The planet of low ovarian reserve: how can we best manage POSEIDON groups 3 and 4?

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Ology Medical Education | Event Planet

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Disclosures

- Receipt of honoraria for lectures from Merck

Educational objectives

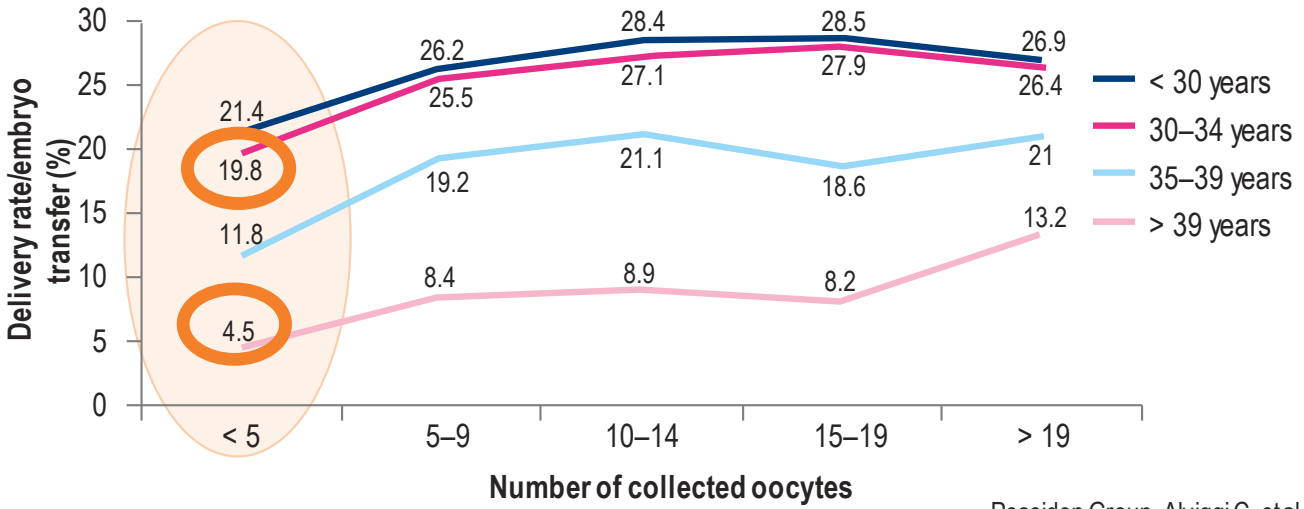
- Identify current unmet needs and therapeutic challenges
- Describe strategies for managing patients in POSEIDON groups 3 and 4
- Evaluate adjuvant therapy for patients in POSEIDON groups 3 and 4

Oocyte number, age, and delivery rates

20 years' experience – the Swiss ART registry

POSEIDON group 3
Young patients (< 35 years) with
poor ovarian reserve pre-stimulation parameters
(AFC < 5; AMH < 1.2 ng/mL)

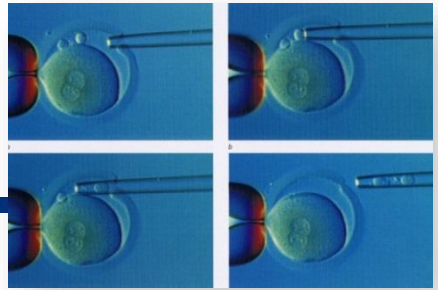
POSEIDON group 4
Older patients (≥ 35 years) with
poor ovarian reserve pre-stimulation parameters
(AFC < 5; AMH < 1.2 ng/mL)

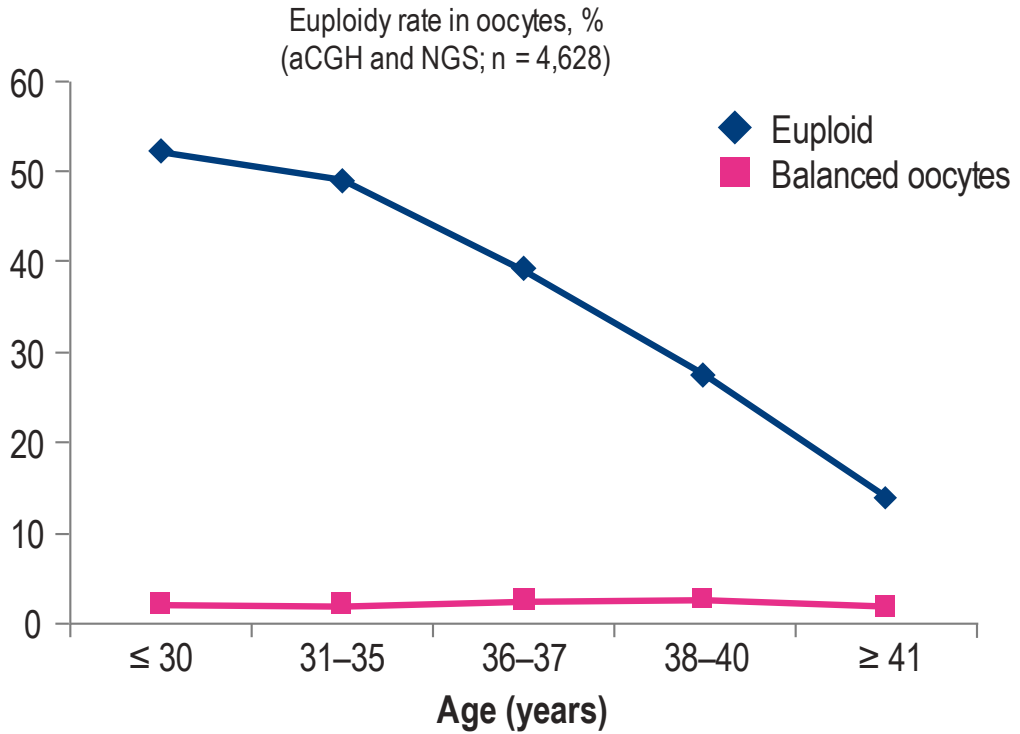


AFC, antral follicle count; AMH, anti-Müllerian hormone;
ART, assisted reproductive technology.

Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.
Humaidan P, et al. F1000Res. 2016;5:2911.
De Geyter C, et al. Swiss Med Wkly. 2015;145:w14087.

Aneuploidy and oocyte yield: FCH data

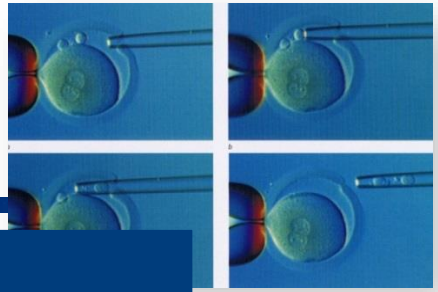




aCGH, array comparative genomic hybridization;
FCH, Fertility Center Hamburg; NGS, next-generation sequencing.

