

“ Womens Business ”
all you ever wanted to know about
female hormones.....
Case Studies

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Outline

- Fertility in younger women
 - Normal cycle (Ovulation tracking)
- Infertility
 - Abnormal cycle (PCOS, and more)



Infertility in women

- Defn: Failure to conceive after 1 yr unprotected intercourse
- Prevalence – 10 % (8-14%) of couples (NEJM 2002)
- Causes

Women	35%
Men	30%
Both	20%
Unknown	15%



Causes of infertility and frequency

- Sperm defects or dysfunction 30%
- Ovulation failure (oligo/amen) 25
- Tubal infection/patency 20
- Unexplained 25
- Endometriosis with scarring 5
- Coital failure or infrequency 5
- Cervical mucus defects/dysf 3
- Other – fibroids, uterine shape <1

History and examination

- **Periods –frequency, regularity**
- Age of patient, early menopause in family
- History of STD, PID
- Any drugs, severe illness, cytotoxics
- Prior pregnancies
- Weight, exercise, stress,
- Glucose tolerance, androgenisation, PCOS
- General physical exam
- ? **PCOS features – overweight, androgenisation**
- Look for underweight
- Thyroid disease
- Genital tract if appropriate



What is the first step?

Is the woman having regular periods or not?

- Regular periods – presume ovulating
- Irregular periods/
Oligo/amenorrhoea
– presume **not** ovulating

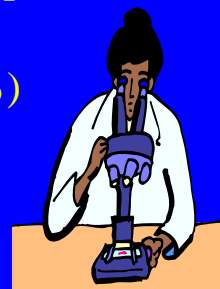


Early in investigation...

- Check “D 21 Prog” -> 20-30 nmol/L
- Tracking cycle

Exclude 2 major causes of infertility-

- Assessment of tubal patency (20%)
- Semen analysis (30%)

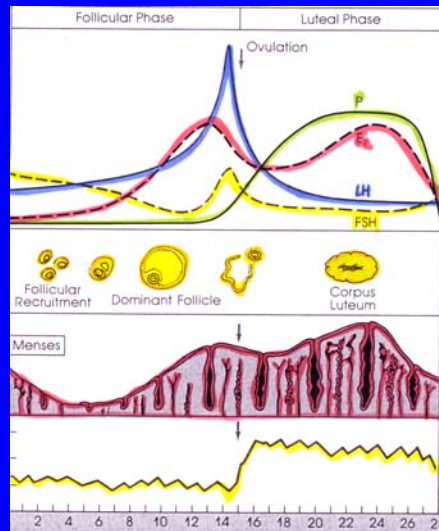


Ovarian reserve

- Day 2-3 FSH > 15 U/L - poor fertility
- AMH early reliable direct indicator of ovarian res.
- AMH - any day cycle
- Pre-antral follicles (< 8 mm) level reflects size of pool
- ↓ AMH with age and ↓↓ menopause
- ↑ with PCOS
- Day 3 Inhibin B - low levels -poor reserve



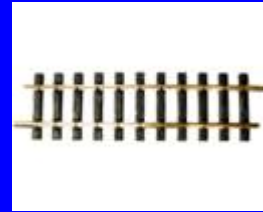
Normal cycle and hormone levels



Normal cycle biochemistry

	FSH	E2	LH	Prog
Day 7	2	430	6	2
Day 12	5	760	9	2
Day 13	7	1300	15	4
Day 14	8	1240	45	6
Day 21	4	220	3	45

How do you "Track" ?



- Regular menses
- Estimate length cycle - eg 28 days
- 1/2 way likely ovulation -eg Day 14
- Start Day 10 (earlier if short cycle)
- Request LH, E2, Prog
- Watch for E2 rise, > 400 Daily
- Watch for LH rise - doubling in a day

Time to try !!



