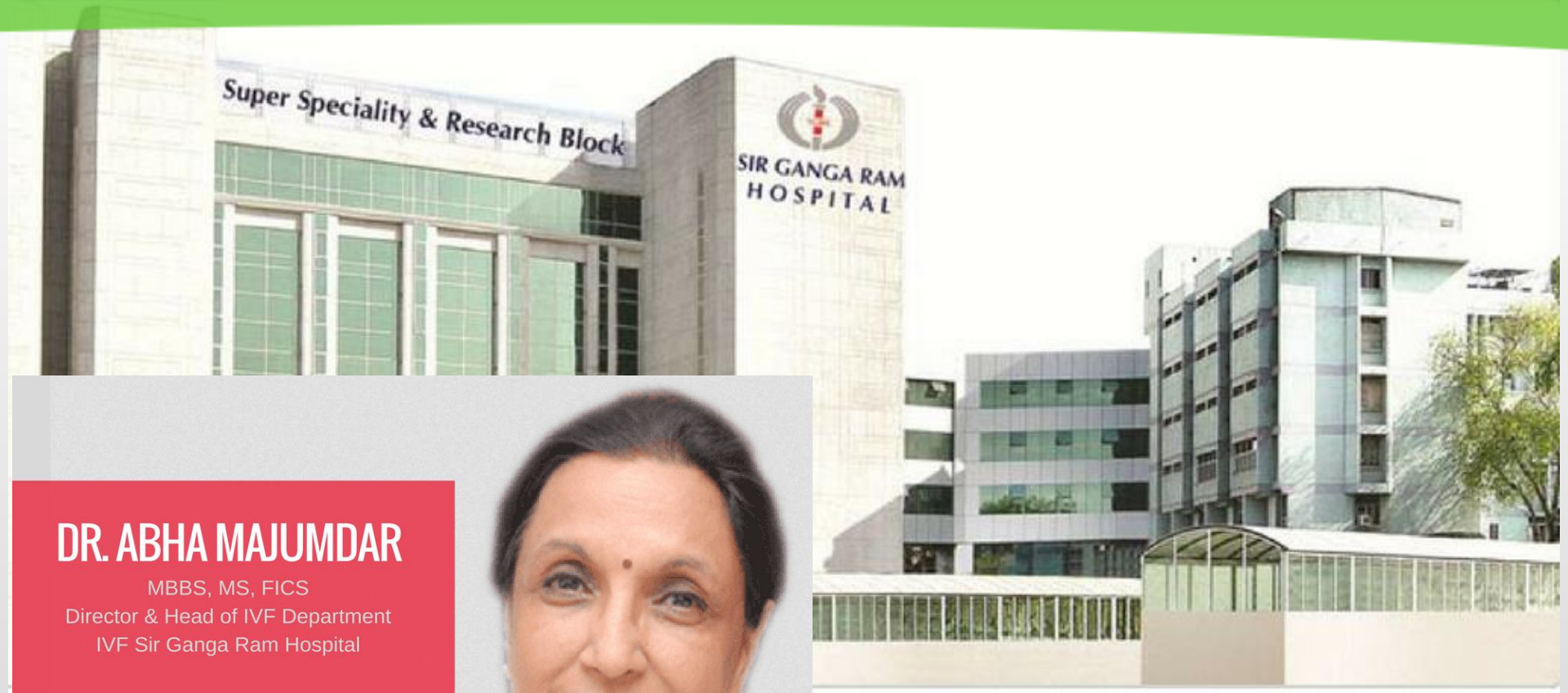
Prof. Abha Majumdar

Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA

President's Medal for best medical graduate of year1970-75
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
Abdul Kalam gold medal 2015 & **Rashtriya Gaurav Gold Medal award** 2017 by Global Economic Progress & Research Association.
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.
Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences',** and member of advisory board for '**Journal of Fertility Science & Research'.**
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection.



DR. ABHA MAJUMDAR

MBBS, MS, FICS
Director & Head of IVF Department
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Expertise

Infertility, assisted reproductive techniques, reproductive endocrinology, endoscopic surgery for pelvic resurrection.

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INDIVIDUALIZATION OF COS TO OPTIMIZE SUCCESS ARE ALL PATIENTS SAME?

Dr. Abha Majumdar
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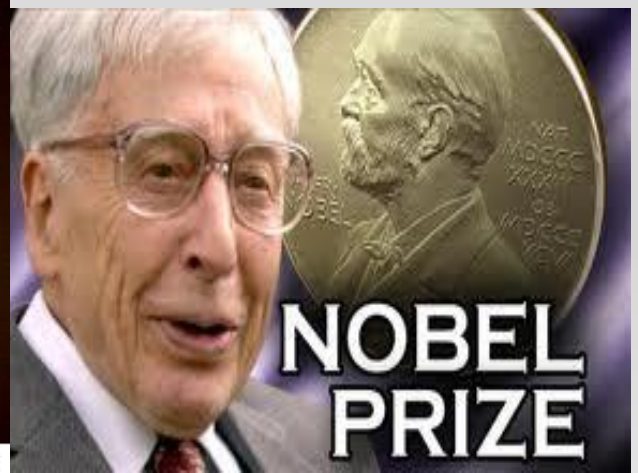
Nobel Prize winner: The work of British physiologist [Robert G. Edwards] waited longest to be recognized. His award for medicine comes 32 years after he figured out how to create the beginnings of human life outside the uterus through in vitro fertilization.

