Treatment of Poor Responders

Pathophysiology of Poor Responders

- Deficiency in systemic IGF-1 levels (Bahceci, 2007)
- Lower intra-ovarian T levels
- Reduced FSH receptor expression (Cai, 2007)

Bahceci, 2007, *Eur J Obstet Gynecol Reprod Biol*. 130:93–98
Cai, 2007,Fertil Steril;87:1350–1356

Predicting Ovarian Response

- The cohort of follicles that can be recruited by FSH is reflected in AFC and AMH measurements.
- A meta-analysis showed that AFC and AMH as single tests both had high predictive value for poor response (AUC 0.78 and 0.76, respectively) and that combining these two tests did not substantially improve prediction (AUC 0.80, P = 0.19)Broer, 2013)
- Other factors such as prior response, female age and, possibly, bodyweight may add to this predictive information.
- Certain SNP variants(Asn/Ser) of the FSH receptor may reflect a higher FSH sensitivity of follicles, leading to a better and more rapid ovarian response compared to the other two SNP variants.

Definition of Poor Responder

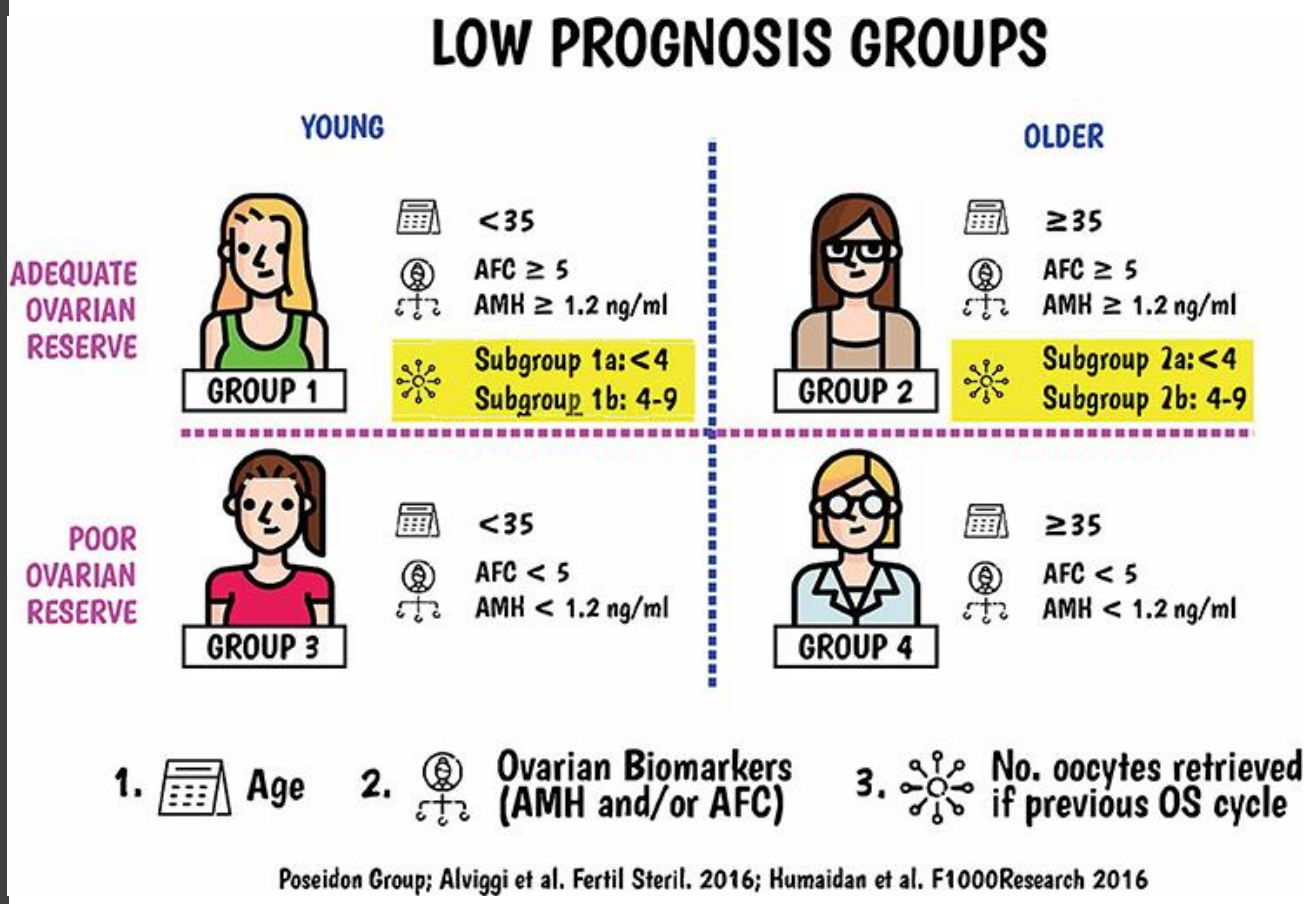
- There is no consistent definition of poor responder in the literature, although ESHRE established the Bologna criteria
- Lack of Uniform Criteria in publications-makes comparison of outcomes from various trials difficult
- A systematic review of 47 randomized controlled trials revealed 41 different definitions of POR
- Incidence: 9-26% of ART cycles

The Bologna criteria

- At least two of the following three features must be present:
  - Advanced maternal age (≥40 years) or any other risk factor for POR;
  - A previous POR (≤3 oocytes with a conventional stimulation protocol);
  - An abnormal ovarian reserve test (i.e. AFC <5–7 follicles or AMH <0.5–1.1 ng/ml).
  - In addition, two previous episodes of poor response after maximal stimulation are sufficient to classify the patient as poor ovarian response

