Prof. Abha Majumdar

Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA

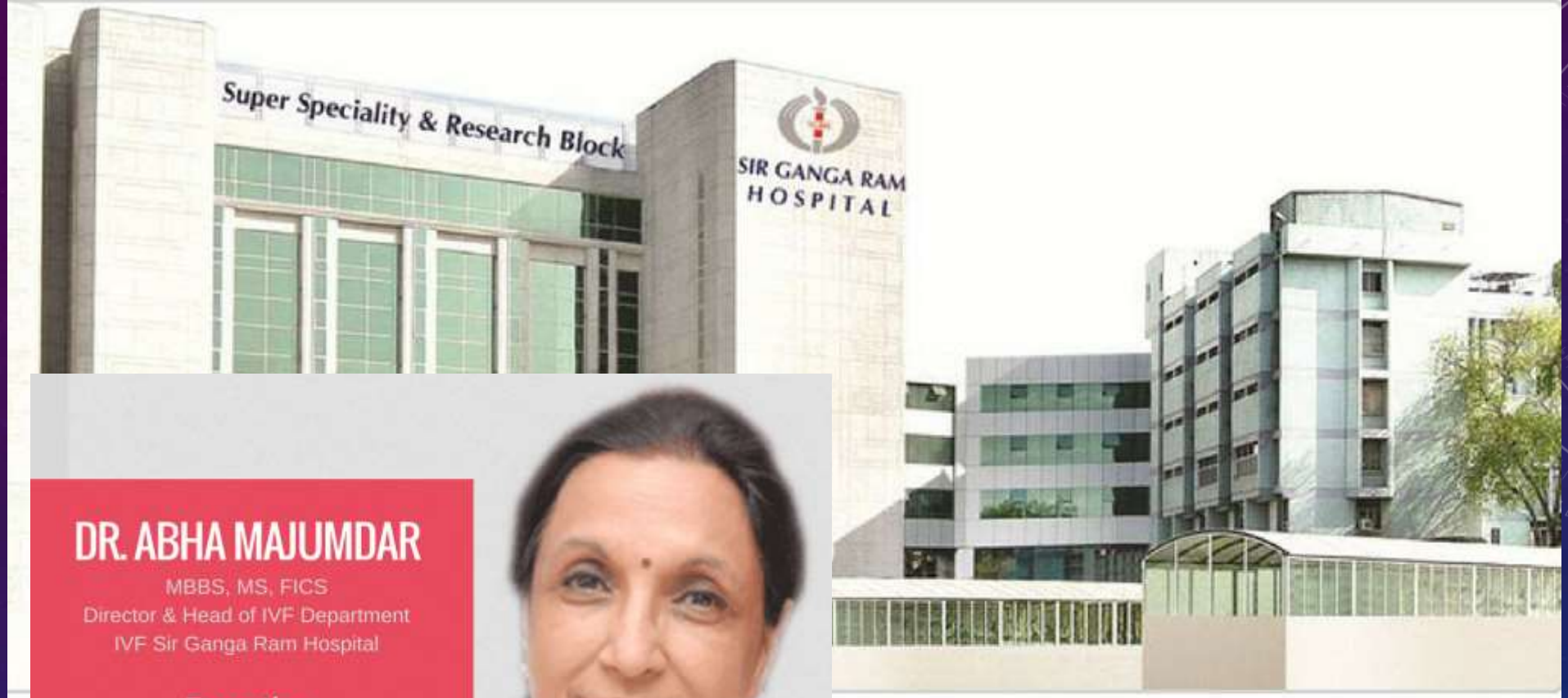
President's Medal for best medical graduate of year1970-75
Award from DMA on Dr. B.C Roy's birthday: outstanding contribution to medicine 1999
Lifetime Medical excellence award Obs & Gyne by Hippocrates foundation 2014
Abdul Kalam gold medal 2015 & **Rashtriya Gaurav Gold Medal award** 2017 by Global Economic Progress & Research Association.
Distinguished teacher of excellence award for PG medical education by ANBAI & NBE 2017**.**

Awarded at the Economic Times Health Care awards as the **"ICON of IVF of North India",** her team awarded as the '**Best integrated national team of IVF'**, & the most coveted award as the **'National IVF Champion of the year 2019'.**

Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE, since 2007, IFS since 2014, ISAR 2014 and by FOGSI for basic & advanced infertility training since 2008.

Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences',** and member of advisory board for '**Journal of Fertility Science & Research'.**

Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection and ART.



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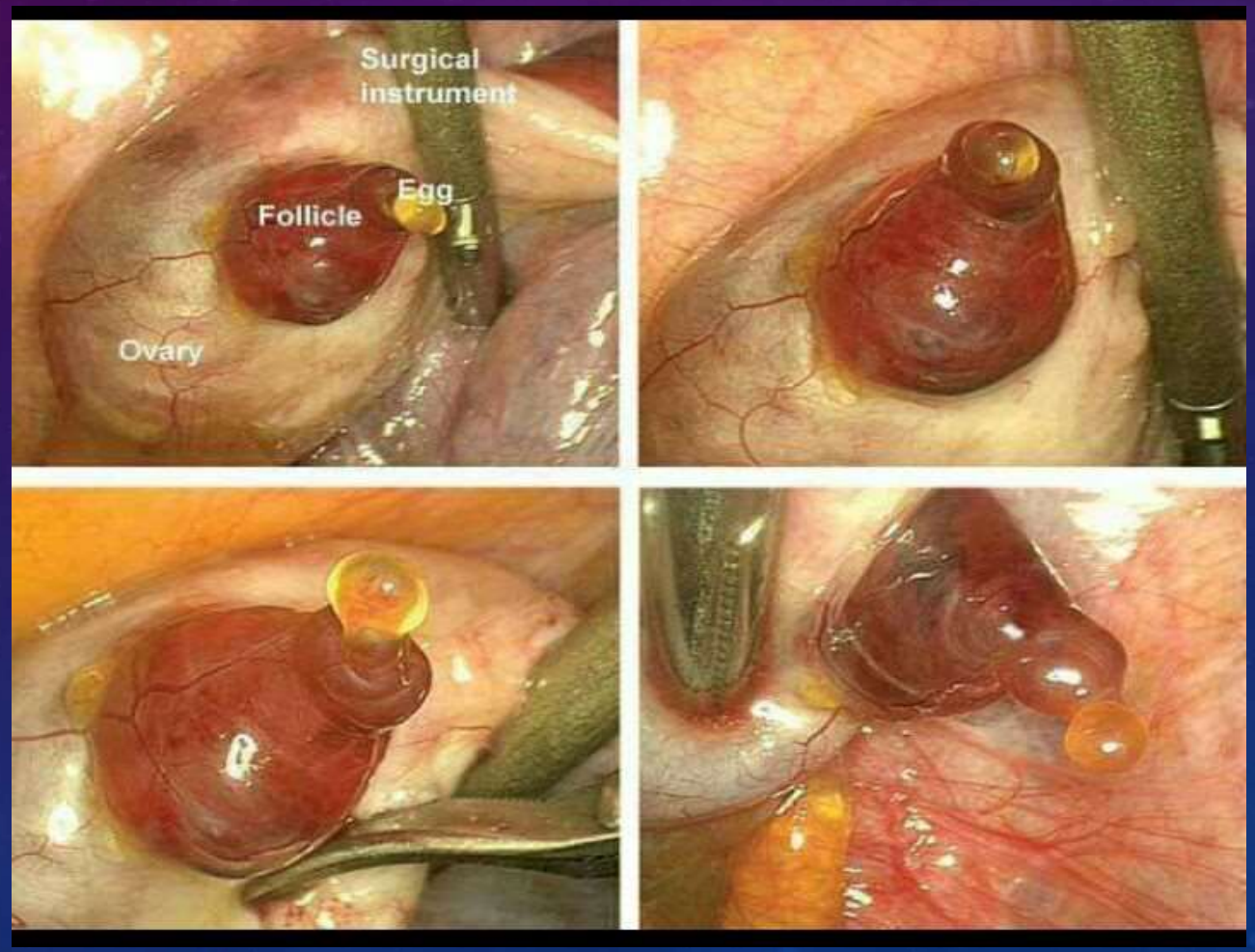
Basics of
Ovulation induction /stimulation

