

Polycystic Ovarian Syndrome Ovulation Induction

Monica Mittal

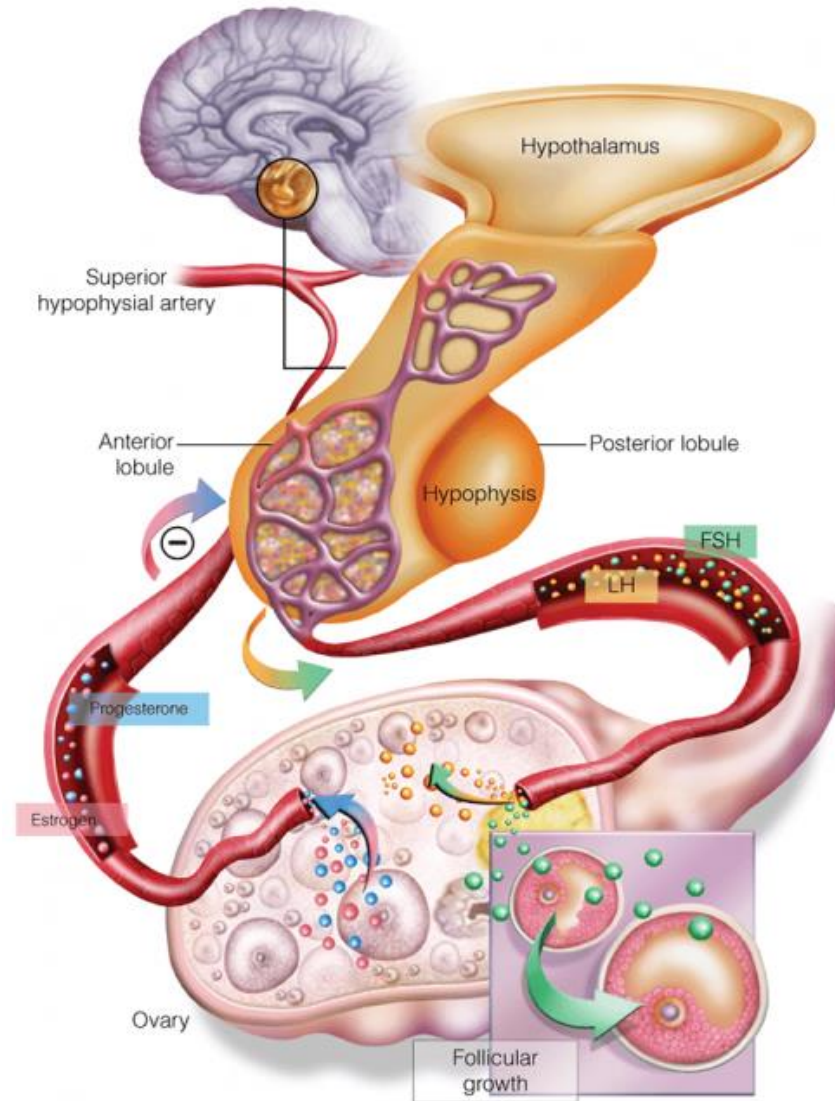
Reproductive Medicine

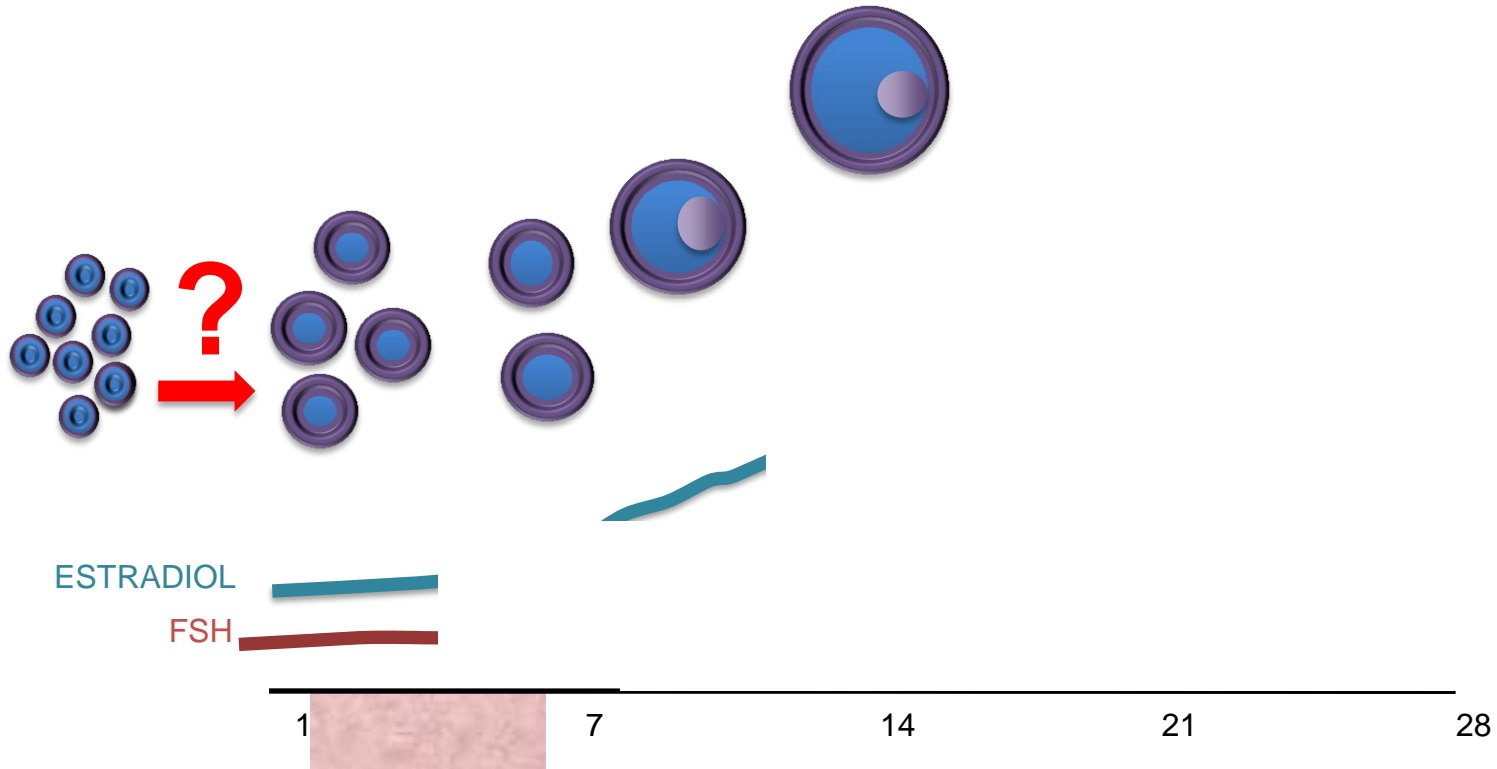
Objectives

WHO classification and Anovulation

