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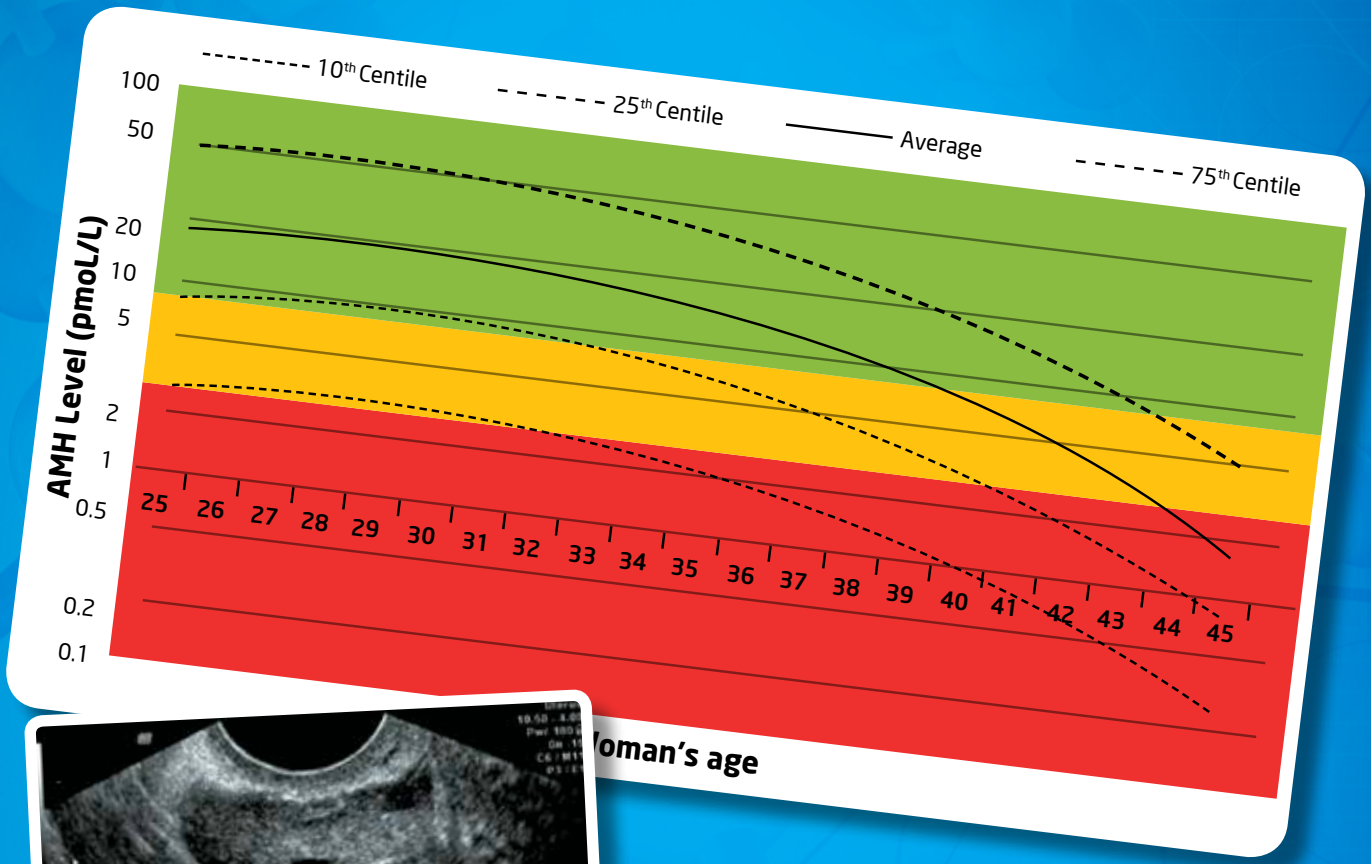
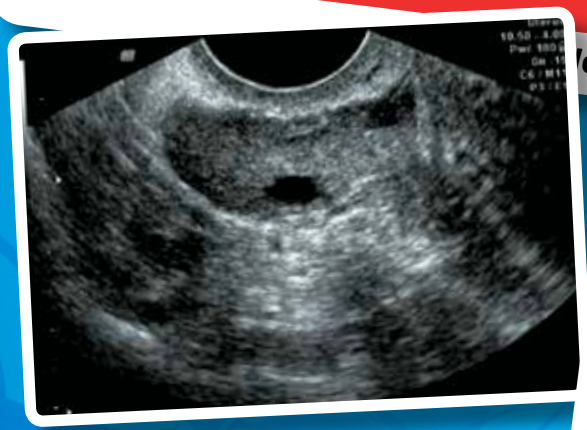
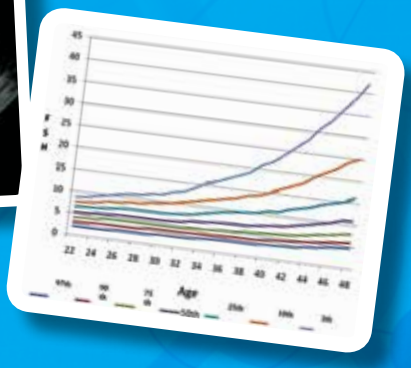
Poor Ovarian Responders







