How PCOS affects fertility and available options

Speaker: Dr Kate Gowling, Fertility Specialist
Date: May 16th, 2024.

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In one word or emoji, how are you feeling this evening?

Nobody has responded yet.

Hang tight! Responses are coming in.

Learning Objectives

- Revise the Rotterdam diagnostic criteria for PCOS
- Understand the implications of PCOS for fertility
- Explore the management options for subfertility in the PCOS patient
  - Periconception Health
  - Lifestyle Modification
  - Ovulation Induction
  - Laparoscopic Ovarian Drilling and IVF
- Understand the increased risks of PCOS in pregnancy

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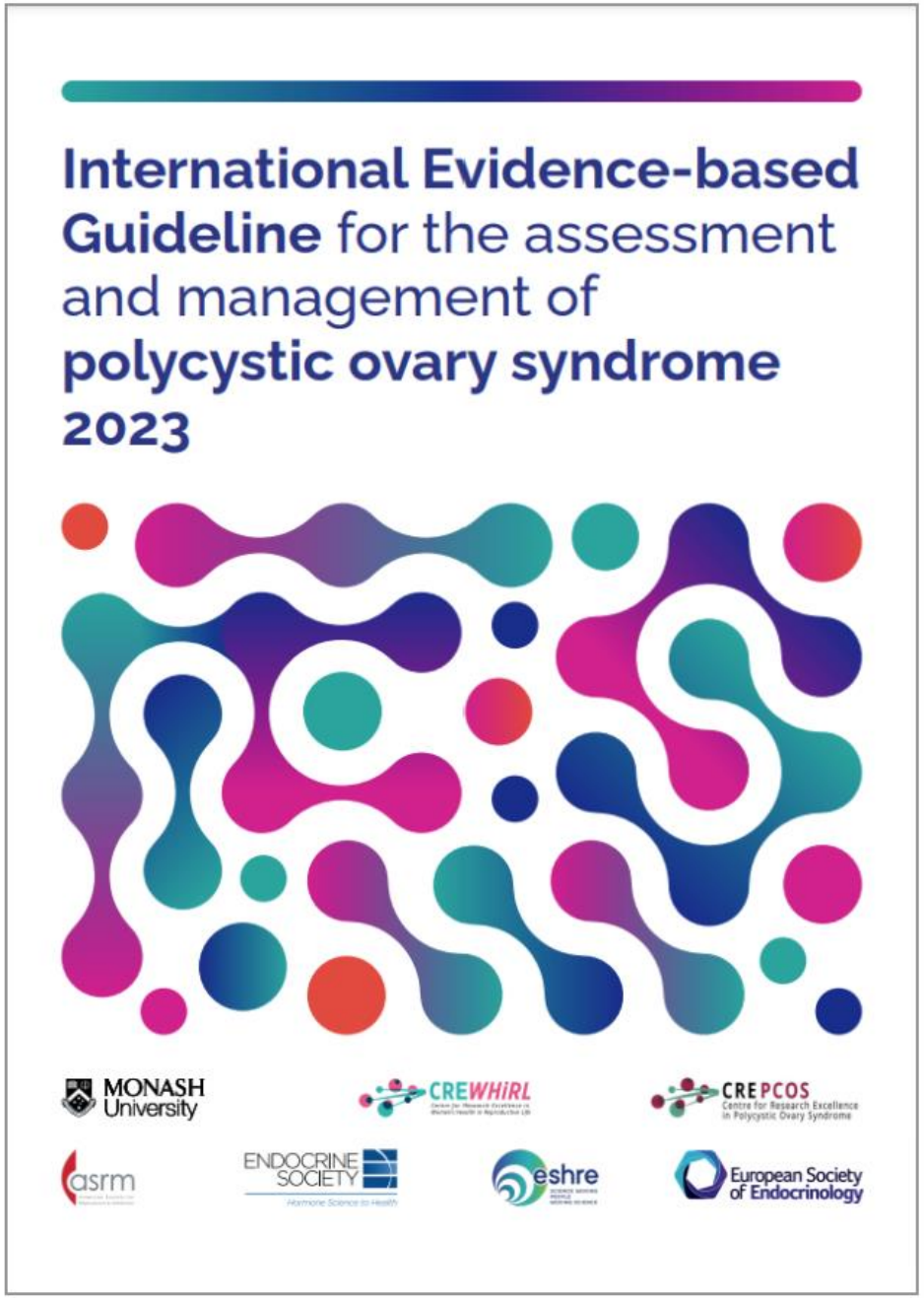
Introduction

- Most common endocrine disorder in reproductive age women
  - Insulin and androgens
- Affects 10% of reproductive aged women
- Not an ovarian disease
- Can cause both short- and long-term health problems
  - Endocrine
  - Reproductive
  - Cardiometabolic
  - Dermatologic
  - Psychosocial
- Heterogeneous condition
- Diagnosis/treatment challenging



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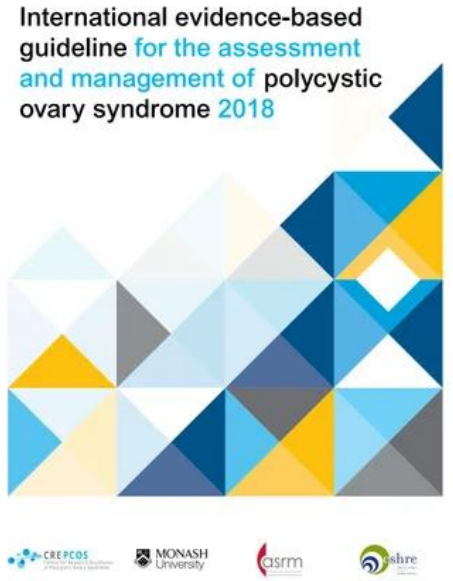

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Diagnostic Criteria

Revised consensus Rotterdam criteria:

In adults this requires the presence of two of

i) clinical/biochemical hyperandrogenism,

ii) ovulatory dysfunction and

iii) polycystic ovaries on ultrasound or elevated anti-mullerian hormone (AMH) levels,

*after other causes of these features are excluded

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Diagnostic Criteria

Step 1: Irregular cycles + clinical hyperandrogenism

(exclude other causes)* = diagnosis

↓

Step 2: If no clinical hyperandrogenism

Test for biochemical hyperandrogenism (exclude other causes)* = diagnosis

↓

Step 3: If ONLY irregular cycles OR hyperandrogenism

Adolescents ultrasound is not indicated = consider at risk of PCOS and reassess later
Adults - **request ultrasound for PCOM***, if positive (exclude other causes)* = diagnosis

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***Exclusion of other causes =s TSH, prolactin, 17-OH progesterone, FSH or if clinically indicated exclude other causes** (e.g. Cushing's syndrome, adrenal tumours etc) Hypogonadotrophic hypogonadism, usually due to low body fat or intensive exercise, should also be excluded clinically and with LH and FSH levels

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Diagnostic Criteria

Irregular menstrual cycles

Normal in the first year post menarche = pubertal transition.

- > 1 to < 3 years post menarche: < 21 or > 45 days,
- > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year
- > 1 year post menarche > 90 days for any one cycle
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development).

With irregular cycles, PCOS should be considered and assessed according to the guidelines,
Ovulatory dysfunction can occur with regular cycles. If anovulation suspected, check progesterone levels.

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Diagnostic Criteria

Biochemical hyperandrogenism
Use total testosterone and free testosterone for diagnosis. If not elevated, then androstenedione and dehydroepiandrosterone sulfate could be measured, but are less specific with a limited role in PCOS diagnosis.
Highly accurate tandem mass spectrometry (LC-MS/MS) assays recommended. Direct free testosterone assays not preferred. Use lab reference ranges.
Reliable assessment of biochemical hyperandrogenism not possible on hormonal contraception. Consider withdrawal for ≥ 3 months with alternative contraception
Biochemical hyperandrogenism role is when clinical hyperandrogenism is unclear.
Where levels are well above laboratory reference ranges, other causes should be considered. History of symptom onset and progression is key in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in hyperandrogenism.

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Diagnostic Criteria

Clinical hyperandrogenism
Comprehensive history and physical examination needed. Adults: acne, female pattern hair loss and hirsutism. Adolescents: severe acne and hirsutism.
Note negative psychosocial impact of clinical hyperandrogenism. Patient perception is important, regardless of apparent clinical severity.
Standardised visual scales are preferred including modified Ferriman Gallway score (mFG), a score of ≥ 4-6 = hirsutism, noting self-treatment impacts assessment.
Ludwig visual score preferred for assessing female pattern hair loss.

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Diagnostic Criteria

Ultrasound and polycystic ovary morphology

With irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for diagnosis.

In diagnosis, follicle number per ovary is most effective, followed by follicle number per cross-section and ovarian volume as ultrasound markers in adults.

Ultrasound should not be used for PCOS diagnosis in adolescents, due to the high incidence of multi-follicular ovaries in this life stage.

