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ARText

Poor Ovarian Response in ART

Editor
Dr. Rupali Bassi Goyal
M: +91 9818331760
E: rupalibassi@hotmail.com

Dr Pankaj Talwar
President

With great pride and honor, I write this message for the Eighth E-bulletin of IFS-ARTexT. ARText is our initiative to disseminate scientific and ethical (subject-related) knowledge, and to constantly update everyone with new researches and developments across the world. Through this endeavor, we aim to discuss and simplify the various complexities in clinical ART.

In the current issue, we will be discussing "Ovarian Hyperstimulation Syndrome" (OHSS). It is a potentially fatal complication of ovulation induction increasingly being recognised with the greater usage of various Assisted Reproductive Techniques. As the treatment of the syndrome is currently empirical, prevention is the most important aspect of its management and thus needs in depth discussion of its pathophysiology and various preventive measures.

I am sure that you would be benefited from this academic initiative of publication wing of IFS. Indian Fertility society feels proud and congratulates the editors for this bulletin.

Dr Shweta Mittal
Secretary General

To start with, I would like to thank all the readers for appreciating and acknowledging the previous bulletins of ARTexT. Your encouragement motivates us to present more such bulletins in the field of the Assisted Reproductive Techniques. We have always believed in spreading awareness about the common issues in ART and tried to gather and present the evidence that will undoubtedly help both the clinicians and the patient.

In this bulletin we are going to dwell in detail "Ovarian Hyperstimulation Syndrome" a complication of ART which can progress from mild to critical OHSS if not timely recognized and intervened. OHSS is an iatrogenic disorder due to ovarian stimulation by gonadotropins resulting in ovarian enlargement and fluid shift from intravascular to extravascular compartment and multiple consequences which can prove to be fatal with a downhill course. This edition of ARText will highlight the pathophysiology, risk factors, clinical presentation and how prevention is of paramount importance in the treatment of OHSS.

I am sure that you would appreciate and learn from this academic initiative of IFS and will be able to apply the take home message in your busy daily clinical practice.

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1 Introduction

POR is one of the main challenges of modern Reproductive Medicine. It is an important limiting factor in success of any treatment modality for Infertility. Basically, POR indicates a reduction in quantity and quality of oocytes in women of reproductive age group.

Evaluating Ovarian Reserve and individualizing the therapeutic strategies are very important for optimizing success rate.

Early detection and active management are essential to minimize the need for egg donation.

2 Incidence

10% of the women undergoing IVF will show poor response to gonadotrophin stimulation.9 – 24% of infertile women are poor responders. Data from ASRM/SART registry showed 14.1% of initial cycles were cancelled: 50% were poor responders. *(Ubaldi FM, et al., 2005)*

3 Definition

Majority of attempts at definition of POR have considered certain parameters noted during ovarian stimulation for IVF:

- Low peak estradiol concentration following conventional ovarian stimulation [300 to 500 pgm/ml].
- Low number of follicles [<5] / Less number of retrieved oocytes [<5].
- Some define age of > 40 years, previous poor response for diagnosing POR. In fact, a review in 1999 had already documented 35 definitions of POR.

((Barrenetxea G et al,. 2008), (Yarali H et al,. 2009), (Surrey ES et al., 2000).

Limitation in defining POR

To overcome limitations imposed by lack of universality in definition or conduct of any research and implementation of meaningful interventions, Bologna criteria have been introduced following consensus meeting of ESHRE Working Group on POR definition held in 2011. ***(Ferraretti AP et al., 2011)***

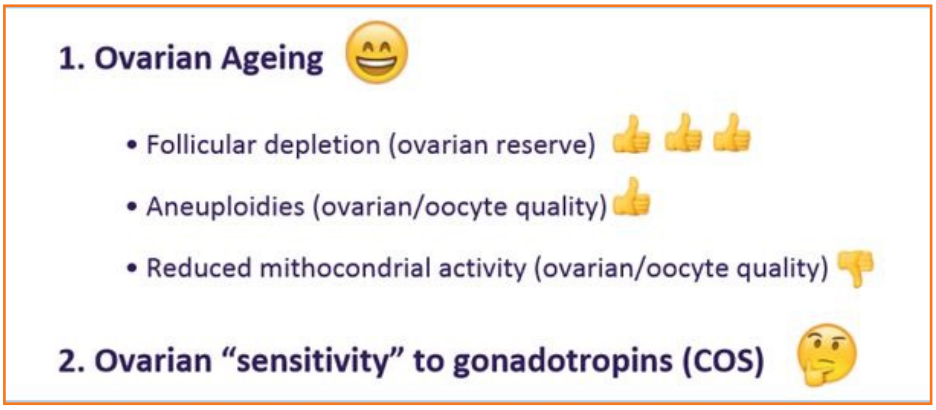
Bologna Criteria recommends the presence of at least two of the following three features for diagnosis of POR:

- Advanced maternal age [> 40 years] or any other risk factor for POR.
- A previous Poor Ovarian Response [< 3 oocytes with conventional stimulation protocols].
- An abnormal Ovarian Reserve Test [i.e. AFC 5-7 follicles or AMH .5 – 1.1 ngm/ml].