The POSEIDON (**P**atient-**O**riented **S**trategies **E**ncom passing **I**ndividualize**D** **O**ocyte **N**umber) group—founded in 2015

- Purpose: to stratify patients with "expected" or "unexpected" impaired ovarian response to exogenous gonadotropins. Proposed a new measure for successful ART treatment, namely, the ability to retrieve the number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient



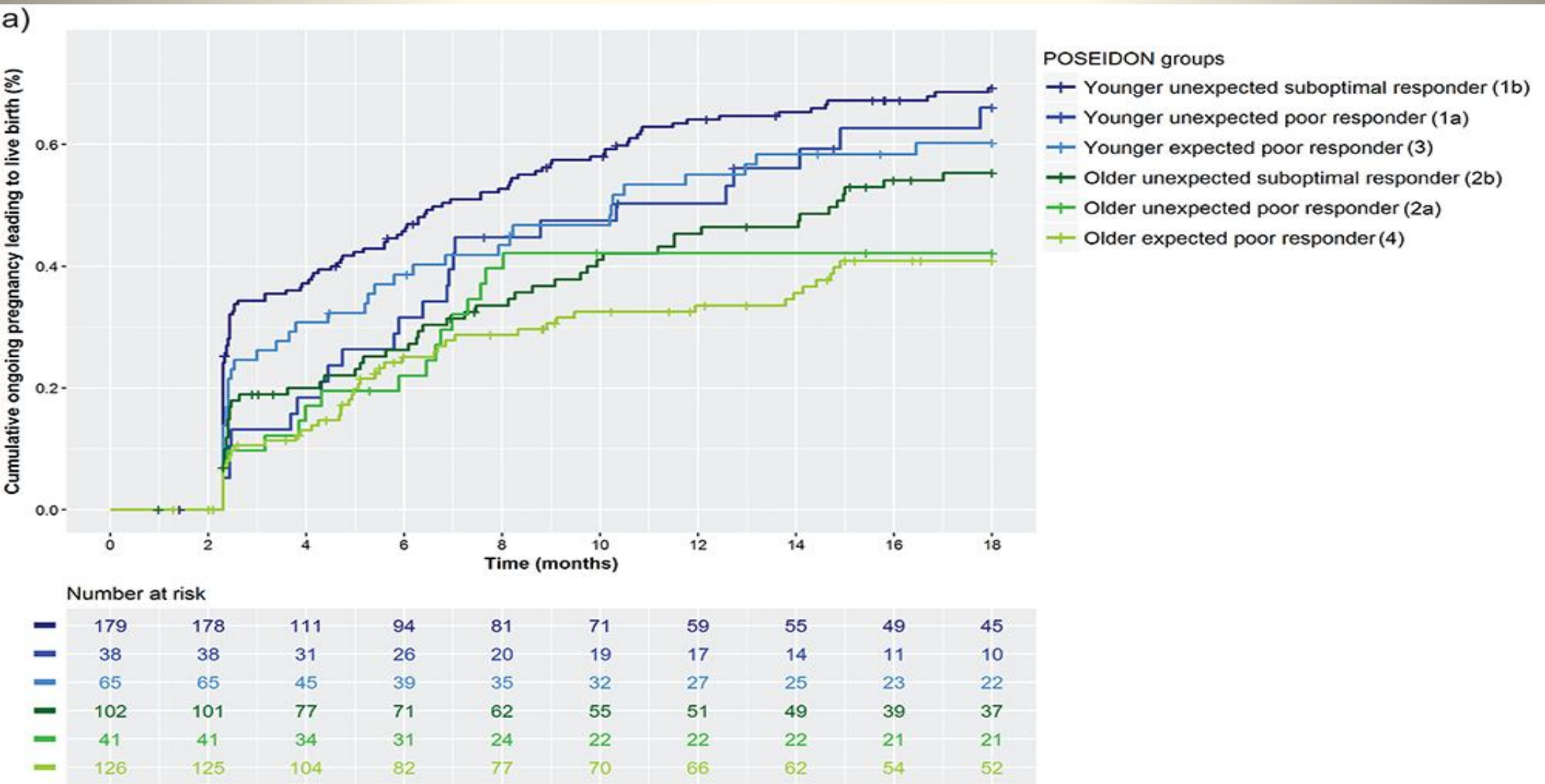
Cumulative live birth rates in low-prognosis women

Leijdekkers, *Human Reproduction*, Volume 34, Issue 6, June 2019, Pages 1030–1041,