Transvaginal ultrasound approach is preferred in diagnosis of PCOS, if sexually active or if acceptable to the individual

Using ultrasound transducers with a frequency bandwidth including 8 MHz, the PCOM threshold is a follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10 ml on either ovary, avoiding corpora lutea, cysts or dominant follicles

Serum AMH could be used for defining PCOM in adults as an alternative to pelvic ultrasound. Either serum AMH OR ultrasound may be used but not both to avoid overdiagnosis*

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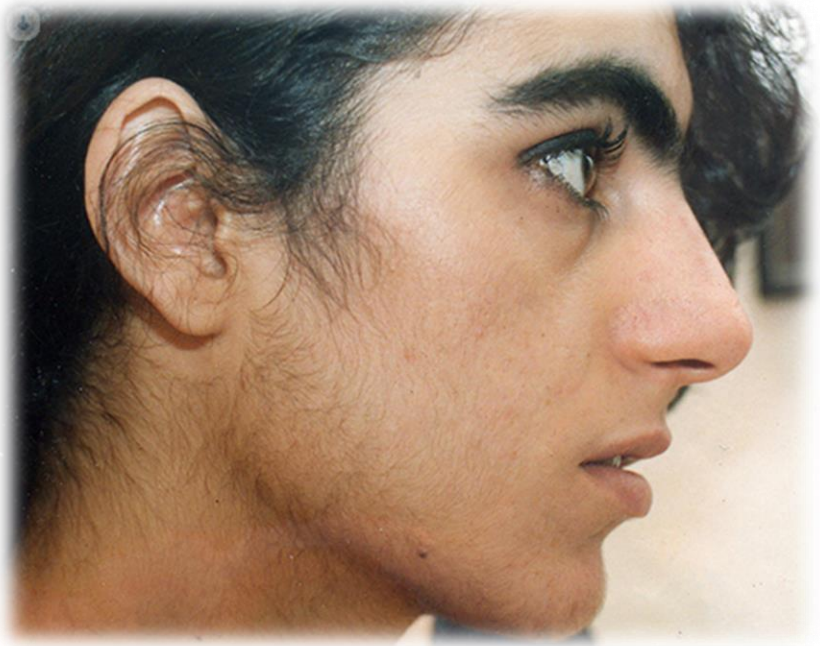
Diagnostic Criteria

- Menstrual irregularity
  - Oligomenorrhoea (<21 or >35 days, <8 periods/yr)
  - Amenorrhoea
- Clinical and/or biochemical hyperandrogenism
  - Acne, hirsutism, increased total or free testosterone
  - Exclude other causes (CAH, Cushing's, androgen secreting tumours)
- Ultrasound Scan PCOM or AMH
  - Either ovary ≥ 20 follicles, or ovarian volume ≥ 10ml



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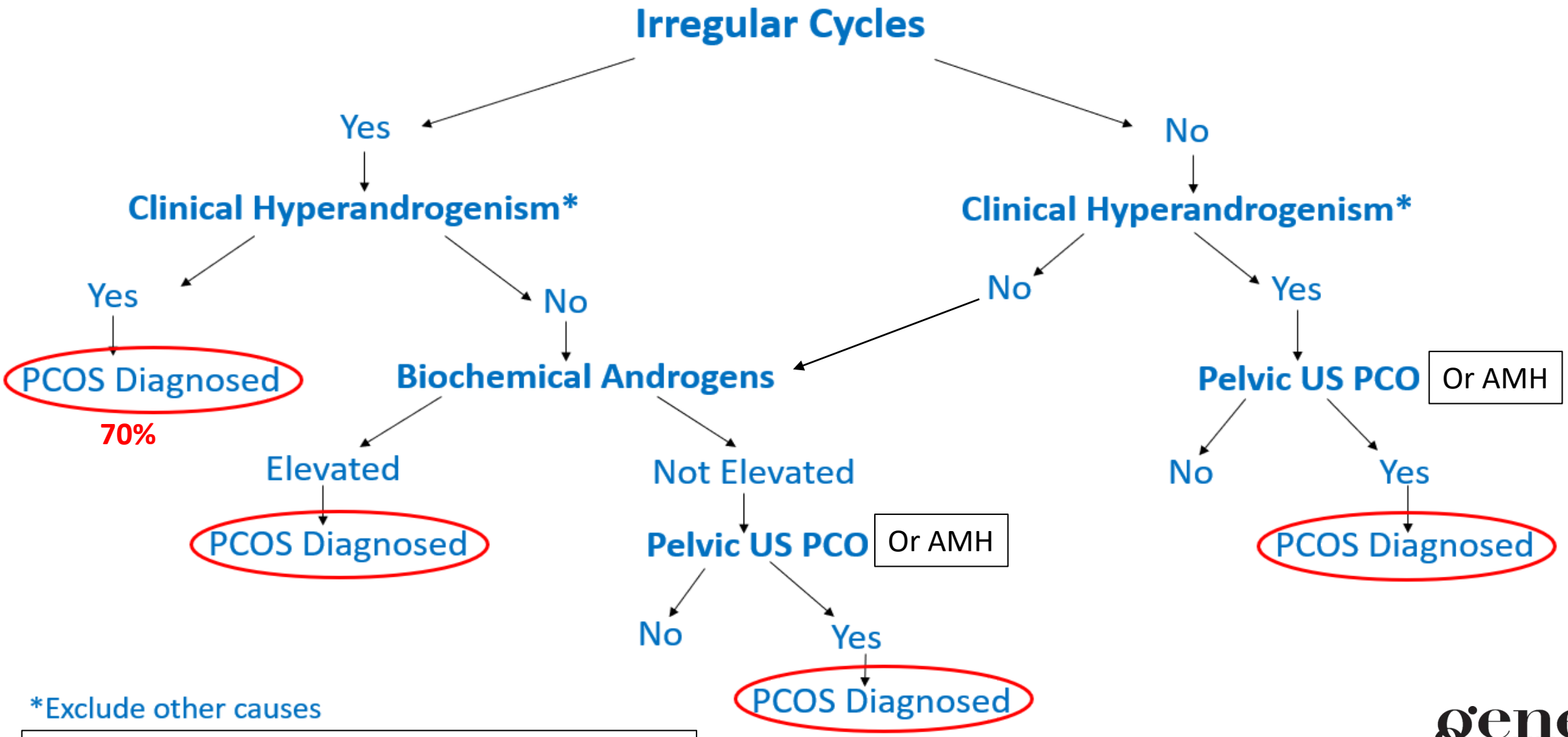

*Exclude other causes

AMH – in adults only, ?cut off level, as alternative to US (not in addition)

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Challenges

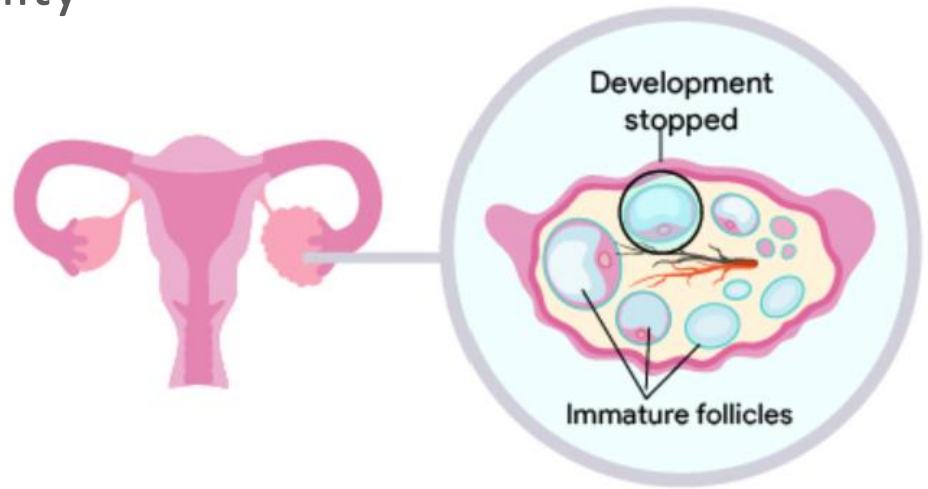
- Accurately defining individual diagnostic criteria
- Marked clinical heterogeneity
- Influence of excess weight
- Ethnic differences
  - Only evaluate terminal, not vellus, hair for pathologic hirsutism
- Variation across the life course
  - Overlap of normal pubertal development and PCOS features, US not recommended within 8 years of menarche

Health Problems

- Reproductive
  - irregular menstrual cycles, infertility, endometrial cancer and pregnancy complications
- Cardiometabolic
  - insulin resistance, metabolic syndrome, type 2 diabetes (T2D), cardiovascular risk factors and increased cardiovascular disease (CVD)
- Dermatologic
  - hirsutism, acanthosis nigricans and acne
- Psychosocial
  - anxiety, depression, sleep and eating disorders

PCOS and Fertility

- One of the most common but treatable causes of infertility in women
- 70% may experience issues conceiving
- Main issue oligo/anovulation
  - Low-grade inflammation
  - Endometrial dysfunction
- Most will achieve pregnancy with simple, non-invasive interventions
- Contraception still required if not wanting a pregnancy
- Preconception care important, as with any chronic disease