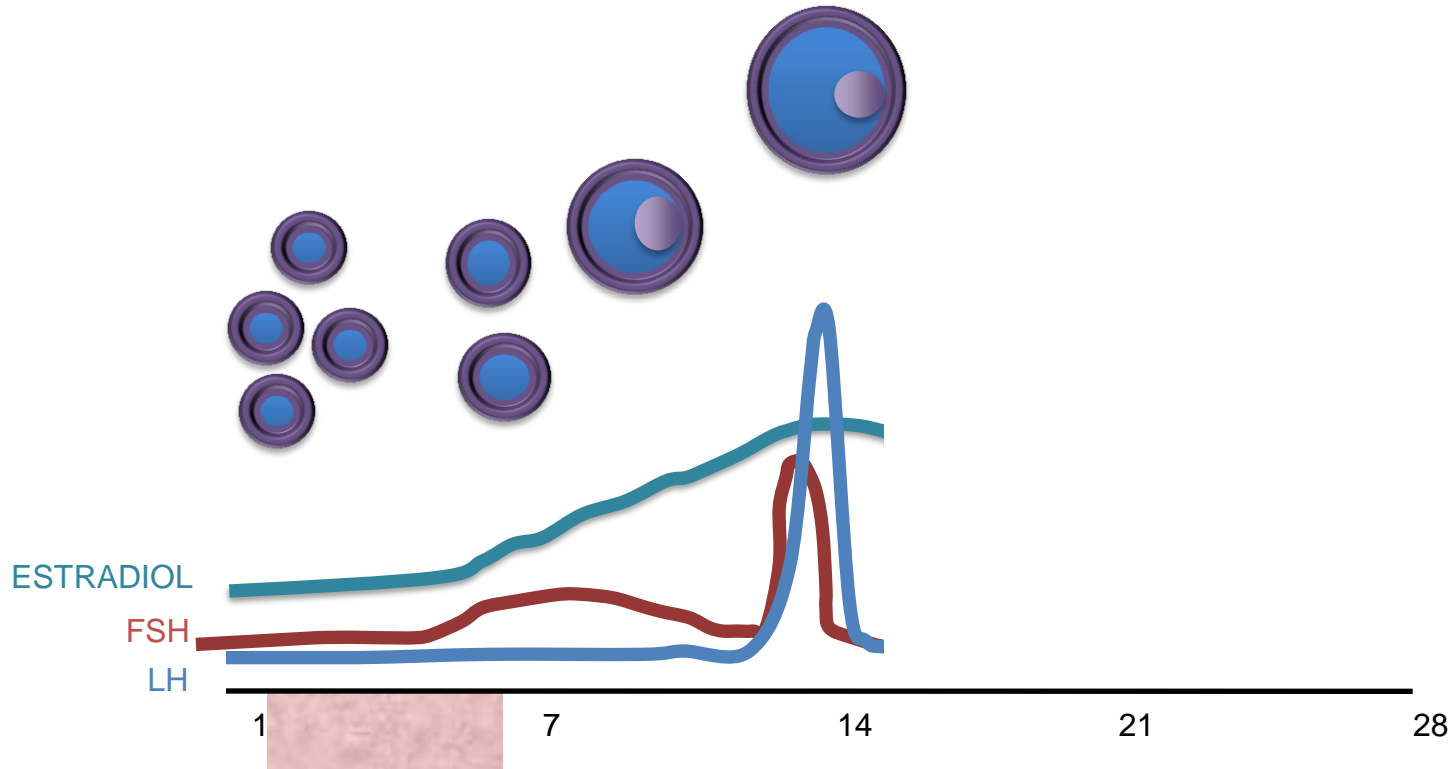
Anovulation and WHO classification

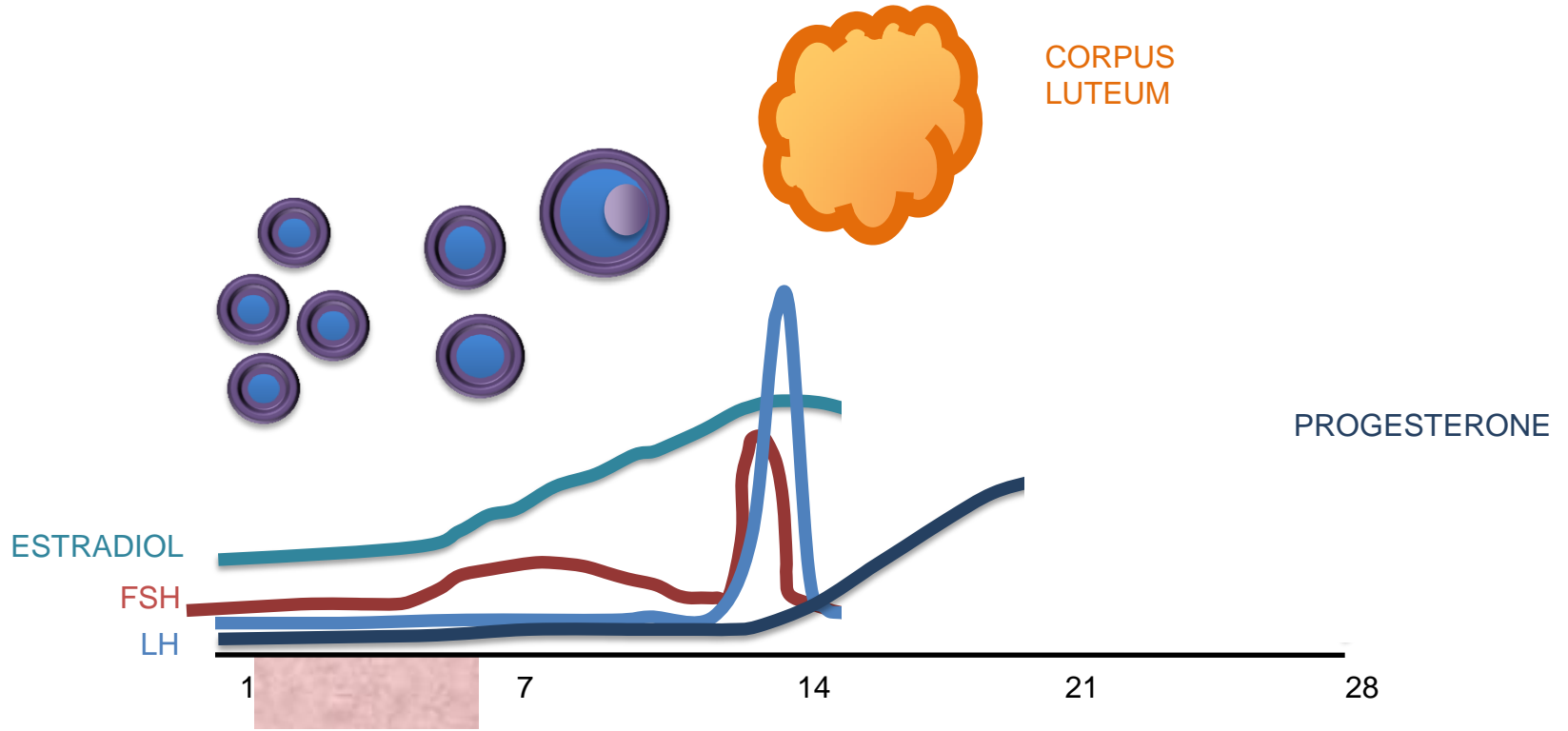
- Ovulation requires a functioning HPO axis, responsive target organ and interrelated feedback mechanism