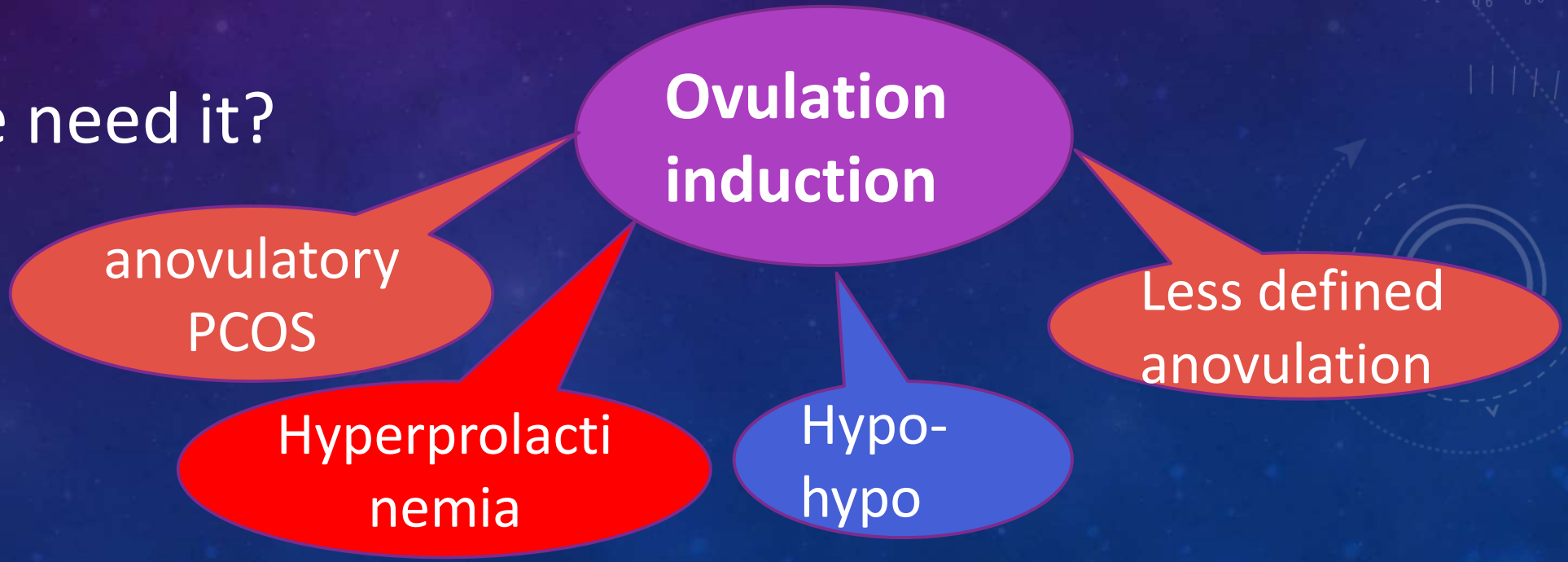


OVULATION INDUCTION

- What is ovulation induction?

Development of one dominant follicle to cause ovulation in women who do not ovulate naturally on their own

Where do we need it?



- Is there any other parallel technique of ovulation induction?

OVULATION STIMULATION (OS)

- What is ovulation stimulation?

Stimulation of ovulation for purpose of multi-follicular development in women who ovulate spontaneously or with medicines.

- When do we need ovulation stimulation?
  - IUI
  - IVF

Synonyms: OS, OH, COH, COS

DIFFERENCES IN DRUGS USED FOR OI & OS?

Drugs used for OI:

These vary according to cause of anovulation

- Clomiphene citrate
- Aromatase inhibitor
- Gonadotropins
- Dopamine agonist

Drugs for OS:

- Oral ovulogens- CC/AI/ gonadotropins for IUI with aim to make 2 dominant follicles
- Gonadotropins with GnRh analogues for COS in IVF to make 10 to 15 follicles.

DIFFERENCE IN METHOD OF OI/OS?