Single oocyte
Single embryo
Single baby

Jonathan Nackstrand, AFP/Getty Images

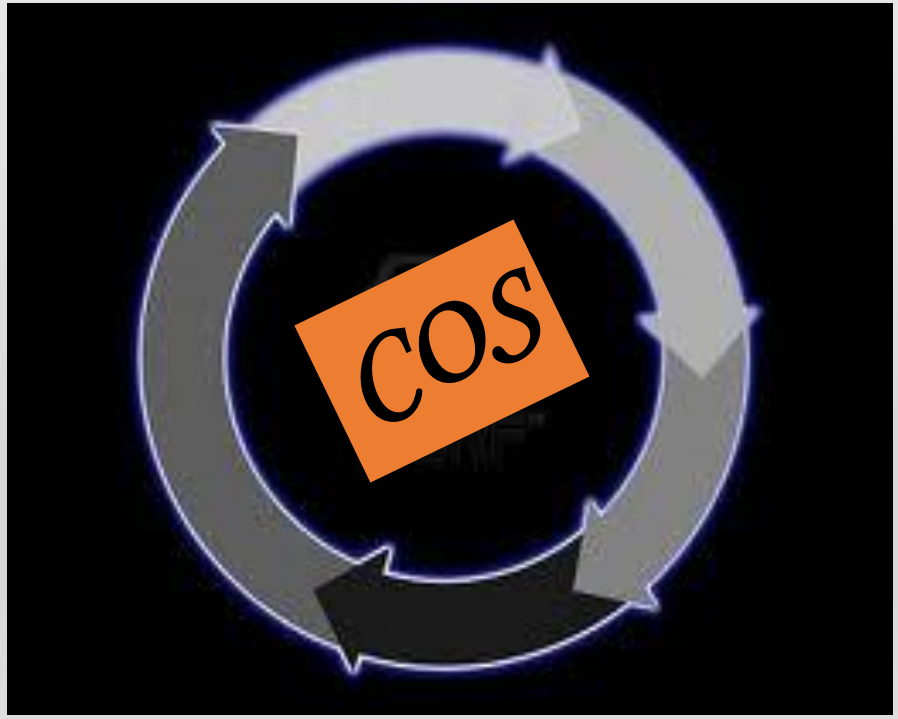


IVF started to develop fast with the aim of maximizing pregnancy rates per cycle

COH for h**igher 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

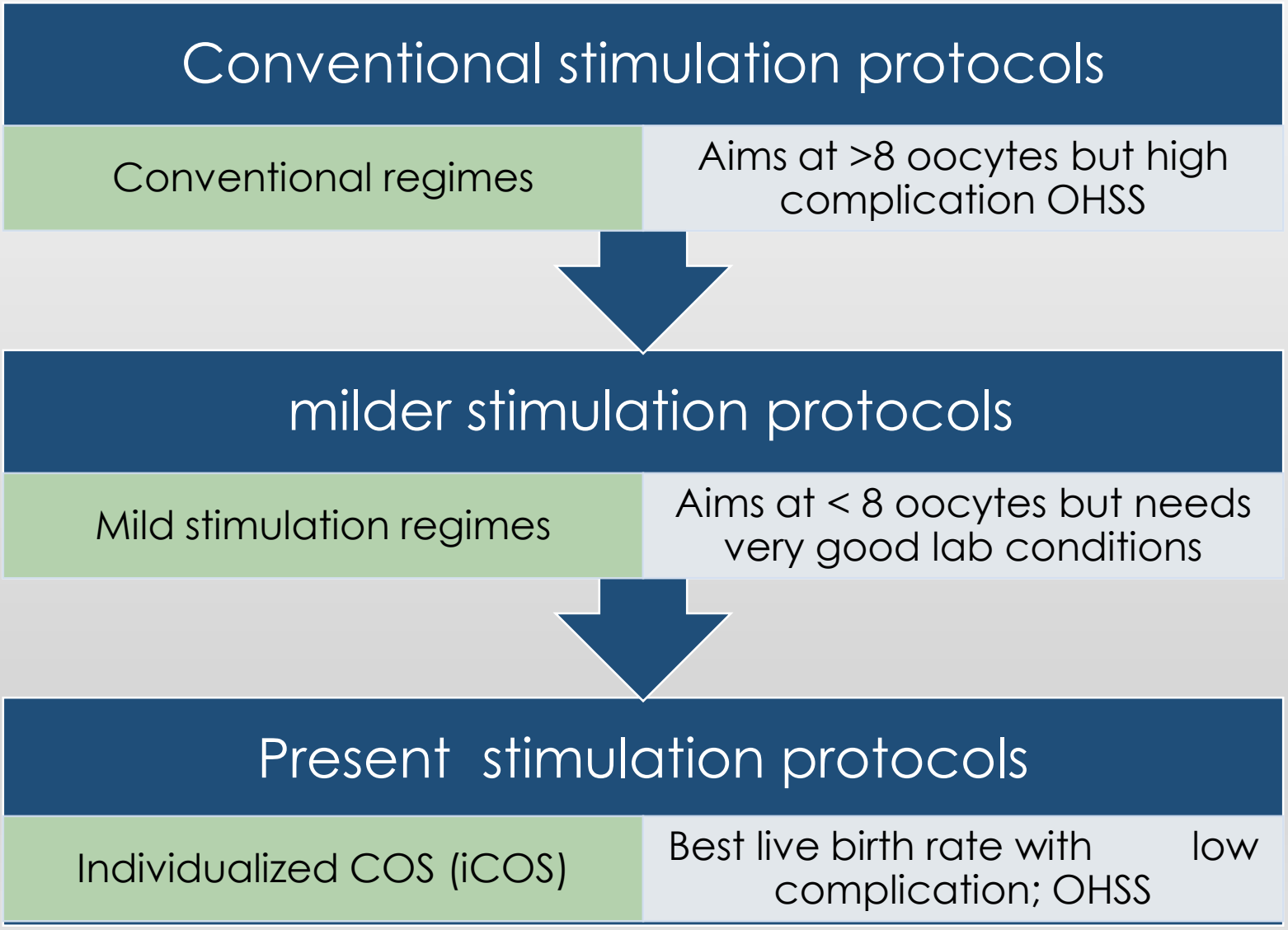
Definition of success in IVF started shifting from pregnancy rate per cycle towards achieving healthy singleton child per started course of treatment.

