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TIPS AND SECRETS FOR A SUCCESSFUL OVARIAN STIMULATION IN ART

By

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TOGETHER WE CAN, WE WILL.

TIPS AND SECRETS FOR A SUCCESSFUL OVARIAN STIMULATION IN ART



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INTRODUCTION:-

Stimulation in ART is an art. Ultimately the success lies in the live birth rate. No book can teach the exact stimulation protocol or dosage as it varies from individual to individual. Our own experience with the population we deal with teaches a lot with which we can improve our protocols and outcomes.

PRE-STIMULATION REQUIREMENTS:-

Counselling the couples by an expert is an important aspect before starting any treatment since they are mentally, physically, financially drained, socially suppressed. Proper understanding about the diagnosis, nature and cost of treatment, success rate of the treating centre, and complications following treatment are to be counselled. Previous detailed treatment history will tell the protocol details, drug dosage and the response to the treatment. Tender loving care from day one is essential. Normal BMI is ensured. Hormone imbalance, if any, is to be corrected. Folic acid supplementation is to be started. Pelvic infection, if present, is to be treated

Day two hormone analysis (FSH, LH), AMH, thyroid function test are to be done. Other investigations like virology, infectious screenings, HbA1C, Hb, Hb electrophoresis are to be done. Day two baseline scan (high resolution scan) is mandatory. Transabdominal and transvaginal USG is to be done to look for subserous, intramural fibroids indenting the cavity, adenomyosis, endomyometrial junction disruption, 3D-US cavity assessment for uterine abnormalities, endometrial polyp, submucous fibroid, Asherman's syndrome, antral follicle

count, any ovarian masses, adnexal masses, hydrosalpinx, POD for any adhesions or endometriosis. Any abnormalities detected is to be treated before stimulation. Accessibility of both ovaries by TVS is to be noted.

STIMULATION PROTOCOLS:-

Before starting stimulation, the individual is to be provisionally diagnosed as normal, poor or hyper-responder.

1. Expected poor responder:

Poor ovarian response:

According to Bologna criteria, at least two of the following three criteria:

- i. Advanced maternal age ≥ 40 years or any risk factors for poor ovarian reserve
- ii. A previous poor ovarian response (< 3 oocytes with conventional stimulation protocol)
- iii. An abnormal ovarian reserve test (AFC– 5 to 7 follicles or AMH– 0.5 to 1.1 ng/ml)

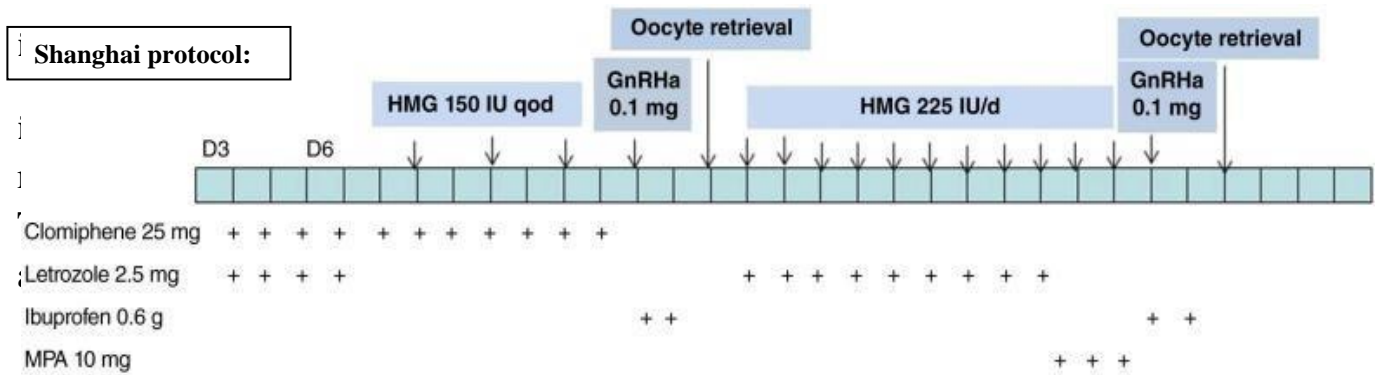
According to POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number):

Parameters	Poor ovarian response	
	Group 3	Group 4
Age	<35 years	≥ 35 years
AMH	<1.2 ng/ml	<1.2 ng/ml
AFC	<5	<5

Stimulation of expected poor responder:

High doses of Gonadotropin in poor responders are questionable as the problem is with the limited number of recruited follicles. High doses of Gonadotropin result in high levels of estrogen which have a negative impact on oocyte quality and Endometrium leading to compromised success rate. Embryo pooling and transfer in remote cycle has promising results in poor responders.

