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Director, Center of IVF and Human Reproduction  
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**President's Medal** for best medical graduate of year 1970-75

**Award from DMA** on Dr. B.C Roy's birthday: outstanding contribution to medicine, 1999

**Vikas Ratan Award** by Nations economic development & growth society 2002, **Chitsa Ratan Award** by International Study Circle in 2007, **Life time 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 and **Inspiring Gynecologists of India** by Economic Times 2017. Highest Merck Serono honor award in 2018. Awarded at the Economic Times Health Care awards the **"ICON of IVF of North India"**, her team as the **'Best integrated national team of IVF'**, & the most coveted award as the **'IVF National Champion of 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.



## DR. ABHA MAJUMDAR

MBBS, MS, FICS

Director & Head of IVF Department  
IVF Sir Ganga Ram Hospital

### Expertise

Infertility, assisted reproductive techniques,  
reproductive endocrinology, endoscopic surgery  
for pelvic resurrection.



## Director

## Centre of IVF and Human Reproduction

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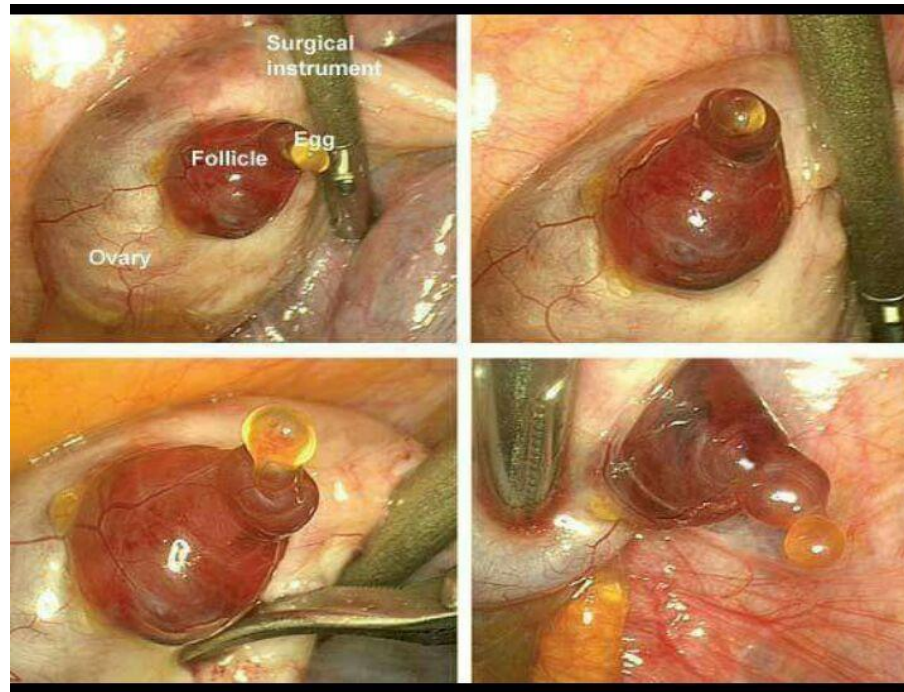
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# Stimulating the stubborn ovaries

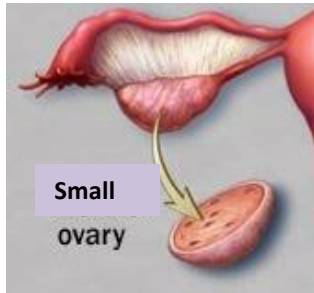


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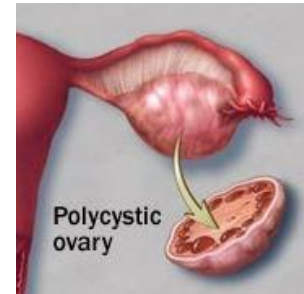


# Low responding Ovaries to stimulation



## Failing ovaries

low AMH, low AFC and higher FSH



## Stubborn ovaries

1: High AMH, High AFC and Very high Basal FSH  
>40miu/ml with amenorrhea  
& only E2 + P4 withdrawal bleeding

2: High AMH & AFC & high



# PCOS like stubborn ovaries



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- Stubborn ovaries present as PCOS (high AMH and high AFC)
- Serum FSH levels determine the subtype.



