MANAGEMENT AND TREATMENT OPTIONS FOR POOR PROGNOSIS PATIENTS

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Disclosures

Declare receipt of honoraria for lectures from Merck

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Four groups of patients with lower prognosis

Group 1

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

Subgroup 1a: < 4 oocytes[a]

Subgroup 1b: 4–9 oocytes retrieved[a]

Group 2

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

Subgroup 2a: < 4 oocytes[a]

Subgroup 2b: 4–9 oocytes retrieved[a]

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)

[a] After standard ovarian stimulation.
AFC, antral follicle count; AMH, antimullerian hormone.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.
Humaidan P, et al. F1000Res. 2016;5:2911.

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Poseidon classification for low-prognosis women

Group 1

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

Subgroup 1a: < 4 oocytes[a]

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Group 2

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

Subgroup 2a: < 4 oocytes[a]

Subgroup 2b: 4–9 oocytes retrieved[a]

Unexpected impaired ovarian response (hyporesponse)

[a] After standard ovarian stimulation.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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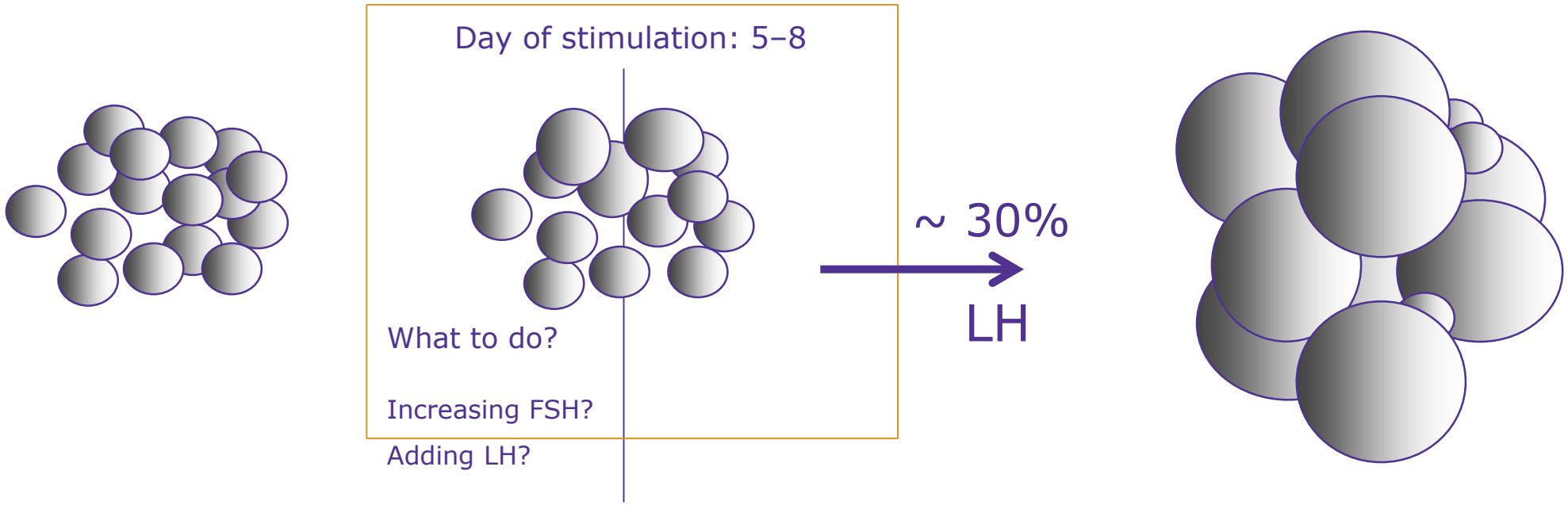
The meaning of hyporesponse: conclusions



15% of normogonadotropic women

+ rLH > + rFSH > + hMG

(rLH 150 IU > rLH 75 IU)

FSH, follicle-stimulating hormone; hMG, human menopausal gonadotropin; LH, luteinizing hormone; rFSH, recombinant FSH; rLH, recombinant LH; IU, international unit.

Alviggi C, et al. Reprod Biomed Online. 2006;12:599-607. Alviggi C, et al. Reprod Biomed Online. 2009;18:9-14. De Placido G, et al. Hum Reprod. 2001;16:1874-9. De Placido G, et al. Clin Endcrinol. 2004;60:637-43. De Placido G, et al. Hum Reprod. 2005;20:390-6. Devroey P, et al. Hum Reprod Update. 2009;15:391-408. Ferraretti AP, et al. Fertil Steril. 2004;82:1521-6. Kailasam C, et al. Hum Reprod. 2004;19:1544-7.

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Role of LH during folliculogenesis

Follicular recruitment (oocyte quantity)

Oocyte competence (quality)

EGF, epidermal growth factor; IGF1, insulin-like growth factor-1.

Spinder T, et al. Psychoneuroendocrinology. 1989;14:97-102. Vendola K, et al. Biol Reprod. 1999;61:353-7. Weil S, et al. J Clin Endocrinol Metab. 1999;84:2951-6. Filicori M, et al. Hum Reprod. 2003;18:1357-8. Jeppesen JV, et al. J Clin Endocrinol. Metab 2012;97:E1524-31.