The main points of debate and concern regarding Bologna Criteria:

- Homogeneity of population.
- Cut off values for age, number of retrieved oocytes, AFC and AMH.
- Risk factor other than age.
- Oocyte quantity versus quality.
- Over Diagnosis.
- Large scale validation.

The POSEIDON GROUP [Patient Oriented Strategies encompassing Individualized Oocyte Number] was recently established to focus specifically on the diagnosis and management of low prognosis patients.
(Alviggi C., et al., 2016)



4 Etiopathalogy

Reproductive ageing is a continuous process from before birth till menopause. Women have a finite number of germ cells whose number peaks at 6-7 million by gestation week 20. From midgestation onwards and throughout reproductive life; an irreversible attrition progressively diminishes the germ cell pool of Gonads. After the age of 30 fertility declines gradually due to reducing primordial follicular pool as a consequence to ovulation but predominantly because of follicular atresia. Nongrowing follicular pool at different ages may have a differing response to changes in hormone levels associated with age.

Women of all age groups with Nongrowing follicles below the normal range would have a suboptimal response to ovarian stimulation and experience a shortened reproductive life span. Considering a fixed time interval between end of fertility and menopause, these women would undergo an early menopause.

Risk factors for Poor Ovarian Response

- Short menstrual cycle length.
- Single Ovary.
- Previous Ovarian Cystectomy.
- Chronic Smokers.
- Unexplained Infertility.
- Previous Chemotherapy and Radiotherapy.
- Genital Tuberculosis.
- Uterine Artery Embolization for Fibroids.
- Ethnicity: Indian Women undergoing IVF, Ovarian ageing was found to be approximately 6 years older.
- Genetic risk factors:
- Family history of Premature Menopause.
- Fragile X mental retardation 1[FMR].
- FSH Receptor [FSH -R] Polymorphism is considered to be important case of unexplained Poor Ovarian Response in young women.
- Genetic risk factors:

The mechanisms involved are:

- Decreased number of FSH receptors in Granulose cells.
- Defective signal transduction after FSH receptor binding.
- Inappropriate local vascular network for distribution of gonadotrophins.
- Auto antibodies against Granulosa cells.
- Excess of vascular growth factor receptor [VEGFR-I].
- Abnormality in IGF-1 and IGF-2 levels.
- Diminished circulating Gonadotrophins Surge –attenuating Factor [GnSAF] bioactivity.

(Younis JS 2011), (Martinez F et al., 2002), (Ulug U et al., 2007), (Neulen J et al. ,2001), (Hernandez ER et al., 2000), (Lee DW et al., 1993),

PREDICTORS OF POR

It is of extreme importance to predict who will be a poor responder, because stimulation protocols should be ideally individualized according to the conditions of each case. There are several tests proposed to predict ovarian reserve, which can give an idea about the ovarian response.

Static Tests

These are biochemical testing of ovarian reserve based on a single measurement of early follicular phase [cycle day 2-4].

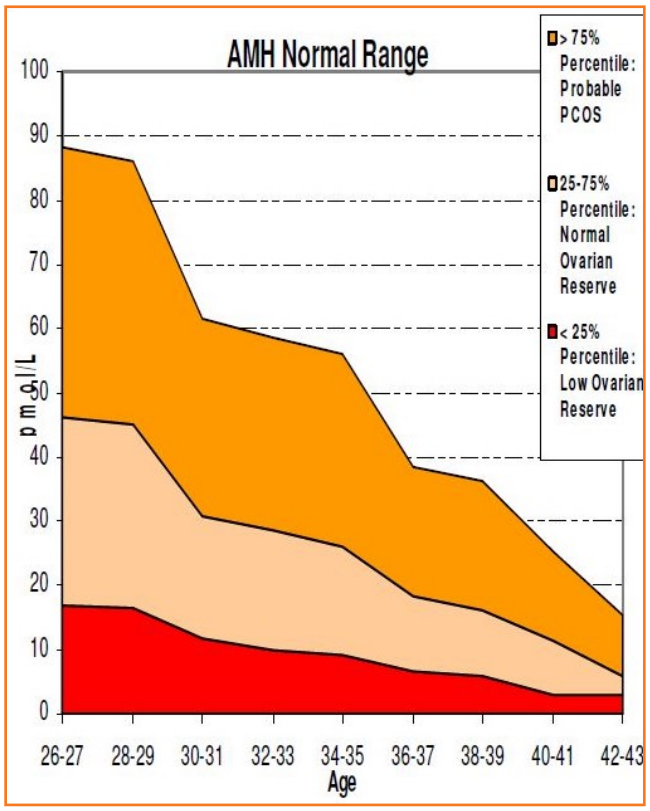
SERUM FSH
High levels [>12 or >15 mIU/ml] on cycle day 2 or 3. It is only screening test.

