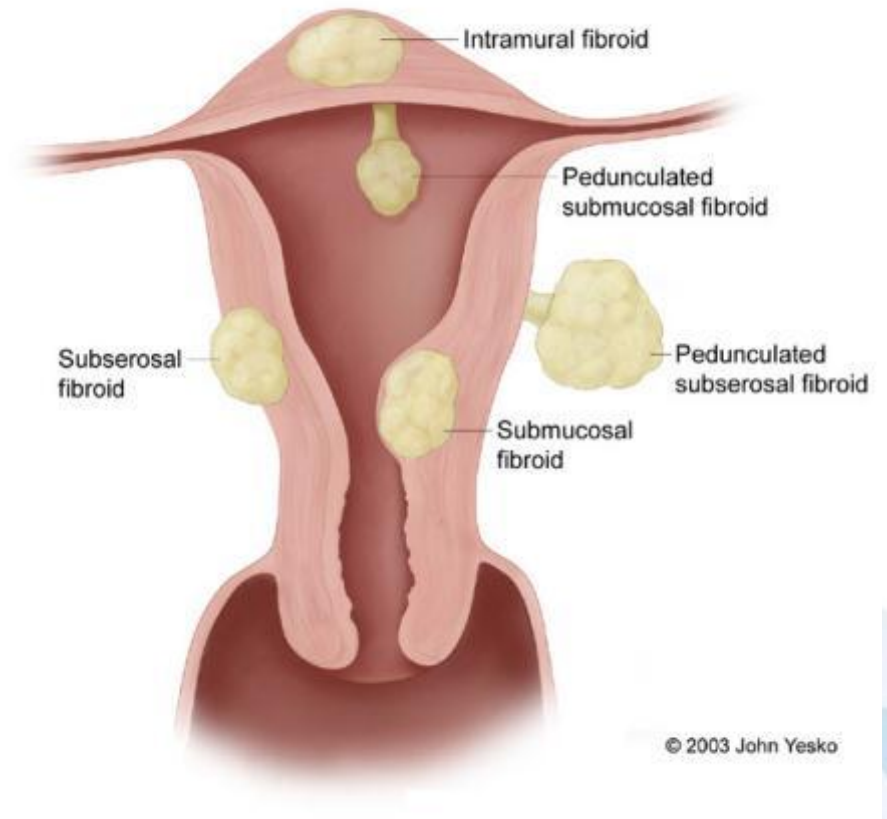
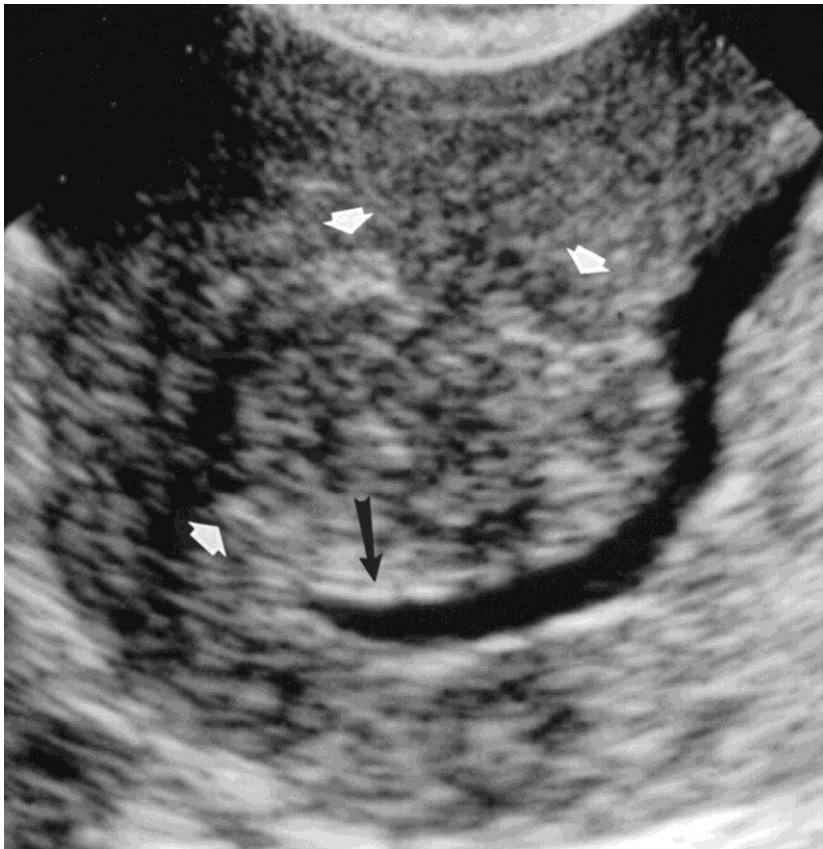
Endometriosis



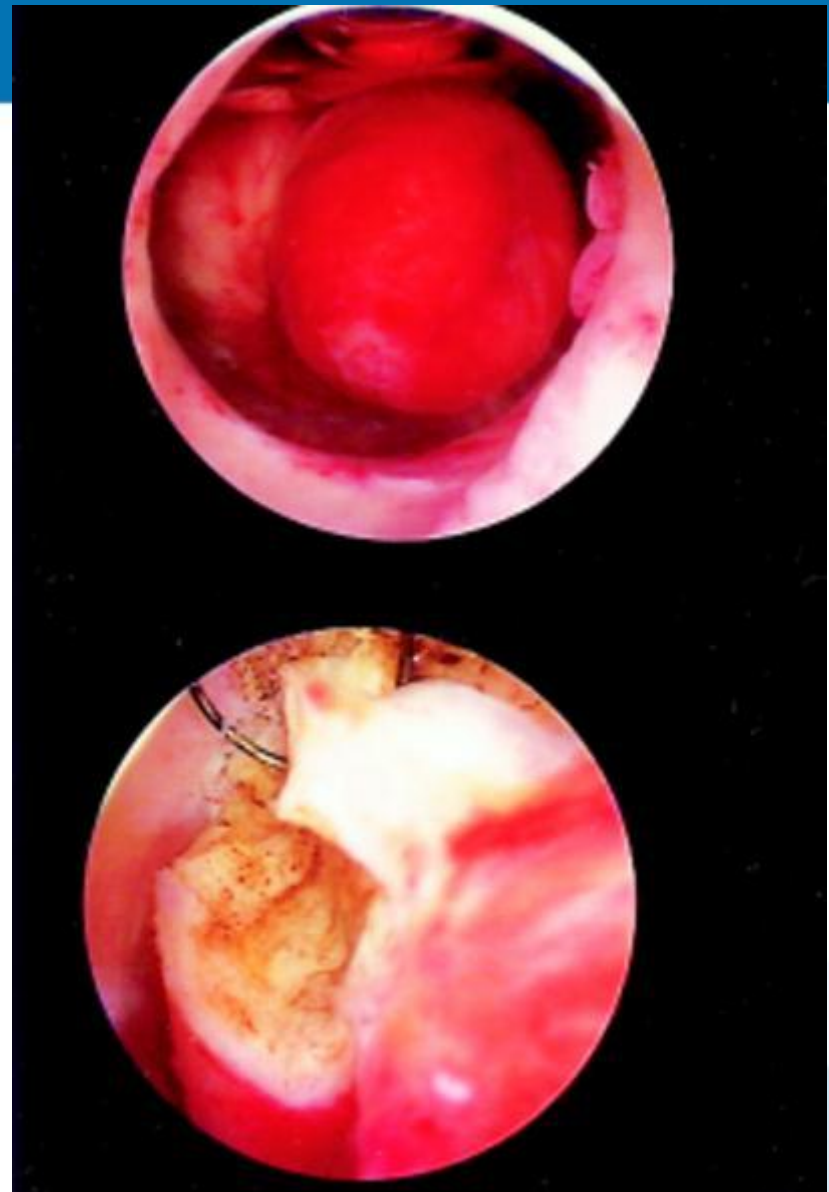
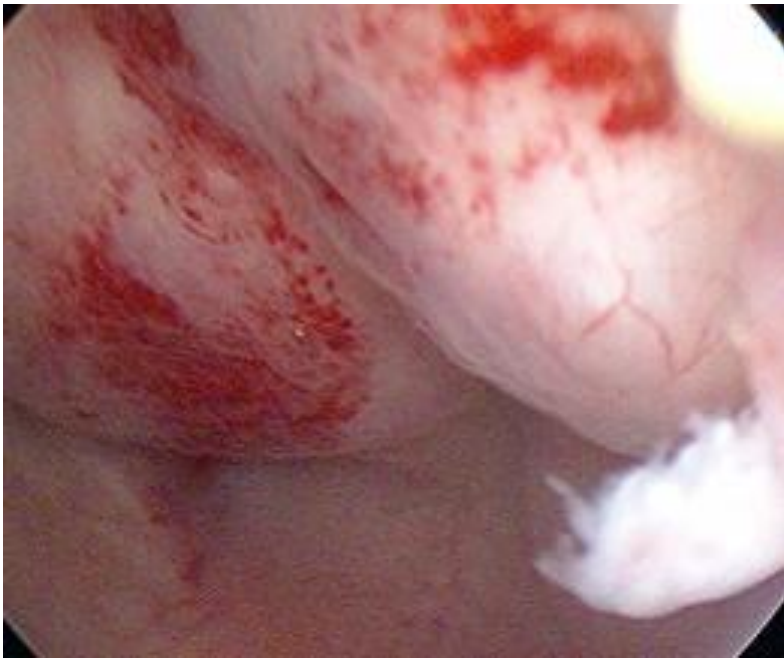
Polyps



Fibroids

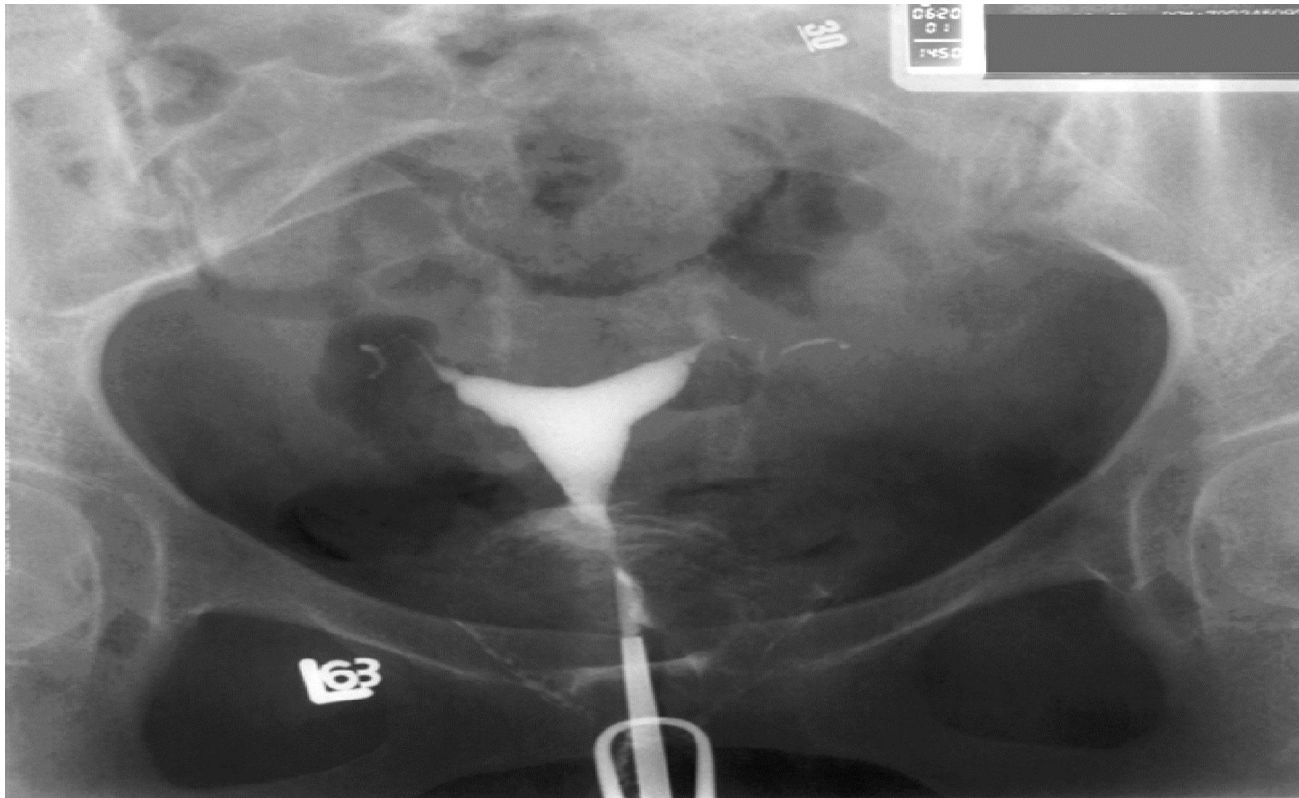


Fibroids



Leaders in Fertility

Tubal ligation reversal



Tubal Obstruction Post Bilateral Tubal Ligation

Male Fertility History

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

Male Examination



Male Examination





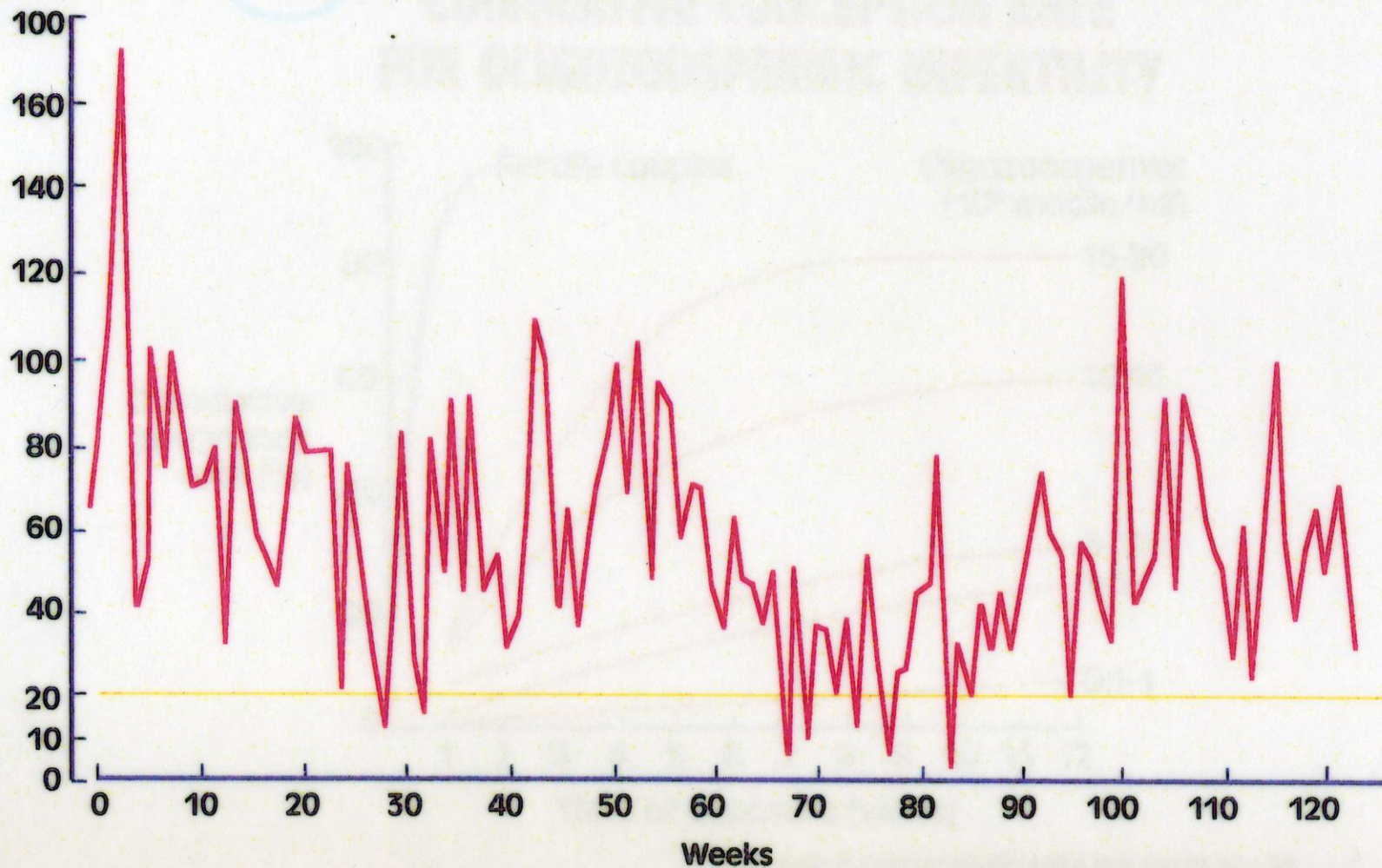
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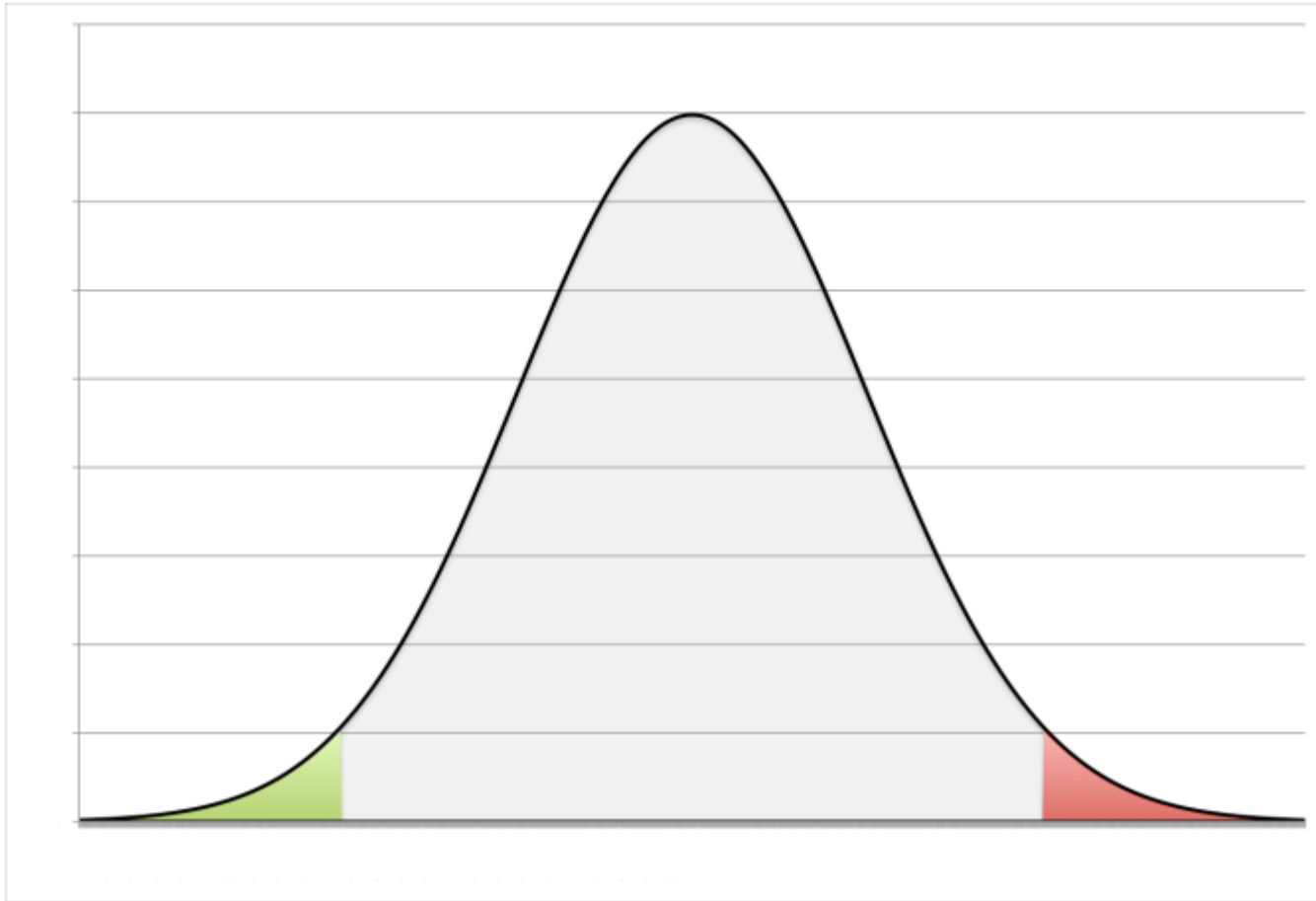
A FERTILE MAN'S SPERM COUNT OVER 2 YEARS