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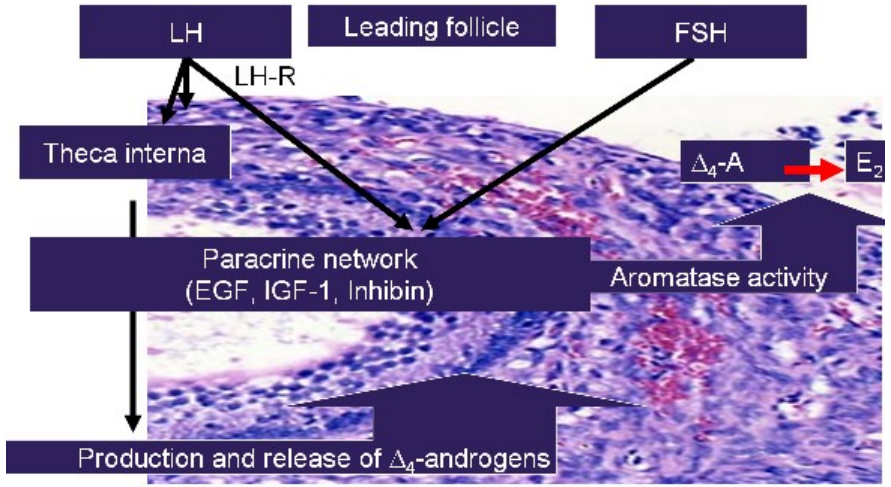
Adaptation mechanisms to 'abnormal'



Exogenous (supra-physiological) FSH activity

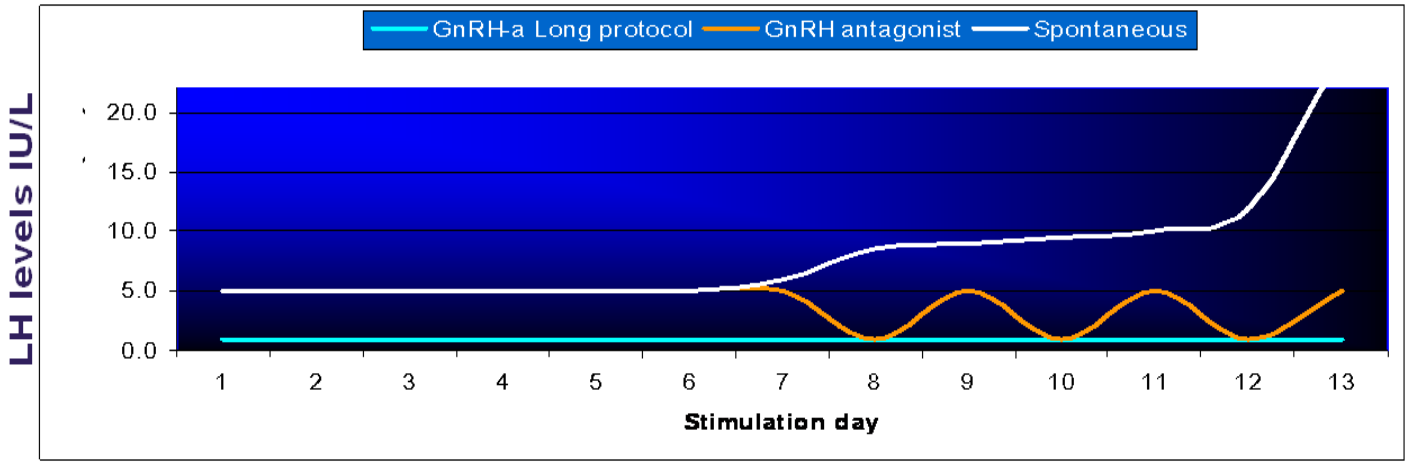
⇩

Enhancement of paracrine network
(inhibin and GFs)

⇩ ⇩

Theca cells (all follicles)
Increase in sensitivity to LH activity: optimal androgen production with <1% of LH receptors occupied (spare receptor hypothesis)

Granulosa cells
Compensation in the reduction of LH



GF, growth factor; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone analogue; LH-R, luteinizing hormone receptor.

Courtesy of C. Alviggi.

Authors' conclusions

Cochrane Database of Systematic Reviews

We included 36 RCTs (8125 women). The quality of the evidence ranged from very low to moderate. The main limitations were risk of bias (associated with poor reporting of methods) and imprecision.

Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles (Review)

Mochtar MH, Danhof NA, Ayeleke RO, Van der Veen F, van Wely M

We found no clear evidence of a difference between rLH combined with rFSH and rFSH alone in rates of live birth or OHSS. The evidence for these comparisons was of very low-quality for live birth and low quality for OHSS.

We found moderate quality evidence that the use of rLH combined with rFSH may lead to more ongoing pregnancies than rFSH alone. There was also moderate-quality evidence suggesting little or no difference between the groups in rates of miscarriage. There was no clear evidence of a difference between the groups in rates of cancellation due to low response or imminent OHSS, but the evidence for these outcomes was of low or very low quality.

We conclude that the evidence is insufficient to encourage or discourage stimulation regimens that include rLH combined with rFSH in IVF/ICS I cycles.

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; rFSH, recombinant follicle-stimulating hormone.

Mochtar MH, et al. Cochrane Database Syst Rev. 2017;5:CD005070.

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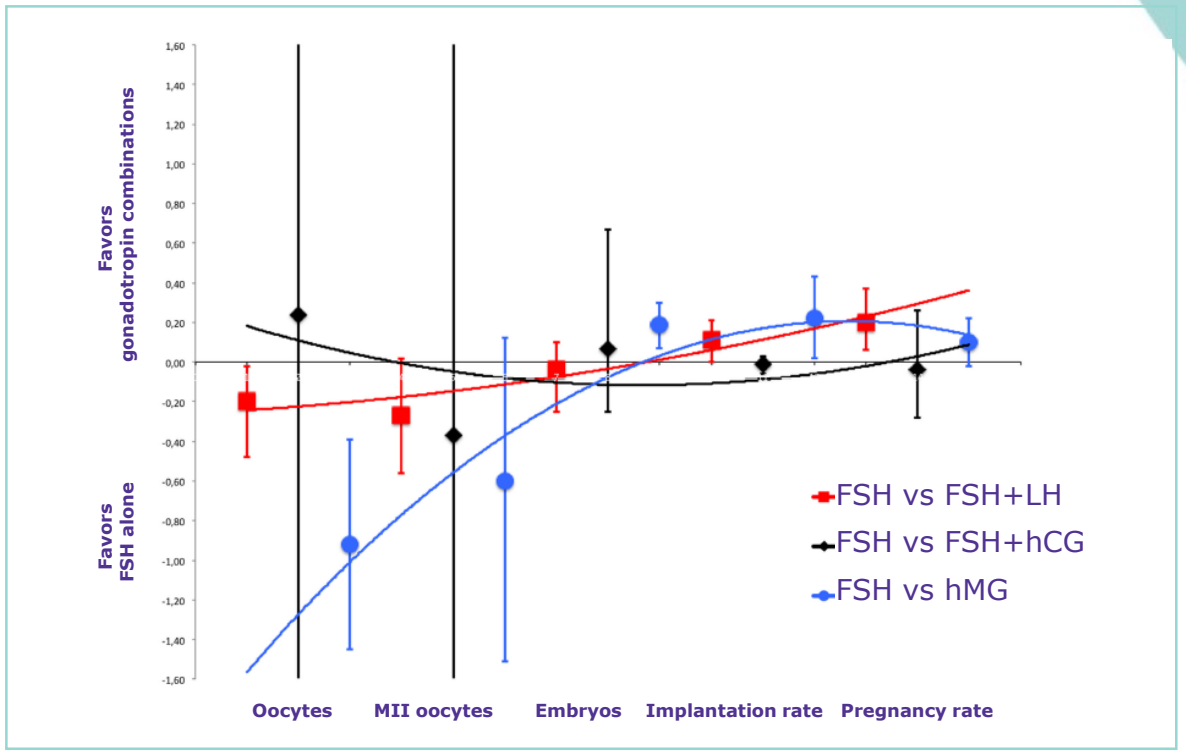
Authors' conclusions