SERUM ESTRADIOL [E2]
Elevated levels [>30 – 75 pgm/ml] on cycle day 2 or 3. Limited by its very low predictive accuracy for poor response.

SERUM INHIBIN-B
Decreased levels [45pgm/ml] on cycle day 2 or 3. Accurate only at a very low threshold level.

IGF-1
Low levels of IGF-1 in follicular fluid are poor predictor in follicular fluid.

AMH
A Glycoprotein produced by the granulose cells within preantral and early antral follicles. Serum AMH has become an increasingly popular and established method for assessment of ovarian reserve.

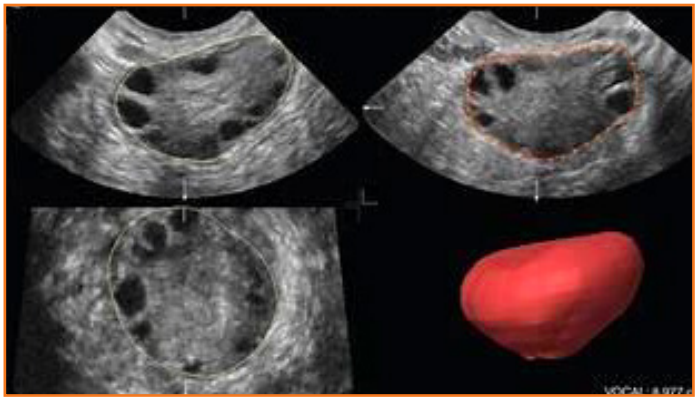


(Cameron IT, et al 1988), (Scott RT et al., 1989), (Toner JP et al., 1991), (Broekmans FJ et al., 2006), (Mukherjee T et al., 1996), (Licciardi FL et al., 1995), (Seifer DB et al., 2007), (Oosterhuis GJ et al., 1998), (Scott RT et al.,1990), (Scott RT et al., 1995), (Seifer DB et al., 1997), (Van Rooij IA et al., 2002).

Sonographic Tests

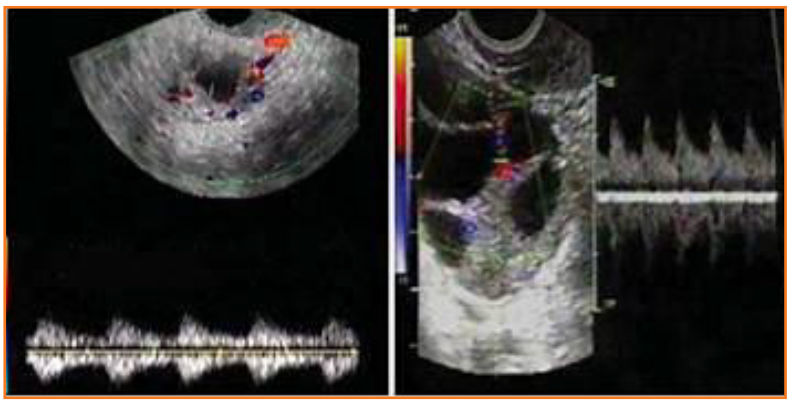
Mean ovarian diameter (length + width/2) provided a comparable degree of predictability of OR as the ovarian volume in infertile women undergoing ART . Ovarian volume measurement, at a cut off value of 3 cm3showed specificity for prediction of cycle cancellation and non-pregnancy of 92%. Some authors demonstrated, the individual ovarian parameters (width, length or an average of the two) reliably reflect ovarian reserve in pre-menopausal infertile women.

(Frattarelli JL et al ,2002),(Stacea Bowen et al ,2007), (Gibreel A et al 2009)



Antral Follicle Count (AFC)
AFC's less than 4 are more likely to have cancelled cycles.

OVARIAN STROMAL BLOOD FLOW
The clinical value of Doppler studies for ovarian stromal blood flow has been unclear.
(Lass A et al., 1997), (Gibreel A et al., 2009), (Chang MY et al,. 1998).



(Ernest Hung Yu Ng et al, 2005)

Dynamic Tests

Clomiphene challenge test [CCT], Exogenous FSH ovarian reserve test [FSHORT] and GnRH agonist stimulation test [GSAT] is Dynamic tests but evidence suggests that dynamic tests should be abandoned.
(Maheshwari A et al., 2009)

DIAGNOSIS

Identifying POR whether age related or otherwise is important; as such these women have a lower pregnancy rate and higher pregnancy loss.