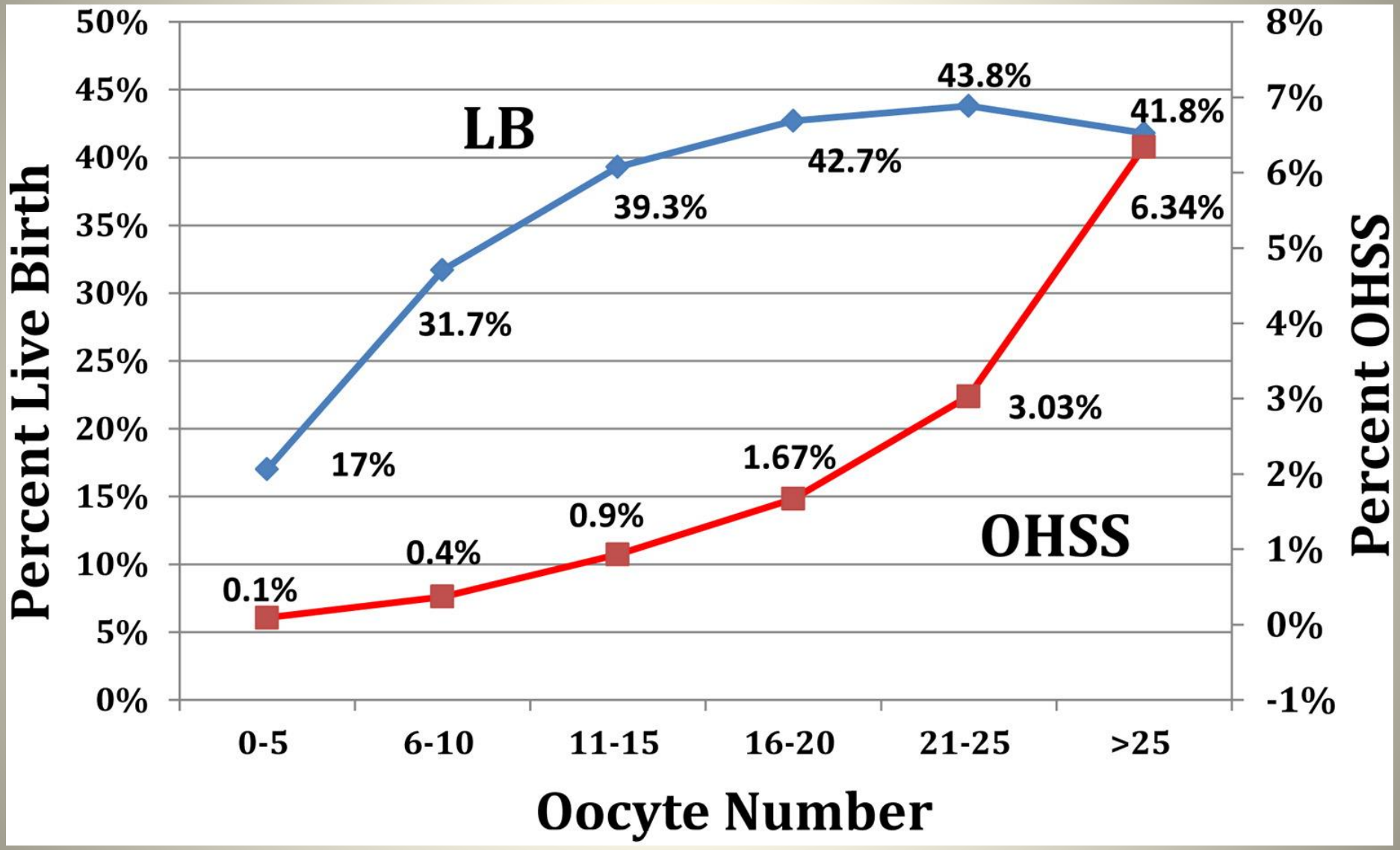
Low-prognosis women in IVF/ICSI treatment		
	Younger	**Older**
Unexpected	**POSEIDON group 1**	**POSEIDON group 2**
	• Female age: <35 years	• Female age: ≥35 years
	• Ovarian biomarkers: AFC ≥ 5 and/or AMH ≥ 1.2 ng/ml	• Ovarian biomarkers: AFC ≥ 5 and/or AMH ≥ 1.2 ng/ml
	• Ovarian response:	• Ovarian response:
	subgroup 1a, poor (<4 oocytes);	**subgroup 2a**, poor (<4 oocytes);
	subgroup 1b, suboptimal (4–9 oocytes)	**subgroup 2b**, suboptimal (4–9 oocytes)
Expected	**POSEIDON group 3**	**POSEIDON group 4**
	• Female age: <35 years	• Female age: ≥35 years
	• Ovarian biomarkers: AFC < 5 and/or AMH < 1.2 ng/ml	• Ovarian biomarkers: AFC < 5 and/or AMH < 1.2 ng/ml

Cumulative live birth curves for low-prognosis women over 18 months of IVF/ICSI treatment

