Treatment strategies in assisted reproduction for the poor-responder patient

Dr Mina Ataei

Infertility Felloeship

Avicenna Fertility Center

Iran Health and Medical Tourism - irhto.com

- In a spontaneous menstrual cycle, **only one follicle** out of a cohort **of 10–20** usually completes maturation and ovu- lates to release a mature oocyte.
- The aim of controlled ovar- ian stimulation (COS) in assisted reproductive technology (ART) protocols is to ***overcome the selection of a domi- nant follicle and to allow the growth of a cohort of follicles.*** This strategy leads to an increase in the number of oocytes and hence embryos available for transfer, thereby increas- ing the chance ***of transferring viable embryos***.
- However, the chance of ***pregnancy and also live birth begins to dra- matically decline after the age of 35 years***, and successful treatment for these patients continues to be a major chal- lenge in ART programs

- The human ovary has a finite number of non-growing fol- licles **(NGFs)** established before birth that decline with increasing age, culminating in menopause at age 50–51 years.
- For **95%** of women, only **12%** of their pre-birth NGF population is present by the age of 30 years, declin- ing to only **3%** by the age of **40** years
- This provides the basis for decline in female fecundity with increasing age.
- This decline in fecundity can be based on a variety of **age**- related conditions, including an increase in gynecological disorders such as endometriosis or fibroids, an increase in ovulatory disorders due to effects on the hypothalamic– pituitary–ovarian axis, or a compromised **uterine vascu- lar** supply that may impede implantation

- using contraceptives showed that natural pregnancies and deliveries after the age **of 45** years constitute only **0.2%** of total deliveries, and **>80%** of these are in *grand* multipa- ras
- In infertile couples, IVF may be a rea- sonable option for such women of advanced maternal age **(AMA)** who are **aged >40** years, but at the age of ≥45 years, deliveries are a rare event
- The peak number of oocytes present in the human ovary occurs **during fetal gestation**, and follicles are continually lost thereafter through the mechanism of **apoptosis,** a process known **as atresia**

- A cohort of growing fol- licles is recruited each month, and the cohort enters *the final stages of follicle maturation during the first half of the menstrual cycle*.
- **This maturation phase is gonadotro- pin dependent**.
- Painstaking histological and *in vitro* stud- ies carried out by Gougeon suggest that follicles require a period of approximately **70** days from the time they enter the preantral stage **(0.15 mm) to reach a size of 2** mm
- These 2-mm follicles have **very low steroidogenic** activ- ity, and they **are impervious** to cyclic follicle-stimulating hormone (FSH) and luteinizing hormone (LH) changes in terms of granulosa cell (GC) proliferation.
- Over **a four- to five-day** period during **the late luteal** phase, follicles that are **2–5 mm** in diameter enter a recruitment stage, and cyclic changes in FSH drive the development of the fol- licle and proliferation of GCs; GC aromatase activity is not affected during this stage.
- Thus, as the follicle develops, it becomes ***increasingly responsive to gonadotropins***

- From the perspective of treatment management, this means that in order to influence the size of the recruitable pool of follicles, it would be necessary to "boost" contin- ued healthy follicle development over a protracted period of time **(≥70 days).**
- However, gonadotropins play a role only during the phases of **recruitment and final follicular maturation**, which occur over the last **20 days** or so of this 70-day period.
- Therefore, extrapolating from knowledge about basic physiology, ***different agents would be required at different times*** in order to successfully overcome the age-related decline in follicle numbers

- Women who postpone childbearing until their late **30s or early 40s** are therefore frequently faced with the distress- ing realization that their chance of achieving a pregnancy is **significantly reduced**, and that they may require the help of **ART**, with further complex difficulties that can jeopar- dize their quest for successful conception.
- In Europe for the year 2010, women undergoing IVF or intracytoplas- mic sperm injection (ICSI) procedures in the age group >40 years represented approximately **16.7% and 17.3%,** respectively, of those attending IVF clinics
- A number of different variables can affect success rates in ART, and the **negative impact of increasing age** is one feature that is well recognized.
- Not only does the response to stimulation steadily deteriorate, requiring **larger amounts of gonado- tropins**, but also the **cancelation rate is higher**, and there is a **significant increase in the rate of miscarriage.**

- Data from the U.S.A. (Center for Disease Control 2013 report on ART success rates) clearly show that the potential for embryo implantation and successful delivery of a live birth **decreases rapidly in women >35 years**
- This same report also documents **the increased incidence of pregnancy loss that is related to increased maternal age**, going from less *than 15% in women ≤36 years of age, increasing rapidly among women in their late 30s to reach 29% at 40 years of age, and over 50% in women ≥44 years*.
- These data suggest that the lower age limit to defining women of **AMA** should be considered **as ≥35 years**.

- Although **chronological age** is the most important pre-
- dictor of ovarian response to stimulation, the rate **of repro- ductive aging and ovarian sensitivity to gonadotropins** varies considerably among individuals
- **Biological and chronological age** **are not** always equivalent, and **biological age** is more important in predicting the outcome of ART
- Biological aging often renders the ovaries increasingly ***resistant to gonadotropin stimulation***, with the result that *the number of oocytes harvested may be very low.*
- Any strategy that might enhance the efficacy of treat- ment for these women would be of great benefit, and dif- ferent areas of research have recently been explored, such as the use of pharmacogenomics to assess response to gonadotropin stimulation, manipulating the endocrinol- ogy of the treatment cycle, and screening of embryos for aneuploidy.

- To this effect, the European Society of Human Reproduction and Embryology **(ESHRE)** working group attempted to standardize the definition of POR to stimu- lation in a simple and reproducible manner (**the Bologna consensus**) . The consensus defi- nition recommends **that two of the following three** features should be present for a diagnosis of POR:
- (1) **AMA (≥40** years) or other risk factor for POR;
- (2) a **previous** POR (≤3 oocytes with a conventional stimulation protocol); and (3)an abnormal ovarian reserve test (ORT) (i.e., antral fol- licle **count [AFC] <5–7** follicles or anti-Mullerian hor- **mone [AMH] <0.5–1.1 ng/mL [3.57–7.85 pmol/L]).**
- **Two episodes of POR after maximal stimulation** were consid- ered sufficient to define a patient as a poor responder in the ***absence*** of AMA or abnormal ORT.
- Patients of **AMA** with an abnormal ORT may be more properly defined as "**expected poor responders**