Editor :
Prof (Dr) Pankaj Talwar

An initiative by
Gynova
MAKES DREAM COME TRUE

ARText

Poor Ovarian Responders

DR SOHANI VERMA

PRESIDENT-IFS

This is my privilege and honour to write this message for E-bulletin of IFS: ARText. Through this academic venture, IFS has taken the initiative to simplify the complexities in clinical ART. In this issue we will be covering the challenging issue of ART - Poor Ovarian Reserve in detail and discuss its clinical implications.

Poor Ovarian Reserve is like opening a Pandora Box. In this bulletin we would learn about the various aspects of POR and apply them in our clinical practice.

I thank "Cadilla healthcare "for associating with IFS in this academic pursuit.

DR. K. D. NAYAR

SECRETARY GENERAL IFS

It is a matter of great prestige to write best wishes message for this E-bulletin of IFS-ARText on "POR".

For an ART specialist POR becomes a limiting factor for the success of any treatment modality for infertility. Through this E-bulletin we will be able to demystify the challenge of POR. We would learn about predictors of POR, various protocols for optimizing successful pregnancy, the recent POSEIDON criteria and a new concept of ovarian reserve screening.

I am sure you would thoroughly enjoy, learn and imbibe from the bulletin.

Best wishes to the Editorial team.

Prof (Dr) Pankaj Talwar

Joint Secretary-IFS

Editor ARText

At the very onset, the editorial team would like to thank all of you for reading our previous bulletins ARTexT pertaining to Hydrosalphinx , endometriosis and responding positively. The present issue deals with poor ovarian reserve.

Poor ovarian reserve (POR) is nightmare for both patient and the clinician .The difficulties in managing POR are due to lack of evidence based guidelines and ultimate poor results .

In this edition we have tried to summarize all the literature available to enhance our understanding of the paradoxes associated with POR. We would also like to place on record our truthful thanks to Cadilla health care limited that are helping us in this publication and off course I promise that there is no conflict of interest at any level. We from the editorial wing wish you a very happy reading and yes don't forget to file this issue. I would formally like to thank my friend Dr. Namita Kotia from Jaipur who has worked un-relentlessly towards bringing out this issue from conception to end.

Jaihind

Dr. Namita Kotia

M S (OBGYN)

Subeditor

Poor ovarian response, premature ovarian ageing and premature ovarian failure represent a continuum of premature ovarian senescence. Providing poor ovarian responders, IVF pregnancy with autologous oocytes remains the most challenging aspect of fertility care .In this issue we have tried to summarize all the literature available to understand the enigma related to poor ovarian responders. However, further research is needed to individualize therapeutic strategies for optimizing success rate before embarking on donor oocyte.

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Part -1

ARText

Poor Ovarian Responders

1. POOR OVARIAN RESPONSE

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. It 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.