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

Progression of technology



There is no possibility

"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

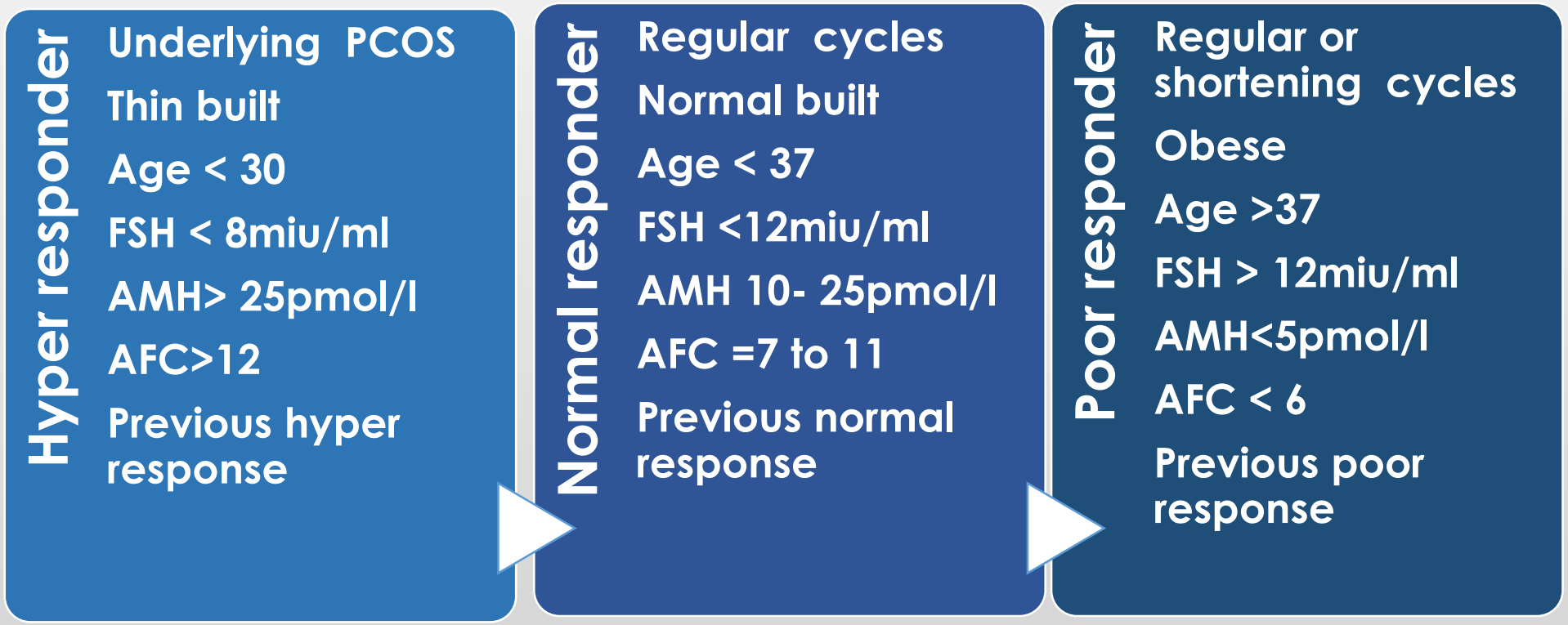
Age

Weight

Ovarian reserve test (ORT)