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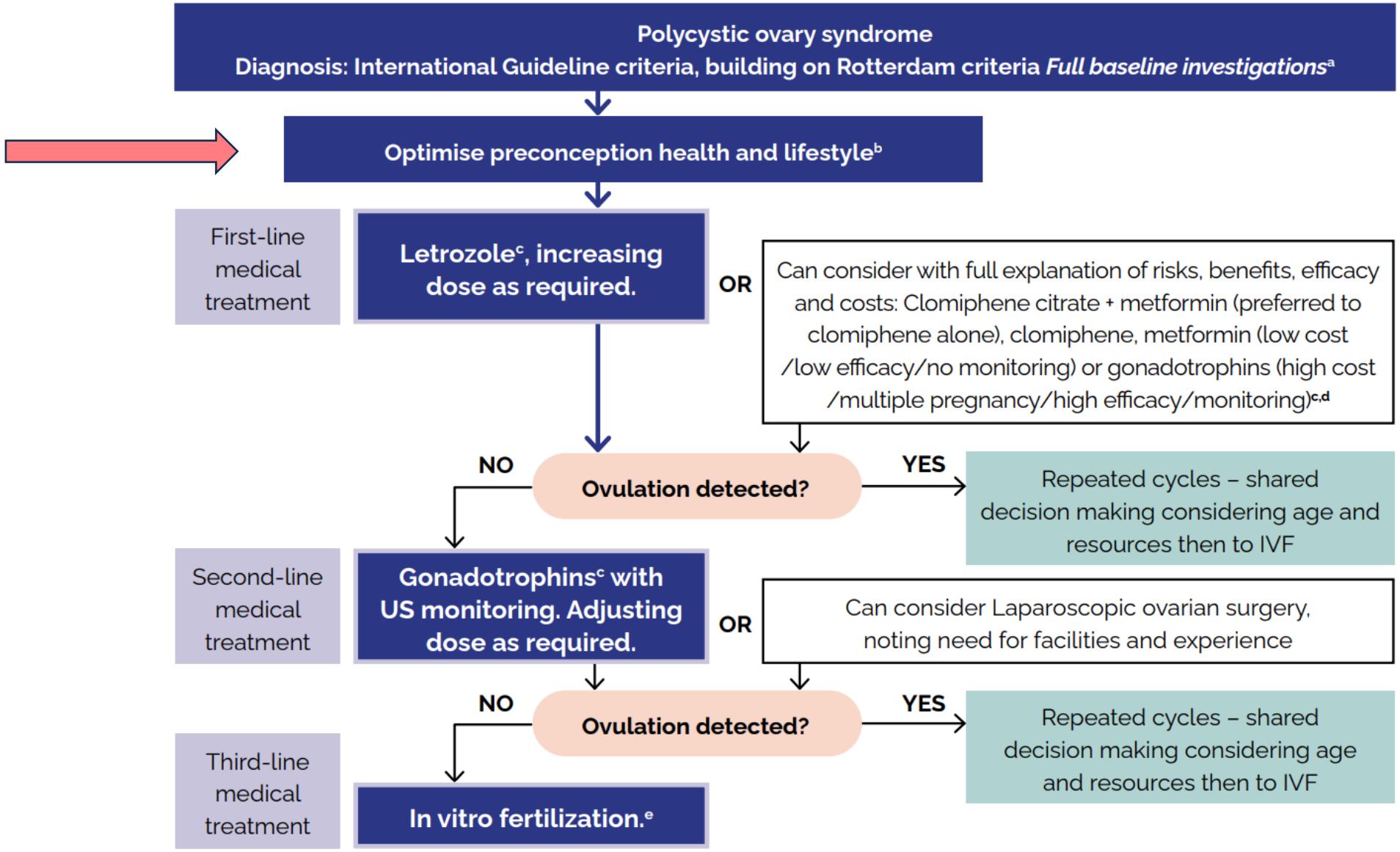
Management of infertility in PCOS



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Preconception Health

- Assessment of BMI, BP & glycaemic status (OGTT/HbA1c)
- Counselling re adverse impacts of excessive weight
  - Many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI
  - Aware of weight stigma
  - Acknowledge weight is just one risk factor
- Routine preconception
  - Infective serology
  - Advice re smoking, alcohol
  - Supplementation
    - Folic acid 500mcg/day, or if BMI >30 5mg/day (MegaFol)
    - Iodine 150mcg/day
  - Reproductive Carrier Screening
  - Optimise co-existing medical conditions
    - eg. HTN, diabetes, depression/anxiety
  - Age
- Additional investigations
  - semen analysis, consider tubal patency assessment

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Lifestyle Modifications

- Healthy eating and regular physical activity
- Limit adverse impacts on fertility and fertility treatment outcomes
- Optimise health during pregnancy
- Weight: Aim for healthy weight, realistic goal setting (3-8% of body weight) ("weight-centric")
  - Negative biopsychosocial impacts of weight stigma
  - Alternative "weight-inclusive" care, without focusing on intentional weight loss
- Behavioural support: e.g. SMART goals (Specific, Measurable, Achievable, Realistic and Timely)
- Dietary advice: population guidelines, no specific "PCOS" diet recommended, tailor to individual
  - Calorie deficit 500 – 750cal/day for weight loss (1200 – 1500 cal daily intake)
- Exercise: population guidelines, 250min moderate or 150min vigorous exercise/wk for weight loss
- Consider referral for Multi-D care arrangement
  - Dietician, Exercise Physiologist, Psychologist, Group Support

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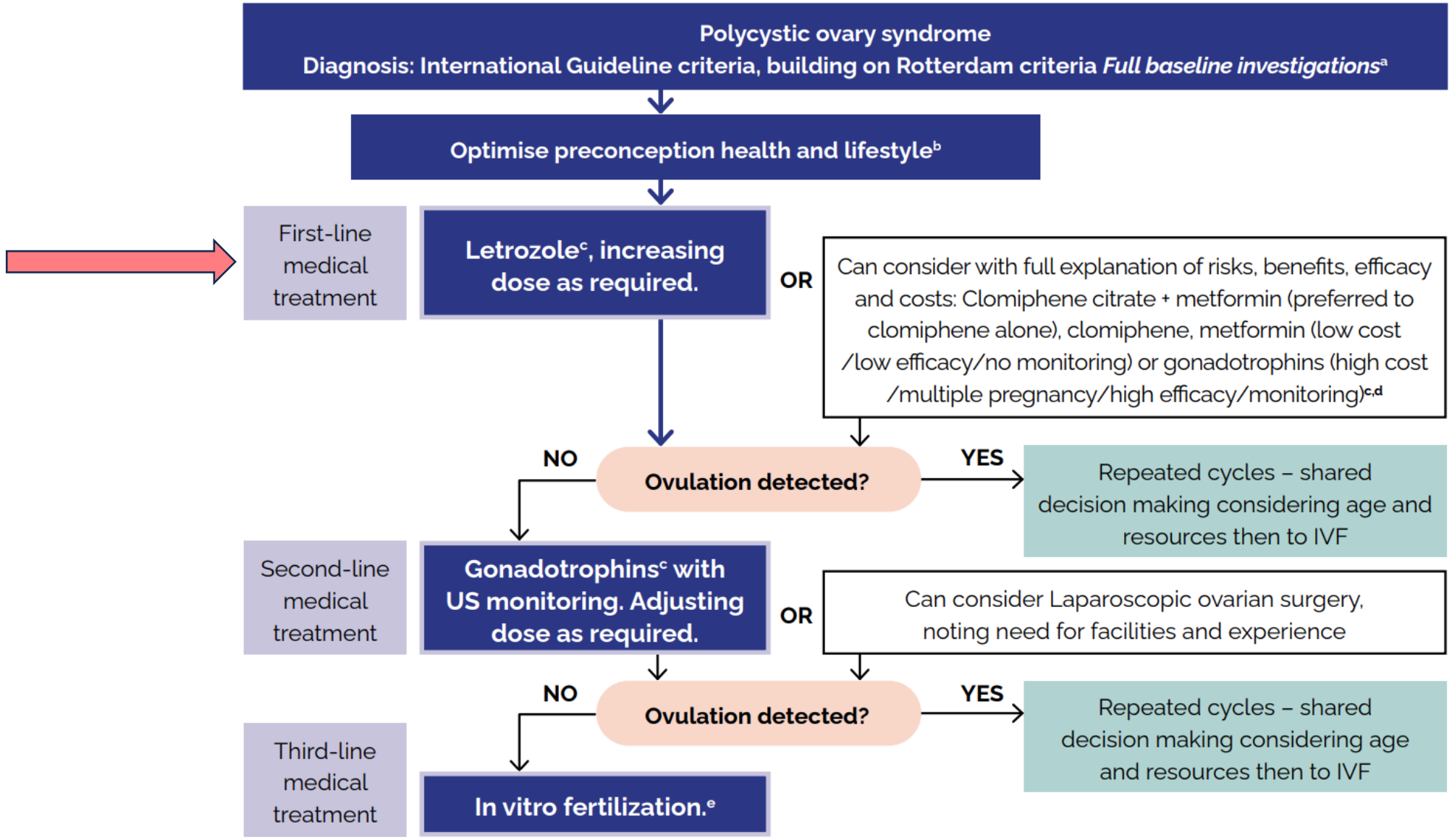
What is your next holiday destination? (single word, no spaces)

Nobody has responded yet.

Hang tight! Responses are coming in.

Management of infertility in PCOS



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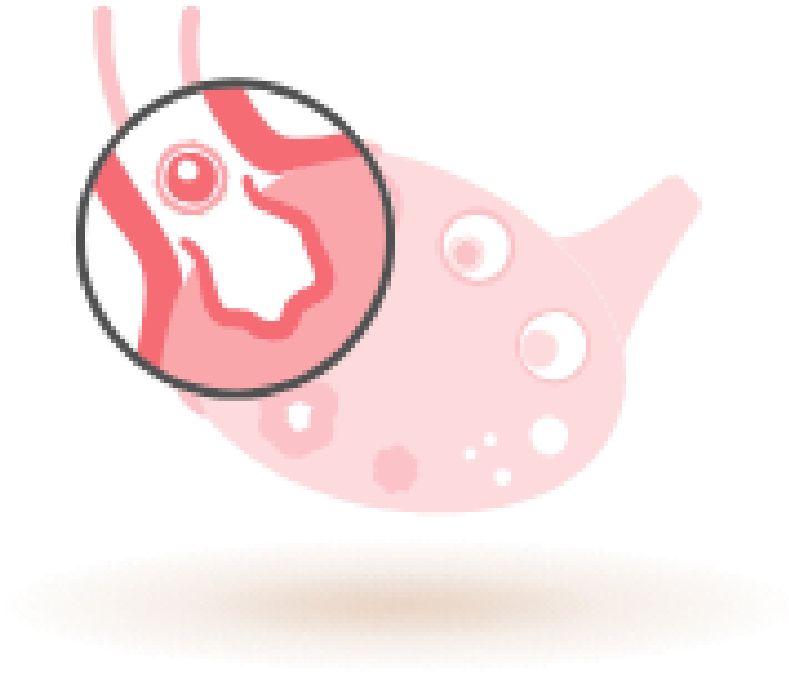
Ovulation Induction

- 1st line – letrozole
  - Can consider
    - Clomiphene + metformin
    - Clomiphene
    - Metformin
    - Gonadotrophins
- 2nd line – gonadotrophins
- Off-label use but evidence based
  - letrozole, metformin