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 that of 14.1% of initial cycles cancelled: 50% were poor responders.

(Ubaldi FM, et al., 2005),

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.

(Keay SD et al., 1997), (Faddy MJ et al., 1992), (Raga F et al,1999), (Surrey ES et al., 1998), (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** were 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 between 0.5 - 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 factors other than age.
- Oocyte quantity versus quality?.
- Over Diagnosis.
- Large-scale validation.

(Younis JS, 2012), (Venetis C., 2014), (Ferraretti AP et al, 2014)

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)

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. Non-Growing follicular pool at different ages may have a differing response to changes in hormone levels associated with age.

Women of all age groups with Non Growing 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[FMR1].
- FSH Receptor [FSH R] Polymorphism is considered to be important cause of unexplained Poor Ovarian Response in young women.

The mechanisms involved are :

- Decreased number of FSH receptors in Granulosa 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.
- Variability in the gene that encodes FSH receptor [FSHR] gene .

(Younis JS 2011), (Martinez F et al., 2002), (Ulug U et al., 2007), (Neulen J et al. ,2001), (Pellicer A et al., 1994), (Hernandez ER et al., 2000), (Lee DW et al., 1993), (Zeleznik AJ et al., 1981).

2. 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.

A. 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.

Insulin like growth factor 1 (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).

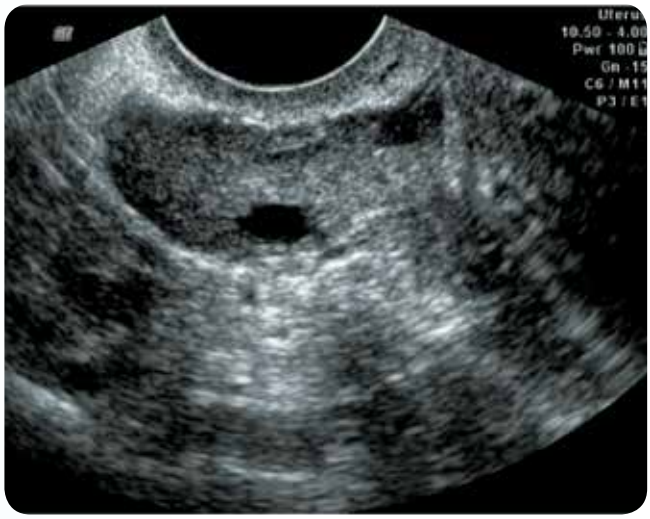
SONOGRAPHIC TESTS

- **Ovarian Volume**

  Decreased ovarian volume is hardly suitable as a routine test for ovarian reserve assessment.

- **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).

b. DYNAMIC TESTS

Clomiphene challenge test [CCT], Exogenous FSH ovarian reserve test [FSHORT] and GnRH agonist stimulation test [GSAT] are Dynamic tests but evidence suggests that **dynamic tests should be abandoned.**

(Maheshwari A et al., 2009)

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

3. 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 Individualise controlled ovarian stimulation 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 pmol/L or 0.28 Ngm/ml is also discriminatory for POR.

(Satwik R et al., 2012)

4. 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:

- Age and expected Aneuploidy rate.
- Ovarian Biomarkers i.e. AFC and AMH.
- Ovarian Response, in the previous stimulation cycle.

GROUP 1

Young patients <35 years with adequate ovarian reserve parameters (AFC>5; AMH ≥1.2ng/ml) and with an unexpected poor or suboptimal ovarian response

Subgroup 1a: <4 oocytes*

Subgroup 1b : 4-9 oocytes retrieved *

*** after standard ovarian stimulation**

GROUP 2

Older patients ≥ 35 years with adequate ovarian reserve parameters (AFC≥5; AMH≥1.2 ngm/ml) and with an unexpected poor or suboptimal ovarian response

Subgroup 2a: <4 oocytes*

Subgroup 2b : 4-9 oocytes retrieved *

*** after standard ovarian stimulation**

GROUP 3

Young patients (<35 years) with poor Ovarian reserve Pre-stimulation parameters (AFC<5; AMH <1.2 ng/ml)

GROUP 4

Older patients (≥ 35 years) with poor Ovarian reserve Pre-stimulation parameters (AFC<5; AMH <1.2 ng/ml)

The POSEIDON concept is based on

- A better stratification of women with "low prognosis" in ART
- Individualized therapeutic approaches in each group, having as endpoint the number of oocytes required to have at least one euploid embryo for transfer in the patient.

