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
Lifetime 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.

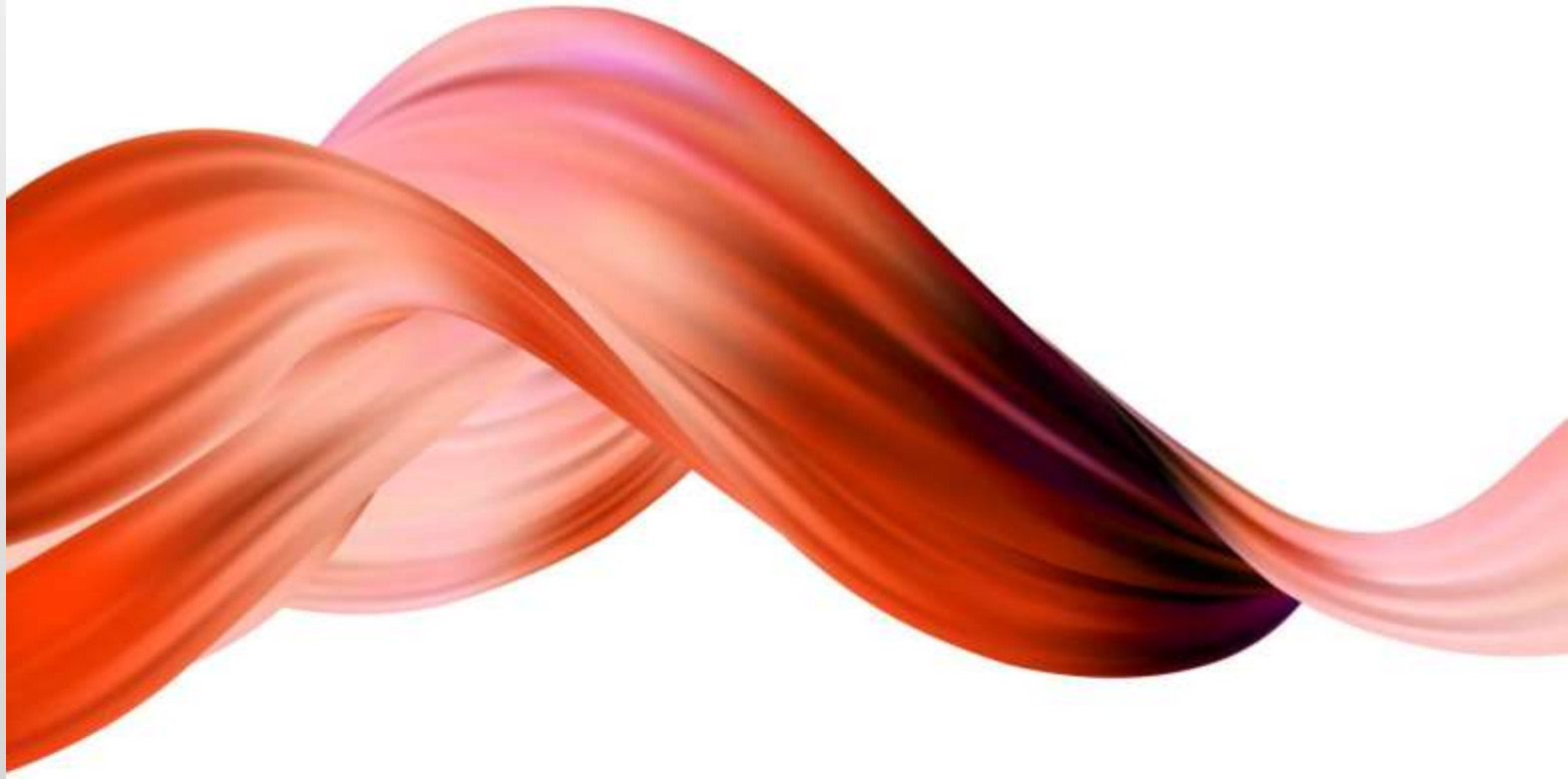
Director
Centre of IVF and Human Reproduction

Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, 110060
Ph: 011 4225 4000/ 011 4225 1800/ 011 4225 1777/ 8375990881
Website: www.ivfgangaram.com

SGRH
IVF SIR GANGARAM HOSPITAL

EVIDENCE BASED MANAGEMENT OF POOR RESPONDER

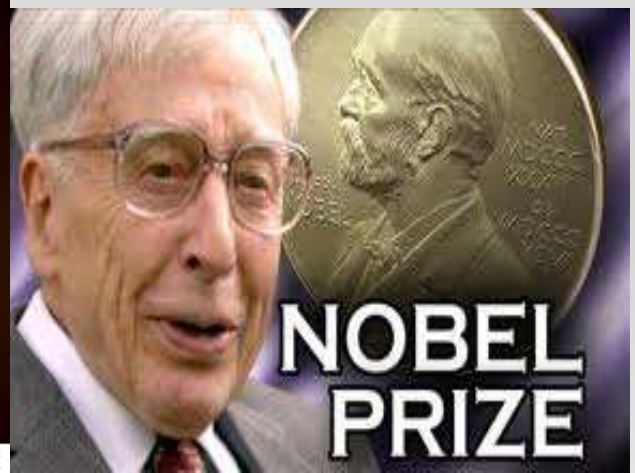
POSEIDON 1 & 2



New twists in ovarian stimulation

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

Louise Brown, was born in 1978 without any fertility drugs

Start of IVF

Gonadotropins 1970's

↑ cost & complications

Agonist: convenience & ↓ cancellation 1980's

↓ complications

Antagonist safer, patient friendly 1990's

↓ success only good labs

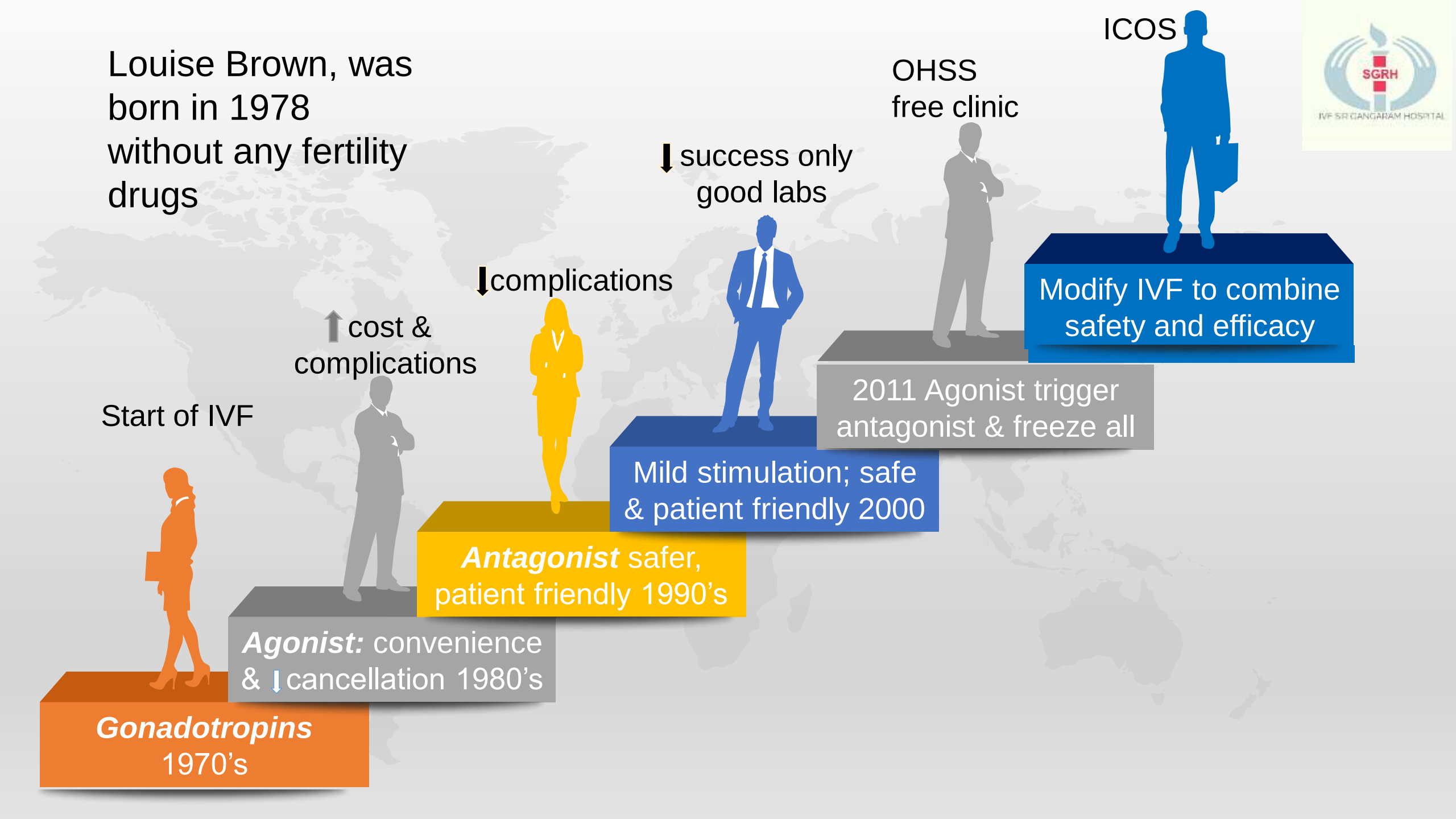
Mild stimulation; safe & patient friendly 2000