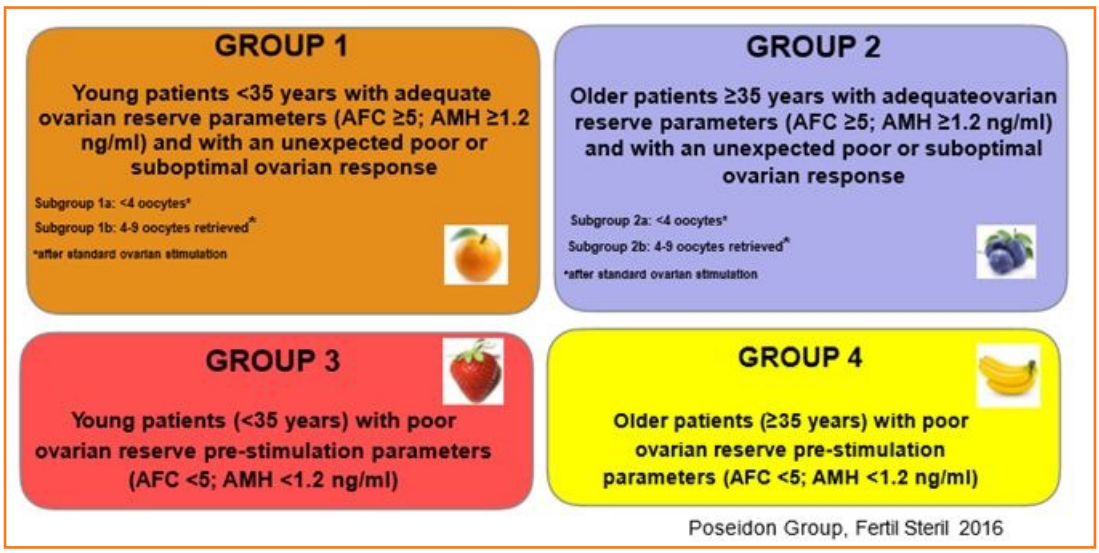
AFC and AMH are the most sensitive markers for diagnosing POR. These markers together are sensitive enough to iCOS protocols.

AFC is defined as the number of follicles smaller than 10 mm in diameter detected by Transvaginal Sonography in early follicular phase. AFC less than 4 is discriminatory for POR. Serum AMH levels of 2 pmole/L or .28ngm/ml is discriminatory for POR.
(Satwik R et al., 2012)

POSEIDON CRITERIA

The POSEIDON Criteria was recently established in 2016 by a group composed of Reproductive Endocrinologists and Reproductive Medicine Specialists from 7 countries. They proposed a new stratification to classify patients with reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotrophins.

These 4 subgroups are based on quantitative and qualitative parameters:
1. Age and expected Aneuploidy rate.
2. Ovarian Biomarkers i.e. AFC and AMH.
3. Ovarian Response, provided in previous stimulation cycle.



Comparison between Bologna criteria and Poseidon's stratification.

Bologna Criteria

1. Maternal age ≥40 years + A previous POR
2. An abnormal ORT (AFC <5–7 follicles or AMH < 0.5 –1.1 ng/ml) + A previous POR
3. Maternal age ≥40 years + An abnormal ORT (AFC <5–7 follicles or AMH <0.5 –1.1 ng/ml)
4. Maternal age ≥40 years + An abnormal ORT (AFC <5–7 follicles or AMH < 0.5 –1.1 ng/ml) + A previous POR
5. 2 previous POR

In the POSEIDON classification a poor ovarian reserve pre-stimulation is defined on the basis of ovarian reserve markers, precisely AFC <5 or AMH <1.2 ng/ml. This identifies the so-called "expected poor ovarian responders": these patients belong to GROUP 3 if they are aged < 35 years or GROUP 4 if they are > 35 years old; the 2 groups with the same low ovarian reserve are thus differentiated for the oocyte quality and therefore for the expected aneuploidy rate of the oocytes taken.

Presently AMH and AFC are the most reliable for assessing ovarian reserve.

MANAGEMENT

Despite the fact that in last two decades an enormous number of papers have been published in the literature, so far it has been impossible to identify any efficient treatment to improve the ovarian response and the clinical outcome.

However, the approach to management can be divided into Pretreatment, Protocols for Controlled Ovarian Stimulation and Adjuvant Treatment.

Pretreatment

Pretreatment with oral contraceptive pills [OCP], Progesterone and Ethinyl Estradiol is used with the aim to improve follicular synchronization, prevent premature ovulation, reduces cyst formation, and shortens the length of stimulation and schedule cycles.

OCP is started from day 3/4 of previous cycle given for a minimum of 21 days and maximum of 42 days.

Progesterone [Medroxy progesterone acetate 10 mg] twice daily from day 15 of cycle preceding IVF treatment for a period of 2-3 weeks.

Cochrane review on OCP Pretreatment found fewer clinical pregnancies and a higher amount of gonadotrophin therapy required. Therefore, routine use of OCP in Poor Responders may not be advisable.

Protocols

Although many protocols with different doses types of gonadotrophins have been proposed but to date the question is still which is the ideal protocol?