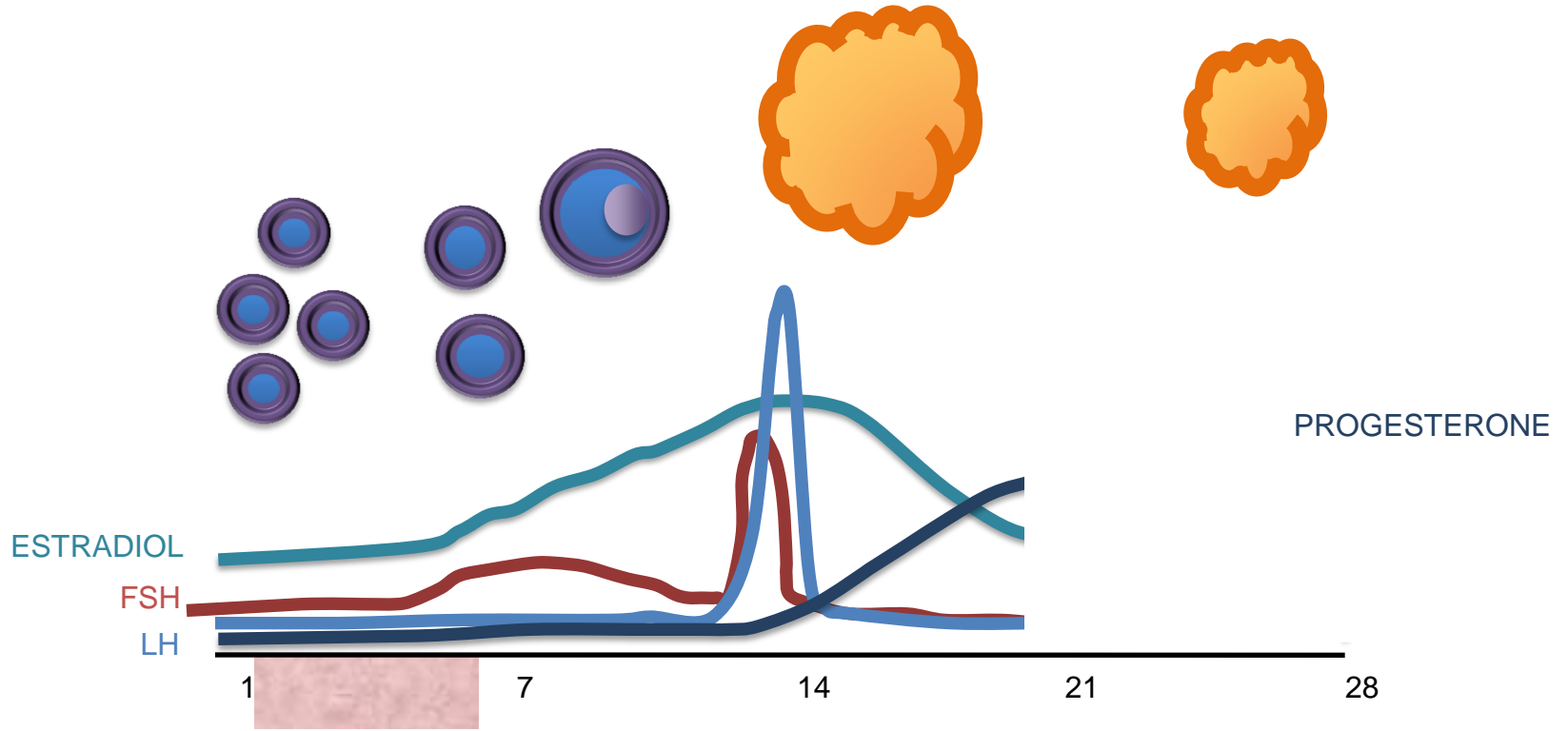


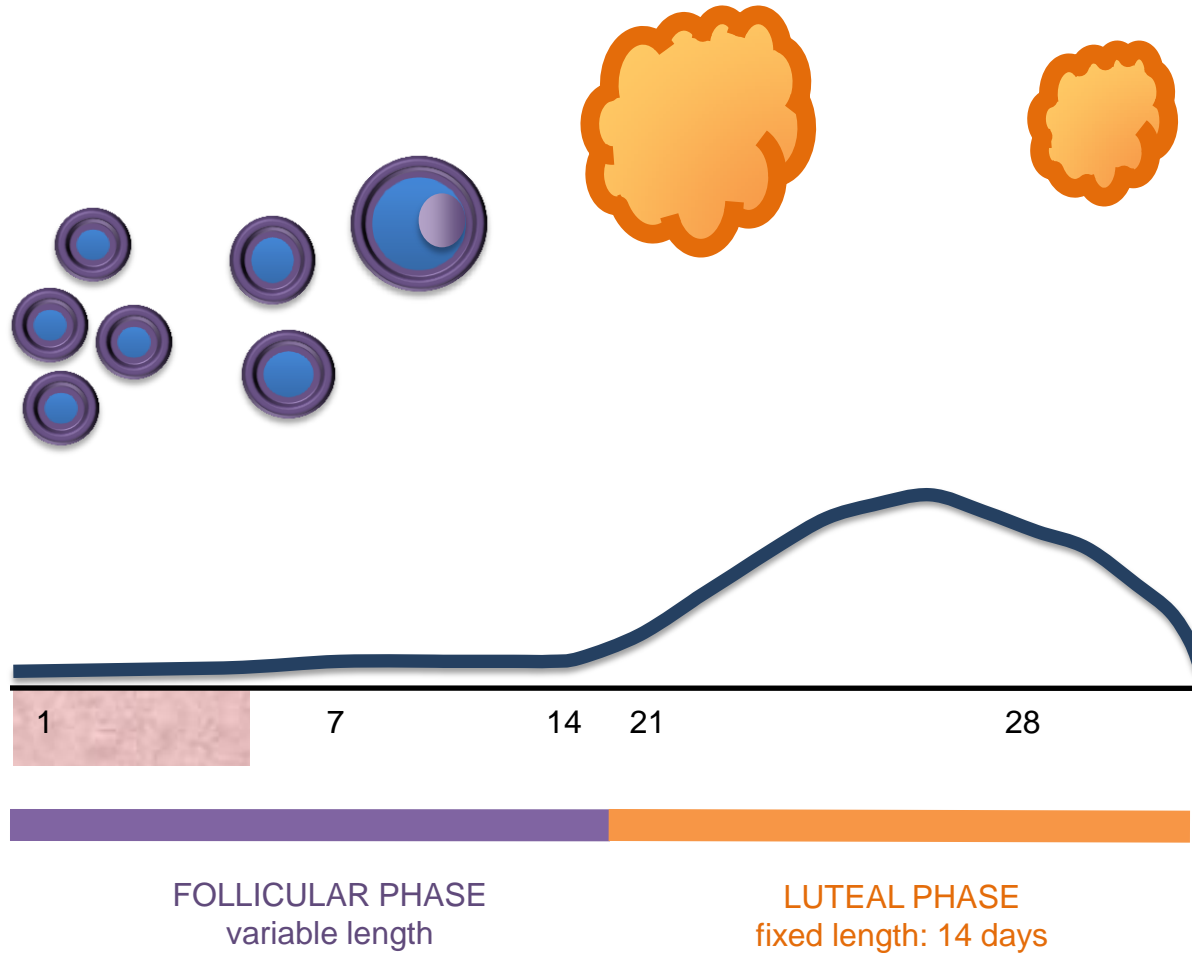


The menstrual cycle









Anovulation and WHO classification

- **Group I:** hypothalamic pituitary failure 5%
- **Group II:** HPO dysfunction 95%
- **Group III:** ovarian failure 5%

Anovulation and WHO classification

- **Group I:**
 - Weight loss – weight stabilisation for 6-15/12, percentage weight gain 90% of ideal / stress / exercise
 - Sheehan's syndrome/infarction (MOH)
 - Prader-Willi (hypothalamic)
 - Laurence-Moon-Biedl (pituitary)
 - Kallmann's syndrome – GnRH deficiency + anosmia
 - Iron overload
 - Trauma/radiotherapy
 - Tumours

Anovulation and WHO classification

- **Group II:**
 - **Predominantly PCOS**
 - Hyperprolactaemia
 - Hypo/hyper-thyroidism
 - Adrenal insufficiency

Anovulation and WHO classification

- **Group III:**
 - POI

Anovulation

	FSH	LH	E2	Testosterone	SHBG
Group I	Low	Low	Low	Low/normal	
Group II	Low/normal	High/normal	High/normal	Mildly raised	Low
Group III	High	High	Low		

History

- Menstrual history from menarche
- Weight changes – eating behaviour
- Exercise history – past and current
 - Ballet / gymnastics / frequency
- Stress / anxiety
 - Exams/new school
- Symptoms
 - Androgenic / low oestrogen / visual / headaches / vomiting / galactorrhoea

- PMHx:
 - Surgery / radiotherapy / head injury
 - Thalassaemia / haemochromatosis / sarcoidosis
 - Steroids / narcotics / dopamine antagonists
 - MOH – Sheehan’s syndrome

Examination

- Height, weight, BMI
- Androgenic features
- Striae, bruising
- Visual fields
- Gravid uterus

Investigations

- UPT
- Bloods:
 - FSH, LH, oestradiol, total free testosterone, FAI, OGTT, TSH, free T4, prolactin, +/- DHEAS, 8am 17-OH progesterone, +/- AMH, +/- IGF-1
 - Androstenedione and dehydroepiandrosterone sulphate (DHEAS) if total testosterone levels are not elevated – provide limited additional information in the diagnosis of PCOS
 - Specialised tests depend on the cause
- Imaging: pelvic / brain MRI / bone DEXA