OHSS free clinic

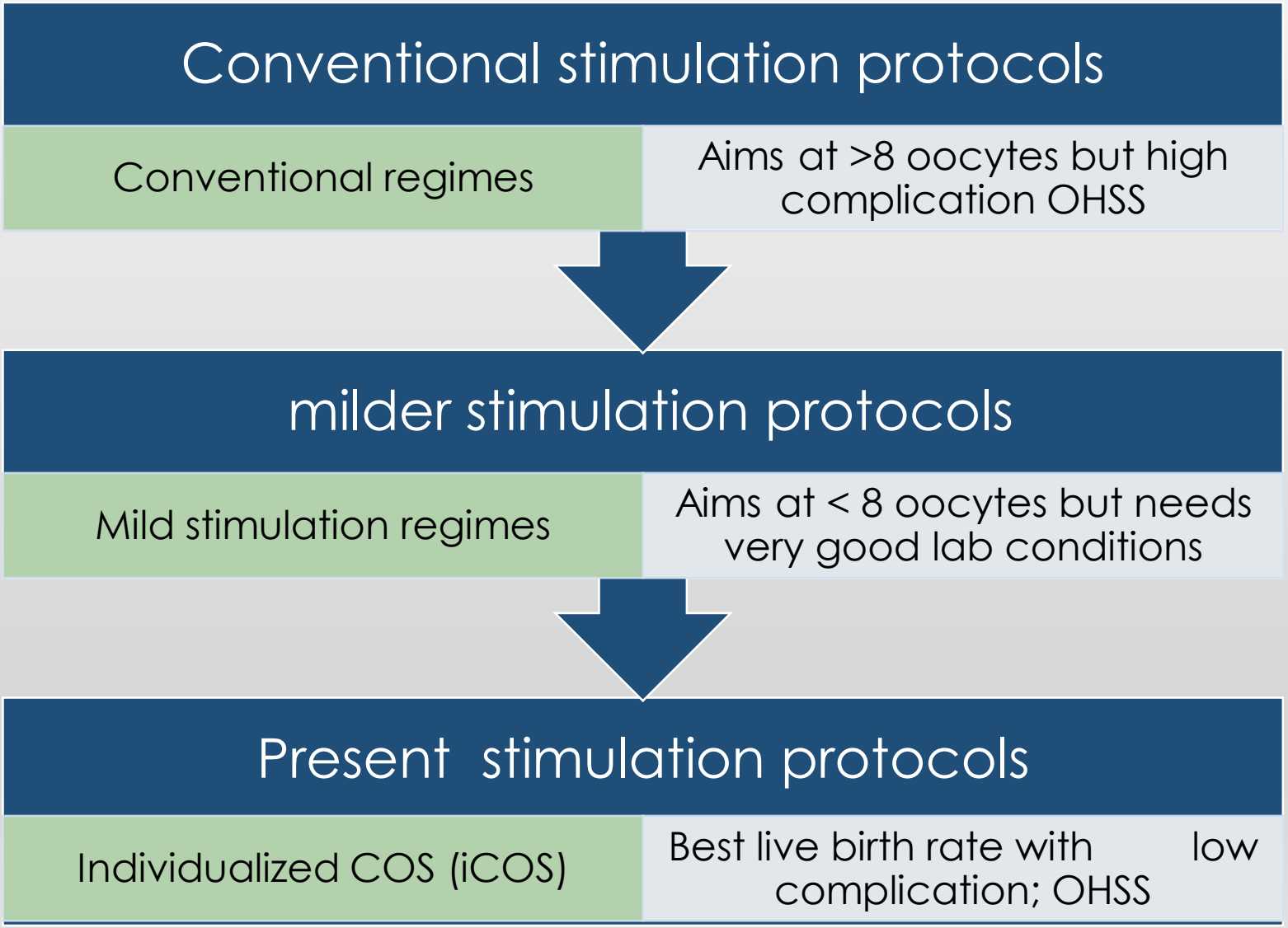
2011 Agonist trigger antagonist & freeze all

ICOS

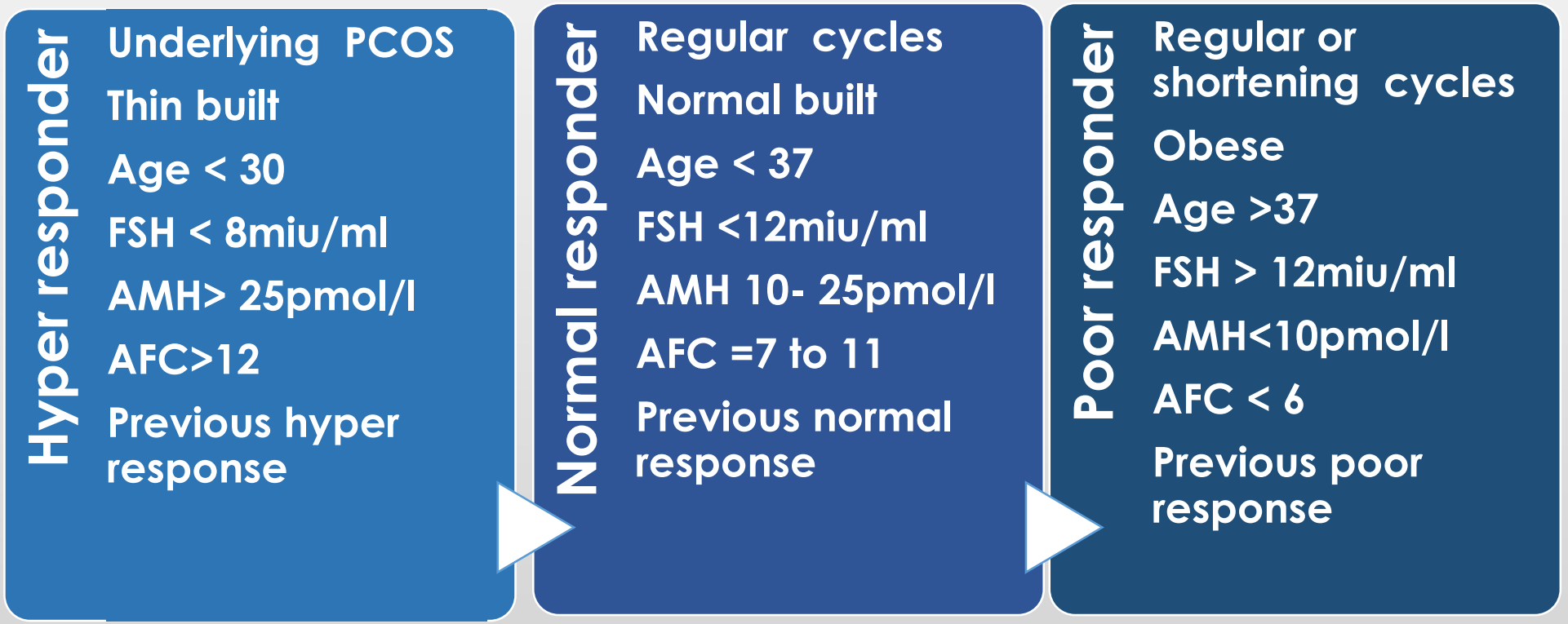
Modify IVF to combine safety and efficacy



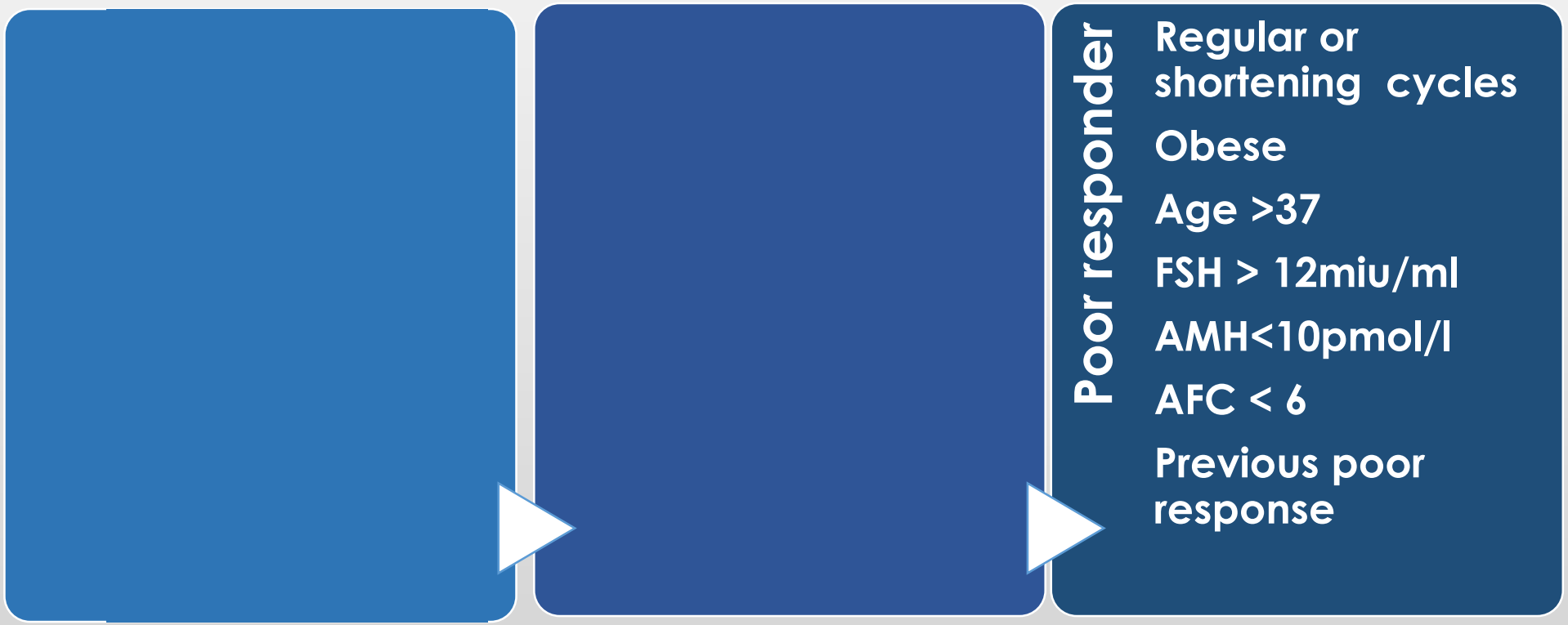
Progression of technology regarding stimulation