Type 1: FSH receptor resistance - Donor oocyte & IVF



Type 2: FSH receptor polymorphism or  $V\beta$  LH gene mutation



Type 3: V. high serum AMH inhibiting serum FSH levels to recruit follicles into dominance

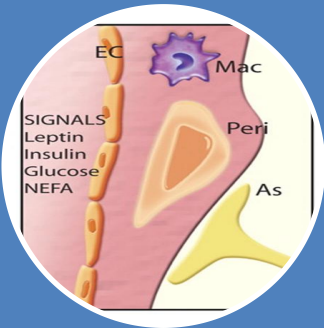


# Ovulation disorder in PCOS

- Infrequent Ovulation/Oligo-ovulation
- Complete absence of Ovulation/Anovulation.



# Various theories postulated for ovulation disorder in PCOS



**PERIPHERAL**

**Insulin resistance**



**OVARY**

**Hyper-androgenism**



**PIT-HYPOTHALAMUS**

**LH hypersecretion**





**Generally these women  
are not absolutely  
infertile but sub-fertile**

**Often challenging  
to treat these  
PCOS women  
successfully and  
safely with various  
ovulation inducing  
agents**

**Sporadic  
ovulation and  
one may  
conceive  
naturally**

**We encounter a complete  
spectrum of ovulatory  
dysfunction in PCOS**





**Respond to small  
or standard doses  
of Clomiphene**

**Exaggerated  
response to CC**



**Resistance to  
clomiphene**

**Respond/ hyper-  
respond to small  
incremental  
doses of FSH**

**Resistant to  
incremental doses  
of FSH**



**Respond/hyper-  
respond to only high  
doses of FSH or hMG**



# Monitoring with CC, letrozole, tamoxifen



## CC/letrozole day 3 to day 7

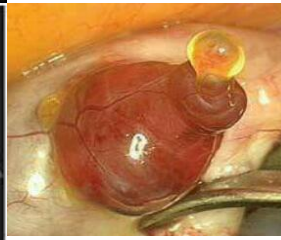
Day 3 of menses  
Baseline ET and ovary



Day 10/11 of menses  
dominant follicle & ET



Ovulation  
will follow



after 7 days

OR



P4

withdrawal

Progesterone  
< 1 ng/ml on  
day 18 to 25

Cervical  
mucous  
estrogenic

# Monitoring with inj FSH/gonadotropin

Daily inj. FSH from day 3 till ovulation

Day 3 of menses  
Baseline ET  
and ovary



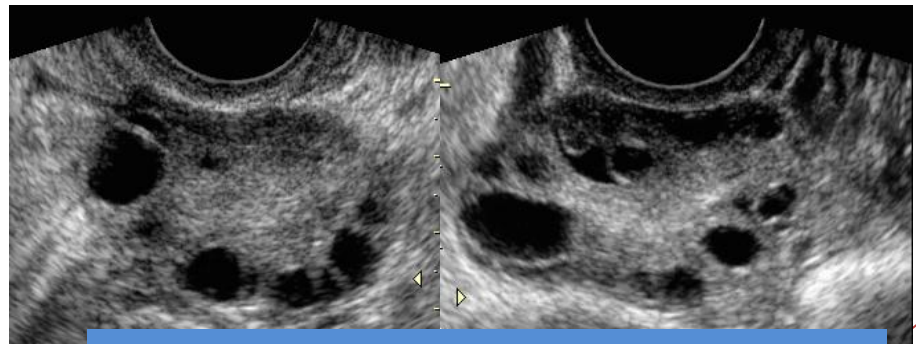
Day 6 of stimulation  
follicle & ET



After every 2 to 3  
days to prevent  
hyper-response

**Estradiol > 120 or  
follicle size  $\geq 15$  is  
good indicator to  
stop or reduce  
gonadotropin  
dose**

**Trigger ?**



**Desired response in PCOS**



18 to 25 days of  
incremental 25-50 iu  
FSH no increase in  
follicle size and E2  
30pg from baseline



# RESISTANT PCOS OR Stubborn ovaries

Problems in such cycles:

- I. Follicles do not increase in size nor the E2 levels
- II. Endometrium continues to be low
- III. Intermittent bleeding sometimes
- IV. Injections for 18 to 25 days with no change seen
- V. Confidence of patient and clinician go down
- VI. Hyper response when dose is jumped up



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There exists a definite group of anovulatory PCOS, who appear to be resistant to ovulation induction when treated with small incremental doses of FSH over time for the purpose of OI.