In conclusion, we found that different performance in ART is depending on gonadotropin combination used for COS, reflecting the physiological role of these molecules as previously indicated by *in vitro* data. This leads to important implication for clinical practice, where pregnancy rate or oocyte numbers might be the preferentially selected outcome.

Especially, LH addition to FSH decreases FSH need and progressively improves ART outcomes and pregnancy rate……

……Pregnancy rate was significantly higher in FSH + LH-treated group *vs.* others



Overall model of meta-analysis results

Each scatter plot represents the mean differences and 95% CI per outcome. Lines represent polynomial trend lines: FSH + LH supplementation (red), FSH + hCG supplementation (black); hMG (blue)

ART, assisted reproductive technology; COS, controlled ovarian stimulation; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; MII, metaphase II.

Santi D, et al. Front Endocrinol (Lausanne). 2017;8:114.

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Recombinant LH supplementation in ART

An initiative of the International Collaborative Group for the Study of r-hLH (iCOS-LH)

- Carlo Alviggi
- Alessandro Conforti
- Sandro C. Esteves
- Claus Yding Andersen
- Ernesto Bosch
- Klaus Bühler
- Anna Pia Ferraretti
- Giuseppe De Placido
- Robert Fischer
- Peter Humaidan

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

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More than 5,500 records screened
Total of 30 RCTs

iCOS, individualized controlled ovarian stimulation;
RCT, randomized controlled trial; r-hLH, recombinant human LH.

Alviggi C, et al. Fertil Steril. 2018;109:644-64.

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Summary of rhLH supplementation in ART according to population treated

TABLE 2

Summary of recombinant luteinizing hormone supplementation in assisted reproductive technology according to population treated.

Population	No. studies/ participants	Intervention	Comparison	Effect	Dosage and timing or r-hLH
Hyporesponders	4/672	r-hFSH + r-hLH	r-hFSH	Better number of oocytes retrieved and implantation rate	150 IU/d started on stimulation day 8 (Ferraretti et al. 2004; de Placido et al. 2005)
Advanced age (35–39 y)	4/578	r-hFSH + r-hLH	r-hFSH	Better implantation rate	Antagonist: 75 IU/d started on stimulation day 1 (Bosch et al. 2011); Agonist: 150 IU/d started on stimulation day 6–8 (Humaidan et al. 2004; Marrs et al. 2004; Matorras et al. 2009).
Cotreatment with GnRH antagonist	10/1,689	r-hFSH + r-hLH	r-hFSH	No difference	Not evaluated
Profoundly suppressed LH levels after GnRH agonist	5/332	r-hFSH + r-hLH	r-hFSH	No difference	Not evaluated
Prevention of OHSS	1/999	r-hFSH + r-hLH	r-hFSH	Lower OHSS cases	75 IU/d started on stimulation day 8
Poor responders	7/1,483	r-hFSH+r-hLH	r-hFSH	No difference	Not evaluated

d, day; r-hFSH, recombinant human FSH; y, year.

Alviggi C., et al. Fertil Steril. 2018;109:644-64.

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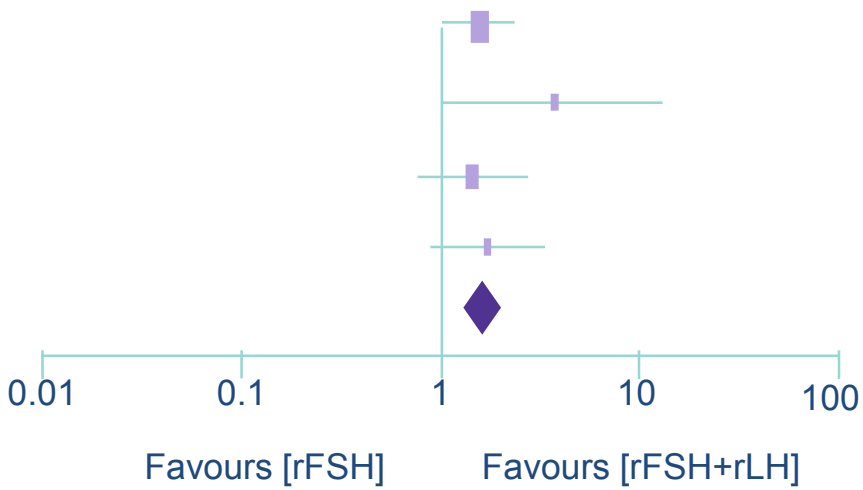
In women 35–39 years old, r-hLH supplementation improves implantation rate compared with r-hFSH alone

Implantation rate

Study or subgroup	Log (OR)	SE	Weight	Odds ratio IV, random, 95% CI
Bosch et al. 2011	0.4574	0.2134	51.7%	1.58 [1.04, 2.40]
Humaidan et al. 2004	1.311	0.6489	5.6%	3.71 [1.04, 13.23]
Marrs et al. 2004	0.3577	0.3225	22.6%	1.43 [0.76, 2.69]
Matorras et al. 2009	0.5423	0.3419	20.1%	1.72 [0.88, 3.36]
Total (95% CI)			100%	1.65 [1.22, 2.23]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.81$, df = 3 ($p = 0.61$); $I^2 = 0\%$

Test for overall effect: $z = 3.26$ ($p = 0.001$)



df, degrees of freedom; CI, confidence interval; IV, inverse variance; OR, odds ratio; SE, standard error.