Sperm count
(million/ml)



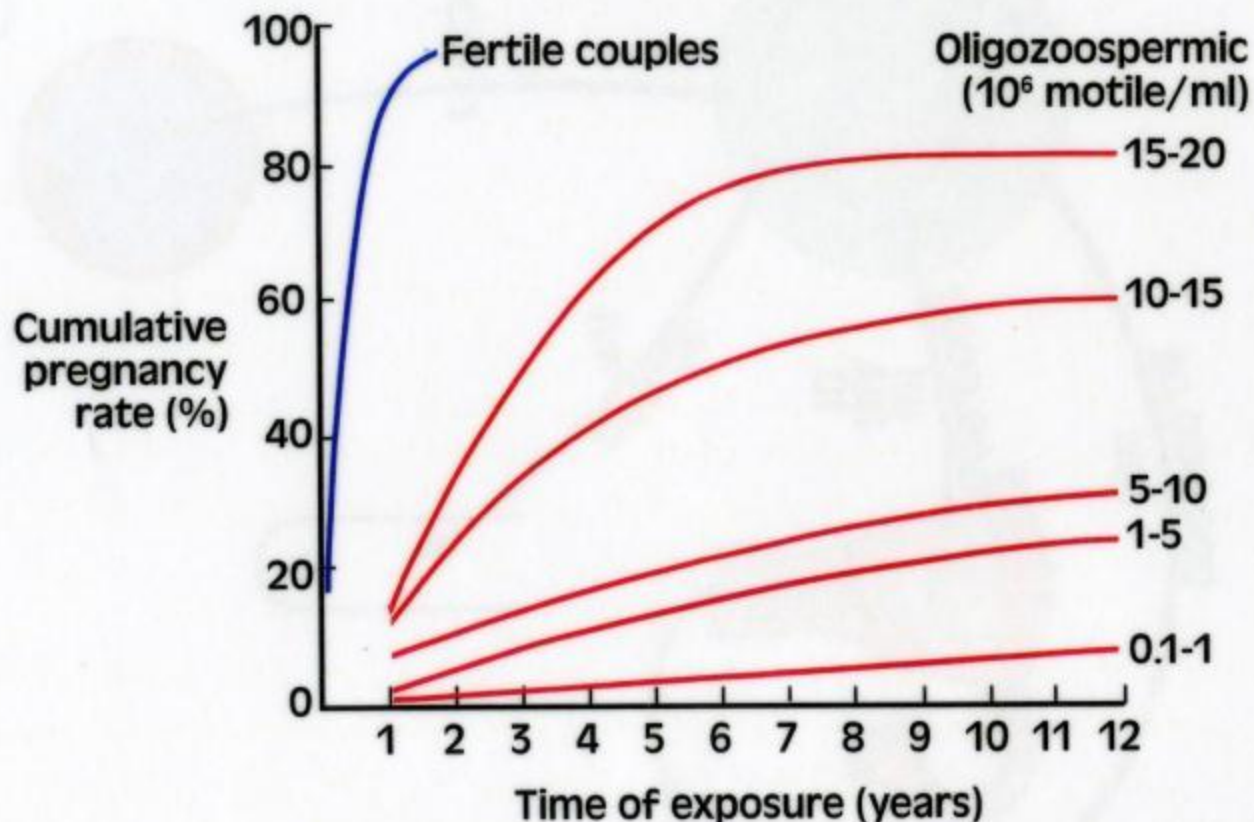
FERTILITY ASSOCIATES

Bell curve, the normal distribution





CUMULATIVE CONCEPTION RATE FOR OLIGOZOOSPERMIC INFERTILITY



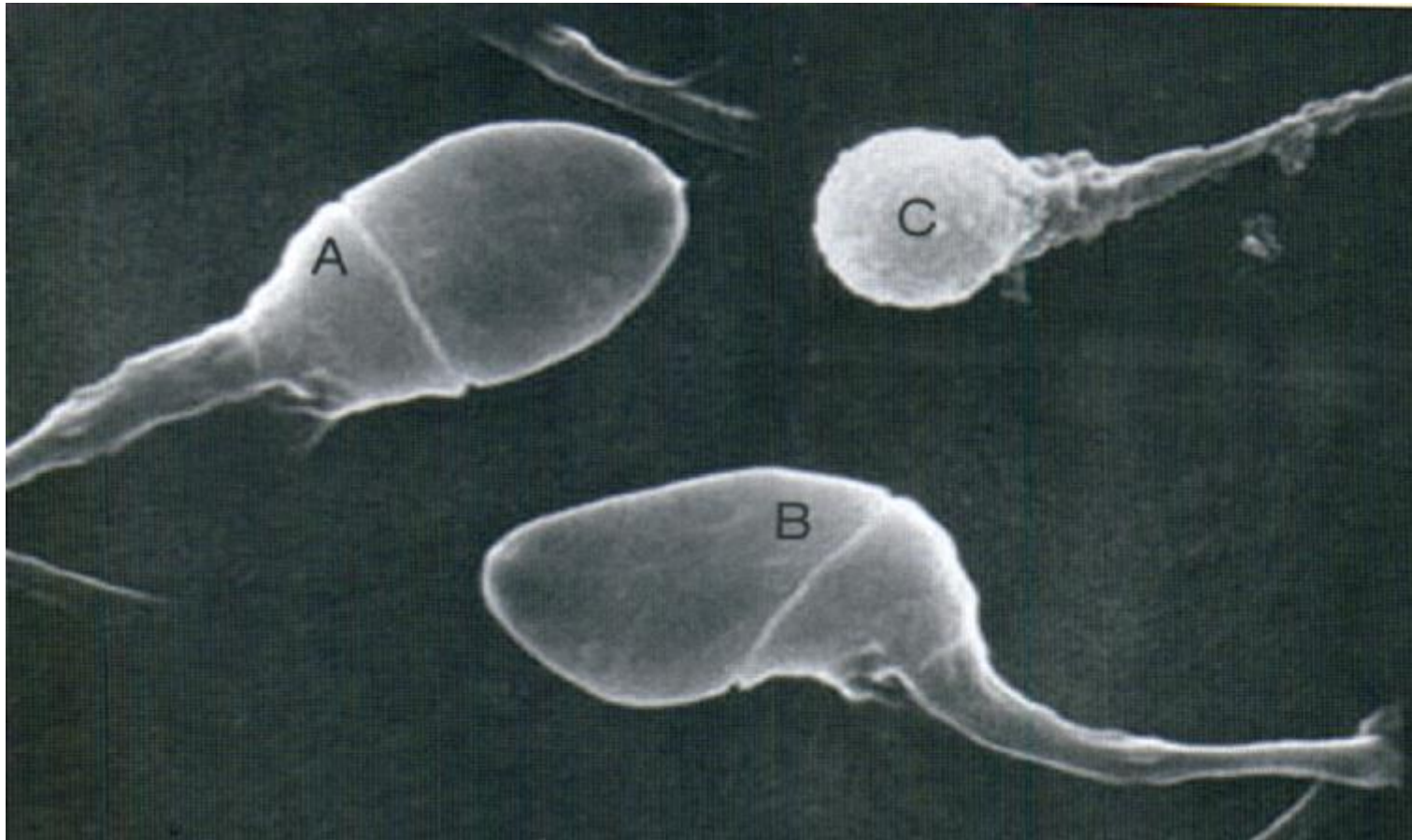
Schoysman & Gerris (1983) Aeta Eur Fertil 14 : 51

WHO revised semenanalysis 2009

Table A1.2 Distribution of values for semen parameters from men whose partners became pregnant within 12 months of discontinuing contraceptive use

Parameter (units)	N	Centile								
		2.5	5	10	25	50	75	90	95	97.5
Semen volume (ml)	1941	1.2	1.5	2.0	2.7	3.7	4.8	6.0	6.8	7.6
Total sperm number (10 ⁶ per ejaculate)	1859	23	39	69	142	255	422	647	802	928
Sperm concentration (10 ⁶ per ml)	1859	9	15	22	41	73	116	169	213	259
Total motility (PR+NP, %)	1781	34	40	45	53	61	69	75	78	81
Progressive motility (PR, %)	1780	28	32	39	47	55	62	69	72	75
Non-progressive motility (NP, %)	1778	1	1	2	3	5	9	15	18	22
Immotile spermatozoa (IM, %)	1863	19	22	25	31	39	46	54	59	65
Vitality (%)	428	53	58	64	72	79	84	88	91	92
Normal forms (%)	1851	3	4	5.5	9	15	24.5	36	44	48

Sperm Morphology





Conservative measures for men with suboptimal semen analyses

- Stop smoking—Nicotine reduces seminal plasma antioxidants
 - Have frequent intercourse—Increases output of non-senile spermatozoa
 - Reduce alcohol intake—Alcohol can suppress spermatogenesis
 - Wear boxer shorts and avoid hot baths—Heat suppresses spermatogenesis
 - Avoid pesticides, herbicides, heat, and radiation at work—All impair spermatogenesis
-

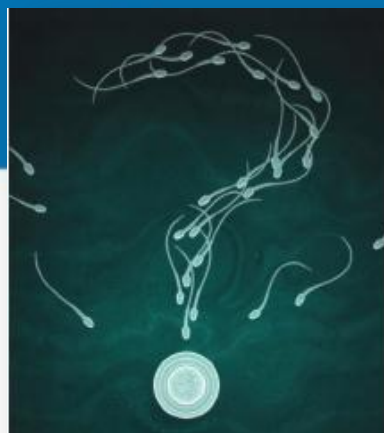
What doesn't work

- Abstaining from coitus until ovulation does not improve the semen or likelihood of conception. Increasing coital frequency (alternate days) supplies more viable spermatozoa that normally remain motile in the female tract for two to three days
- Treatment with gonadotrophin injections, androgens (mesterolone) or antioestrogens (clomifene or tamoxifen) is not indicated because although they may improve the sperm count, fertility rates are not improved as the spermatozoa remain dysfunctional

Menevit ?

- Sperm DNA fragmentation
- TUNEL SCSA
 - Abnm > 15%
- Zn Se Antioxidants
- Farming evidence
- Dietary insufficiency
- No improvement in Semen
- Improved IVF / Miscarriage





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.

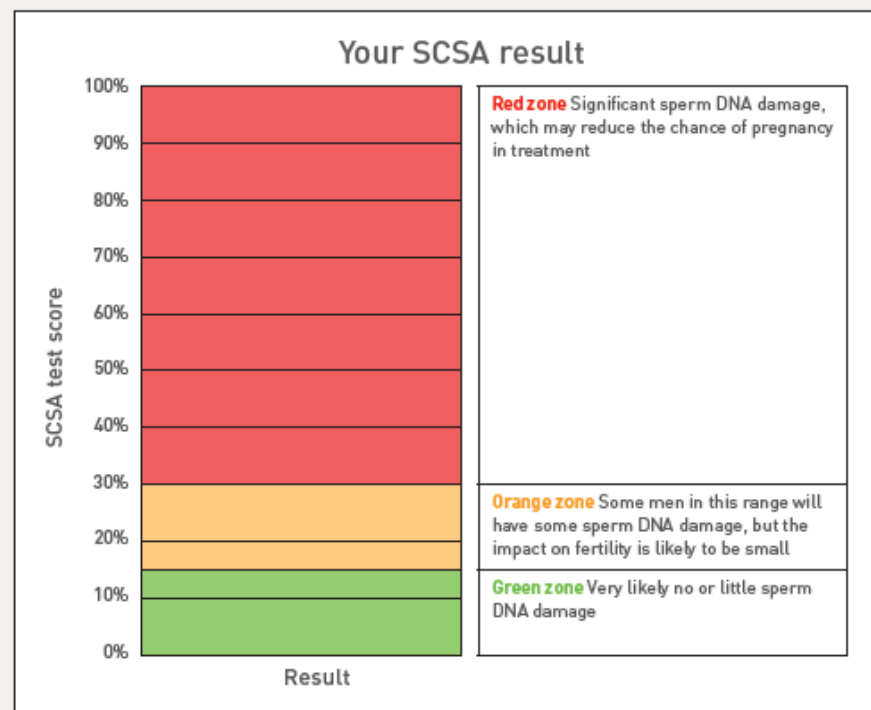
The body's main defence against ROS damage is to maintain an optimal antioxidant environment for sperm maturation and storage before ejaculation. This is one of the reasons why Fertility Associates promotes a healthy lifestyle, healthy eating and considering the use of antioxidant supplements.

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, Ramuera	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.



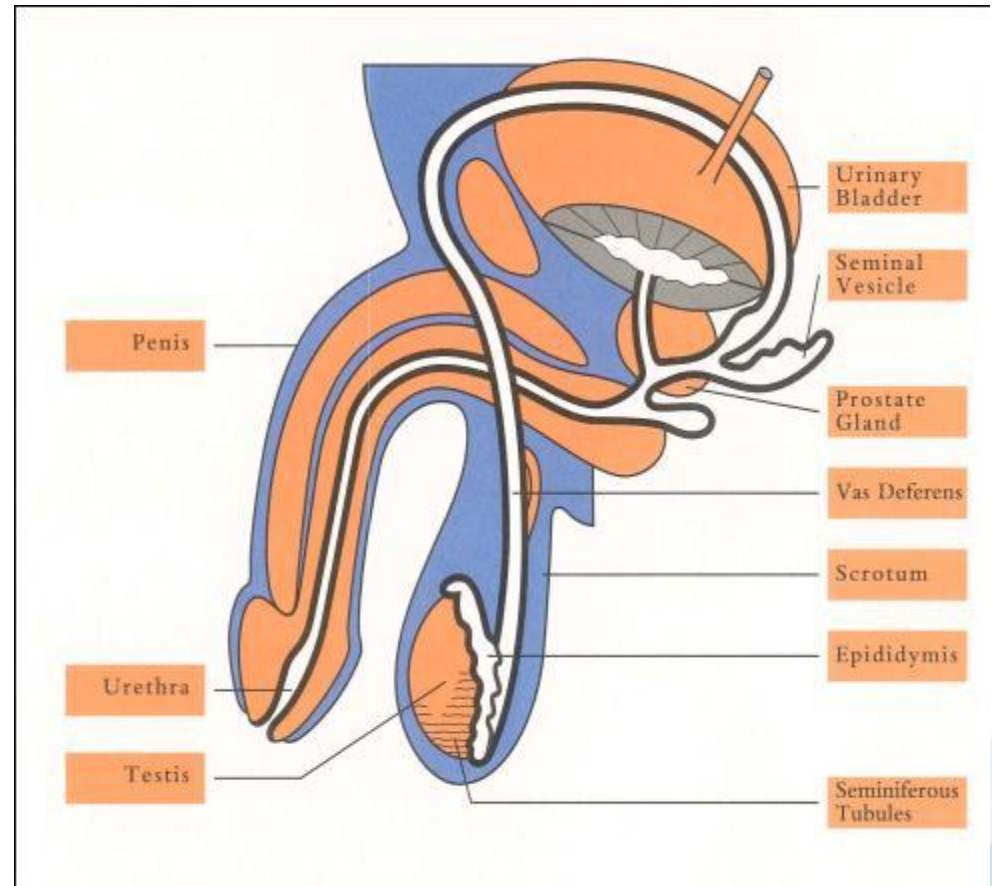
Azoospermia

Investigating azoospermia, by site of abnormality

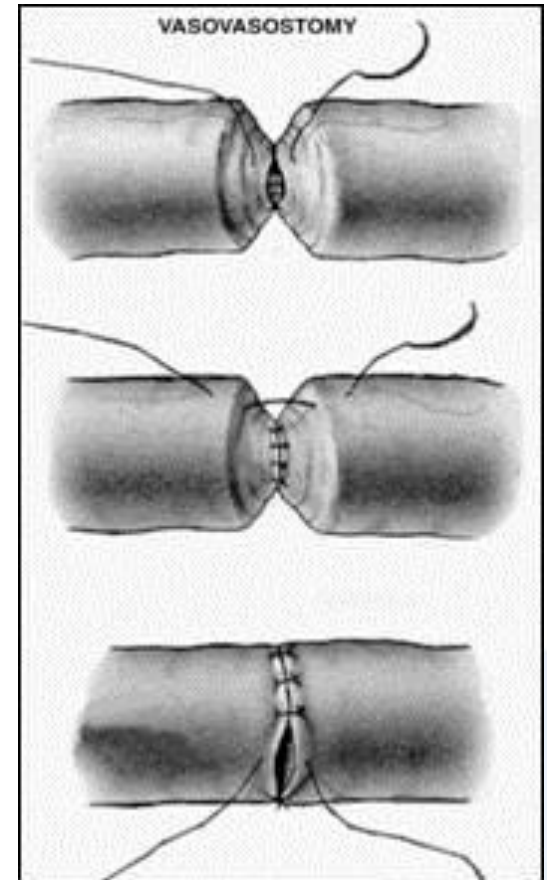
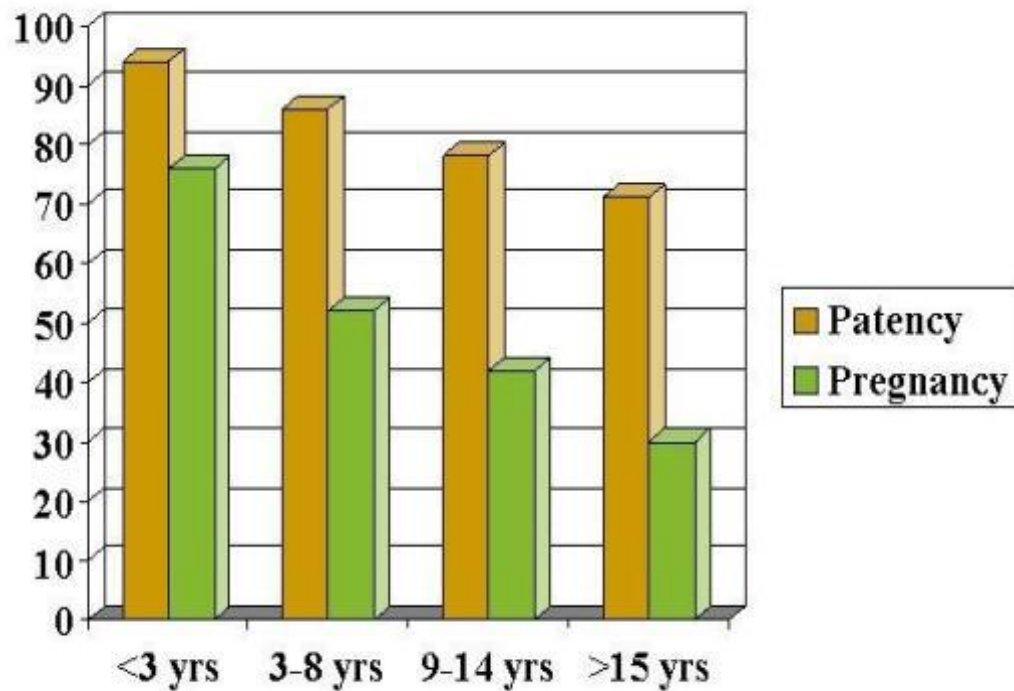
	Obstructive	Non-obstructive	
	<i>Post-testicular</i>	<i>Testicular</i>	<i>Hypothalamic-pituitary</i>
Congenital causes	Vasal aplasia, cystic fibrosis, mullerian cysts	Genetic causes, cryptorchidism, anorchia	Kallman's syndrome, isolated FSH deficiency
Acquired causes	Gonorrhoea, chlamydia, tuberculosis, prostatitis, vasectomy	Radiotherapy, chemotherapy, orchitis, trauma, torsion	Craniopharyngioma, pituitary tumour, pituitary ablation, anabolic steroids
Testicular size	Normal	Small, atrophic	Small, prepubertal
FSH	Normal	Raised	Low
Testosterone	Normal	Low	Low