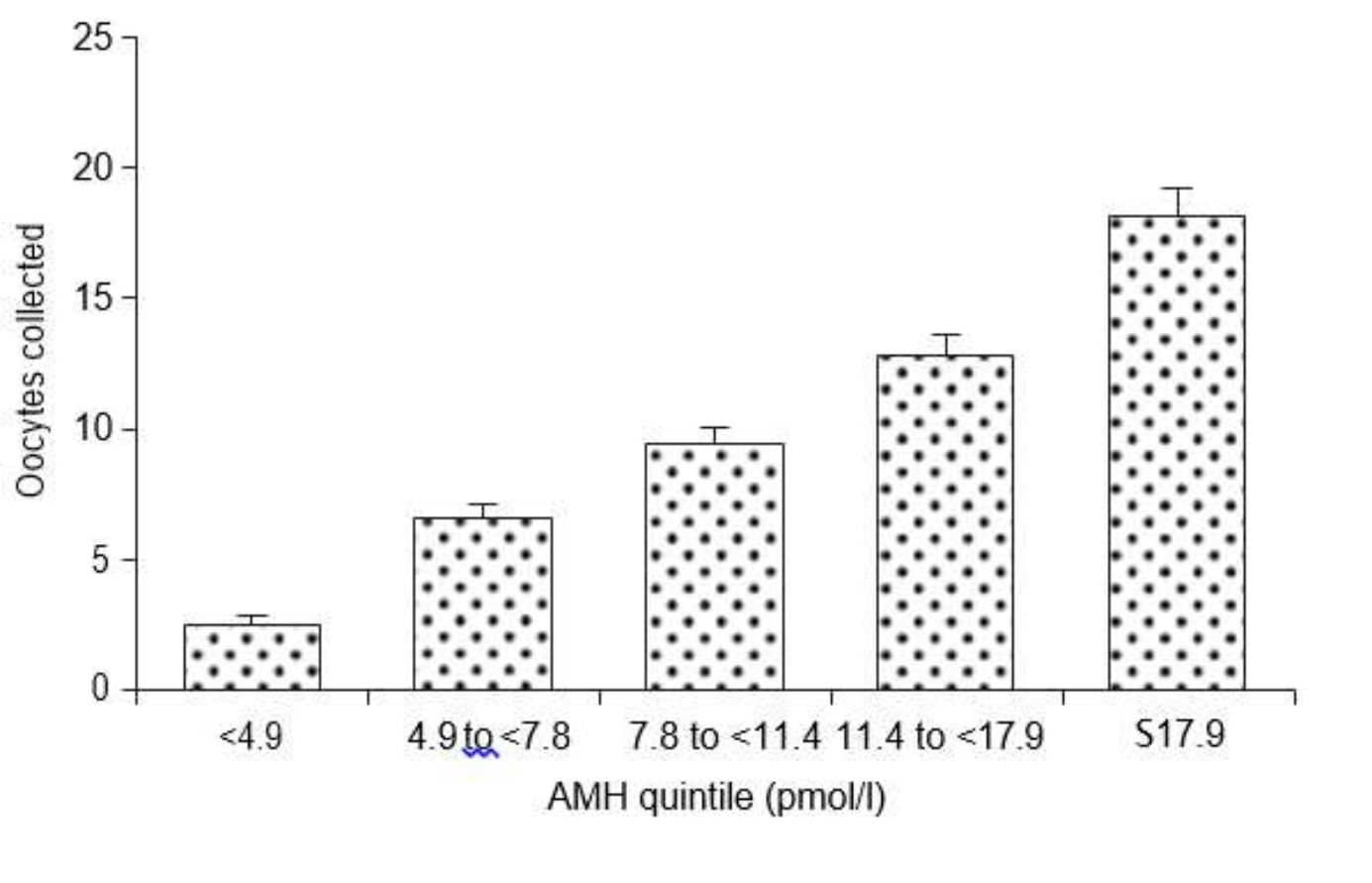
ASSESSMENT AND PREDICTION OF OVARIAN RESPONSE TO STIMULATION

- The ability to accurately assess and predict ovarian response would reduce the burdens imposed by fail- ure because of inadequate response to stimulation.
- Unfortunately, the response to stimulation cannot be reli- ably predicted, even for young patients with no evidence of endocrine disorders.
- Parameters that have been identified as exerting an influence include age, cause of infer- tility , body weight and body mass index (BMI)
- Ovarian characteristics have also been assessed by ultrasound, such as the number and size of antral folliclesovarian volume, and ovarian **vascular resistance** mea- sured by Doppler ultrasound

- There is a clear correlation between the **number of antral follicles** (defined as ≥2 mm to ≥10 mm) seen at the begin- ning of the follicular phase during a natural cycle (NC) and subsequent ovarian response to stimulation.
- However, there is as yet no consensus of agreement regarding the minimum number of antral follicles below which an influ- ence can be seen a minimum of fewer than **five follicles of 2–5** mm in diameter has been suggested as a predictive parameter
- One of the major reasons for this was a lack of standardized definition for assessment of the AFC, whose accuracy of measurement is highly operator dependent
- Klinkert et alsuggest that patients with **an AFC of fewer than five** follicles of 2–5 mm

- Basal hormone assessment at follicular phase has been used to predict ovarian response, including FSH estradiol (E2) and inhibin-B
- AMH is an accurate marker of ovarian reserve and oocyte yield.
- Circulating levels of AMH decline with increasing biological ovarian age, but remain relatively stable throughout each menstrual cycle leading to it being measureable with accuracy **at any time during the cycle**.
- A comparison of AMH and FSH as predictors of retrieved oocyte numbers showed that AMH was clearly superior at predicting ovarian response
- AMH was a **significantly better predictor** of poor response com- pared with FSH but not AFC.

- . Various AMH cutoff values to predict a poor response have been explored.
- It has been suggested that an AMH cutoff level of <1.0 ng/mL (7.14 pmol/L) may have modest sensitivity and specific- ity in predicting a poor response to COS
- The four factors identified as significantly predictive of ovarian response were baseline serum FSH levels, BMI, age, and AFC.


25
20
15
10
5
0
Oocytes collected
<4.9
4.9 to <7.8
7.8 to <11.4
11.4 to <17.9
S17.9
AMH quintile (pmol/l)

HIGH-DOSE GONADOTROPINS

- It is generally believed that the dose of gonadotropins should be adjusted upwards in an attempt to overcome the age-related decline in ovarian response to FSH stimula- tion.
- Patients who responded poorly to conventional doses **(150–225 IU of FSH) may produce more follicles when given 300–450 IU or even 600 IU per day**
- **increasing the starting dose of gonado- tropins in poor responders is a rational approach that is widely practiced.**
- **A common starting dose would be at least 300 IU/day.**
- **Nevertheless, further dose increments are of limited effectiveness, and clinically meaningful improve- ments are only rarely obtained with doses >300 IU/day.**

GONADOTROPIN-RELEASING HORMONE AGONISTS IN THE TREATMENT OF POOR RESPONDERS

Long gonadotropin-releasing hormone agonist protocols

- The aim of the long protocol is to achieve pituitary down-regulation with **suppression of endogenous gonadotropin secretion** before stimulation with exogenous gonadotropins.
- Once pituitary down- regulation and ovarian suppression are achieved, ovarian stimulation with exogenous gonadotropins is commenced, while GnRHa administration is continued concomitantly until the day of hCG administration.
- In the general IVF population, the long protocol has been found to be supe- rior in terms of efficacy compared with the short proto- col and is therefore used most frequently.
- **However, the matter of which GnRHa protocol is preferable in poor responders remains controversial**

- It has been well established that there is a **dose-depen- dent duration of ovarian suppression after single implant injections of GnRHa,** and that in a suppressed pituitary gland the dose needed to maintain suppression gradu- ally decreases with the length of treatment
- **Ovarian cyst formation** is a common complication of the long GnRHa protocol. It has been suggested as being typical for poor responders and as being a reliable predic- tor of poor stimulation and low pregnancy rates in a given cycle
- the higher the serum progesterone level at the time of commencing GnRHa administration, the lower the incidence of cyst formation .
- Summarizing the above evidence, the ***long GnRHa*** protocol seems to be a suitable option for poor responders

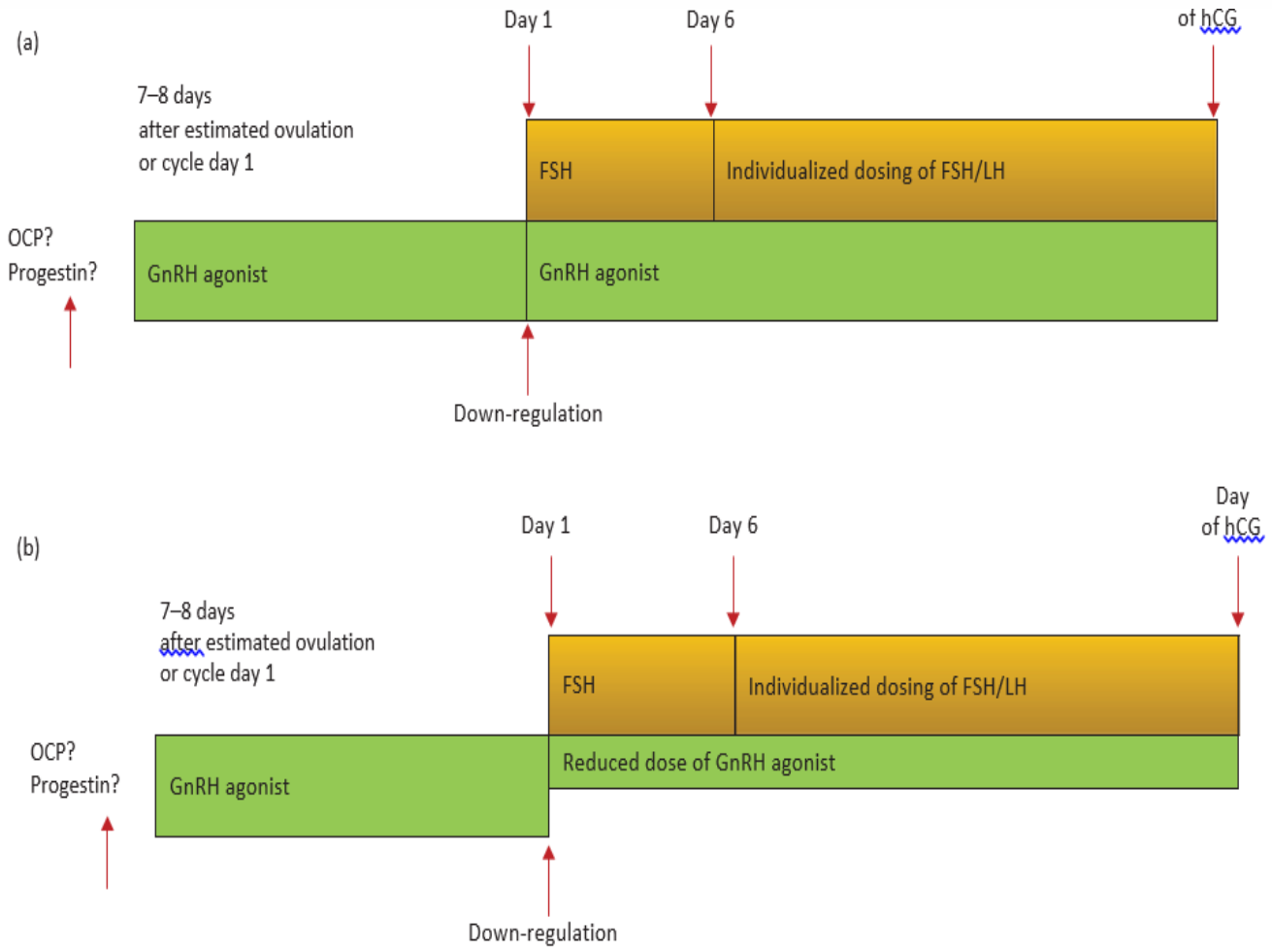


Figure 50.3 (a) The long GnRH agonist protocol. (b) The "mini-dose" long agonist protocol. *Abbreviations*: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; OCP,

