

Hormones and fertility

Stephen Franks

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

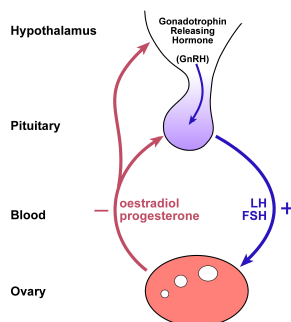
Imperial College
London

TSN Master Class, Norwich
July 12 2011

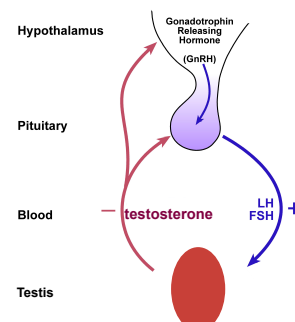
Reproductive hormones

- Pituitary hormones
 - stimulate ovaries and testes to produce germ cell development
 - stimulate the (mainly steroid) hormones from ovaries (or testes) that control
 - normal sexual development of the fetus and infant
 - the onset of puberty
 - production of hormones in the adult that affect reproductive capacity, sexual desire, general wellbeing

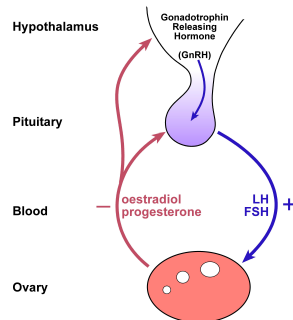
The hypothalamic-pituitary-ovarian axis



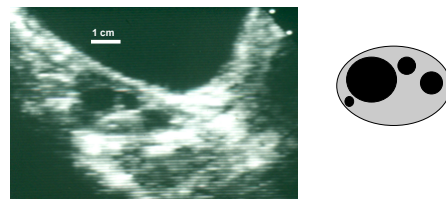
The hypothalamic-pituitary-testicular axis



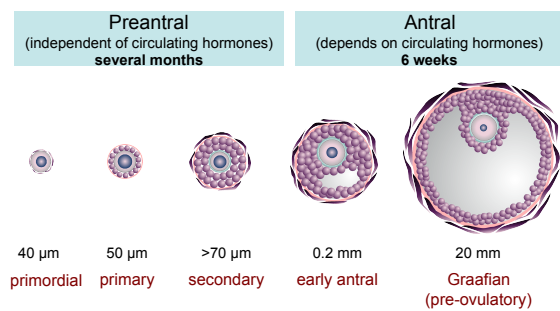
The hypothalamic-pituitary-ovarian axis



The ovary as seen by ultrasound



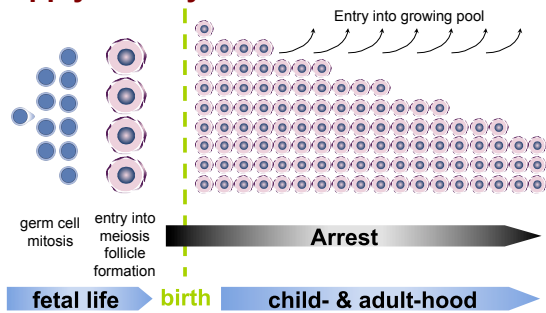
Human egg and follicle development



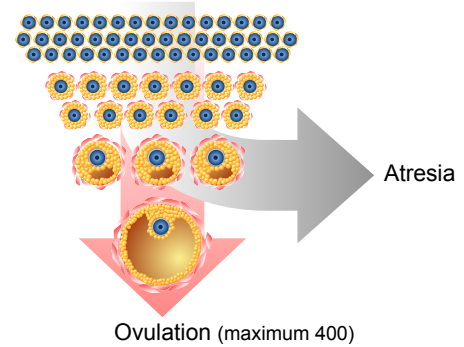
Eggs and follicles



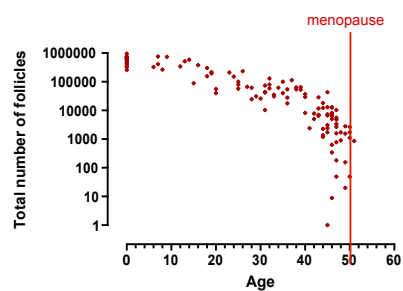
Females born with lifetime's supply of oocytes