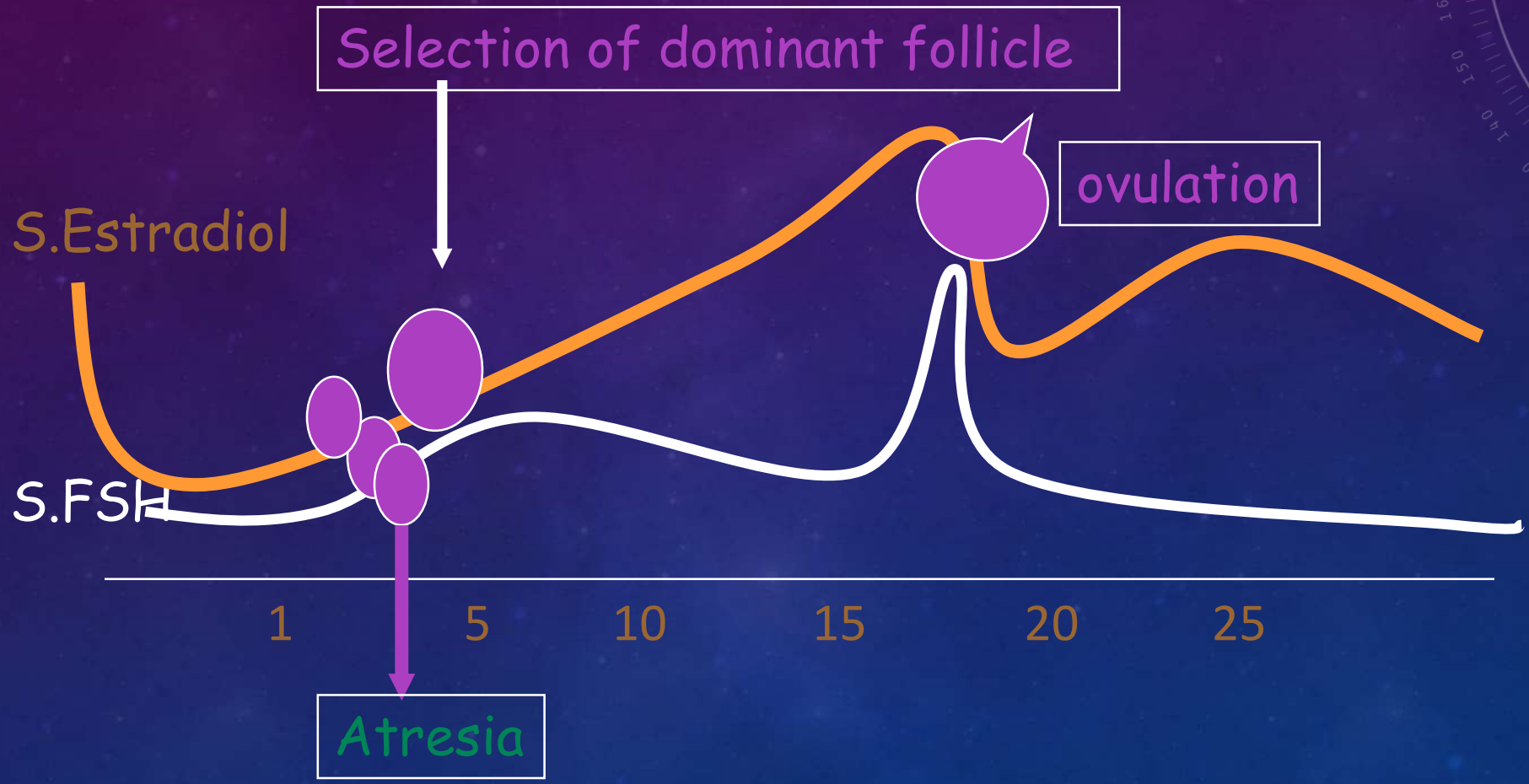
Ovulation induction:

- No need to suppress LH surge before ovulation is allowed
- Ovulation trigger/HCG not mandatory
- Lower risk of OHSS; if occurs dependent on the intensity of ovulatory response, drug & dosage used