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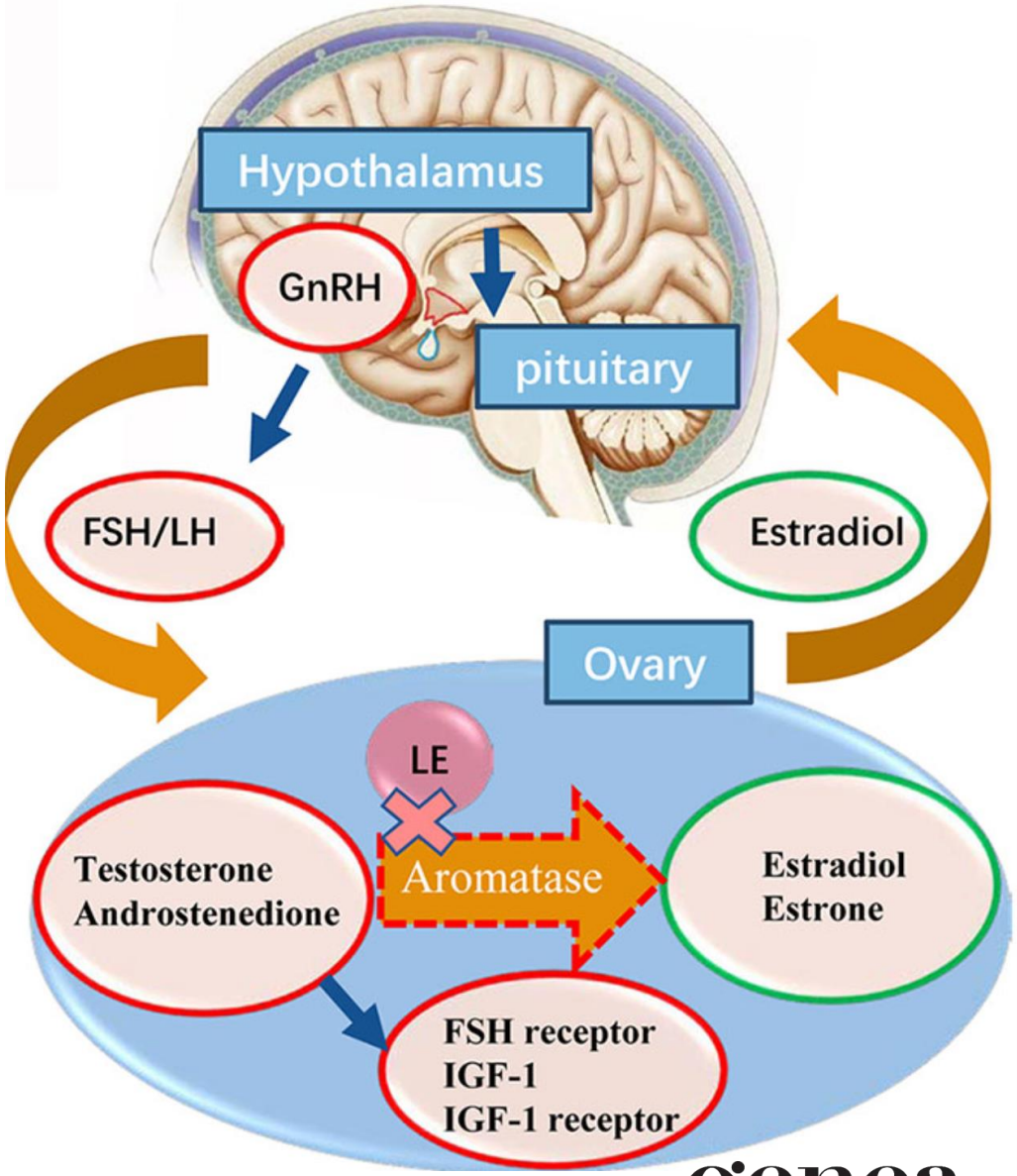
Letrozole

- 1st line pharmacological infertility therapy in PCOS
- Aromatase Inhibitor
  - prevent conversion of androgens to oestrogens including in the ovary
  - increase FSH secretion
  - Increase follicular FSH sensitivity
- Proposed as OI agent in 2001
- Start 2.5mg PO daily for 5 days
  - start day 5 (ie day 5-9, or can do 2-6)
  - Max 5mg daily for 5 days



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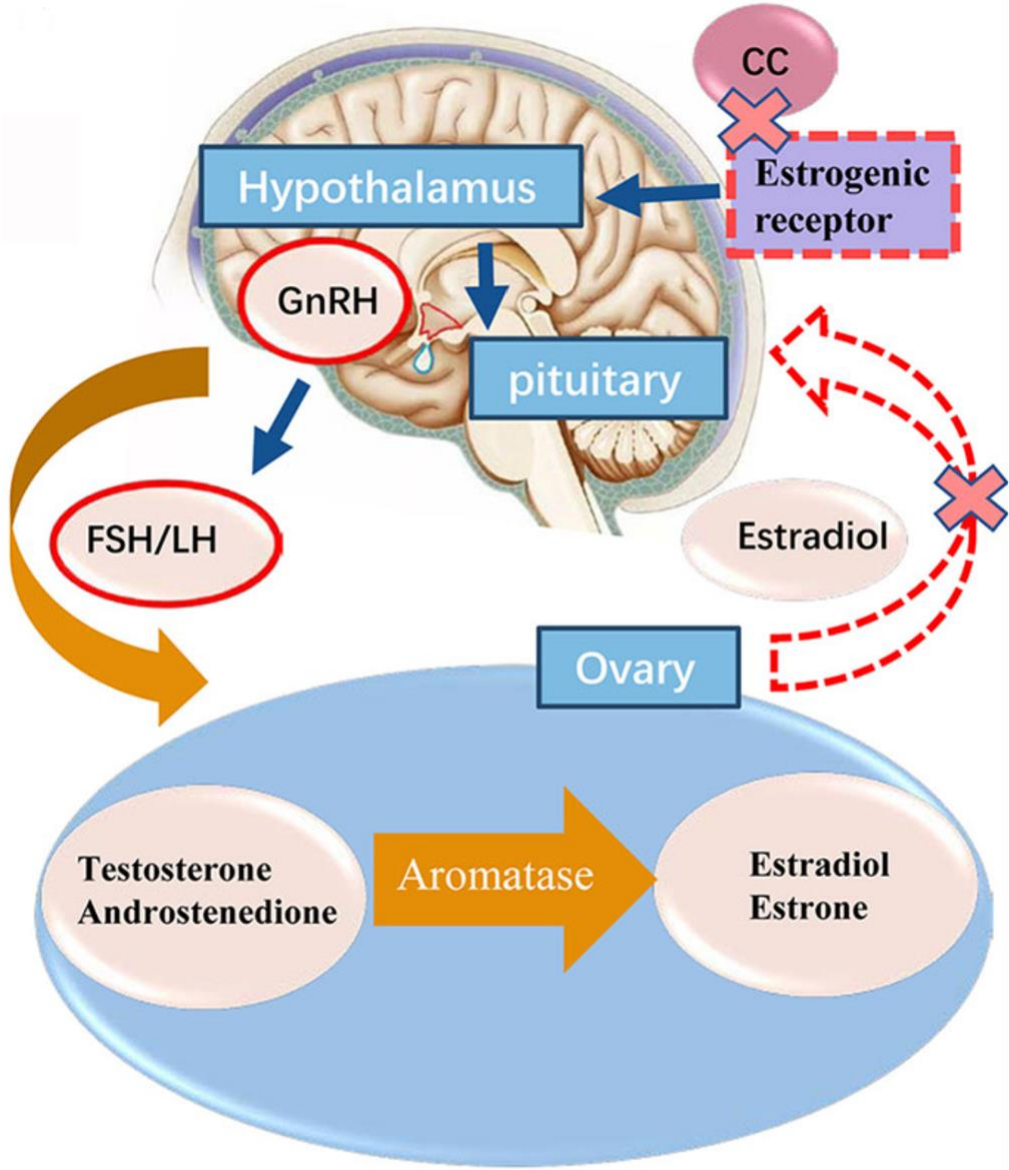
Letrozole

- Side effects
  - GI disturbance, asthenia, hot flushes, headaches, back pain
- No increased congenital abnormality risk
- Short half-life (approx. 2 days) therefore less side effect persistence
- Risk of multiples = 5% twins, 0.5% triplets
- Advantages over SERM (eg CC)
  - higher ovulation rate, clinical pregnancy and LBR (OR 1.68, NNTB =10)
  - lower MPR through single follicle recruitment*
  - better SE profile with fewer vasomotor Sx
  - more rapid clearance thus reducing potential periconceptual exposure
  - lacks the antiestrogenic effect; hence it does not alter cervical mucus and endometrial growth

Clomiphene Citrate

- Could consider as alternative 1st line agent
  - clomiphene plus metformin preferred
- Selective estrogen receptor modulator (SERM)
  - antagonizes negative feedback of estrogen at hypothalamus
  - increase ovarian stimulation by endogenous gonadotropin
- Used as OI agent for 50yrs
- Start 50mg PO daily for 5 days
  - start day 5 (ie day 5-9, or can do 2-6)
  - LH surge 5-12 days after last dose
    - Ovulation 14-26hrs after
  - 2nd daily intercourse for 1/52 from 5 days after finishing
- Max 150mg daily for 5 days
  - clomiphene resistant if no ovulation at max dose