Human Reproduction, Volume 34, Issue 6, June 2019, Pages 1030–1041

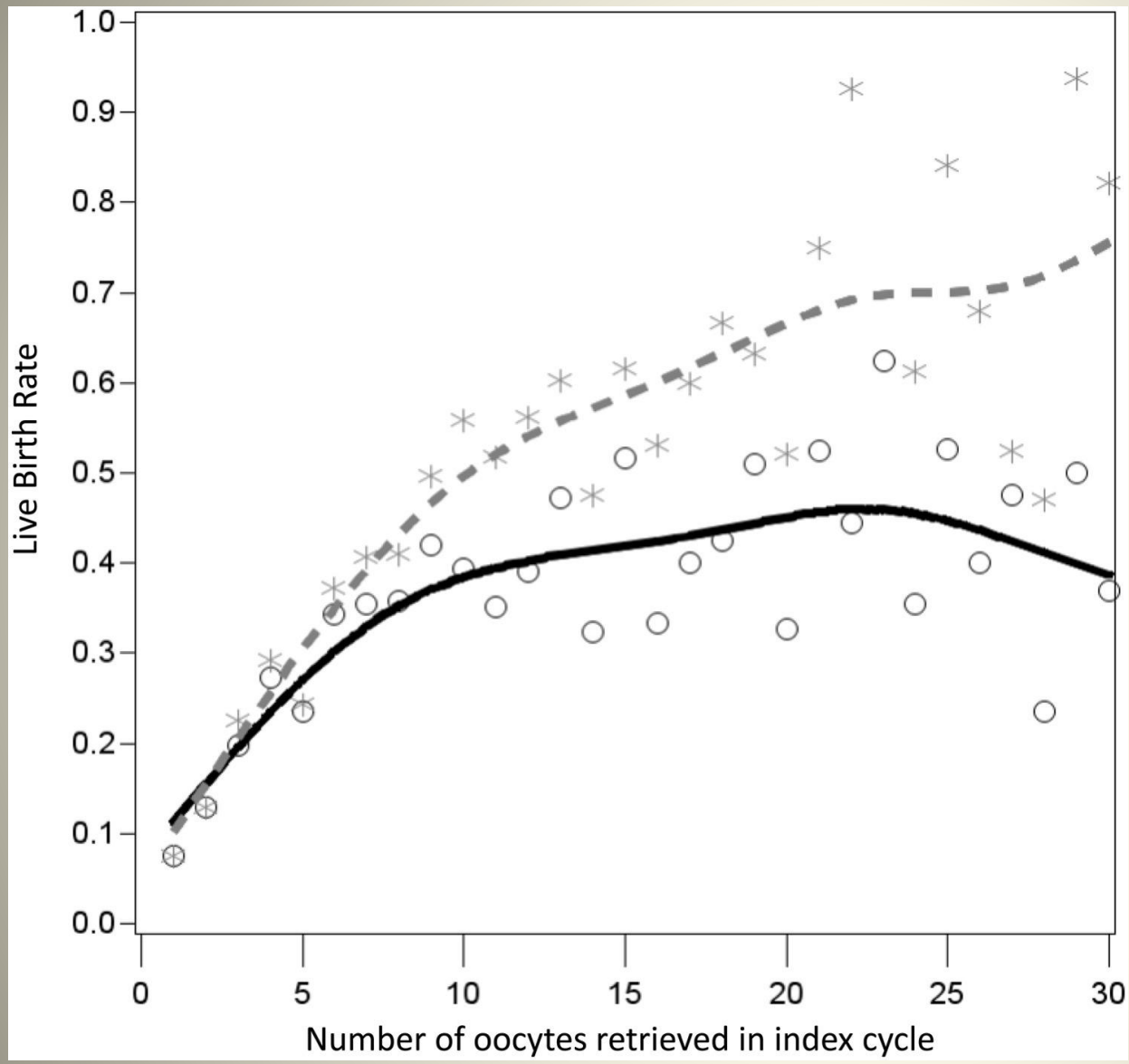


Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles



Steward, Fertility and Sterility 2014 101, 967-973DOI: (10.1016/j.fertnstert.2013.12.026)

How many oocytes are optimal to achieve multiple live births with one stimulation cycle? The one-and-done approach