GnRHa "stop" protocols

- Pituitary recovery and resumption of gonadotropin secre- tion following GnRHa treatment may take up to several weeks, depending on the dose and route of administra- tion of the agonist.
- For example, with intranasal busere- lin acetate (BA), suppression of endogenous gonadotropin secretion seems to continue for at least **12 days** after the discontinuation of the agonist as was also reported for s.c. BA
- Interestingly, using the "ultrashort proto- col," suppression of endogenous LH secretion was more profound when LA administration was stopped after **five days** of administration, compared with continuous LA administration, and no premature LH peak was recorded
- This forms the basis for a variety of discontinuous or "stop" GnRHa protocols.
- It was concluded that the stop proto- col combined with high doses of gonadotropins permitted the retrieval of a significantly **higher number of oocytes, but did not influence the reproductive outcome**

Short GnRHa regimens

- The short protocol consists of **early follicular-phase** initia- tion of GnRHa, with minimal delay before commencing gonadotropin ovarian stimulation.
- It takes advantage of the initial agonistic stimulatory effect of GnRHa on endog- enous FSH and LH secretion, also known as the flare-up effect.
- In theory, it eliminates excessive ovarian suppres- sion associated with prolonged agonist use.
- The dura- tion of the endogenous gonadotropin flare has not been completely characterized, but pituitary **desensitization** is generally achieved within **five days** of initiating treatment and therefore patients are protected from premature LH surges by the end of the stimulation phase.
- The short protocol has been proposed by many authors as a better stimulation protocol for poor responders

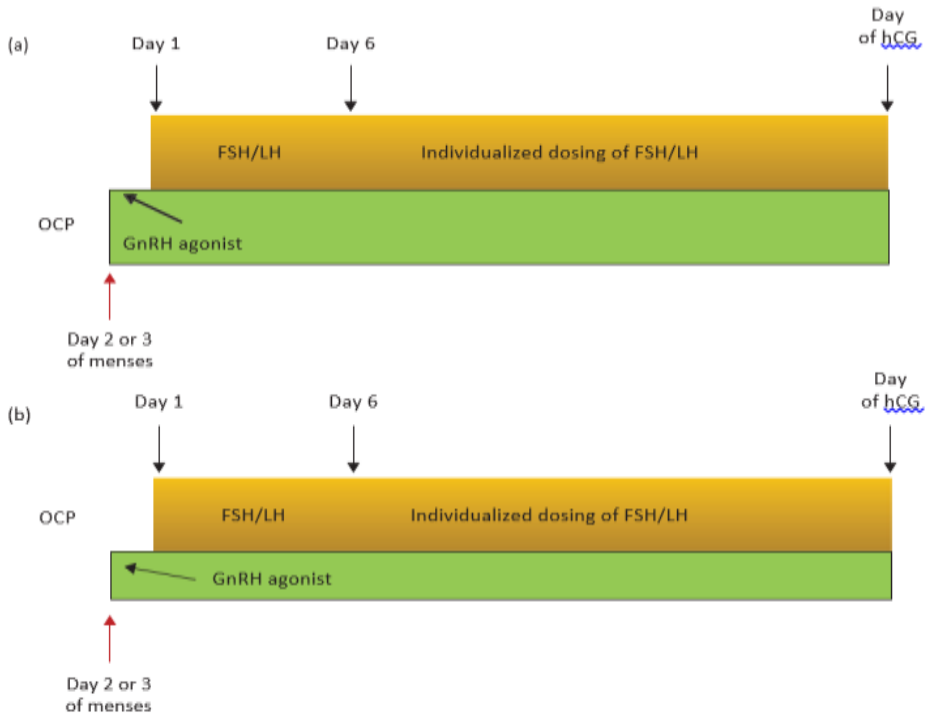


Figure 50.4 (a) The short GnRH agonist protocol. (b) The "micro-dose" flare GnRH agonist protocol. *Abbreviations*: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; OCP, oral contraceptive pill.

GnRH-ANTS IN THE TREATMENT OF POOR RESPONDERS

- GnRH-ants **competitively block** the GnRH receptor in the pituitary gland, producing an immediate dose-related suppression of gonadotropin release.
- **Within six hours of** GnRH-ant administration, LH levels are significantly reduced.
- On the principle of maximizing potential endog- enous pituitary stimulation, a GnRH-ant can be adminis- tered later in the follicular phase to **suppress the LH surge** thus avoiding suppression during the phase of early follicular recruitment
- In the general IVF population, the GnRH-ants offer comparable thera- peutic efficacy to agonists and have a number of potential advantages over agonists for use in ovarian stimulation protocols**, such as avoiding the initial "flare-up" of LH, shortening the overall treatment period, reducing the risk of OHSS, and reducing menopausal side effects**

- The GnRH-ants are administered in the late follicu- lar phase, either according to **the fixed or according to the flexible protocol**

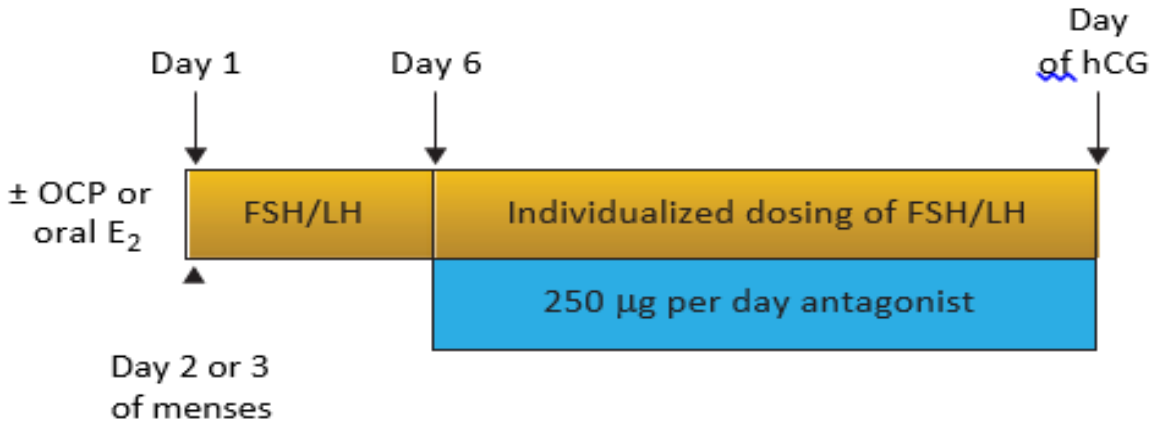


Figure 50.5 Gonadotropin-releasing hormone antagonist protocol. *Abbreviations*: E2, estradiol; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; OCP, oral contraceptive pill.

NCs AND MODIFIED NCs

- The yield of lengthy, high-dose, and cost-stimulation regi- mens used in poor responders to increase the number of oocytes retrieved is often disappointing
- It was therefore suggested to perform NC-IVF in such cases, an approach that is less invasive and less costly for the patient
- It was concluded that pregnancies and live births can be achieved in poor-prognosis/poor-responder patients with elevated basal FSH levels, and **age was found to be a more adverse infertility factor than** elevated serum FSH.

Modified NC

- The efficacy **of NC-IVF is hampered by high cancelation rates** because of premature LH rises and premature ovu- lations
- The possibility of enhancing the efficacy of unstimulated IVF cycles by the concomitant addition of a **GnRH-ant and exogenous gonadotropins** in the late follic- ular phase was introduced by Paulson et al. as early as 1994
- This protocol, later known as the MNC, is expected to reduce the rate of premature ovulation and to improve control of gonadotropin delivery to the developing follicle

- . Kolibianakis et al. (175) evaluated the use of the MNC for IVF in poor respond- ers with an extremely poor prognosis as **a last resort prior to oocyte donation. Thirty-two patients with** regular menstrual cycles, basal FSH levels >12 IU/L, and one or more failed IVF cycles with five or fewer oocytes retrieved were included.
- **Recombinant hFSH 100 IU and ganirelix 0.25 mg/day** were started concomitantly when a follicle with a mean diameter of 14 mm was identified. hCG was administered as soon as the mean follicular diameter was ≥16 mm.
- Twenty-five out of 78 cycles performed (32.1%) did not result in oocyte retrieval. In nine out of 53 cycles (16.9%) in which oocyte retrieval was performed, no oocytes were retrieved

- While many authors regard follicle size ≥16 mm as the threshold
- other prefer to **administer hCG at 17–18** mm or even ≥18 mm
- Segawa et al. prefer the use **of GnRHa** for ovulation trig- gering than hCG.
- While no consensus exists, the best estimate is that early ovulation triggering (i.e., ≥16 mm) is beneficial
- Are oocyte and embryo quality improved in NCs? While there is a common belief that **"natural" is better,** this assumption has never been directly tested.