IDENTIFYING RESPONSE FOR ICOS



IDENTIFYING RESPONSE FOR ICOS



IS POOR OVARIAN RESERVE DIFFERENT FROM POOR OVARIAN RESPONSE?

- **Poor ovarian reserve**

- Tests for ovarian reserve show a poor reserve: Low AFC, low AMH, high basal FSH, age > 37 which translates into poor response on stimulation

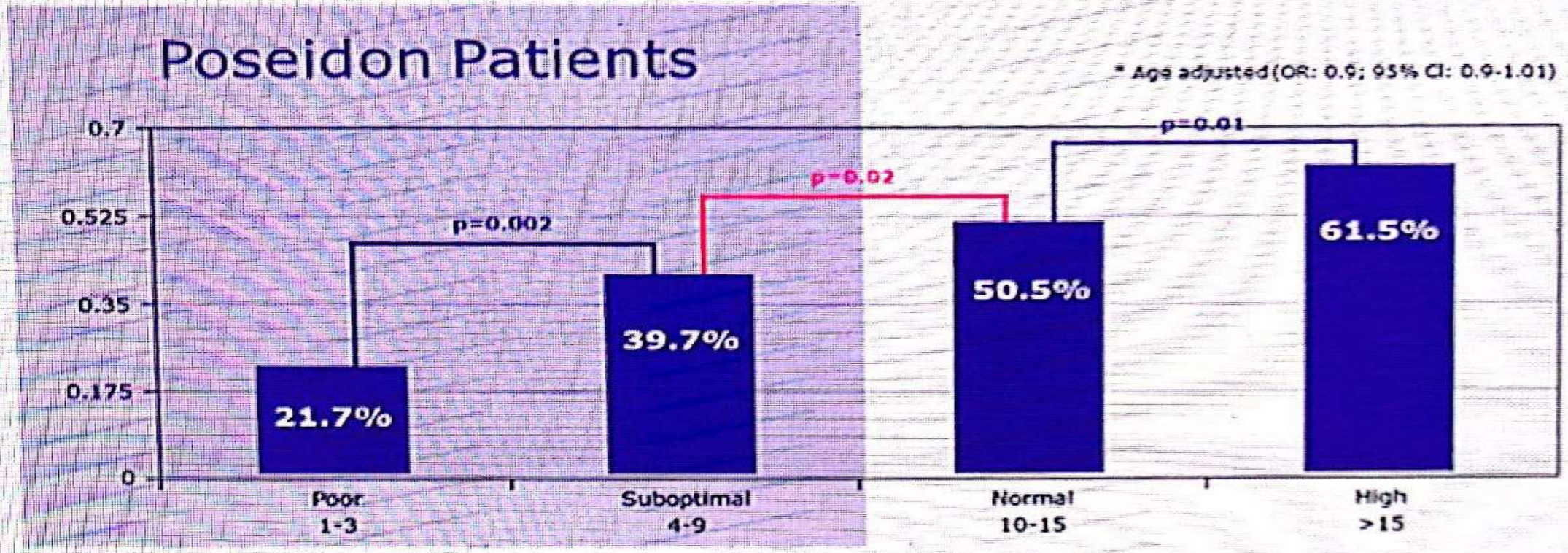
- **Poor ovarian response**

- All ovarian reserve tests show a normal ovarian reserve but on standard stimulation for IVF the response is poor in terms of number of oocytes collected

