

# What's new in PCOS?

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Excellence in fertility care

# Key Learning Objectives

- Understand how to diagnose PCOS
- Understand the National Evidence-based guideline for the assessment and management of polycystic ovary syndrome. Jean Hailes Foundation for Women's Health on behalf of the PCOS Australian Alliance
- Understand the modern management of different symptoms related to PCOS
- Be able to manage the long-term safety of women with PCOS



# PCOS: Diagnostic Criteria

Rotterdam

Rotterdam diagnostic criteria requires two of:

1. Oligo- or anovulation;
2. Clinical and/or biochemical signs of hyperandrogenism;
3. Polycystic ovaries;

**and** exclusion of other aetiologies such as hypothyroidism, hypoprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome (14).

NIH

NIH diagnostic criteria requires:

1. Oligo- or anovulation; and
  2. Clinical and/or biochemical signs of hyperandrogenism;
- and** exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome (15).

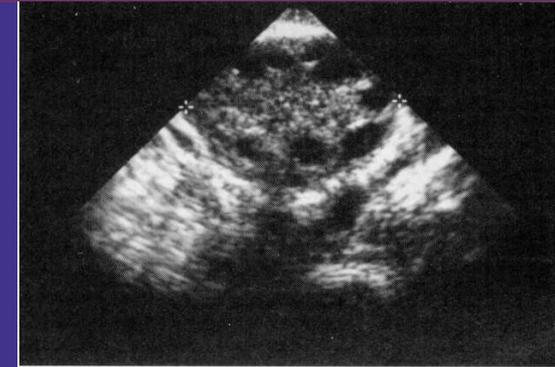
# What does this mean in practice

- Polycystic ovaries very common on ultrasound
- The syndrome, and all its consequences, only present when there is clinical evidence of either anovulation or androgen excess
- Polycystic ovaries on their own are NOT bad news

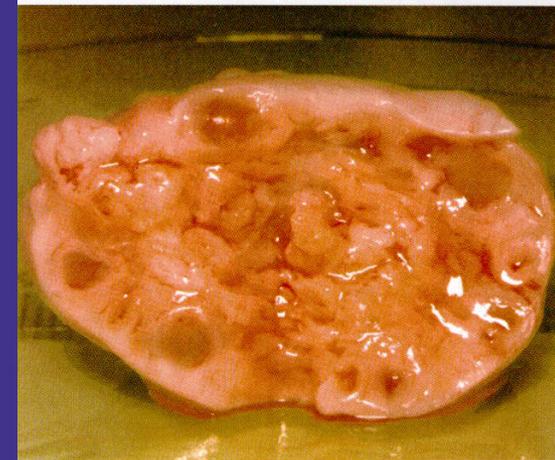


# Diagnosis: PCO on ultrasound

- At least 1 ovary with 12+ follicles 2-9mm &/or ovarian volume > 10mls
- NB: US picture on 1 occasion suffices for diagnosis