**OBESITY  
BMI**

**AMH**

**high LH**

**ANDROGENS**





Studied underlying characteristics of a subset of PCOS women requiring stimulation of ovulation with high doses of FSH/hMG after not having responded to normal dose step up regimes of FSH

- Prospective study
- Centre: IVF Centre, SGRH, New Delhi
- No of patient (n) = 18 ( 6 months duration)
- Selected from a cohort of clomiphene resistant women undergoing FSH stimulation for ovulation induction



Case Study

# Series of 18 Cases of Clomiphene Resistant Anovulatory Women with Polycystic Ovary Syndrome and Altered Response to FSH Stimulation

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## Abstract

The outcome of ovulation induction in anovulatory polycystic ovarian syndrome (PCOS) may depend, in part, on the pharmacologic compounds used, but also on individual patient characteristics, such as age, body mass index (BMI), hyper-androgenism, luteinizing hormone (LH), hyper-secretion, anti mullerian hormone (AMH) levels and possibly antral follicle count (AFC) with ovarian volume of these women. There exists a subset of clomiphene citrate (CC) resistant PCOS women who require stimulation of ovulation with high doses of human menopausal gonadotropin (hMG), after not having responded to chronic low dose step up regimes of recombinant follicle stimulating hormone (r-FSH).

**Keywords:** Polycystic ovarian syndrome; Hyperstimulation

## Case Represewntation

We report a case series of 18 such PCOS women selected from 100 CC resistant women undergoing r-FSH stimulation with the purpose of ovulation induction.

These women were labeled as 'FSH resistant PCOS' and were further stimulated with high doses of injection hMG (Humog Bharat Serum, India). The starting dose of hMG was 150 units which were subsequently increased to 225 units if there was no response after 6 days in terms of rise in S. E2 and USG evidence for dominant follicle. Surprisingly all patient responded or hyper responded within 10 days of stimulation.



## Series of 18 cases of Clomiphene resistant Anovulatory Women with Poly Cystic Ovary Syndrome



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**Citation:** Majumdar A, Mishra P (2016) Series of 18 Cases of Clomiphene Resistant Anovulatory Women with Polycystic Ovary Syndrome and Altered Response to FSH Stimulation. JFIV Reprod Med Genet 4: 194. doi: [10.4172/2375-4508.1000194](https://doi.org/10.4172/2375-4508.1000194)

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S. No.	Characterstics	Min	Max	Mean	SD	Normal physiological index
1	BMI (kg/m <sup>2</sup> )	29	36	33	3.32	18-24.9
2	WC (cm)	98	124	108	5.0	<80
3	AMH (pmol/L)	60	145	106	37.7	7.7-22.5
4	FSH (mIU/ml)	4	8	5.6	1.09	3-10
5	LH (mIU/L)	3.3	12	6.4	6.12	3-10
6	Oral GTT (2 h value)	151	198	178	13.47	<140
7	Lipid profile (TG in mg/dl)	170	220	193	14.27	<150
8	Ovarian volume (cc)	12	21	18	3.7	3-10
9	Antral Follicle Count	30	56	42	10.17	5-10 (in each ovary)

**Table 1:** Characteristics evaluated to identify features common to this group of FSH resistant PCOS.



# Ovulation induction



In all these CC resistant cases, ovulation induction was started with injection of r-FSH 50/75 IU which was increased by 25 units every 5 to 7 days according to low dose step up protocol. Follicular response was monitored by serum estradiol (E2) levels and ultrasound (USG) follicle monitoring (FM). 18 PCOS were selected from this cohort of women as they showed no ovulatory response in terms of rise in serum E2 levels (at least rise of 30 pg/ml from baseline serum estradiol levels (20-80 pg/ml) or presence of a follicle of 13 mm or larger, even after 18-25 days of stimulation with incremental doses of r-FSH of up to 150 IU.