Alviggi C., et al. Fertil Steril. 2018;109:644-64.

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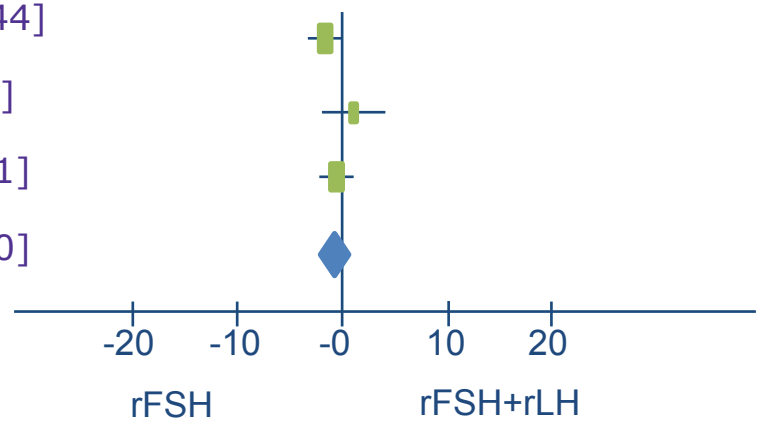
r-LH in women 35–39 yrs: increase in implantation rate is associated with similar number of oocytes retrieved

Number of oocytes

Study or subgroup	rFSH+rLH Mean	rFSH+rLH SD	rFSH+rLH Total	rFSH Mean	rFSH SD	rFSH Total	Weight	Mean difference IV, random, 95% CI
Bosch et al. 2011	8.4	4.5	150	10.1	6.3	142	45.0%	-1.70 [-2.96, -0.44]
Humaidan et al. 2004	10.3	4.1	21	9.4	4.1	18	19.3%	0.90 [-1.68, 3.48]
Matorras et al. 2009	8.3	4.7	68	8.9	4.7	63	35.6%	-0.60 [-2.21, 1.01]
Total (95% CI)			239			223	100%	-0.81 [-2.12, 0.50]

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 3.50$, df = 2 (p = 0.17); $I^2 = 43\%$

Test for overall effect: z = 1.21 (p = 0.23)



Improved oocyte quality

Alviggi C., et al. Fertil Steril. 2018;109:644-64.

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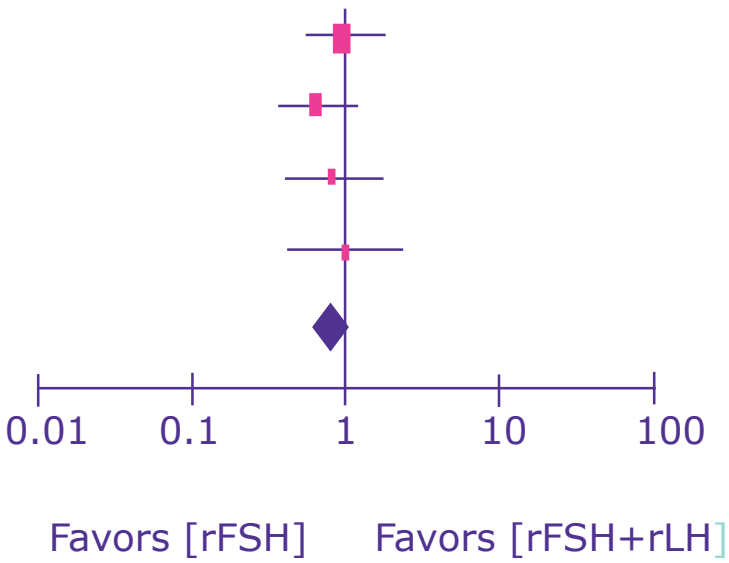
The effect of r-hLH on implantation rate disappears when patients aged above 40 years are included

Study or subgroup	Log (OR)	SE	Weight	Odds ratio IV, random, 95% CI
Fabregues et al. 2006	-0.0408	0.2842	35.0%	0.96 [0.55, 1.68]
Konig et al. 2013	-0.4359	0.3085	29.7%	0.65 [0.35, 1.18]
Nyboe Anderson et al. 2008	-0.1985	0.3663	21.1%	0.82 [0.40, 1.68]
Vuong et al. 2015	0.0164	0.4447	14.3%	1.02 [0.43, 2.43]
Total (95% CI)			100%	0.83 [0.60, 1.16]

Heterogeneity: $Tau^2=0.00$; $Chi^2=1.13$, df=3 (P=0.77); $I^2=0\%$

Test for overall effect: Z=1.09 (P=0.28)



The effect of age-related aneuploidies becomes more relevant

Alviggi C., et al. Fertil Steril. 2018;109:644-64.