OVULATION TRACKING (Serum) -Early Ovulation

Date	Day of Cycle	FSH U/L	LH U/L	E'diol pmol/L	Prog nmol/L
	8		6	760	
	9		10	1400	4
	10		56	910	
	11		14	220	8
	21				81

OVULATION TRACKING (Serum) Later Ovulation

Date	Day of Cycle	FSH U/L	LH U/L	E'diol pmol/L	Prog nmol/L
14/02/10	14	2	5	500	3
15/02/10	15		5	720	2
16/02/10	16		13	820	4
17/02/10	17		29	1200	
24/02/10	24				42

OVULATION TRACKING (Serum) Long pre-ov phase

Date	Day of Cycle	FSH U/L	LH U/L	E'diol pmol/L	Prog. nmol/L
23/02/10	10		6	110	2
25/02/10	12	5	5	150	2
27/02/10	14		5	160	2
02/03/10	16		6	700	1
03/03/10	17		6	690	2
04/03/10	18		7	1100	2
05/03/10	20	3	8	1300	2
06/03/10	21		17	1600	2
07/03/10	22	8	31	1000	6

OVULATION TRACKING (Serum) "PCOS"

Date	Day of Cycle	FSH U/L	LH U/L	E'diol pmol/L	Prog nmol/L
17/02/10	10	5	16	< 100	2
19/02/10	12	4	15	< 100	4
22/02/10	15	3	11	120	3
25/02/10	18	3	14	< 100	2
27/02/10	20		9	130	2
02/03/10	23		6	280	3
04/03/10	25		5	390	3
06/03/10	27		9	980	3
07/03/10	28	26	52	660	5

OVULATION TRACKING (Serum) 1 day warning...

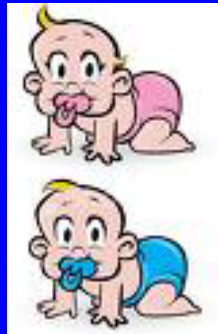
Date	Day of Cycle	FSH U/L	LH U/L	E'diol pmol/L	Prog. nmol/L
03/03/10	10	4	9	1200	4
04/03/10	11	10	40	1300	5
11/03/10	18	3	2	620	72

Irregular cycles/Amenorrhoea

Probable anovulation !

Commonest cause of 2^o amenorrhoea

- Pregnancy !!
- Do hCG



What to do ?



1. 2 sets Hormones, 2 weeks apart -
LH, FSH, E2, Prog – eg “D7 & D21”
2. Prolactin & TSH
3. Androgens – SHBG and testosterone
If testo is high-
DHEAS, Androstenedione, 17 hydroPrg

Causes of irregular abnormal periods / disrupted ovulation

Polycystic ovarian syndrome

Hypothalamic amenorrhoea – psychogenic, exercise, weight

Thyroid disease

Premature ovarian failure

Hyperprolactinaemia

Hypopituitarism

Late onset CAH

Cushings syndrome

Ovarian and adrenal tumours

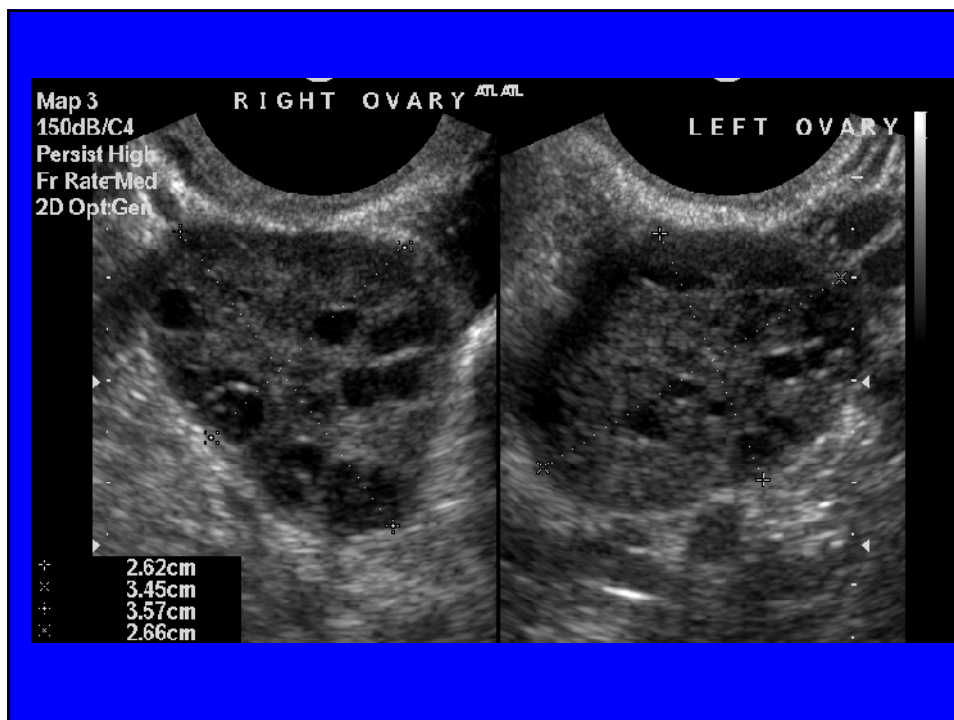
PCOS

- Polycystic Ovarian Syndrome
- Stein Leventhal Syndrome
- Ovarian Resistance Syndrome
- Metabolic syndrome