- Schimberni et al. have reported fairly constant implantation and preg- nancy rates **through five NC** cycles
- What is the role of follicle **flushing**
- **Should cleavage- or blastocyst-stage transfers be performed?**
- **Which dose of gonadotropins should be administered in the MNC protocol?**
- **Should LH be included in the gonadotropin regimen**

The Prediction and Management of Poor Responder

- Dr Ataei Mina

- The trends of child bearing have changed in the past few decades with **late pregnancies** becoming an increasing phenomenon in present days.
- Whether the reasons are **late marriage, sterility, lack of awareness of treatment, career development, or other social reasons**, more and more women are crossing the age of **35 or even 40 before** thinking of pregnancy.
-

- As the age increases, the need for in vitro fertilization (IVF) increases and the ovarian reserve is compromised.
- In such patients poor response (POR) is a pesky problem.
- It represents one of the few unresolved problems of modern infertility care.
- First described in 1983 **as reduced follicular response and E2 levels** following controlled ovarian stimulation (COS), which lead to production of less oocytes and transferable embryos

What is Meant by Poor Ovarian Response?

- Poor response in IVF can be defined as **development of**

mature follicles in insufficient number following stimulation ***with gonadotropin*** leading to retrieval of few oocytes or cycle cancellation.

Goal of ovarian stimulation in IVF ***is multiple*** follicular recruitment so that *inefficiencies* in embryology culture, embryo selection, and implantation are compensated. But poor responders **fail** to serve this goal.

- But one of the main problems for POR in literature is the absence of a standard definition.

INCIDENCE

- The incidence of POR varies between **9 and 24%** in the literatures depending upon various definitions.

VARIABLE DEFINITIONS USED IN THE LITERATURE

- Various definitions were used in the past like with **one previous cancelled IVF cycle, age greater than 40 years, day 3 follicle-stimulating hormone (FSH) greater than 7–15 IU/L, etc.**
- A study analyzed 47 randomized trials and found that 41 different definitions were used in the past.
- In that not more than three trials used the same definition. Even different definitions were used by same research group across different trials. And none of the criteria used was adopted in more than 50% of the trials.But all were inconclusive, insufficient, inadequate, inconsistent, and uncertain. So there came an urgent need for uniform definition.

BOLOGNA CONSENSUS

- In order to provide a uniform definition worldwide ESHRE consensus in 2011 proposed a definition for POR and named it to bologna criteria.
- It should meet at least two of three following criteria:
- 1. Advanced maternal age or any risk factors for POR**(≥40 years).**
- **2. A previous POR (<3 oocytes with conventional stimulation protocol).**
- **3. An abnormal ovarian reserve tests (i.e. AFC—5–7 follicles or AMH 0.5–1.1 ng/mL).**

- Of all the above parameters, ***minimum of one previous stimulated cycle is essential*** to make a diagnosis.
- And also if previous episode of poor response at least twice after maximal IVF stimulation is present it is sufficient to a make diagnosis.
- Advanced maternal age with reduced ovarian reserve
- is defined as expected poor responder in the absence of
- IVF stimulation.
- Studies in poor responder patients categorized according to bologna criteria were found to have low prognosis
- consistently irrespective of age or number of criteria used,
- live birth rate per cycle of about 6%.7
- Although Bologna criteria gave uniform definition
- worldwide, there exist some drawbacks for the same.

Limitations of Bologna Criteria

- • Heterogeneous populations with different prognosisare clubbed together.
- • Specific characteristic profiles of unexpected poor suboptimal responders are not included.
- • No definition for hypo/suboptimal responders.
- • It failed to distinguish between **alteration of oocyte quantity and those of oocyte quality as reflected by ART outcome, the real oocyte quality is not included**.
- • ORT predicts magnitude of **COS response but do not foretell pregnancy chances.**

POSEIDON STRATEGY (POSEIDON—Patient-Oriented Strategies Encompassing Individualized Oocyte Number)

- In order of improve treatment outcome and guide the physicians in more detailed way, a new more clinically relevant criteria were introduced.
- It combines **quality and quantity** for stratification of patients as low prognosis in ART cycle.
- The following factors are considered:
- • New categorization of patients based on ***their impaired response to COS.***

- • Includes both qualitative and quantitative ovarian response into consideration.
- • Ability to generate number oocytes to produce at least one euploid embryo.
- Consideration of ovarian sensitivity to gonadotropins into account.
- • More clarity in implementing COS in impaired response.
- Include four groups with difference in degree of low prognosis, so each requires a more personalized treatment

Fig. 23.1: Poseidon strategy for poor responders.

Table 28.1. POSEIDON strategy for poor responders.			
Good ovarian reserve		*Poor ovarian reserve*	
Group 1 Age <35 years AMH ≥1.2 AFC ≥5 (Sub Groups Ia <4 Oocytes Ib 4–9 Oocytes)	Group 2 Age >35 years AMH ≥1.2 AFC ≥5 (Sub groups Ia <4 Oocytes Ib 4–9 Oocytes	Group 3 Age <35 years AMH <1.2 AFC <5	Group 4 Age >35 years AMH <1.2 AFC <5

POOR OVARIAN RESPONSE Pathophysiology

- 1. **Depletion of ovarian follicle pool**
- • **Insufficient** initial follicle number
- • **Accelerated** follicle loss
- • **Iatrogenic**
- **2. Ovarian follicle dysfunction**
- • **Signaling** defect
- • **Enzymatic** deficiency
- • **Autoimmunity**
- • **Idiopathic**

Risk Factors

- 1. Advanced maternal **age**
- 2. **Lifestyle**-related factors
- 3. ***Acquired*** factors
- 4. **Genetic** factors

Advanced Maternal Age

- As age advances there occurs a decrease **in number and**
- **quality of oocyte**.
- The quality of the oocyte is affected by the following
- ways:
- • Impairment **of mitochondrial function** (less energy)
- • Increased **granulosa cell apoptosis**
- • Increased **oxidative stress**.
- Because of theca cell ageing there ***is reduced production of androgen.***
- There is decrease in percentage of ***euploid blastocyst*** as age increases irrespectiveof increase in number of blastocyst

Lifestyle-related Factors

- ***• Smoking***
- ***• Obesity***
- ***Acquired Factors***
- ***• Endometriosis***
- ***• Ovarian surgery***
- ***• Previous pelvic inflammatory diseases (PID)***
- ***• Chemotherapy/radiotherapy***

Genetic Factors

- • **Structural and numerical abnormalities** of X chromosome
- ***Turners*** syndrome/Turner mosaicism
- Fragile X syndrome **(FMR1** premutation)
- • **Balanced** translocation
- • **Autosomal** functionally relevant genetic variants
- **FSH receptor mutation**
- FSH receptor single nucleotide polymorphisms **(SNPs**)
- Luteinizing hormone **(LH) receptor mutation**
- LH beta polypeptide **(v-LHβ).**

Table 28.2. Gonadotropin receptor polymorphism.	
LH Receptor	*FSH Receptor*
v-βLH Trp8-Arg/Ile15-Thr Short T1/2-5 to 9 min More potent action Resistance to FSH stimulation	FSH-R Asn680/Ser—most common (75%) High AFC Slightly elevated basal FSH Resistance to FSH stimulation

GONADOTROPIN RECEPTOR POLYMORPHISM

- Carriers of v-beta LH variants and FSH-R Ser680 were found to have higher FSH consumption
- **Ser/Ser** carriers of FSH receptor polymorphism require 75IU more than Asn/Asn carriers to achieve the same steroidogenesis.

Predicting a Poor Response to IVF Stimulation

- The ability to accurately assess and predict ovarian response would reduce the burden imposed by failure because **of inadequate** response to stimulation.
- I

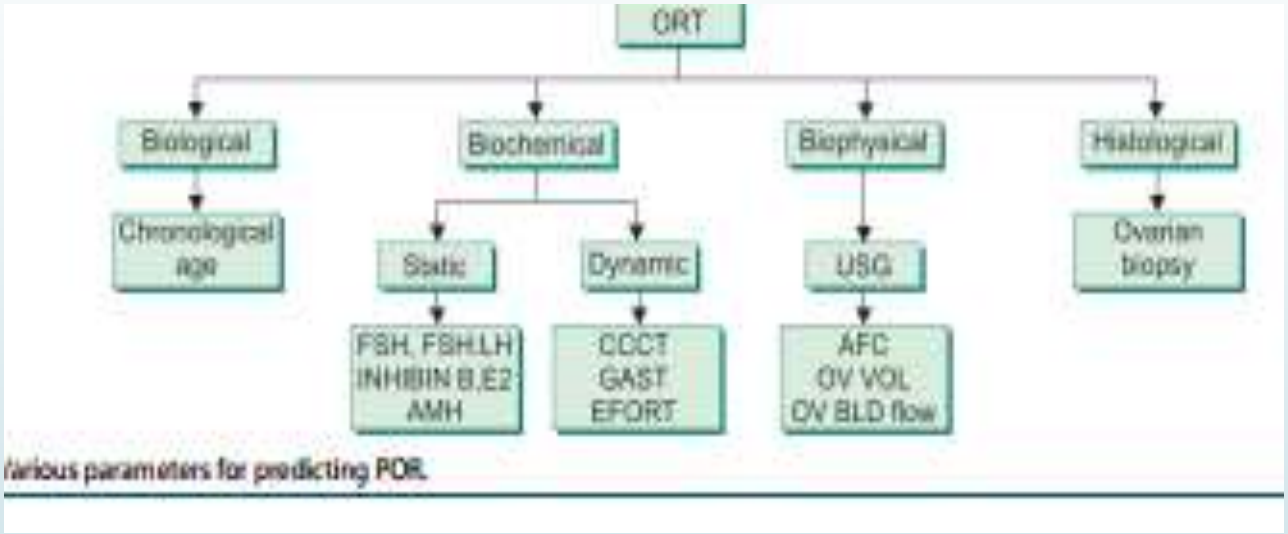
Interpretation of Various Ovarian

- Both AMH and AFC correlate well with response of the ovary to COS.