It is important to further discuss the issue of quantity versus quality regarding oocytes. It is difficult to deny that counting the number of oocytes retrieved or estimating their numbers using ovarian biomarkers may not be sufficient for clinical management.

Equally important is the age-related decrease in oocyte quality, which largely depends on chromosomal abnormalities occurring prior to meiosis II.

This is a novel initiative as an important working and counseling tool for the ART specialist who handles the low prognosis patient.

(Humaidan P, Alviggi C, Fischer R and Esteves SC. The novel POSEIDON stratification of 'Low prognosis patients in Assisted Reproductive Technology' and its proposed marker of successful outcome 2016)

5. 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:

- Gonadotrophins
- GnRH Analogues
- GnRH Antagonist
- Natural cycle / Modified Natural cycle
- 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 ANALOGUES

From past two decades the combination of gonadotropins and gonadotropin-releasing hormone (GnRH) agonists, started on the late luteal phase of the previous cycle, has been considered the protocol of choice in normo responder patients.

Such approach lowers cancellation rate and raises the number of preovulatory follicles and the number of oocytes retrieved and good quality embryos for transfer, leading to better pregnancy rates.

However this protocol could have a detrimental effect in poor responders because it may induce an excessive ovarian suppression that could lead to a reduced or absent follicular response.

For this reason, in patients with poor ovarian reserve the options could be -

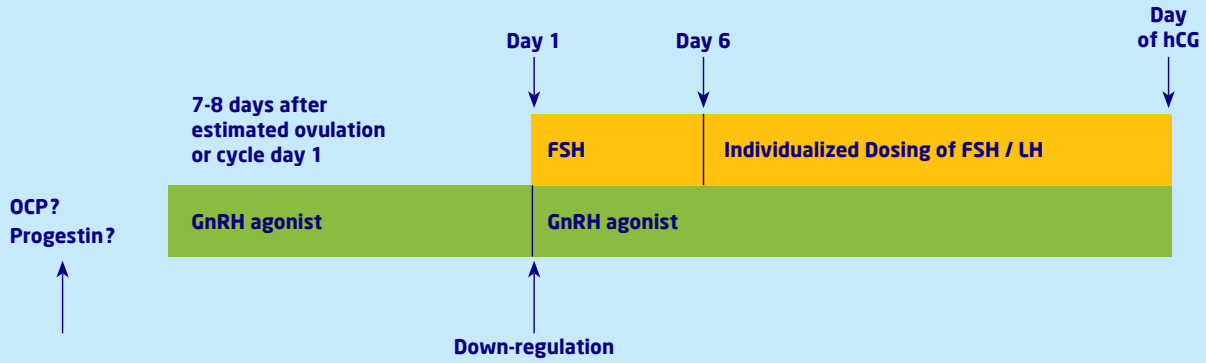
- To decrease the length of suppression by decreasing the duration of GnRH agonist use (short and ultra- short, mini- and microdose flareup regimens)
- To lower or to stop (after pituitary suppression) the dose of GnRH agonists initiated during the luteal phase
- To use the GnRH antagonists in combination with gonadotropins to prevent premature LH rise during the mid-late follicular phase.