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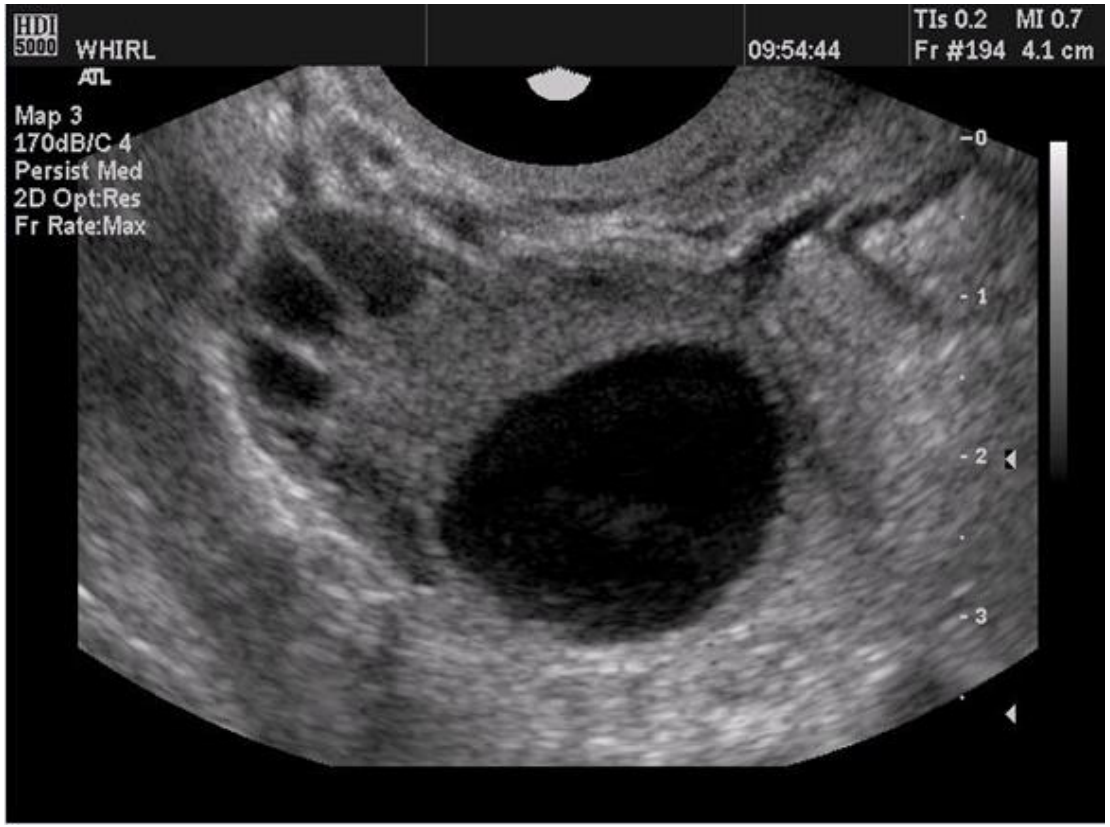
Clomiphene Citrate

- Side effects
  - Hot flushes 10%, headache, abdominal distention, breast tenderness, N & V
- Half-life approx 5 days
- Risk of multiples = 5% twins, 0.5% triplets
- OHSS 1/1,000
- Visual Symptoms 1/1,000



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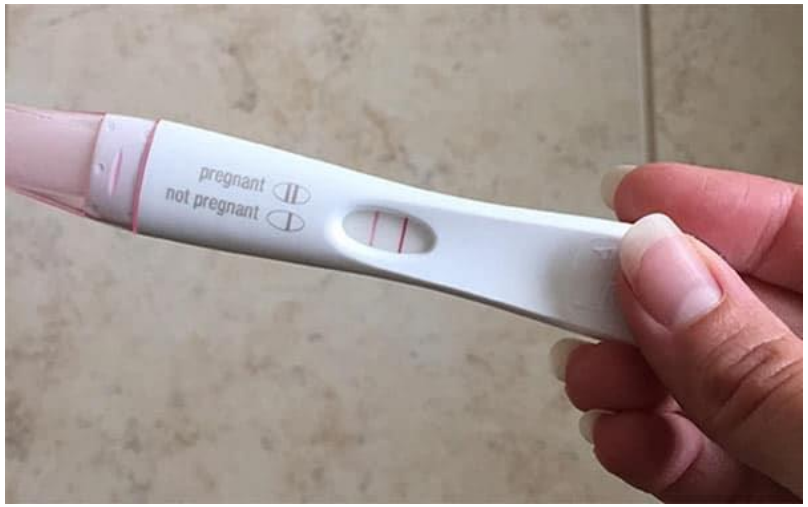
Clomiphene Efficacy

- Ovulation Rate = 80%
- Cumulative Pregnancy Rate = 30-40%
- 75% of pregnancies occur in first 3 ovulatory cycles
- Duration of treatment 3 – 6 cycles
  - Pregnancy rates low after 6 cycles despite ovulation
- No additional benefit from hCG trigger



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Metformin

- Insulin sensitising agent
- Used to address the insulin resistance in PCOS that leads to increased local ovarian androgens and subsequent follicle atresia and anovulation
- Widely studied in PCOS but therapeutic regimens vary widely
- Start 500mg/day, increase by 500mg/d every 1-2 weeks
  - switch to XR, max 2.5g/day
- Side effects – GI
- Improves clinical pregnancy and live birth rates (OR 1.8)
- Compared to letrozole - has lower efficacy, cost, multiple pregnancy rate
- Benefit when added to clomiphene, compared to clomiphene alone
- No benefit with addition to letrozole
- Cheap

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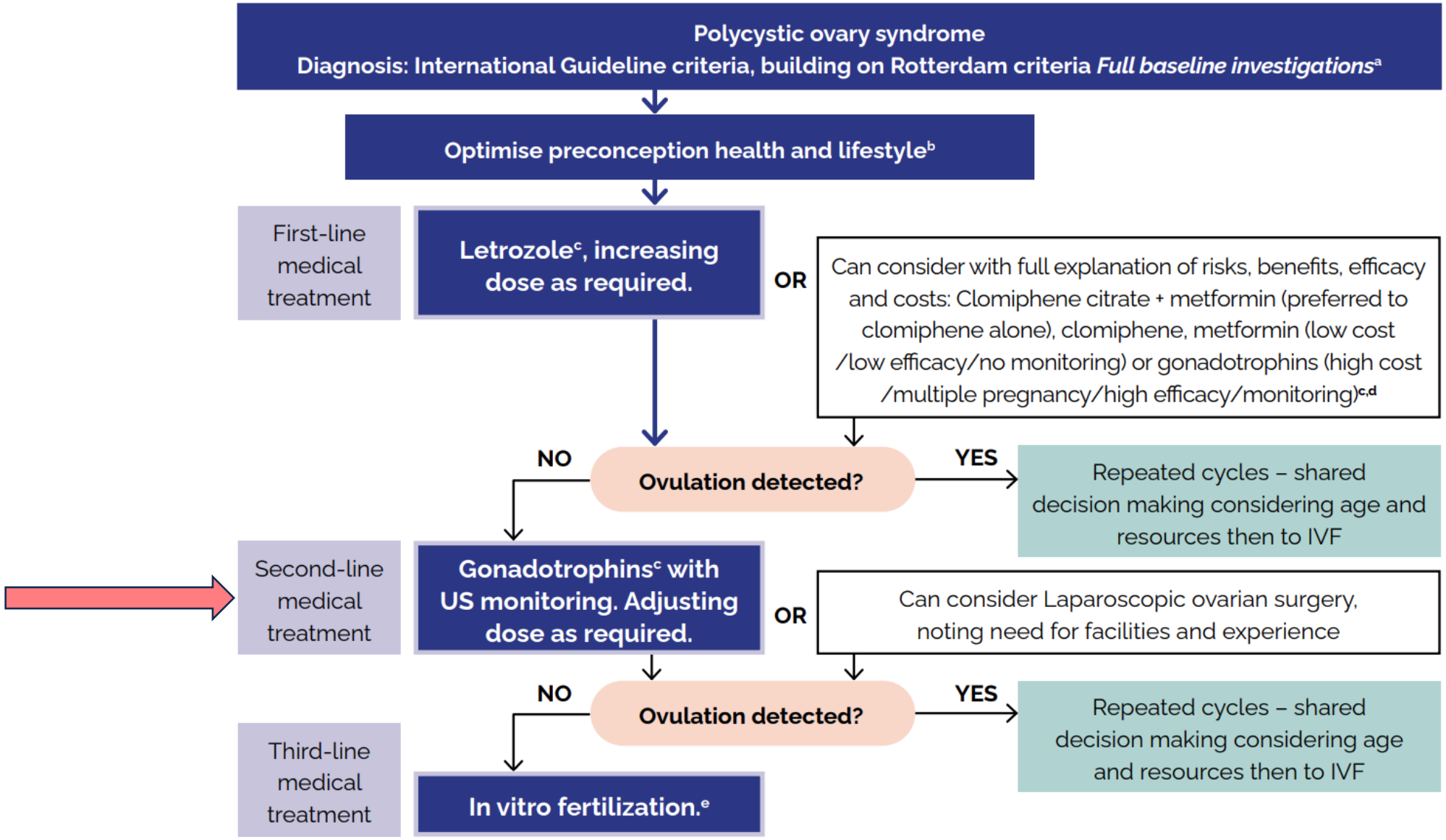
Management of infertility in PCOS



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Gonadotrophins

- 2nd line pharmacological infertility therapy in PCOS
- Multiple low dose FSH injections
- 70% pregnant in 6 months
- 20% Multiple Pregnancy
- OHSS 1/1,000
- Cycle Monitoring
- Compared to letrozole - higher efficacy, cost and multiple pregnancy rate
- Can use in clomiphene resistant patient

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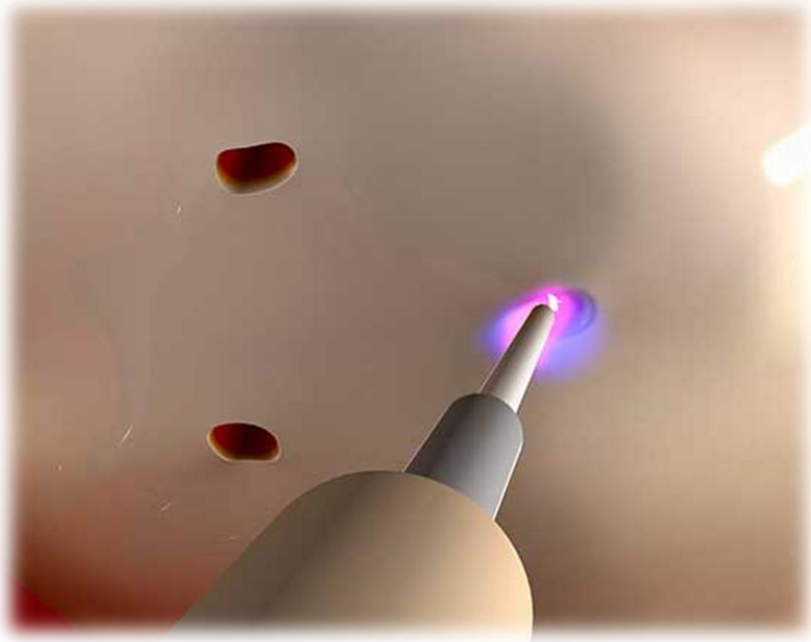
Laparoscopic Ovarian Drilling (LOD)