The ideal test is the ovarian response to COS itself.

AFC and AMH alone or in combination were not found to improve the prediction of response of the ovary to COS.

Most important factor related to live birth rates is the age of the women

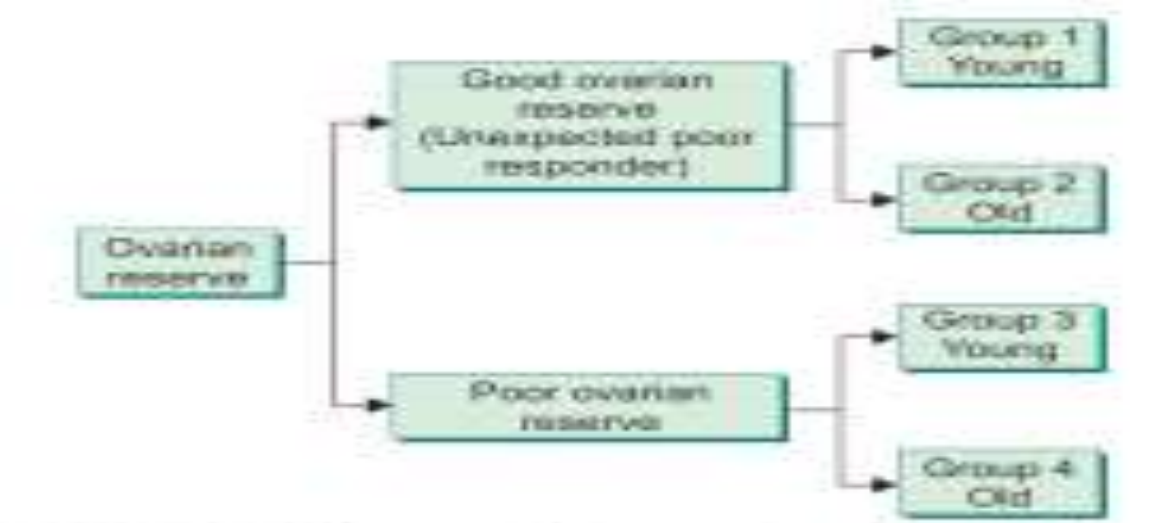


Various parameters for predicting POR

Table 23.3. Parameters for predicting POR and their interpretation.								
		Poor pregnancy		*Non response*				
		Sensitivity	*Specificity*	*Sensitivity*	*Specificity*			
TEST	*Cut point*	%	%	%	%	*Reliability*	*Advantages*	*Limitations*
FSH	10–20 IU/L	10–80	83–100	7–58	43–100	Limited	Widely used	Reliable, low sensitivity
AMH	0.2–0.7 ng/mL	40–97	78–92	*	*	Good	Reliable	Do not predict non pregnancy
AFC	3–10	9–73	73–100	8–33	64–100	Good	Reliable, widely used	Low sensitivity
Inhibin B	40–45 pg/mL	40–80	64–90	*		Limited		Reliable, do not predict non pregnancy
CCCT	10–22 IU/L	35–98	68–98	23–61	67–100	Limited	High sensitivity than FSH	Reliable limited additional value

*Limited evidence

Source: Practice Committee. Ovarian reserve testing. Fertil Steril. 2015.



. 23.3: POSEIDON strategy for low prognosis patients.

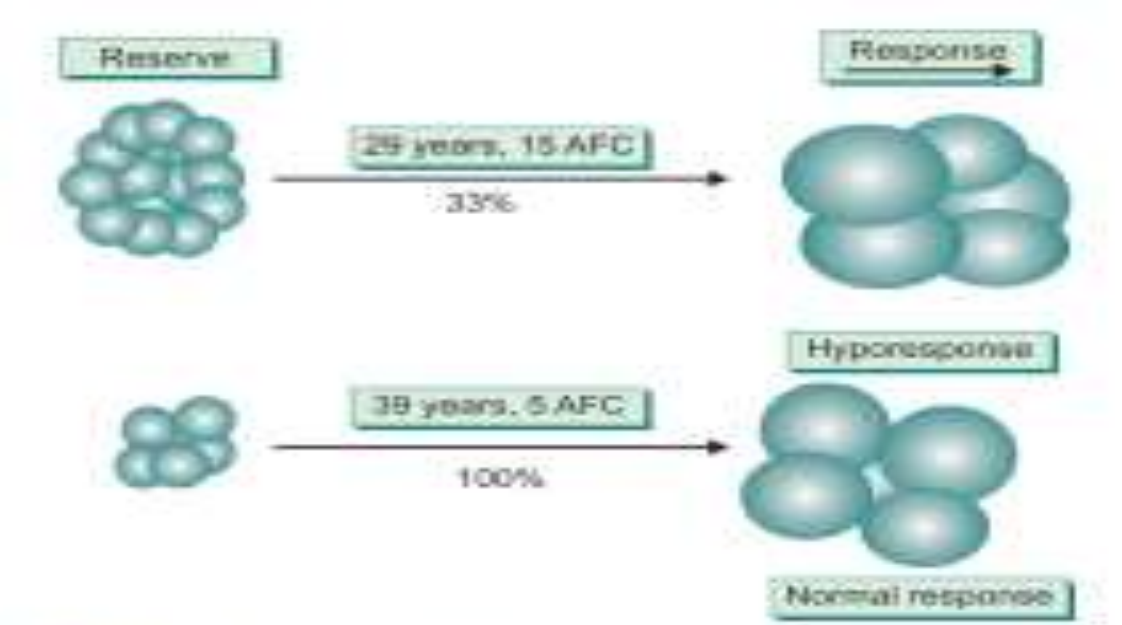


Fig. 23.4: FORT index (Follicular output ratio).

Table 23.4. POSEIDON strategy—Group 1 (Young women with good ovarian reserve).	
Reason	*Interventions*
• FSH dose does not reach the threshold • Genetic polymorphism of FSH-R, LH-R, V-LH-β • Trigger problem	• Change the protocol • Increase FSH dose • Add LH activity • hCG or agonist trigger

MANAGEMENT

- GROUP 1
- Young women with good ovarian reserve. Oocyte quality
- will be good

CONCEPT OF OVARIAN SENSITIVITY

- FORT Index (Follicular Output Ratio)
- • Ratio of preovulatory follicle to small antral follicle

Hyporesponders

- • About **15%** of normogonadotropic good prognosis patient are hyporesponders.
- • Incidence with long agonist protocol **is 19.8 and 15.2%** in antagonist protocol.
- • FSH hyposensitivity is defined as normogonadotropic normo-ovulatory young patients who will have **to r-hFSH an initial slow response** (stagnation between day 7 and 10 or no follicle >10 mm on day 8 of stimulation with normal follicular cohort).

- • **Reflects hyposensitivity** of the granulosa cell to FSH.
- • These are the women with good ovarian reserve and can achieve adequate number of retrieved oocytes.
- • But they **need higher dosage of FSH** (i.e. 3,000 IU) and prolonged stimulation cycle with low FORT, unexpected poor response (i.e. <3 eggs retrieved) and lower PRs.
- • If **hyporesponse** is identified **early** (i.e. day 5–8 of COS), r-h LH is effective in rescuing follicle/oocyte number (FORT) and embryo competence.

Sub-optimal Responders

- • Women with good ovarian reserve who obtain less number of oocyte **(4–9)** compared to normal responders (10–15).
- • They have a lower prognosis compared to normal responders in terms of cumulative live birth.

INCREASING DOSAGE OF GONADOTROPINS

- Useful in patients with good ovarian reserve and FSH threshold not reached or due to FSH receptor polymorphism.
- There is **a little benefit** in increasing the daily dose of gonadotropins to 450 IU in patients who poorly respond to standard protocol.
- **No benefit** in increasing the starting dose of FSH above 300 IU in terms of live birth rate.
- Study published regarding personalized protocol in FSH starting dose in patients, categorized according to their expected response to COS.
- They in patients expected to have poor response there is **no benefit in increasing FSH starting dose to more than 300** IU.