Rotterdam 2003 (any 2 of 3) and also Dx of exclusion

- Lack of cycling
Oligo/amenorrhoea &/or anovulation
History &/or 2 sets hormones 2 weeks apart
- Hyperandrogenism -
Clinical and/or biochemical
Free calc. Testo/DHEAS or androstenedione
- Polycystic ovaries (on Ultrasound)



28 y.o. mother of 2, failure to get pregnant and irregular periods

O/E Mild hirsutism, acne and overweight

Day "7"

FSH 4 LH 14 E2 180 Pg 3



Normal cycle biochemistry

	FSH	E2	LH	Prog
Day 7	2	430	6	2
Day 12	5	760	9	2
Day 13	7	1300	15	4
Day 14	8	1240	45	6
Day 21	4	220	3	45

28 y.o. mother of 2, -repeat bloods

O/E Mild hirsutism, acne and overweight

Day "7"

FSH 4 LH 14 E2 180 Pg 3

Day "21"

FSH 6 LH 18 E2 220 Pg 2

History and lack of cycling –
Suspicious of PCOS ? What other Ix's



Testosterone	3.8 nmol/L ↑	(0.7-2.5)
SHBG	19 nmol/L ↓	(30-90)
Calc free testosterone	90 ↑	(9-32)
Prolactin	N	
TFT's	N	
Androstenedione	mildly ↑	
DHEAS	mildly ↑	
17OH Prog	N	
24 hour UFC	N	

“Metabolic” Parameters

Fasting BSL **6.1 mmol/L** ↑ (< 5.5 mmol/L)
Insulin **26 mU/L** ↑ (< 10 mU/L)

Consider OGTT

Lipids

Chol **8.0** Tg **3.6**
HDL **1.3** LDL **5.1** (<3.4)



Ovarian U/S

“PCOS” Case 2

22 y.o. irregular menses, increased weight.

HORMONES (Serum)

FSH.....: 6 U/L
LH.....: 21 U/L
Oestradiol.....: 140 pmol/L
Progesterone.....: 3 nmol/L
Prolactin.....: 160 mU/L (< 500)

- TSH 2.5 mU/L
- T4 16 pmol/L

Repeat Bloods...

HORMONE VALIDATION

Date	Lab No	FSH	LH	E2	PROG
24/02/10		6	21	190	2
10/03/10		6	23	140	3
Prolactin	160				

Pattern is suggestive of PCO.

Persistent elevation of LH to FSH ratio with low oestradiol and associated menstrual disturbance suggestive of polycystic ovarian

Androgen Profile



Testosterone 1.9 nmol/L (< 1.8) ↑
SHBG 25 nmol/L (30-90) ↓
Calculated free testosterone ↑

Mild increase in testo and calc. testo is common in PCOS

* Androstenedione : 18.7 nmol/L (1.6 - 12.0) *

* DHEA Sulphate : 10.8 umol/L (2.7 - 9.2) *

Mild increase in testosterone with low SHBG may occur in PCOS.
Mildly increased DHEAS and Androstenedione may occur in PCOS.

Unusual causes of amenorrhoea

- 30 year old woman- 2 children, irregular menses- amenorrhoea
- History “ ? PCOS”



FSH 7	LH 5	E2 120	Prog 5
Testo 4.6	↑↑	(0.5-2.6)	
SHBG 17		(30-90)	
Free calc testo 116		(9-32)	