Ata B, et al. Reprod BioMed Online. 2012;24:614-20.
Fischer R. Personal data.

Aneuploidy and oocyte yield: FCH data



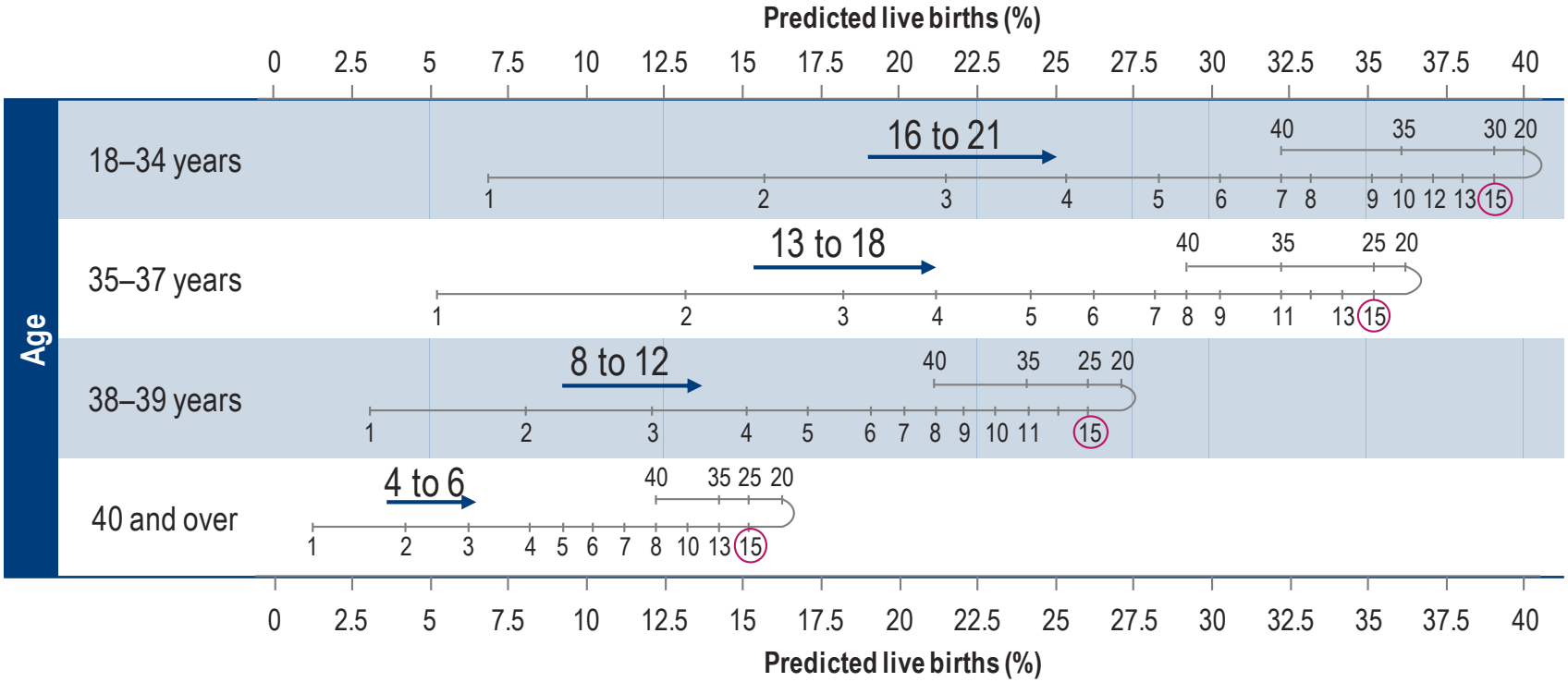
Day 5 embryos, n	Abnormal embryos				
	Egg donors	< 35 years old	35–39 years old	40–42 years old	> 42 years old
1–3	30%	40%	50%	70%	85%
4–6					
7–10					
> 10	7,753 embryos from 900 IVF cycles and 60 clinics				

60
50
40
30
20
10
0

aCGH, array comparative genomic hybridization;
FCH, Fertility Center Hamburg; NGS, next-generation sequencing.

Ata B, et al. Reprod BioMed Online. 2012;24:614-20.
Fischer R. Personal data.

The significance of one more oocyte



Sunkara SK, et al. Hum Reprod. 2011;26:1768-74.

Treatment strategies

- Pituitary suppression regimens
- Stimulation approaches
  - Conventional stimulation: gonadotrophin dose
  - Mild stimulation, natural cycle
  - Double stimulation
- Adjuvant therapies
  - DHEA, testosterone, LH
  - Growth hormone
- Oocyte/embryo accumulation

DHEA, dehydroepiandrosterone; LH, luteinizing hormone.

Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial

POR definition:

- Previous cancelled IVF cycle or ≤ 3 oocytes following stimulation with gonadotrophin ≥ 300 IU/ day
- Mean AFC < 7

POR, poor ovarian reserve.

Sunkara SK, et al. Fertil Steril. 2014;101:147-53.

Comparison of stimulation regimens

Characteristic	Agonist long regimen Group A (37)	Agonist short regimen Group B (37)	Antagonist regimen Group C (37)	Overall p value	A vs B p value	A vs C p value	B vs C p value
Stimulation days, mean ± SD	12.4 ± 2.7	10.5 ± 2.4	10.5 ± 2.5	0.006	0.005	0.009	0.91
Cancelled cycles, n	3 (8.1%)	4 (10.8%)	6 (16.2%)	0.82			
Oocytes retrieved, mean ± SD	4.42 ± 3.06	2.71 ± 1.60	3.30 ± 2.91	0.04	0.01	**0.21**	0.34
Fertilization rate	52.4%	48.6%	49.4%	0.28	0.52	0.18	0.61
Pregnancies, n	8	4	6				
Ongoing pregnancies, n	3	3	6				

SD, standard deviation.

Sunkara SK, et al. Fertil Steril. 2014;101:147-53.