Previous response to stimulation

IDENTIFYING RESPONSE



Optimizing treatment protocols for normal responder

- Long protocol (GnRH agonist down regulation followed by gonadotropins)

- Antagonist protocol *(flexible / fixed protocol)*

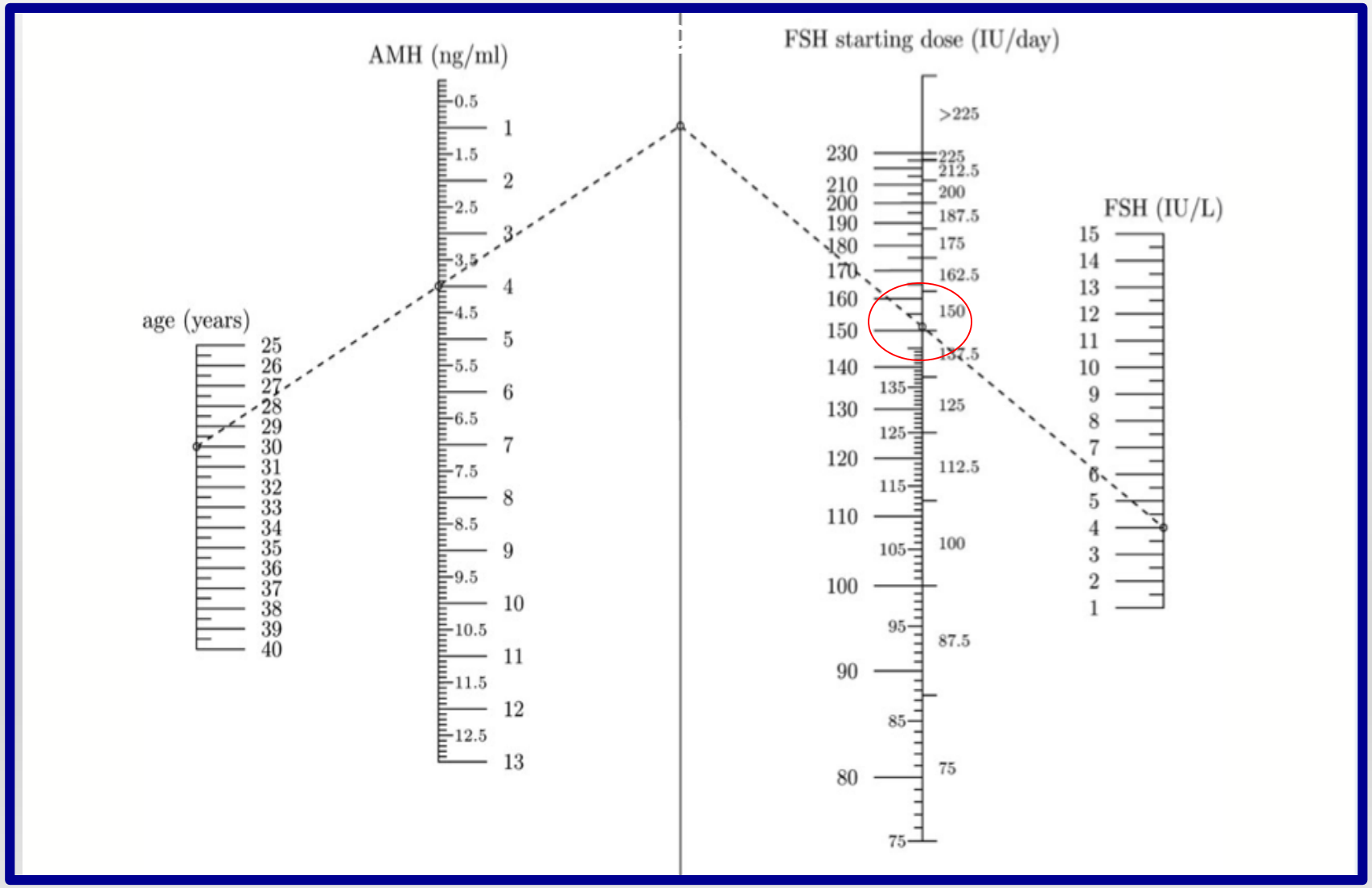
Dose of gonadotropin = 150 to 225 iu/day