Azoospermia

- Prevalence 1%
- CBAVD
- Genetic
- Vasectomy
- Donor sperm
- Donor embryo



Vasectomy Reversal



Management Unexplained delay

- Wait
- Clomiphene 50mg for 5 days
 - Empiric
 - 3-6 months only
 - Multiple pregnancy risk
- IUI
 - Empiric
 - 3-6 months only
 - Multiple pregnancy risk
- IVF

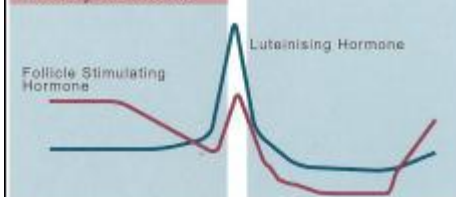
Unexplained Infertility

- One third of couples have no obvious diagnosis
- If young
 - ? Wait
 - ? Clomiphene
 - ? IUI
 - IVF
- If older female partner
 - ? Clomiphene while waiting
 - ? IVF

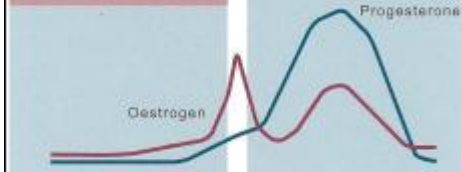


The Normal Menstrual Cycle

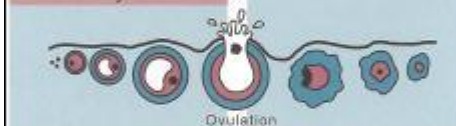
Pituitary Hormones



Ovarian Hormones



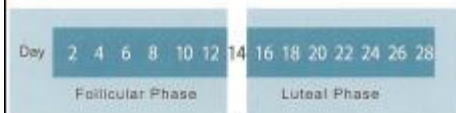
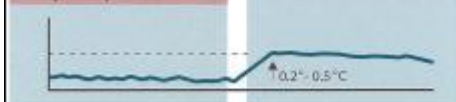
Follicular Cycle



Endometrial Cycle

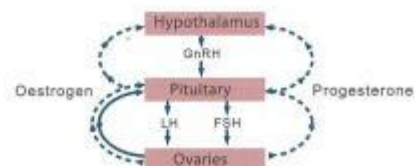
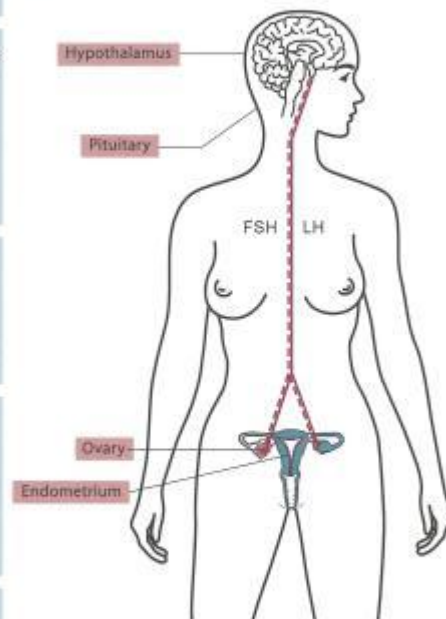


Body Temperature



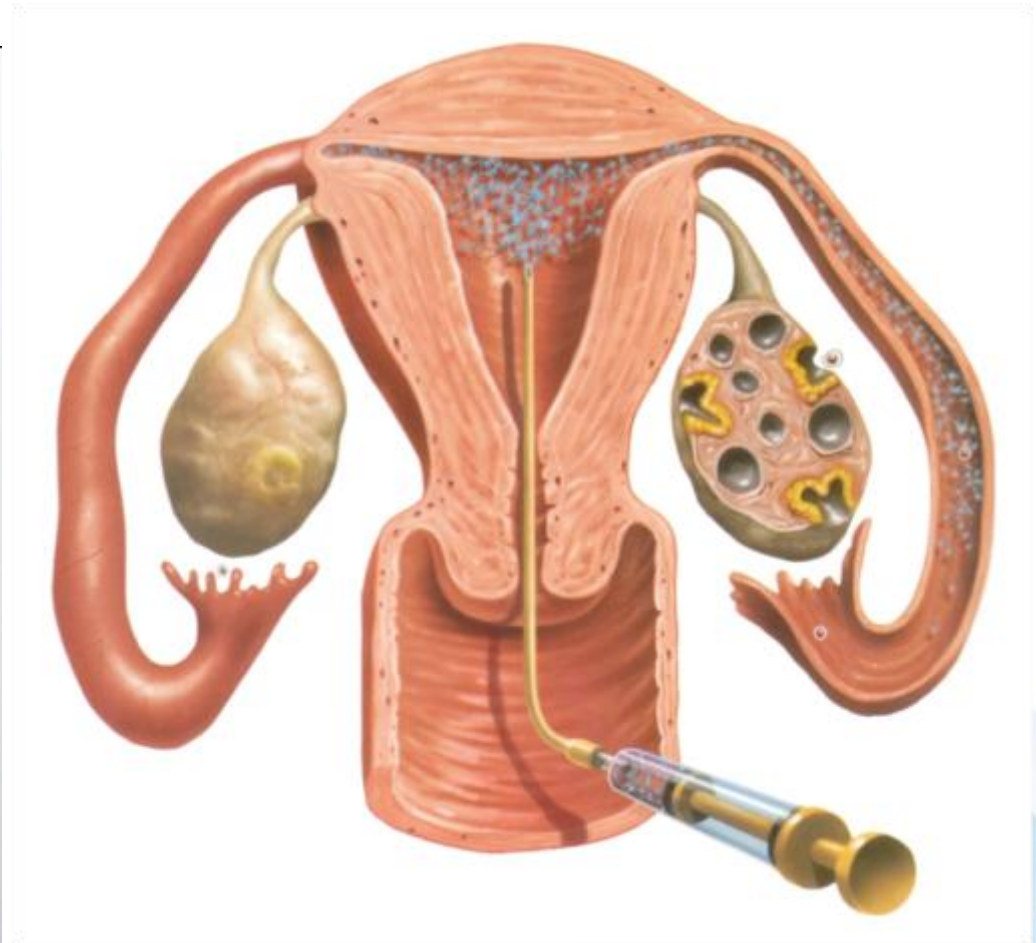
Ovulation

Notes



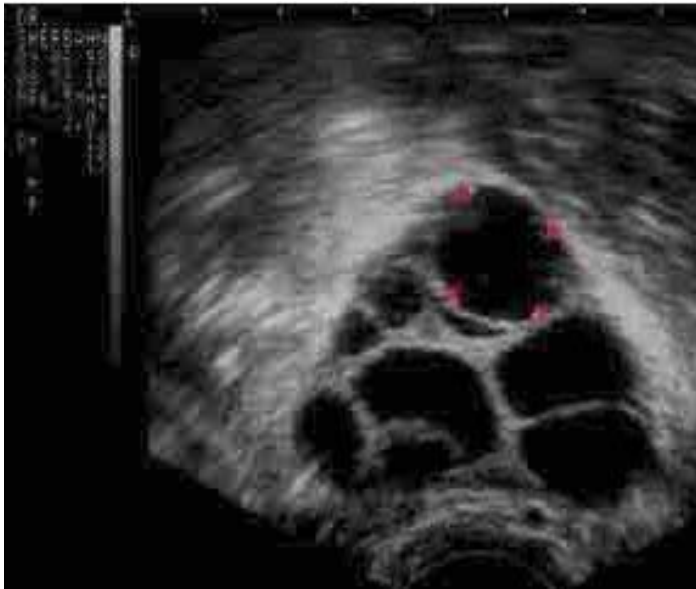
----- Reduces hormone release
———— Stimulates hormone release

IUI

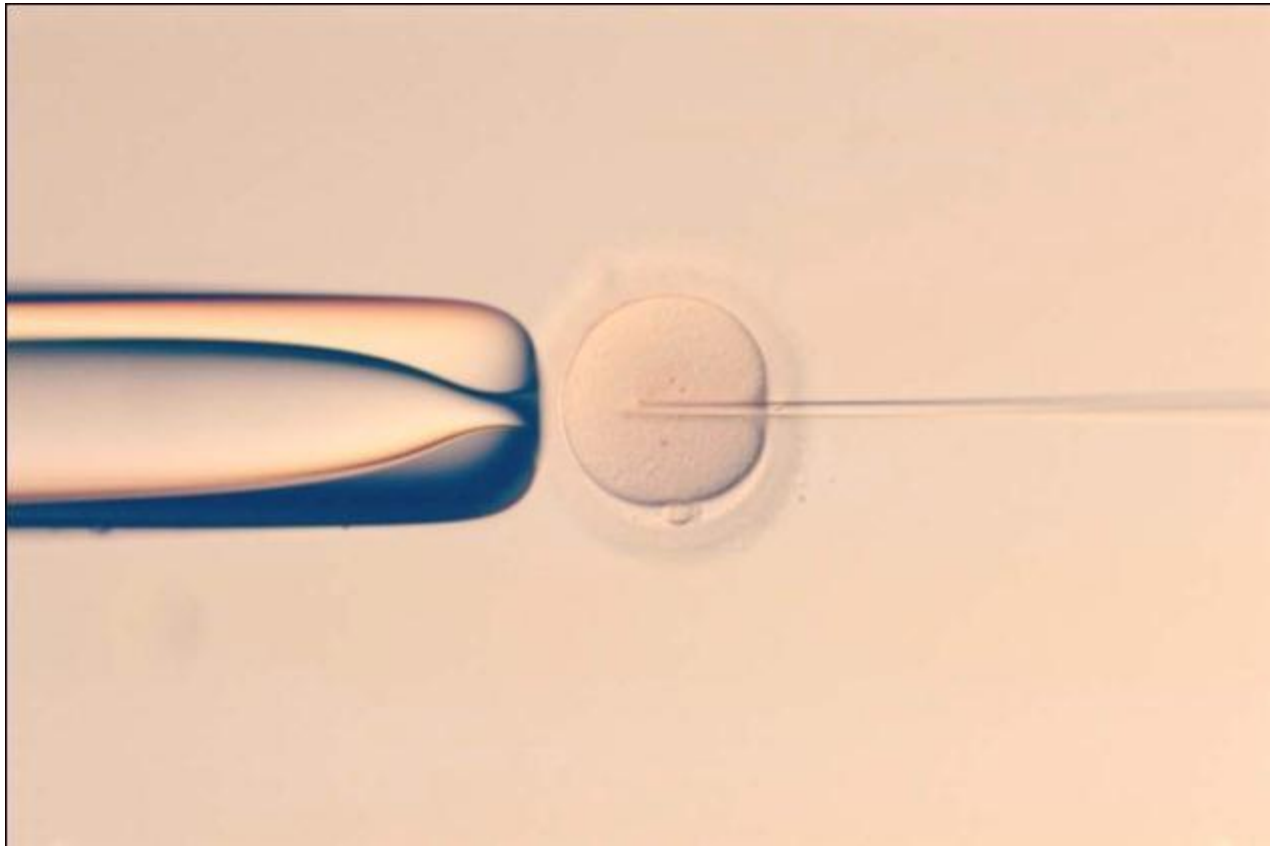


Leaders in Fertility

IVF



IVF ICSI

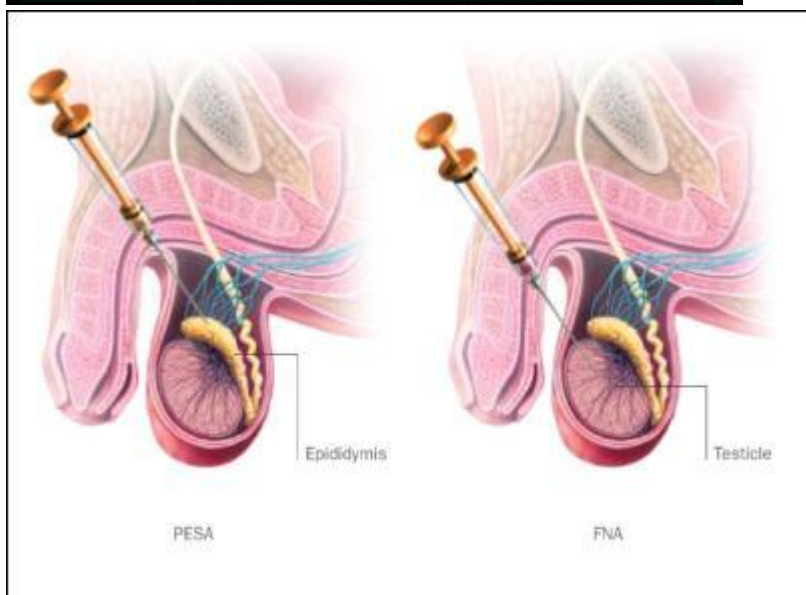
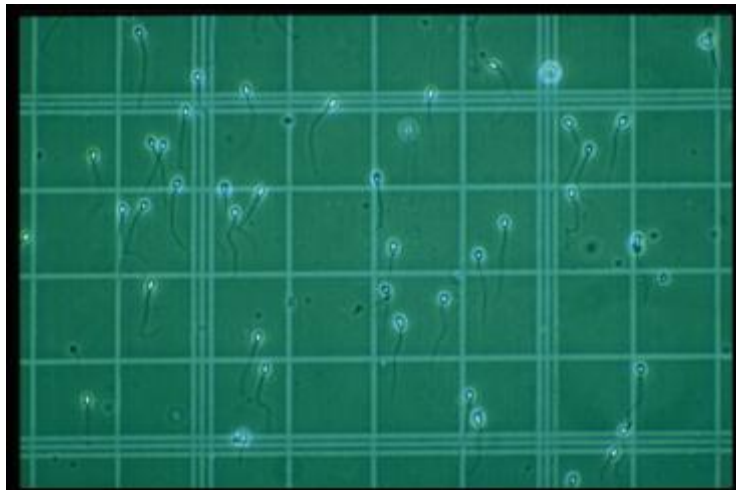




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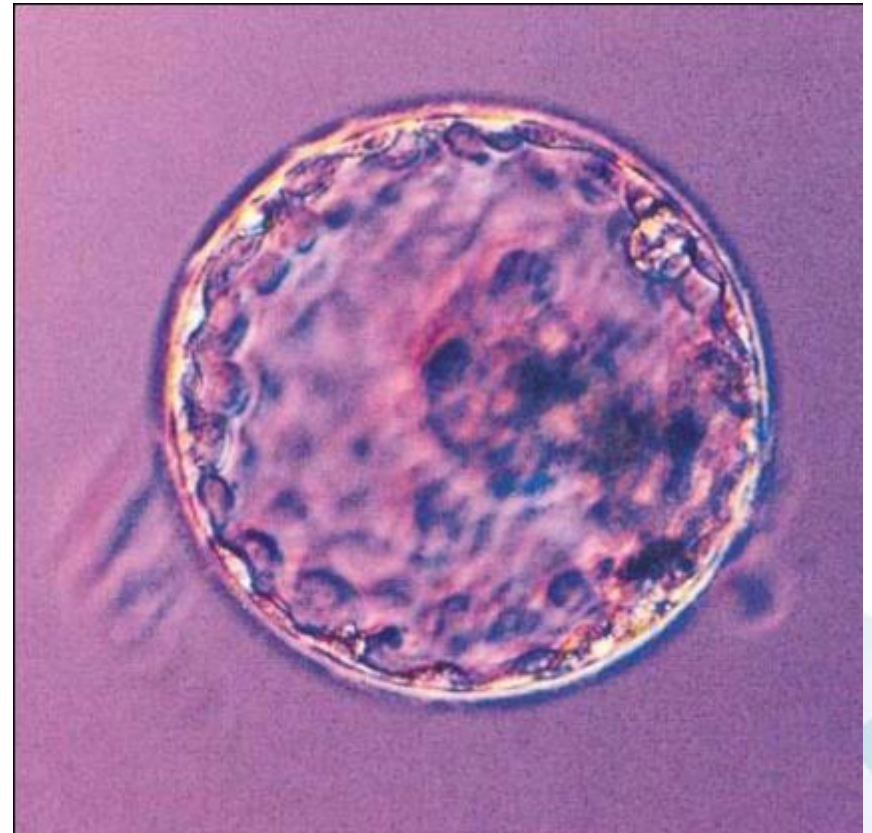
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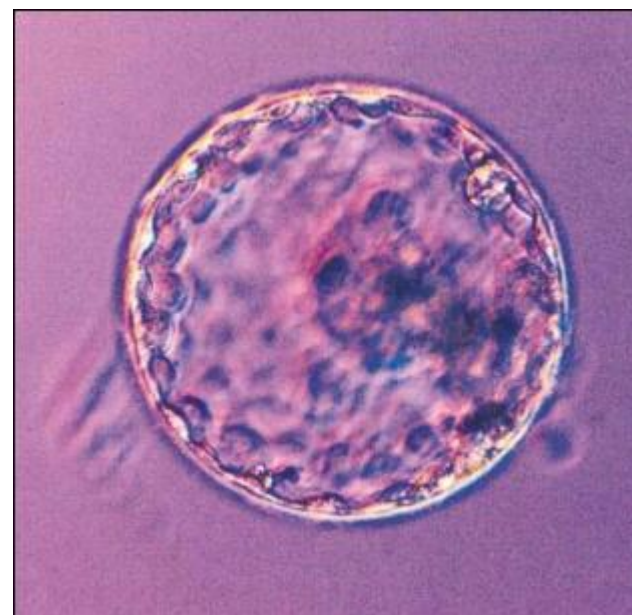
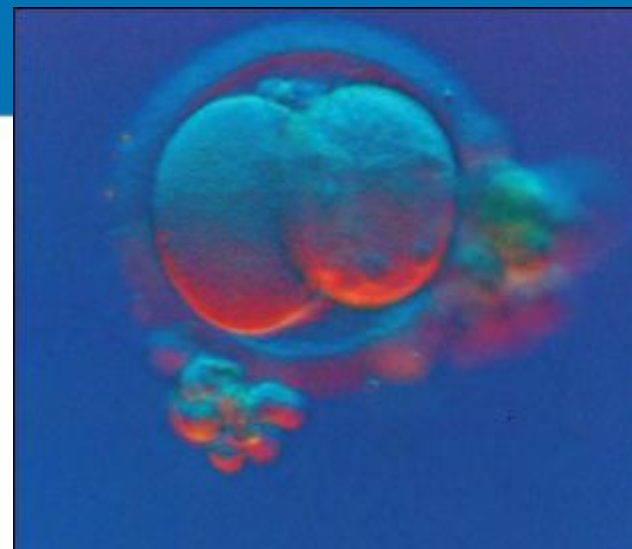
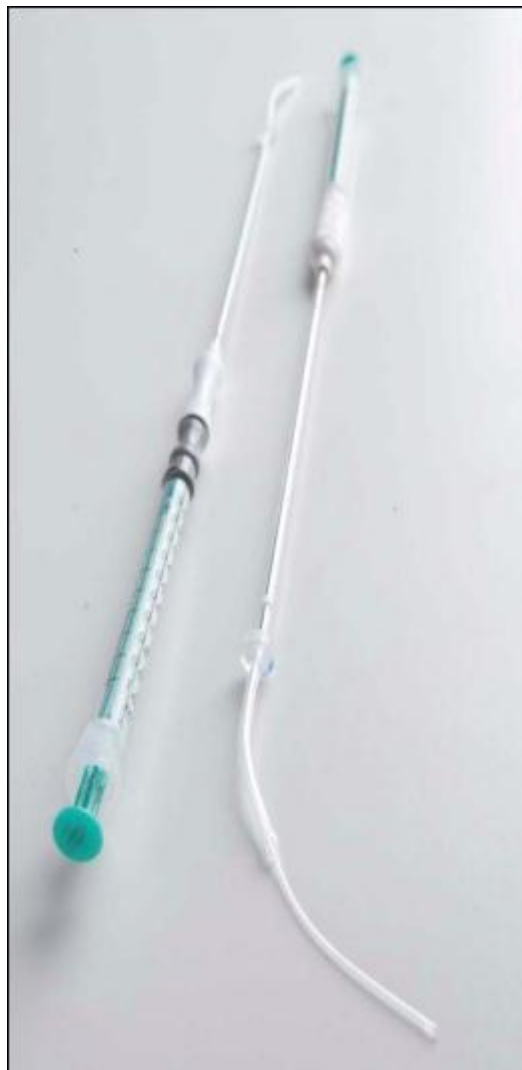
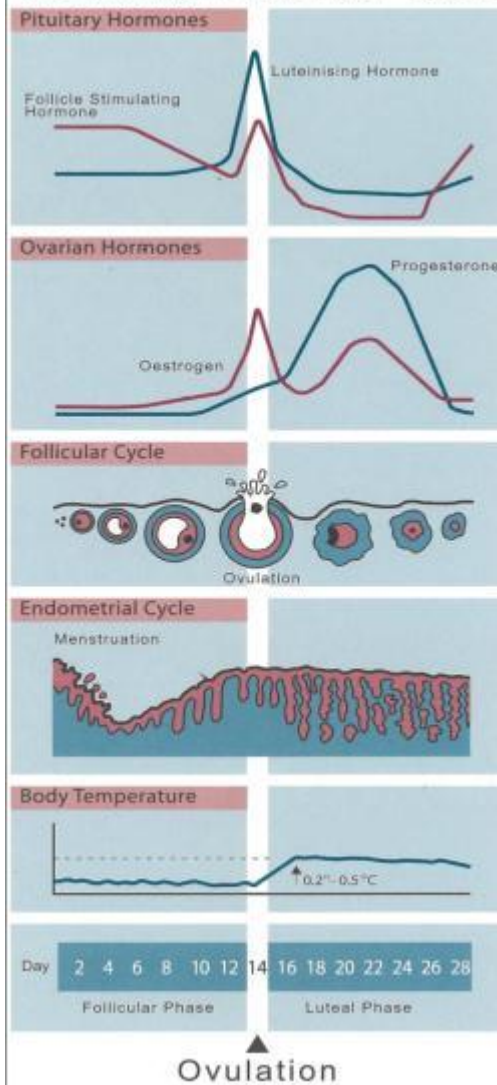