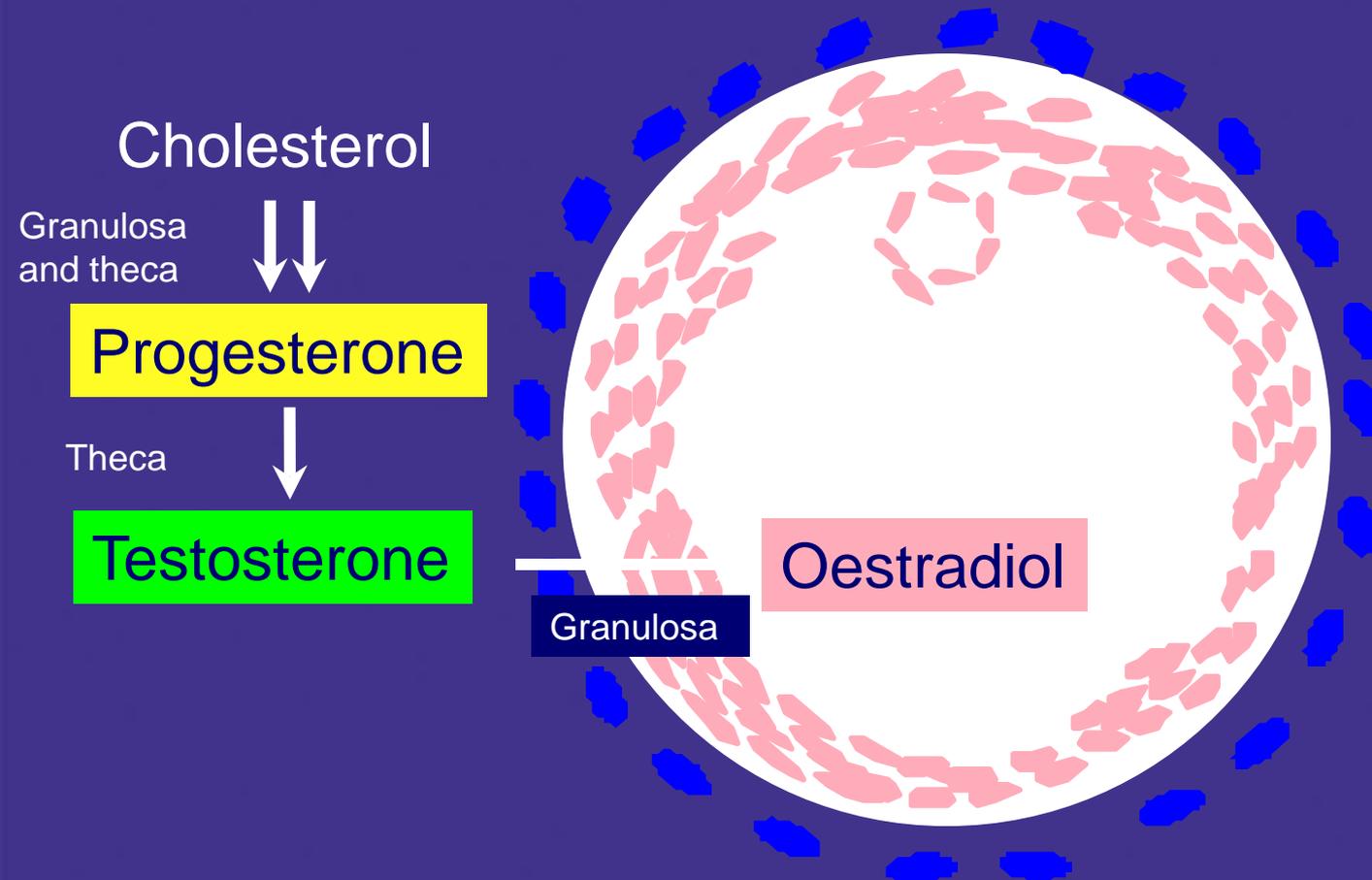


A

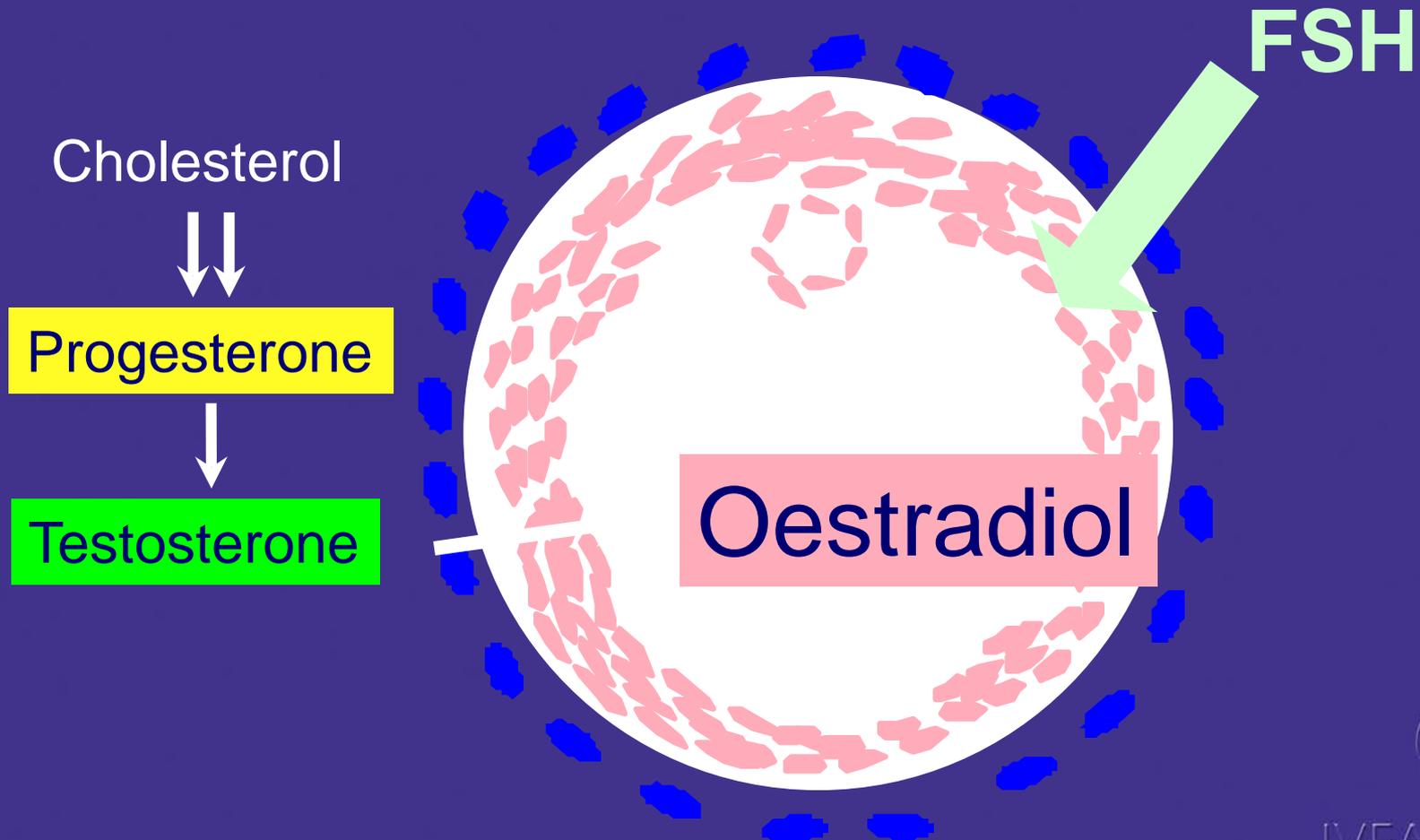


B

# Ovarian follicle development

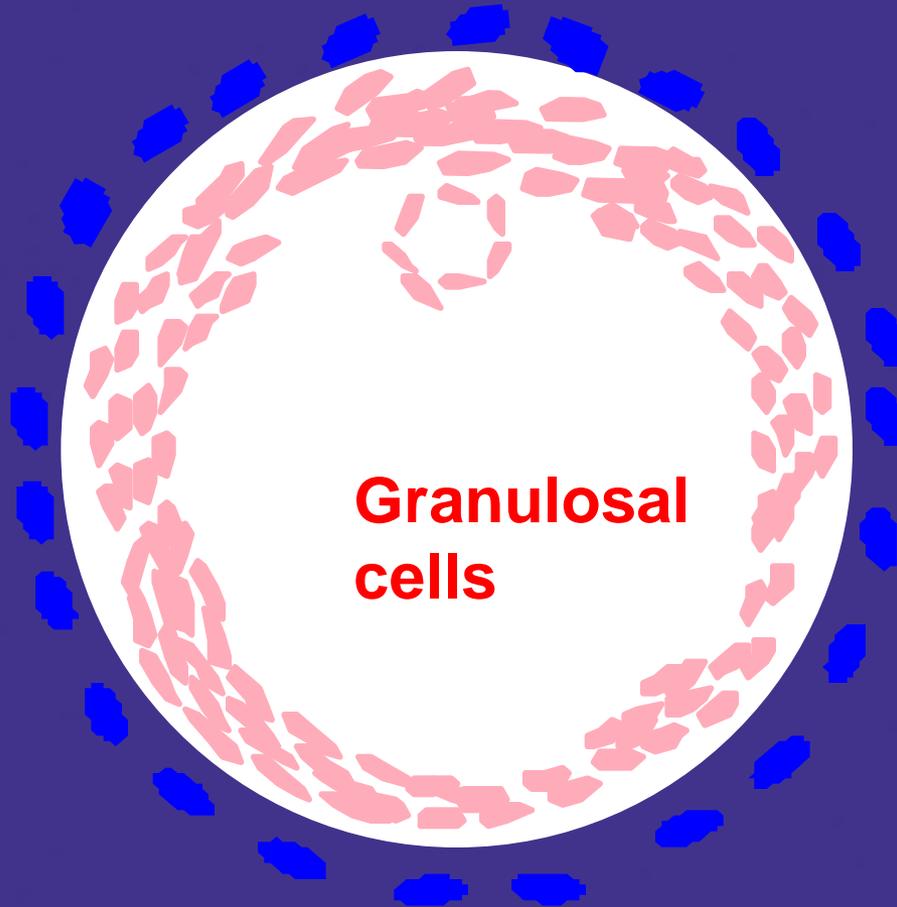


# Ovarian follicle selection



# The follicle in PCOS

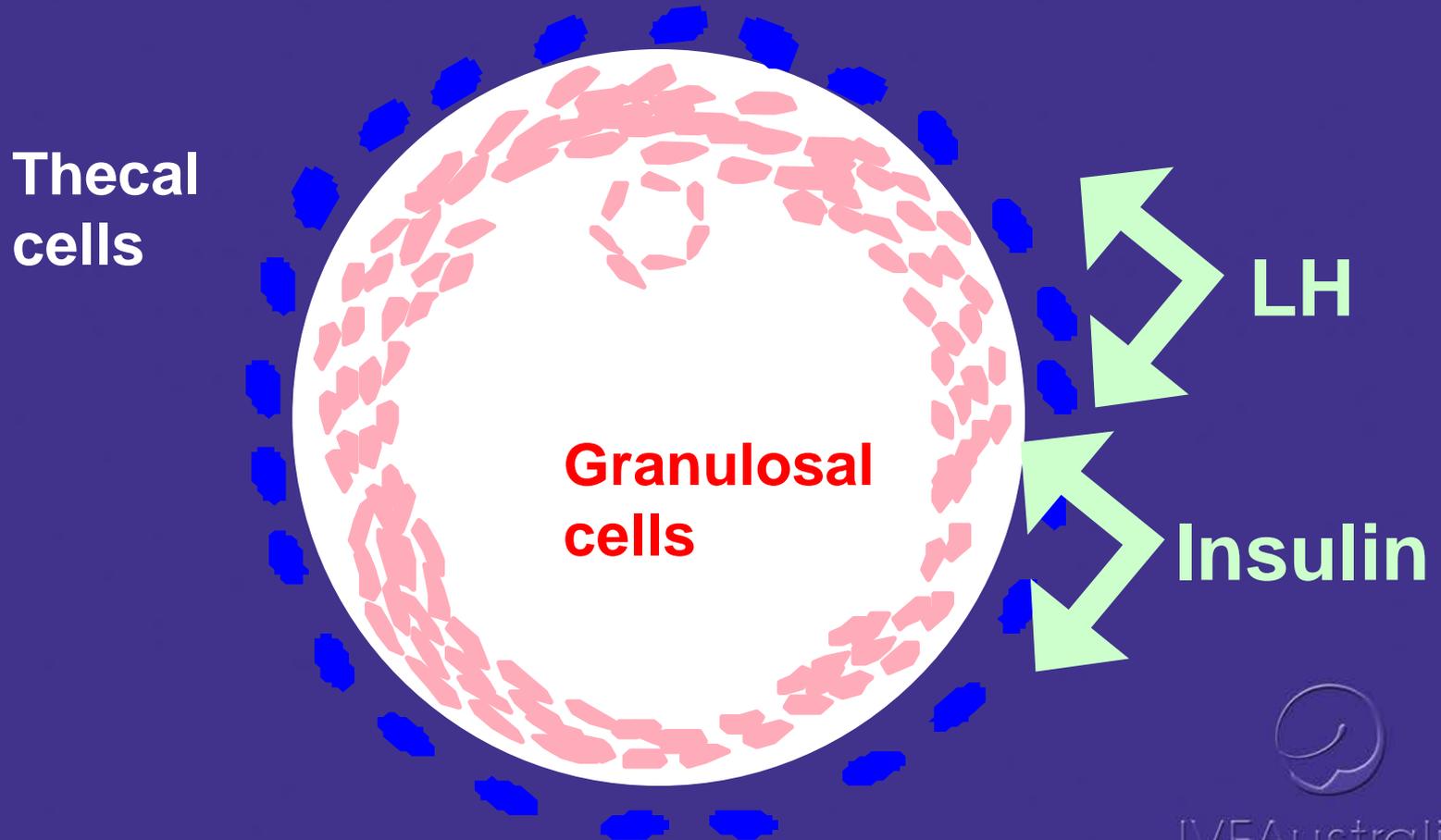
Thecal  
cells



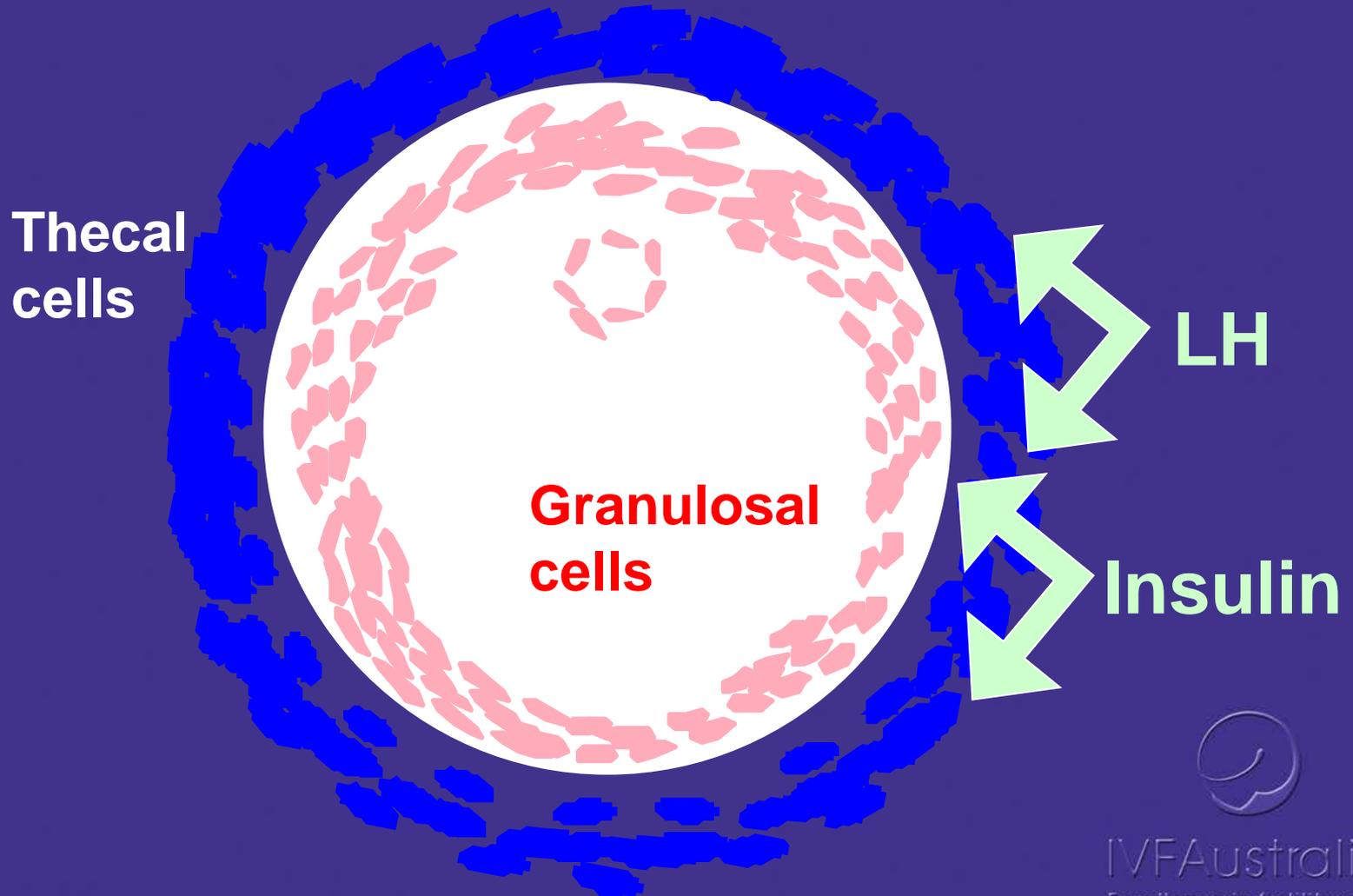
Granulosa  
cells



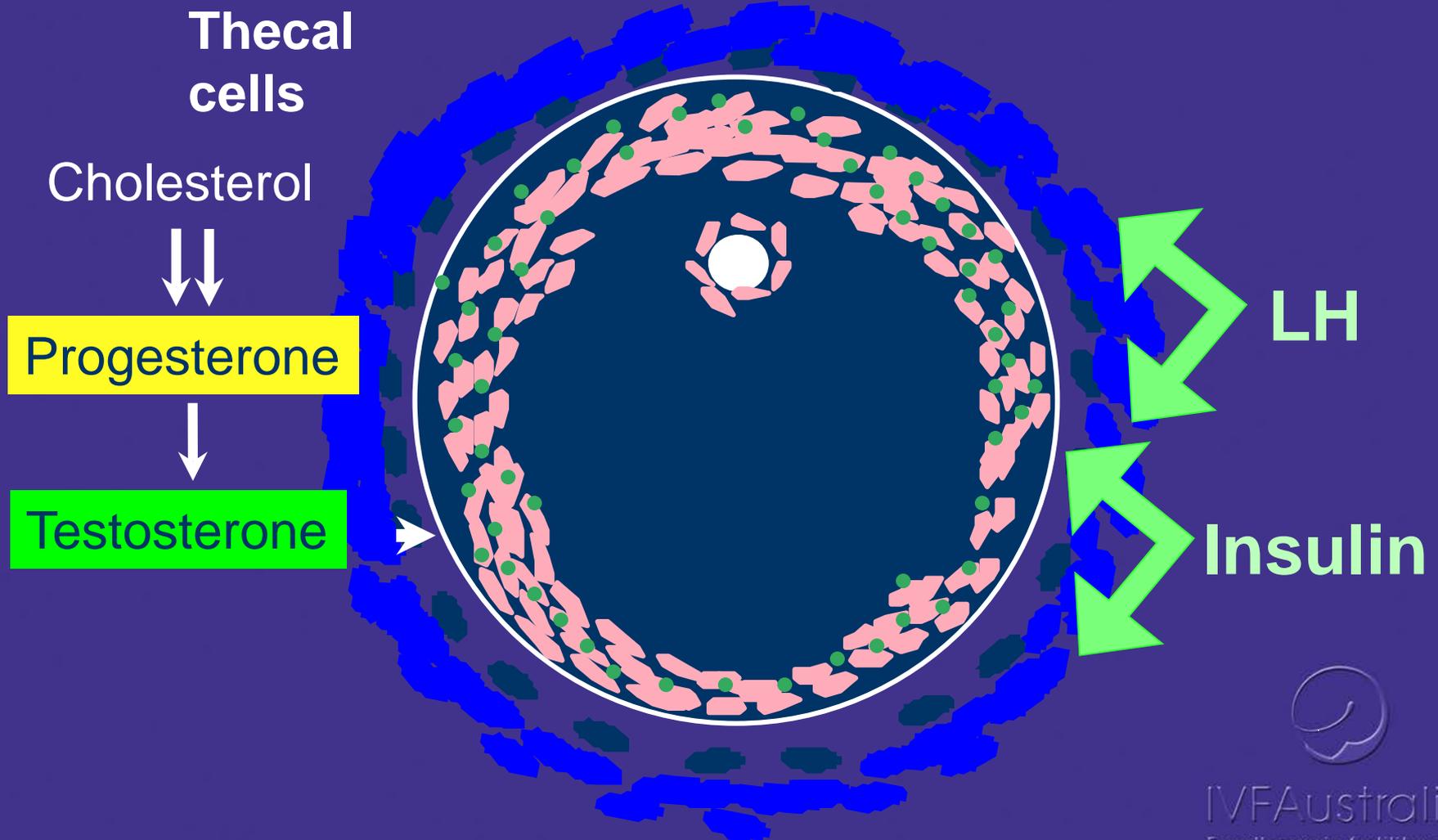
# The follicle in PCOS



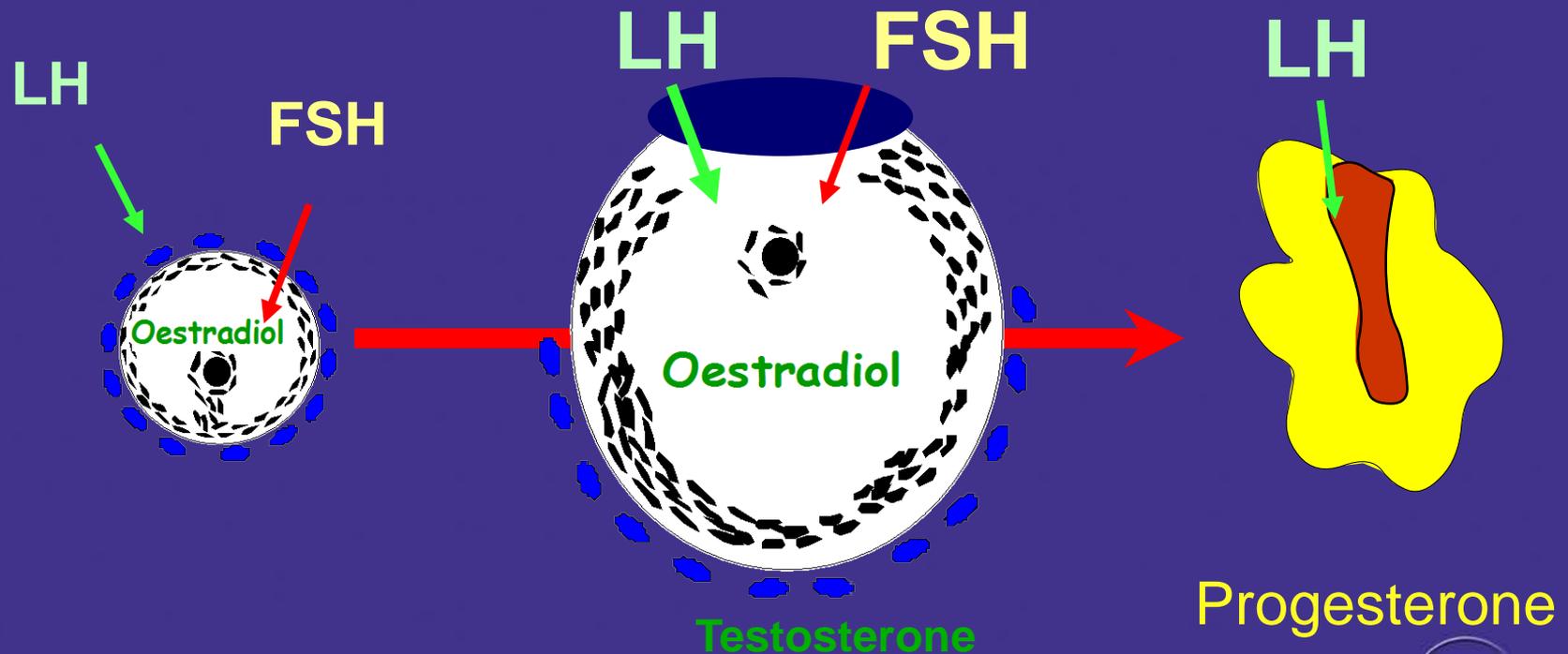
# The follicle in PCOS



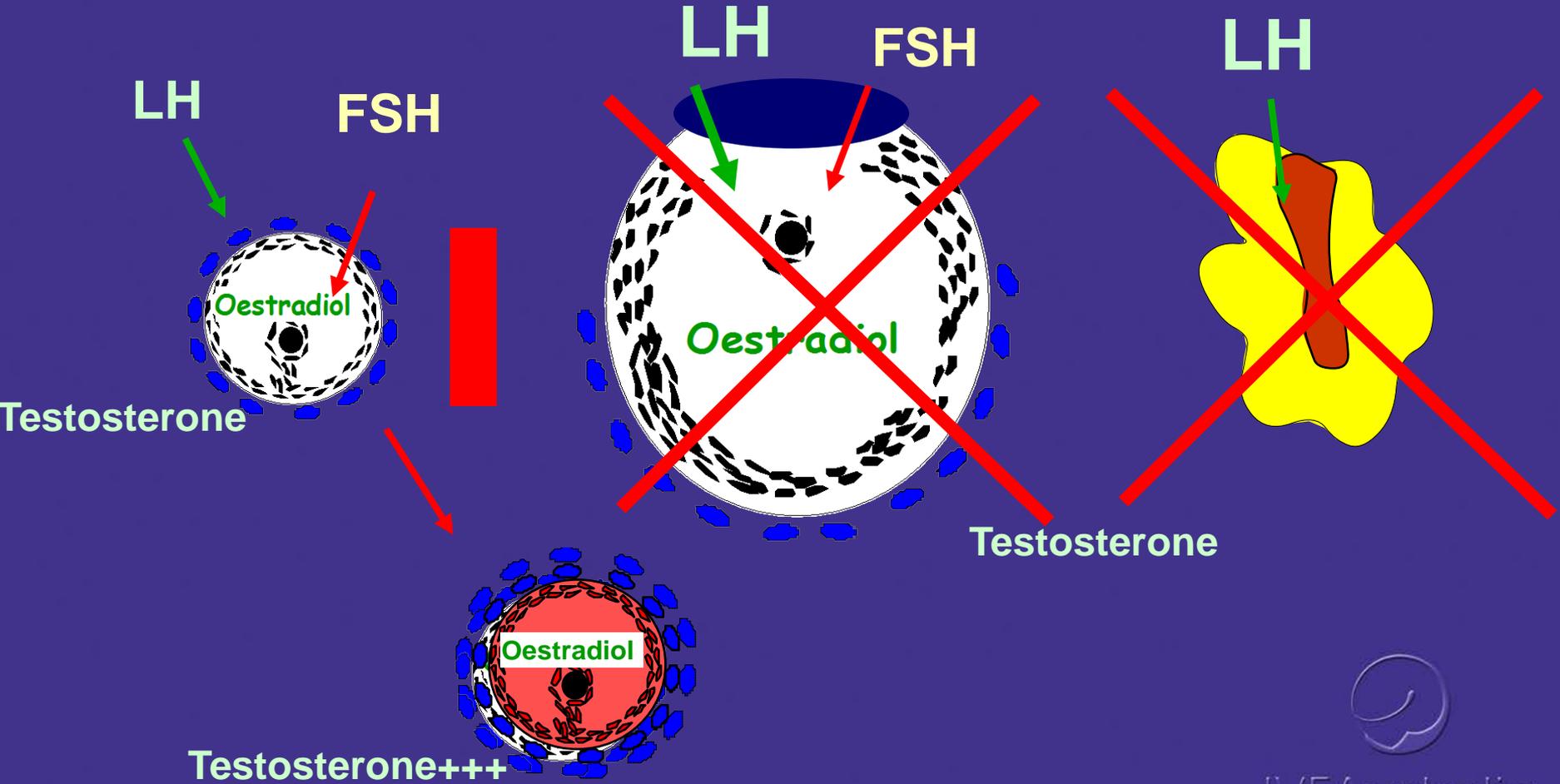
# The follicle in PCOS



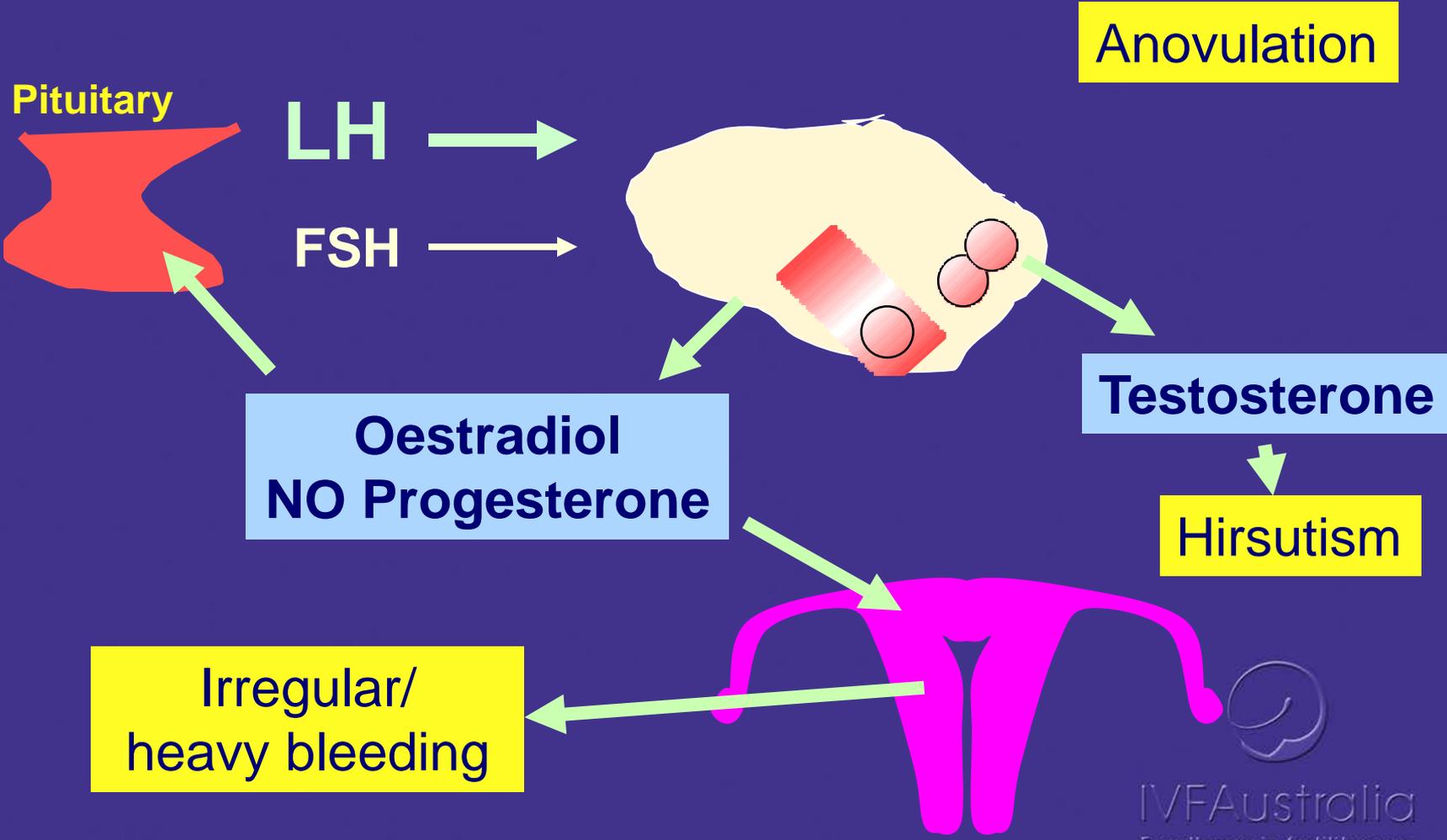
# The normal menstrual cycle



# Pathophysiology of PCOS



# Pathophysiology of PCOS



Anovulation

Oestradiol  
NO Progesterone

Testosterone

Hirsutism

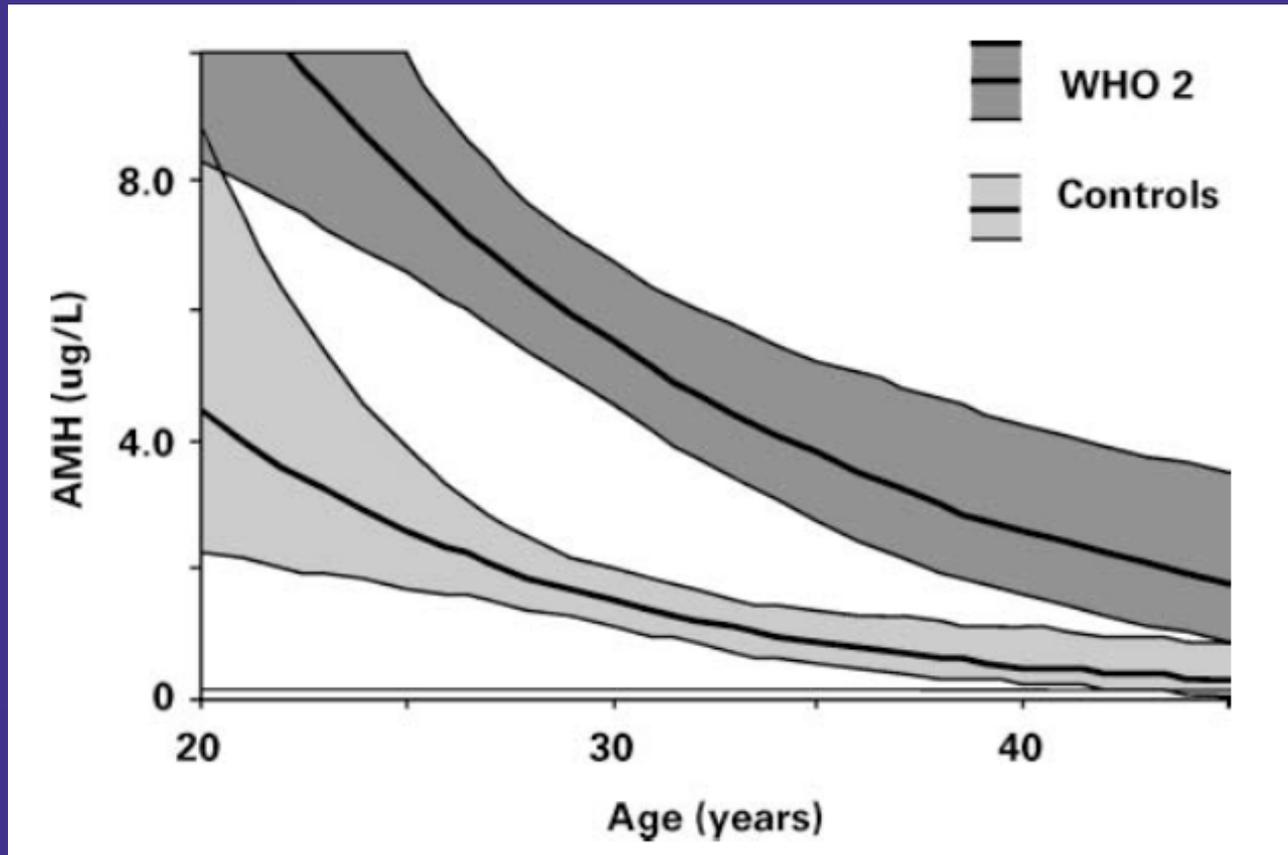
Irregular/  
heavy bleeding