Optimizing treatment protocols for high responder / PCOS

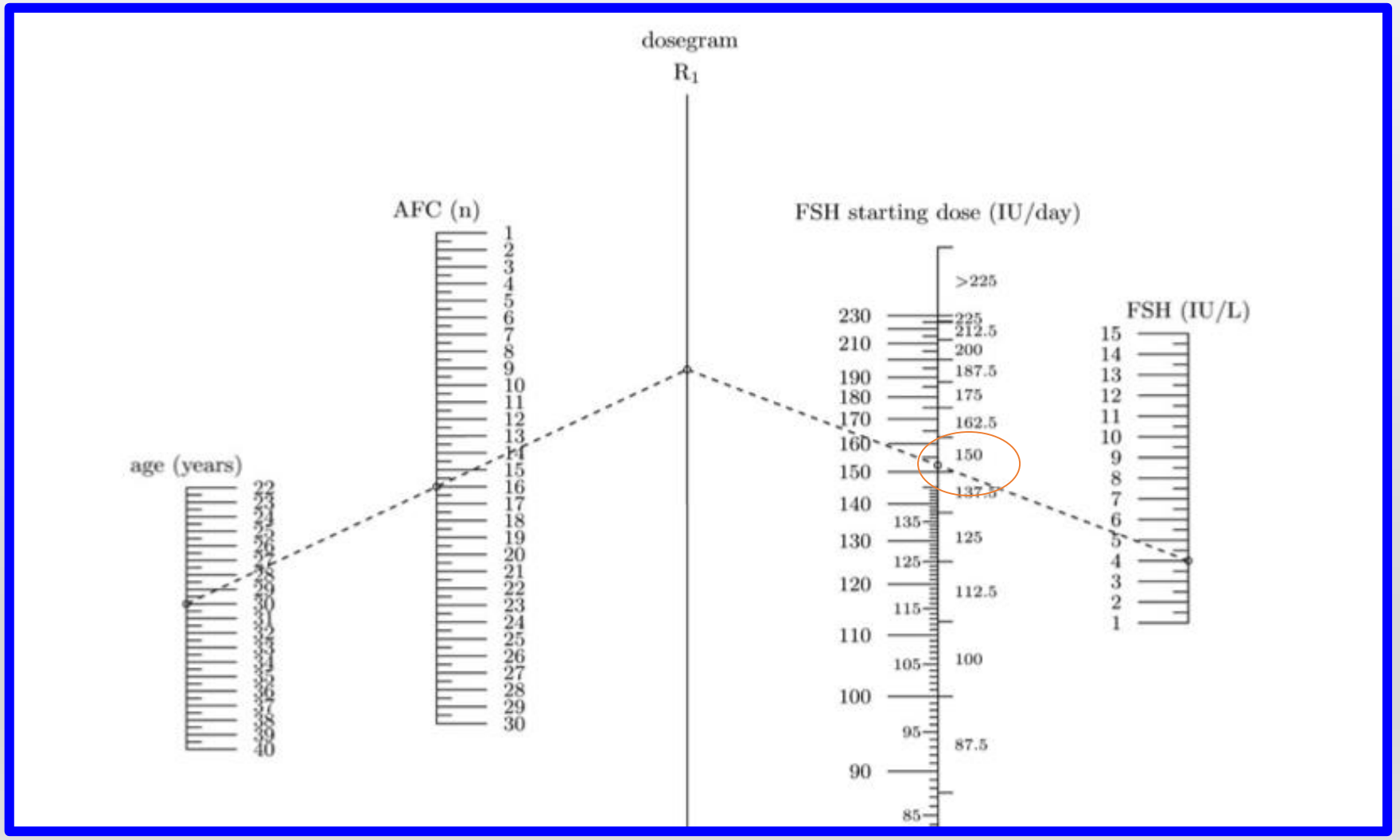
COS with Antagonist protocol (fixed/flexible dose)
Agonist trigger
Freeze all embryos if over stimulated