Leaders in Fertility

Embryo Transfer



The Normal Menstrual Cycle

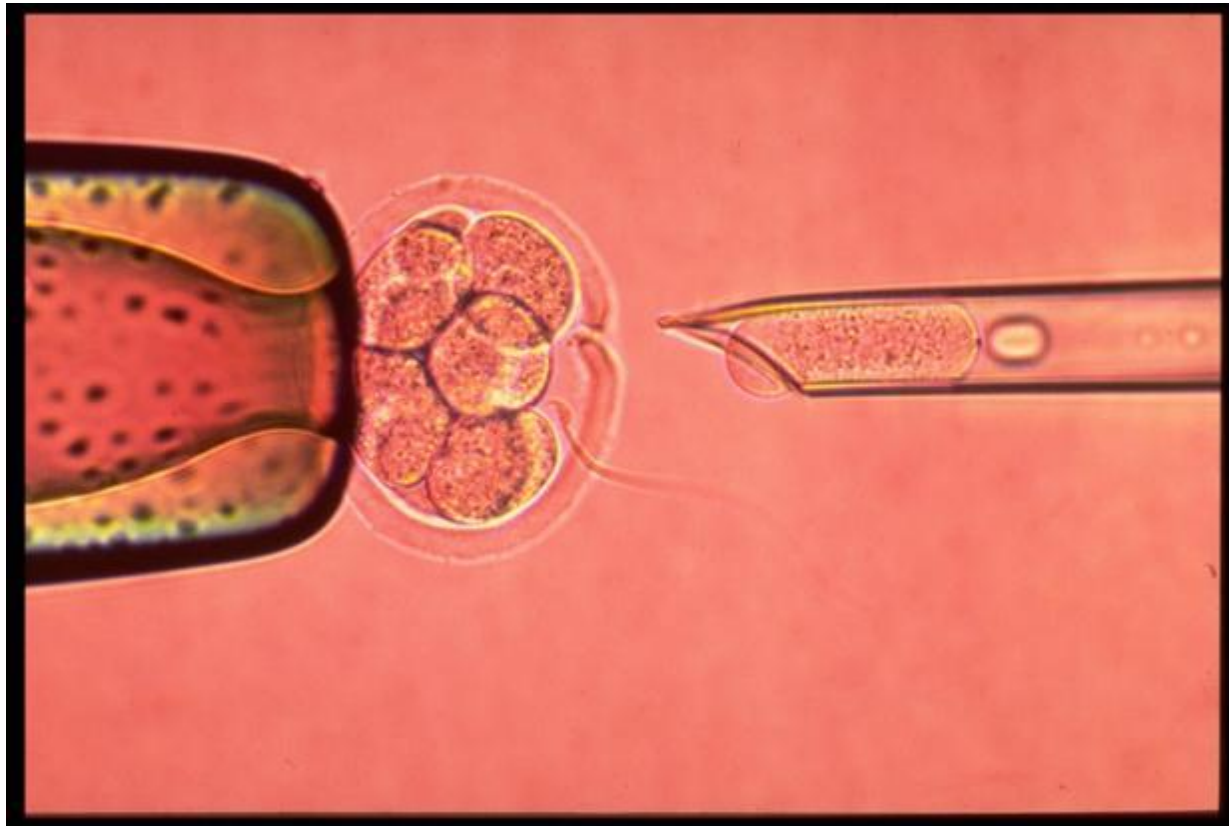


Leaders in Fertility

IVF: the current results

- Clinical pregnancy rates
- Natural conception
- Frozen embryos
- Female age and IVF pregnancy rate

Pre implantation Diagnosis



Public Funded Fertility Treatment

- Fertility assessment
- Primary (GP, nurse practitioner)
- Secondary (Hospital)
- Tertiary
 - DHB contracted providers (Fertility Associates, OFS)
 - Specialist first assessment is covered if the criteria are met
 - Two treatment “cycles” (IVF, DI x4, Donor eggs = 1 cycle)

Eligibility for Public Funding

- Eligibility is determined by CPAC (Clinical Priority Access Criteria) specifically defined for fertility services throughout New Zealand.
- Couples require a CPAC score of more than 65 to access treatment.
- The scoring is complex and includes some factors which make patients ineligible for Public Funding:
 - Women who smoke are required to stop and be smoke free for three months to become eligible
 - Women with a BMI greater than 32 or less than 18 are required to lose or gain weight
 - Women aged 40 or older are excluded
 - Patients with two children in their current relationship or two children from previous relationships aged 12 or younger living at home

Eligibility for Public Funding

- Severe causes of infertility (anovulation, bilateral tubal damage, poor sperm) score a higher CPAC score.
- Previous vasectomy or tubal ligation, duration of infertility and history of unsuccessful other treatments are taken into account.
- Lesbian couples and single women may be eligible for Public Funded treatment if they have a biological reason for fertility delay or have not achieved pregnancy after 12 cycles of donor insemination.
- Funding covers the most appropriate treatment for that patient and may include ovulation induction, insemination of sperm, donor insemination, IVF, egg donation or surrogacy.

Public Funded Fertility Treatment

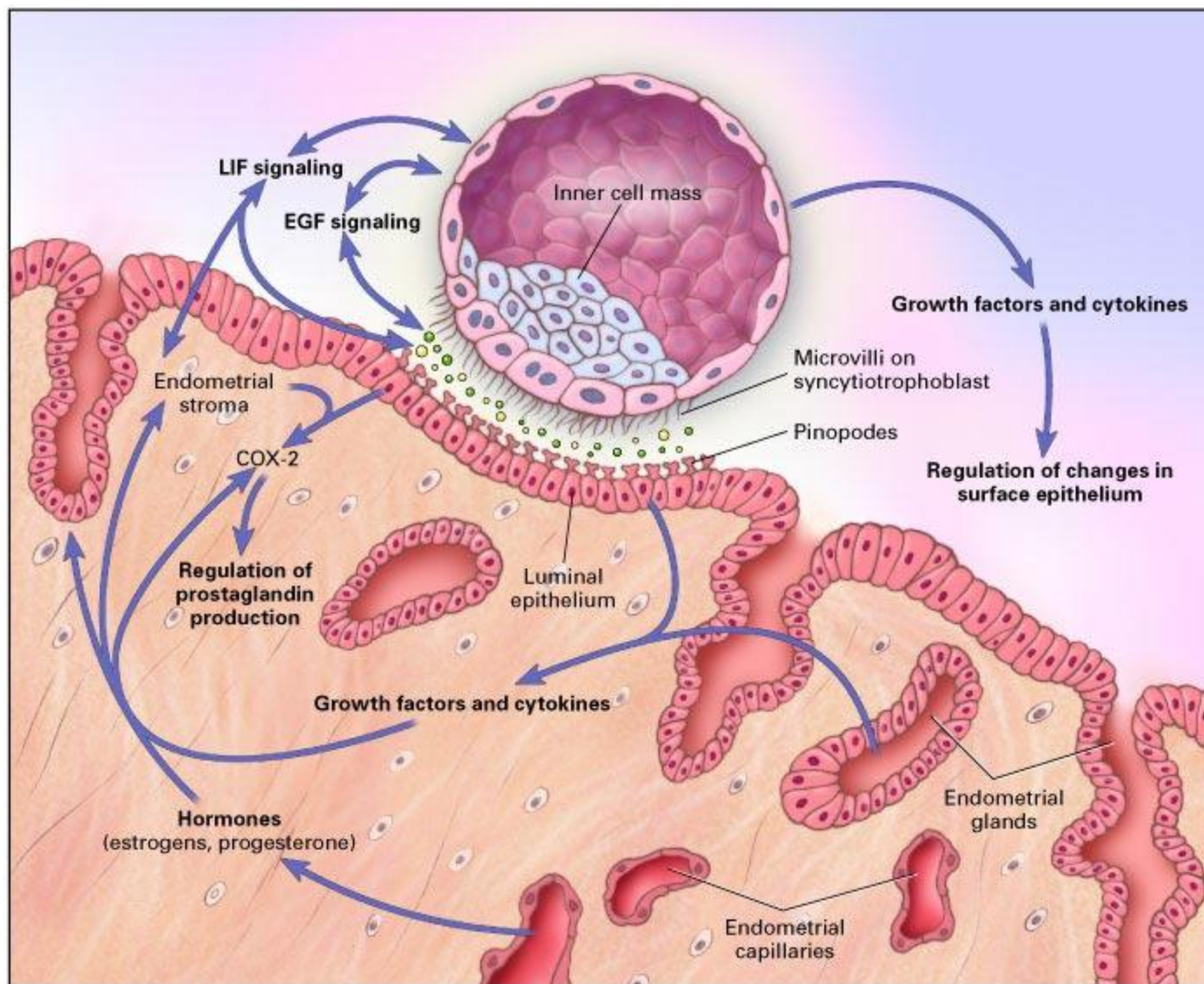
- Specialist assessment
- Scoring
- Waiting time until treatment starts
- Second scoring and treatments
- Other options

Private treatment costs

- Private specialist assessment vs FSA
- Clomiphene ...
 - Cycle monitoring, blood tests, Ultrasound scanning
- IUI (prev AIHusband)
- IUDI (donor sperm)
- IVF...ICSI
- Oocyte freezing (oncology....social)

- Lifestyle, environmental and nutritional issues
- Cost effective and timely investigation
- **Recent developments**
 - **endocrine, radiology and genetics**
- New developments in IVF
- Early pregnancy management miscarriage and ectopic
- Ethical issues and medical tourism

- Radiology
 - Saline scanning
 - 3 d ultrasound
 - MRI fro uterine anomalies
- Endocrinology
 - AMH
- Genetics
 - Sperm DNA
 - Endometrial and impalntation factors



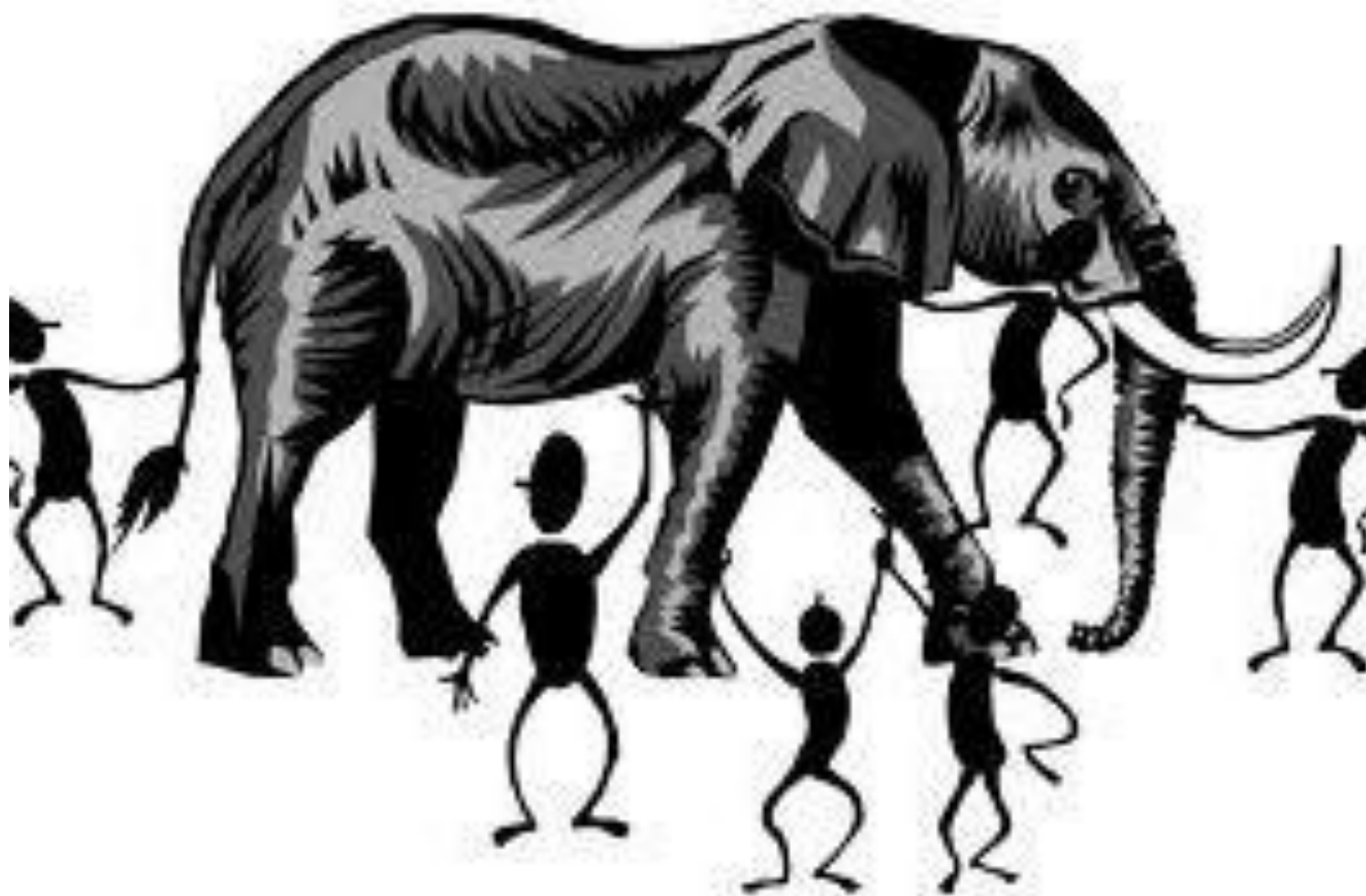
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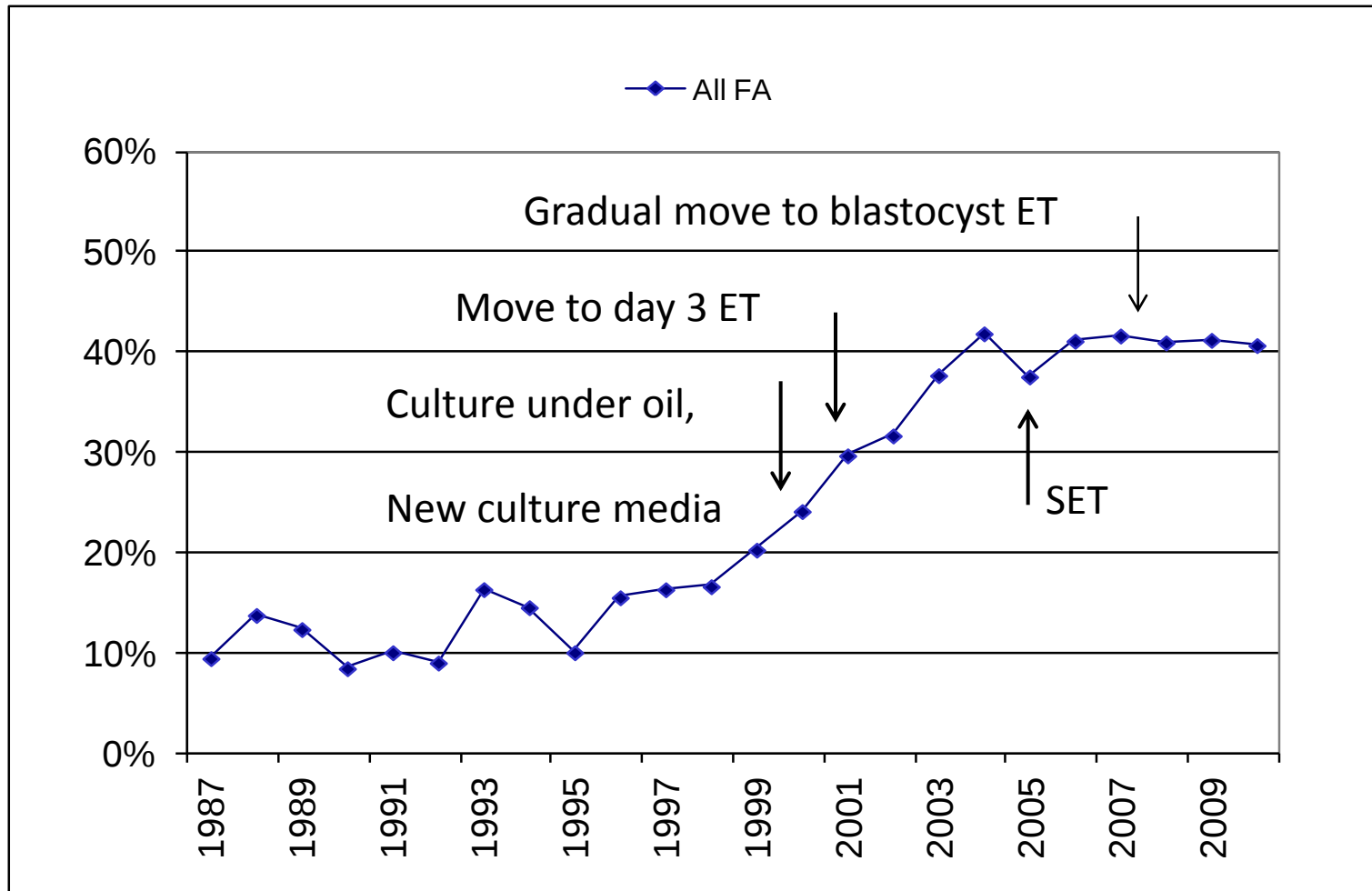


Leaders in Fertility

IVF in 2012

- All causes, both male and female
- Blood tests
- Drugs to block ovulation
- Ultrasound egg retrieval & embryo replacement
- Common to be in 40's
- Single women and lesbian couples increasingly represented
- Fertility preservation now an option