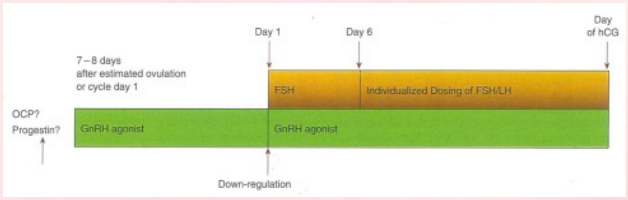
The various protocols are:

1. Gonadotrophins
2. GnRH Analogues
3. GnRH Antagonist
4. Natural cycle / Modified Natural cycle
5. Dual Stimulation
6. Oocyte Cryopreservation

Gonadotrophins

When the standard dose of gonadotrophins [225-300 IU] fails to induce proper multifollicular growth, high doses of gonadotrophins have been used. Prospective and Retrospective studies did not report enhanced ovarian response and/or pregnancy rates when starting dose of gonadotrophins was increased up to 450 IU. In poor responders; the recruitable follicles are fewer and the gonadotrophins, independently of the dosage administered, can only support, the cohort of follicles receptive to stimulation without manufacturing follicles de novo.

GnRH-a



LIMITATIONS

(a) High cancellation rate

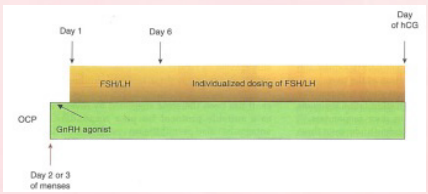
(b) Prolonged hormonal stimulation

(c) High cost

(d) Only marginal benefit in yield of mature oocytes

GnRH Analogues: Gonadotrophins and GnRH Agonist started in late luteal phase.

SHORT GnRH-a



- MOA- Initial agonistic stimulation effect on endogenous FSH and LH (Flare up effect).

ADVANTAGE

(a) Decrease in Exogenous gonadotrophin requirement

(b) Higher pregnancy rate

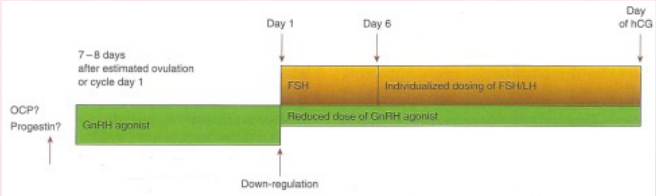
(c) Decrease miscarriage rate.

LIMITATION

Significant increase in LH and Progesterone levels leading to atresia of follicles

Short GnRH Agonist Protocol

MICRO-DOSE GnRH-a

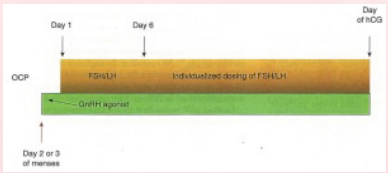


ADVANTAGES

(a) Decrease Gonadotrophin requirement
(b) Shorter duration of stimulation
(c) Increase E2 concentration on day of stimulation.
(d) Increase number of mature oocytes
(e) Good quality embryos.
(f) Decrease cancellation rate.

Micro Dose Protocol

MICRO DOSE FLARE GnRH-a



- BASIS - Low dose of leuprolide acetate (25-50ugm) is needed to cause a pituitary flare of gonadotrophins

ADVANTAGES

- More physiological
- Rapid rise in E_2 levels
- Development of mature follicles
- No premature L.H. surge

LIMITATION

- Most studies are retrospective
- Efficiency is yet to be proved

Micro Dose Flare Up Protocol

GnRH-a "STOP"

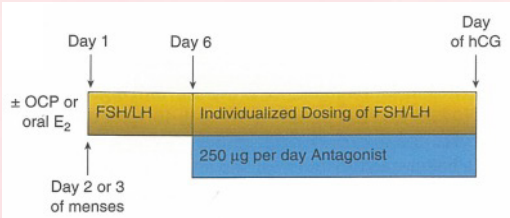
- GnRH-a administered as in long protocol from D-21.
- Withheld once gonadotrophin stimulation has started.
- No premature LH Surge

LIMITATIONS

Prospective studies, showed that in spite of higher number of oocytes there was no improvement in reproductive outcome.