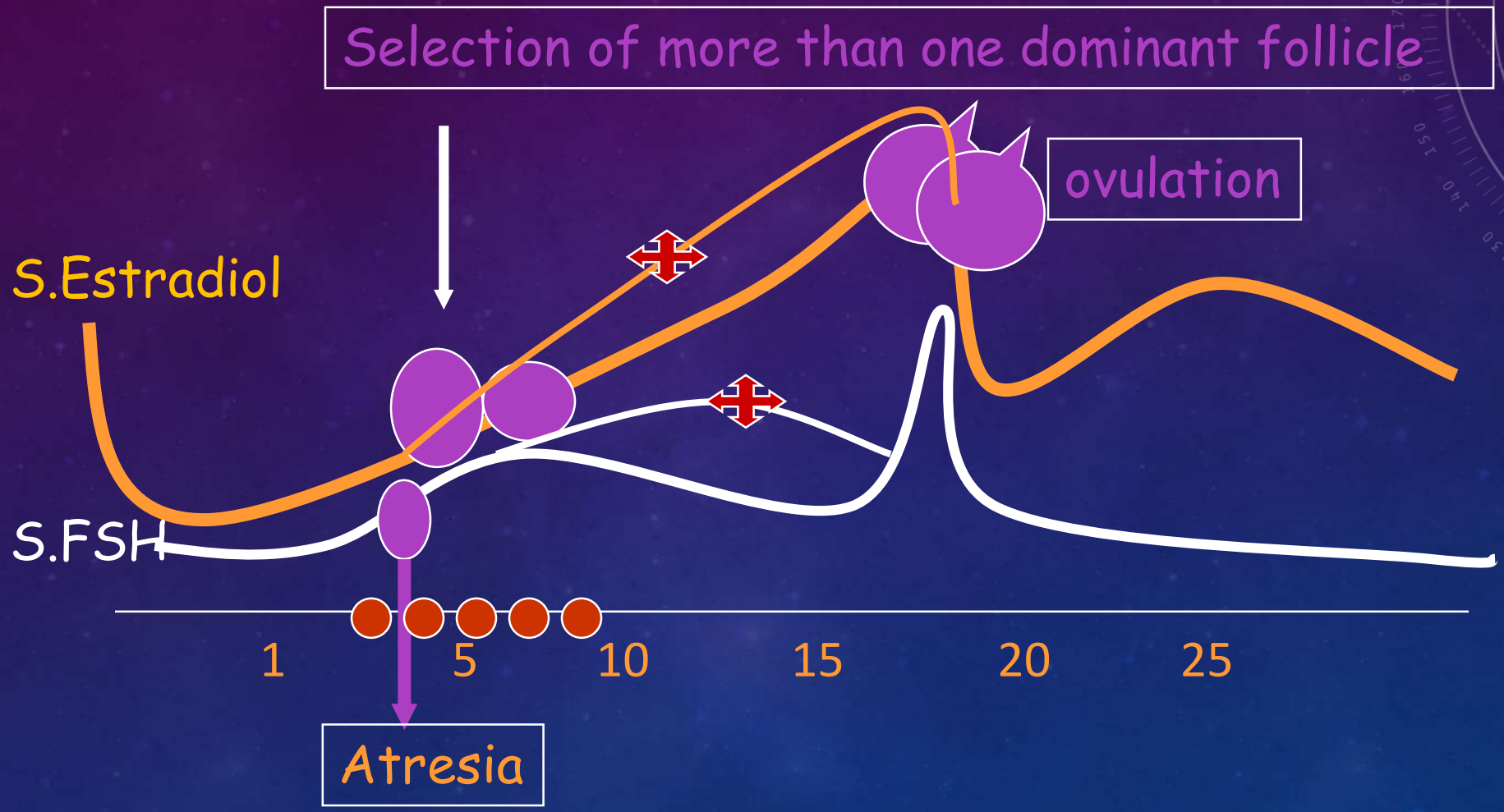
Ovulation stimulation

- LH surge needs to be controlled in IVF cycles but rarely in IUI cycles (only to overcome weekend IUI)
- Ovulation trigger is required to time ovulation precisely
- Higher risk of OHSS independent of PCOS may occur in any patient

Events in a natural cycle or in ovulation induction



Events in a stimulated cycle for IUI



Steps to start ovulation induction with CC/letroz in PCOS with amenorrhea?

- Ultrasound: endometrial thickness
  - *Endometrial thickness > 5 mm with silent ovary: give progestin to induce withdrawal bleeding*
  - *Endometrial thickness ≤5 mm- start stimulation directly or give OCPs 21 days for withdrawal*
- OI/OS started by day 2 to 5 of cycle:
  - *longer CC-free period before ovulation if started early*
- OI can be started on any day post menses with variable results in anovulatory PCOS (after ruling out pregnancy)

Dickey RP, Taylor SN, Curole DN, et al. Hum Reprod. 1996;11(12):2623-8.

Administration of CC/letrozole as single agent in anovulatory PCOS?