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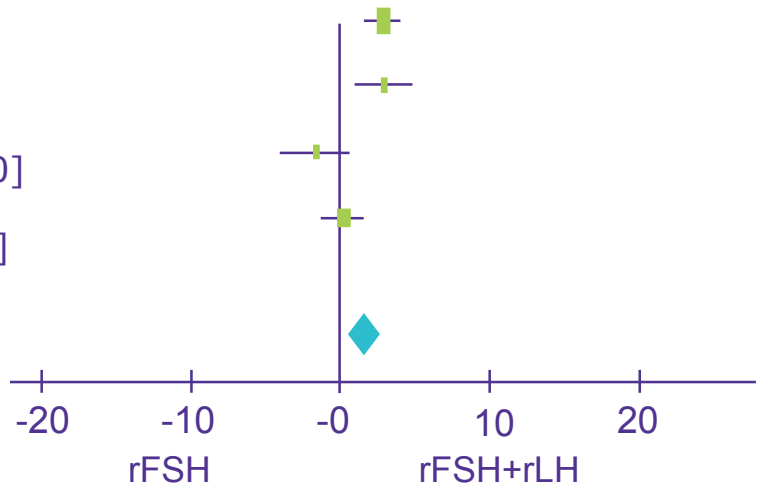
Hyporesponders: r-hLH significantly increases FORT

Study or subgroup	rFSH+rLH Mean	rFSH+rLH SD	rFSH+rLH Total	rFSH Mean	rFSH SD	rFSH Total	Weight	Mean difference IV, fixed, 95% CI
De Placido et al. 2005	9	4.3	59	6.1	2.6	58	38.9%	2.90 [1.16, 4.19]
Ferraretti et al. 2004	11.1	4.8	54	8.2	4.8	50	18.8%	2.90 [1.05, 4.75]
Ruvolo et al. 2007	5.33	4.8	24	7	3	18	11.5%	-1.67 [-4.04, 0.70]
Yilmaz et al. 2015	6.6	3.4	50	6.4	3.3	35	30.8%	0.20 [-1.24, 1.64]
Total (95% CI)			187			161	100%	1.54 [0.74, 2.35]

Heterogeneity: $Chi^2 = 16.75$, $df = 3$ ($p = 0.0008$); $I^2 = 82\%$

Test for overall effect: $z = 3.78$ ($p = 0.0002$)



FORT, follicle output rate.

Alviggi C., et al. Fertil Steril. 2018;109:644-64.

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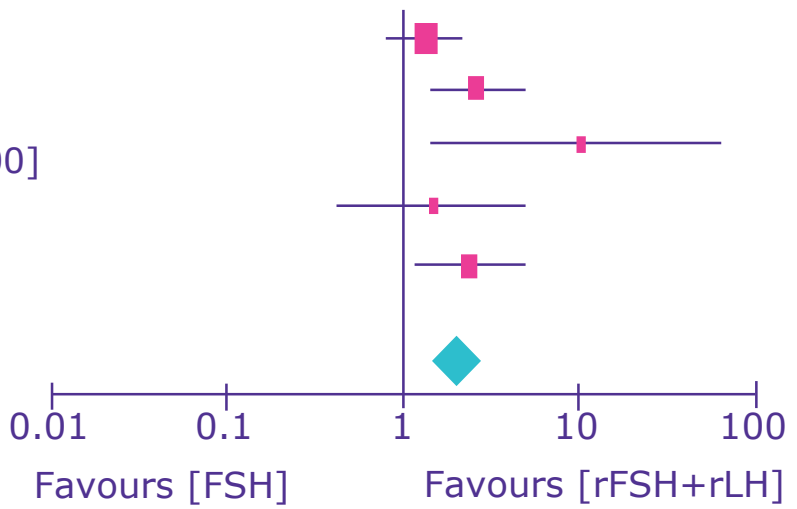
Hyporesponders: r-hLH significantly increases implantation rate

Study or subgroup	rFSH+rLH Events	rFSH+rLH Total	rFSH Events	rFSH Total	Weight	Risk ratio M-H, random, 95% CI
De Placido et al. 2005	29	206	18	174	31.8%	1.36 [0.78, 2.36]
Ferraretti et al. 2004	24	65	12	85	28.3%	2.62 [1.42, 4.83]
Lisi et al. 2002	5	7	1	14	4.5%	10.00 [1.43, 70.00]
Ruvolo et al. 2007	11	69	3	28	10.7%	1.49 [0.45, 4.93]
Yilmaz et al. 2015	22	61	9	60	24.6%	2.40 [1.21, 4.79]
Total (95% CI)		408		361	100%	2.08 [1.36, 3.19]

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.74$, df = 4 ($p = 0.22$); $I^2 = 30\%$

Test for overall effect: $z = 3.36$ ($p = 0.0008$)



M-H, Mantel–Haenszel test.

Alviggi C., et al. Fertil Steril. 2018;109:644-64.

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Role of LH in specific subgroups of low prognosis patients

1. Poseidon classification may be helpful

2. In which Poseidon groups?

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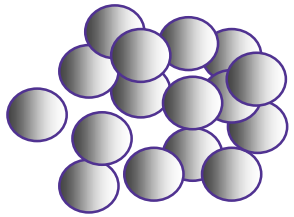
Four groups of patients with lower prognosis

Group 1

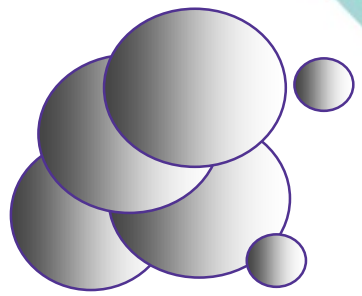
Young patients < 35 years with adequate ovarian reserve parameters (AFC ≥ 5; AMH ≥ 1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response

Subgroup 1a: < 4 oocytes[a]

Subgroup 1b: 4–9 oocytes retrieved[a]



~30%



Hyposensitivity to standard doses of FSH (low FORT)

[a] After standard ovarian stimulation.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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POSEIDON Group 1

Reasons for low response:

- FSH dose does not reach threshold
- Genetic polymorphism of *FSHR*; *LHR*; *V-LHβ*
- (Asynchronous development)

"Good reserve – good quality"

iCOS treatment:

- GnRH antagonist
- Increase rFSH dose
- Add LH activity
- Synchronize follicle wave before COS (E_2, NETA)

- **Fresh transfer**

E_2, estradiol; NETA, norethisterone acetate.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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Four groups of patients with lower prognosis

Number of blastocysts	% normal embryos				
	< 35 y	35–37 y	38–40 y	41–42 y	> 42 y
1–3	61%	51%	39%	22%	13%
4–6	60%	52%	38%	23%	17%
7–10	62%	51%	36%	21%	14%
> 10	63%	55%	37%	25%	n/a

Group 2

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

Subgroup 2a: < 4 oocytes[a]