Poor ovarian reserve =Poor response √

Normal ovarian reserve = Poor response X

Low Prognosis Owing to Decreased Number of Oocytes and thus lower CLBR

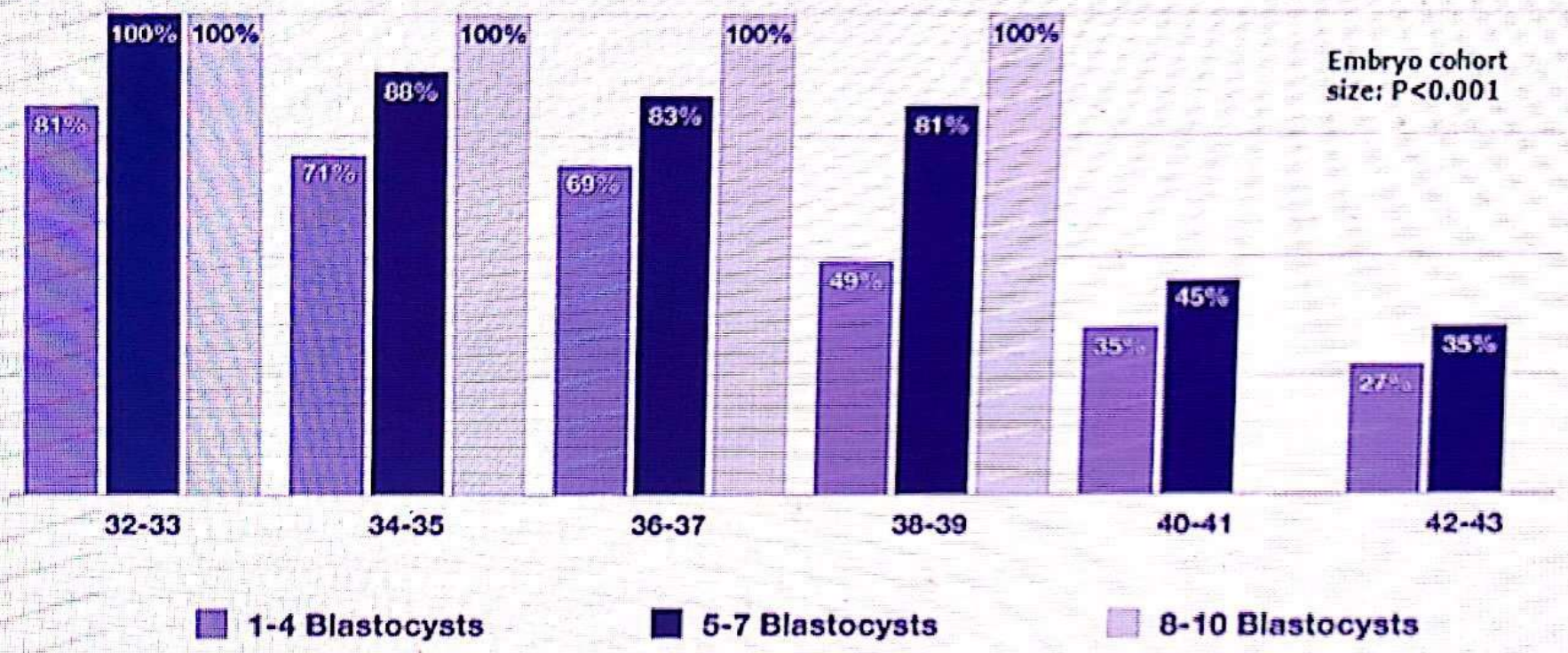


Age-adjusted CLBR strongly influenced by oocyte number

Modified from Drakopoulos et al. Hum Reprod 2016

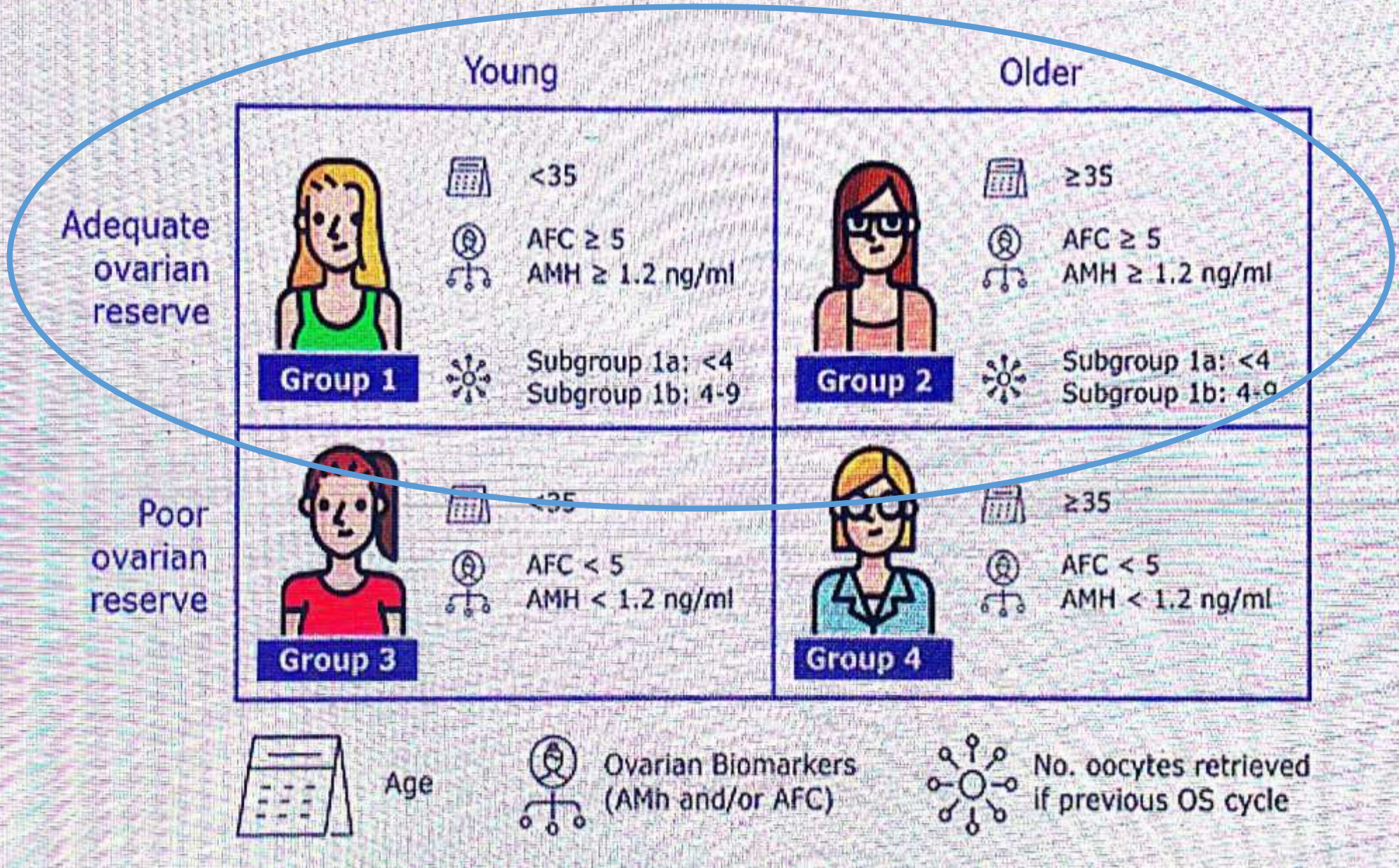
To increase LBR/CLBR we need to maximize the number of oocytes

% women with at least one euploid blastocyst as a function of age and embryo cohort size



12. Esteves et al. Panminerva Medica, 2019

Low prognosis groups Poseidon classification



A Valid Biomarker Should be Highly Sensitive and Highly Specific

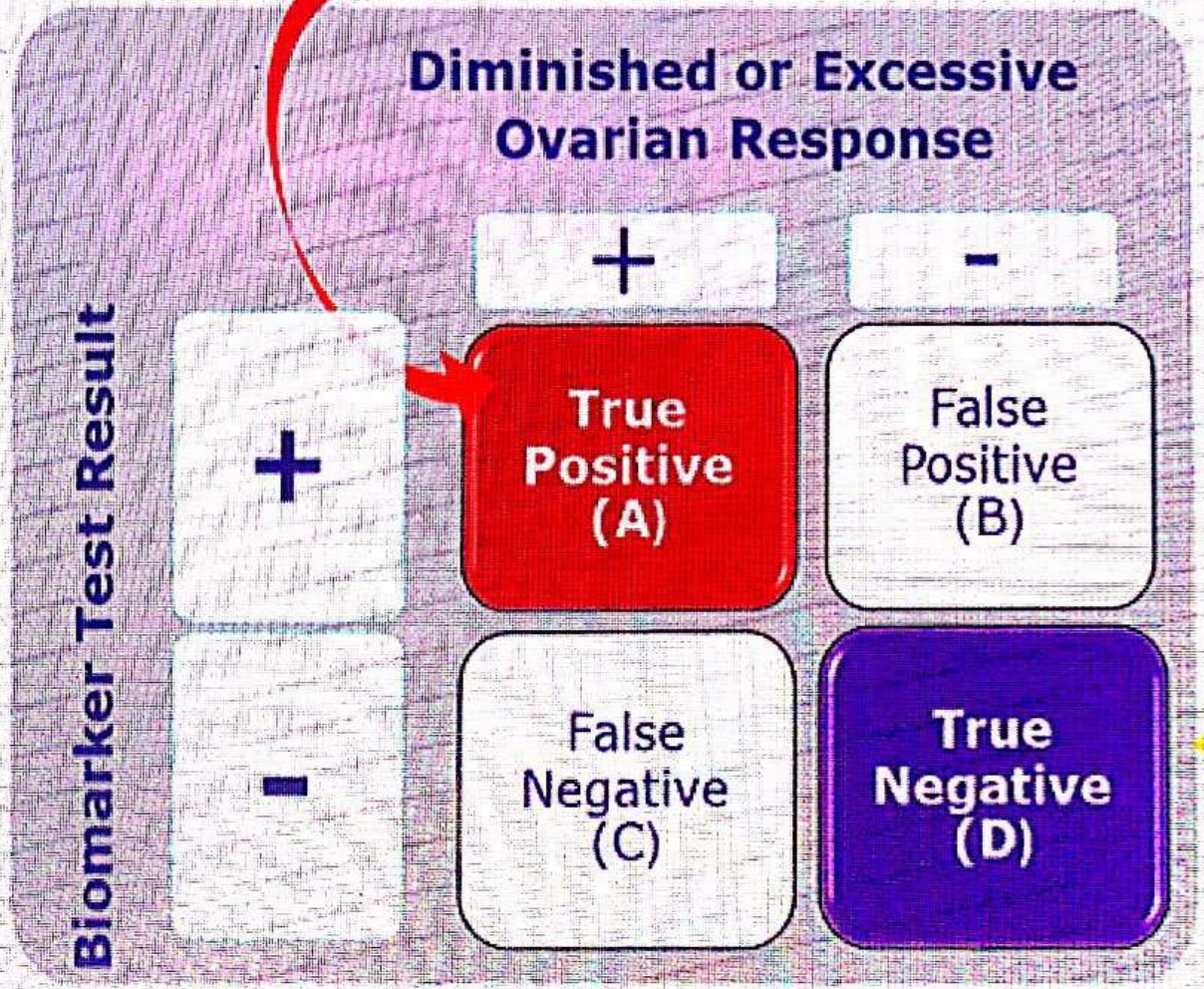
Sensitivity (A/A+C)

Specificity (D/B+D)

Predictive Value
(PPV=A/A+B; NPV=D/C+D)

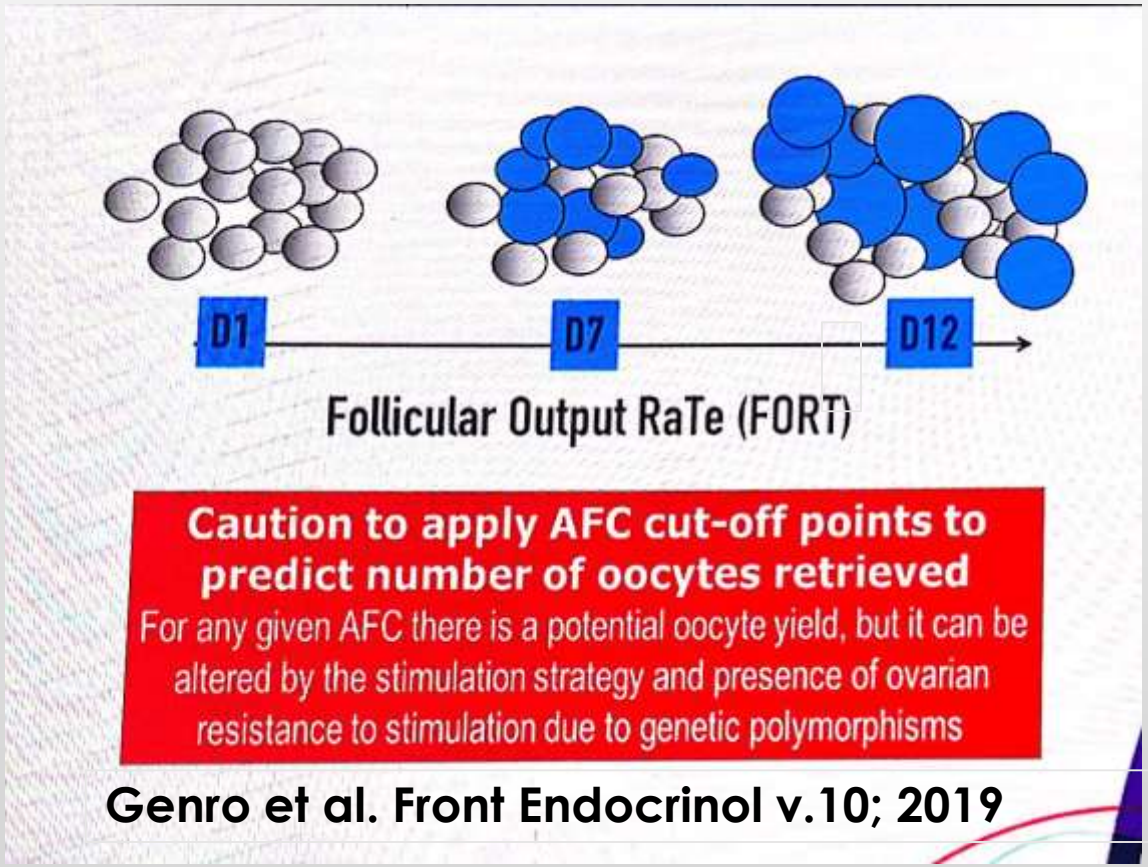
Accuracy
(A+D/A+B+C+D)