- Starting dose for CC 50/day or let 2.5 mg/day for 5 days
- ↑ dose for CC to 100 mg or let 5 mg/day in subsequent cycle if no ovulation
- No need to increase dose if ovulation happens with CC 50 mg/day or let 2.5 mg/day
- 3 cycles no ovulation with CC 100 mg/day or let 5mg/day revise strategy of treatment
- Maximum dose allowed of CC is 500 mg in one cycle

Medically reviewed by Drugs.com. Last updated on Feb 10, 2022.

Duration of treatment with CC?

Limited to six ovulatory cycles

1. no pregnancy clomiphene failure
2. no ovulation clomiphene resistance

Absence of ovulation →

- Administration of gonadotropins with or without oral ovulogens
- Medical pre treatment (metformin)
- Surgical pre-treatment (laparoscopic ovarian drilling)

Absence of pregnancy despite ovulation 3 to 6 cycles→

- IUI
- IVF

Eijkemans MJ, Imani B, Mulders AG, et al Hum Reprod.
Fluker MR. In: Homburg R (Ed). Polycystic Ovary Syndrome. London: Martin Dunitz Ltd.; 2001

HOW DO YOU OR YOUR PATIENT MONITOR CYCLES WITH USE OF CC OR LETROZOLE?

Clinicians monitoring

TVS before start of drug: Ensure endometrial shedding (4mm or less) and no persistent ovarian cyst.

Restart monitoring: Day 11, then every 2 to 4 days till ovulation

Last monitoring Day 21 : no follicle selected or serum P4 <1ng/ml give withdrawal

Patients self monitoring

1. Urine LH surge by urinary kit from day 11 alternate day or daily as per the mucous discharge of the woman
2. S. progesterone on day 21/25: take withdrawal if P4 not over 1ng/ml

Principle of gonadotropin regimens used in PCOS patients for ovulation induction?

Chronic low dose regimens used in step up, step down and constant dose regimens.

These regimens fulfil two essential requirements for successful OI in PCOS:

(i) Allow slow rise of FSH to just above the FSH threshold level (high in PCOS)

(ii) Avoid explosive ovarian response because of exquisite sensitivity of PCOS to exogenous gonadotropin

Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril. 2008; 89(3):505-22.

Which Gonadotropins used?

- Human menopausal gonadotropin (hMG) = FSH:LH / 75:75
- Urinary FSH preparations = FSH:LH / 75:1
- Highly purified FSH (HP) = impurities less than 5% FSH:LH / 75:1
- Recombinant FSH filled by mass 75iu=5.5mcg derived from recombinant technology.

Pen device or multi-dose vials ideal for PCOS as options for small increments (8.5iu/25iu/50iu) vs urinary where all increments are of 75 units only.

How do you use gonadotropins in PCOS women for OI? Can You monitor without USG?

- Low starting dose of gonadotropin of 50 to 75 iu
- Small increments of 25 to 50 iu of gonadotropin doses are desirable after first 5 days of constant dose administration.
- USG monitoring is a must before starting gonadotropins and then 5 days after gonadotropin administration then every 2 to 3 days
- Trigger not needed if 1 /2 dominant follicle.
- Sexual intercourse is mandatory not IUI

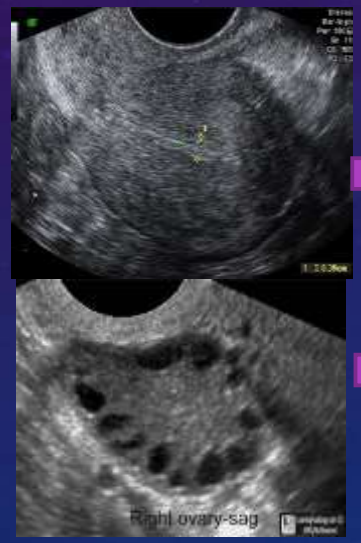
Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril. 2008; 89(3):505-22.