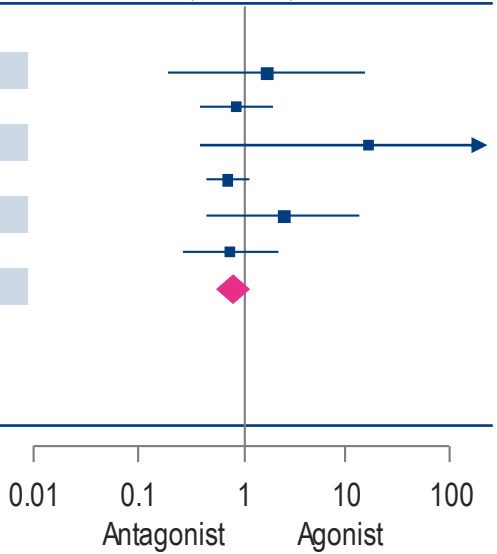
POR: GnRH antagonist vs long GnRH agonist

Ongoing pregnancy

Study or subgroup	GnRH antagonist Events	Total	GnRH agonist Events	Total	Weight	Risk ratio M–H, random, 95% CI
1.1.3 poor responders						
Cheung 2005	3	33	2	33	0.1%	1.50 (0.27–8.40)
Kim 2011	20	80	11	40	1.1%	0.91 (0.48–1.71)
Marci 2005	4	30	0	30	0.1%	9.00 (0.51–160.17)
Prapas 2013	39	182	51	182	3.3%	0.76 (0.53–1.10)
Sunkara 2014	6	37	3	37	0.3%	2.00 (0.54–7.40)
Tazegul 2008	8	48	10	48	0.6%	0.80 (0.35–1.85)
Subtotal (95% CI)		**410**		**370**	**5.5%**	**0.87** (0.65–1.17)
Total events	80		77			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.12$, df = 5 (p = 0.40); $I^2 = 2\%$

Test for overall effect: z = 0.89 (p = 0.37)



CI, confidence interval; GnRH, gonadotropin releasing hormone; M–H, Mantel–Haenszel.

Lambalk CB, et al. Hum Reprod Update. 2017;23:560-79.

FSH dose and number of oocytes retrieved

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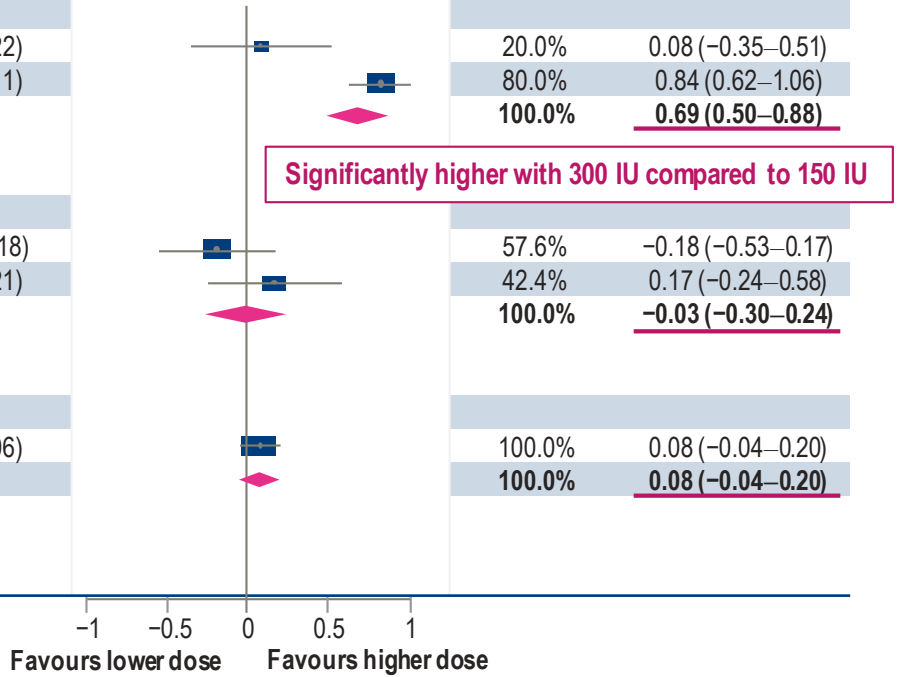
Study or subgroup	Mean difference (SE)	Weight	Mean difference IV, fixed, 95% CI
1 300/450 IU vs 150 IU			
Klinkert 2005	0.08 (0.22)	20.0%	0.08 (−0.35–0.51)
Van Tilborg 2017	0.84 (0.11)	80.0%	0.84 (0.62–1.06)
Subtotal (95% CI)		**100.0%**	**0.69 (0.50–0.88)**
Heterogeneity: $Chi^2 = 9.55$, df = 1 (p = 0.002); $I^2 = 90\%$			
Test for overall effect: z = 6.99 (p < 0.00001)			
2 400/450 IU vs 300 IU			
Bastu 2016	−0.18 (0.18)	57.6%	−0.18 (−0.53–0.17)
Harrison 2001	0.17 (0.21)	42.4%	0.17 (−0.24–0.58)
Subtotal (95% CI)		**100.0%**	**−0.03 (−0.30–0.24)**
Heterogeneity: $Chi^2 = 1.60$, df = 1 (p = 0.21; $I^2 = 38\%$)			
Test for overall effect: z = 0.23 (p = 0.82)			
3 600 IU vs 450 IU			
Lefebrve 2015	0.08 (0.06)	100.0%	0.08 (−0.04–0.20)
Subtotal (95% CI)		**100.0%**	**0.08 (−0.04–0.20)**
Heterogeneity: not applicable			
Test for overall effect: z = 1.33 (p = 0.18)			
Test for subgroup differences $Chi^2 = 34.43$, df = 2 (p = 0.00). $I^2 = 94\%$			



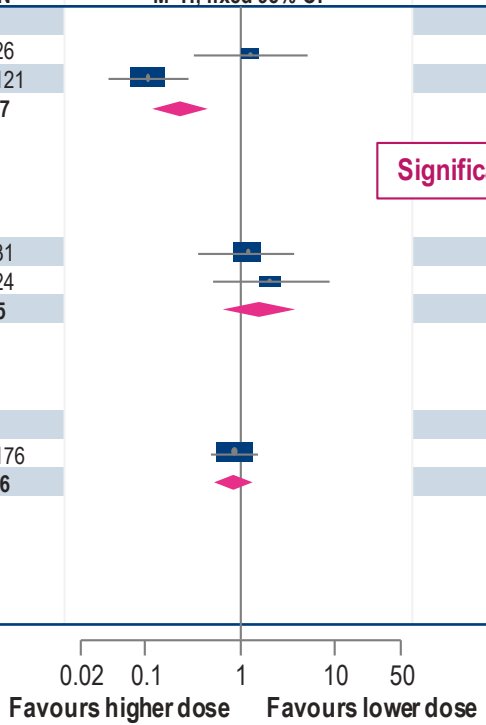
IV, instrumental variable; SE, standard error.

Lensen SF, et al. Cochrane Database Syst Rev. 2018;2:CD012693.