Fresh implantation rates, women aged ≤ 37



‘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

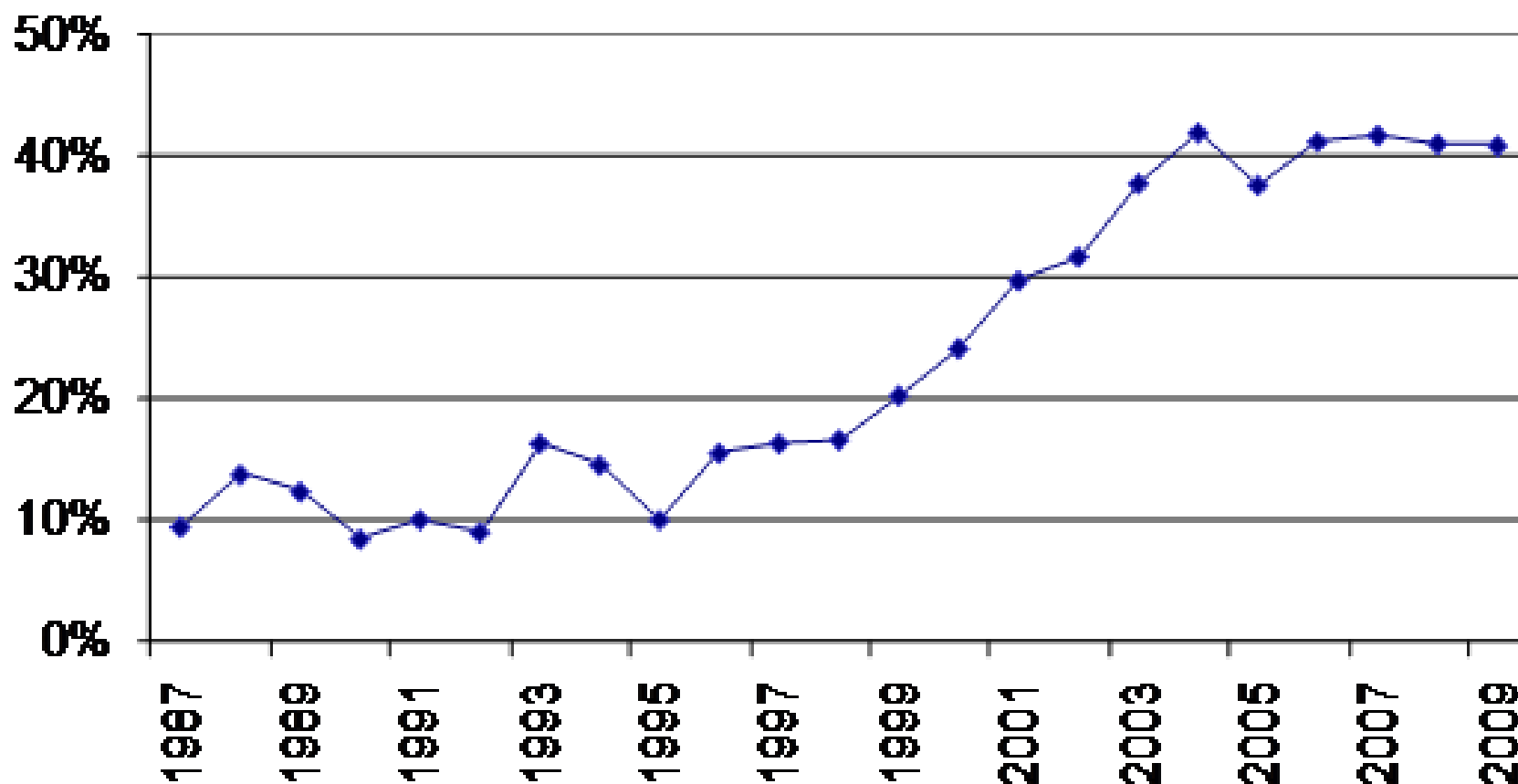
Efficacy of fertility treatment

- 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)



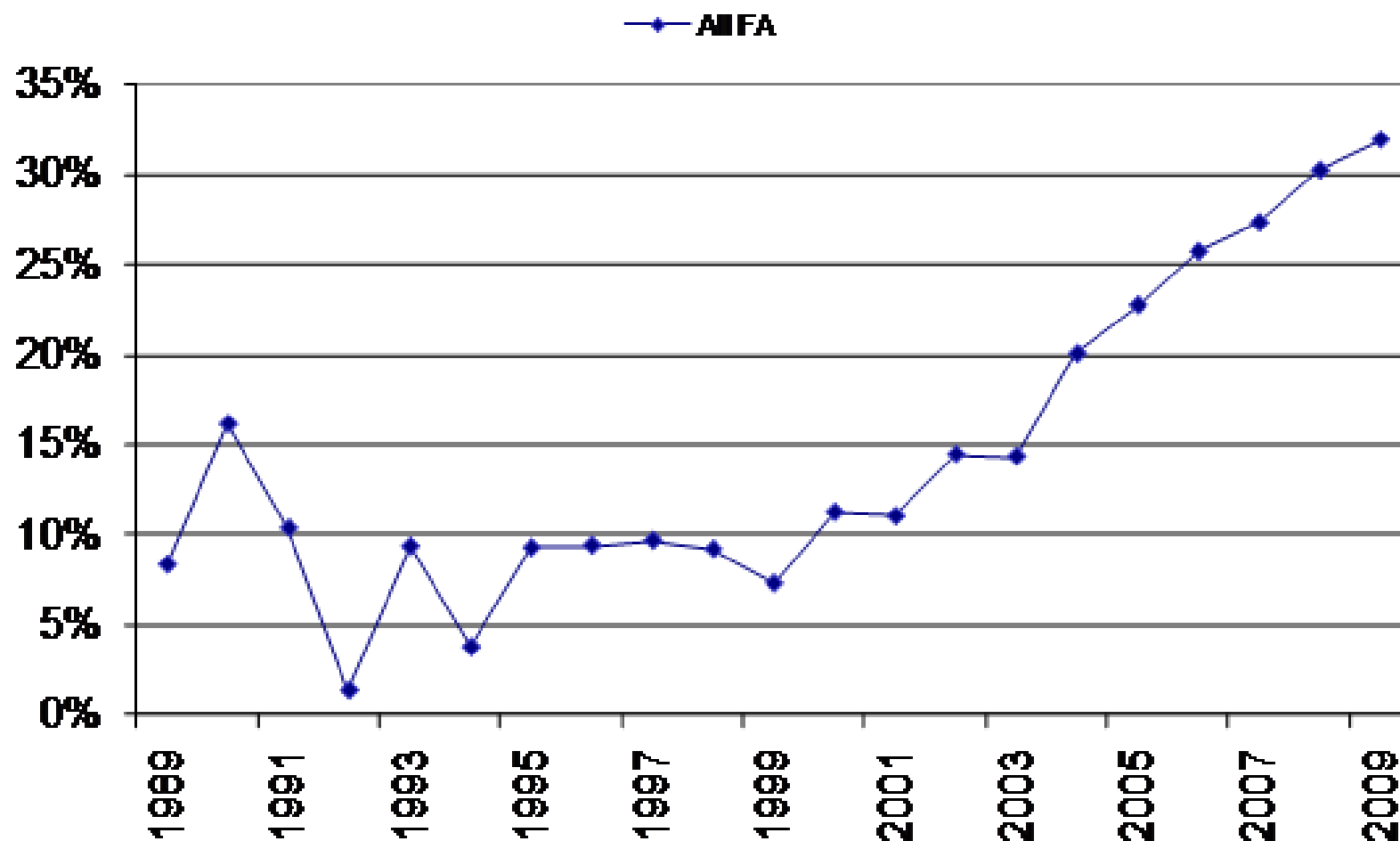
Implantation rates in women ≤ 37 per ET

—♦— All FA

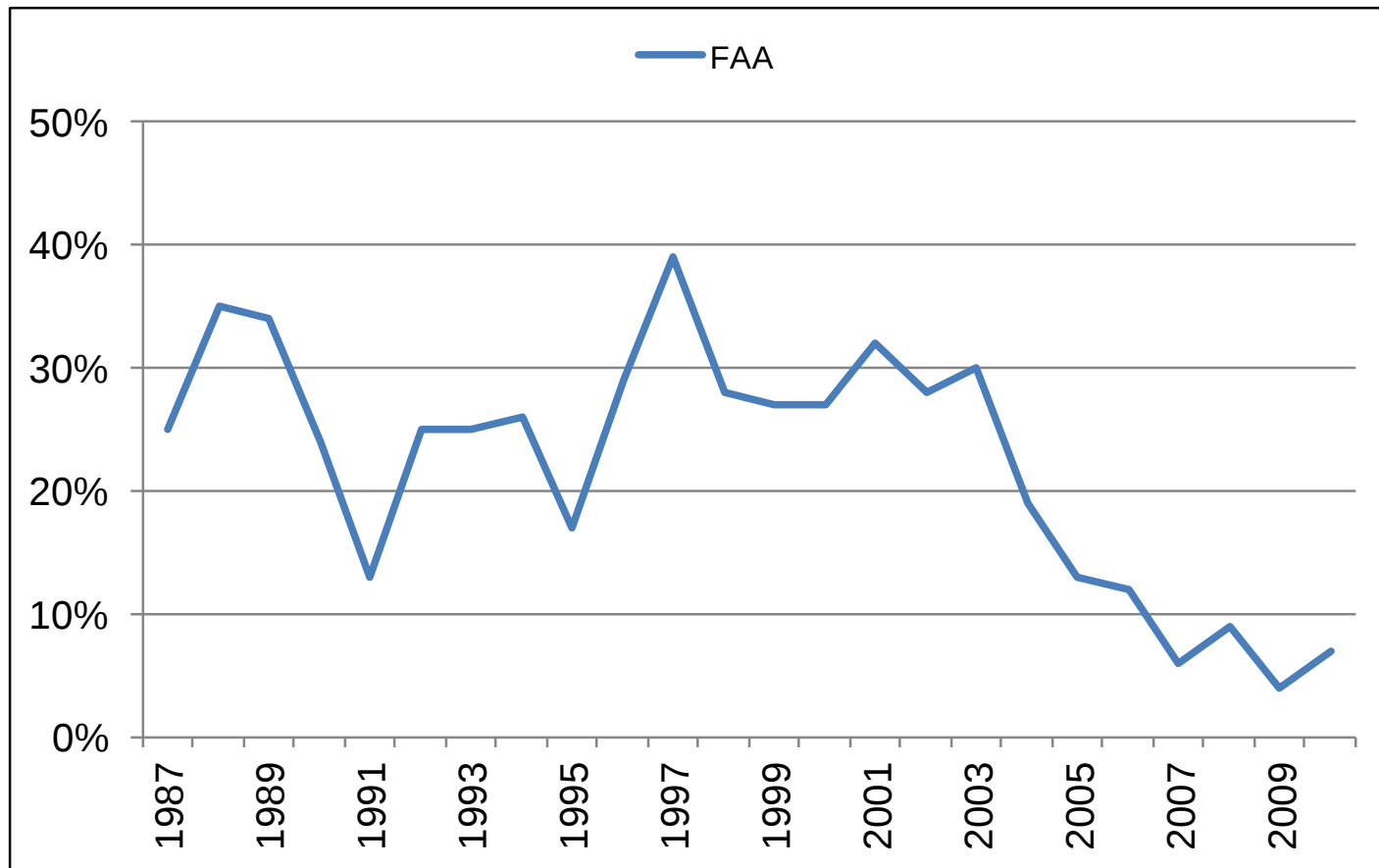




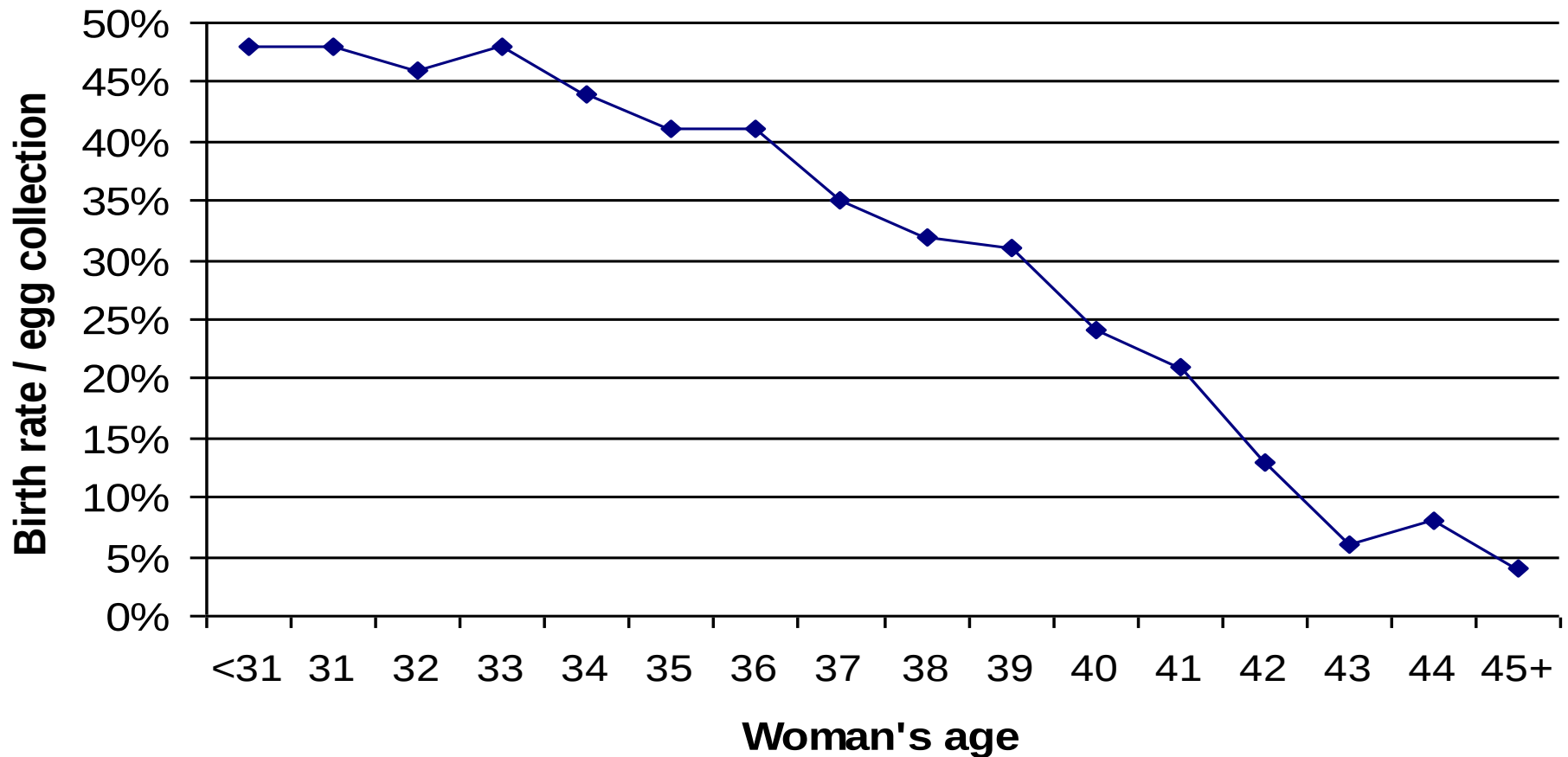
Implantation rates in women ≤ 37 per TER



Multiple IVF birth rate fresh IVF



IVF success rates



Freezing things

- Sperm
- Ovarian Tissue
- Eggs



Sperm freezing - who might benefit?

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



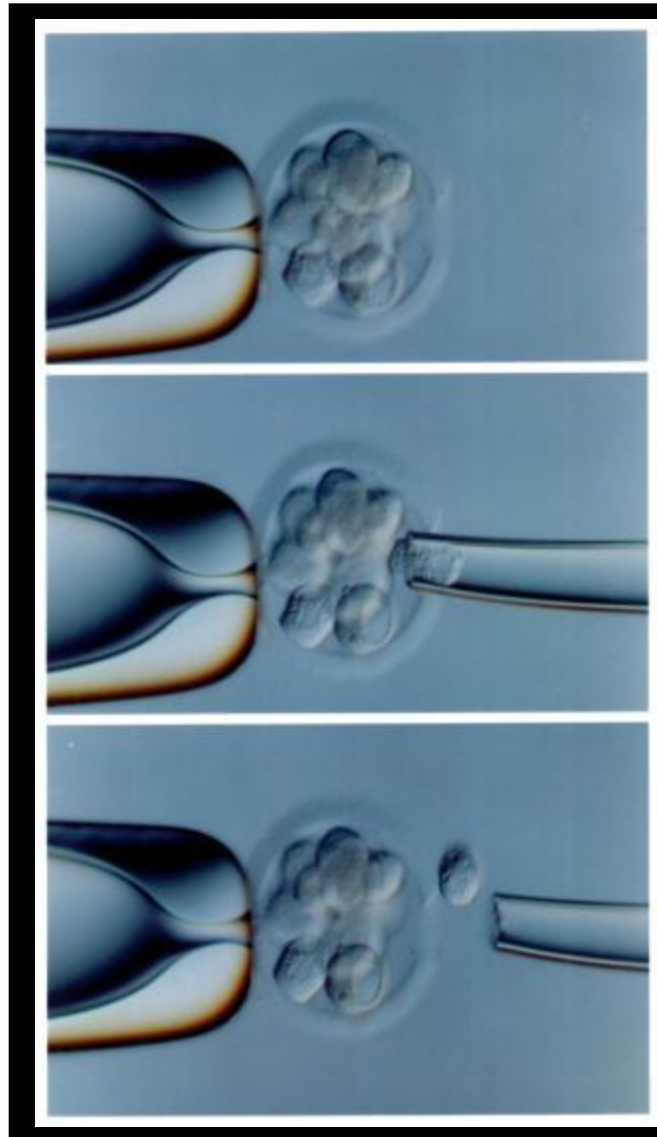
Cryopreservation of ovarian tissue

- 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’