Marked increase in calc. Free testosterone

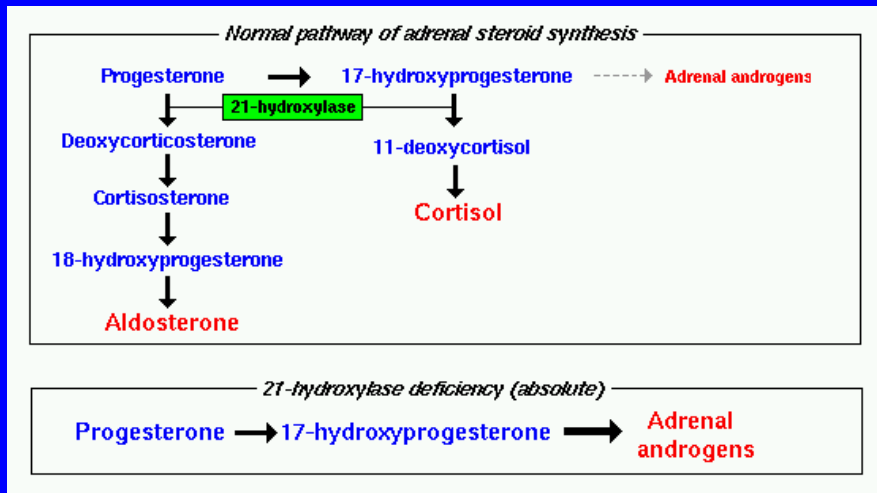
“Check DHEAS, androstenedione, 17 OH Prog and screen for Cushings”



- Repeat testosterone 6 nmol/L (Confirm LCMS)
- Androstenedione ↑ 15.7 (1.6-12 nmol/L)
- DHEAS ↑ 8.3 (1.2-7.3 umol/L)
- 17 OH Prog ↑↑ 18.2 (< 6 follicular.)
- Cortisol 229 nmol/L (11 am.)

(AM. ref range 150-600)

Late onset CAH



Synacthen stimulation test

Basal cortisol	294	17 Oh Prog	18.3
30 min	281		20.9
60 min	457		210.0

- Cortisol should exceed 550 nmol/L during Synacthen to exclude adrenal insufficiency
- 17 Oh Prog > 60 consistent with late onset CAH

Late onset CAH (non classic)



- 90 % CAH is 21 OH defic (AR)
- Can have children / present late
- Generally **not** salt wasting (Aldo normal)
- Partial defect of 21 OH enzyme -low cortisol, XS drive for androgens
- Genetic tests- can detect some mutations
- Rx - Steroid !! Testosterone ↓

Other common hormone patterns...

Worth knowing....



Hormones on the OCP



- FSH < 1 LH < 1 E2 < 100 Prog 2
- Testo < 0.3 and SHBG 140 nmol/L
- Ethinyl Oestradiol and Medroxyprogesterone acetate - high dose
- Not measured in assays
- Negative feedback suppresses FSH, LH
- Also - high SHBG and low testo

Young woman, med student, 3 periods in the last year, very slim, feels very stressed...runs daily....

No hormone therapy

Day -? (random)



FSH 5 LH 3 E2 260 Prog 1

FSH 5 LH 3 E2 263 Prog 1

Day -14 days later

FSH 4 LH 3 E2 200 Prog 1

TSH 2.1 U/L T4 14 pmol/L

Prolactin 300 Testosterone 1.2 nmol/L

No evidence of cycling, no evidence of
hypothalamic GnRH drive



“Functional” hypothalamic anovulation

- *Dx by excluding Pathologic causes*
- 15% of secondary amenorrhoea
- 3 periods missed in previous year OR absence of menses for 6 months = amenorrhoea
- May have oligo or amenorrhoea
- “Female athlete triad” – eating disorder, amenorrhoea and osteoporosis
- Check hCG, Prol, TFT, Hormones



Causes of functional hypothalamic anovulation

- Underweight (BMI <19) and ↓ body fat
- Excessive dieting, nutritional imbalance
- Excessive exercise
- Psychiatric or physical illness stress
- May take time for cycling to resume once precipitants are corrected

EXCLUDE

Pregnancy !!

Hyperprolactinaemia

Hypothyroidism

Excessive androgens – eg tumour

Hypothalamic Amenorrhoea

Date	FSH	LH	E2	PROG	PRL
16/01/08	2	2	< 100	2	
31/01/08	3	4	< 100	2	420

- TFT's - Normal
- Normal Prolactin noted. No evidence of cycling so far with low levels of FSH, LH and E2 persisting. If contraceptive therapy is excluded, this pattern may occur in functional (Hypothalamic) amenorrhoea.
- Patients may have very low BMI, or history of excess stress, chronic illness or excess dieting/exercise. Hypothalamic amenorrhoea may take some months to resolve even if precipitating causes are removed.