Cycles cancelled due to POR

Cochrane Library
Cochrane Database of Systematic Reviews

Study or subgroup	Higher dose n/N	Lower dose n/N	Odds ratio M–H, fixed 95% CI	Weight	Odds ratio M–H, fixed 95% CI
1 300/450 IU vs 150 IU					
Klinkert 2005	6/26	5/26		10.4%	1.26 (0.33–4.79)
Van Tilborg 2017	5/113	36/121		89.6%	0.11 (0.04–0.29)
Subtotal (95% CI)	**139**	**147**		**100.0%**	**0.23 (0.11–0.47)**
Total events 11 (higher dose), 41 (lower dose)					
Heterogeneity: $Chi^2 = 8.46$, df = 1 (p = 0.004); $I^2 = 88\%$					
Test for overall effect: z = 4.06 (p = 0.000049)					
2 400/450 IU vs 300 IU					
Bastu 2016	9/31	8/31		66.7%	1.18 (0.38–3.60)
Harrison 2001	7/24	4/24		33.3%	2.06 (0.51–8.25)
Subtotal (95% CI)	**55**	**55**		**100.0%**	**1.47 (0.62–3.49)**
Total events: 16 (higher dose), 12 (lower dose)					
Heterogeneity: $Chi^2 = 0.38$, df = I (p = 0.54); $I^2 = 0.0\%$					
Test for overall effect: z = 0.87 (p = 0.38)					
3 600 IU vs 450 IU					
Lefebrve 2015	29/180	32/176		100.0%	0.86 (0.50–1.50)
Subtotal (95% CI)	**180**	**176**		**100.0%**	**0.86 (0.50–1.50)**
Total events 29 (higher dose), 32 (lower dose)					
Heterogeneity: not applicable					
Test for overall effect: z = 0.52 (p = 0.60)					
Test for subgroup differences: $Chi^2 = 12.70$, df = 2 (p = 0.00). $I^2 = 84\%$					



Lensen SF, et al. Cochrane Database Syst Rev. 2018;2:CD012693.

Live birth/ongoing pregnancy rates

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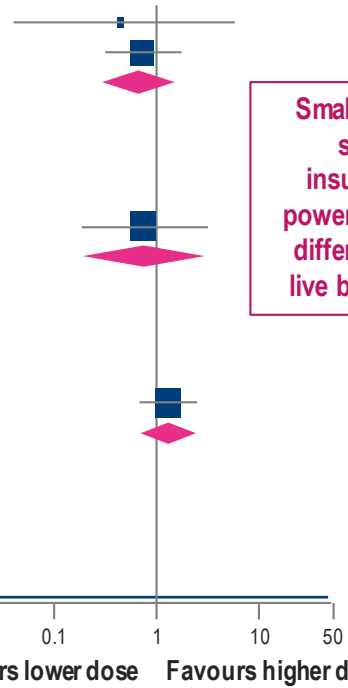
Study or subgroup	Higher dose Events	Higher dose Total	Lower dose Events	Lower dose Total	Weight	Odds ratio M–H, random, 95% CI
1.1.1 300/450 IU vs 150 IU						
Klinkert 2005	1	26	2	26	13.5%	0.48 (0.04–5.85)
Van Tilborg 2017	10	113	14	121	86.5%	0.74 (0.32–1.75)
Subtotal (95% CI)		**139**		**147**	**100.0%**	**0.71 (0.32–1.58)**
Total events	11		16			
Heterogeneity: $Chi^2 = 0.11$, df = 1 (p = 0.74); $I^2 = 0\%$						
Test for overall effect: z = 0.94 (p = 0.40)						
1.1.2 400/450 IU vs 300 IU						
Bastu 2016	4	31	5	31	100.0%	0.77 (0.19–3.19)
Subtotal (95% CI)		**31**		**31**	**100.0%**	**0.77 (0.19–3.19)**
Total events	4		5			
Heterogeneity: not applicable						
Test for overall effect: z = 0.36 (p = 0.72)						
1.1.3 600 IU vs 450 IU						
Lefebrve 2015	25	180	19	176	100.0%	1.33 (0.71–2.52)
Subtotal (95% CI)		**180**		**176**	**100.0%**	**1.33 (0.71–2.52)**
Total events	25		19			
Heterogeneity: not applicable						
Test for overall effect: z = 0.88 (p = 0.38)						
Test for subgroup differences: $Chi^2 = 1.62$, df = 2 (p = 0.44), $I^2 = 0\%$						



Small sample sizes, insufficient power to detect differences in live birth rates

Lensen SF, et al. Cochrane Database Syst Rev. 2018;2:CD012693.

Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria

N.P. Polyzos*, C. Blockeel, W. Verpoest, M. De Vos, D. Stoop, V. Vloeberghs, M. Camus, P. Devroey, and H. Tournaye

STUDY DESIGN, SIZE, DURATION: In this retrospective cohort trial, 164 consecutive patients, undergoing 469 natural cycle IVFs between 2008 and 2011 were included. Patients were stratified as poor and normal responders: 136 (390 cycles) were poor ovarian responders according to the Bologna criteria, whereas 28 women (79 treatment cycles) did not fulfil the criteria and were considered as normal responders.

MAIN RESULTS AND THE ROLE OF CHANCE: Live birth rates in poor responders according to the Bologna criteria were significantly lower compared with the control group of women; the live birth rate per cycle was 2.6 versus 8.9%, $P = 0.006$ and the live birth rate per treated patient was 7.4 versus 25%, $P = 0.005$. In poor responders according to the Bologna criteria, live birth rates were consistently low and did not differ among different age groups ($\leq$35 years, 36–39 years and $\geq$40 years), with a range from 6.8 to 7.9%.

SUMMARY ANSWER: Although natural cycle IVF is a promising treatment option for normal responders, poor ovarian responders, as described by the Bologna criteria, have a very poor prognosis and do not appear to experience substantial benefits with natural cycle IVF.

Polyzos NP, et al. Hum Reprod. 2012;27:3481-6.

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,i] and Laura Rienzi, M.Sc.[a,b,c]

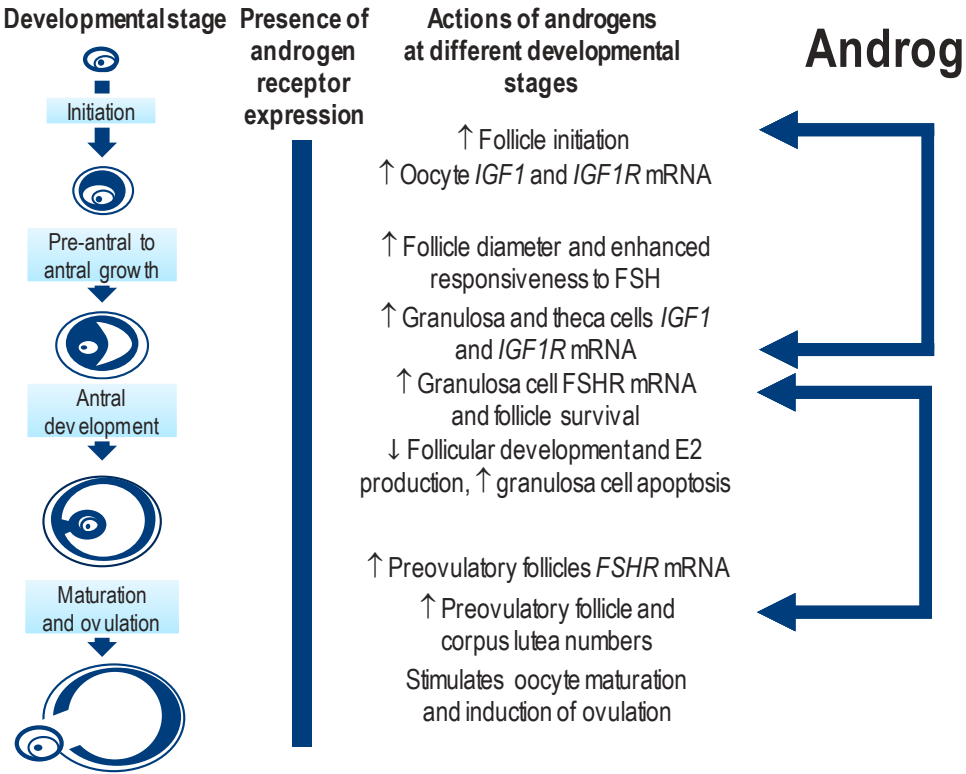
Preliminary clinical outcomes according to FPS or LPS