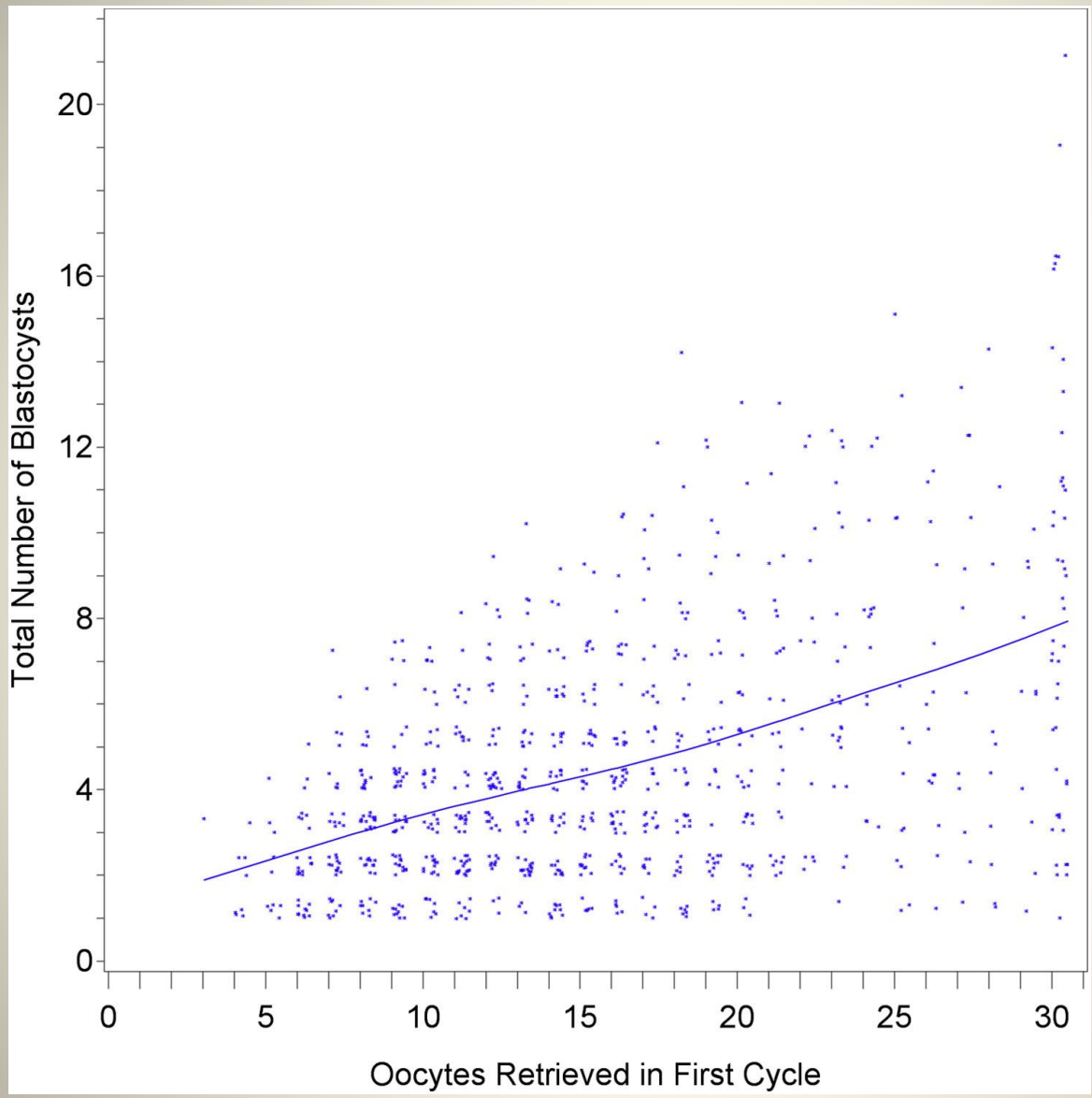


live-birth rate in the index cycle (*solid line*)

live-birth rate across all cycles (*broken line*) in relation to the number of oocytes retrieved.

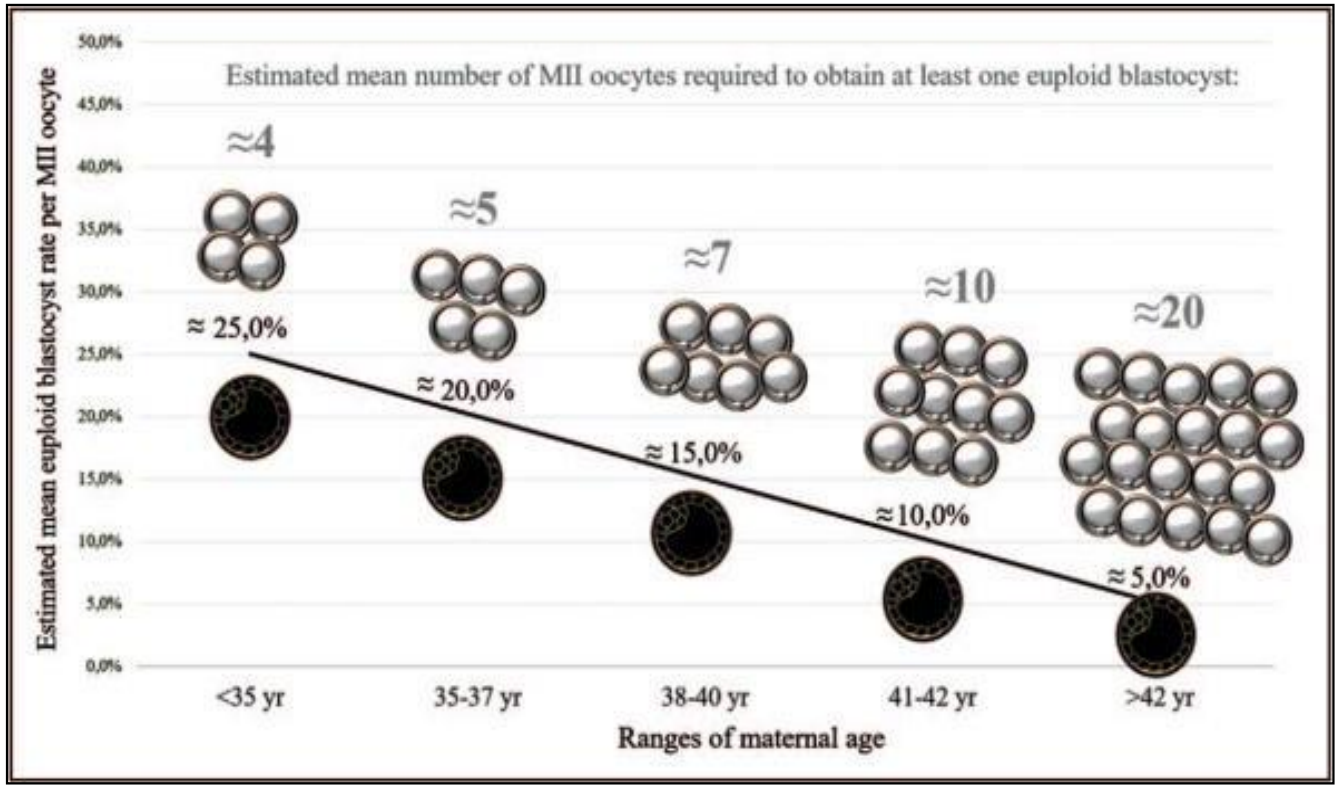
Vaughn, Fertility and Sterility 2017 107, 397-404.e3DOI: (10.1016/j.fertnstert.2016.10.037)

The number of useable blastocysts on days 5 and 6 in relation to the number of oocytes retrieved



Fertility and Sterility 2017 107, 397-404.e3DOI: (10.1016/j.fertnstert.2016.10.037)

FIGURE 1



What is new in the management of poor ovarian response in IVF?.
Vaiarelli, Alberto; Cimadomo, Danilo; Ubaldi, Nicolo; Rienzi, Laura; Ubaldi, Filippo

Current Opinion in Obstetrics & Gynecology. 30(3):155-162, June 2018.
DOI: 10.1097/GCO.0000000000000452

FIGURE 1 . Estimated mean number of metaphase II oocytes required to obtain at least one euploid blastocyst. The mean euploid blastocyst rates per MII oocyte according to the ranges of maternal age have been estimated based on an average 35% blastocyst rate per MII oocyte, which is independent from maternal age (GENERA data under review), and on the euploidy rate per blastocyst reported by Franasiak et al.[24] and Capalbo et al.[23[black small square]]. The blastocyst rate per MII oocyte has been estimated in the absence of male factor infertility. MII, metaphase II.