Further results

- **ACTH** 09:10 (Reference Range < 10 pmol/L)
2.5 pmol/L
- **Cortisol** 09:10
596 nmol/L (150-600 nmol/L)

Normal AM. cortisol level and normal ACTH noted.

ANDROGENS (Serum)			
Testosterone	SHBG	Free Testo.	FAI
(0.5 - 2.6)	(30 - 90)	(9 - 32)	
nmol/L	nmol/L	pmol/L	
0.7	72	7	1.0

“Routine check of hormones”

? Day - 35 yo woman

FSH < 1 U/L Estradiol < 100 pmol/L

? What does this mean

“Suppressed FSH and E2 may occur in women on the OCP, however if this is not the case, suggest repeat in 2 weeks together with TSH, T4 and Prolactin level”

Day ?

“Not on OCP – suppressed hormones- repeat suggested with Prolactin”

14 Days later

FSH < 1 U/L Estradiol < 100 pmol/L

LH < 1 U/L Prog 2 nmol/L

Prolactin to follow.....

Prolactin level.....

Prolactin 19,000 !!!!

Pituitary macroadenoma

? Hypopituitarism and ↑Prolactin

Check other pituitary hormones – Cortisol, T4 and TSH, Gr Hormone, ACTH, Electrolytes



22 year old woman,

- History of secondary amenorrhoea
- FSH 92 E2 <100
- Repeat and confirm



Premature ovarian failure (POF)

Current therapeutics, 2002

- Ovarian failure < 40 yrs
- FSH > 40 2x -a month apart
- Permanent or Temporary
- Common - 1 in 100 women
- Usually no signs/symptoms prior
- POF occurs often in families
- 5-10% pregnancy rate
- HRT important for symptoms, CVS, Bones



22 year old woman, FSH 92 and E2 <100

- Secondary amenorrhoea
- ? Premature ovarian failure -perm/temp.
- Confirm diagnosis with repeat in 1-2 months time

Idiopathic - majority of causes

Genetic – Karyotype – Turners

Premutations Fragile X – FMR-1 gene, 55-200 CGG

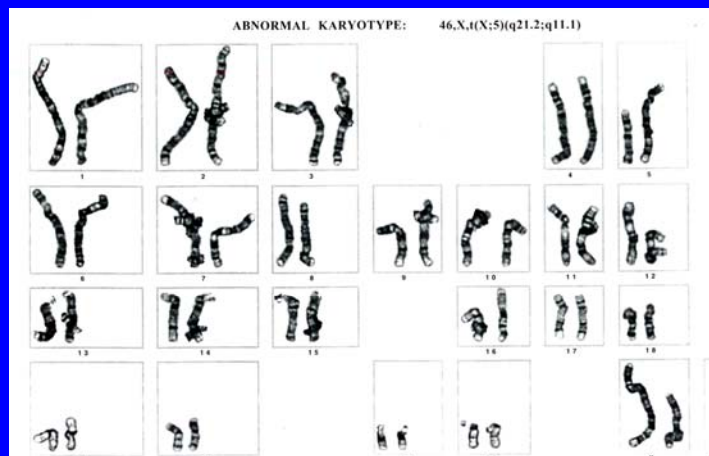
Autoimmune –adrenal AB's, TFT, thyroid AB's,
+/- Ovarian AB - Polyglandular I/II

Iatrogenic – chemo, radiation, surgery

Toxins - ? Mumps, cigg smoke, chemo

22 year old woman, FSH 92 and E2 <100

Mosaic Karyotype



25 y.o woman

↓ LH / FSH

Hx – Amenorrhoea, unwell,
Not on OCP



FSH < 1 LH < 1

Prolactin 850 U/L ↑ (<550)

Testosterone 4.5 nmol/L ↑ (0.7-2.5)

Suppressed LH and FSH

Hx – Amenorrhoea, unwell

FSH < 1 LH < 1

Prolactin 850 U/L (<550)

Testosterone 4.5 nmol/L (0.7-2.5)

SHBG 180 nmol/L (30-90)

Estradiol 2,300 pmol/L

Progesterone 130 nmol/L



Final Diagnosis ...

hCG 6,000 U/L

PREGNANT!!



Thank you !!