Protocols used:



Pre-treatment adjuvants for poor responders:

- Androgens - Transdermal testosterone gel 12.5mg in the cycle prior to that of stimulation for 21 days; DHEA 75 mg/day for 60 days prior to stimulation.
- Growth hormone - Though very expensive, many studies have shown promising results when used in a dosage of 4-24 IU starting from previous cycle day 21 until trigger in poor responders.
- Antioxidants – Melatonin 3mg/day, Coenzyme-Q10 200mg TDS for 60 days prior to stimulation

2.Expected normal responder:

According to POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number):

Parameters	Good ovarian response	
	Group 1	Group 2
Age	< 35 years	≥35 years
AMH	≥ 1.2 ng/ml	≥1.2 ng/ml
AFC	≥5 Subgroup 1a) <4 oocytes* 1b) 4 to 9 oocytes* *after standard ovarian stimulation	≥5 Subgroup 2a) <4 oocytes* 2b) 4 to 9 oocytes* *after standard ovarian stimulation

Stimulation protocol:

- Either agonist or antagonist protocol
- Starting dose of gonadotropins (either rFSH or HMG) 225-250 IU
- Aim to get 8-14 oocytes

3.Expected hyper responder:

AMH > 3.5ng/ml ; AFC > 15

Stimulation protocol:

- Antagonist protocol
- Starting dose of gonadotropin (preferably rFSH, rarely HMG) 125-150 IU
- Pre-treatment with metformin significantly reduces the risk of OHSS in PCOS

MONITORING THE STIMULATED CYCLES:-

Why?

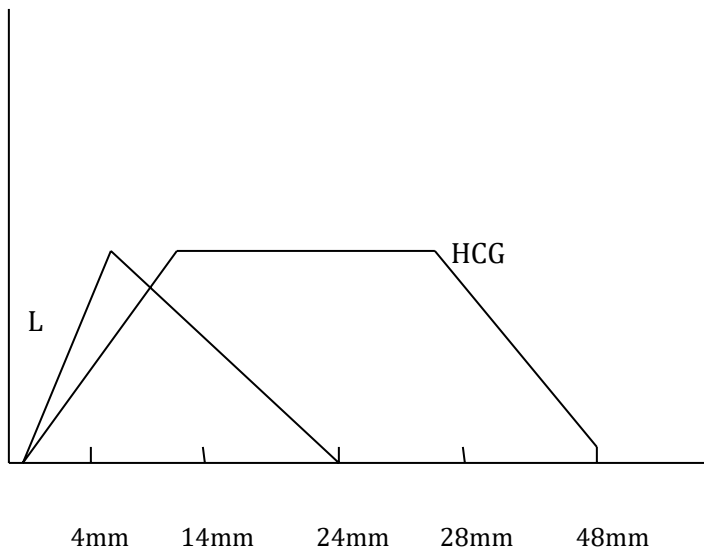
- Predicting ovarian response
- Monitoring the effect of pituitary down-regulation
- Dosage of gonadotropin
- Deciding optimal timing of administration of trigger
- Identifying optimal time for transfer of frozen thawed embryos

Clinically used methods:

- i. E2 and progesterone – In high responders, large number of follicles produce more progesterone which affects the endometrium which will be advanced causing drop in implantation and pregnancy rates. If serum progesterone before trigger is more than 1.4ng/ml, it will reduce the pregnancy rate. Hence freeze all will be a better option.
- ii. 2D Ultrasound monitoring of follicular diameter, endometrial thickness and pattern
- iii. Combined hormone analysis and 2D Ultrasound – This will be useful in dealing with poor responders or women at risk for OHSS.
- iv. 3D volume and Doppler parameters – Follicular volume of 3-7cc, presence of cumulus, perifollicular velocity index of 6-20 and perifollicular FI > 35 are associated with better pregnancy rates. Uterine artery Doppler – optimum receptivity can be obtained when average PI of uterine artery is between 2- 3 and RI < 0.9 on the day of transfer. Absent subendometrial and intraendometrial vascularization on the day if trigger appears to be a useful predictor of failure of implantation in IVF irrespective of morphological appearance. Pregnancy rate with Zone-3 endometrial vascularity is around 30-50% and for Zone-4 vascularity 65-75%. Subendometrial Doppler indices VI > 1, FI > 31, VFI > 0.25 on the day of trigger is found to have high pregnancy rate.
- v. Colour Doppler studies of Ovarian circulation – Studies have shown that Doppler parameters of follicles that have > 75% of their surface perfused,

ovarian stromal PSV $> 10\text{cm/second}$ and RI $< 0.4-0.48$ contain mature oocyte of satisfactory quality and results in better grade embryos. Follicle with PSV $< 10\text{cm/second}$ contribute oocyte to have high chances of chromosomally abnormal embryos.

TRIGGER:-



- i. HCG – It is given in normal and poor responders
- ii. GnRH agonist (Triptorelin, leuporide, buserelin) – It is given in hyper responders with antagonist protocol. GnRH agonist trigger brings up FSH surge in addition to LH surge. It is short acting. No difference is noted in oocyte/embryo quality. Early corpus luteolysis and inadequate steroidogenesis result in decreased pregnancy rate and miscarriage rate. Freeze all will be a good option. If opting for fresh transfer, luteal phase support with 50mg IM progesterone daily with estradiol support and low dose HCG.

- iii. Dual trigger (Low dose HCG 1000-2500 IU + GnRH agonist) – OHSS risk will be minimized. This trigger shows good improvement in patients with empty follicle syndrome or immature oocyte syndrome.

CONCLUSION:-

‘One size fits all’ concept has to be replaced by a more ‘custom made’ concept. Individualised stimulation protocols and appropriate dosage of gonadotropins will definitely improve the success rate.