Subgroup 2b: 4–9 oocytes retrieved[a]

Hyposensitivity to standard doses of FSH (low FORT)

In these women, the recruitment of more eggs is crucial because they have high aneuploidy rate (dual stimulation)

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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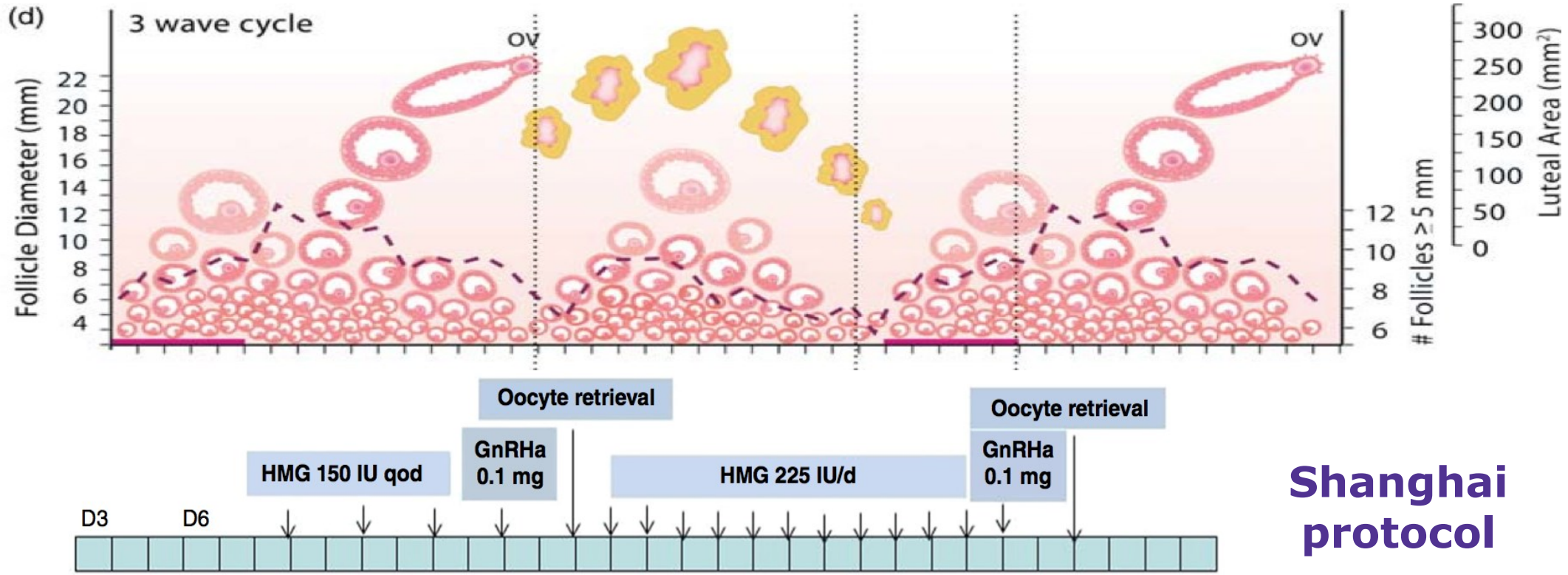
Two consecutive stimulations within the same cycle

Concept: 2 or 3 waves of follicular recruitment



Shanghai protocol

56.5% pregnancy rate per transfer

38 patients **oocytes: 1.7 ± 1** **oocytes: 3.5 ± 3.2**

GnRHa, GnRH agonist; qod, every other day.

Figures reproduced from Baerwald AR, et al. Human Reprod Update. 2012;18:73-91.
Kuang YP, et al. Reprod BioMed Online. 2014;29:684-91.

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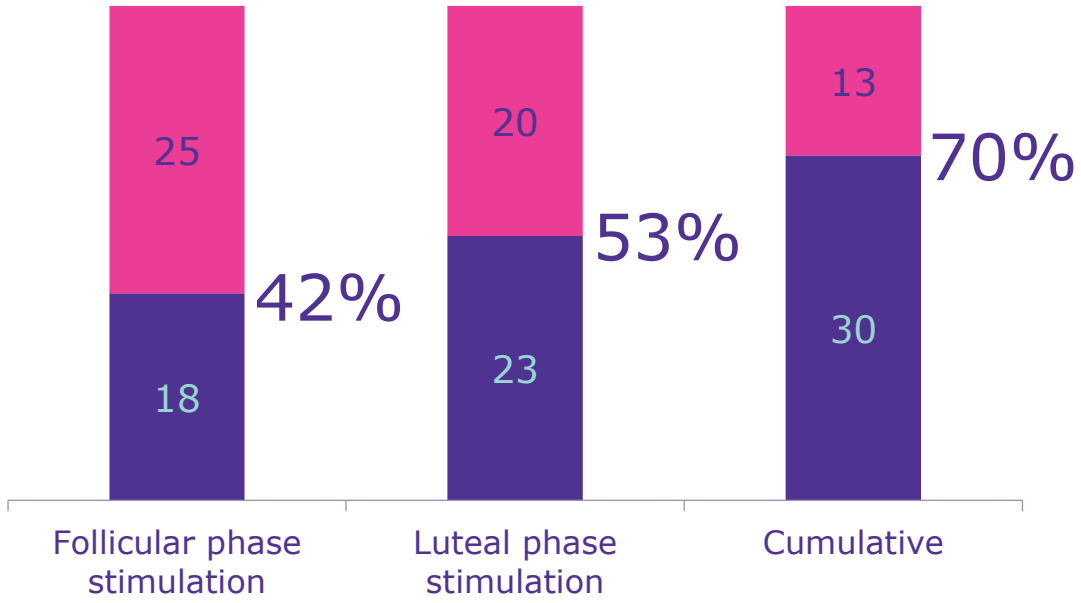
DuoStim in POR/ poor prognosis patients



ORIGINAL ARTICLE: ASSISTED REPRODUCTION

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

Filippo Maria Ubaldi, M.D., M.Sc.,[a,b,c] Antonio Capalbo, Ph.D.,[a,b,c] Alberto Vaiarelli, M.D., Ph.D.,[a,b] Danilo Cimadomo, M.Sc.,[a,b,d] Silvia Colamaria, M.D.,[a,b] Carlo Alviggi, M.D., Ph.D.,[d,e] Elisabetta Trabucco, M.D.,[a,b] Roberta Venturella, M.D.,[a,b,f] Gábor Vajta, Ph.D.,[g,h] and Laura Rienzi, M.Sc.[a,b,c]

Preliminary clinical outcomes according to follicular or luteal phase stimulation.