GnRH Analogue Stop Protocol

GnRH ANTAGONIST

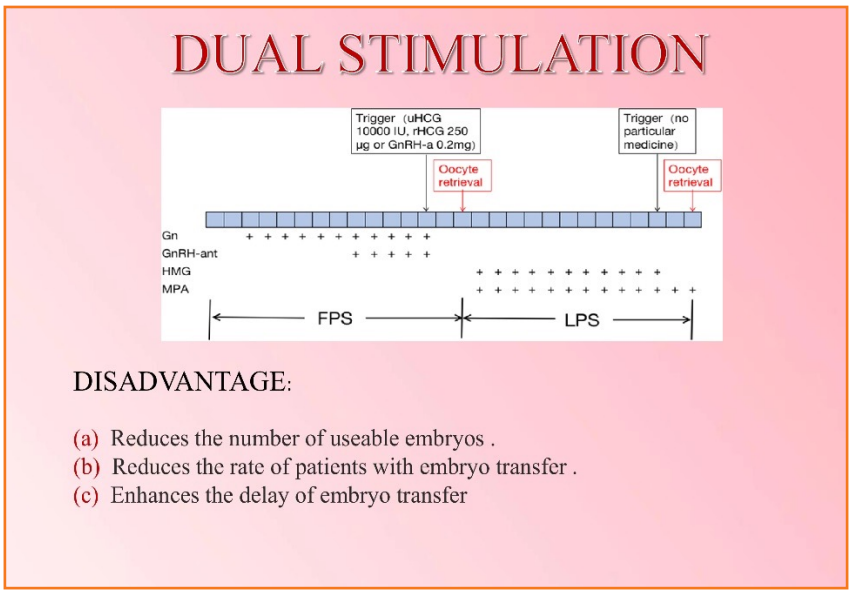


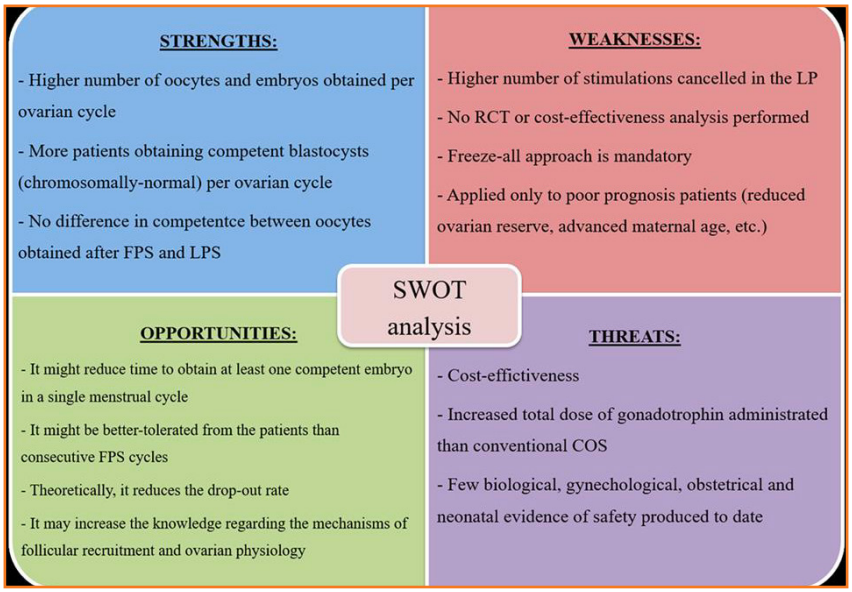
ADVANTAGES

(a) Suppresses LH surge of late follicular Phase.
(b) Shortens treatment period.
(c) Allows natural follicular recruitment
(d) Cost effective due to decreased Gonadotrophin requirement.

GnRH Antagonist

Dual Stimulation





(M. A. Akman et al., 2000.) , (Yanqun Luo et al, 2020).

Natural Cycle / Modified Natural Cycle

Natural cycles IVF with or without minimal can be considered as an easy and cheap approach to poor responders. Natural cycle IVF was associated 50% cancellation rate due to premature LH surge, failed fertilization and overall clinical pregnancy rate was 10%. In Modified Natural cycle addition of GnRH antagonist and endogenous gonadotrophins reduced incidence of premature LH surge.

(M. Schimberni et al., 2009)

Oocyte Cryopreservation

Obtaining a large cohort of oocytes in poor responders by accumulating vitrified oocytes over several cycles of stimulation could result in higher live birthrate per patient and potentially reduce dropout.

(A. Cobo et al., 2012).

Adjuvant Therapy

1. **Addition of Estradiol in Luteal Phase:** The addition of estradiol in luteal phase with or without the simultaneous use of GnRH antagonist decreases the risk of cycle cancellation and increase the chance of clinical pregnancy improving synchronization of pool of follicles available for controlled ovarian stimulation. *(R. Fanchin, L et al., 2003), (N. P. Polyzos et al., 2014)*
2. **Addition Of Androgens:** Evidence for role of androgens arises from pharmacological observations that testosterone, androstenedione and dihydrotestosterone can promote early follicular growth and enhance FSH mediated action.

a. Testosterone

The effect of testosterone on follicular response is mediated by increasing FSH receptor activity and by stimulating IGF-1. This improves number of follicles recruited, oocytes retrieved, implantation rate, clinical pregnancy rates and decrease in cycle cancellation rates. 10 mg of testosterone gel is applied on external side of thigh for 21 days starting from first day of menstruation prior to initiation of ovarian stimulation. However routine use of testosterone in poor responders is a matter of debate.