IMPORTANCE OF ADDITION OF LH

- Role of LH in **Folliculogenesis**
- Basically LH through androgen production improves the **sensitivity of the granulosa cell to FSH** by increasing the number of FSH receptor
- If hyporesponse is identified early (i.e. day **5–8 of** COS**), r-h LH** is effective in rescuing FORT and embryo competence.

Table 28.6. Role of LH in folliculogenesis.	
Early Follicular Phase (Induction of Androgen Production in Theca Cells)	*Intermediate Follicular Phase (Expression of LH Receptors in Granulosa Cells)*
• FSH receptor induction in Granulosa Cells • Increases responsiveness • Acts synergistically with IGF-1 • Increases recruit ability of pre-antral and antral follicles	• Sustain of FSH-dependent granulosa activities, including aromatase induction and growth factors release • Regulation of final follicle/oocyte maturation • Optimization of steroidogenesis

- A meta-analysis26 done with 43 trials and 6,443 patients evaluated the benefit of addition of adding r-LH with r-FSH.
- Bologna criteria were not used. They found that addition of **r-LH increased the pregnancy rate by 30% in patients with poor response** but not so in patients with normal response.
- ESPART trial27 randomized 939 poor responder patients selected according to bologna criteria to receive either r-FSH+ r-LH (2:1) (Pergovaris) or r-FSH alone.

- No difference in outcome was observed in terms of pregnancy rate and live birth rate.
- A meta-analysis28 showed that addition of r-LH in COS protocol **improves implantation rate and clinical pregnancy rate in patients with advanced maternal age (>35 years).**

PREFERRED COS PROTOCOL IN POOR RESPONDERS

- A study29 analyzed regarding the preferred protocol in poor responder patients over 45 countries worldwide in total of 196 centers.
- Majority were in favor of GnRH antagonist protocol (56%) followed by short agonist protocol (20%).
- In a Cochrane review,30 it was concluded that there is not much evidence to promote any particular intervention either in **adjuvant therapy**, pituitary down-regulation or ovarian stimulation in poor responder patients.
- f

- Two meta-analyses31,32 compared GnRH antagonist and long agonist protocol in poor responder patients.
- They found **no difference in number of oocyte** retrieved, pregnancy rate, and cancellation rate. However, with **antagonist protocol, there is reduction in dose and duration of gonadotropins**.
- A randomized controlled trial (PRINT) performed in poor responders33 categorized the patients according to bologna criteria into three groups each receiving either antagonist, long and short protocol.

- **Higher numbers of oocytes were retrieved in long and antagonist** protocol compared to short protocol.
  - So they concluded that long agonist and antagonist protocol are the suitable ones in poor responder.
- **Using Corifollitropin-alfa in older women** was found to be equally effective compared to daily recombinant FSH in terms of, number of oocytes retrieved, pregnancy rate, and live birth rates.
  - .

- If conventional protocol fails we can try with mild stimulation protocol.
- A meta-analysis found compared to **micro flare** protocol, in antagonist/letrozole protocol CPR was lower.
- By natural cycle IVF overall treatment burden to the couple is reduced. However, there is an increased risk **of cycle cancellation**.
- So it should be considered before deciding for donar oocyte, especially in less than 38 years

GROUP 2

- Older women with **good ovarian reserve**. The oocyte quality may be affected due to age factor (Table 23.6).

Table 23.8. POSEIDON strategy—Group 2 (Older women with good ovarian reserve).

Reason	Interventions
• Ageing—reduced androgen production • Asynchronous development of follicle • Genetic polymorphism of FSH-R, LH-R, LH β (rare)	• Protocol • Add LH activity • Synchronize follicle wave • Increase FSH dose • Aneuploidy screening—PGS

HOW TO SYNCHRONIZE FOLLICLE DEVELOPMENT?

- The following treatment will synchronize the follicle development (Table 23.7).
- • **OCP** pretreatment
- • **Luteal phase** manipulation:
- **Estradiol priming**
- **GnRH antag**
- **AACEP**

Table 23.7. Treatments used to synchronize the follicle development.

Drugs	*Rationale*	*Regimen*	*Advantages*	*Disadvantage*	*Evidences*
OCPs	Pituitary suppression No increase in FSH level in luteal phase So no early recruitment of follicles Role in enhancement of ER sensitization	Day 5–25 of menstrual cycle of previous month	Decrease in ovarian cyst formation Increase in homogeneity of cohort	Due to profound pituitary suppression there is an increase in need of dose and duration of the gonadotropin	A meta-analysis found that there is increase in dose and duration of gonadotropins and no difference in other outcome of IVF[37] A Cochrane review showed improved pregnancy outcomes with progesterone pretreatment and poorer outcomes with OCP pretreatment[38]
Luteal Phase Manipulations					
Estradiol	With its negative feedback effect on pituitary, E2 levels prevents early rise in FSH levels in late luteal phase thereby preventing early recruitment of follicles in follicular phase	4 mg daily from D20 to D2 of next cycle	Aides in follicular synchronization	Further large scale studies required	A meta-analysis showed increased number of retrieved oocytes but no difference in clinical pregnancy rate (CPR)[39] Another meta-analysis found decrease in cycle cancellation and an increase in CPR[40]

Contd...

Table 23.7. Treatments used to synchronize the follicle development.

Drugs	*Rationale*	*Regimen*	*Advantages*	*Disadvantage*	*Evidences*
GnRH antagonist	Causes immediate, rapid gonadotropin suppression by competitively blocking GnRH receptors in anterior pituitary, thereby preventing FSH rise and follicular discrepancy in early follicular phase	3 mg on D25	Aides in follicular synchronization	Large scale studies required	reduced size disparity of early antral follicle[67]
AACEP (GnRH agonist antagonist coonversion with E2 priming)	Uses agonist flare effect for recruitment of follicles and estrogen supplementation increases estrogen dominance in follicles leading to better quality oocytes in POR	Pretreatment with OCPs with GnRH-agonist overlapping last 5–7 days of OCPs till onset of menses, on D2—Low dose GnRH-antagonist (0.125 mg/day) and Estradiol 2 mg IM 2 doses every 3 days along with FSH/hMG stimulation, F/B Estrogen supplementation till dominant follicle	Focuses on promoting Estrogenic dominance in the stimulated ovaries thus avoiding the ill effects of LH flare and androgens—may improve prognosis in POR	Large well designed studies required	Helps in Estrogenic dominance in the stimulated cycles, avoiding the ill effects of LH flare and androgens[68]

Table 23.8. POSEIDON strategy—Group 3 (Young women with poor ovarian reserve).

Reason	*Interventions*
• Poor ovarian reserve • Asynchronous development of follicle	• Protocol • Maximum FSH dose • Synchronize follicle wave • Androgens • Dual stimulation

GROUP 3

- Young women with poor ovarian reserve.
- In spite **of poor ovarian reserve**, the quality of oocytes is good (Table 23.8).

ROLE OF ANDROGENS

- • **Follicular recruitment, growth, and survival**
- • **Increases intraovarian** concentration of androgens
- • Act via **androgen receptor** predominant on the granulosa cells
- • **Up regulation of IGF1, IGF1-R, FSH-R**.

DRUGS USED FOR ANDROGEN SUPPLEMENTATION WHY TO INCREASE NUMBER OF OOCYTE?

- A study analyzed the association between number of oocytes and cumulative live birth.
- There exists **a significant increase in cumulative live** rate if more number of oocytes are retrieved.
- There exist a nonlinear relationship between live birth rate and number of oocytes obtained following COS regardless of age.