	Stimulation phase		
Outcome	**Follicular**	**Luteal**	**Total**
Number of SET	7	8	51
Number of clinical pregnancies	6	6	12
Number of miscarriages	1	1	2
Number of ongoing pregnancies	5	5	10

FPS, follicular phase stimulation;
LPS, luteal phase stimulation; SET, single-embryo transfer.

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

Should androgen supplementation be used for poor ovarian response?



Androgen studies: role in folliculogenesis

- Enhance initial recruitment and follicle development into small antral stages by decreasing atresia
- Enhance cyclic recruitment by improving FSH sensitivity of larger antral follicles

Walters KA, et al. Biol Reprod. 2008;78:380-9.

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journal homepage: www.elsevier.com/locate/ijgo

REVIEW ARTICLE

A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection

Jie Li [a,1], Hua Yuan [a,1], Yang Chen [b,1], Hongbo Wu [a], Huimei Wu [a], Liuming Li [a,*]

- **DHEA: 8 studies (2 RCT)**

Outcome	Pooled RR (95% CI)	I^2, %	p value for heterogeneity
Implantation rate	1.89 (0.91–3.94)	0.00	0.40
Clinical pregnancy rate	2.13 (1.12–4.08)	50.90	0.06
Spontaneous abortion rate	1.09 (0.39–3.07)	0.00	0.74
Number of oocytes retrieved	−0.23 (−1.43–0.96)	97.60	< 0.001

- Oocytes, n = 585: **decreased**
- Ongoing PR, n = 555: globally improved but **NS in RCT and case-control studies**
- Implantation rate, n = 306: **NS**
- Miscarriage rate, n = 281: **NS**

NS, not significant; PR, pregnancy rate;
RCT, randomized controlled trial; RR, relative risk.

Li J, et al. Int J Gynaecol Obstet. 2015;131:240-5.

DHEA supplementation

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When DHEA was compared with placebo or no treatment, pre-treatment with DHEA was associated with higher rates of live birth or ongoing pregnancy (OR 1.88, 95% CI 1.30 to 2.71; eight RCTs, N = 878, I^2 statistic = 27%, *moderate quality evidence*). This suggests that in women with a 12% chance of live birth/ongoing pregnancy with placebo or no treatment, the live birth/ongoing pregnancy rate in women using DHEA will be between 15% and 26%. However, in a sensitivity analysis removing trials at high risk of performance bias, the effect size was reduced and no longer reached significance (OR 1.50, 95% CI 0.88 to 2.56; five RCTs, N = 306, I^2 statistic = 43%). There was no evidence of a difference in miscarriage rates (OR 0.58, 95% CI 0.29 to 1.17; eight RCTs, N = 950, I^2 statistic = 0%, *moderate quality evidence*). Multiple pregnancy data were available for five trials, with one multiple pregnancy in the DHEA group of one trial (OR 3.23, 95% CI 0.13 to 81.01; five RCTs, N = 267, *very low quality evidence*).

Nagels HE, et al. Cochrane Database Syst Rev. 2015;11:CD009749.

Studies assessing DHEA supplementation

Conclusion:

- No scientific evidence for a clinically relevant benefit
- DHEA: weak androgenic activity partly converted into testosterone

Advantages:

- Low cost
- Administration for several months without side effects

MORE TRIALS NEEDED

Testosterone pretreatment

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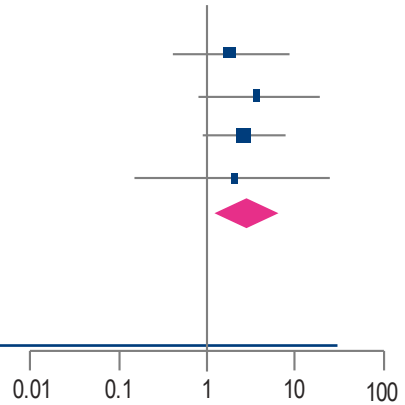
Live births

Study or subgroup	DHEA/T Events	DHEA/T Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Odds ratio M–H, Fixed, 95% CI
1.1.2 Testosterone						
Fabregues 2009	5	31	3	31	23.0%	1.79 (0.39–8.27)
Kim 2010	19	90	2	30	21.7%	3.75 (0.82–17.15)
Kim 2011	15	55	7	55	46.6%	2.57 (0.96–6.92)
Maasin 2006	2	27	1	26	8.6%	2.00 (0.17–23.49)
Subtotal (95% CI)		**203**		**142**	**100.0%**	**2.60 (1.30–5.20)**
Total events	41		13			

Heterogeneity: $Chi^2 = 0.49$, $df = 3$ ($p = 0.92$); $I^2 = 0\%$

Test for overall effect: $z = 2.69$ ($p = 0.007$)



Testosterone TRANSdermal gel for Poor Ovarian Responders Trial: T-TRANSPORT (PI: Nikos Polyzos)

- 400 patients
- Testosterone transdermal gel 65 days
- Control: placebo gel
- Long agonist regimen
- 300 IU hMG
- Multicentre (7); 4 countries

T, testosterone.

Nagels HE, et al. Cochrane Database Syst Rev. 2015;11:CD009749.

Studies assessing testosterone supplementation

Conclusion:

- No scientific evidence for clinically relevant benefit
  - In patients with DOR, a short-term (21 days) testosterone application does not increase the number of recruitable follicles
  - In patients with normal FSH, short-term testosterone supplementation might improve ovarian sensitivity to FSH
- Further studies are required for long-term administration!
  - Timing of theca cell stimulation
  - Stimulate recruitment prior to follicular growth

"Priming effect of LH"

MORE TRIALS NEEDED

DOR, diminished ovarian response.

LH pretreatment as a novel strategy for poor responders

	LH pretreatment	Previous cycles
Cycles	79	154
Cancellation rate	22%	51%
Number of collected oocytes	3.5	2.5
Fertilization rate	80%	83%
Cleavage rate	92%	62%
Transferred cycles (mean embryos/ET)	54	58
Implantation rate	22.3%	4%
Clinical pregnancy rate/ET	37%	7%
Early miscarriages	1	4
Live birth rate/started cycle	24%	0%
Live birth rate/patient	29%	0%

Long agonist 150 IU rLH for 4 days followed by 400 IU rFSH

ET, embryo transfer; rFSH, recombinant FSH; rLH, recombinant LH.

