Anovulation

Stephen Franks

Institute of Reproductive & Developmental Biology,
Imperial College, Hammersmith Hospital, London
W12 0NN

and St Mary's Hospital, London W2 1PG

Imperial College London

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Anovulation: learning objectives

- To understand the importance of anovulation as a cause of infertility
- To learn the common causes of anovulation and what tests are required to make a diagnosis
- To be able to discuss the approach to restoration of fertility in anovulatory women - especially those with hypothalamic amenorrhoea

Suggested reading

- Balen A. Anovulatory infertility and ovulation induction. Policy and Practice subcommittee of the British Fertility Society.*Hum Reprod* 1997 12(11 Suppl) 83-7.
- Franks S. assessment and management of anovulatory infertility in polycystic ovary syndrome. *Endocrinol Metab Clin N Am* 2003 32 639-51
- Messinis I. Ovulation induction: a mini-review *Hum Reprod* 2005 20 2688-97

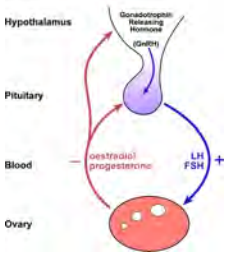
Anovulation is a common cause of infertility

- Disorders of ovulation account for about 25% of causes of infertility
- Most are due to abnormal endocrine environment
- Most are treatable

Presentation of anovulatory infertility

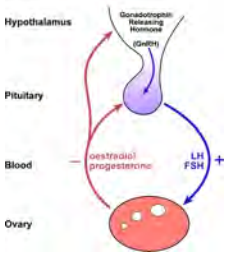
- Amenorrhoea (primary or secondary)
- Oligomenorrhoea (cycle >42 days)
- Irregular menses (eg cycles varying between 2 and 6 weeks in duration)

Causes of anovulation



- Primary ovarian failure (8%)
- Deficiency or disordered regulation of gonadotrophins (32%)
- Polycystic ovary syndrome (55%)
- Miscellaneous (5%)

Investigation of anovulation



- High FSH, low E2 = **primary ovarian failure**
- Normal/low FSH, low E2 = **hypothalamic/pituitary disorder**
  - Measure prolactin
- Normal FSH, normal E2 (± high LH) = **PCOS**

Induction of ovulation

- Antioestrogens (clomiphene) (PCOS)
- Pulsatile GnRH (hypothalamic amenorrhoea)
- Dopamine agonists (hyperprolactinaemia)
- Gonadotrophins (hypothalamic/pituitary causes; PCOS)

Induction of ovulation and superovulation

- Aim of ***induction of ovulation*** is to restore physiological (single follicle) ovulation in anovulatory women
- Aim of ***superovulation*** is to override physiology and stimulate multiple follicle development for IVF

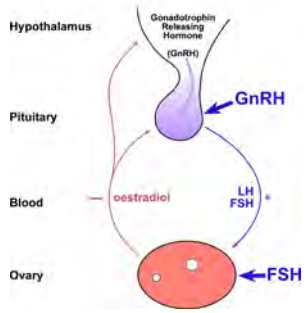
Complications of multiple follicle development in induction of ovulation and superovulation

- Mutiple pregnancy (twins bad; triplet or higher order, disastrous)
- Ovarian hyperstimulation syndrome (OHSS)

Hypothalamic amenorrhoea

- **Treat underlying cause**
  - eg weight loss-related, hyperprolactinaemia
- **Induce ovulation with GnRH**

Induction of ovulation: disordered hypothalamic regulation of gonadotrophins



Case 1

Mrs JK aged 19

- Primary amenorrhoea
- Investigated aged 17: low FSH & LH; laparoscopy: small uterus and “no ovaries”
- Told that uterus too small to be able to have children

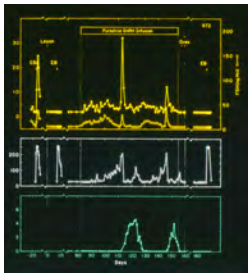
Investigations at St Mary's

- LH 0.6 u/l; FSH 1.8 u/l
- Prolactin 120 mu/l
- Oestradiol <70 pmol/l
- Ultrasound: small uterus and ovaries
- No evidence of other endocrine abnormalities