# Too many follicles in PCOS?

- No actual cysts in PCOS
- Poly “follicular” syndrome



# Higher ovarian reserve in women with PCOS



# Clinical implications of high follicle number

- Women in their 30s with polycystic ovaries may actually be better off than their peers by having a better ovarian reserve
- The worst excesses of PCOS improve as time passes and the follicle number drops
- Ovulation induction in PCOS is more likely to produce multiple follicle development
- Problems of follicle excess such as Ovarian Hyperstimulation syndrome are more common

# Australian PCOS Evidence Based Guidelines:

Evidence-based guideline for  
the assessment and management  
of polycystic ovary syndrome

PCOS  
Australian  
Alliance

A single voice for polycystic ovary syndrome

# Australian PCOS Evidence Based Guidelines:

- **Guideline Booklet** (127 pages)
- **5 Clinical Algorithms** (each 1 page)
- **Evidence Report** (761 pages)
  - all available free at [www.managingpcos.org.au/pcos-evidence-based-guidelines](http://www.managingpcos.org.au/pcos-evidence-based-guidelines)
- **MJA September 2011 Supplement** (clinical summary of the guideline) (43 pages)
  - Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BGA, Wong JLA, Norman RJ and **Costello MF**. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust 2011;195(6): S65-S112.



# Infertility management in PCOS

## Recommendation (summary)

**Lifestyle modification** should be **first-line therapy** for 3 to 6 months in PCOS women with BMI  $\geq 30$  to determine if ovulation is induced (with due consideration given to age-related infertility). (*Some evidence C*)

## Clinical implications

- Weight loss will certainly help, particularly when BMI is  $>35$