**Day 3
embryo
(8 cells)**



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

**Insertion of glass
micropipette**

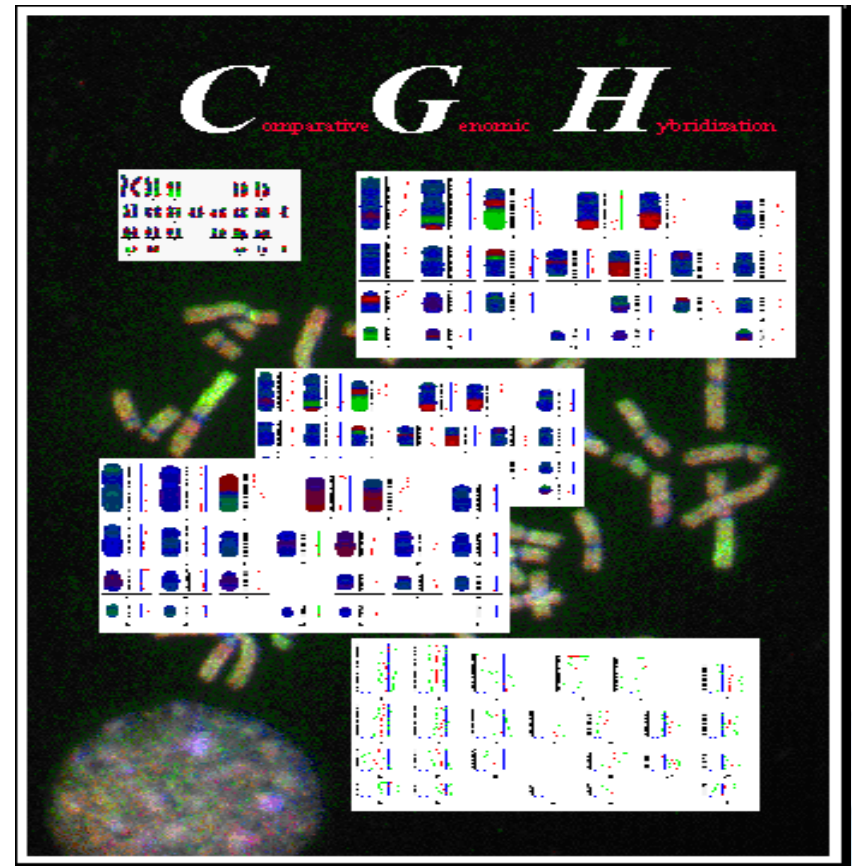
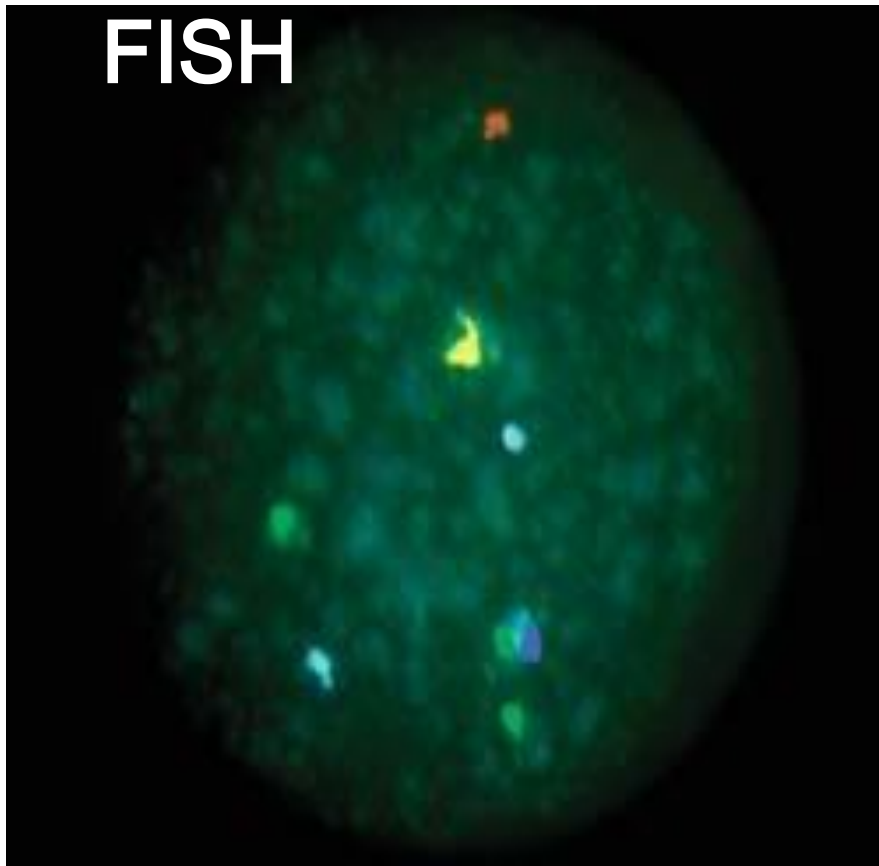
**Removal of a single
blastomere for genetic
analysis**



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FISH



Leaders in Fertility

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

- Lifestyle, environmental and nutritional issues
- Cost effective and timely investigation
- Recent developments
 - endocrine, radiology and genetics
- New developments in IVF
- **Early pregnancy management miscarriage and ectopic**
- Ethical issues and medical tourism

Early Pregnancy

- Normal
- Ectopic
- Miscarriage
- Recurrent Miscarriage
 - Immune disorders
 - Thrombophilias
 - Genetics
 - PGD

Early Pregnancy hCG

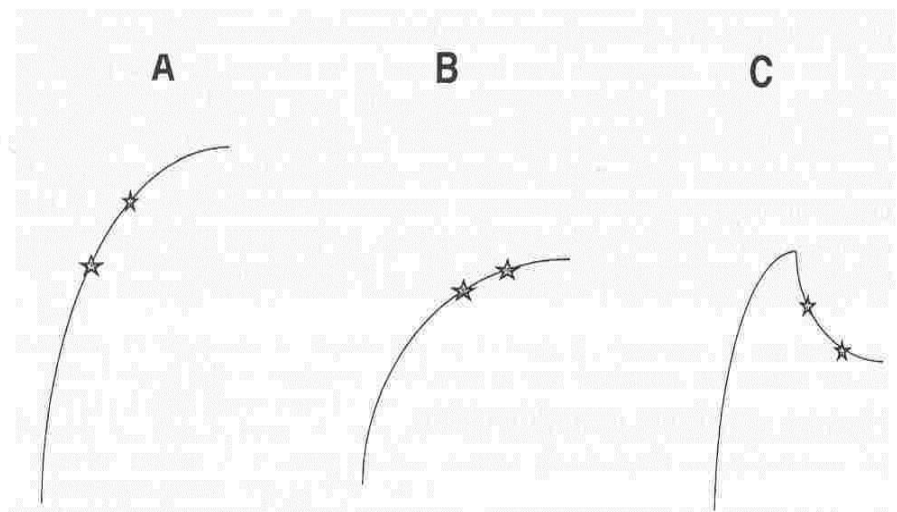
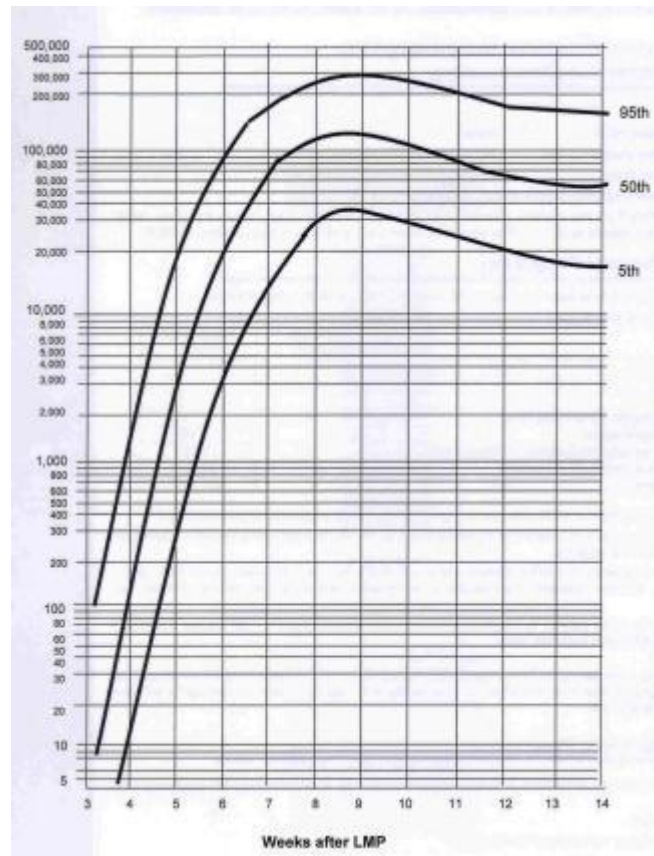


Fig. 9.1. Different hCG patterns in early pregnancy. A, normal increase of hCG; two consecutive samples will show the rate of hCG production (iu/l $\times$ day). B, subnormal increase, where the 'hCG score' can give diagnostic information. C, initial normal increase followed by decline.

Early pregnancy scanning

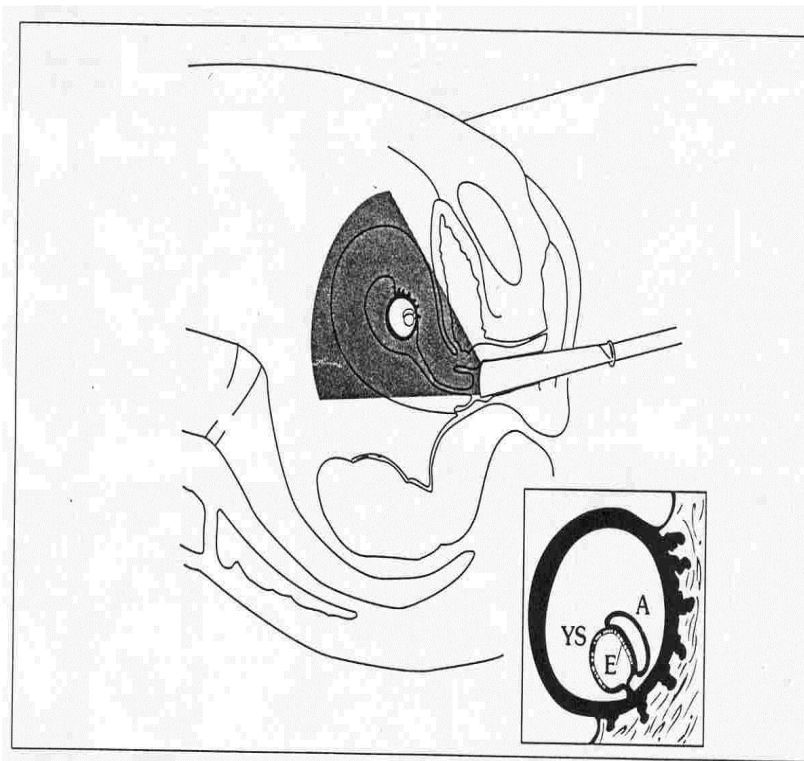
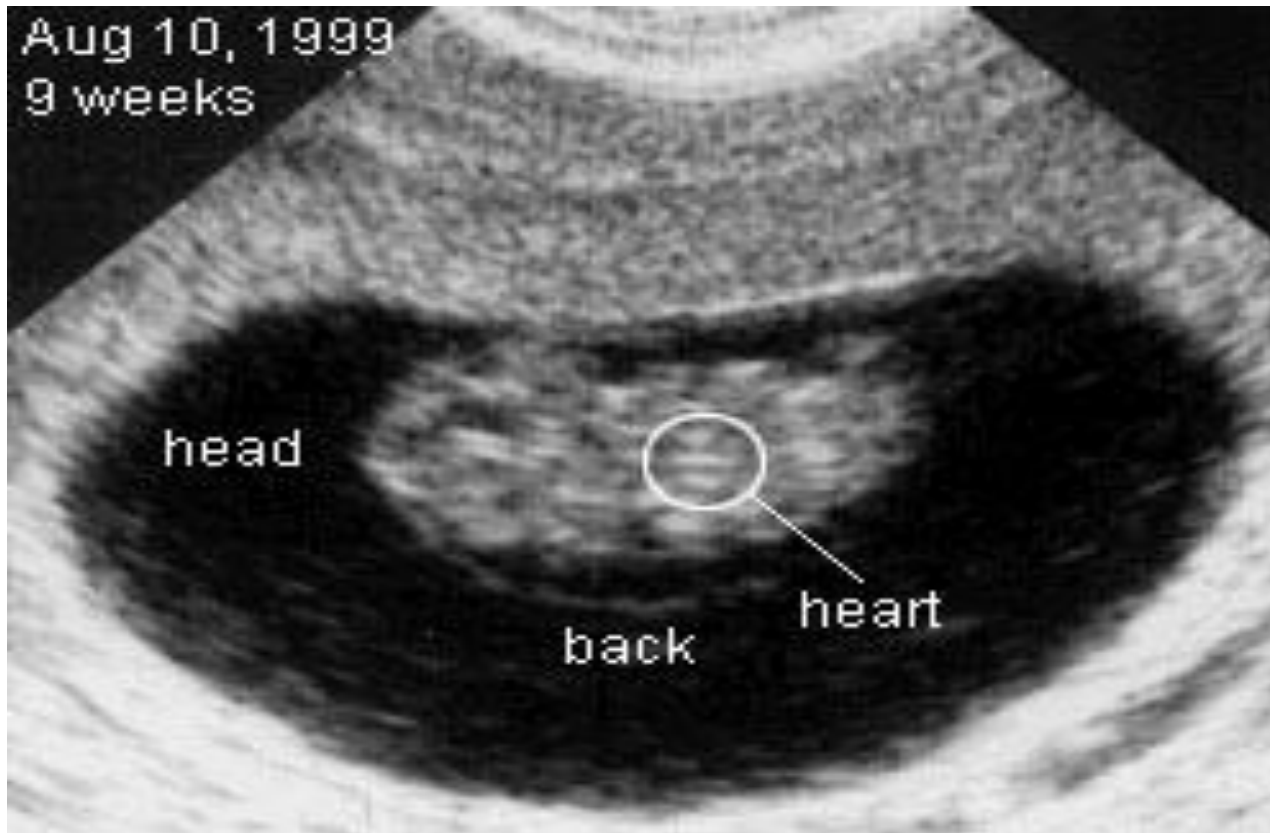


Figure 8-2. Early intrauterine pregnancy and its relationship with the transvaginal probe. Note that the embryonic disk (E) lies between the developing amnion (A) and yolk sac (YS).

	28.	35.	42.	49.	56.	63.	70.	day p.m.
	5.	6.	7.	8.	9.	10.		week
Chorionic Cavity	○	●	●					
Yolk Sac		○	●	●				
Embryo		○	●	●				
Heart Motion		○	●	●				
Amniotic Cavity		○		●	●			
Cephalic Pole (BPD)			○	●	●			
Abdomen Diameter			○	●	●			
Umbilical Cord				○	●	●		

○ = earliest detection
● = usually detected
● = always detected

Early pregnancy scanning



Early pregnancy, hCG and scans

Pregnancy Hormones

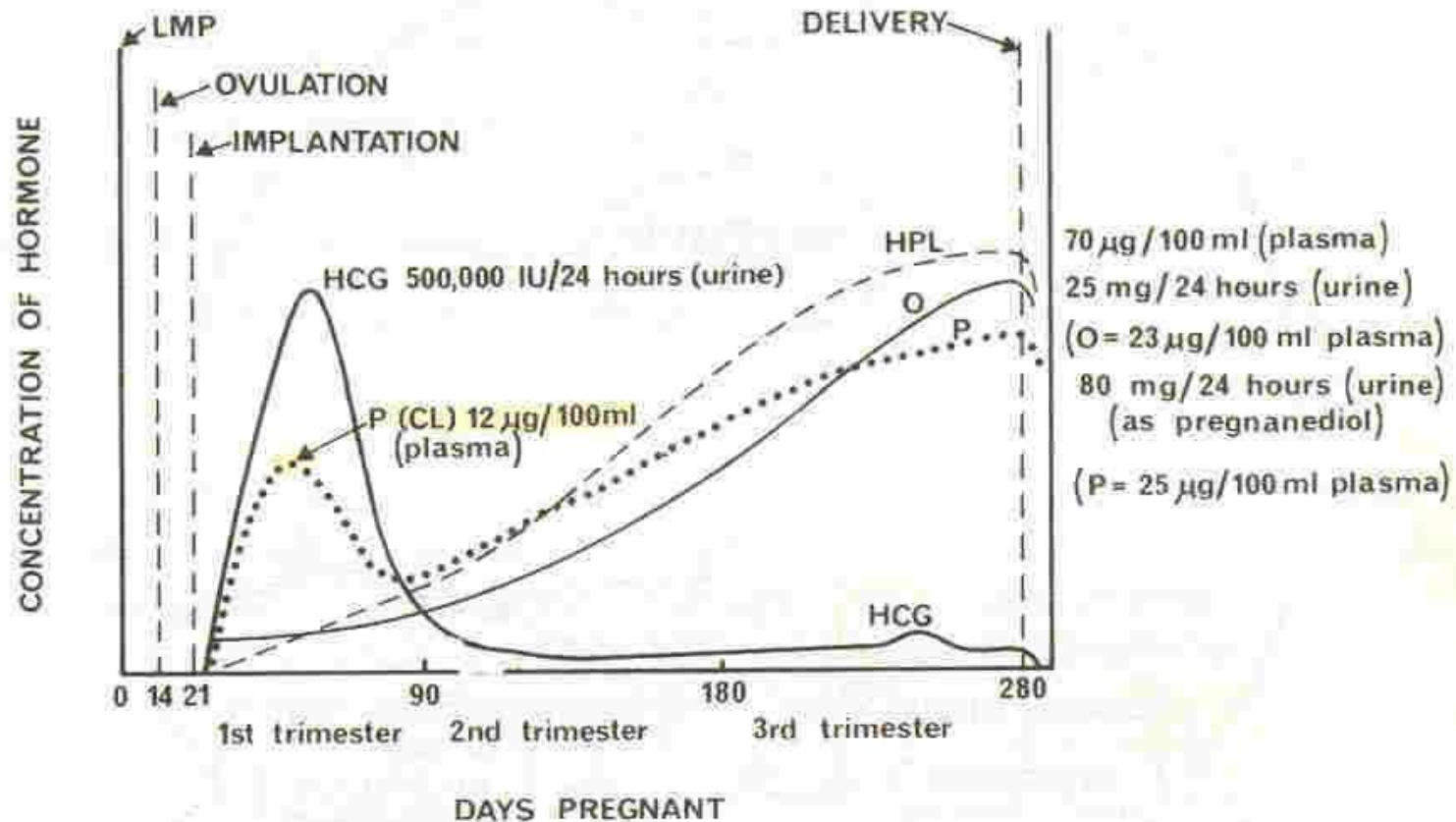
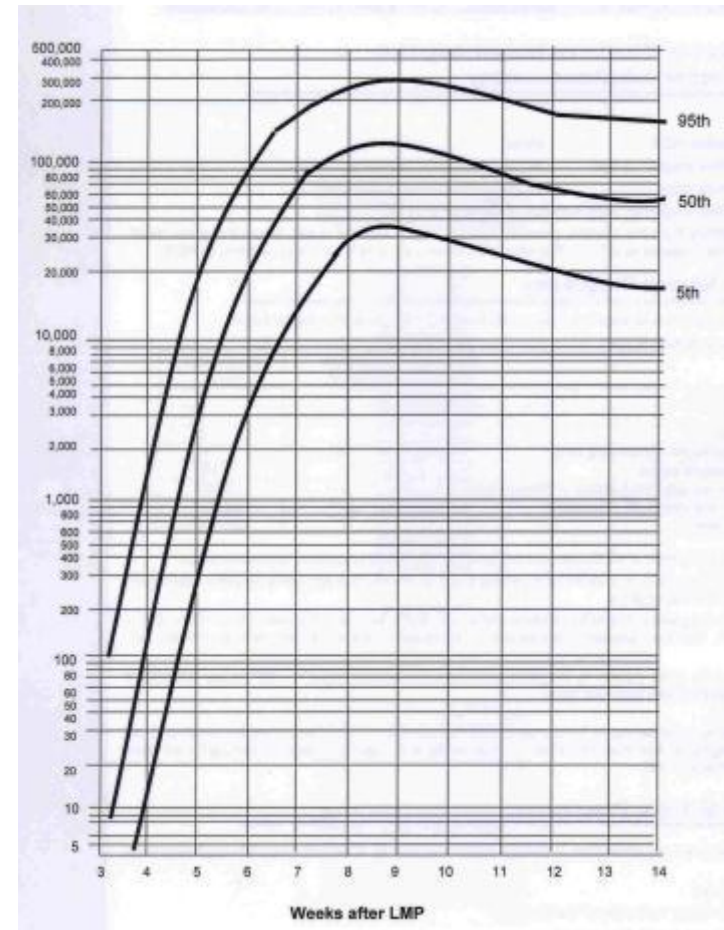


Fig. 11.9 Hormone levels during pregnancy

First trimester β hCG centiles

- mRNA from embryo day 4
- Serum HCG from day 6 (immuno radiometric assay)
- Wilcox 1988:
30 % pre-clinical loss
- Luteal phase
 - doubles over 16 hrs
- from 4w to 7w (ELISA)
 - doubles over ~48 hrs
- Peak ~7-8w 100,000iu+