(Filippo Ubaldi ,Management of Poor Responders in IVF: Is There Anything New? 2014)

The common protocols used are -

1. Gonadotrophins and GnRH Agonist started in late luteal phase.

GnRH-a



Limitations

(a) High Cancellation rate

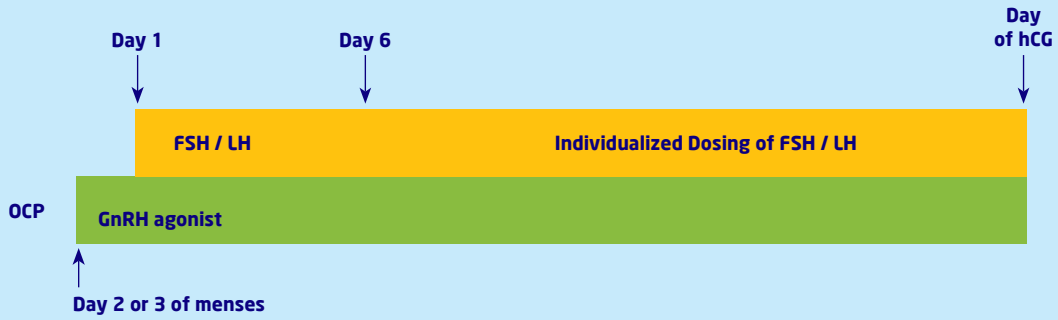
(b) Prolonged hormonal stimulation

(c) High Cost

(d) Only marginal benifit in yield of mature oocytes

2. Short GnRH agonist protocol

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

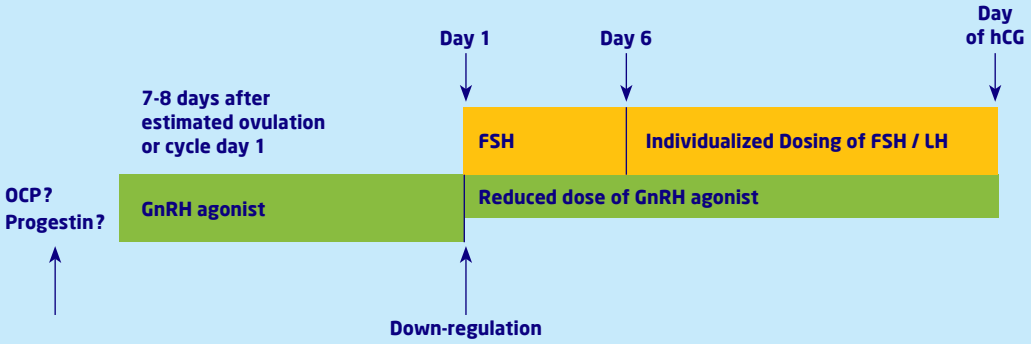
(C) Decrease miscarriage rate

Limitations

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

3. Micro dose protocol

MICRO DOSE GnRH-a



Advantage

(a) Decrease Gonadotrophin requirement

(b) Shorter duration of stimulation

(C) Increase E2 concentration on day of stimulation

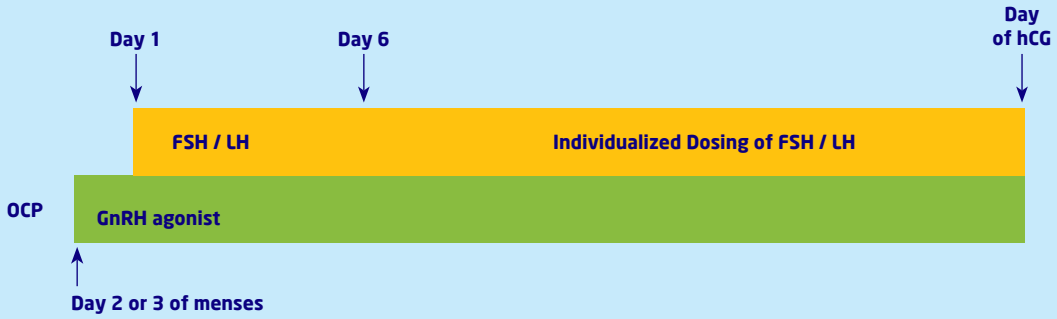
(d) Increase number of mature oocytes

(e) Good quality embryos

(f) Decrease cancellation rate

4. Micro dose flare up protocol

Micro Dose Flare GnRH-a



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

Advantage

(a) More physiological

(b) Rapid rise in E_2 levels

(c) Development of mature follicles

(d) No premature L.H.surge

Limitations

(a) Most studies are retrospective

(b) Efficiency is yet to be proved

5. GnRH analogue stop protocol

GnRH-a "STOP"

(1) GnRH-a administered as in long protocol from D-21

(2) Withheld once gonadotrophin stimulation has started.