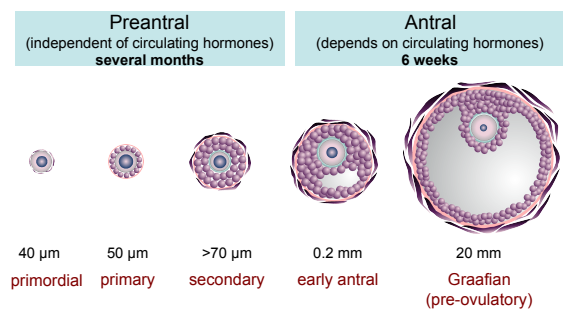
Fate of oocytes

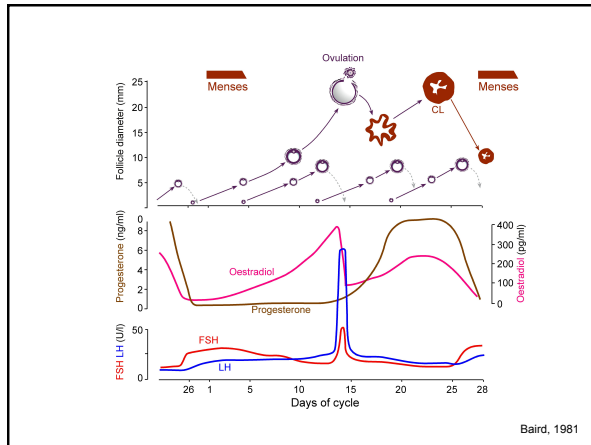


Declining number of oocytes



Human egg and follicle development





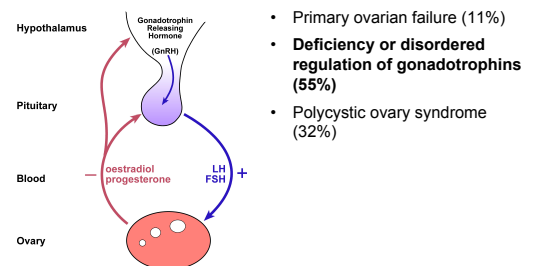
Infertility

- Involuntary infertility affects 1 in 6 couples
- Commonest causes are:
 - Infrequent or absent ovulation (25-30%)
 - endocrine causes very common
 - Abnormal, insufficient or absent sperm (25%)
 - endocrine causes rare
 - Blocked Fallopian tubes (25%)
 - Unexplained (20-25%)

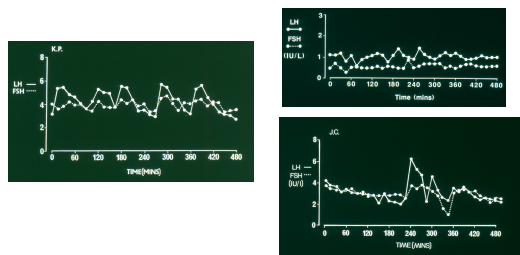
Infertility

- Involuntary infertility affects 1 in 6 couples
- Commonest causes are:
 - Infrequent or absent ovulation (25-30%)
 - endocrine causes common
 - Abnormal, insufficient or absent sperm (25%)
 - Blocked Fallopian tubes (25%)
 - Unexplained (20-25%)

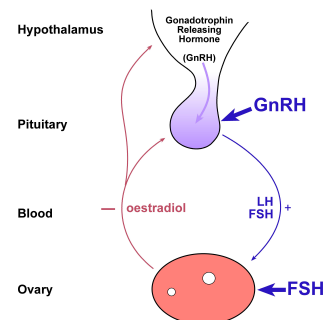
Hormone deficiency can cause lack of periods and infertility