Dehydroepiandrosterone [DHEA]

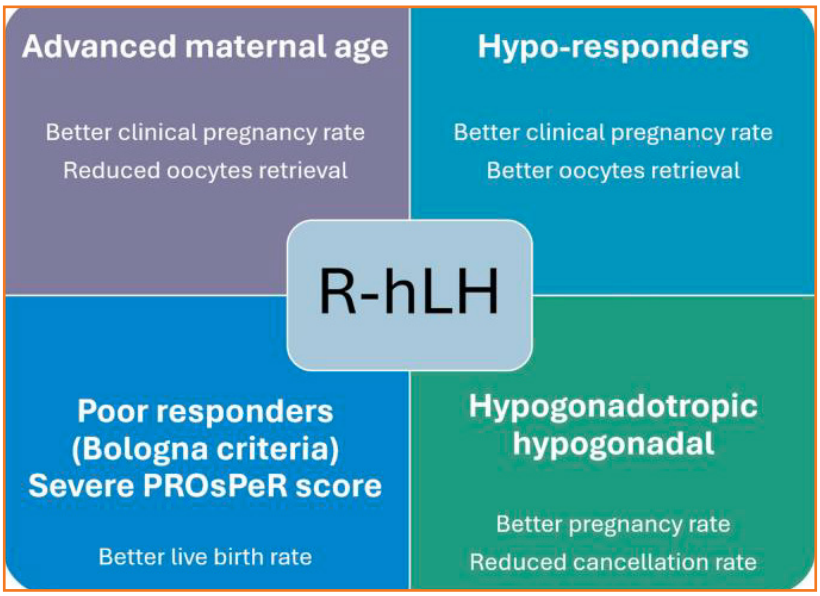
DHEA is the prohormone for up to 48% of follicular fluid testosterone, which itself is the prehormone for estradiol.75 mg/day of DHEA causes improvement in AMH concentration, AFC, peak estradiol, number of oocytes retrieved, number of metaphase 2 oocytes and high-quality embryos.
(P. R. Casson et al 1998.)

Growth Hormone

GH stimulates ovarian steroidogenesis, follicular development and enhances the ovarian response to gonadotrophins.GH is started concomitantly with gonadotrophins. The dose ranges from 4 IU to 8 IU daily or 10 to 24 IU on alternate days. Till date available evidence shows that GH supplementation improves pregnancy and live birth rates in poor responders without any adverse effects.
(E. M. Kolibianakis et al., 2009.), (D. Kyrou et al 2009).

Recombinant LH

Addition of r-LH with r-FSH in poor responders significantly increases number of oocytes retrieved with relative increase in clinical pregnancy rates.
(P. Lehert et al., 2014).



COQ10

CoQ10 supplementation significantly increased the clinical pregnancy rate in women with POR. CoQ10, DHEA and GH adjuvant therapy before IVF may have a positive effect on pregnancy outcome in POR patients compared with the conventional COS regimen. TEAS was the worst at improving clinical pregnancy rates, even though it was a noninvasive ex vivo intervention.

(Xu Y, Nisenblat, V et al 2018), (Florou P, et al 2020)

VASOACTIVE SUBSTANCES

Vasoactive substances like aspirin and L-arginine enhance ovarian vascularity required for folliculogenesis which could contribute to improved response in poor ovarian responders.

(U. Waldenström et al., 2004), (J. L. Frattarelli et al., 2008).

OVARIAN PRP

Autologous PRP has the potential to enhance tissue functionality through the stimulation of angiogenesis. A potential positive impact of PRP on the regulation of sex hormone levels, ovarian response, and pregnancy outcome. Women with diminished ovarian reserve or premature ovarian failure experience improvements in follicular count, hormone levels, and successful pregnancy outcomes after undergoing intraovarian PRP treatment

(Farimani M, et al 2021) (,Lingling Wu et al 2024)

Autologous stem cell ovarian transplant [ASCOT]

Women receiving ASCOT showed a positive response in terms of AFC and AMH. Autologous stem cell ovarian transplant could represent a paradigm shift for fertility treatment for PRs and women with severe DOR. Combined Use of Autologous Bone Marrow-derived Stem Cells and Platelet-rich Plasma for Ovarian Rejuvenation in Poor Responders could represent a paradigm shift for fertility treatment for poor responders.

(Mindy S, et al 2018 .) (Sunita Tandulwadkar ,et al 2020)

FREQUENTLY ASKED QUESTIONS

1 Does DHEA supplementation improve ooyte / embryo quality?

DHEA supplementation seems to improve the ovarian environment by acting on the androgen receptors that are expressed on the granulosa cells and ovarian stroma, resulting in increasing antral follicle counts and AMH levels, and therefore ovarian reserve. DHEA is increasingly being used by many IVF centers in poor responders despite the lack of convincing data. The current suggestion is that utilization of DHEA is suitable in consented and well-informed patients considering absence of side effects, low cost, and the increase in spontaneous pregnancies as it may improve ovarian reserve, response to ovarian stimulation, and potentially pregnancy outcome.

2 DHEA dose and duration of use?

There is no consensus on the optimal or maximal dose of DHEA, or duration of use, though most studies suggest 75 mg of micronized and oral DHEA for maximum 6 months.
(Mazen R et al 2013)

3 What cut off value of AMH can predict poor ovarian response?

AMH levels of 2 pmol/l [=.28 ng/ml] seems to be discriminatory for poor ovarian response, however no value of AMH could identify non-response but available evidence suggests that although no women can be excluded from IVF programme but counseling should be done regarding avoidance of repeated cycles of IVF if first cycle confirms poor response. With AMH levels between 2 – 10 pmol/l, there is suspicion of poor response hence; alternative protocols may be helpful for a better response.