Potential Treatments for the Poor Responder

- Increase Gonadotropin dose
- Microdose Agonist Flare
- GnRH antagonists
- Luteal estrogen priming
- Luteal antagonist
- Addition of LH
- Aromatase inhibitors
- Clomiphene
- Adjunctive treatment with Testosterone or Growth hormone
- Minimal stimulation/natural cycle

450 IU versus 600 IU gonadotropin for controlled ovarian stimulation in poor responders: a randomized controlled trial

Characteristic	450 IU/d FSH (n = 171)	600 IU/d FSH (n = 175)	*P* value
No. of follicles at last US	7.0 (4.0–10.5)	8.0 (5.0–11.0)	.3
No. of oocytes retrieved	5 (0–8)	5 (3–9)	.15
No. of mature (MII) oocytes	4 (0–6)	4 (2–7)	.17
Fertilization rate	0.67 (0.50–0.86)	0.61 (0.33–0.80)	.22
No. of normally day 2 embryos	1 (0–3)	1 (0–3)	.54
No. of embryos (day of transfer)	1 (0–2)	1 (0–2)	.60
No. of transferred embryos	1 (0–1)	1 (0–1)	.91
No. of vitrified embryos	0 (0–1)	0 (0–1)	.26
Cycle outcome, % [b]			
Cycles with embryo transfer	56.7	60.0	.61
Biochemical pregnancy rate[c]	20.5	22.9	.68
Clinical pregnancy rate[c]	16.4	18.3	.74

Lefebvre, F&S, December 2015:104; 6, 1419

Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: The predicted poor responder

- Aimed to assess whether an increased gonadotrophin dose in women scheduled for IVF/ICSI with a predicted poor response based on a low AFC resulted in higher cumulative live birth rates.
- Women assigned to the higher dose group received 450 IU/day FSH if they had an AFC ≤ 7, In the standard dose group, women received 150 IU/day FSH

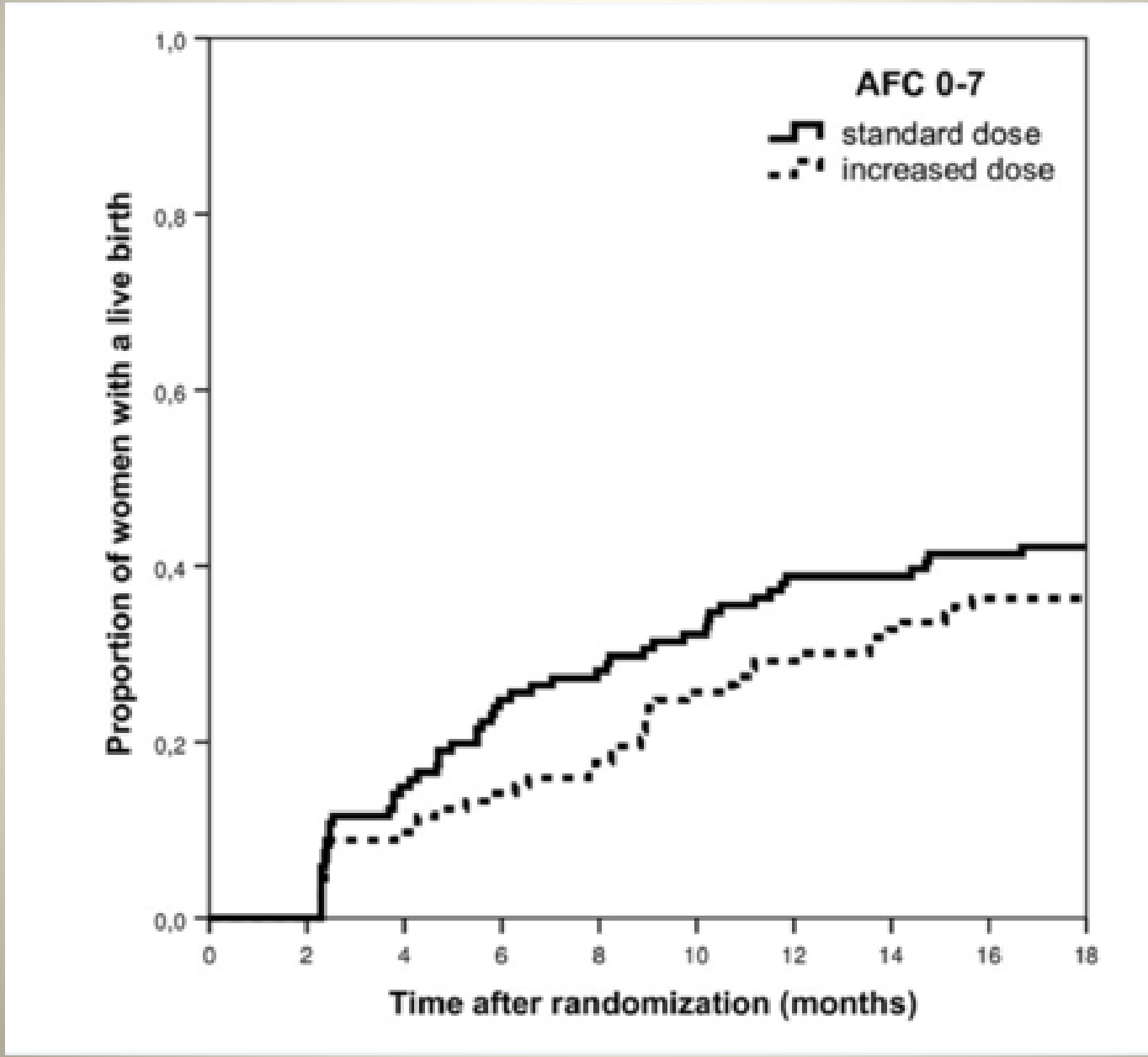
Tilborg, Human Reproduction, Volume 32, Issue 12, 1 December 2017, Pages 2496–2505