- Needle point diathermy to ovary at laparoscopy
- Reduces ovarian androgens
- Compared to letrozole - No difference in LBR
- Compared to FSH – lower LBR, lower MPR
- Ability to treat concomitant pelvic pathology
- Avoids Multiple Pregnancy
- Cost of surgery and need for surgical expertise



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In-vitro Fertilization (IVF)

- 3rd line for treatment of infertility in PCOS
  - Or unless other infertility factors eg male factor or tubal blockage
- Not indicated for anovulation alone
- Risk of OHSS
  - PCOS specific protocols should be use
- Cost, invasive

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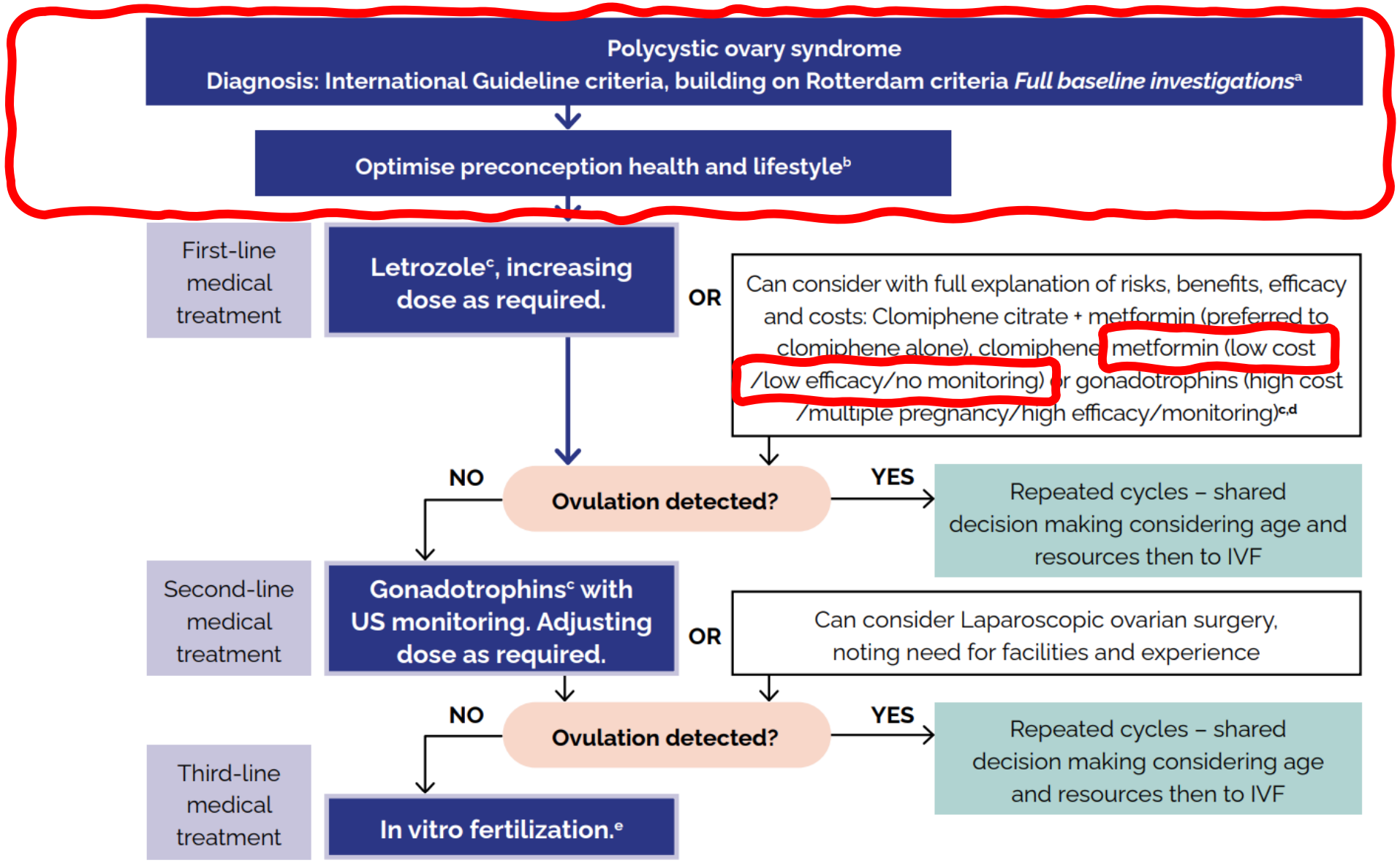
Management of infertility in PCOS in Primary Care



Refer to fertility specialist if TTC.

≥ 12 months if <35

≥ 6 months if >35

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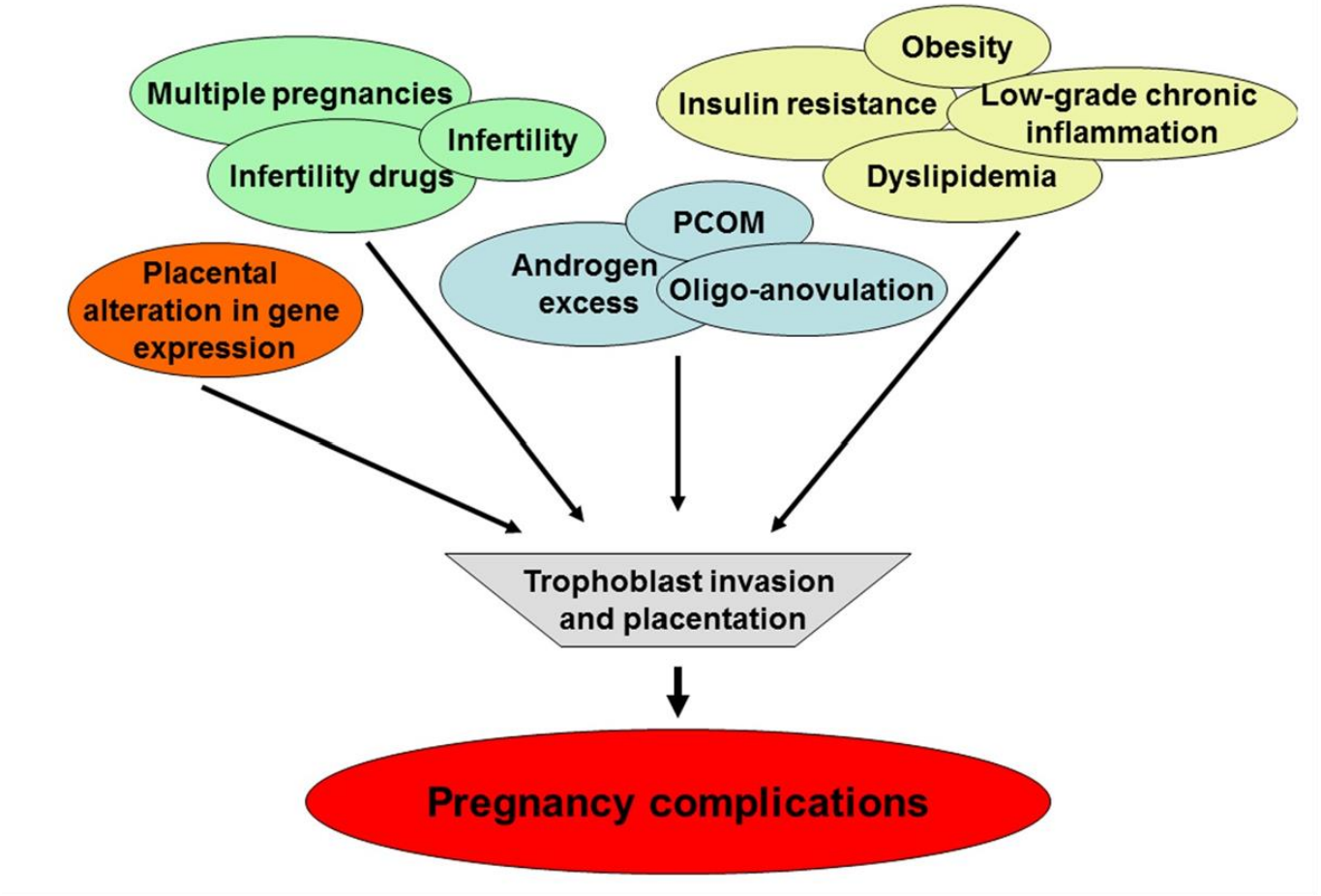
PCOS and Pregnancy

- Should be considered a high-risk condition in pregnancy



Palomba et al 2015

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PCOS and Pregnancy

- Increased risk of:
  - higher gestational weight gain
  - Miscarriage (OR 1.5)
  - GDM (OR 2.35)
  - hypertension in pregnancy (OR 2.2) and preeclampsia (OR 2.28)
  - IUGR (OR 1.77), SGA (OR 1.12) and low birth weight (OR 1.28)
  - preterm delivery (OR 1.54)
  - Caesarean section (OR 1.23)
- NO difference in: LGA, macrosomia, instrumental delivery

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PCOS and Fertility Summary

- Most common endocrine disorder in reproductive age women
  - insulin and androgens
- Affects 10% of reproductive aged women
- Approx 70% may experience problems conceiving
- Most will achieve their desired family size with simple interventions
  - lifestyle modifications +/- ovulation induction
- Should be considered a high-risk condition in pregnancy
- GP plays an important role in identifying and optimising health of patients with PCOS