4 How much does AMH really vary in normal WOMEN?

AMH levels reflect the ovarian follicular pool of women of reproductive age. Fluctuations in the menstrual cycle appear to be random and minor. Hence in clinical practice, AMH can be measured independently of cycle phase. Prolonged ovarian suppression by physiological or pharmacological interventions may reduce AMH levels.
(Antonio La Marca et al., 2013)

5 What are the best tests to determine ovarian reserve?

Ovarian reserve tests provide an indirect estimate of a woman's remaining follicular pool. Inspite of availability of multiple ORTs; the present evidence shows AFC and AMH appear to be the most useful markers of ovarian reserve in addition to chronological age.

6 Is there an ideal stimulation protocol for poor responders?

Ovulation stimulation protocols for poor responders are constantly under review in an attempt to improve follicular recruitment and pregnancy rates. Retrospective studies compared the efficacy of four different protocols including GnRH agonist [long, short and Mini flare] and GnRH antagonist on pregnancy outcomes in poor responders showed no significant differences in implantation, pregnancy and overall cancellation rates between four groups. Presently the commonly used protocol is gonadotrophin / GnRH antagonist. Addition of r-LH to ovarian stimulation protocol may benefit poor responders. Empirical use of adjuvants should be avoided.

Pharmaceutical advances in recombinant technology resulted in introduction of corifollitropin alfa [a hybrid molecule with sustained FSH activity and reduced injection frequency] along with HP-HMG in a GnRH antagonist regimen may be a promising protocol in poor responders.
(A. van Schanke et al., 2010), (N. P. Polyzos et al., 2013)

7 Should ovarian reserve screening be done?

Screening for ovarian reserve is a complex medical and social question. WHO have developed certain criteria for assessing adequacy of screening test and serum AMH testing for ovarian reserve currently meets almost all WHO screening criteria.

Proposed protocol for OR screening.

1. Ovarian reserve screening should be offered to all women at 30 years of age who potentially seek future fertility. Screening must be voluntary. Screening may be offered earlier if significant risk factors are present
2. Pre-screening counseling regarding the decline in fertility with age and the merits and potential actions related to ovarian reserve screening must be performed before the test is ordered
3. AMH is the ideal screening test of ovarian reserve as it is the least expensive and intrusive, has the least inter-observer variability and can be taken at any stage in the menstrual cycle
4. A serum AMH result below the 10th percentile for age suggests that the individual has diminished ovarian reserve. A repeat confirmatory AMH and FSH test (Days 3–5, off hormonal contraception for 2 months) should be performed, together with an AFC scan. A final risk assessment is made after consideration of all results, in the context of any known individual risk factors for diminished ovarian reserve.
5. Abnormal results must be discussed with a reproductive medicine physician with an understanding of the relative merits of the test and the available treatment options.
6. Women seeking pregnancy after a poor ovarian reserve screen result should be encourage to attempt natural conception for 6 months, unless natural conception is impossible or highly improbable (e.g. in the case of tubal factor infertility, severe semen defect or no partner). If conception does not occur within 6 months, early recourse to treatment should be considered.
7. Patients with borderline low ovarian reserve screening results may elect to have follow-up ovarian reserve testing 12 months later to assess the rate of decline in ovarian reserve before acting on the result.

(Kelton Tremella et al., 2014)

IMPLICATIONS

Ovarian follicular pool undergoes progressive decline from before birth to menopause. Even though oogonal stem cells have been identified in adult ovaries, there is no conclusive evidence towards their contribution to size of follicular pool in postnatal period.

The impact of poor ovarian responders is often seen in context of infertility, when time available to achieve pregnancy is limited in such patients offers highest probability for pregnancy. Irrespective of age women with poor ovarian response have lower pregnancy rates than those with normal ovarian reserve. With repeated attempts of failure, the only option is oocyte donation / adoption which imposes financial and emotional burden.

Ovarian reserve testing should be offered to women who wish to delay childbearing in order to make an informed decision remains debatable. However, AMH is being used to predict fertility potential of such women. These women can make a choice not

Overenthusiastic pelvic surgery for endometriomas and laparoscopic ovarian drilling in PCO may induce iatrogenic poor ovarian reserve.

Besides fertility, poor ovarian responder women will have early menopause so long-term health implications involving bone and cardiovascular status are to be considered.

CONCLUSION

Poor ovarian response is an indicator of reduced size of primordial follicle pool and the resulting eggs are likely to be of suboptimal quality as well. IVF remains only option of achieving pregnancy in such women. None of the stimulation protocols, pretreatment and adjuvant therapy can guarantee successful pregnancy outcome. High cost of treatment with emotional stress in women with poor ovarian response has to be considered while counseling.

At present there is no known mechanism to reduce follicular atresia and prolong fertility.

Social freezing is an alternative but does not ensure pregnancy and childbirth. Finally. the last resort remains oocyte donation / adoption.

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