(3) No Premature LH Surge

Limitations

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

GnRH Antagonist

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 Gonadotropin requirement

(E. S. Surrey et al., 1998), (W. Schoolcraft et al., 1997), (S. L. Padilla et al., 1996.), (V. Karande et al., 1999.), (I. Craft et al., 1999.), (M. A. Akman et al., 2000.).

NATURAL CYCLE / MODIFIED NATURAL CYCLE

Natural cycles IVF with or without minimal stimulation can be considered as an easy and cheap approach to poor responders. Natural cycle IVF was associated with 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 birth rate per patient and potentially reduce dropout.

(A. Cobo et al., 2012).

ADJUVANT THERAPY

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)

ADDITION OF ANDROGENS

Evidence for role of androgens arises from pharmacological observations that testosterone, androstenodione and dihydrotestosterone can promote early follicular growth and enhance FSH mediated action.

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]

48- 50 % of follicular fluid testosterone during ovarian stimulation comes from circulating DHEAS , and DHEA could therefore act as a precursor for testosterone in the follicular fluid. .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.)

In women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates. The overall quality of the evidence is moderate. There is insufficient evidence to draw any conclusions about the safety of either androgen. Definitive conclusions regarding the clinical role of either androgen awaits evidence from further well-designed studies.

(Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database of Systematic Reviews 2015)

GROWTH HORMONE

GH-releasing hormones increase the sensitivity of ovaries to gonadotropin stimulation and enhance follicular development. It enhances oocyte quality by accelerating and coordinating cytoplasmic and nuclear maturation. There are some propositions that GH-releasing factor supplementation may improve pregnancy rates in poor responders.

It 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. However, none of the studies had independently found any significant benefit with GH supplementation.

(E. M. Kolibianakis et al., 2009.), (D. Kyrou et al 2009).

RECOMBINANT LH

LH maintain adequate concentrations of intraovarian androgens and promote steroidogenesis and follicular growth. It has been proposed that addition of LH to ovarian stimulation protocol may benefit poor responders.

Addition of r-LH with r-FSH in poor responders significantly increases number of oocytes retrieved with relative increase in clinical pregnancy rates. Meta-analysis of eight trials did not show significant improvement in CPR with use of recombinant LH.

(Jeve YB, Bhandari HM. Effective treatment protocol for poor ovarian response: A systematic review and meta-analysis. *Journal of Human Reproductive Sciences. 2016), (P. Lehert et al., 2014).*

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. The modality is debatable. It is recommended that the empirical use of adjuvants should be avoided pending good quality evidence from well-designed studies.

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

Part -2

ARText

Poor Ovarian Responders

FREQUENTLY ASKED QUESTIONS

a. 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. It may improve ovarian reserve, response to ovarian stimulation, and pregnancy outcome.

b. 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 oral DHEA for maximum 6 months.

(Mazen R et al 2013)

c. WHAT CUT OFF VALUE OF AMH CAN PREDICT POOR OVARIAN RESPONSE?

AMH levels of 2 pmol/l [≤ 0.28 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.

d. 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)

e. 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 to be the most useful markers of ovarian reserve in addition to chronological age.

f. 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 comparing the efficacy of four different protocols including GnRH agonist [long, short and Miniflare] 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)

g. 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.

- 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
- 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
- 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
- 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.
- 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.
- Women seeking pregnancy after a poor ovarian reserve screen result should be encouraged 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.
- 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 oogonial 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. IVF 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 to delay childbearing or may undergo IVF for vitrification of eggs / embryos.

Over enthusiastic pelvic surgery for endometrioms 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 resulting infertility.

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

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