Ferraretti AP, et al. Biomed Res Int. 2014;2014:926172.

Rationale for GH supplementation in POR

GH exerts its effects through

- Its own receptor on granulosa cells
- Stimulation of IGF production (liver and ovary)

GH is an important regulator of ovarian function

- Steroidogenesis[1]
- Follicular development[2]
- Oocyte maturation[3]
- Increased expression of FSH and LH in granulosa cells[4]

GH and IGF1 act as co-gonadotrophins within the ovary

1. Nakamura E, et al. Endocrinology. 2012;153:469-80.
2. Bachelot A, et al. Endocrinology. 2002;143:4104-12.
3. Bevers MM, Izadyar F. Mol Cell Endocrinol. 2002;197:173-8.
4. Regan SL, et al. Mol Cell Endocrinol. 2017 May 5;446:40-51.

GH, growth hormone; IGF, insulin-like growth factor.

GH supplementation in POR

Does the addition of growth hormone to the in vitro fertilization/ intracytoplasmic sperm injection antagonist protocol improve outcomes in poor responders? A randomized, controlled trial

Prospective randomized study POR: Bologna criteria

Concept: GH acts as a co-gonadotropin

Gr A: hMG (300-450 IU)/d D3 + GH 2.5 mg (7.5 IU)/d D6 + Antagonist when foll ≥ 13 mm

Gr B: hMG (300-450 IU)/d D3

Variable	Group A, GH/hMG/GnRHant (n = 68)	Group B, GH/hMG/GnRHant (n = 73)	p value
Duration of hMG treatment, days	10.77	12.02	< 0.001
Duration of GnRHant treatment, days	6.86	7.98	< 0.001
Total doses of gonadotropin, IU	3,900	4,906	< 0.001
E2 levels on hCG day, pg/mL	1,862.47	854.44	< 0.001
P levels on hCG day, ng/mL	0.70	0.80	0.099
Endometrial thickness, mm	12.14	11.56	0.029
Number of collected oocytes	7.58	4.90	< 0.001
Number of MII oocytes	4.53	2.53	< 0.001
Number of fertilized oocytes	4.04	2.42	< 0.001
Number of transferred embryos	2.89	2.03	< 0.001
Number of frozen embryos	1.50	1.15	0.054
Number of cycles with frozen embryos per cycle start, n/n	20/68	13/73	0.104
Number of cycles with frozen embryos per embryo transfer n/N (%)	20/57 (35.1)	13/59 (22.0)	0.119

Improvement in ovarian parameters, but no significant difference in pregnancy rate

E2, estradiol; foll =, follicle; MII, metaphase II; P, progesterone.

Bassiouny YA, et al. Fertil Steril. 2016 Mar;105:697-702.

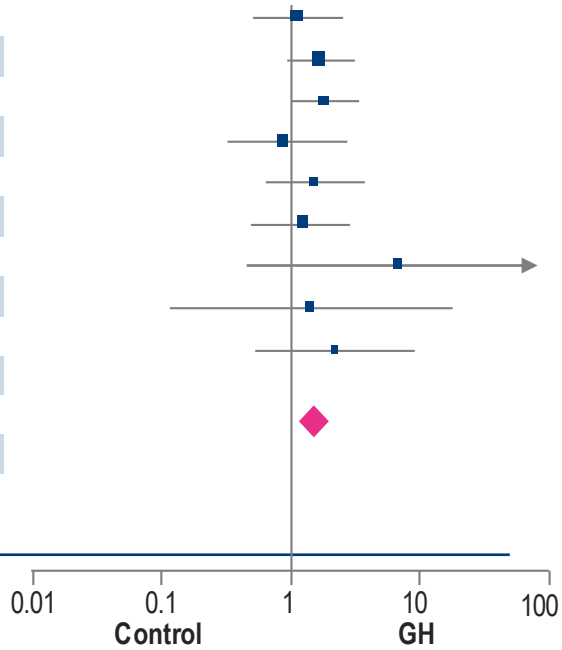
GH supplementation

Live births

Study or subgroup	GH Events	GH Total	Control Events	Control Total	Weight	Risk ratio M–H, Fixed, 95% CI
Bassiouny YA 2015	10	57	8	59	17.6%	1.29 (0.55–3.04)
Bayoumi YA 2015	22	72	12	73	26.7%	1.86 (1.00–3.47)
DE Liu 2005	12	31	9	49	15.6%	2.11 (1.01–4.41)
Erflekhar M 2013	5	33	5	33	11.2%	1.00 (0.32–3.13)
Guan Q 2007	7	20	4	20	9.0%	1.75 (0.61–5.05)
Kucuk T 2008	10	31	5	22	13.1%	1.42 (0.56–3.58)
Owen EJ 1991	4	13	0	12	1.2%	8.36 (0.50–140.56)
Suikkari A1996	2	8	0	2	1.7%	1.67 (0.11–25.83)
Zhuang GL 1994	4	12	2	15	4.0%	2.50 (0.55–11.41)
Total (95% CI)		**277**		**285**	**100.0%**	**1.73 (1.25–2.40)**
Total events	76		45			

Heterogeneity: $Chi^2 = 3.25$, $df = 8$ ($p = 0.92$); $I^2 = 0\%$

Test for overall effect: $z = 3.31$ ($p = 0.0009$)



Li XL, et al. Medicine (Baltimore). 2017;96:e6443.

Conclusions for GH therapy

- It is still uncertain whether GH therapy may actually improve LBR
- More evidence is needed for a positive effect on oocyte and embryo quality

Several issues to be addressed:

- Daily dose of GH
- Duration of GH therapy
- Cost effectiveness

MORE TRIALS NEEDED

LBR, live birth rate.

