Presdent’s Medal for best medical graduate of year 1970-75
Award from DMA on Dr. B.C Roy’s birthday: outstanding contribution to medicine, 1999
Vikas Ratan Award by Nations economic development & growth society 2002
Chitsa Ratan Award by International Study Circle in 2007
Life time Medical excellence award Obs & Gyne by Hippocrates foundation 2014
Distinguished teacher of excellence award for PG medical education by ANBAI & NBE 2017 and Inspiring Gynecologists of India by Economic Times 2017. Felicitated by highest Merck Serono honor award at times healthcare achievers award 2018
Course director for post doctoral Fellowship in Reproductive Medicine by NBE, since 2007, IFS since 2014, ISAR 2014 and by FOGSI for basic & advanced infertility training since 2008.
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection.
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INDIVIDUALIZATION OF COS TO OPTIMIZE SUCCESS
ARE ALL PATIENTS SAME?

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Nobel Prize winner: The work of British physiologist Robert G. Edwards waited longest to be recognized. His award for medicine comes 32 years after he figured out how to create the beginnings of human life outside the uterus through in vitro fertilization.
IVF started to develop fast with the aim of maximizing pregnancy rates per cycle

COH for higher number of oocytes, thus > embryos
- Use of unphysiological high doses of gonadotropins
- Time consuming protocols
- Higher costs
- Patient discomfort
- Higher risk of OHSS
- Very high risk of multiple gestation

Rapid progression of protocols and technology
This magic wheel had to slow down
Definition of success in IVF started shifting from pregnancy rate per cycle towards achieving healthy singleton child per started course of treatment.

For achieving this aim the first change had to be in COS and stimulation protocols with the aim of:

• Less oocytes
• Less pain /stress
• Less cost
• Less complications
• Obtaining a good oocyte / embryo/ implantation rate

Further progression of technology aimed at minimizing complication rate yet maintaining optimal pregnancy rates

Careful individualized COH
Progression of technology

Conventional stimulation protocols

Conventional regimes
Aims at >8 oocytes but high complication OHSS

milder stimulation protocols

Mild stimulation regimes
Aims at < 8 oocytes but needs very good lab conditions

Present stimulation protocols

Individualized COS (iCOS)
Best live birth rate with low complication; OHSS
There is no possibility of "one-size-fits-all"
Choice of right gonadotropin for COH will depend upon:

**Expected response**
- Age
- Weight
- Ovarian reserve test
- Previous response to stimulation

**Underlying pathology**
- Severe endometriosis
- Oocyte donor
- Hypo-gonadotropic hypogonadim

**Time constraint**
- Fertility preservation before cancer therapy

**Low E2 requirement**
- Pro-thrombotic cases for COS
- Estrogen sensitive cancers
Type of response expected

Age
Weight
Ovarian reserve test (ORT)
Previous response to stimulation
IDENTIFYING RESPONSE

Hyper responder
Underlying PCOS
Thin built
Age < 30
FSH < 8miu/ml
AMH > 25pmol/l
AFC > 12
Previous hyper response

Normal responder
Regular cycles
Normal built
Age < 37
FSH < 12miu/ml
AMH 10-25pmol/l
AFC = 7 to 11
Previous normal response

Poor responder
Regular or shortening cycles
Obese
Age > 37
FSH > 12miu/ml
AMH < 5pmol/l
AFC < 6
Previous poor response
Optimizing treatment protocols for normal responder

- Long protocol (GnRH agonist down regulation followed by gonadotropins)
- Antagonist protocol (flexible / fixed protocol)

Dose of gonadotropin = 150 to 225 iu/day
Optimizing treatment protocols for high responder / PCOS

COS with Antagonist protocol (fixed/flexible dose)
Agonist trigger
Freeze all embryos if over stimulated

All protocols require low starting dose of FSH 100 -200 IU/day and have more chances of over or under stimulation
ALGORITHM FOR DOSE OF FSH: CONSIDERING AGE, AMH AND BASAL FSH
ALGORITHM FOR DOSE OF FSH: CONSIDERING AGE, AFC AND BASAL FSH
Optimizing treatment protocols for poor responder/poor prognosis group

- Antagonist protocol with flexible regime
- GnRHa long protocol
  - Conventional protocol
    - GnRH agonist ‘stop’ or ‘mini’ dose protocol
- Milder stimulation regimes

**Pre treatment for better cohort:**
- OCP from day 2 for 14-21 days
- Estradiol valerate 4mg/day from day 22 till menses
- Progestin for 5 days from day 21

- Higher dose of FSH 300 units/day
- Add LH or HMG to FSH from day of stimulation
### Low prognosis groups