	Stimulation phase		
Outcome	**Follicular**	**Luteal**	**Total**
No. of SET	7	8	15
No. of clinical pregnancies (%)	6 (85.7)	6 (75.0)	12 (80.0)
No. of miscarriages (%)	1 (16.7)	1 (16.7)	2 (16.7)
No. of ongoing pregnancies (%)	5 (71.4)	5 (62.5)	10 (66.7)

POR, poor ovarian response; SET, single-embryo transfer.

Courtesy of F. Ubaldi. Ubaldi FM, et al. Fertil Steril. 2016;105:1488-95.

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POSEIDON Group 2

"Good reserve – poor quality"

iCOS treatment:

- GnRH antagonist
- Increase rFSH and add rLH
- HCG or GnRHa trigger
- Blastocyst culture
- Synchronize follicle wave before COS (E_2, NETA)

- **Fresh transfer or segmentation-DuoStim**

Reasons for low response:

- FSH dose does not reach threshold
- Genetic polymorphism of *FSHR*, *LHR*, *V-LHβ*
- Asynchronous development

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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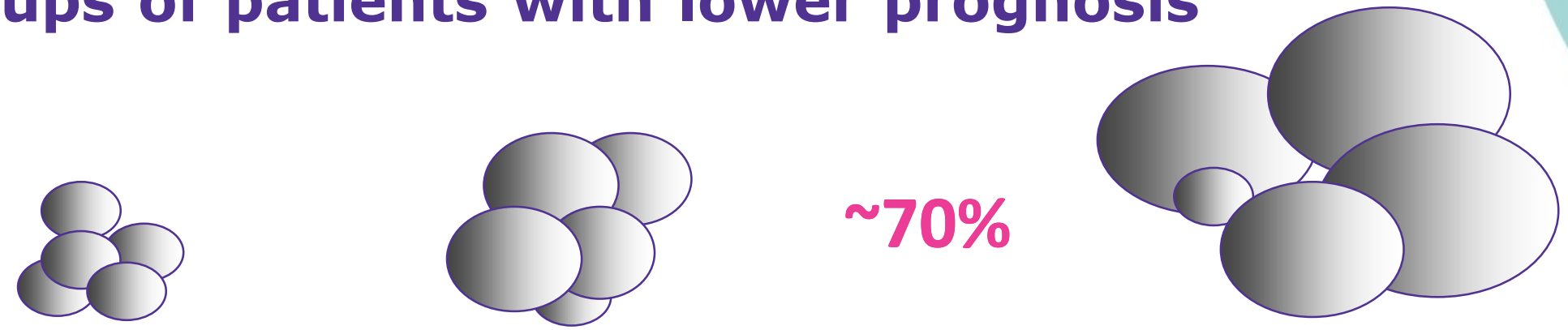
Four groups of patients with lower prognosis



If ovarian reserve is low and FORT is high, no gonadotrophin can compensate!!!
Most of Bologna (ESPART) patients fall in these groups!!!
DuoStim can be an option in young patients where aneuoploid rates are still low

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)

ESPART, Efficacy and Safety of Pergoveris in Assisted Reproductive Technology.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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What about POR?

After ESHRE Bologna criteria, 2011

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human reproduction ORIGINAL ARTICLE *Infertility*

Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders

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STUDY QUESTION: How does the efficacy and safety of a fixed-ratio combination of recombinant human FSH plus recombinant human LH (follitropin alfa plus lutropin alfa; r-hFSH/r-hLH) compare with that of r-hFSH monotherapy for controlled ovarian stimulation (COS) in

> 900 patients

Patients selected according to ESHRE Bologna criteria for POR

1) Fixed-dose r-hFSH plus r-hLH in a 2:1 ratio

2) r-hFSH monotherapy

- No differences in oocyte quantity between groups
- Lower pregnancy loss with r-hFSH + rLH than with rFSH
- Higher LBR with r-hFSH + rLH than with rFSH in moderate/severe POR compared with mild POR
- Indicating heterogeneity in POR (Bologna criteria) population

post hoc analysis

ESHRE, European Society of Human Reproduction and Embryology.

Humaidan P, et al. Hum Reprod. 2017;32:544-55.

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Poseidon Group 3

"Low reserve – good quality"

iCOS treatment:

- Long GnRHa protocol
- GnRH antagonist (E_2, NETA)
- Stimulation up to 300 IU/day rFSH
- DuoStim (Ubaldi et al., 2015)
- Androgens? (testosterone)

- **Fresh transfer**
- **Oocyte/embryo accumulation and FET**

Reasons for low response:

- Poor ovarian reserve
- Asynchronous development
- (Genetic polymorphism of *FSHR*, *LHR*, *V-LHβ*)

FET, frozen embryo transfer.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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Poseidon Group 4

Reasons for low response:

- Poor ovarian reserve
- Asynchronous development
- (Genetic polymorphism of *FSHR*, *LHR*, *V-LHβ*)

"Poor reserve – poor quality"

iCOS treatment:

- Long GnRHa protocol
- GnRH antagonist (E_2, OCP)
- Stimulation up to 300 IU/day rFSH and LH
- Androgens (testosterone)?
- GH?
- DuoStim (Ubaldi et al., 2015)
- **Fresh transfer**
- **Segmentation – oocyte/embryo accumulation and FET**
- **(Oocyte donation)**

OCP, oral contraceptive pill.

POSEIDON Group. Fertil Steril. 2016;105:1452-3.

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How many oocytes are needed for at least 1 euploid embryo?