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

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

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

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

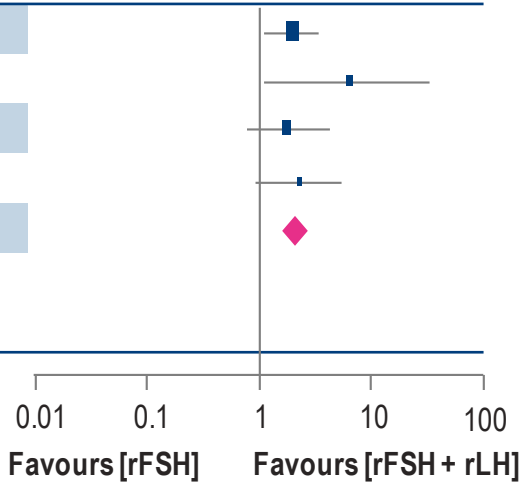
In women 35–39 years old, r-hLH supplementation improves implantation rate vs r-hFSH alone

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)



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

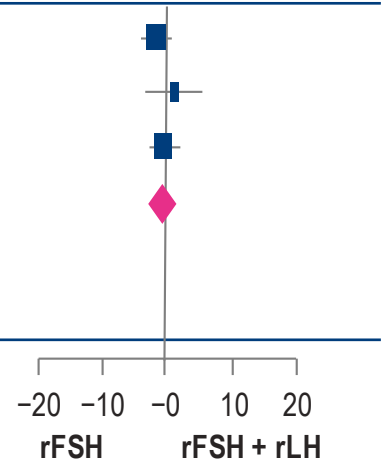
rLH in women 35–39 years: increase in implantation rate is associated with similar number of oocytes retrieved

Number of oocytes

Study or subgroup	rFSH + rLH			rFSH			Weight	Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total		IV, random, 95% CI	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 competence

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

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

P. Humaidan[1,2,*], W. Chin[3], D. Rogoff[4,†], T. D'Hooghe[5], S. Longobardi[5], J. Hubbard[4], and J. Schertz[4] on behalf of the ESPART Study Investigators[‡]

- 939 women aged 36-40 years, Bologna criteria for poor responders
- Long GnRH agonist regimen
- Randomized to:
  - rFSH (300 IU) + rLH (150 IU) (2:1 ratio), or
  - rFSH (300 IU)

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

ESPART trial

- No significant difference overall
  - Oocytes retrieved: 3.3 ± 2.71 vs 3.6 ± 2.82; p = 0.182
  - Live birth rate: 10.6% vs 11.7%; p = 0.663

Post hoc analysis:

- Significantly lower rate of pregnancy failures (miscarriage + ectopic pregnancy) with rFSH + rLH
  - 6.7% vs 12.4%; p = 0.005
- Significantly higher LBR rate in moderate and severe POR with rFSH + rLH
  - 11.0% vs 7.5%; p < 0.001
  - 9.6% v 4.5%; p = <0.001

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

POSEIDON group 3:
"Low reserve – good quality"

POSEIDON group 3
Young patients (< 35 years) with
poor ovarian reserve pre-stimulation parameters
(AFC < 5; AMH < 1.2 ng/mL)

Reasons for low response:
- Poor ovarian reserve
- Asynchronous development
- (Genetic polymorphisms in *FSHR*, *LHCGR*, *V-LHβ)*

iCOS treatment:
- Long GnRHa protocol
- GnRH antagonist (E2, NETA)
- Stimulation up to 300 IU/day rFSH (+rLH)
- DuoStim[2]
- Androgens? (testosterone)
- **Fresh transfer**
- **Oocyte/embryo accumulation and FET**

FET, frozen embryo transfer; FSHR, FSH receptor; LHR, LH receptor; NETA, norethisterone acetate.

1. Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.
2. Ubaldi FM, et al. Fertil Steril. 2016;105:1488-95.

Probability for one euploid blastocyst

Number of blastocysts	Probability of Patients with Euploid Embryos, % (Euploidy Rate, %)				
	Egg donors	< 35 years old	35–39 years old	40–42 years old	> 42 years old
1–3	**99** (69)	**95** (68)	**79** (49)	**61** (34)	**37** (17)
4–6	**100** (77)	**100** (73)	**97** (52)	**81** (31)	**67** (13)
7–10	**100** (62)	**100** (58)	**100** (48)	**97** (27)	**95** (22)
> 10	**100** (67)	**100** (59)	**100** (51)	**100** (41)	**100** (17)

Adapted from Ata B, et al. Reprod BioMed Online. 2012;24:614-20.

POSEIDON group 4:
"Poor reserve – poor quality"

POSEIDON group 4[1]
Older patients (≥ 35 years) with
poor ovarian reserve pre-stimulation parameters
(AFC < 5; AMH < 1.2 ng/mL)

Reasons for low response:
- Poor ovarian reserve
- Asynchronous development
- (Genetic polymorphism in *FSHR*, *LHR*, *V-LHβ)*

iCOS treatment:
- Long GnRHa protocol
- GnRH antagonist (E2, NETA)
- Stimulation up to 300 IU/day rFSH **and rLH**
- Androgens (testosterone)?
- GH?
- DuoStim[2]
- **Fresh embryo transfer**
- **Segmentation – oocyte/embryo accumulation and FET**
- **(Oocyte donation)**

NETA, norethisterone acetate.

1. Poseidon Group, Alviggi C, et al. Fertil Steril. 2016;105:1452-3.
2. Ubaldi FM, et al. Fertil Steril. 2016;105:1488-95.

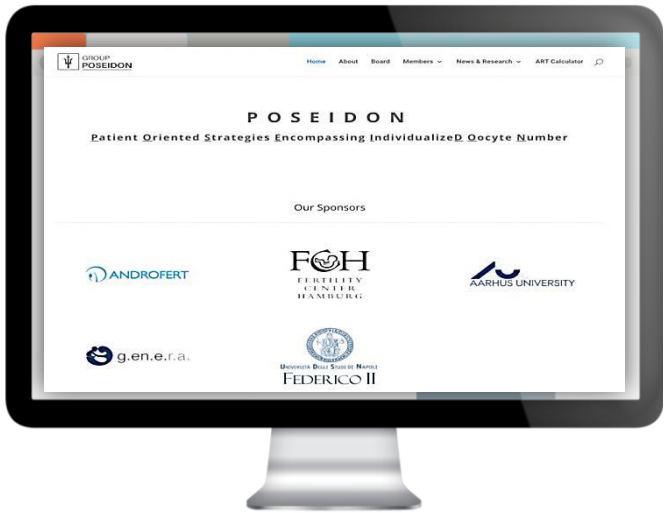
Transfer of euploid embryos eliminates the age-related decrease in implantation

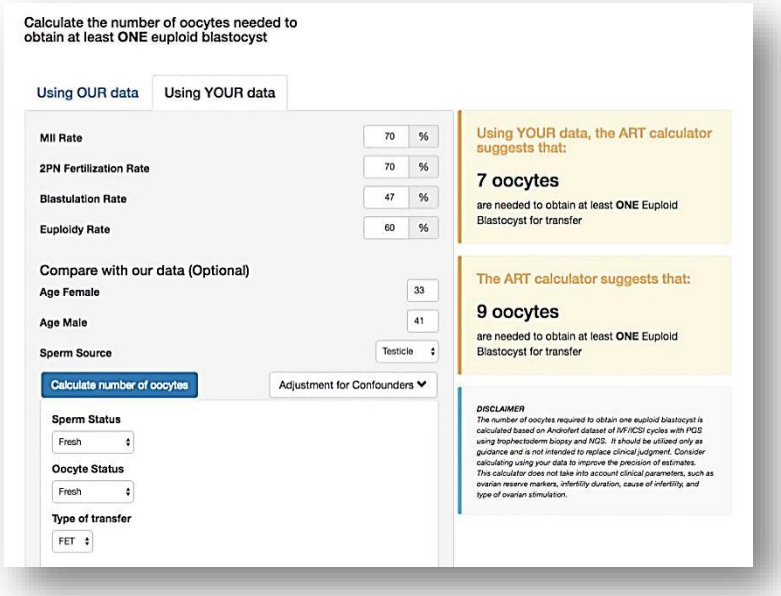
- In advanced maternal age, preliminary data comparing age-related implantation rates using:
  - aCGH (N = 258)
  - Polar bodies aneuploidy testing with PGS (FCH data)

PGS, preimplantation genetic screening.