#### Poseidon classification

<table>
<thead>
<tr>
<th></th>
<th>Adequate ovarian reserve</th>
<th>Poor ovarian reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup 1a: &lt;4</td>
<td>Subgroup 1b: 4-9</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>AFC ≥ 5</td>
<td>AMH ≥ 1.2 ng/ml</td>
</tr>
<tr>
<td>Group 3</td>
<td>AFC &lt; 5</td>
<td>AMH &lt; 1.2 ng/ml</td>
</tr>
<tr>
<td>Older</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup 1a: &lt;4</td>
<td>Subgroup 1b: 4-9</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>AFC ≥ 5</td>
<td>AMH ≥ 1.2 ng/ml</td>
</tr>
</tbody>
</table>

- **Age**
- **Ovarian Biomarkers (AMH and/or AFC)**
- **No. oocytes retrieved if previous OS cycle**
POSEIDON MANAGEMENT OF LOW PROGNOSIS PATIENTS
Adequate AFC and/or AMH
Previous cycle with poor or suboptimal oocytes number

<table>
<thead>
<tr>
<th>GROUP 1, young (age &lt; 35)</th>
<th>GROUP 2 OLD (age &gt; 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good reserve good quality</strong></td>
<td><strong>Good reserve poor quality</strong></td>
</tr>
</tbody>
</table>

**Possible reasons**
- Low starting dose of gonadotropin (gn)
- Asynchronous development
- Polymorphism of FSH-R, LH-rvLHβ
- Trigger or OCR issues

**iCOS treatment**
- GnRH Antagonist COS with E2/ocp/progestin
- rFSH in preference to uFSH/HMG
- Higher FSH dose + LH supplementation

**Transfer strategy**
- hCG/GnRHa/dual trigger, fresh transfer if no risk of OHSS, freeze all if OHSS risk or need for PGT-A

**Measure of success**
- Min. of 5 mature oocytes for 1 euploid embryo

**Possible reasons**
- Low starting dose of gonadotropin (gn)
- Asynchronous development
- Polymorphism of FSH-R, LH-rvLHβ
- Trigger or OCR issues

**iCOS treatment**
- Antagonist COS with E2/ocp/ prog priming
- Increase rFSH dose
- Add rLH, Duostim

**Transfer strategy**
- hCG/GnRHa/dual trigger, fresh transfer or FET for oocyte/embryo accumulation or PGT-A

**Measure of success**
- 10 to 12 mature oocytes for 1 euploid embryo
POSEIDON MANAGEMENT POOR POGNOSIS PATIENTS
<5 AFC and/or AMH <1.2ng/ml

GROUP 3, young (age<35)
Poor reserve, good quality

Possible reasons
Poor ovarian reserve
Asynchr development
Polymorphism of FSH-R, LH-r vLHβ

iCOS treatment
Long GnRH agonist
GnRH Antagonist E2/ocp priming)
Start rFSH 300 units androgens?

Transfer strategy
Fresh transfer, freeze all oocyte or embryo accumulation or PGT-A

Measure of success
4-7 oocytes for 1 euploid blastocyst

GROUP 4 OLD (age >35)
Poor reserve, poor quality

Possible reasons
Poor ovarian reserve
Asynchronous cohort development
Polymorphism of FSH-R, LH-r vLHβ

iCOS treatment
Long GnRH agonist
Antagonist E2/ocp/Start rFSH 300 add rLH, Androgens? Duostim

Transfer strategy
Fresh transfer, Freeze for oocyte/embryo accumulation, PGT-A, oocyte donation

Measure of success
>12 oocytes for 1 euploid blastocyst
Underlying pathology

- Severe endometriosis
- Hypo-gonadotrophic-hypogonadism
- Oocyte donor
SEVERE ENDOMETRIOSIS
Administration of GnRH agonists for 3–6 months prior to IVF in patients with endometriosis increases clinical PR (4 fold) and the live birth rate significantly (9 fold).

Long term down regulation for 60 to 90 days before IVF for women with endometriosis is better than long protocol: 3 RCTs with 165 women
  
  Live BR/ woman OR 9.19: Clinical PR: OR 4.28
HYPOGONADOTROPIC
HYPOGONADISM

- LH control not required, no need of agonist or antagonist

- Step 1: Pretreatment with estrogen and progesterone cyclically for 6 to 9 months till the midcycle endometrium appears ideal for implantation.