Patterns of β hCG rise 1st trimester

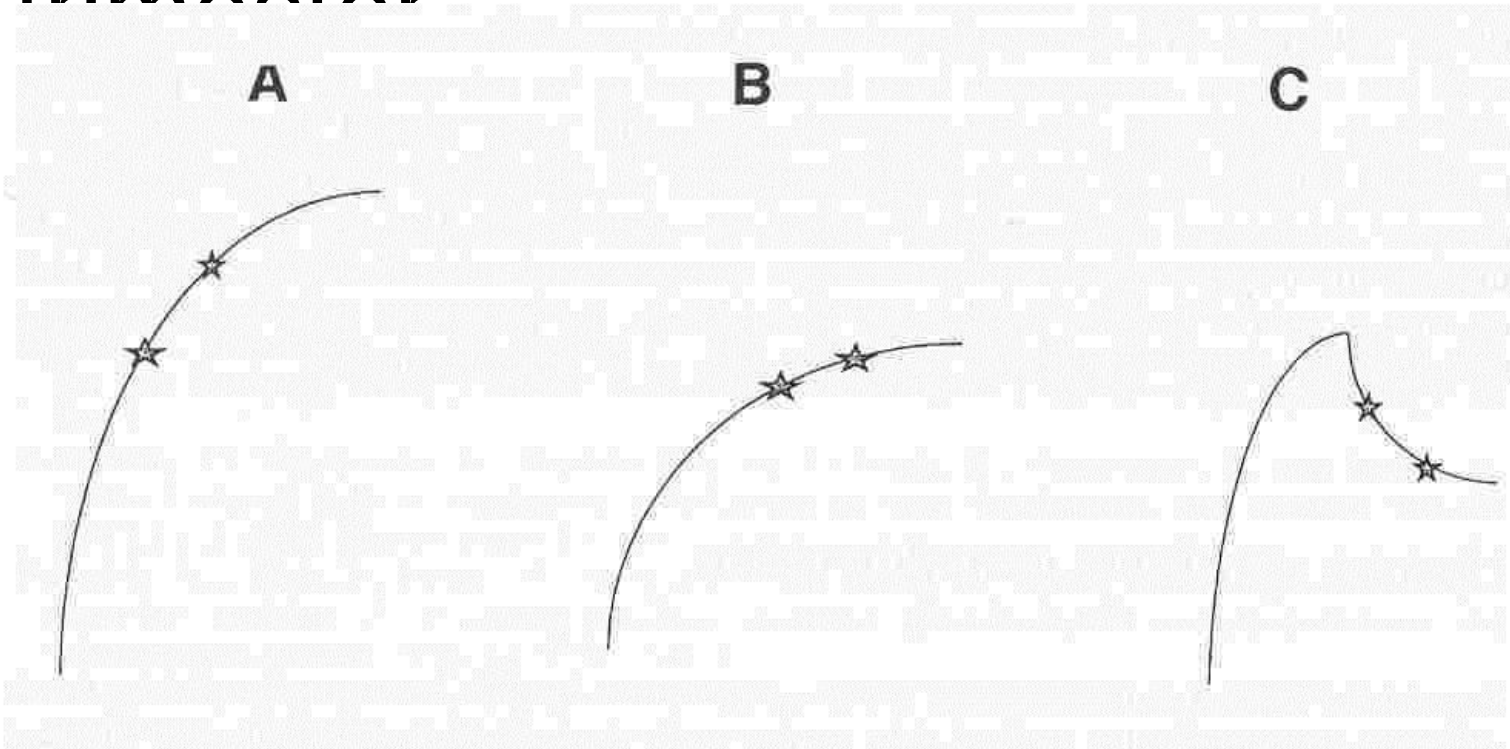


Fig. 9.1. Different hCG patterns in early pregnancy. A, normal increase of hCG; two consecutive samples will show the rate of hCG production (iu/l $\times$ day). B, subnormal increase, where the 'hCG score' can give diagnostic information. C, initial normal increase followed by decline.



Early pregnancy ultrasound

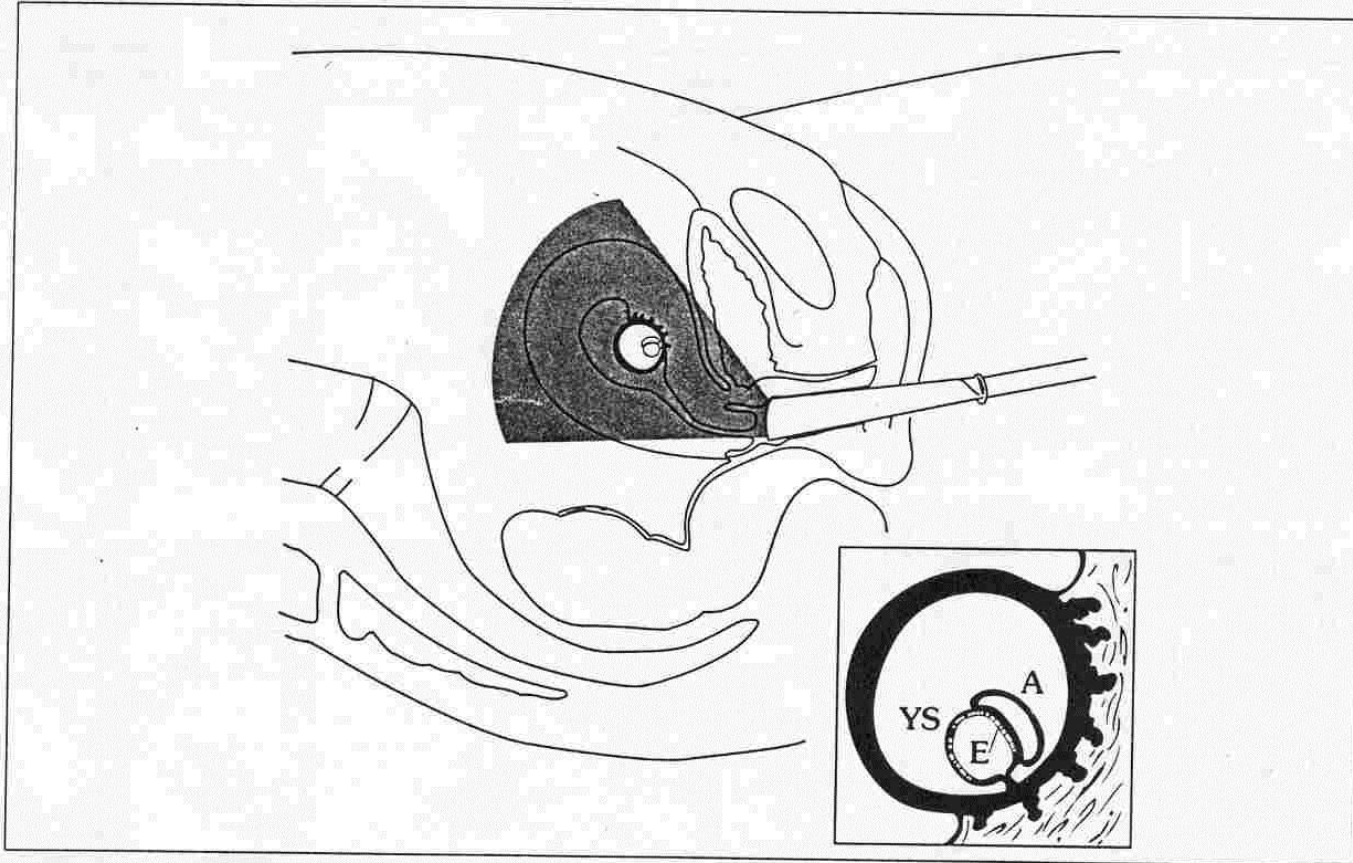


Figure 8-2. Early intrauterine pregnancy and its relationship with the transvaginal probe. Note that the embryonic disk (E) lies between the developing amnion (A) and yolk sac (YS).



Eai

ies

	28.	35.	42.	49.	56.	63.	70.	day p.m.
	5.	6.	7.	8.	9.	10.		week
Chorionic Cavity	○	●	●					
Yolk Sac		○	●	●				
Embryo		○	●	●				
Heart Motion		○	●	●				
Amniotic Cavity		○		●	●			
Cephalic Pole (BPD)			○	●	●			
Abdomen Diameter			○	●	●			
Umbilical Cord				○	●	●		

- = earliest detection
● = usually detected
● = always detected

Early pregnancy ultrasound

- Mean Gestational Sac diameter
 - If $>20\text{mm}$ with no Yolk Sac , no embryo = EPL
- Crown Rump Length
 - If $> 6\text{mm}$ without fetal cardiac activity = EPL
 - But if CRL $<6\text{mm}$, repeat in 7 days
 - Expect CRL increase $\sim 1\text{mm/day}$ and +FH
- Heterotopic pregnancy (1% IVF...1/3000)

Pregnancy of unknown location

- (PUL) ? 8-31% of presentations
- = + HCG with no sign of intra or extra uterine pregnancy with no evidence retained POC
- 4 possible reasons
 - Failing pregnancy
 - Early viable pregnancy
 - Early ectopic
 - Persistent PUL

Serum progesterone in

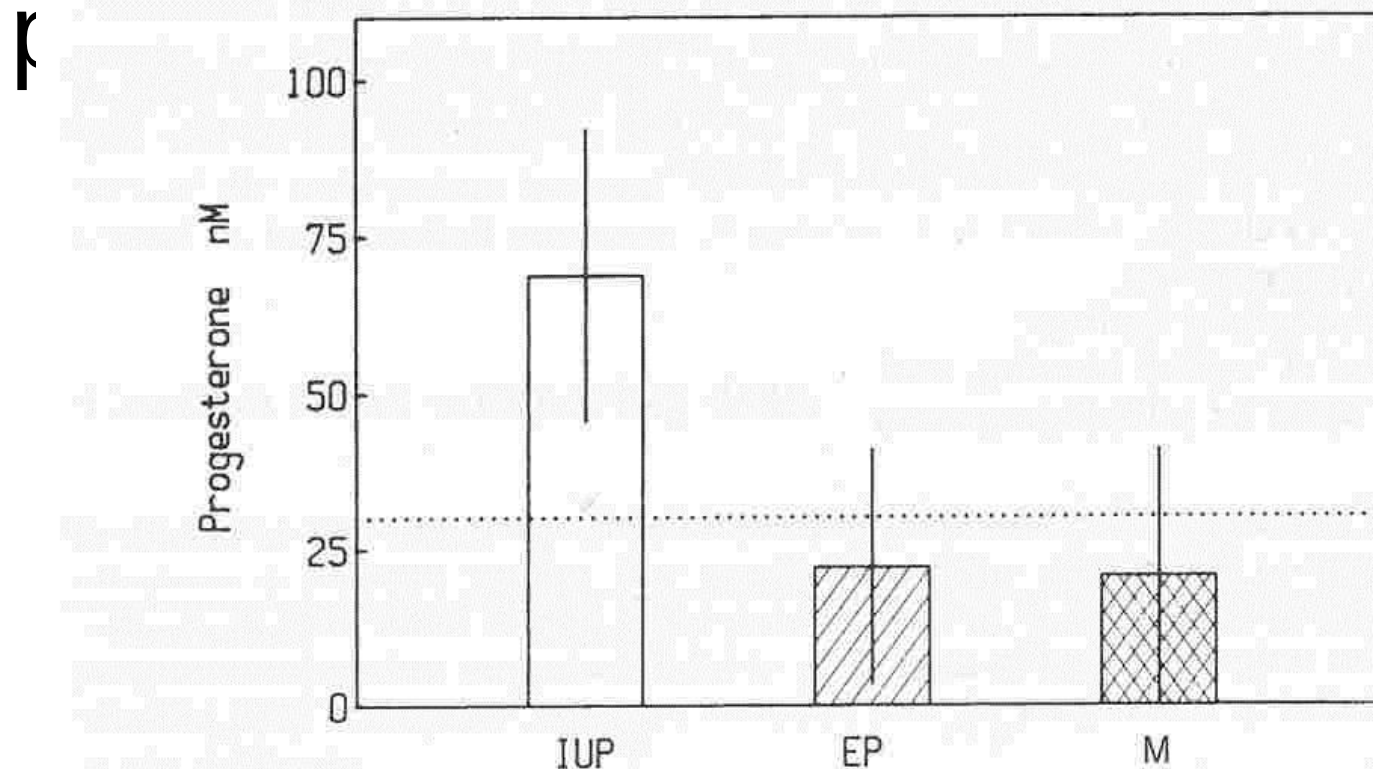


Fig. 9.2. Initial serum level of progesterone in viable intrauterine pregnancy (IUP) ($n = 24$), in miscarriage (M) (SPAB) ($n = 37$) and in ectopic pregnancy (EP) ($n = 97$). Values are given as means $\pm$ standard deviation. The values for M and EP are significantly different from IUP ($P < 0.001$). The dotted line is the discriminatory level of progesterone (30 nM) below which no viable intrauterine pregnancies were found. Reproduced, with permission, from Hahlin *et al.* (1990).

Discriminatory zone

- Correlation of HCG with GSD (but note centiles)
- Limitations:
 - Twin gestation (higher than expected HCG)
 - USS hardware (TV USS 1000-1500iu cf Abdo USS 5000iu)
 - USS operator experience
- HCG doubling over 48 hrs in ongoing pregnancy
 - cf Complete EPL HCG should fall to <20% in 48hrs
 - cf after ERPOC HCG should fall by ~15% in first 12 hrs
- ?serum progesterone
 - <15 nmol implies non-viable pregnancy
 - >80 nmol 97% sensitivity to exclude ectopic
 - BUT many patients between 15 to 80 nmol

Ectopic Pregnancy:

? Expectant management

- If stable + no haemato peritoneum or signs of tubal rupture
- HCG <200iu (?<1000iu)
- ??60% resolve.
- Careful followup USS and HCG

Ectopic Pregnancy:

? Medical management

- If stable + no haemato peritoneum
- HCG <5000 iu
- EP diameter <30mm
- No fetal cardiac activity
- No contraindication to Methotrexate
 - (Viable pregnancy, liver, renal , bone abnm.)
- Follow up USS and HCG. ?80% resolve
- But 10% persist or rupture even if HCG falls
 - (possible even if HCG falls to non-pregnant levels)

Summary

- Understanding of physiology
- Correlation of history, dates, HCG and USS
- Careful follow-up @ 48 hours
- HCG doubling expected 4-7weeks
 - if plateau or failure to fall after presumed intrauterine loss / ERPOC ?ectopic
- Limitations of single HCG, P, USS <6/40

- Lifestyle, environmental and nutritional issues
- Cost effective and timely investigation
- Recent developments
 - endocrine, radiology and genetics
- New developments in IVF
- Early pregnancy management miscarriage and ectopic
- **Ethical issues and medical tourism**

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)

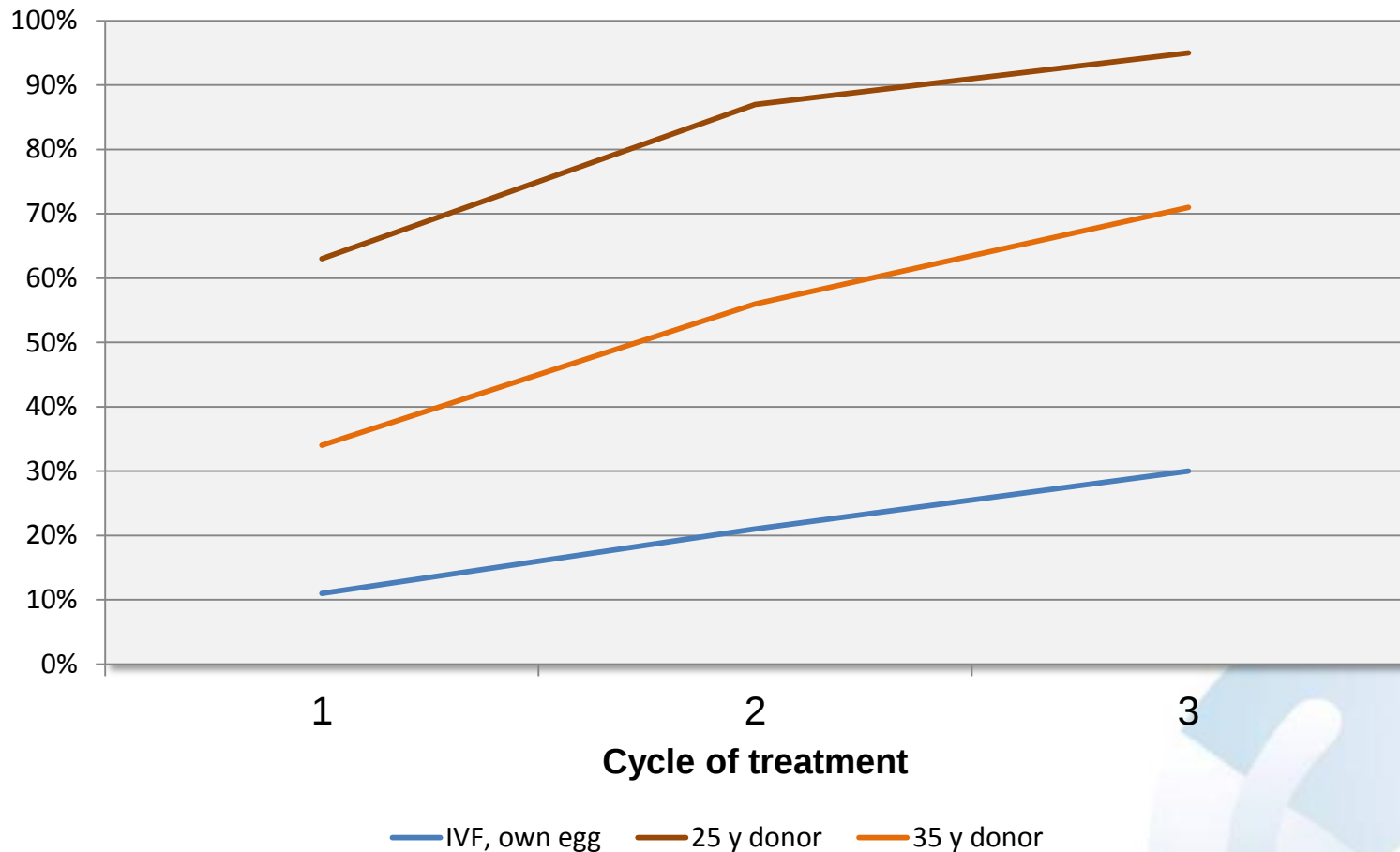
Prohibitions (ii)

- 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

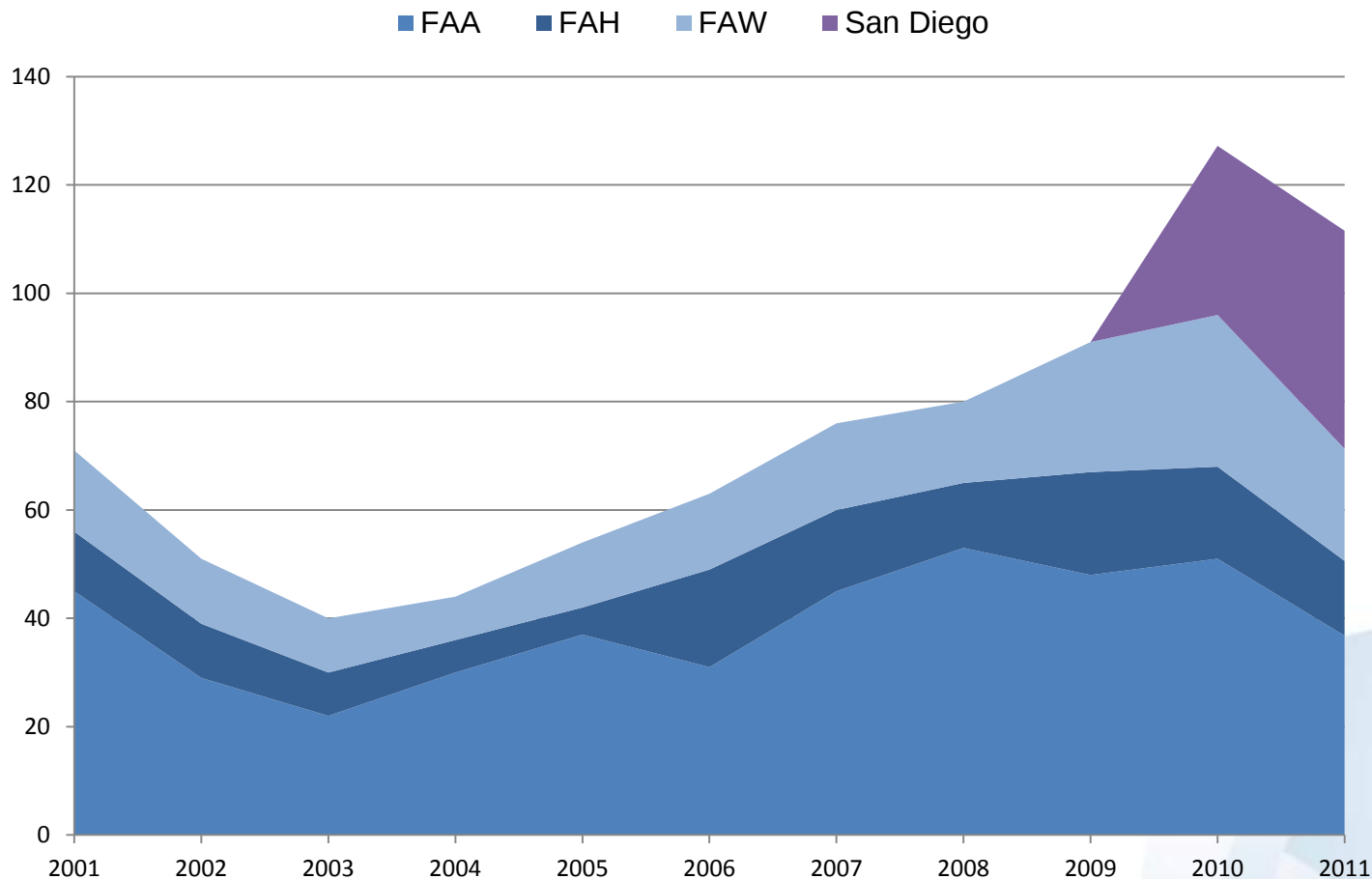
HART Act (2004)