Overall treatment results in the 18 months follow-up

	AFC 0–7		
First cycle results	**450 IU (n = 113)**	**150 IU (n = 120)**	**P-value**
Total number of cycles started	236	255	
Dose increase between first and second cycle	0/78	61/84(72.6%)	
Cycles without cancellation	220/236(93.2%)	190/254(74.8%)	.001
No of oocytes	6.9 (4.8)	5.2 (4.0)	0.006
Poor response*	98/235(41.7%)	163/254(64.2%)	0.001
Live birth (fresh and cryo)	41(36.3%) 51(42.1)	0.36	

Tilborg, Human Reproduction, Volume 32, Issue 12, 1 December 2017, Pages 2496–2505

Cumulative live birth incidence curve in women with an AFC 0–7.



Tilborg, Human Reproduction, Volume 32, Issue 12, 1 December 2017, Pages 2496–2505

Do poor-responder patients undergoing IVF benefit from splitting and increasing the daily gonadotropin dose?

	Cycle using daily gonadotropin dose of 450 IU	Cycle using daily gonadotropin dose of 300IU bid	p
Patients' age <42 years			
Peak E2	1997.17 ± 1403.27	3889 ± 2908.53	0.02
Num fol >15	1.75 ± 1.29	3.67 ± 2.96	0.04
Mean number of oocytes retrieved	1.33 ± 0.89	2.75 ± 2.53	0.05
Patients' age ≥42 years			
Peak E2	2451.9 ± 1255.49	2912.1 ± 1497.72	0.5
Num fol >15	2 ± 0.94	3.5 ± 2.06	0.015
Mean number of oocytes retrieved	1.9 ± 0.99	3.5 ± 2.64	0.125