AFC & AMH



AFC

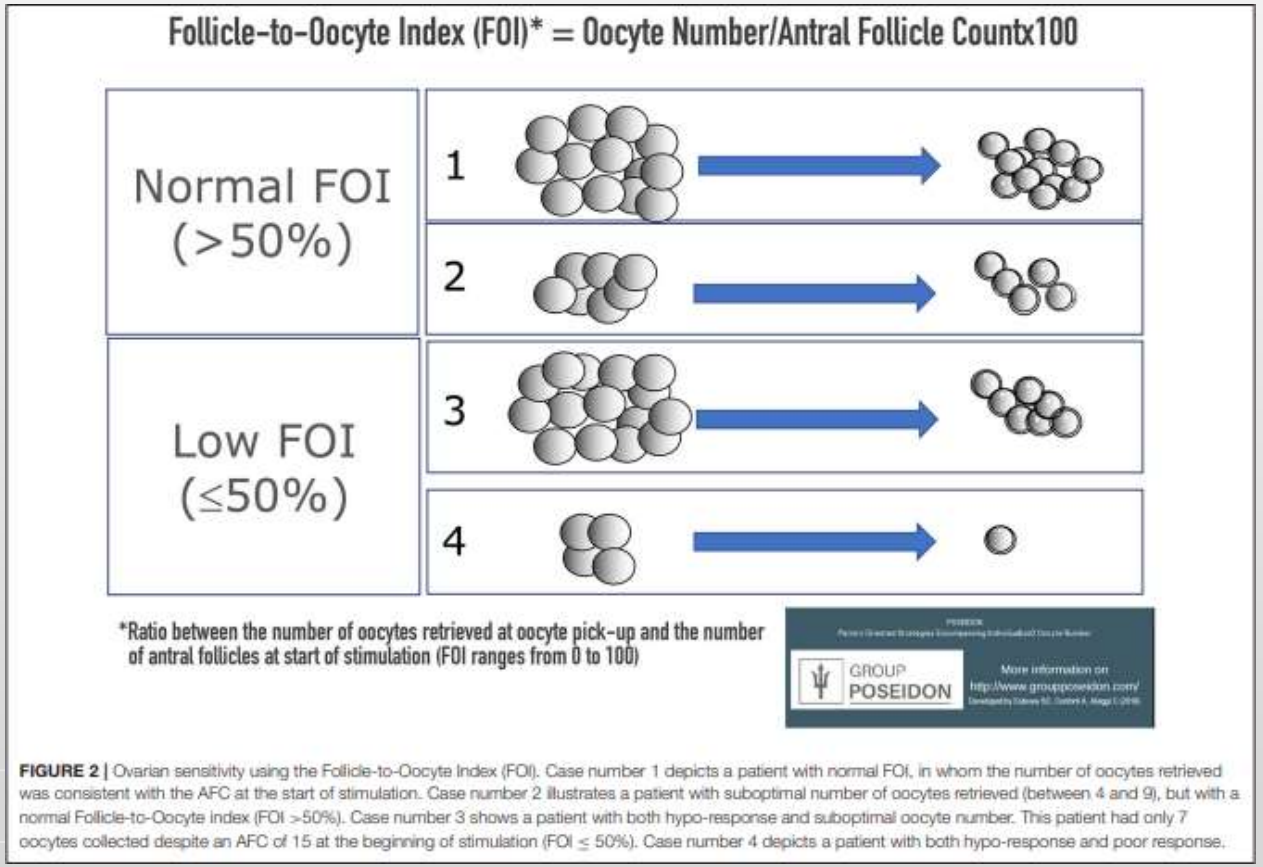
FORT



Genro et al. Front Endocrinol v.10; 2019

FORT is ratio of pre-ovulatory follicle (16–22 mm in diameter) count (PFC) on hCG day X 100/small antral follicle (3–8 mm in diameter) count at baseline.

FOI



FOI is Ratio between total oocytes collected X AFC/100 at the start of stimulation

Carlo Alviggi et al; 2018:

CLINICAL USE:

- FOI may be used alone or combined with FORT to most optimally reflect the ovarian resistance to OS.
- The results of FOI can also help to understand whether it is possible to exploit the ovarian reserve further by using pharmacologic interventions.
- FOI could be useful to predict likelihood of success in ART, the so-called POSEIDON marker of successful outcome as well as pregnancy success.
- Technical aspects related to oocyte retrieval and triggering for final oocyte maturation, can influence FOI results,

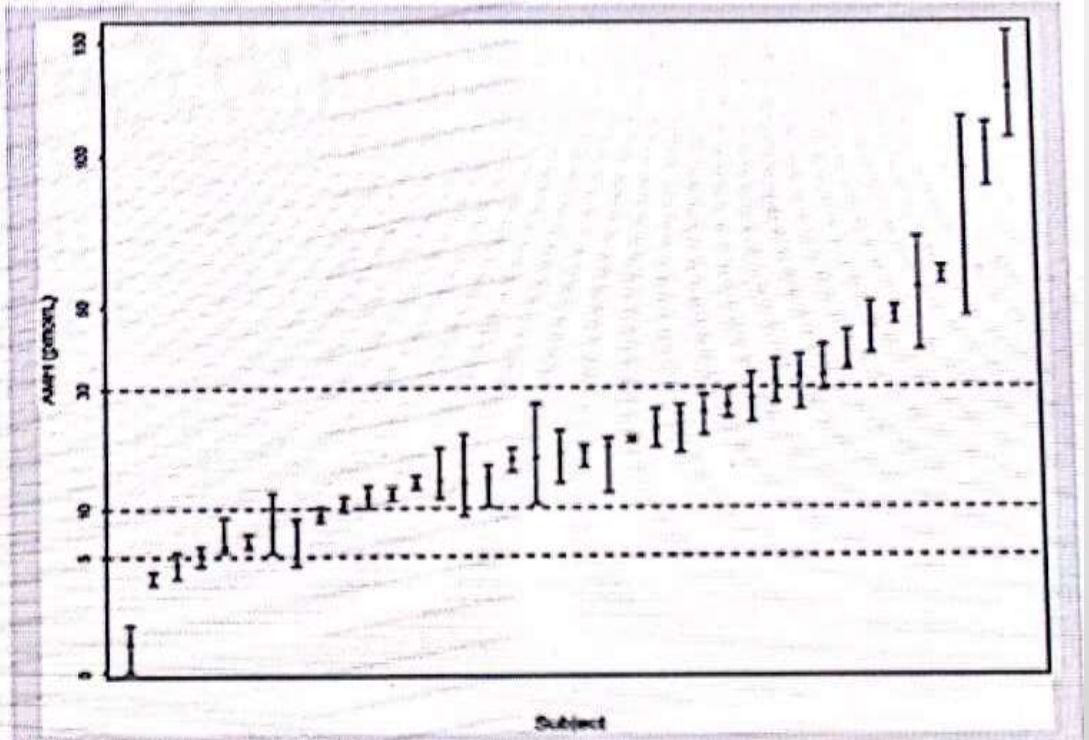
AMH

Hadlow et al. FS 2016

Average total intra-individual AMH variability: 20% (range: 2.1% to 73%)

Biological variation: 19% (range: 0 to 71%) and at least twice the analytical variation of 6.9% (range: 4.5% to 16%)

Inconsistency in AMH-measurements is mainly of biological origin



Median and range of antimüllerian hormone (AMH) results in each individual. The median and range of results in each woman, displayed in order of ascending median AMH. The *dashed lines* represent relevant clinical cutoffs (5, 10, and 30 pmol/L).

Hadlow. Biological and analytical variation of AMH. Fertil Steril 2016.

Beckman-Couter generation II assay

Hum Reprod. 2017 Aug 1;32(8):1710-1715. doi: 10.1093/humrep/dex219.

Non-equivalence of anti-Müllerian hormone automated assays-clinical implications for use as a companion diagnostic for individualised gonadotrophin dosing

Stamatina Iliodromiti [1], Barbara Salje [1], Didier Dewailly [2], Craig Fairburn [3], Renato Fanchin [4], Richard Fleming [3], Hang Wun Raymond Li [5], Krzysztof Lukaszuk [6 7 8], Ernest Hung Yu Ng [5], Pascal Pigny [9], Teddy Tadros [4], Joseph van Helden [10], Ralf Weiskirchen [11], Scott M Nelson [1]

- Overall, 29.3% women would have received an inappropriate follitropin delta dose if the Beckman Coulter Access assay was used.
- Substantial proportion of women (ranging from 49% to 90% depending on the AMH category) would receive a lower dose of follitropin delta based on the Access AMH assay.
- 2.5% to 10% of women with high ovarian reserve would have been misclassified to a greater dose of follitropin delta based on the Access AMH assay.