# Ovulation induction



These women were labeled as 'FSH resistant PCOS' and were further stimulated with high doses of injection hMG (Humog Bharat Serum, India). The starting dose of hMG was 150 units which were subsequently increased to 225 units if there was no response after 6 days in terms of rise in S. E2 and USG evidence for dominant follicle. Surprisingly all patient responded or hyper responded within 10 days of stimulation.



# Why don't some PCOS respond to exogenous FSH when administered in appropriate doses for OI?

## **FSH/LH receptor polymorphism**

### **Type 2**

Follicles resistant to lower doses of FSH alone. Respond to higher doses of FSH/HMG to overcome this.

## **Very high AMH**

### **Type 3**

Inhibitory effect on follicular recruitment. Especially on low dose step up FSH administration.



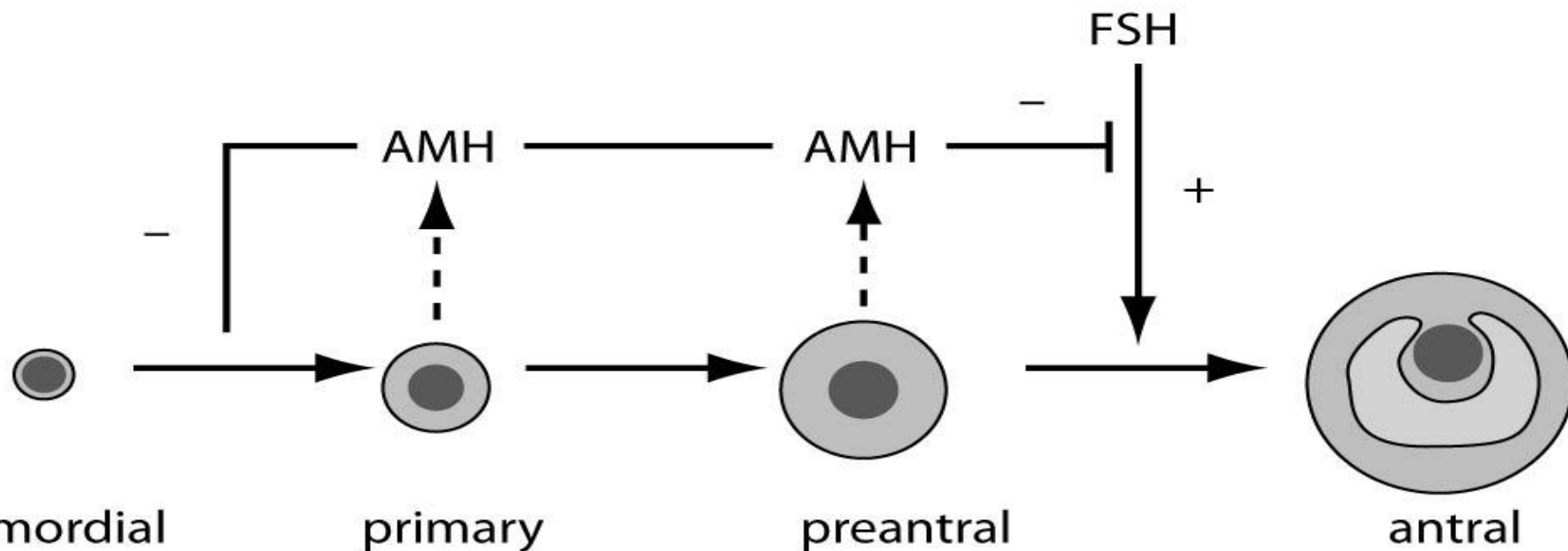
# Very high AMH



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## Possible actions of AMH in the ovary:

- Inhibition of follicular activation and growth
- Inhibition of FSH stimulated growth
- Inhibition of granulosa cell growth
- Inhibition of aromatase

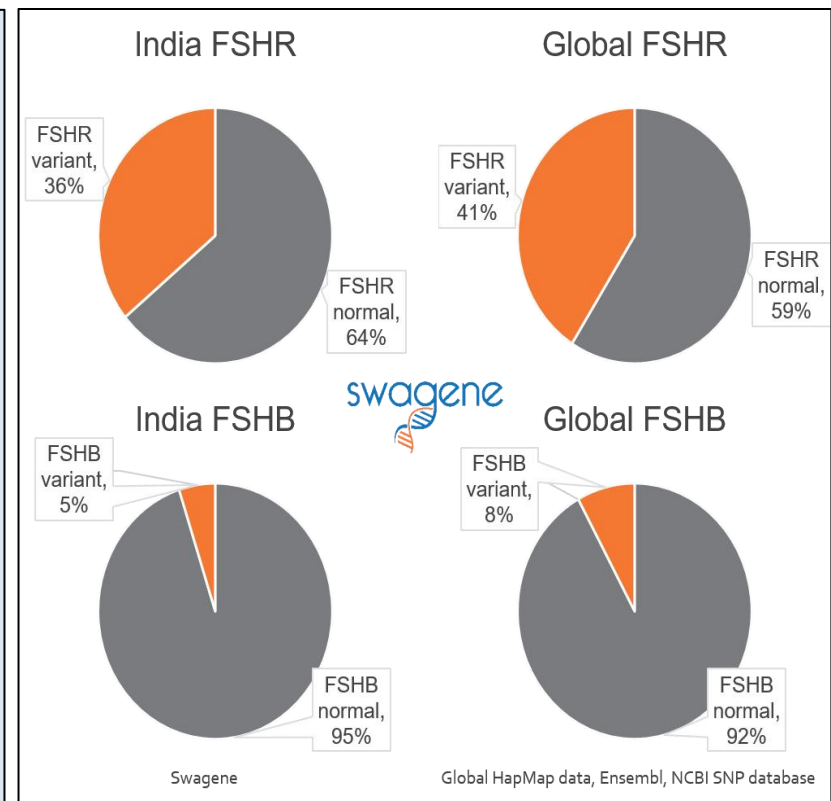




# FSH receptor polymorphism/ v beta LH gene mutation

Frequency of FSH-R Ser680 variant is high in hypo-responders with good OR and consumption of FSH is higher in carriers of this polymorphism

v-beta LH is a common genetic variant of LH  $\beta$ -sub-unit gene & is associated with higher exogenous FSH consumption during COH



Alviggi et al., Reproductive sci. 2015,

[C Alviggi](#), - Reproductive ..., 2013 - [rbej.biomedcentral.com](http://rbej.biomedcentral.com)



# Adjuvants with uncertain effect



- Metformin
- Steroids
- Growth hormone
- Drilling
- Inositol's



# Résistance to FSH in PCOS



NON IVF OI

Ovulation induction where small incremental doses of FSH used show resistance to FSH due to high AMH or FSH receptor polymorphism

COS FOR IVF

COS for IVF where higher doses of FSH are used from beginning, may overcome the inhibitory effects of high AMH or the FSH receptor polymorphism.





# Resistant PCOS

## Good news for IVF clinicians



Inhibition to dominant follicular selection is imposed by

- ☐ Very high AMH
- ☐ FSH receptor polymorphism
- ☐  $V \beta$  LH gene mutation

over come by high doses of FSH/hMG



# Take home message



- Ovulation induction with CC & exogenous FSH preparations are commonly used as first- and second-line therapy for anovulatory PCOS.
- Ovarian response to CC or FSH is hampered by limited control due to large inter & intra-individual variability.
- The outcome of ovulation induction in PCOS appears to depend, in part, on the pharmacologic compounds used but also on individual patient characteristics, such as BMI, very high AMH levels or genetic predisposition
- Such PCOS require longer duration and higher doses of gonadotropins to have ovulatory response and then often tend to hyper-respond.