USE OF FSH/HMG IN PCOS

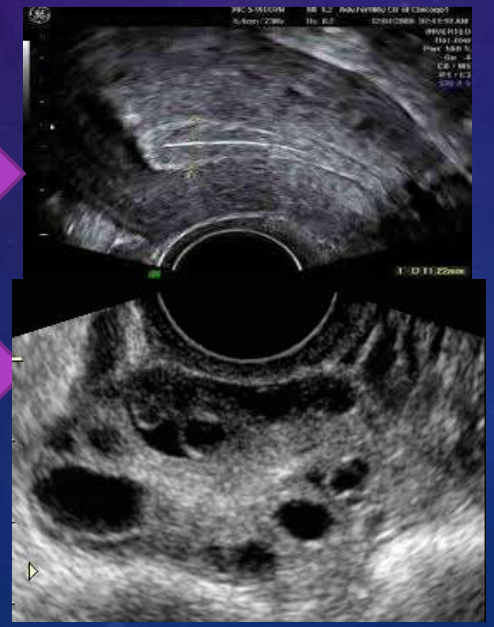
FSH 50/75iu/day from day 3 X 5 days

First type of response

Day 3 of menses Baseline ET and ovary

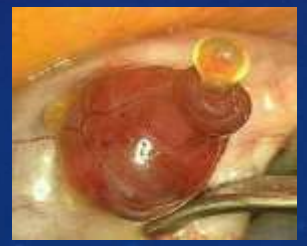


Day 6 of stimulation follicle & ET



Continue inj. FSH repeat usg FM every 3-5 days till Dom. follicle 15 mm to prevent hyper-response

Ovulation will follow

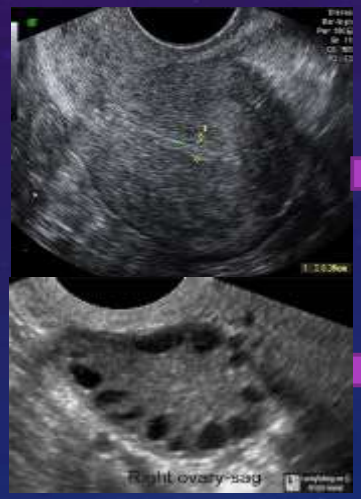


FSH/HMG IN PCOS WITH NO RESPONSE

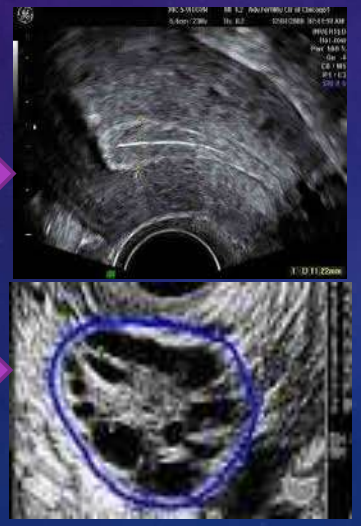
Daily inj. FSH 50/75 from D3 with slow increments

Second type of response

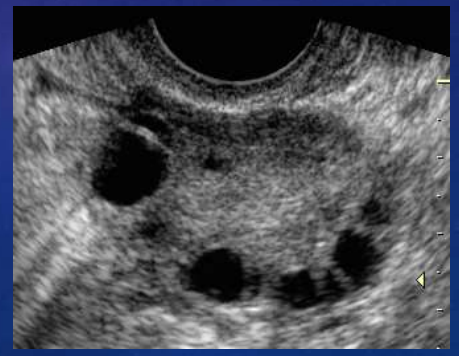
Day 3 of menses Baseline ET and ovary



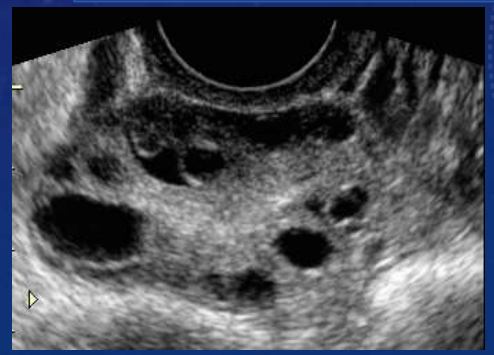
Day 6 of stimulation follicle & ET



After every 3-5 days to prevent hyper-response



18 to 25 days of incremental 25-50 iu FSH- no increase in follicle size or in E2 levels (> 30pg from base) think of RESISTANT PCOS



Refer to specialist

Is hCG necessary in patients having received ovulation induction in PCOS by any drug including gonadotropins?

NO

And

Is IUI necessary in these patients?