Polycystic Ovarian Syndrome

PCOS

- Significant public health issue
- Incidence: 8-13% of reproductive aged women
- May have significant long term consequences:
 - Reproductive features – subfertility
 - Metabolic features – DM / cardiovascular risk factors
 - Psychological features – anxiety / depression / body image
 - Endometrial carcinoma – 2-6 fold increased risk

Rotterdam criteria

- 2 out of the 3 features
 - Menstrual irregularity
 - Clinical or biochemical evidence of hyperandrogenism
 - US evidence of PCO (only if >8 years from menarche)



PCOS Sonogram

Menstrual irregularity

- Normal in the first year post menarche as part of 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)

Features of PCOS

Feature	Percentage
Irregular cycles	70-85%
Regular cycles	15-30%
Subfertility	42-75%
Hirsutism	64-69%
Acne	7-35%
Alopecia (frontal)	
Obesity	35-41%

Management of hyperandrogenism

Treatment	Comments
COCP	Suppresses ovarian hormones; raises SHBG +/-blocks testosterone; regulates cycle; contraception
Antiandrogens Cyproteroneacetate Spironolactone	Contraception required – can add to COCP after 6/12 and cosmetic therapy have been unsuccessful: 25-50mg x 10 days/month – check LFTs; some cycle regulation 100-150mg OD mane; check LFTs and U&Es
Eflornithine cream (Vaniqa)	Blocks hair development; skin irritation common but usually improves
Cosmetic electrolysis laser	Plucking/threading/waxing but in-grown hairs Laser/electrolysis – top ups usually required Best in combination with hormone suppression

Which COCP?

- antiandrogen
- least androgenic
- mildly androgenic
- most androgenic

Combined Hormonal Contraception and Risk of Venous Thromboembolism	
Progestogen in Combined Hormonal Contraceptive	Estimated incidence per 10 000 women per year of use
Non-pregnant, not using combined hormonal contraception	2
→ Levonorgestrel(1)	5–7
→ Norgestimate(1)	
→ Norethisterone(1)	
Etonogestrel(1)	6–12
Norelgestromin(1)	
→ Gestodene(1)	9–12
→ Desogestrel(1)	
→ Drospirenone(1)	
→ Dienogest(2)	Not known—insufficient data
Nomegestrol acetate(2)	

Management of menstrual irregularities

- Why?
 - To protect against endometrial cancer
 - To prevent heavy anovulatory bleeding
 - Convenience
 - To control PMT-like symptoms

Management of menstrual irregularities

- How?
 - COCP
 - Cyclical progesterone – MPA 10mg OD for 10/7 each month
 - Mirena

Management of anovulation/subfertility

- Ovulation induction
 - Letrozole (1st line)
 - Gonadotrophins (2nd line)
- IVF (3rd line)

Ovulation Induction

Aim

- Successful ovulation induction is measured on confirmation of ovulation and not on conception
- Restorative treatment of fertility

Criteria for treatment

- Anovulation subfertility and no other cause
- BMI 18.5-35kg/m²
 - If BMI >35kg/m² + coexistent morbidity consider referral for metabolic surgery

Methodologies

- Weight loss
 - 5-10% (1200 – 1500 kcal/day)
 - BMI and waist circumference
- Clomiphene citrate
 - Cumulative pregnancy rate (6 months) 50%
 - Cumulative pregnancy rate (9 months) 67%
 - Headache / visual disturbances / breast tenderness / bloating / thin endometrium
- Letrozole
 - First line pharmacological therapy for subfertility
 - Beneficial in women who are clomiphene citrate resistant / raised BMI
 - Higher ovulation rates
 - Lower multiple pregnancy rates and miscarriage rates
 - Unlicensed
- Metformin
- Gonadotrophins
 - Second line therapy
 - Cumulative pregnancy rate (6 months) 70%
- Laparoscopic ovarian drilling
 - Cumulative pregnancy rate after 12 months after LOD is equivalent to after 6 cycles of ovulation induction with hMG

Weight loss / gain

- Weight loss
 - Increased ovulation frequency
 - Increased pregnancy rate
 - Increased sensitivity to ovulation induction
 - Reduction in androgenic symptoms
 - Reduced risk of DM
- Weight gain
 - Increased frequency of all symptoms
 - Increased risk of DM

Letrozole versus clomiphene citrate

- Lower risk of multiple pregnancies with letrozole versus clomiphene citrate

Cochrane review 2014

- Live births
 - 9 RCTs – higher with letrozole
n=407, OR 1.64, 95% CI 1.32 to 2.04
- Clinical pregnancy
 - 15 RCTs – higher with letrozole
n=2816, OR 1.4, 95% CI 1.18 to 1.65