GENETIC POLYMORPHISM:
Exogenous FSH consumption higher in carriers of FSH-R Ser680 & v-beta LH variants in OS

Frequency of FSH-R Ser680 variant is higher in patients selected as hyporesponders . *(p value 0.02 and 0.04 respectively in Ser/Ser & Asn/Ser variants)*
Alviggiet al., Reproductive sci. 2015

A common polymorphic allele of the LH beta-subunit gene is associated with higher exogenous FSH consumption during controlled ovarian stimulation for IVF

v-betaLH is a common genetic variant of LH caused by two polymorphic base changes in the beta subunit gene, altering the amino acid sequence (Trp8Arg and Ile15Thr).
***C Alviggi*, - Reproductive …, 2013 - rbej.biomedcentral.com**

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:

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

GROUP 2 OLD (age >35)

Good reserve poor quality

Possible reasons:

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

ASYNCHRONOUS DEVELOPMENT OF FOLLICLES ON OS

- FSH elevation during the luteo- follicular transition in some patients with POR may cause accelerated growth of few follicles, suppressing less sensitive ones, resulting in poor response to OS.
- Pretreatment with GnRH antagonist, estrogen, or OCPs is offered to patients with POR in the late luteal phase preceding OS, aiming to achieve endogenous gonadotropin suppression and a uniform follicular recruitment and synchronization during the subsequent OS cycle
- Mid luteal GnRH agonist long protocol synchronizes follicles but uses higher doses of gonadotropins.

PRE-TREATMENT PITUITARY SUPPRESSION IN COS WITH ANTAGONIST PROTOCOL

- **Late luteal phase GnRH antagonist pretreatment:** Abrupt decrease in gonadotropin levels, luteolysis, and a uniform cohort of follicles. Olgan and Humaidan. Reprod Biol 2017
- **Estradiol pretreatment:** Luteal estradiol results in suppression of pit FSH & significantly longer duration of OS, higher no. of oocytes & mature oocytes retrieved, but no significant difference in the clinical pregnancy rate.
  Another meta-analysis was associated with decreased cycle cancellation and increased chance of clinical pregnancy.
  Chang and Wu. Gynecol Endocrinol 2013; Reynolds et al.Human Reproduction 2013
- **Oral contraceptive pills:** OCP pretreatment in POR showed no significant differences in the duration of OS, gonadotropin dose consumed, number of oocytes or clinical pregnancy rate. Li et al. Gynecol Endocrinol 2021

ASYNCHRONOUS DEVELOPMENT OF FOLLICLES

- GnRH agonist long protocol
- Estradiol valerate 4 mg/day from day 23 till menses of ovulatory cycle
- OCP from day 3 for 15 or 21 days
- Antagonist 0.25 mg/day X 5 days from Day 21

ORIGINAL RESEARCH ARTICLE
Front. Endocrinol., 25 July 2018 | https://doi.org/10.3389/fendo.2018.00361

The Effect of Dose Adjustments in a Subsequent Cycle of Women With Suboptimal Response Following Conventional Ovarian Stimulation

Panagiotis Drakopoulos[1,2,3], Samuel Santos-Ribeiro[1,2,4], Ernesto Bosch[5], Juan Garcia-Velasco[6], Christophe Blockeel[1,2,3], Alessia Romito[2], Herman Tournaye[1,2] and Nikolaos P. Polyzos[1,2,7]*

frontiers in Endocrinology

The number of oocytes retrieved was significantly higher in the second IVF cycle [6 (5–8) vs. 9 (6–12), $p < 0.001$]. According to our results, a dose increment of rFSH remained the only significant predictor of the number of oocytes retrieved in the subsequent IVF cycle (coefficient 0.02, p-value = 0.007) after conducting GEE multivariate regression, while adjusting for relevant confounders. A regression coefficient of 0.02 for the starting dose implies that an increase of 50 IU of the initial rFSH dose would lead to 1 more oocyte.

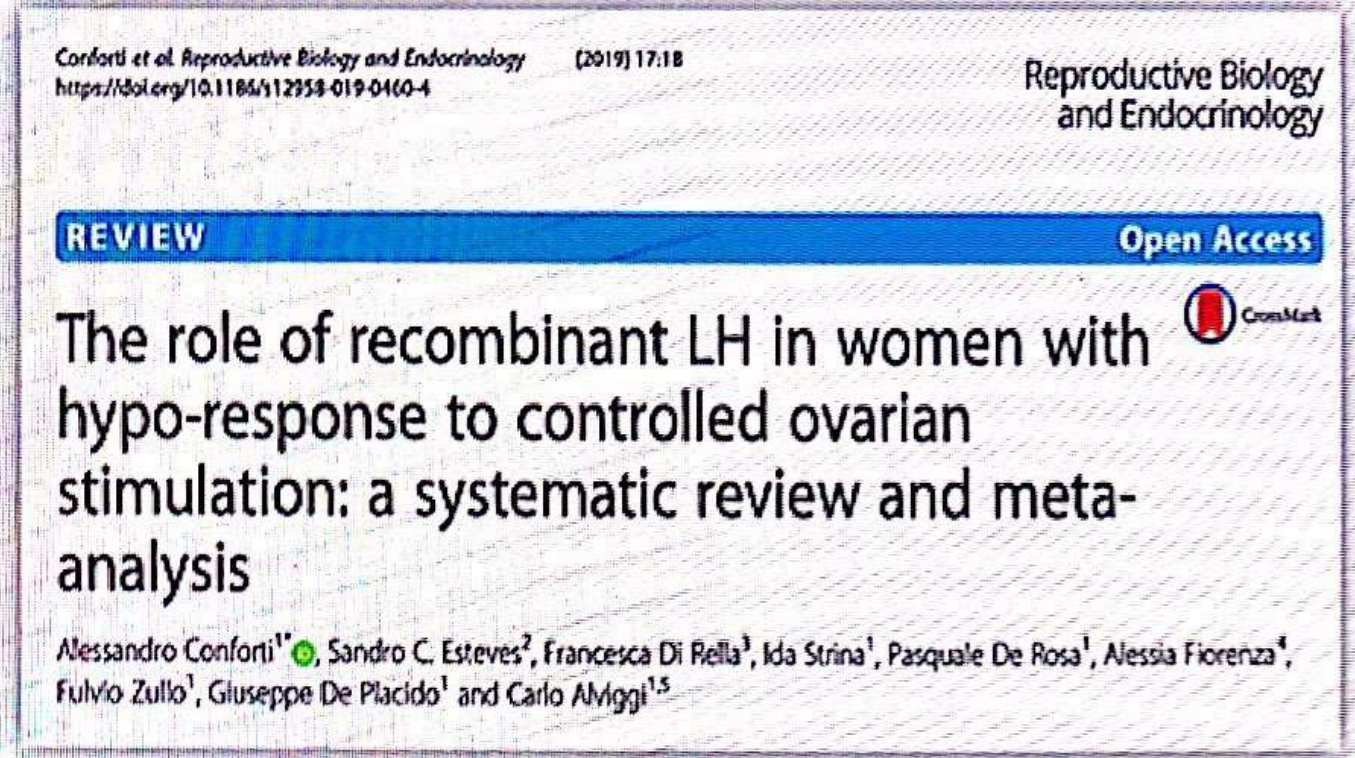
Drakopoulos et al. Front Endocrinol 2018

Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review

Carlo Alviggi, M.D., Ph.D.,[a] Alessandro Conforti, M.D.,[a] Sandro C. Esteves, M.D., Ph.D.,[b] Claus Yding Andersen, D.M.Sc.,[c] Ernesto Bosch, M.D.,[d] Klaus Bühler, M.D.,[e] Anna Pia Ferraretti, M.D.,[f] Giuseppe De Placido, M.D.,[a] Antonio Mollo, M.D., Ph.D.,[a] Robert Fischer, M.D.,[g] and Peter Humaidan, M.D., D.M.Sc.,[h] for the International Collaborative Group for the Study of r-hLH (iCOS-LH)

CONCLUSION

Despite differences in study design, r-hLH dosage, and r-hLH starting day, current evidence suggests that the following groups of ART women may benefit from r-hLH supplementation during OS: 1) patients with sufficient prestimulation ovarian reserve parameters that have an unexpected hyporesponse to FSH monotherapy—in these cases r-hLH can be started either during the midfollicular phase to rescue the ongoing cycle or on stimulation day 1 in a subsequent cycle; and 2) women 36–39 years of age—the positive effect in terms of implantation rate and oocyte/embryo quality observed in donor cycles was supported by a single small RCT, so further research is required before any definitive conclusion can be drawn. The effect of r-hLH supplementation in preventing OHSS remains to be established.



Conforti et al. Reproductive Biology and Endocrinology (2019) 17:18
https://doi.org/10.1186/s12958-019-0460-4

Reproductive Biology and Endocrinology

REVIEW Open Access

The role of recombinant LH in women with hypo-response to controlled ovarian stimulation: a systematic review and meta-analysis

Alessandro Conforti[1*], Sandro C. Esteves[2], Francesca Di Rella[3], Ida Strina[1], Pasquale De Rosa[1], Alessia Fiorenza[4], Fulvio Zullo[1], Giuseppe De Placido[1] and Carlo Alviggi[1,5]

Conclusion: In conclusion, our analysis confirms that women with a hypo-response to exogenous gonadotropins might benefit from LH supplementation.