Abnormal LH “pulses” in hypothalamic amenorrhoea



Replacing GnRH can restore fertility



Case report

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

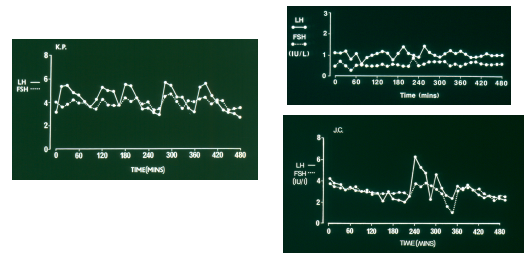
Investigations at St Mary's

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

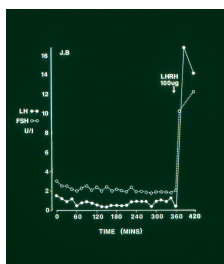
Diagnosis

- Isolated gonadotrophin therapy
- Probable hypothalamic deficiency of GnRH

Abnormal LH pulses in hypothalamic amenorrhoea



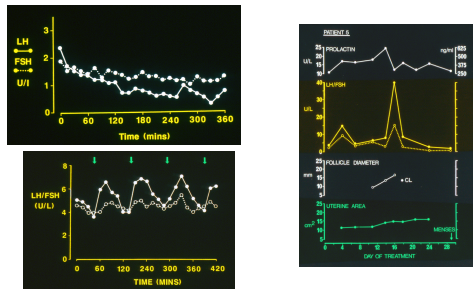
Hypothalamic amenorrhoea: response to a GnRH challenge test



Portable pulsatile infusion pumps



Restoring normal ovulation by pulsatile infusion of GnRH



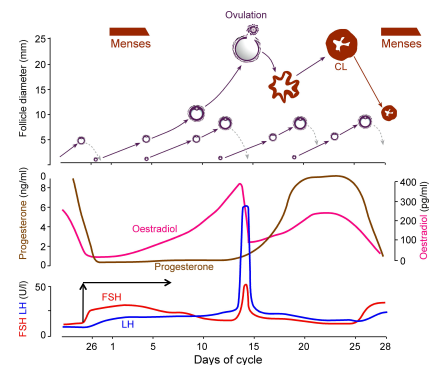
Mrs JK: management

- 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

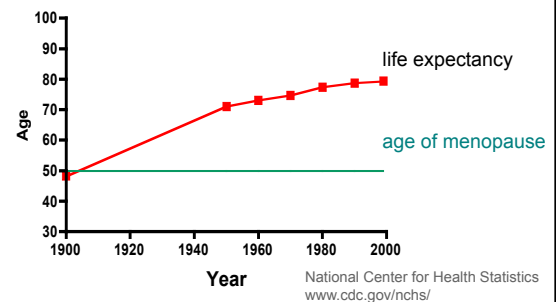
Superovulation for IVF - overriding physiology



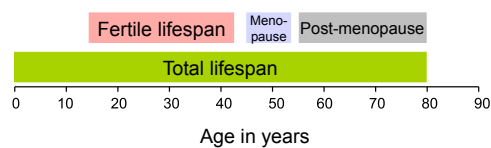
Baird, 1981

**The menopause and
premature menopause:**
Running out of eggs

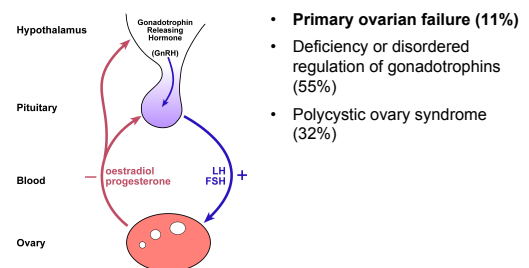
Life expectancy is increasing



Female lifespan 2009



Hormone deficiency can cause lack of periods and infertility



Can we delay the onset of the
menopause?

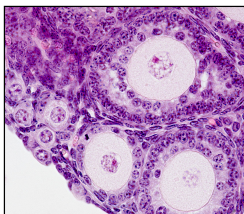
**What controls the “recruitment” of
follicles from the resting to the
growing phase?**

- The answer to that question is the key to understanding premature menopause and other ovarian disorders