Diagnosis

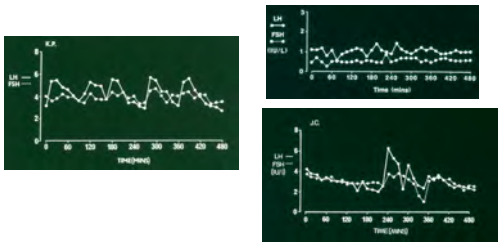
- Isolated gonadotrophin therapy
- Probable hypothalamic deficiency of GnRH

Pulsatile GnRH restores cyclicity to GnRH-deficient Rhesus monkey

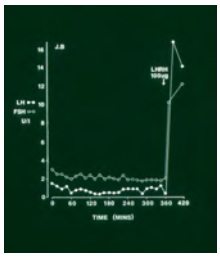


Knobil E, On the control of gonadotropin secretion in the Rhesus monkey *Recent Prog Horm Res*. 1974;30(0):1-46.

Abnormal LH pulses in hypothalamic amenorrhoea

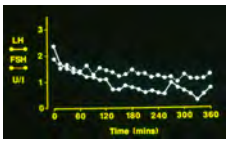


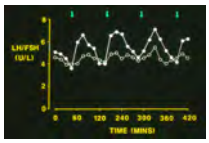
Hypothalamic amenorrhoea: response to a GnRH challenge test

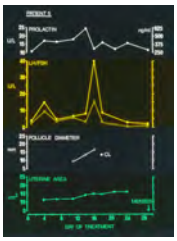


Portable pulsatile infusion pumps

Restoring normal ovulation by pulsatile infusion of GnRH







Mrs JK: management

- Pulsatile GnRH started
- Ovarian follicles visible on ultrasound within 14 days
- Steady enlargement of uterus
- Ovulation confirmed within 6 weeks of starting treatment
- Pregnant after first ovulation
- Uneventful pregnancy and labour and normal baby!

Hypothalamic amenorrhoea

- Most common cause is weight-loss
- May be due to isolated deficiency of GnRH
  - Idiopathic
  - Kallmann's syndrome
- Pulsatile GnRH therapy results in single follicle ovulation and restores fertility

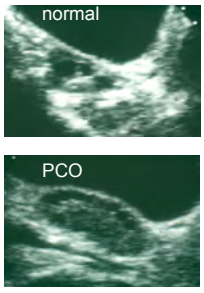
Results of pulsatile GnRH treatment

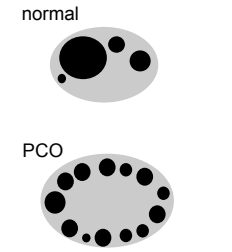
(Homburg et al, *Br Med J* 1989, 289: 809-812)

Cases	146 (118 patients)
Cycles	434
Ovulatory cycles	304 (70%)
Pregnancies	100 (68%)

Conception rate (@6 months) 93%

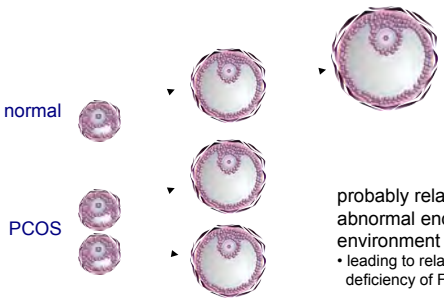
Polycystic ovary syndrome





more follicles, more stroma

Arrested antral follicle development in PCOS

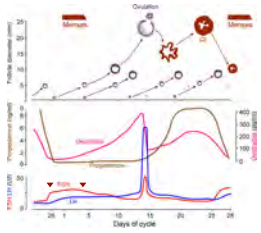


probably related to abnormal endocrine environment

- leading to relative deficiency of FSH

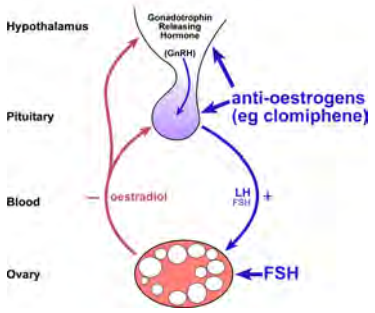
FSH concentrations are inappropriately low in anovPCOS