## However...

- Compliance with weight loss programs limited so needs a lot of work and support
- Often has little effect
- Little randomised trial evidence of long term benefit



# Diagnostic assessment of PCOS: menstrual irregularity

## Recommendation

In **adolescent women** (<18 years), **after two years of irregular cycles** (>35 or <21 days) **following the onset of menarche**, PCOS should be considered and appropriate assessment should be undertaken

## Clinical implications

- Irregular periods are common in adolescence so you don't need to do anything until the problem has been present for two years
- May need to do abdominal ultrasound to make the diagnosis in this group





# Infertility management in PCOS

## Recommendation (summary)

**Clomiphene citrate** should be **first-line pharmacological therapy** in women with PCOS and anovulatory infertility, with no other infertility factors. (Trusted evidence A)

## Clinical implications

- Clomiphene was then the first line for anovulation
- Take early in follicular phase
- Start at 50mg and may need to increase dosage
- Tight monitoring important



# Clomiphene Citrate (Clomid or Serophene)

- Now over 5000 publications
- 1961 first used to induce ovulation
- A competitive anti-oestrogen
- HOWEVER...



# Clomiphene citrate: the problems

- Induces ovulation in 70% but pregnancy in only 30-40%
- Adverse effects on endometrium and mucus
- Side-effects include hot flushes and headaches and eye effects
- No effect in unexplained infertility