AskPCOS Website and App

Get the App

Ask PCOS

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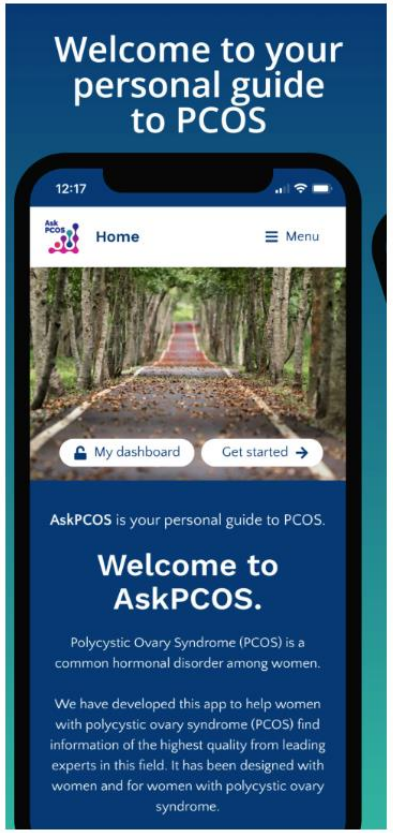

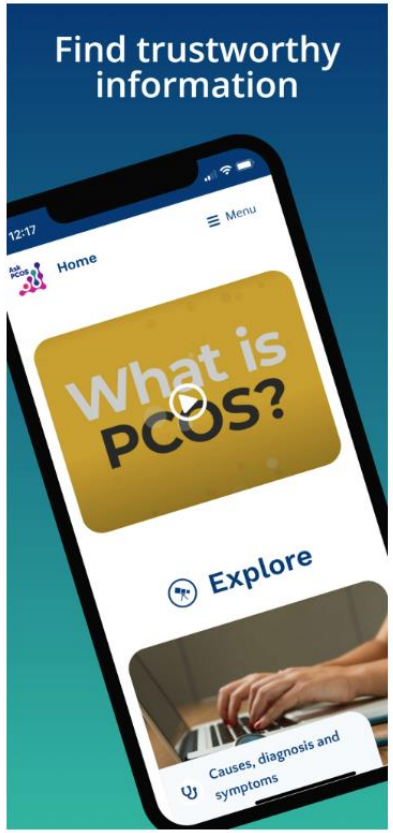

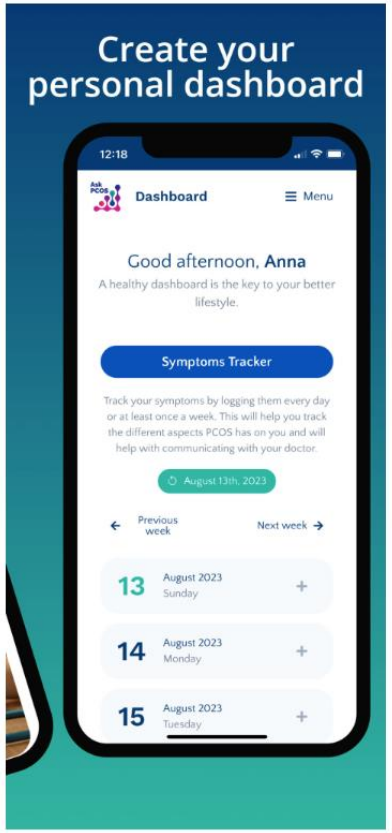

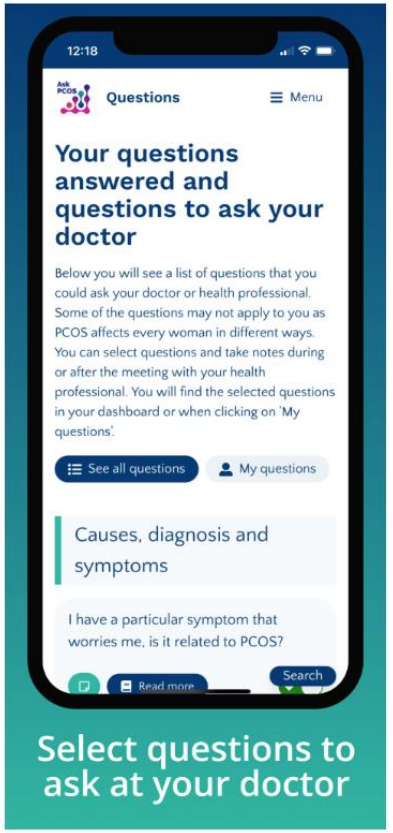

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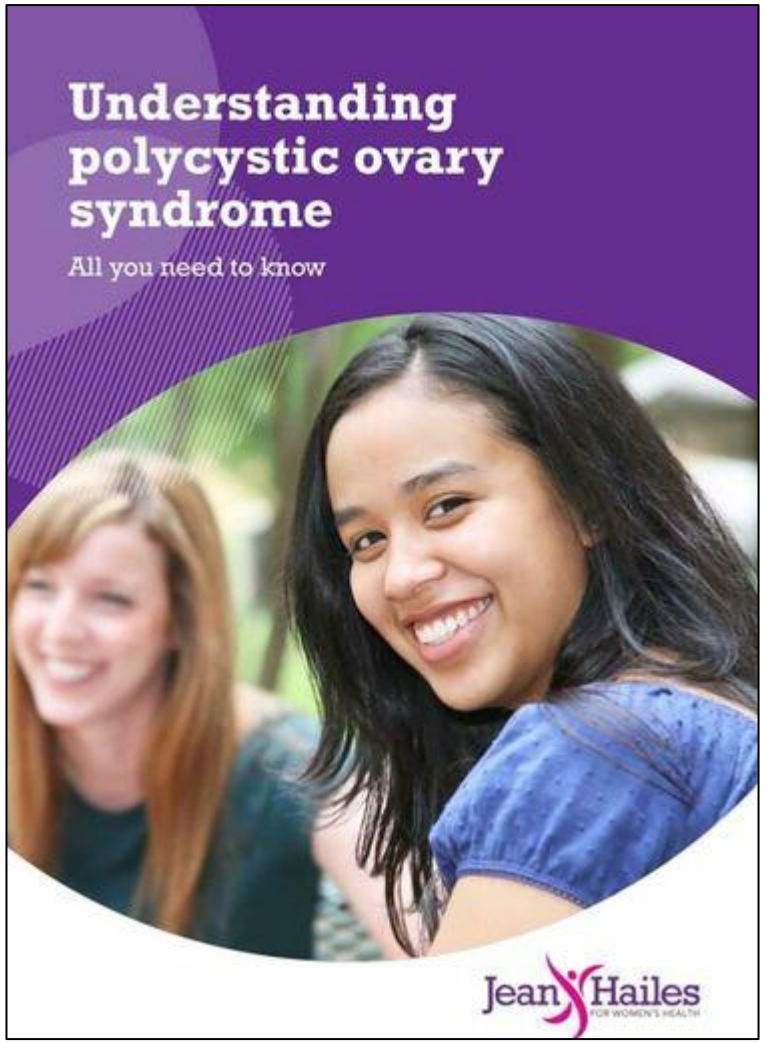
Jean Hailes Website

- www.jeanhailes.org.au
- PCOS fact sheets in various languages
- PCOS booklet



A partnership between:

MCHRI Monash Centre for Health Research and Implementation | MONASH University | Monash Health

- mchri.org.au/PCOS
- Patient resources
- PCOS Health Professional Tool

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- UpToDate
  - Overview of ovulation induction, Ovulation induction with letrozole, Ovulation induction with clomiphene citrate
- www.askPCOS.org
- www.jeanhailes.org.au
- www.mchri.org.au/pcos

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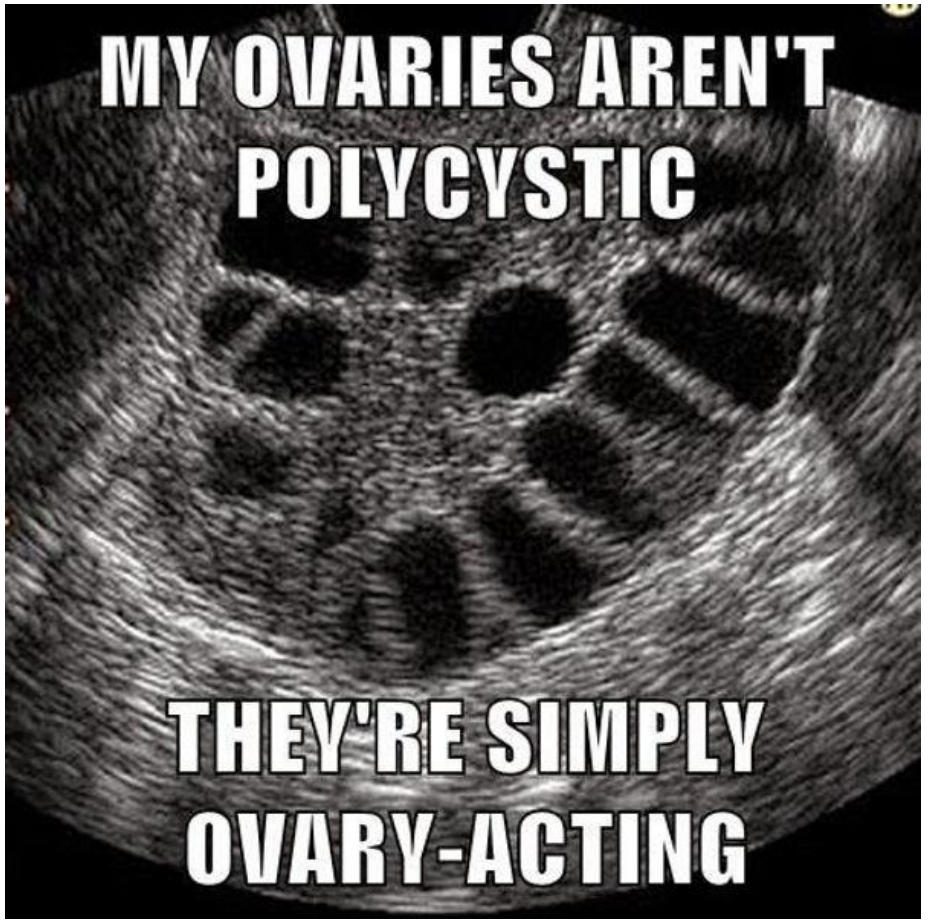
Questions?