Hypo-responders:

- "initial slow response" or "stagnation" in follicle growth during ovarian stimulation with FSH monotherapy (absence or only marginal growth of both follicles and estradiol levels during OS)
- A hypo-response can be retrospectively diagnosed in women who require higher-than-expected doses of gonadotropins on the basis of age, BMI and ovarian reserve


Original Article

Effectiveness of recombinant luteinizing hormone/human menopausal gonadotropin/letrozole as additives to recombinant follicle-stimulating hormone in women with poor ovarian reserve undergoing controlled ovarian stimulation for *in vitro* fertilization/intracytoplasmic sperm injection

CONCLUSION According to current study results, addition of rLH may improve the outcome of IVF/ICSI in patients with POR during early stages of stimulation. The results are evident with the highest clinical pregnancy rate when rLH was used as an additive with rFSH.

Agrawal R, Majumdar A, Gupta SM, Gupta D. Effectiveness of recombinant luteinizing hormone/human menopausal gonadotropin/letrozole as additives to recombinant follicle-stimulating hormone in women with poor ovarian reserve undergoing controlled ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection. Fertil Sci Res 2021;8:166-72

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 instead of uFSH/HMG,
higher FSH dose +LH?

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

Duostim: This protocols are best suited for:

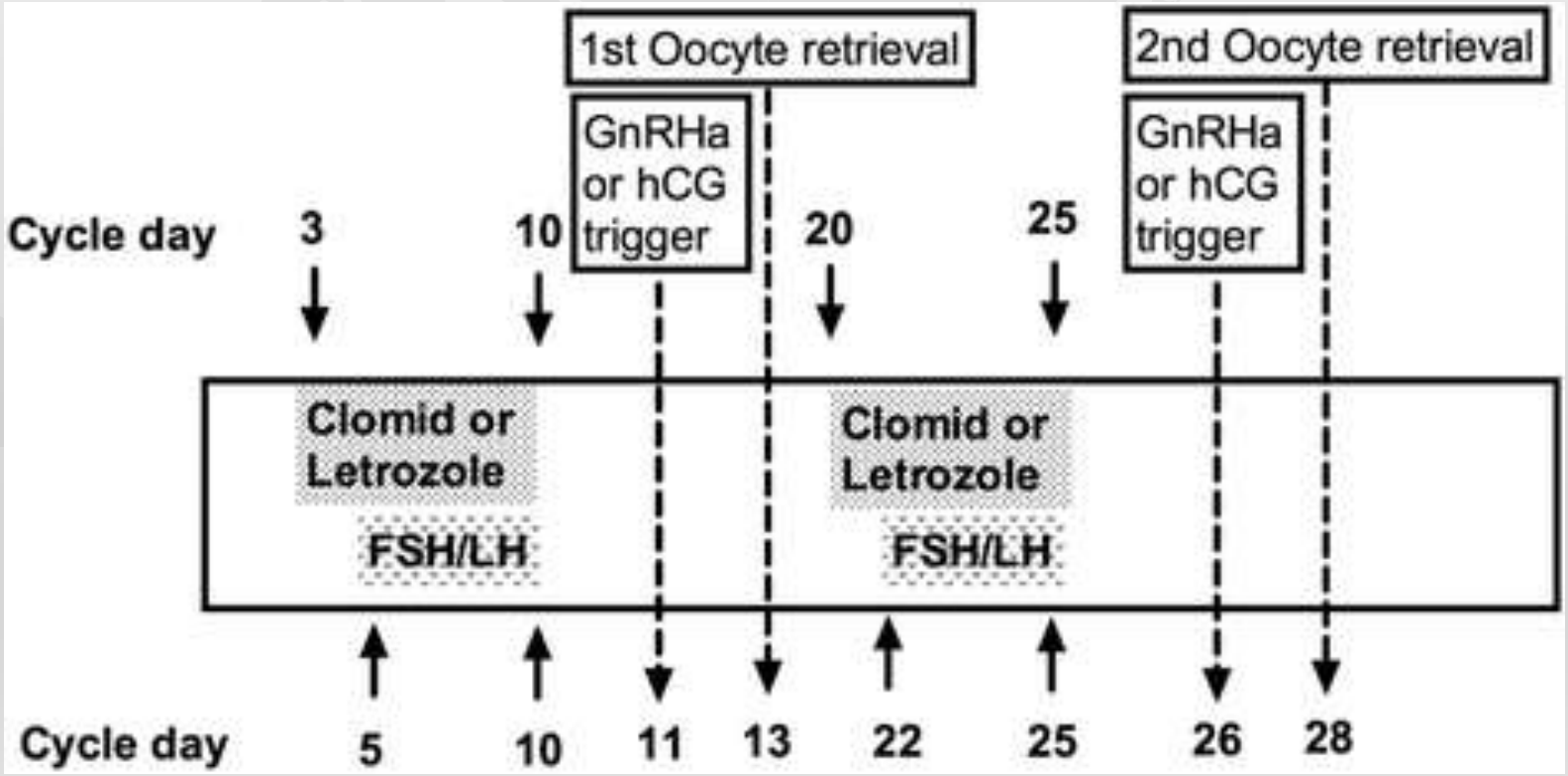
- Low ovarian reserve (AMH <1.5ng/ml, AFC 6 follicles),
- Poor response in the previous IVF cycle with less than 5 oocytes obtained
- Need for PGT of embryos to accumulated more embryos before sending them for genetic testing.

Cakmak, H., Katz, A., Cedars, M.I., Rosen, M.P., 2013. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil. Steril. 100, 1673–1680.

Shanghai protocol

Dual stimulation
(Follicular & luteal stimulation)

Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation



Hum Reprod. 2018 Jun 15. doi: 10.1093/humrep/dey217. [Epub ahead of print]

Luteal phase anovulatory follicles result in the production of competent oocytes: intra-patient paired case-control study comparing follicular versus luteal phase stimulations in the same ovarian cycle.

Cimadomo D[1], Vaiarelli A[1], Colamaria S[1], Trabucco E[2], Alviggi C[3,4], Venturella R[5], Alviggi E[2], Carmelo R[2], Rienzi L[1,2], Ubaldi FM[1,2].

Author information

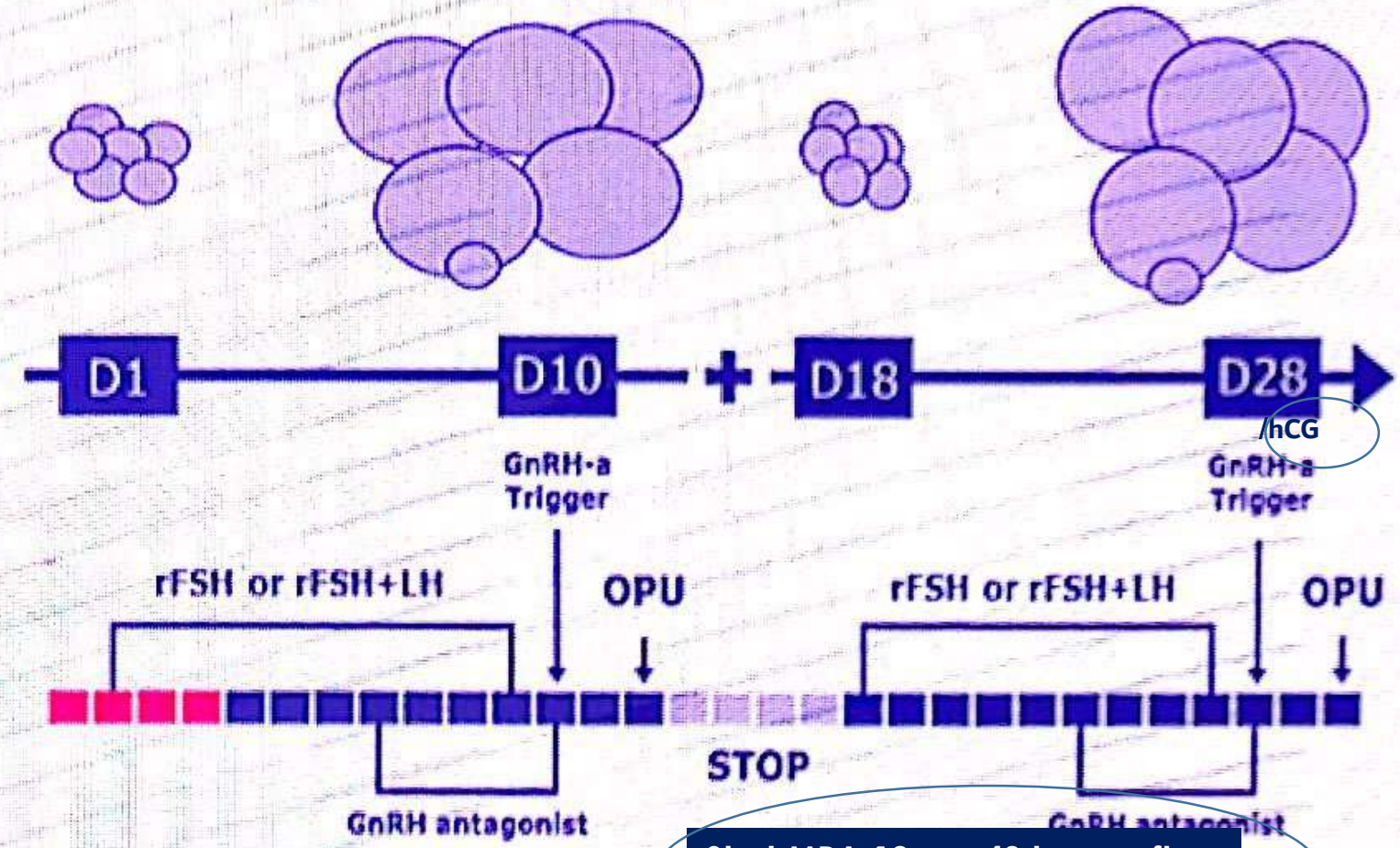
STUDY DESIGN, SIZE, DURATION: This case-control study was conducted with paired follicular phase- and luteal phase-derived cohorts of oocytes collected after stimulations in the same ovarian cycle (DuoStim) at two private IVF clinics between October 2015 and December 2017.