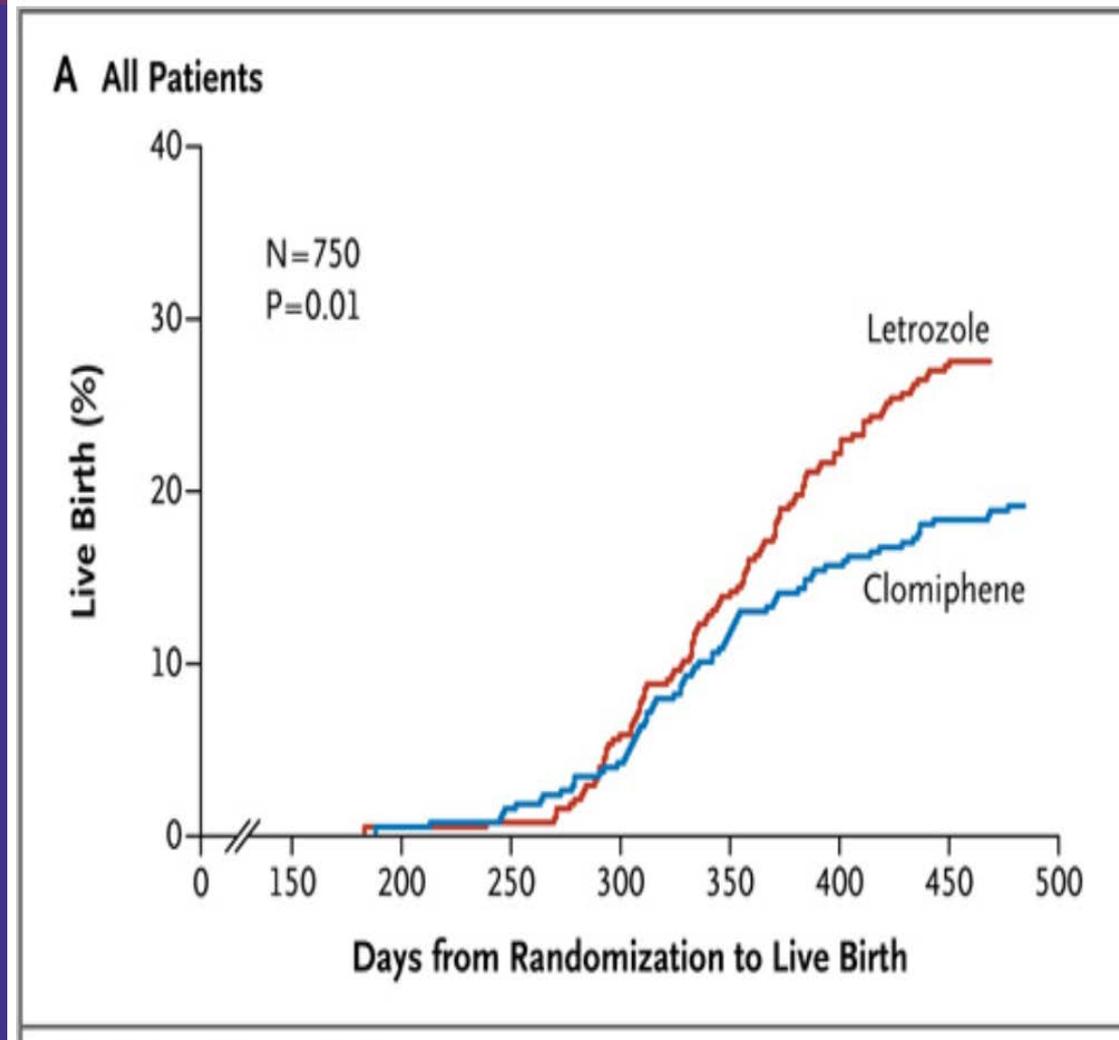


# Letrozole (Femara)

- Aromatase inhibitor
- Used in breast cancer
- Safe and very effective in ovulation induction



# Comparison between letrozole and clomiphene



**Legro RS *et al.*,  
N Engl J Med.  
2014; 371: 119–  
129.**



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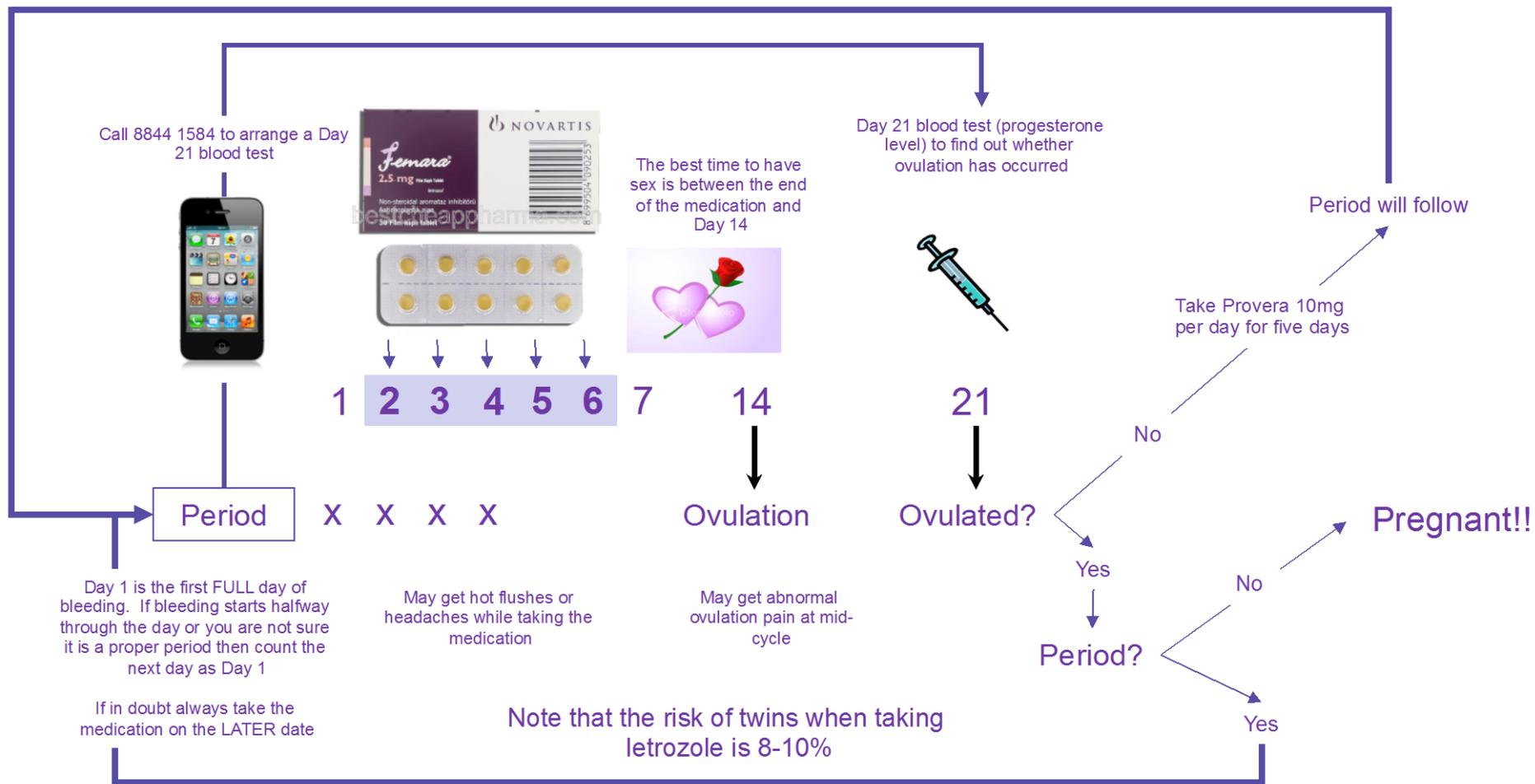
# Ovulation induction with letrozole

- Use 5mg (two tablets) Days 2-6
- Careful instruction and tight monitoring the key to success
- Generally not more than 6 months





# Instructions for taking letrozole



**Don't hesitate to call the nurses on 8844 1584 if you have any questions**

# What do we know about metformin?

- Reduces hyperinsulinemia
- Target dose: 1500 – 2550mg daily
- Prescribing: give with meals and titrate dose
- Significant common side-effects are gastrointestinal
- Rare problem of lactic acidosis



# Metformin proves ineffective in large-scale RCT

- *NEJM 2/2007 largest RCT using Metformin for ovulation induction in PCOS (Legro et.al.)*
- In the study 626 infertile women with PCOS were randomly assigned to:
  - clomiphene citrate plus placebo,
  - an extended-release metformin plus placebo
  - a combination of metformin and clomiphene for up to six months.
- Metformin was associated with lower ovulation rate, lower live birth rate and no reduction in miscarriage rate



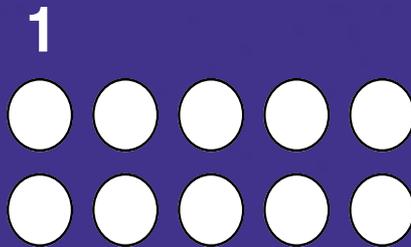
# PCOS, Insulin and metformin

- Clear association between PCOS and insulin resistance with all the long-term sequelae.
- PCOS is probably one manifestation of insulin resistance rather than the other way round
- Obese women with anovulatory PCOS should have an OGTT
- If the glucose concentration is normal, she is healthy (for the moment)
- Role of metformin in PCOS?????