- Oestradiol and progesterone concentrations higher in anovPCOS than in early follicular phase
- Results in suppression of FSH and arrest of follicle maturation (Chavez-Ross *et al, J Math Biol*, 1997 36 95-118)

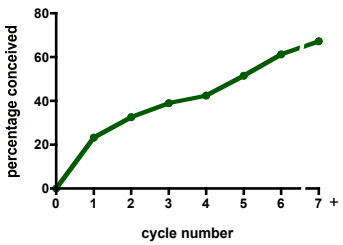


From Baird, 1983

Induction of ovulation: polycystic ovary syndrome

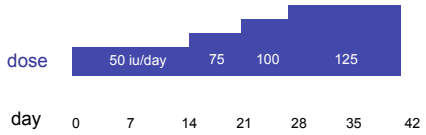


Cumulative conception rate following clomiphene



Kousta, White & Franks, *Hum Reprod Update* 1997 3 359-65

Low-dose, step-up FSH regimen



White *et al, J Clin Endocrinol Metab* 1996 **81** 3821

Patient population

- 199 women with PCOS
- Age 30.3y (20-42); BMI 24.2 (18-45)
- Chronic anovulation; oestrogen-replete amenorrhoea or oligomenorrhoea
- No ovulation after clomiphene or no pregnancy after ≥6 ovulatory cycles

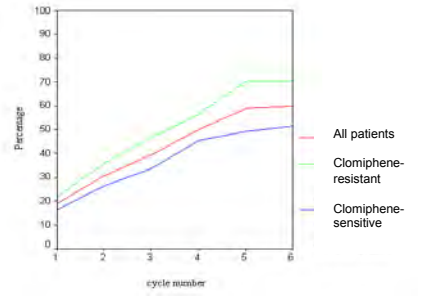
Gorry, White & Franks, *Endocrine* 2006 **30** 27-33

Outcome of treatment with low-dose FSH in 199 women

Cycles	916	
Ovulatory cycles	657	(72%)
Uniovulatory cycles	562	(86%)
Pregnancies	91	(46%)
Miscarriages	21	(23%)
Multiples (all twin)	3	(3%)

mild “OHSS” in 4% of cycles

Cumulative conception rate after low-dose FSH



Factors affecting outcome of treatment

- Endocrine profile:
  - Pre-treatment LH ≥11 iu/l or testosterone ≥3 nmol/l associated with higher "threshold" dose of FSH ($p<0.05$*) but no effect ovulation or pregnancy rate
- BMI:
  - BMI ≥25 associated with higher "threshold" dose of FSH ($p<0.05$*) *and* reduced ovulation and pregnancy rate ($p\leq0.05$**)

*t-test or **logistic regression

Metformin in treatment of PCOS

- Small number of small RCTs
- Significant but modest increase in ovulation rate (23% vs 13% n=92; Fleming *et al, J Clin Endocrinol Metab* 2002, 87 569-74)
- *No* effect independent of weight loss (n=143; Tang *et al, Hum Reprod* 2006 21 80–89,)
- Efficacy and indications for treatment unclear
- Large RCTs needed: ***then along came Moll and Legro!***

Metformin and clomiphene in treatment of PCOS: RCTs

Moll et al	*clomiphene + metformin (111)*	*clomiphene + placebo (114)*
Ovulation rate (%)	64	72
Conception rate (%)	40	46

Legro et al	*clomiphene + metformin (209)*	*clomiphene + placebo (209)*	*metformin + placebo (208)*
Conception rate (%)	38.3	29.7	12.0
Live birth rate (%)	26.8	22.5	7.2

Moll *et al, BMJ* 2006, **332** 1485-8
Legro *et al, New Engl J Med* 2007 **356** 551-66

Anovulation: summary

- Anovulation - common and usually treatable cause of infertility
- Small number of diagnostic tests guide choice of treatment
- Aim is induce single follicle ovulation
- Pulsatile GnRH is the most appropriate treatment for hypothalamic amenorrhoea
- PCOS very common, cause is uncertain but increasing FSH can restore ovulation