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

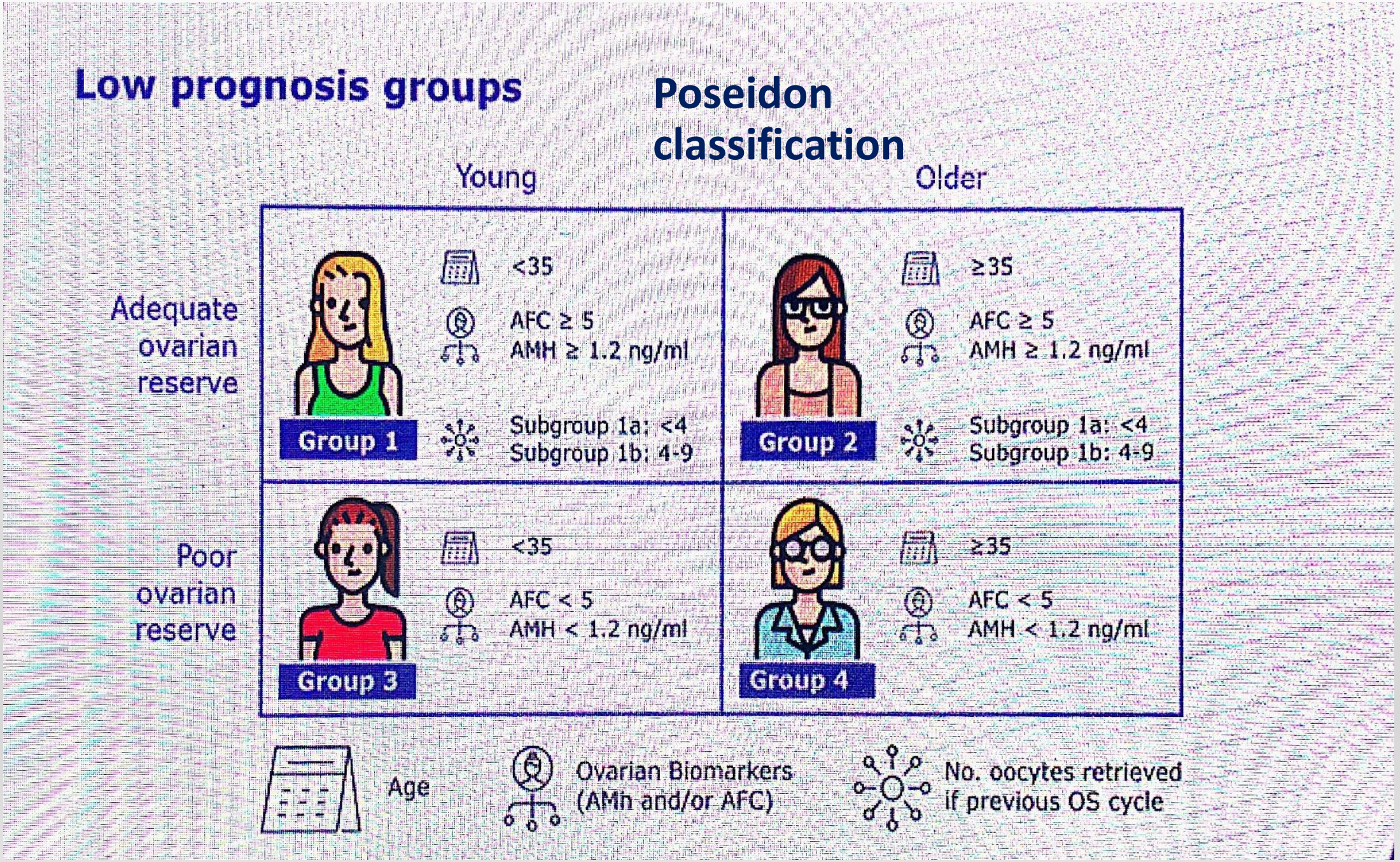
- Antagonist protocol with flexible regime
- GnRHa long protocol
  - ***Conventional protocol***
  - **GnRH agonist '*stop*' or '*mini*' dose protocol**
- Milder stimulation regimes

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

- *Higher dose of FSH 300units/day*
- *Add LH or HMG to FSH from day of stimulation*

Low prognosis groups

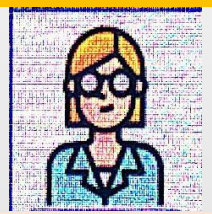
Poseidon classification



POSEIDON MANAGEMENT OF LOW PROGNOSIS PATIENTS

Adequate AFC and/or AMH

Previous cycle with poor or suboptimal oocytes number



GROUP 1, young (age<35)

Good reserve good quality

Possible reasons

Low starting dose of gn
Asynchr development
Polymorphism of FSH-R, LH-rvLHß
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

GROUP 2 OLD (age >35)

Good reserve poor quality

Possible reasons

Low starting dose of gn
Asynchr development
Polymorphism of FSH-R, LH-rvLHß
Trigger or OCR issues

iCOS treatment

Antagonist COS with E2/ocp/ prog priming
Increase rFSH dose
add rLH,
Duostim

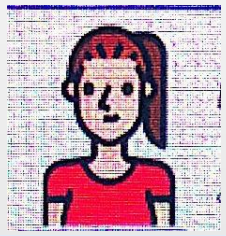
Transfer strategy

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

Measure of success

10 to12 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 vLHß

iCOS treatment

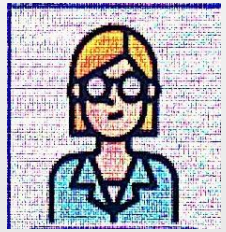
Long GnRH agonist
GnRH Antagonist E2/ ocp priming)
Start rFSH 300 units
androgens?

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 vLHß

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-gonadotropic-hypogonadism
- Oocyte donor

SEVERE ENDOMETRIOSIS

Meta analysis ESHRE 2005
ESHRE guidelines for endometriosis 2008

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).

Cochrane data base systemic review 2006

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 rec… …gonist or antagonist
- Ster… …deal treatment o… …of LH enough with ind… …as per response)
- Lute… …pport mandatory with hCG as well as proges.erone or progesterone and estradiol.

Pretreatment with estrogen and progesterone cyclically for 6 to 9 months till the mid cycle endometrium appears ideal for implantation.