Abstract

STUDY QUESTION: Are the mean numbers of blastocysts obtained from sibling cohorts of oocytes recruited after follicular phase and luteal phase stimulations (FPS and LPS) in the same ovarian cycle similar?

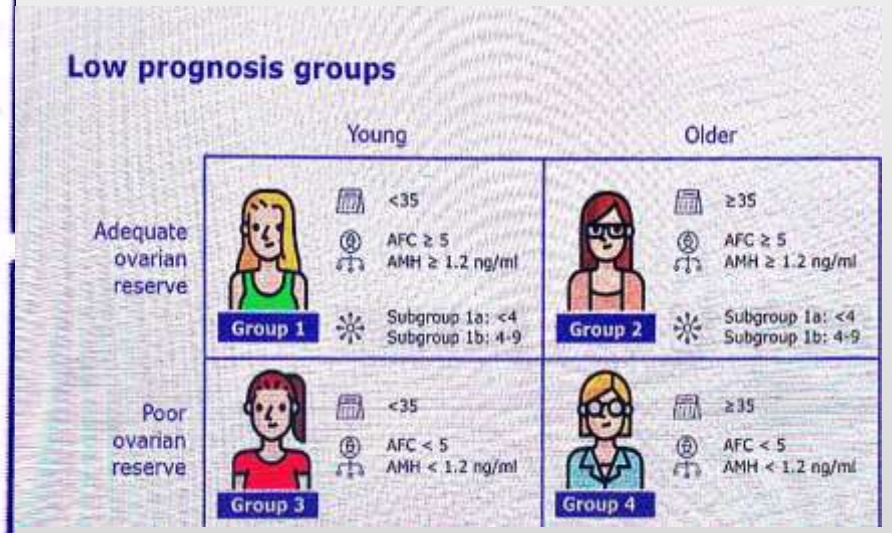
SUMMARY ANSWER: The cohorts of oocytes obtained after LPS are larger than their paired-FPS-derived cohorts and show a comparable competence, thus resulting in a larger mean number of blastocysts.

Dual stimulation SGRH protocol



Modified from Ubaldi et al. Fertil Steril 2016

Start MPA 10 mg 48 hours after OCR till the 2nd trigger



OUTCOME SGRH DUOSTIM protocol

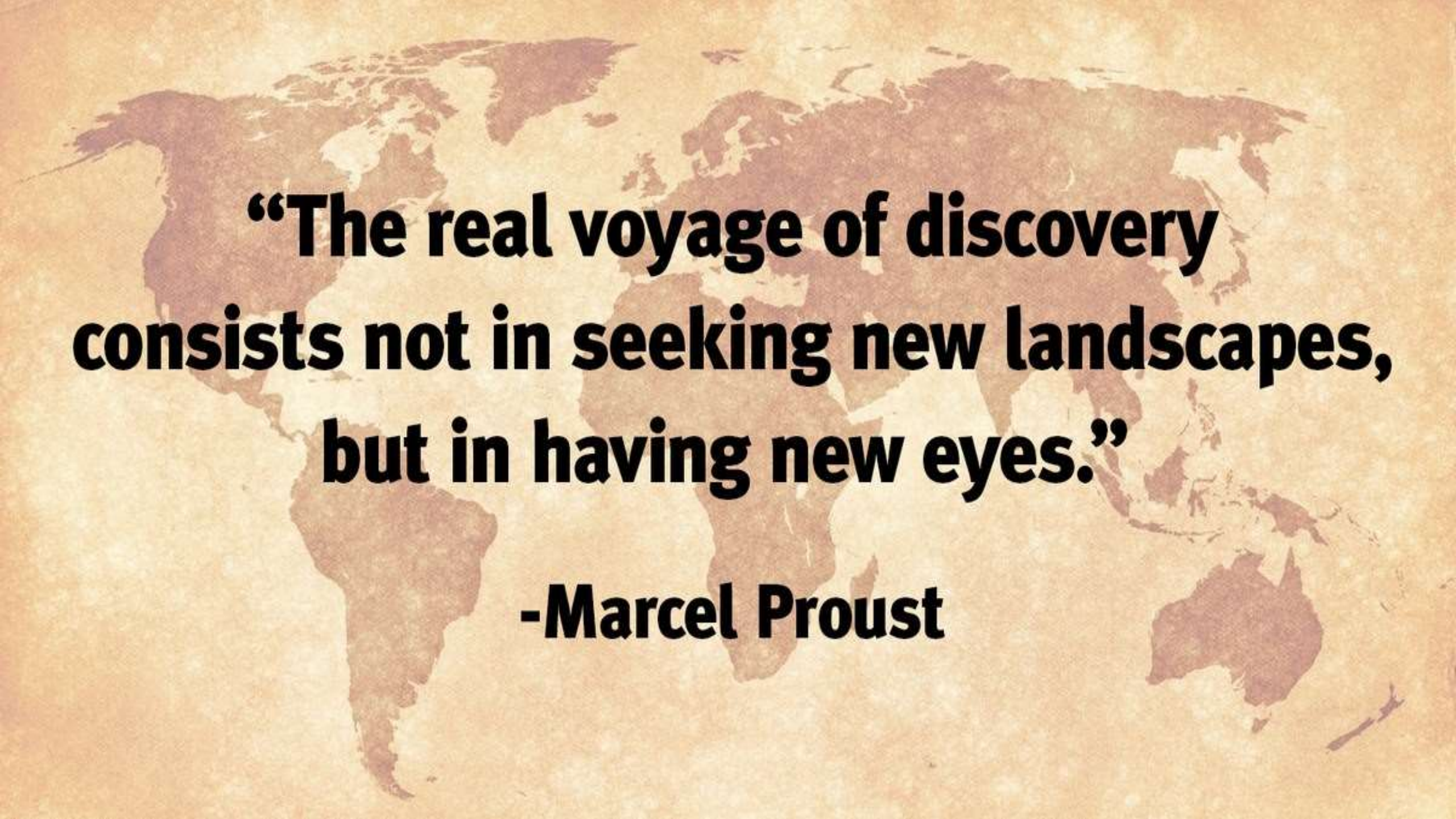
- *poor responders recruited for duo-stim: 103*
- *poor responders underwent both FPS and LPS:87*

Outcome	FPS	LPS	P-value
Oocytes (mean ± SD)	4.84±2.19	5.86± 3.08	0.005

Outcome	FPS(%)	LPS(%)	P-value
Embryo development rate(D3,D5,D6)	36.8	44.59	0.08
Blastocyst development rate(D5,D6)	22.2	30.74	0.03

SUMMARY OF REMEDIES FOR POSEIDON 1 AND 2

1. Synchronize follicular development on OS by using luteal pretreatment (agonist long protocol/Estradiol valerate/OCP/ Antagonist)
2. Increase FSH dose/add LH or HMG
3. Dual trigger with agonist and rec hCG
4. Check aspiration pressure and flow rate/ presence of cumulus cells.
5. DUO-STIM (COS in follicular and luteal phase both)


“The real voyage of discovery consists not in seeking new landscapes, but in having new eyes.”
-Marcel Proust

DESCRIPTIVE ANALYSIS OF PATIENTS UNDERGOING 'DUO-STIM' AT SGRH

- *Total number of poor responders recruited for duo-stim: 103*
- *Total number of poor responders who underwent both FPS and LPS:87*
- *In 16 out of 103 (15.5%) patients LPS was cancelled due to following reasons:*

- 1 or less than 1 follicle in LPS:4
- Poor oocyte quality in FPS:1
- Enough embryos in FPS:6
- Decided to go for Fresh transfer(opted out of LPS):2
- COVID +:1
- Opted Out:2

87 LOW RESPONDER WITH DUO-STIM

- 54% patients had increased oocyte yield in LPS than FPS.
- 32% patients had lesser oocyte yield in LPS than FPS.
- 14% patients had equal oocyte yield in both LPS and FPS.

➢ Comparison between Embryo conversion between LPS and FPS:

- 50% had increased embryo conversion in LPS.
- 19% had lesser embryo conversion in LPS.
- 21% had equal number of embryo conversion in LPS and FPS.
- 10% had Zero embryo conversion in both LPS and FPS.