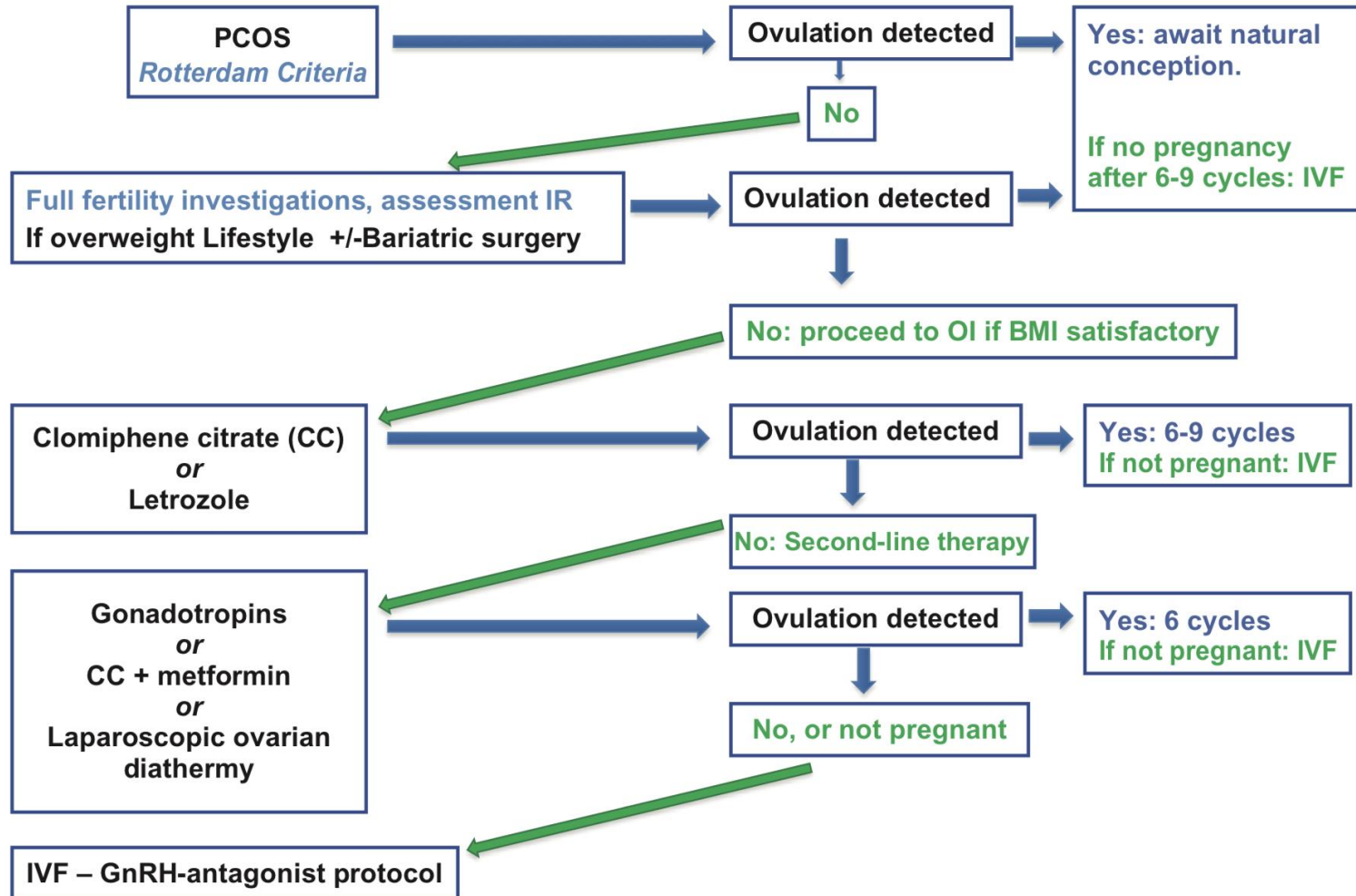
Metformin

- Recommended in the presence of metabolic features
- BMI $\geq 25\text{kg/m}^2$
- Insulin sensitising agent
- Increased but low ovulation frequency
- Lower conception rate per ovulation than all other methods
- If BMI $\geq 30\text{kg/m}^2$, consider metformin in combination with clomiphene citrate
- May improve response rate to clomiphene citrate
- Debatable reduction in androgenic symptoms
- Side effects
- Prescribed off-label