OPTIMUM STIMULATION FOR OOCYTE 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

A qualitative follow-up study of experiences with oocyte donors; A.L. Kalfoglou; *Hum. Reprod. (2000) 15 (4): 798-805.*

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*
- *J.C. Castillo et al, Reprod BioMed Online, Nov. 2011*

Time constraint

Fertility preservation before cancer therapy

Protocols for ovarian stimulation in patients with a small time line

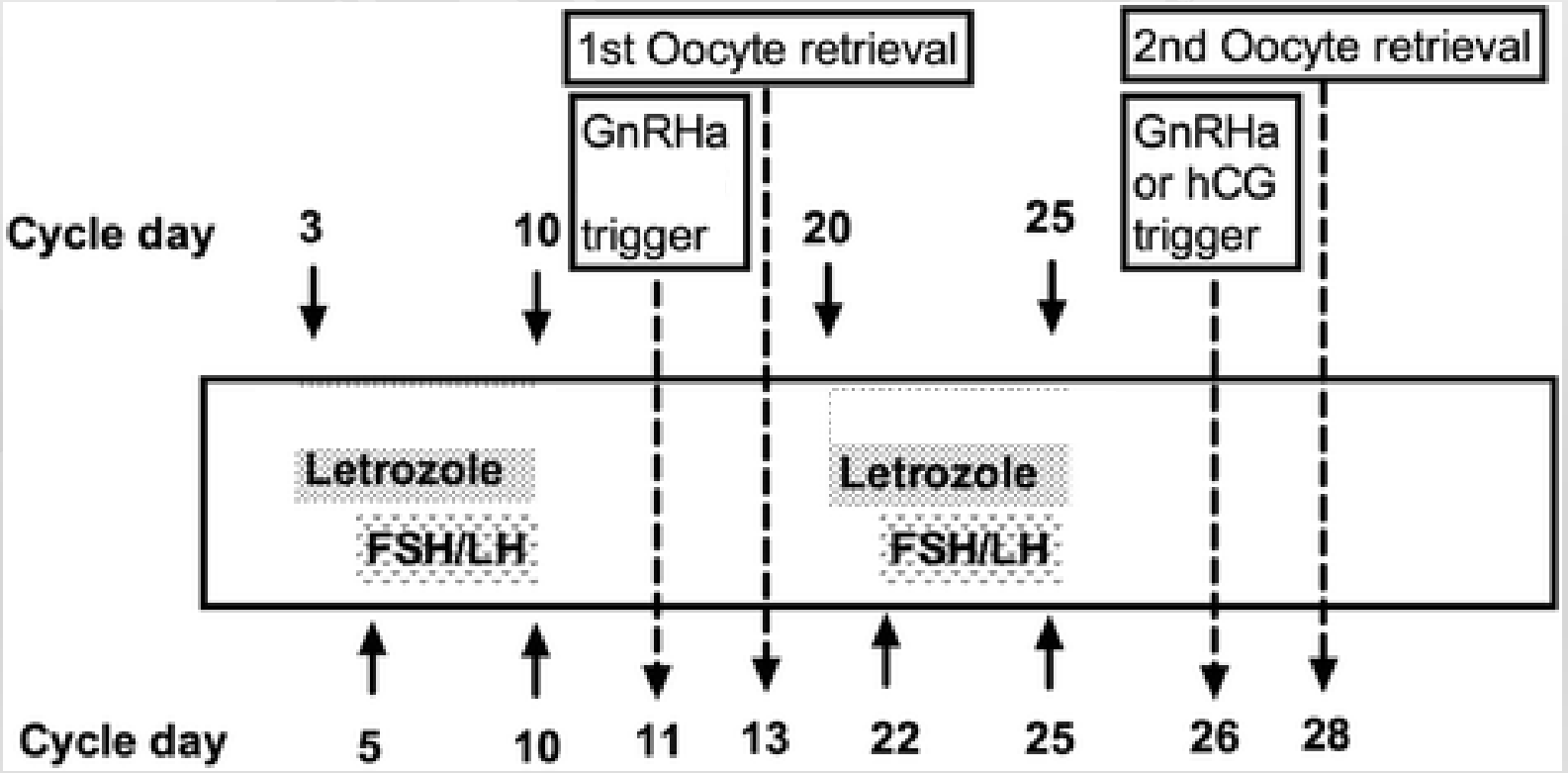
The emergence of these protocols occurred with data coming from researchers which fuelled the concept that OS for IVF can be dissociated from the follicular phase and its hormonal environment, as long as no fresh ET takes place. Oocyte yields of these protocols were found to equal those of OS started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