Ovarian Stimulation and IUI

The rationale behind the use of Ovarian stimulation in IUI is :

- Increase in number of available oocytes for tubal pickup and site of fertilization
- Correction of subtle endocrinological or ovulatory dysfunction
- Higher concentration of energy laden sperms at site of fertilization

Common drugs used for OI in IUI

1. Clomiphene: Day 3 to 7 for 5 days 100 mg/day

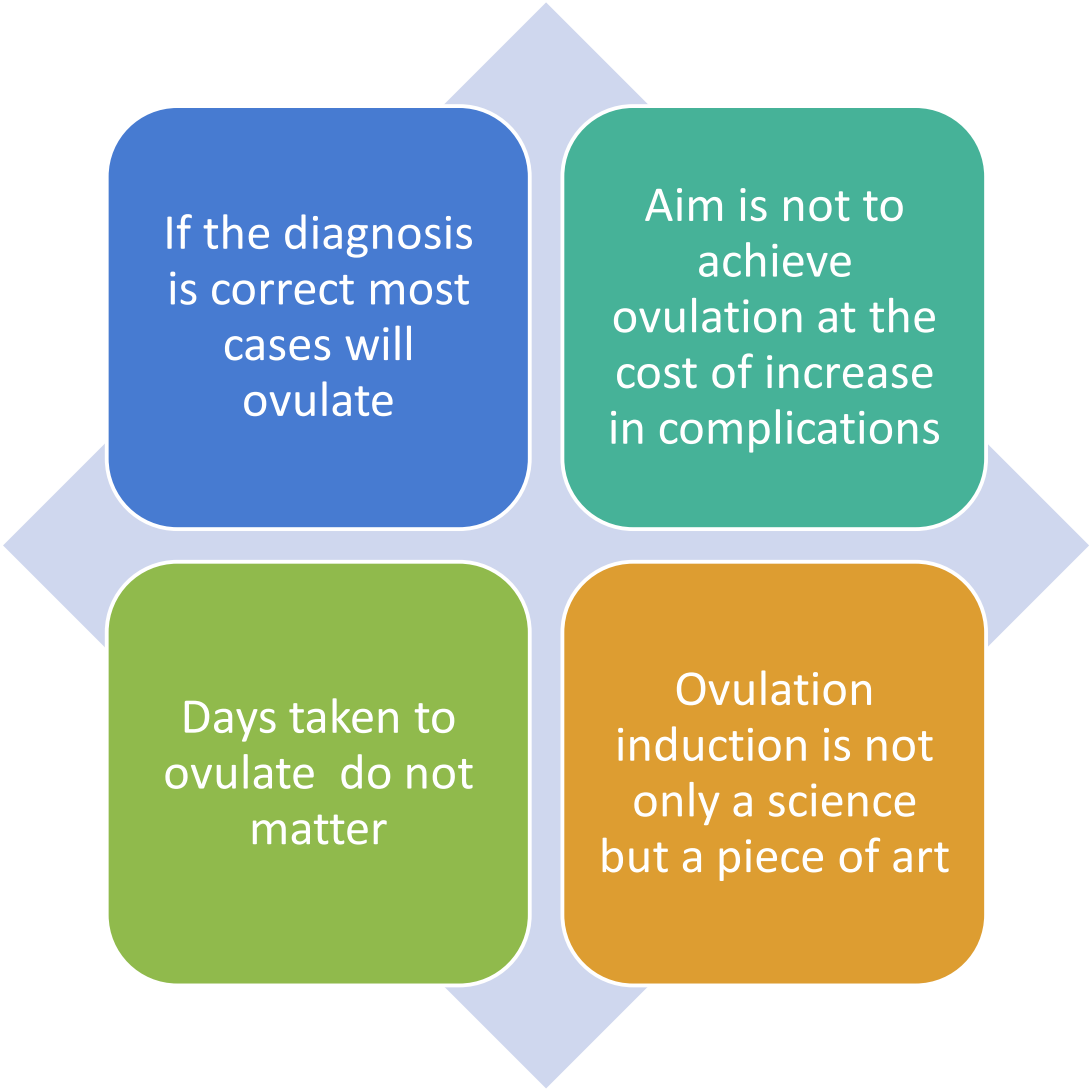
3. Letrozole: Day 3 to 7 for 5 days 2.5 to 5mg/day

4. Gonadotropins: Daily dosing starting with 50 to 75 units/day from day 3 or 4 of cycle till dominant follicle is made

Is hCG a good option in patients having received ovulation induction by any drug including gonadotropins undergoing IUI ?

YES

THE LAST WORD TO OVULATION INDUCTION



OVULATION INDUCTION IS NOT ONLY A SCIENCE BUT ALSO AN ART

THANK YOU

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