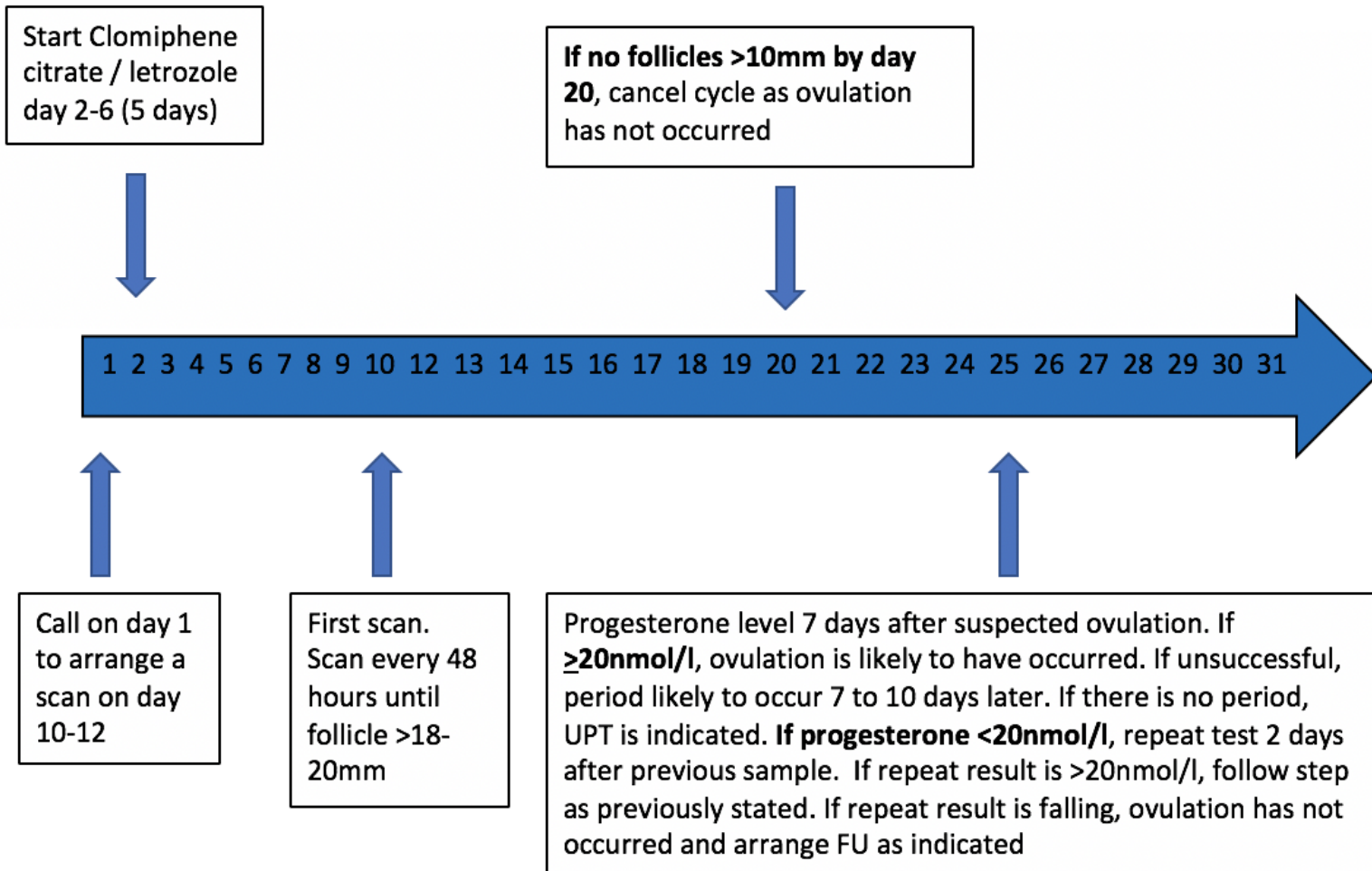
Inositol

- Experimental

Consensus Algorithm for OI in PCOS

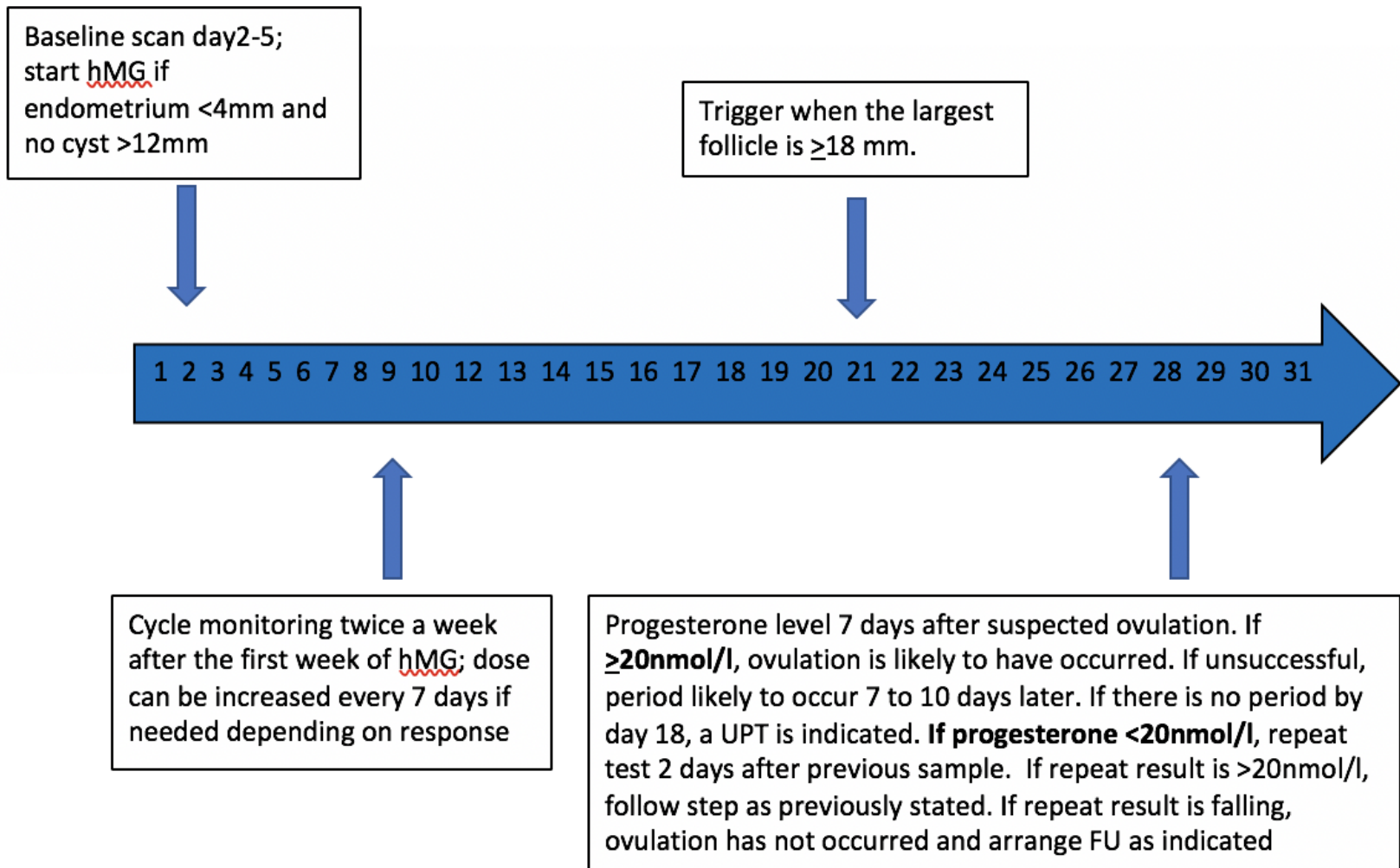


Clomiphene citrate / letrozole



If ≥ 3 follicles of $> 16\text{mm}$, abandon cycle
If endometrium $< 7\text{mm}$, consider alternative protocol
No routine use for trigger or luteal phase support

Human menopausal gonadotrophin



If ≥ 3 follicles of $> 14\text{mm}$, abandon cycle

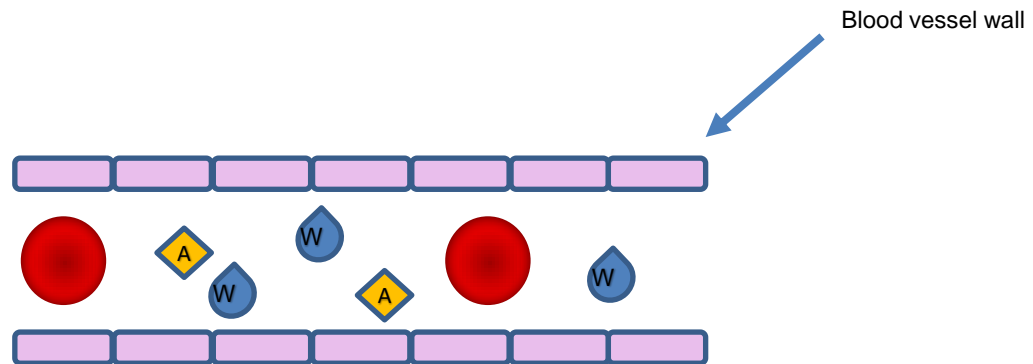
If **endometrium** $< 7\text{mm}$, consider alternative protocol