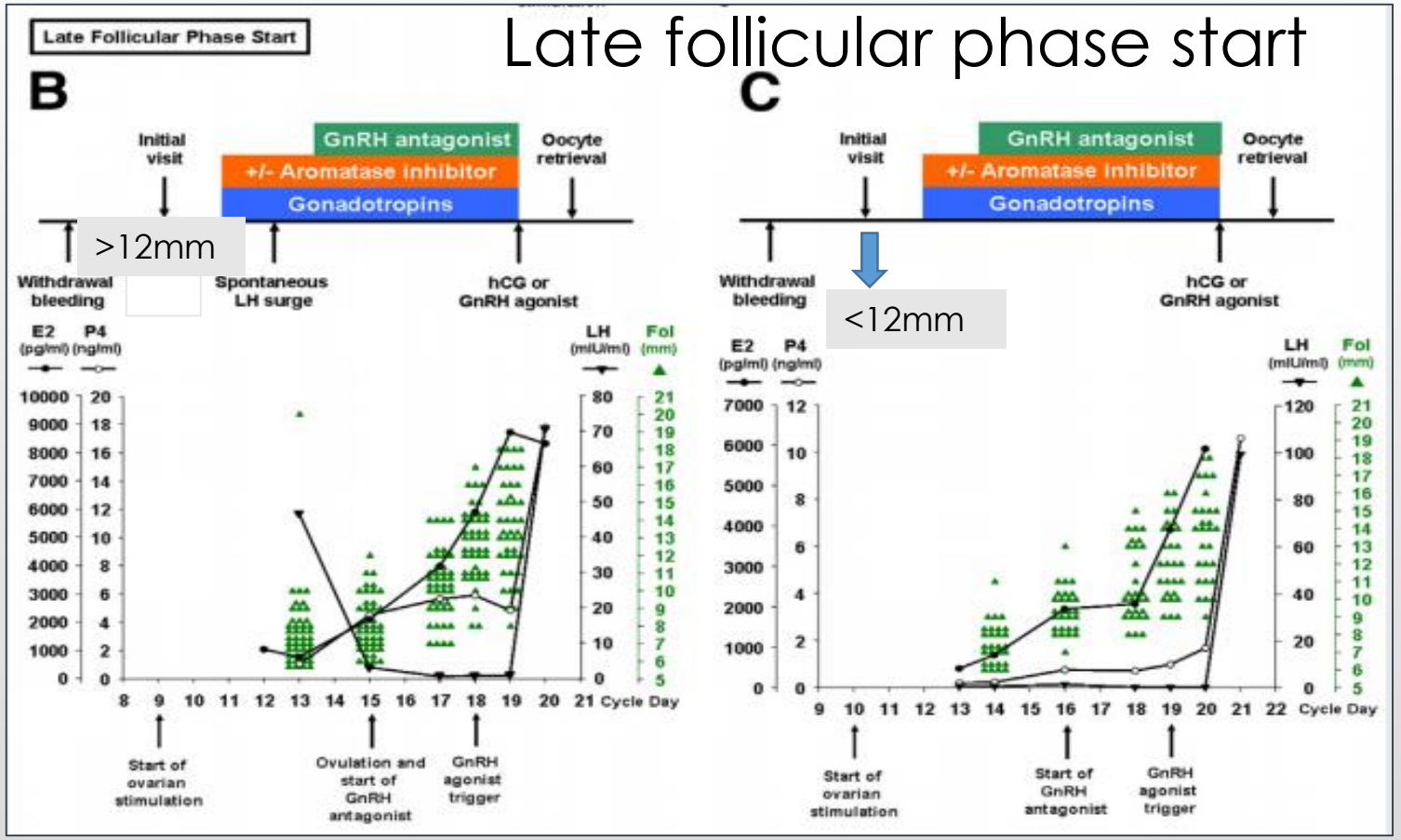


Random start protocols:

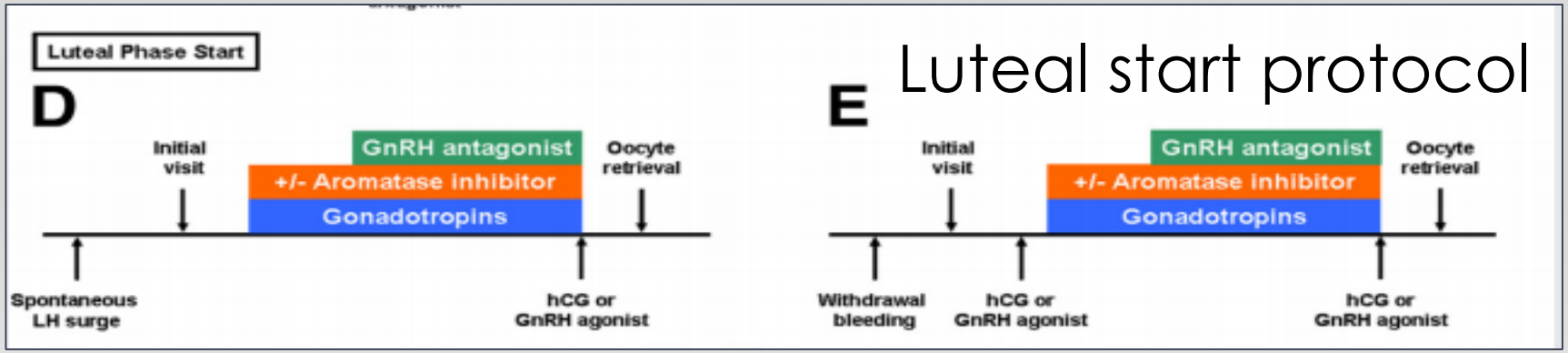
Patient presenting in late follicular phase or luteal phase following COS plans are used:

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



Luteal start protocol



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

BMJ