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After exclusion of other causes, a diagnosis of PCOS can be made in all cases EXCEPT:

Secondary amenorrhoea and hirsutism

0%

Acne and menstrual cycles of 45 days

0%

High AMH and U/S of ovary with 25 antral follicles

0%

U/S with left ovarian volume 12ml and testosterone level 2.5 (elevated)

0%

In regards to fertility and PCOS:

Infertility is usually easily treated

0%

90% will have trouble conceiving

0%

There’s no increased risk of infertility as long as ovulation occurs

0%

Patients should expect to need IVF in order to conceive

0%

Preconception care in PCOS should include:

Commencing 5mg folic acid daily

0%

HbA1c and fasting glucose level

0%

Education on Reproductive Carrier Screening

0%

Tubal patency testing

0%

Lifestyle advice in PCOS is important to:

Improve metabolic dysfunction

0%

Optimise health for pregnancy

0%

Improve chances of spontaneous ovulation

0%

All of the above

0%

Preconception weight loss in PCOS should:

Include 60min vigorous activity a day

0%

Include a calorie deficient diet specifically designed for PCOS patients

0%

Be aiming for 15% loss of body weight

0%

None of the above

0%

Ovulation induction in a patient with PCOS and infertility:

Should always be performed before proceeding with IVF

0%

Is cheap and effective

0%

Is associated with a higher risk of congenital abnormalities in offspring

0%

Should be continued for a minimum of 6 cycles

0%

Compared to letrozole, ovulation induction with clomiphene citrate:

Metformin use in PCOS infertility:

Has added benefit when added to letrozole, compared to letrozole alone

0%

Has added benefit when added to clomiphene, compared to clomiphene alone

0%

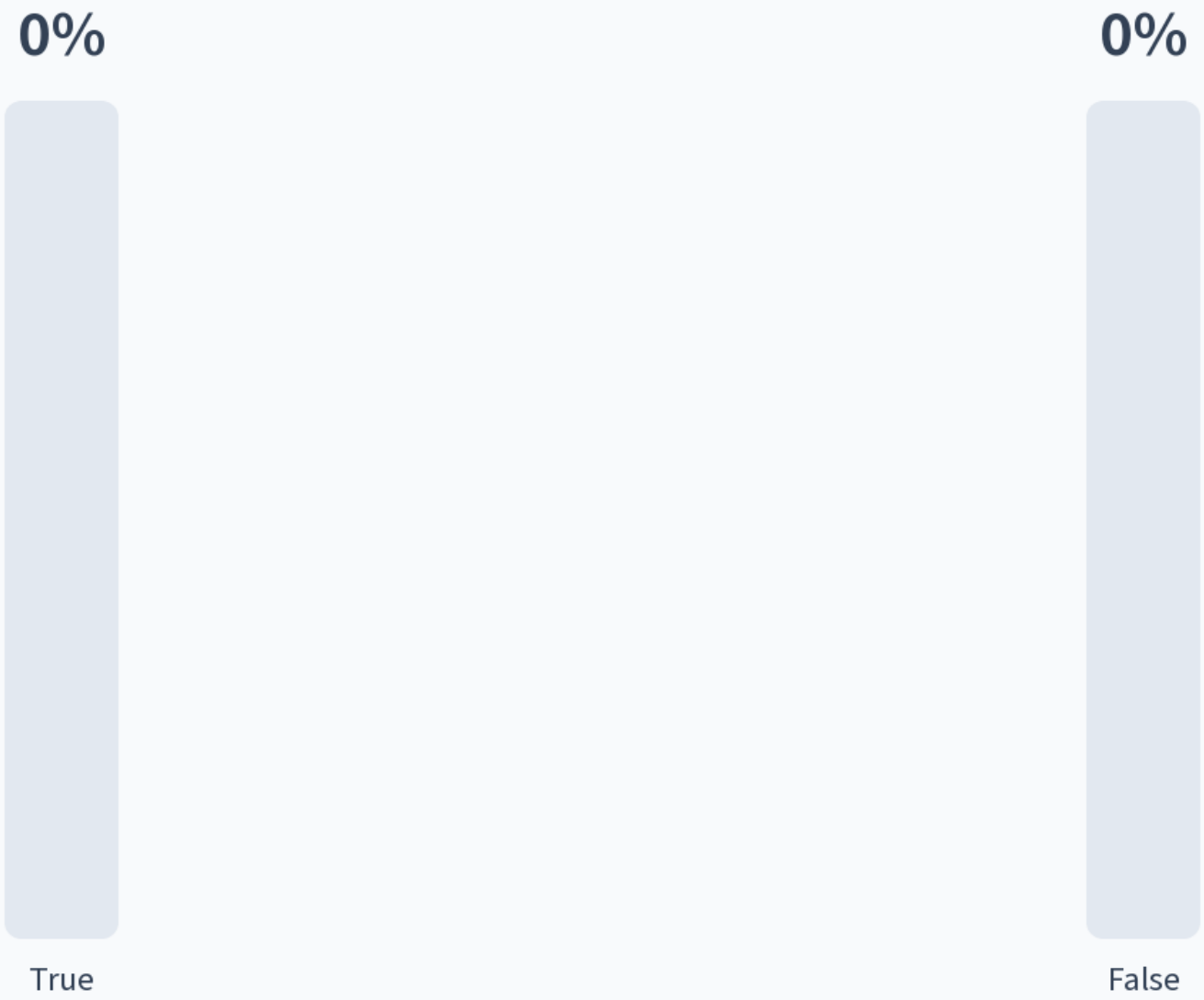
Has higher live birth rates, compared to letrozole

0%

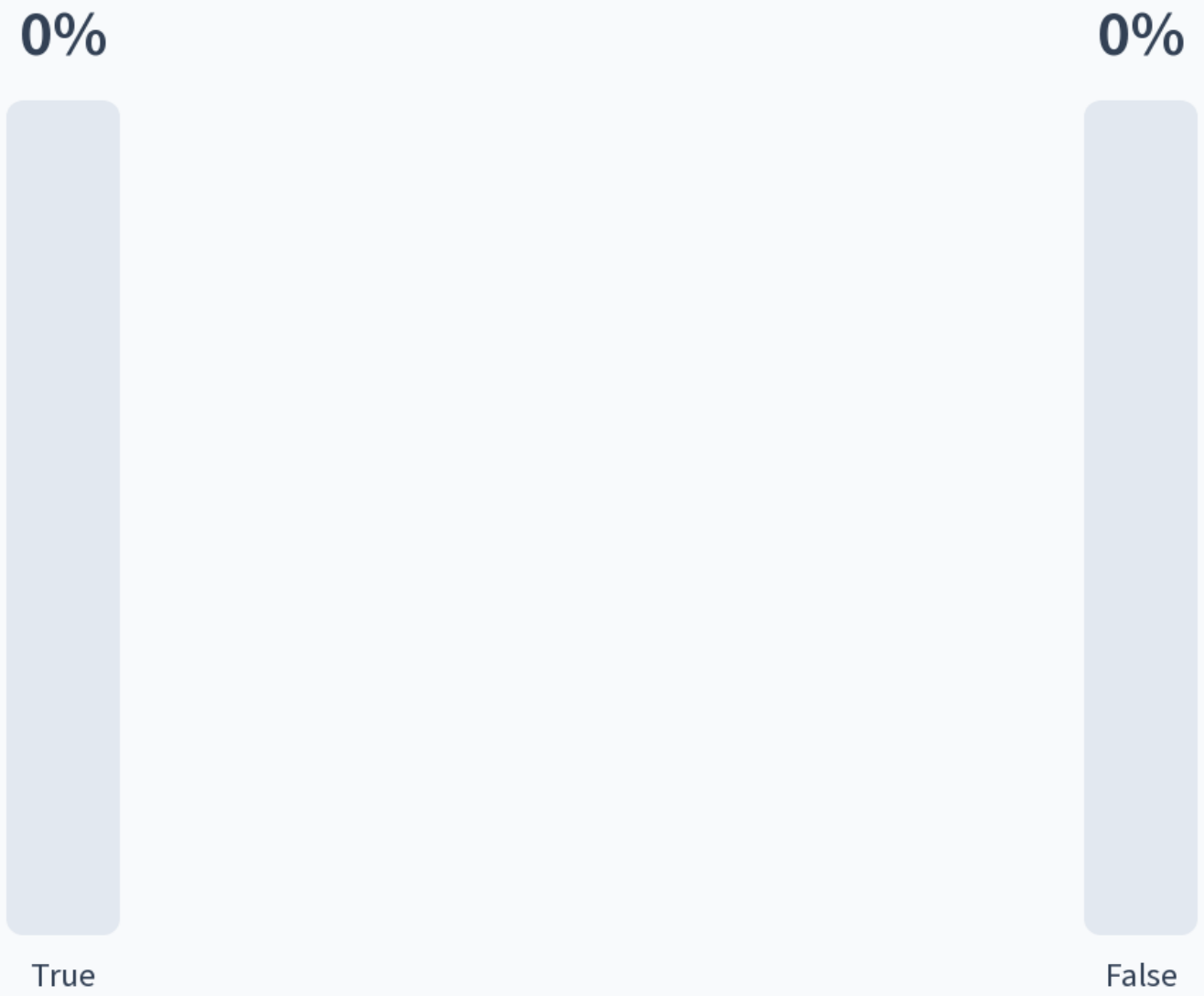
Is off-label so shouldn't be offered

0%

Once pregnant, a patient with PCOS can be treated as per usual care:



PCOS increases the risk of having a macrosomic baby:



In one word or emoji, how are you feeling right now?

Nobody has responded yet.

Hang tight! Responses are coming in.