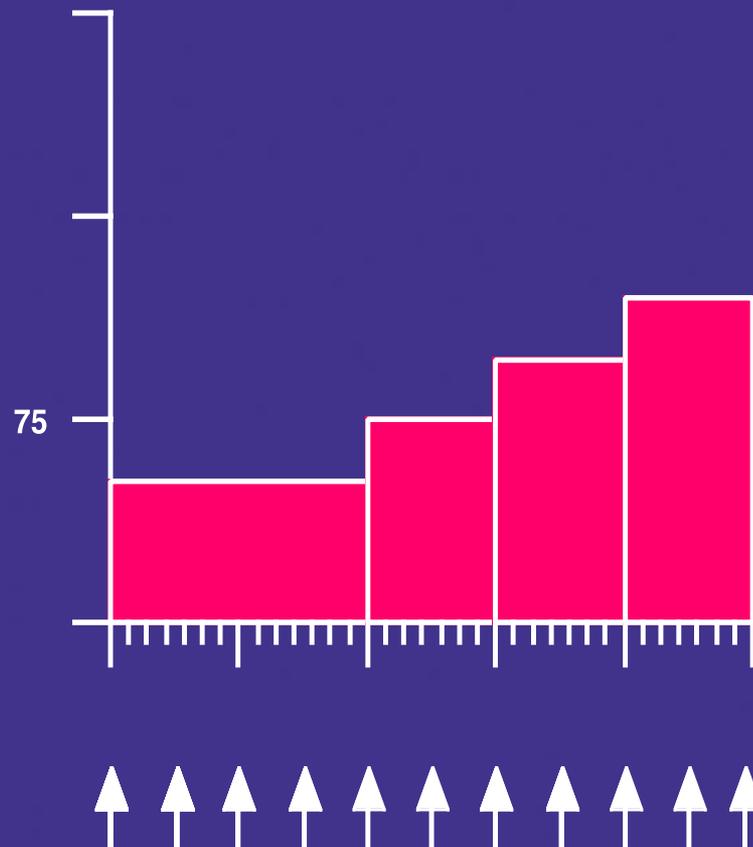
# Low dose gonadotrophin treatment

1. Give gestogen to induce withdrawal bleed



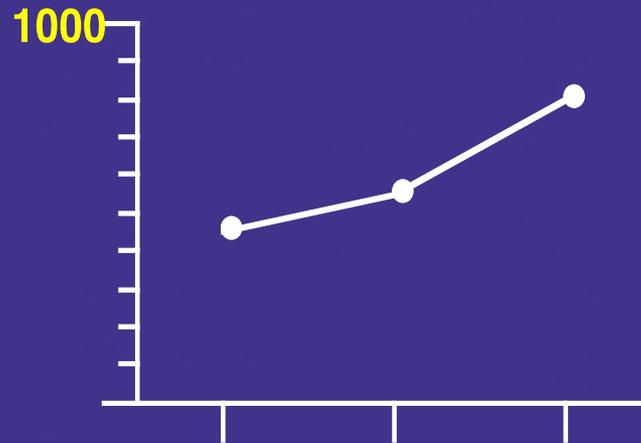
# Low dose gonadotrophin treatment

2. Give slowly increasing doses of gonadotrophin until oestradiol > 400pmol/L



# Low dose gonadotrophin treatment

3. Daily oestradiol measurements and alternate day scans until one (two max.) follicle(s) seen greater than 17mm diameter



4. Give hCG 5000 IU to induce ovulation





# Infertility management in PCOS

## Recommendation (summary)

**Gonadotrophins or laparoscopic ovarian drilling** should be second-line therapy in women with PCOS who have **clomiphene citrate resistance and/or failure**, are anovulatory and infertile, with no other infertility factors. (Evidence in most situations B)

## Clinical implications

- Gonadotrophin treatment is much more involved than clomiphene/letrozole
- No apparent difference between the long-term fertility of gonadotrophins and ovarian drilling
- Gonadotrophins quicker so more widely used in Australia



# Laparoscopic ovarian drilling



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# Infertility management in PCOS

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## Clinical implications

- Gonadotrophin treatment is much more involved than clomiphene
- How quickly patients will move onto these treatments varies and will largely depend on how much of a hurry the couple are in



# PCOS Clinic

## IVFAustralia: Polycystic Ovary Syndrome Clinic

Dispelling the myths and dealing with the issues

### IVFAustralia's PCOS Clinic

IVFAustralia has introduced a PCOS clinic to diagnose PCOS and deal with non-fertility related issues such as:

- menstrual irregularities
- endometrial protection
- hirsutism, acne, hair loss
- metabolic syndrome screening (diabetes, hypertension, hypercholesterolemia, hyperlipidemia)
- miscarriage

#### Appointments

Appointments are available every second Friday between 11 am & 2pm. They are 30 minutes in duration.

#### Referral required

A referral is required for all appointments.

#### Funds to be used for research

This is a not-for-profit clinic consultation fees (\$120 for initial consult and \$60 for follow up) will be used for research and/or patient resources.

#### PCOS Clinic is held at

IVFAustralia  
Level 2, 176 Pacific Highway  
Greenwich NSW 2065

Tel           02 9425 1600  
Toll free   1800 111 483

# Some cases...

- A 35 yo woman with regular cycles and 12 months of unexplained infertility goes for a scan.
- The report says “Normal pelvis. Ovarian appearances appear polycystic”



# Some cases...

- A 35 yo woman with regular cycles and 12 months of unexplained infertility goes for a scan.
- The report says “Normal pelvis. Ovarian appearances appear polycystic”
- REASSURE HER. THIS IS A GOOD RESULT



# Some cases...

- A 16 year-old girl comes in worried about her periods. They come every six months and when they come, they are extremely heavy. Normal bodyweight. No clinical hyperandrogenism.
- Endocrinology: LH 20, FSH 4.5, E2 200pmol/L, P4 <0.5nmol/L, Testosterone 2.6nmol/L



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- PUT HER ON REGULAR PROGESTOGENS – ORAL CONTRACETIVE NORMALLY MOST CONVENIENT



# Some cases...

- A 16 year-old girl comes in worried about her facial hair. Her periods come every six months but it doesn't bother her. Normal bodyweight. Clear evidence of hirsutism but no bodily hair or other stigmata of virilisation.
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- PUT HER ON THE ORAL CONTRACEPTIVE .
- IF NO RESPONSE DISCUSS FINASTERIDE 1mg/day BUT GIVE (AND DOCUMENT) WARNING ABOUT TERATOGENIC RISKS AND NEED TO AVOID PREGNANCY.



# Some cases...

- A 28 year-old woman has been married for 12 months and trying to conceive. Not excess bodyweight. She only has a period every 3-4 months. Everything else normal



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- Letrozole 5mg/ day from days 2-6



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- A 28 year-old woman has been married for 12 months and trying to conceive. Weighs 100kg. She only has a period every 3-4 months. Her husband has severe oligozoospermia.



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- A 28 year-old woman has been married for 12 months and trying to conceive. Weighs 100kg. She only has a period every 3-4 months. Her husband has severe oligozoospermia.
- Do what can be done to lose weight. No rush for IVF at this age.
- If no success (as likely) start IVF with reasonable dose of FSH, antagonist protocol and agonist trigger.



# Conclusions

1. Treat the manifesting problem step by step.
2. Women with PCOS have a tough and frustrating time but usually get there in the end.
3. The therapeutic implications of the long-term health issues still remain unclear