Input variables

X

Maturation rate
2PN fertilization rate
Cleavage or blastulation rate
Euploid rate per age group

Parameter	Rate[a]
MII	~ 75%
2PN	~ 65%
Blastocyst formation	~ 40%
Euploid per age group (years) < 35 35–39 40–42	 ~ 60% ~ 50% ~ 30%

[a] As commonly reported in the literature.
2PN, 2 pronuclei.

Function
Y = f(X)

Adjusted according to maternal and paternal age, sperm source, sperm and oocyte status, and type of embryo transfer (fresh, FET)

Output variable
Y (N oocytes)

Courtesy of S. Esteves.

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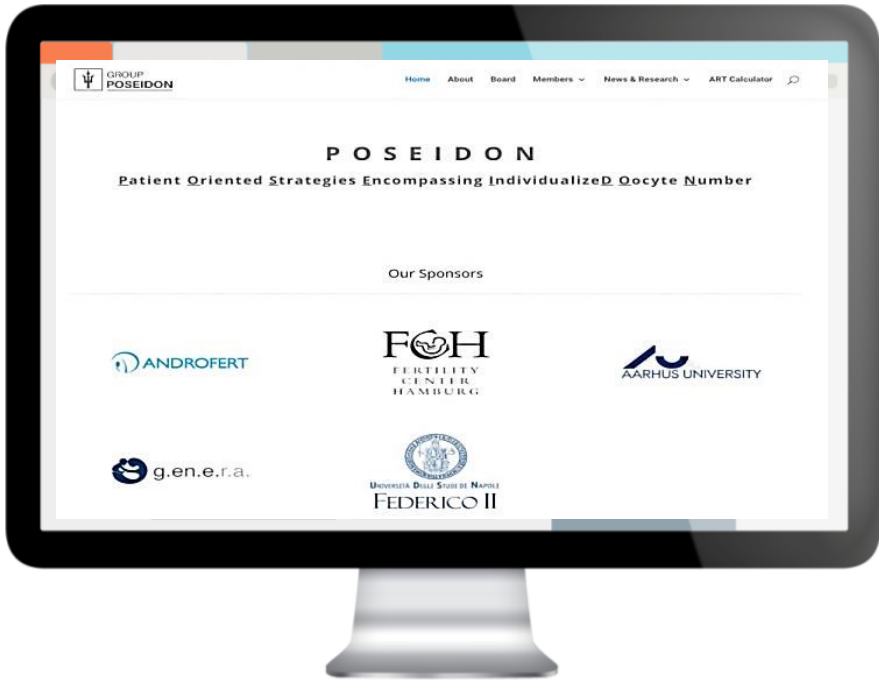
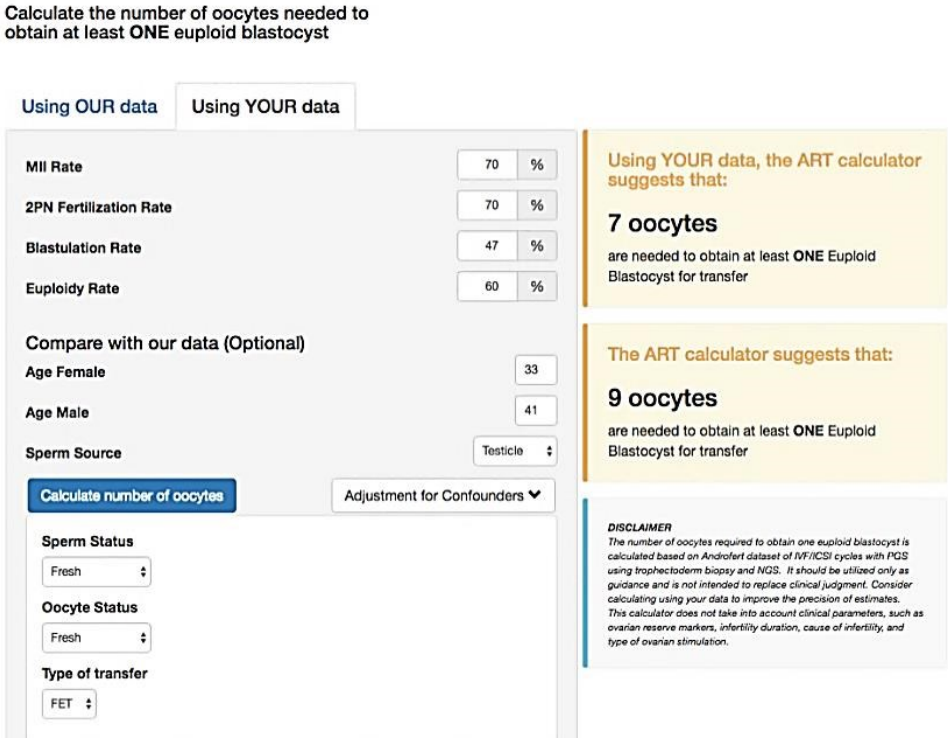
POSEIDON ART CALCULATOR





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Estimation of number of oocytes needed to obtain at least 1 euploid blastocyst for transfer in each patient proposed as an intermediate marker of success in ART

Counseling

- Set patients expectations and facilitate mature discussion about therapeutic alternatives
- Prepare patients financially for treatment journey

Treatment

- Establish an individualized, patient-centered, treatment plan to achieve the estimated number of oocytes needed for at least 1 euploid blastocyst

Reduce TTP

TTP, time to pregnancy.

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The use of LH in COS: conclusions

- R-hLH is beneficial in terms of both oocyte quantity and quality in women with hyporesponse to FSH monotherapy (Poseidon Groups 1 and 2) co-treated with GnRH agonist
- In case of an initial low FORT, r-hLH can be started at the mid-follicular phase (days 6–8) in the attempt to rescue the ongoing cycle and from the first day of stimulation in a subsequent cycle
- R-hLH improves implantation rate in women between 35 and 39 years (Poseidon Group 2)
- Despite the fact that post hoc analysis shows promising results in specific subgroups of POR patients, the role of LH in women with very low ovarian reserve (Poseidon Groups 3 and 4) needs to be studied

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Thank you

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