Unpublished data.

POSEIDON ART Calculator: www.groupposeidon.com

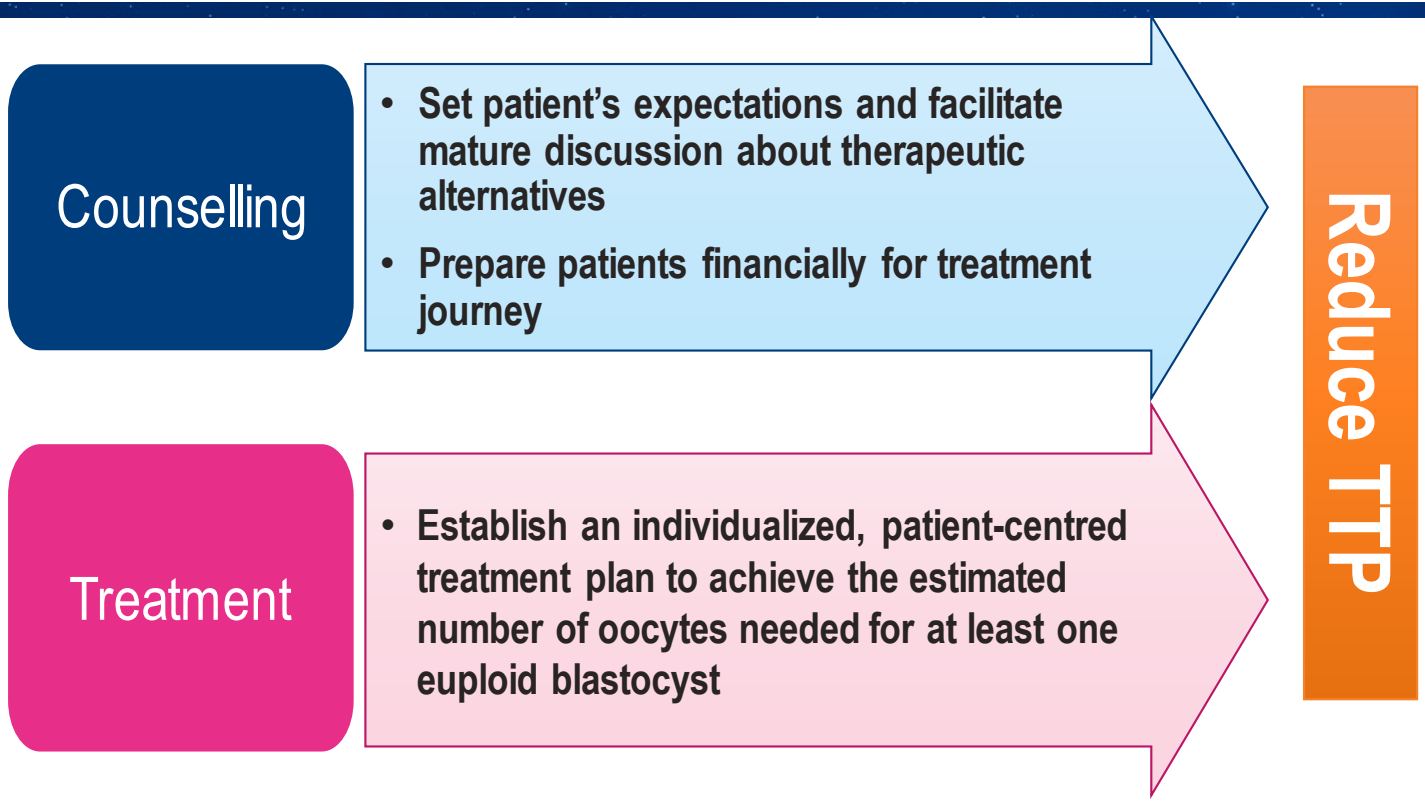




GROUP POSEIDON

Esteves SC, et al. Front Endocrinol (Lausanne). 2019;10:99.

Estimation of number of oocytes needed to obtain one euploid blastocyst for transfer proposed as an intermediate marker of success in ART

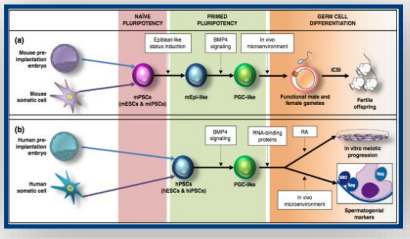


TTP, time to pregnancy.

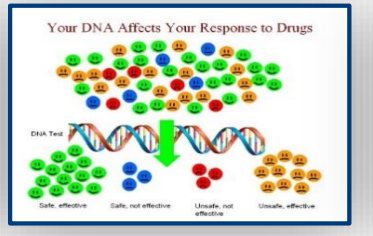
Courtesy of SC Esteves.

Future potential solutions for low prognosis

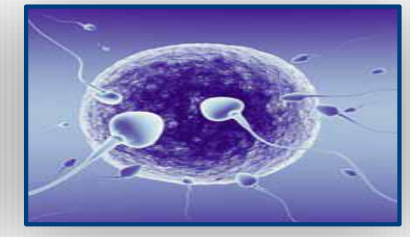
Stem cells



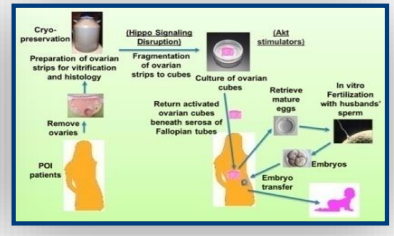
PGX



Gamete repairing



Follicle activation



PGX, pharmacogenetic testing.

Courtesy of P Humaidan.
Hayashi K, et al. Science. 2012;338:971-5.
White YA, et al. Nat Med. 2012;18:413-21.
Kawamura K, et al. Proc Natl Acad Sci USA. 2013;110:17474-9.

Conclusions

- Prediction, counselling, individualization
- GnRH agonist long and antagonist regimens are a suitable choice for poor responders
- Benefit from dose > 150 IU/day, but benefit is unlikely for gonadotrophin dose > 300 IU/day
- DuoStim
- LH supplementation
- Some evidence suggests adjuvant testosterone and GH could be beneficial
- However, robust RCTs are needed to evaluate the potential benefit
- Practical endpoints (i.e. the number of eggs to retrieve to have one euploid embryo) should be considered in clinical practice