- ACART
- ECART

Estimate cumulative birth rate, women 42y using donor eggs



Donor egg cycles



Cross border reproductive care

Oct 2010 to Sept 2011 AUCKLAND

- 28 Patients to San Diego Fertility Clinic alone
- Average age of egg donors around 23
- Clinical pregnancy rate of around 65%
- Returned for thawed embryo replacement 6
- Transport of frozen embryos



Dilemmas

- Age
- Weight
- Marital status
- Cancer care
- Fertility preservation
- Cross border reproductive care
- Embryo disposal
- Embryo research

NZ Census 2006



**9% more women
than men in
30 – 34 year
group**

Indication for Donor Insemination at FA

Social indicators

Year	Proportion of cycles			
	Total	FAA	FAH	FAW
2002	40%	48%	29%	33%
2003	46%	44%	36%	51%
2004	45%	40%	33%	55%
2005	58%	54%	49%	65%
2006	51%	51%	31%	57%
2007	58%	59%	56%	57%
2008	59%	61%	40%	59%
2009	59%	61%	40%	62%
2010	55%	57%	38%	55%
2011 to date	62%	61%	50%	57%

Average age of women at the time of DI treatment

- Social causes 38.3
- Other causes 34.5

Families in NZ

- Couples with child(ren) 447,894
- One parent with child(ren) 193,635
- 30% of children are from one parent families



Statistic NZ 2006 Census

Oocyte freezing

- Prior to chemo/radiotherapy
- Religious reasons
- Legislative restriction
- Strategy for cumulative outcomes
- “Social”

Oocyte freezing

A. Cobo - Vitrification

- 486 cycles
- 2721 oocytes
- 84% survived thawing
- 128 deliveries, 29% / transfer

If >8 oocytes then pregnancy rate (46.4%)

The future



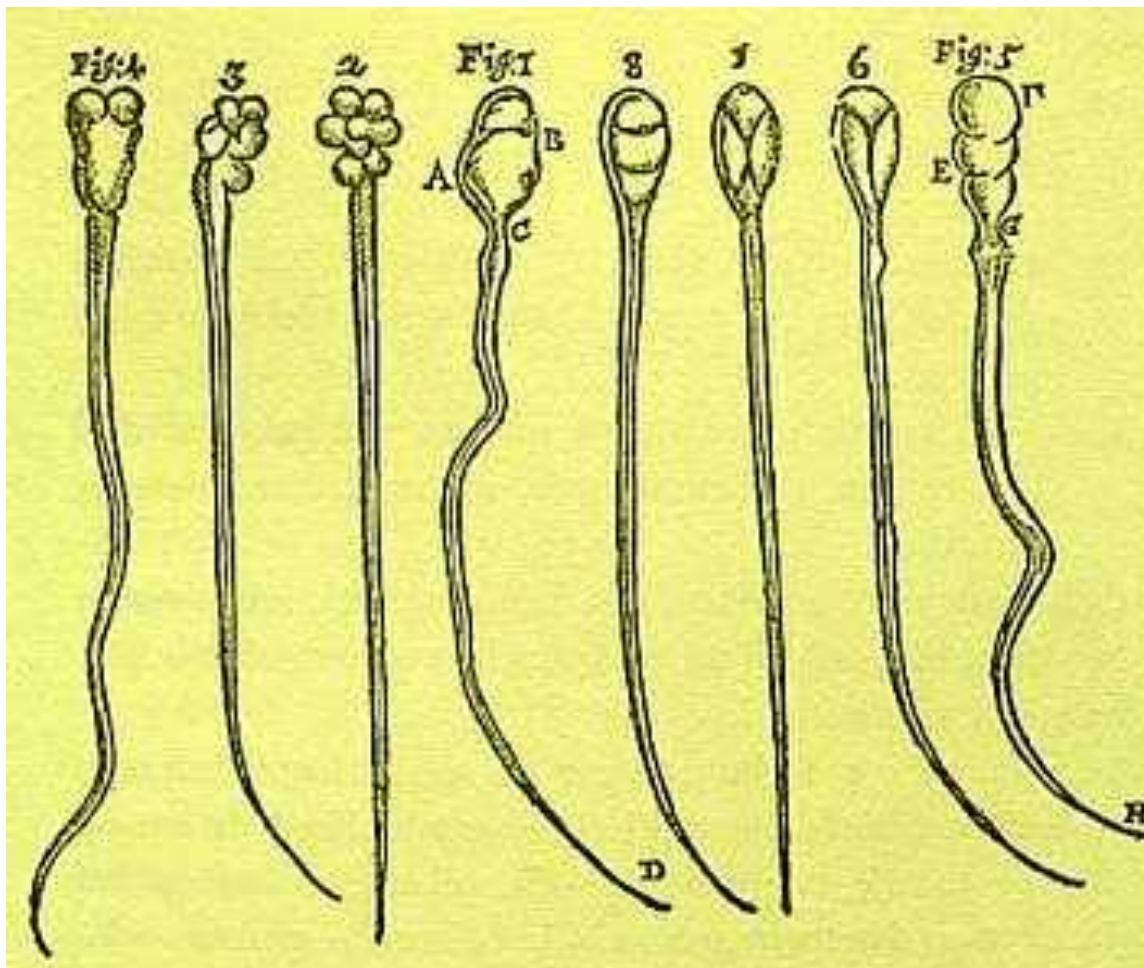
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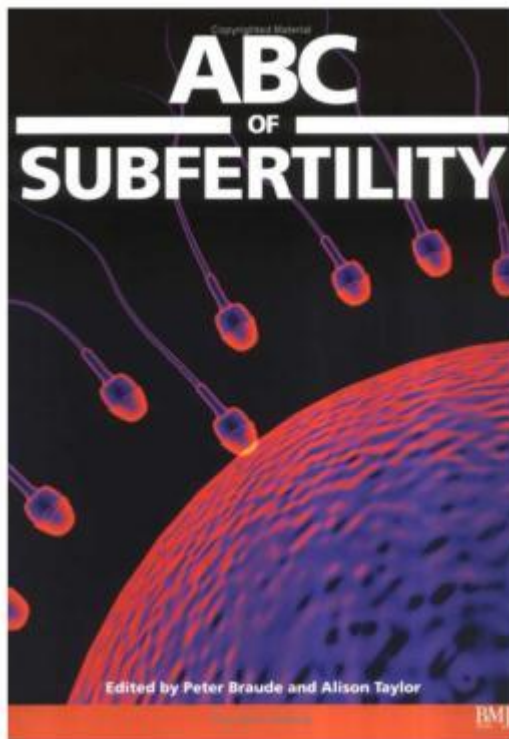


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For more info, please visit our website:

www.fertilityassociates.co.nz/GP



www.nice.org.co.uk



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The future?

- Sperm Transport
 - Sperm selection IIMSI
- Endometrial factors
- Embryo factors
 - Time lapse assessment
 - Genetics



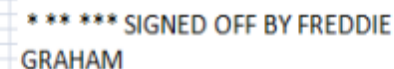
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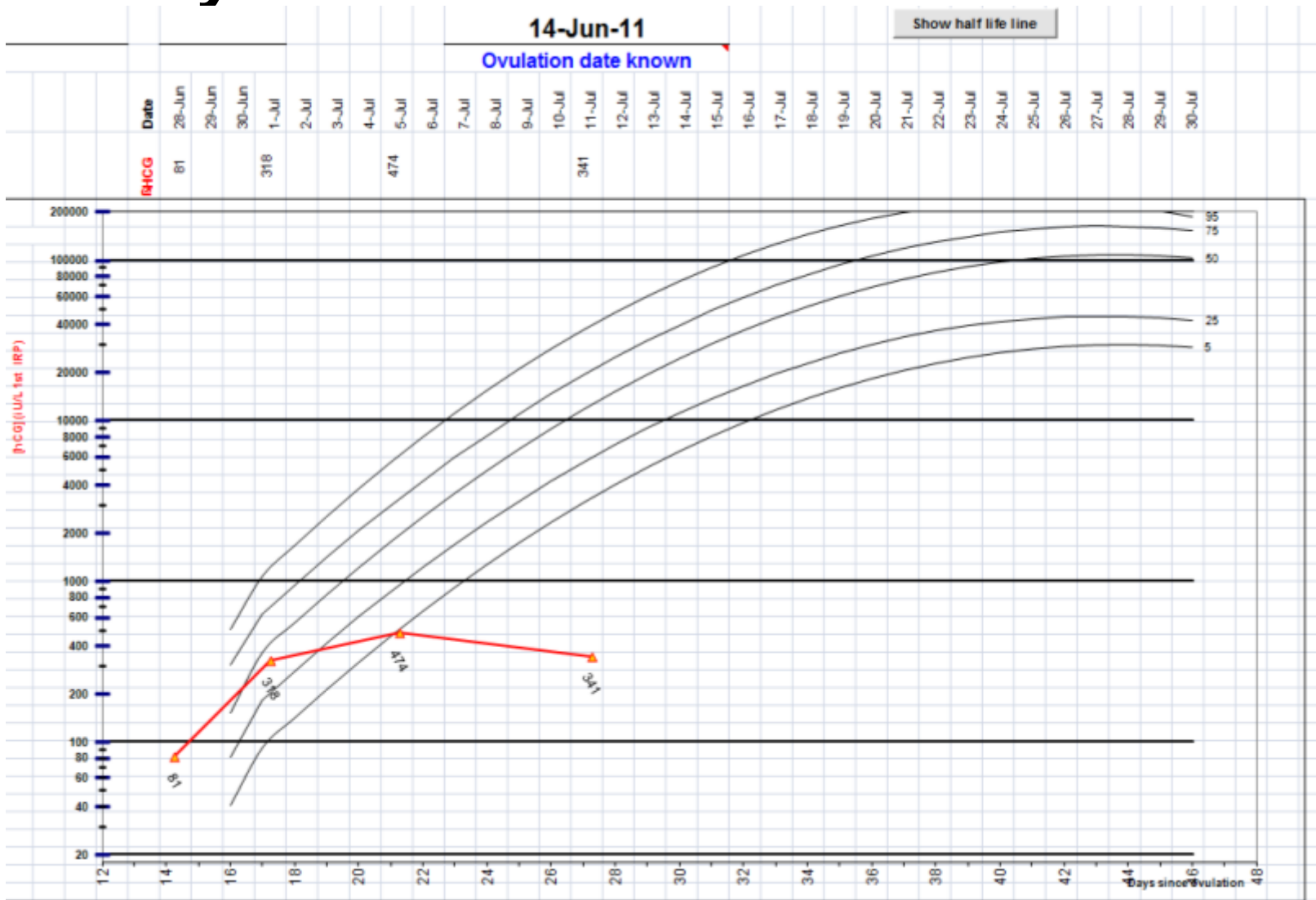
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Case study 1



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

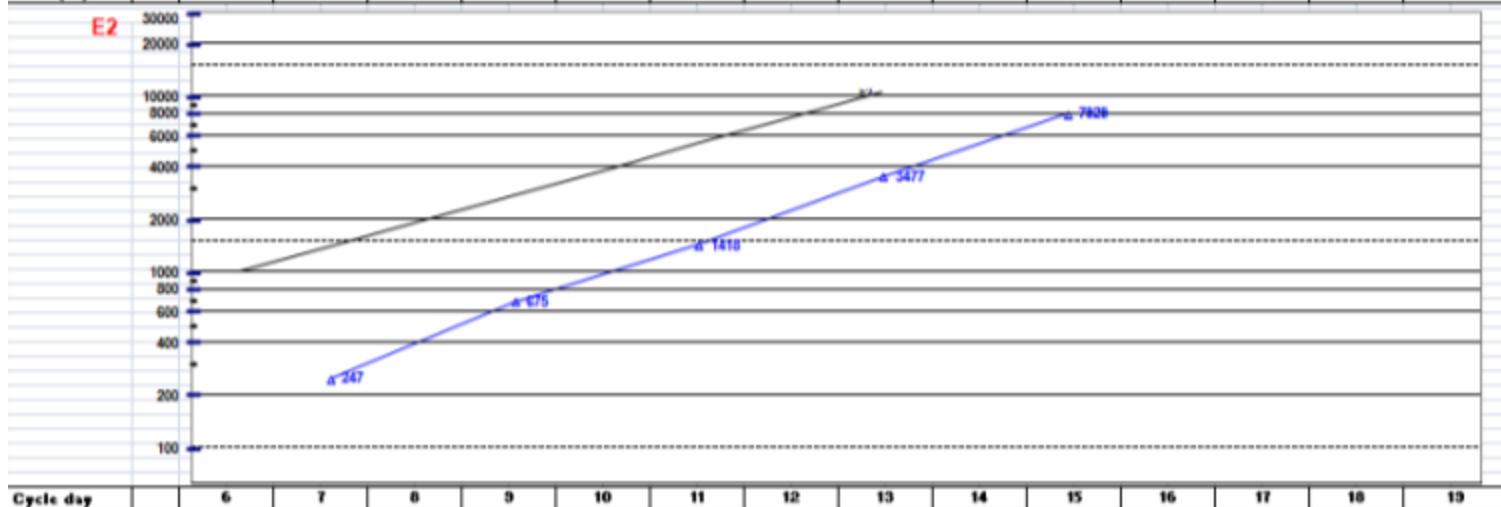
Case study 3 – June 2008

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

Case study 3

Scan Dr's name										sk		pm																
		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										14				16				23	1									
										13				15	3			16	3									
										11	2			12	3			15	3									
										###	4																	
R Ovary										13				13	1			20	1									
										12				12	3			17	1									
										11	2			11	3			16	3									
										10	2			10	2			14	4									
																		12	3									
Cycle day		6		7		8		9		10		11		12		13		14		15		16		17		18		19
Date		8-Mar		9-Mar		10-Mar		11-Mar		12-Mar		13-Mar		14-Mar		15-Mar		16-Mar		17-Mar		18-Mar		19-Mar		20-Mar		21-Mar
Weekday		Mon		Tue		Wed		Thu		Fri		Sat		Sun		Mon		Tue		Wed		Thu		Fri		Sat		Sun
E2 (pM)				247				675				1418				3477				7929								
Lab E2																												
P4																				trigger				opu				
FSH (iu)		150		150		150		150		150		150		150		150		150										

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.

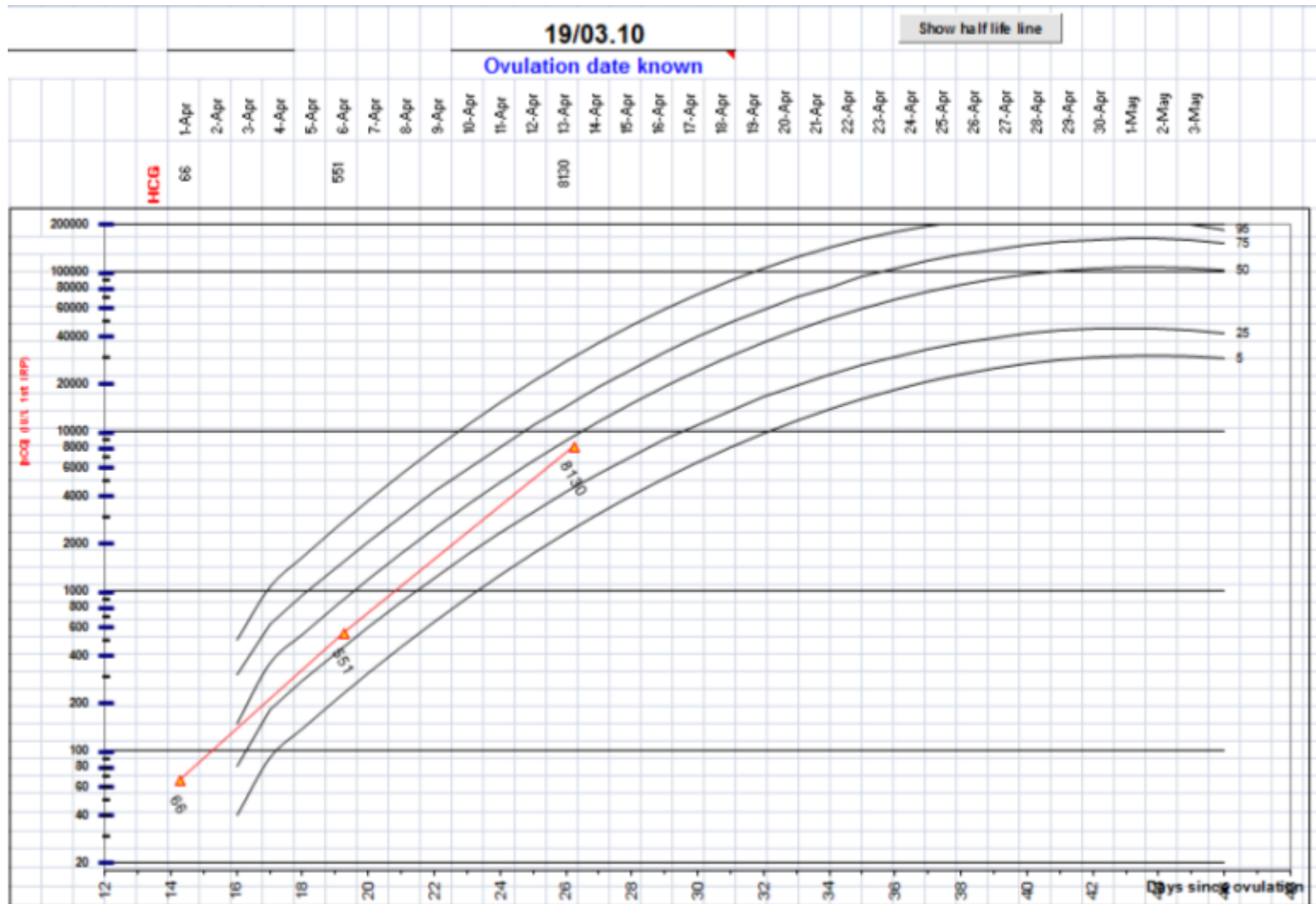


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Case study 3



Case study 3



Case history

6/12 trying

Age 35

Irregular cycles, 35-56 days

BMI 25

- What differential diagnosis?
- What tests to confirm?
- What treatment likely?

Case history

Age 32

3 miscarriages in 1st trimester

- What history matters?
- What tests?
- What treatment?

Case history

8/12 trying

Age 25

Regular cycles

- What history?
- What tests?
- What treatment?

Case history

9/12 trying

Age 39

Partner had vas reversal, normal semen analysis

Regular cycles

Previous pregnancy terminated in prior relationship

- What history?
- What tests?
- What treatment?



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Case study 1

AMH: 12.5