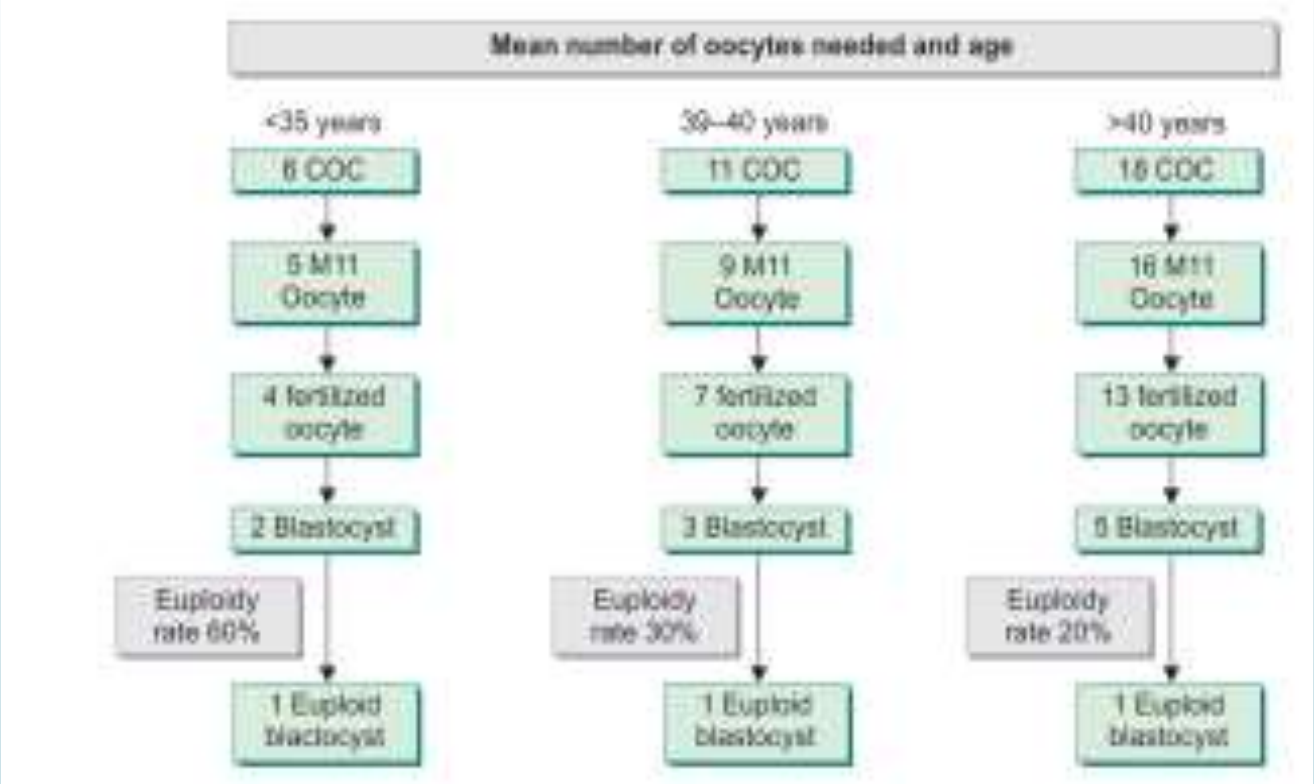
- The number of oocytes to maximize the live birth rate is
- A study was performed analyzing the relationship between number **of mature oocytes retrieved and chance of obtaining a euploid blastocyst**.
- Found that each supplementary **mature oocyte** increased the chance of obtaining euploid blastocyst by 11%.50

WHAT IS CONSIDERED AS GOOD NUMBER TO OBTAIN?

- The below chart explains how many oocytes are required to get an euploid blastocyst across women of different age group

Table 23.9. Drugs used for androgen supplementation.

Drug	MOA	Regimens	Advantages	Disadvantages	Evidence
DHEA	Act during early follicular growth before the gonadotropin sensitive phase Increases the recruitment of follicles Increases IGF & serves as precursor for steroids	75 mg/d 6-8 weeks before stimulation	Provides substrate for folliculogenesis and helps in improvement of antral follicle count	Still large-scale studies are required to prove the effectiveness	Cochrane review found that T and DHEA might be useful in terms of increasing live birth rate, but if we removed high risk bias trials then it showed no significance[45] There is increase in CPR but no improvement in other outcome as shown in a meta-analysis[46] Another recent meta-analysis found improvement in CPR significantly but not so if we consider only RCT[48]
TESTOSTERONE GEL	Enhancing FSH sensitivity during early Gn sensitive phase Improves follicular function and steroidogenesis	20 µg/kg/day from D15 in the preceding cycle	Local application No systemic side effects	Still controversial	A meta-analyses showed an increase in CPR and LBR as well as reduction in dose and duration of gonadotropins[46] A recent randomized clinical trial in bologna poor responders concluded no improvement in ovarian parameters[47] Ongoing RCT is TTRANSPORT (Testosterone TRANSdermal Gel for Poor Ovarian Responders Trial)
Letrozole	Competitive inhibition of Aromatase enzyme—↑ intraovarian androgens and decreases estradiol levels, thereby inhibiting negative feedback on FSH production	2.5 mg for first 5 days of COS	Improves intraovarian micro environment and endometrial receptivity Other uses—oncofertility	Mono follicular growth	The CPR was significantly lower and duration of gonadotropin stimulation is lower with the antagonist/letrozole group compared with microflare protocol[28]


Mean number of oocytes needed and age
<35 years
6 COC
5 M11 Oocyte
4 fertilized oocyte
2 Blastocyst
Euploidy rate 60%
1 Euploid blastocyst
35–40 years
11 COC
9 M11 Oocyte
7 fertilized oocyte
3 Blastocyst
Euploidy rate 30%
1 Euploid blastocyst
>40 years
16 COC
16 M11 Oocyte
13 fertilized oocyte
6 Blastocyst
Euploidy rate 20%
1 Euploid blastocyst

WAYS TO INCREASE NUMBER OF OOCYTES

- 1. **Increasing FSH Dosage**
- • Useful if ovarian reserve is good and FSH threshold not reached or FSH receptor polymorphism.
- • Not of much use if antral follicle counts is low.
- Higher dose of gonadotropins **will not** create follicles in de novo.
- • If ovarian reserve is **low and FORT is high no gonadotropin can compensate.**
- • In such cases dual stimulation is an option.

Double Stimulation or Shanghai Protocol

- • Based on concept that there occur 2 or 3 waves of follicle recruitment
- • It is a combination of two stimulation protocol in one menstrual cycle.
- • It targets the antral follicles in **the both follicular phase and luteal phase.**
- • Two OPU is done in **a single** menstrual cycle.
- • So, **more number of oocytes** and viable embryos are obtained.
- • Studied in 38 POR (Bologa criteria). The number of oocytes harvested was 167. • 26/38 (68.4%) succeeded in producing 1–6 cryopreserved embryos.
- • 21 underwent 23 frozen ET resulting in 11 ongoing pregnancies (47.8%).

- They observed that a good number of oocytes are retrieved in poor responders by using this protocol.
- A study was performed using Duplex protocol and they analyzed the outcome of COS in both phase of menstrual cycle.

COS was done in both follicular and luteal phase by classical antagonist protocol with GnRH trigger for follicular maturation.

COS in both phase of menstrual cycle provided a similar number of oocytes, zygotes, and blastocyst.54

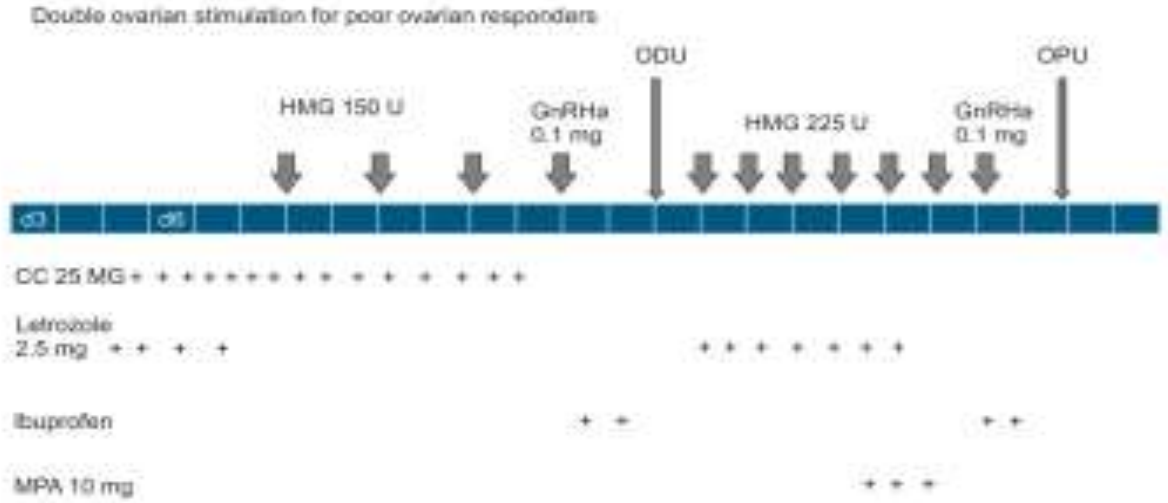
- Hence**, duplex protocol compared** to single COS cycle
- **doubled the final blastocyst** yield.54

GROUP 4

- Older women **with poor ovarian reserve**. Again the quality of oocytes is affected due to age factor
- GROWTH HORMONE
- Its use may be effective in group 4 women

Table 23.10. POSEIDON strategy—Group 4 (Older women with poor ovarian reserve).

Reason	Interventions
• Poor ovarian reserve • Asynchronous development of follicle	• Protocol • Maximum FSH dose • Synchronize follicle wave • Androgens • Dual stimulation • Growth hormone



. 23.6: Double stimulation or Shanghai protocol.

Table 23.11. Growth hormone in poor responder.