- Luteal support mandatory with hCG as well as progesterone or progesterone and estradiol.
OPTIMUM STIMULATION FOR OO CYTE DONORS
DONORS FOR OOCYTES UNDERGOING OVARIAN STIMULATION

Improved donor safety and satisfaction is likely to improve donor recruitment and retention

Minimizing trips to the clinic; protocols to limit number of I/M injections; reduced risk of OHSS

Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyper-stimulation in oocyte donors: A systematic review and meta-analysis

No differences after donor stimulation with **GnRH antagonist protocols** on number or quality of retrieved oocytes or ongoing pregnancy rate. USG follicle monitoring is enough for follow up of donor cycles with antagonist protocol (serum E2 not necessary).

Daniel Bodri; Fertility and Sterility, Volume 95, Issue 1, Pages 164-169, January 2011
GnRH agonist trigger safe treatment option for egg-donors. No compromise on embryo quality and risk of OHSS reduces considerably.

**GnRH antagonist protocol with agonist trigger appears best for oocyte donors**

- Anna Galindo, January 2009, Vol. 25, No. 1 , Pages 60-66
- A. Sismanoglu et al, J. Assist Reprod and Genetics, 26; 5, 251-256
- M Melo et al, ReprodBioMedOnline, 19; 4, October 2009, 486–492
Time constraint

Fertility preservation before cancer therapy
Protocols for ovarian stimulation in patients with a small time line

The emergence of these protocols occurred with data coming from researchers which fuelled the concept that OS for IVF can be dissociated from the follicular phase and its hormonal environment, as long as no fresh ET takes place. Oocyte yields of these protocols were found to equal those of OS started in the early follicular phase.

1. Duo-stimulation protocols ‘Duplex protocol’
2. Random start protocols
Shanghai protocol

Dual stimulation
Follicular & luteal stimulation with GnRHa trigger in first stimulation

Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a woman awaiting chemo or radio therapy results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation
Random start protocols:

Patient presenting in late follicular phase or luteal phase following COS plans are used:

I. Late follicular phase:
   I. lead follicle >12 mm: COS with letrozole and gonadotropin started without antagonist till spontaneous LH surge for that single follicle, continue COS till the secondary follicle cohort reaches 12 mm. Add GnRH antagonist till trigger.
   II. Lead follicle <12 mm before starting COS, start COS and add antagonist from 12 mm cohort size, continue till trigger.

II. Luteal phase COS: Start in 5 to 7 days after hCG or GnRH agonist trigger. Ignore menstruation if happens between stimulation and use antagonist when cohort 12 mm or start progesterone from day of stimulation MPA or DYG till trigger
Late follicular phase start

B

Initial visit
Withdrawal bleeding
Spontaneous LH surge
>12mm
Start of ovarian stimulation
Ovulation and start of GnRH antagonist
GnRH antagonist trigger
GnRH agonist
Oocyte retrieval

C

Initial visit
Withdrawal bleeding
<12mm
LH (mIU/ml)
LH (mIU/ml)
P4 (pmol/l)
P4 (pmol/l)
E2 (pmol/l)
E2 (pmol/l)
Cycle Day
Cycle Day

Luteal Phase Start

D

Initial visit
Spontaneous LH surge
+/- Aromatase inhibitor
GnRH antagonist
GnRH agonist
Oocyte retrieval

Luteal start protocol

E

Initial visit
Withdrawal bleeding
hCG or GnRH agonist
+/- Aromatase inhibitor
GnRH antagonist
Gonadotropins
Oocyte retrieval
hCG or GnRH agonist
hCG or GnRH agonist
Low E2 requirement

Pro-thrombotic cases for COS

Estrogen sensitive cancers
ONCOLOGIC ISSUES OR PROTHROMBOTIC CONDITIONS REQUIRING LOW E2 DURING COS

ESTROGEN SENSITIVE MALIGNANCY: BREAST OR ENDOMETRIUM HISTORY OF DEFINITIVE DVT OR THROMBOTIC EVENT IN PAST

Addition of Letrozole daily with conventional doses of gonadotropins from day 2 of stimulation with antagonist or long agonist protocol till hCG or GnRH agonist trigger

Aim is to keep serum E2 levels lower than 200 pg /ml with dose of letrozole as high as 10mg/day if required

Cakmac H et al; Fertility Sterility; Vol 100, No. 6 Dec 2013
Choosing the right gonadotropin for individual COS

I. Prospective identification of ovarian response

II. Determine co-existing hormonal imbalances affecting COS

III. Determine underlying pathology which could change the need for protocol for optimal iCOS

IV. Ensure complete safety for oocyte donors without compromising on oocyte quality

V. Pro-thrombotic conditions or oestrogen dependent cancers at risk with high oestrogen levels during COS

VI. ICOS for patients with oncologic issues with urgent need for oocyte or embryo cryo preservation.

VII. Optimizing total reproductive potential of a couple by use of embryo cryopreservation technology.
Thank you for giving me a reason to scratch my brains

Abha Majumdar