Luteal phase support is required for women with hypogonadotropic hypogonadism

Risks

- Multiple pregnancies
- OHSS

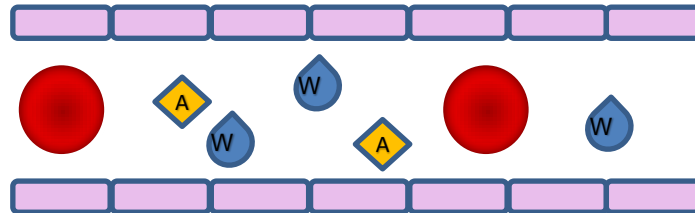
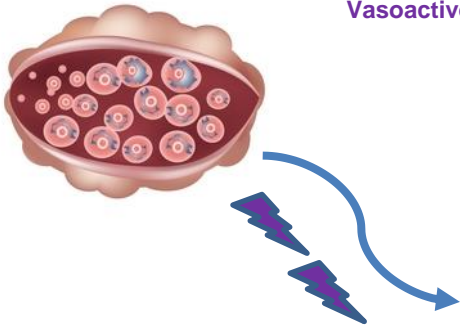
Healthy Woman






	Red blood cell
	Albumin
	Water

OHSS Pathophysiology

Vasoactive substances



	Red blood cell
	Albumin
	Water

Early OHSS: usually presents within 7 days of the hCG injection
Late OHSS: typically presents 10 or more days after the hCG injection

Laparoscopic ovarian drilling

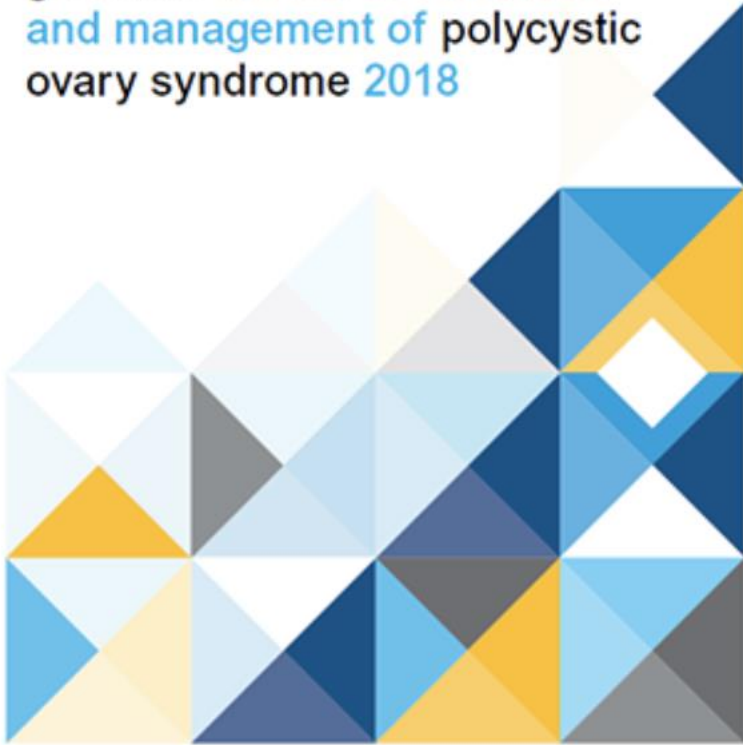
- Aim
 - To induce spontaneous ovulation
 - To render someone clomiphene resistant
clomiphene sensitive
 - To aid ovulation induction with hMG if difficult to control and IVF is not an option

Criteria for LOD

- PCO confirmed on US
- Corresponding high AMH $>25\text{pmol/l}$
- BMI $<35\text{kg/m}^2$

Sources for further information

International evidence-based
guideline for the assessment
and management of polycystic
ovary syndrome 2018



International evidence-based
guideline for the assessment
and management of
ovary syndrome 201



Royal College of
Obstetricians &
Gynaecologists

Long-term Consequences of
Polycystic Ovary Syndrome

Green-top Guideline No. 33
November 2014



International evidence-based guideline for the assessment and management of ovary syndrome 201



Long-term Cons Polycystic Ovary

Green-top Guideline No.
November 2014



Information for you

Published in June 2015

Polycystic ovary syndrome: what it means for your long-term health

About this information

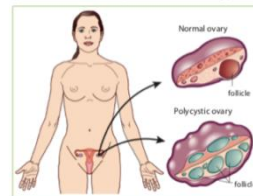
This information is for you if you want to know more about polycystic ovary syndrome (PCOS). It may be helpful if you are a patient, relative or friend of someone who has PCOS.

What is polycystic ovary syndrome?

PCOS is a condition that can affect your periods, fertility, hormones and aspects of your appearance. It can also affect your long-term health. Estimates of how many women it affects vary widely from 2 to 26 in every 100 women. This information is about the effects on your long-term health and does not cover specific treatment options for PCOS.

What are polycystic ovaries?

Polycystic ovaries are slightly larger than normal ovaries and have twice the number of follicles (fluid-filled spaces within the ovary that release the eggs when you ovulate).



International evidence-based guideline for the assessment and management of ovary syndrome 201

Human Reproduction Update, Vol.22, No.6 pp. 687–708, 2016

Advanced Access publication on August 10, 2016 doi:10.1093/humupd/dmw025

human reproduction update

Long-term Polycystic

Green-top Guid
November 2014

The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance

Adam H. Balen^{1,*}, Lara C. Morley¹, Marie Misso², Stephen Franks³, Richard S. Legro⁴, Chandrika N. Wijeyaratne⁵, Elisabet Stener-Victorin⁶, Bart C.J.M. Fauser⁷, Robert J. Norman⁸, and Helena Teede²

Polycystic ovary syndrome: what it means for your long-term health

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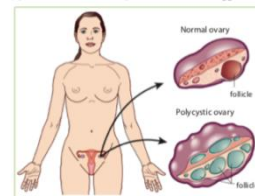
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QUESTIONS...