Rationale	*Regimen*	*Evidences*
• IGF is GH dependent and is involved in potentiating the effect of FSH • *In vitro* GH increase estradiol production • Oocytes from follicles having higher antral fluid GH levels have better developmental potential • Enhances nuclear and cytoplasmic maturation • Stimulates DNA repair • Improves normal fertilization and embryo development	• Varies from 4 IU daily to 24 IU on alternate days • Started on the day of gonadotropin or from day 21 in LBG protocol • Continued till day of hCG	A meta-analysis showed that the probability of pregnancy is increased by addition of GH or by doing day 2 embryo transfer[85] GH was found to increases live birth rate in poor responders, but in which subgroup was not shown in a cochrane review[86] Although GH does not increase COS response or no of oocytes, three meta-analysis concluded the positive effect of adding GH in terms of pregnancy and live birth rate thus showing its effect on oocyte quality[87] Meta-analysis done in poor responders showed no benefit of GH in improving implantation or live birth rate[88] A recent RCT regarding the benefit of adding GH in poor responders diagnosed according to bologna criteria showed some improvement in ovarian parameters but found no difference in pregnancy rate[89]

OTHER INTERVENTION IN POOR RESPONDERS

1. Pyridostigmine

- • **Acetylcholinesterase inhibitor**.
- • ***Increases GH secretion*** by enhancing the action of
- acetylcholine.
- • Was evaluated as a cheaper alternative to GH supplementation (dose—120 mg/day).
- • Very limited no of studies and study population.
- • Addition of pyridostigmine **does not appear to improve** the ongoing pregnancy/delivery rate in poor responders undergoing IVF.

2. Aspirin

- • Poor ovarian response might be due **to impaired ovarian blood flow.**
- • A meta-analysis concluded that there is **no** difference in clinical pregnancy rate by adding aspirin.
- • Due to lack of evidence aspirin cannot be recommended in women undergoing IVF.

3. L-Arginine

- • It is involved in formation of **nitric oxide** (NO).
- • NO is **an intra- and intercellular modulator** that plays a role in follicular maturation and ovulation.
- • In poor responders, the addition of L-arginine ***increases the number*** of retrieved oocytes but has
- no benefit on terms of pregnancy outcome.

4. Assisted Hatching (AH)

- • AH compared to control group **showed no** difference in terms of live birth.
- • In patients with **repeated IVF failure or in FET** cycles AH was found to increase clinical pregnancy rate and multiple pregnancy. But it is of no benefit in women of advanced age or when performed in **unselected patients in fresh embryo transfer cycle.**
- • Currently, there is an insufficient evidence to recommend **AH to patients with AMA or POR**.

5. Day of Embryo Transfer

- • A randomized trial concluded that there is a significant increase in pregnancy rate for day 2 transfer **(27.7%)** compared to day 3 transfer (16.3%).65
- • Another randomized trial including total of 250 patients showed that based on the day of embryo transfer there is no difference in outcome transfer there is no difference in outcome

6. Role of PGS

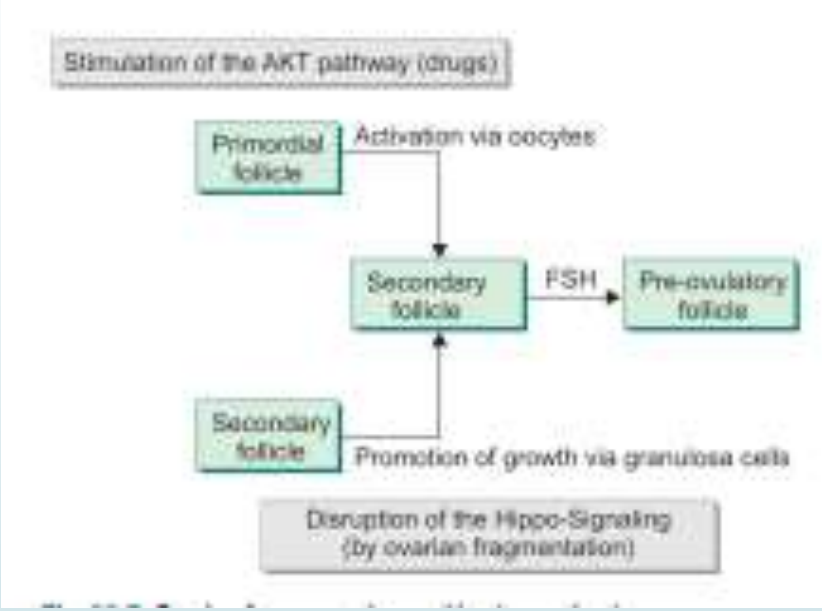
- transfer there is **no difference in outcome**
- • Its benefit in poor responder patients is controversial.
- • Some studies have shown in diminished ovarian reserve there is a chance of having genetically abnormal pregnancy or miscarriage.
- But some say that there is no increased risk of aneuploidy or miscarriage in patients with poor ovarian reserve.
- • So further RCTs are required before suggesting its role.

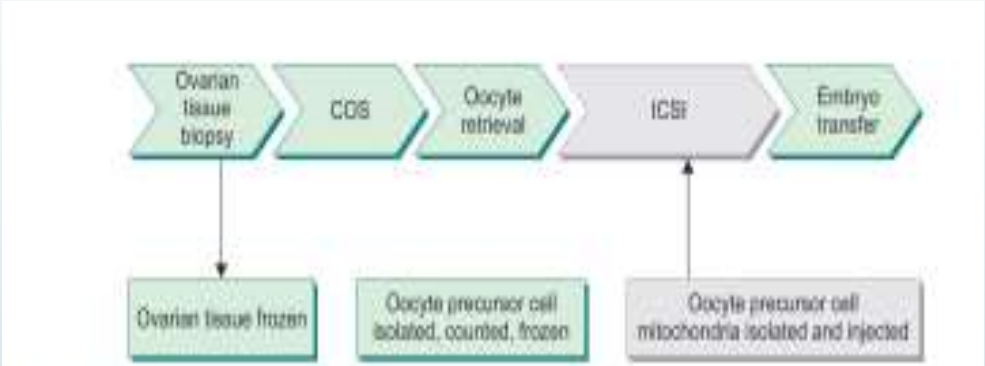
Future in Poor Responders

- • Ovarian fragmentation and in vitro activation
- • Ovarian PRP application (ovarian rejuvenation)
- • Application of mitochondrial activation.
- 1. Ovarian fragmentation and in vitro activation (IVA)
- • Reproductive lifespan of the women is determined
- by her primordial follicular pool. It is maintained
- through a balance between the tensin homolog
- (PTEN) and phosphatidyl inositol 3-kinase (PI3K)
- (Fig. 23.7).

- • PTEN is break and P13K is a gas pedal.
- If PTEN is inhibited follicular growth is enhanced.
- Release of PDK-1 (a protein regulated by the PI3K pathway) leads to premature death of primordial follicles.
- • Ovarian fragmentation and IVA promote follicle growth via different mechanism.
- • Ovarian fragmentation and IVA treatment was given to 27 patients with ovarian failure

- Residual follicles were found in 13/27 patients.
- About 8/13 patients had follicular growth secondary to this method.
- About 5/8 patients had mature oocytes.
- In that 2 had pregnancy following FET.
- One healthy baby was born after this treatment.70


Stimulation of the AKT pathway (drugs)
Primordial follicle
Activation via oocytes
Secondery follicle
FSH
Pre-ovulatory follicle
Secondary follicle
Promotion of growth via granulosa cells
Disruption of the Hippo-Signaling (by ovarian fragmentation)



13.8: Application of mitochondrial activation.

2. Ovarian PRP application (ovarian rejuvenation)

- • PRP is rich in several growth factors that have a significant role in tissue regeneration.
- • In the ovarian cortex, it can possibly stimulate the germ cell line to develop into an oocytes.
- • Studied in total of eight perimenopausal women.

- • PRP was injected into the ovary by **transvaginal ultrasound guidance.**
- • Return of ovarian function was observed within **3** months.
- • But large scale data on ovarian rejuvenation and pregnancy outcomes will be required before a conclusion can be drawn.

3. Application of mitochondrial activation

- • Oocyte is the cell which have large amount of mitochondria.
- **• Mitochondria the power house of the cell** is needed by oocyte to be competent for fertilization and for embryo development.
- • Mitochondrial application at time of ICSI can be used in patients with repeated IVF failure or advanced age group.
- • It increases oocyte energy without altering fetal genome.

CONCLUSION

- • Hyporesponse (impaired response) and poor response
- are not the same.
- • Hyporesponders and poor responders are associated
- with lower chance of live birth rate.

- • Concept of low prognosis should be taken in to
- account during COS considering ORT, sensitivity
- of ovaries to gonadotropins, and ability to produce
- euploid oocytes.
- • Number of oocytes retrieved to obtain one euploid
- embryo should the end point of stimulation in real life
- clinical scenario.

- • Type and dose of gonadotropins will not compensate
- when ovarian reserve is poor.
- • GnRH agonist and GnRH antagonist are equally effective, but GnRH antagonist is more patient friendly.
- • Nonlinear association was found between oocyte

- number and live birth following IVF.
- • Supplementation with r-LH is recommended, especially in hyporesponders.
- • Adjuvant therapy (GH, androgens) do not seem to be
- effective in terms of pregnancy.
- • Accumulation of oocytes–embryos is a new therapeutic way requiring further evaluation

PROBABLE QUESTIONS

- 1. Define POR and describe various classifications used
- and their critical analysis.
- 2. Prediction of POR.
- 3. How will you manage a 28-year-old patient with
- AFC of 10 with previous history of poor response to
- COS.
- 4. Management strategies in a 38-year-old patient with
- AFC of 3.
- 5. Preferred COS protocols in POR.