Prof Kate Hardy

**We need to understand how the cells
change as eggs and follicles start to grow**



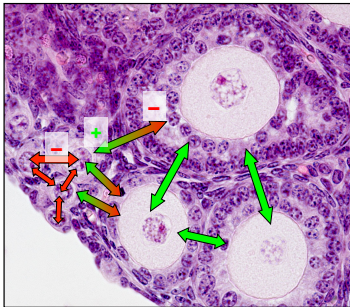
Oocytes get bigger

Granulosa cells change shape,
form lots of layers,
and start dividing

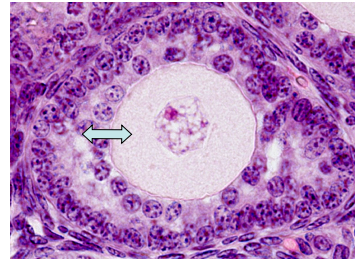
Follicles signal to each other



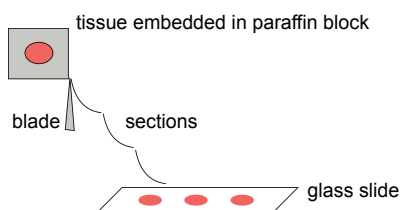
Follicles signal to each other



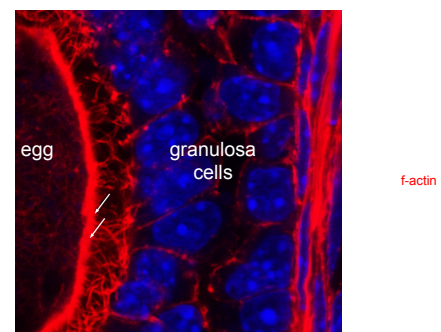
The egg signals to the granulosa cells, and vice versa



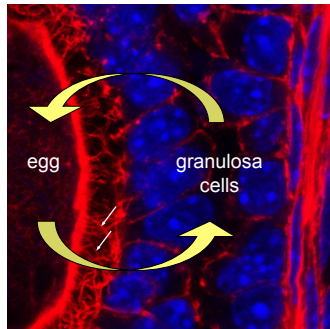
Where are the interesting molecules?



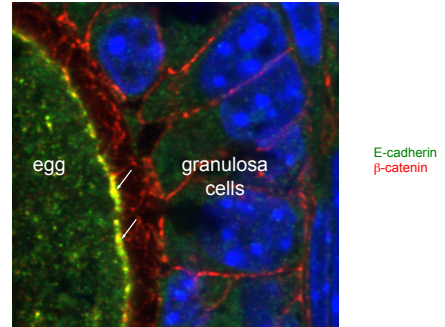
Oocyte and somatic (granulosa) cells communicate directly via tiny trans-zonal processes



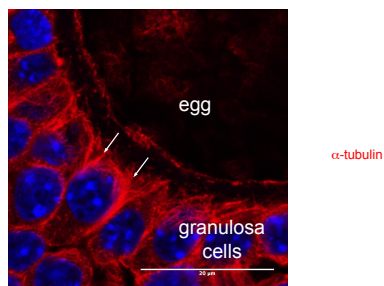
Communication via diffusing proteins



Cells adhere to each other via specific proteins

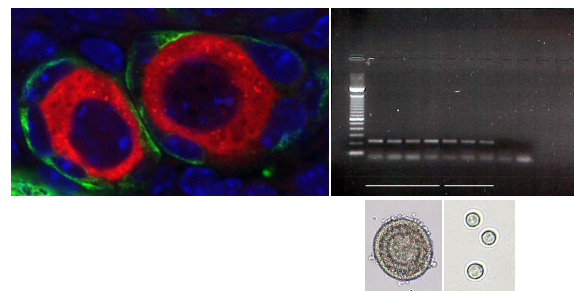


Cells have a skeleton! (a cytoskeleton)

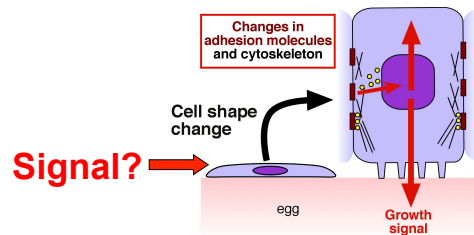


Where.....?

How much.....?



How do cells change shape? What are the signals?



Hormones and fertility

- Hormones control
 - the onset of puberty
 - production of sperm and eggs
 - the ovulation/menstrual cycle
- Hormone disorders are a common cause of infertility in women
- Most hormone disorders of fertility can be treated successfully
- Premature menopause cannot yet be treated
 - We need to know more about the signals that lead follicles to start growing