Osnat, E, Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. , 2019, p.1-4

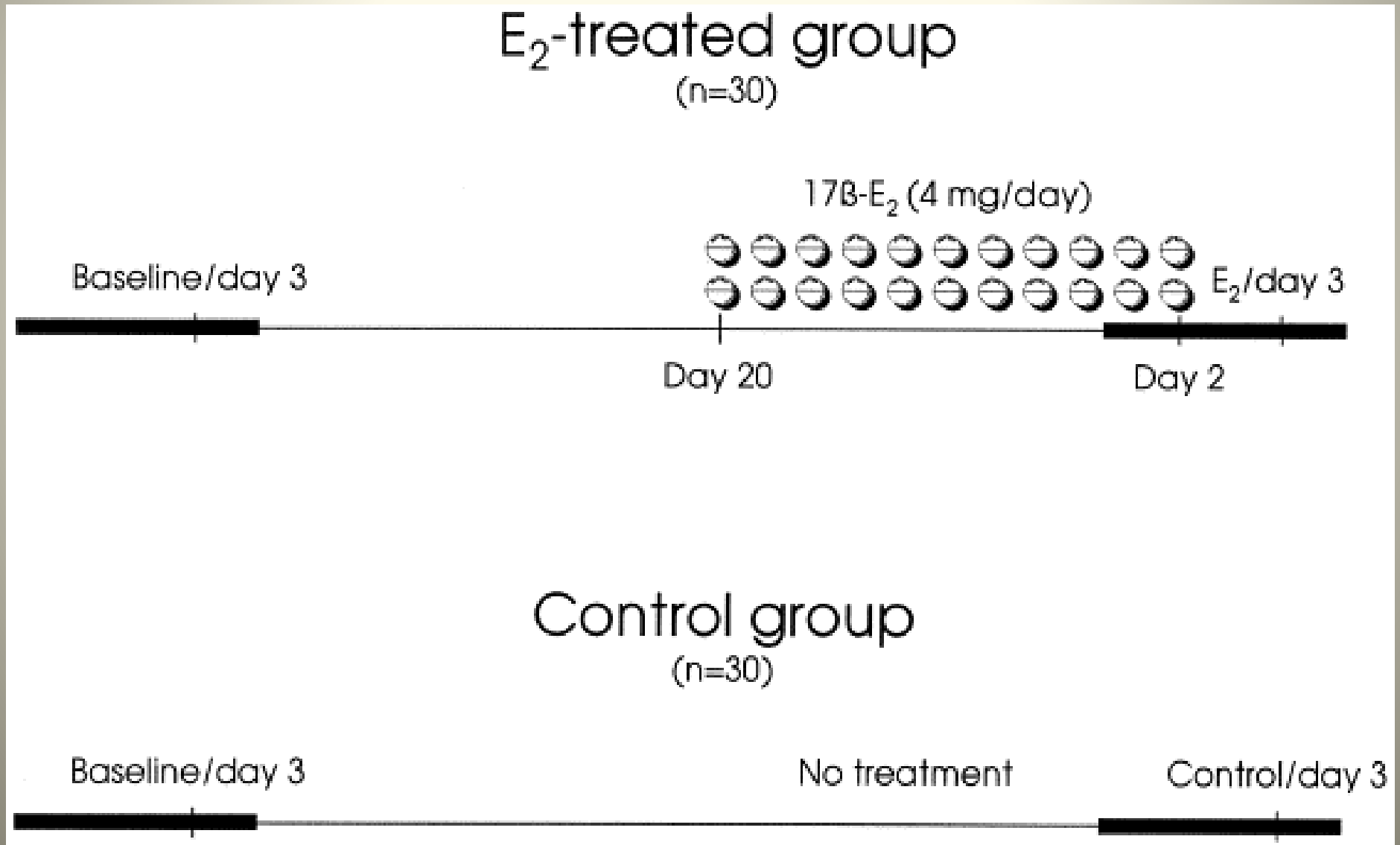
Antagonists for Poor Responders

- Avoid desensitization(seen with long agonist protocols) and thereby the eliminate the suppression of endogenous gonadotropins during the start of stimulation

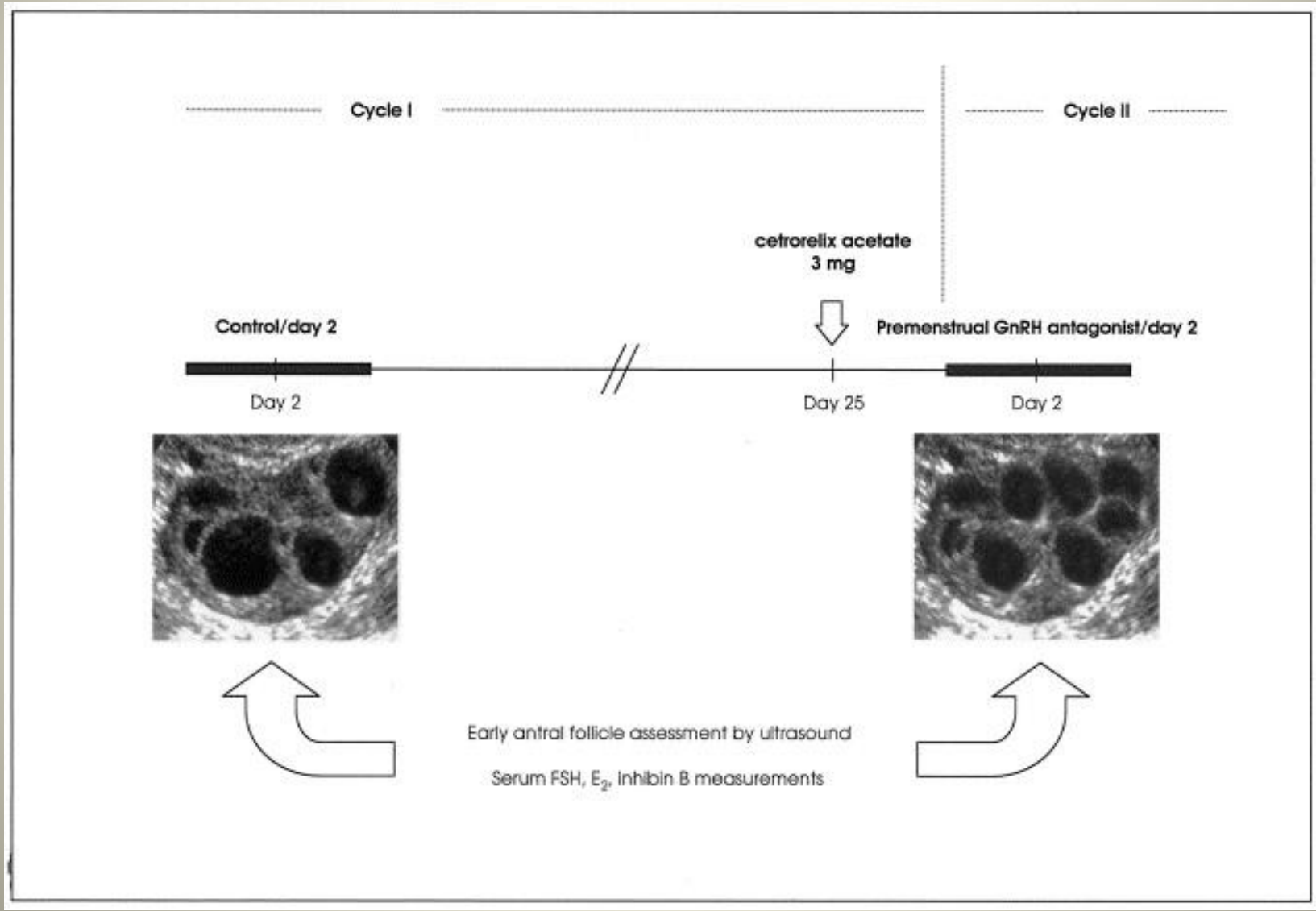
Evolution of luteal Estrogen and Antagonist Protocols

Fanchin, F&S, 2003

Luteal E-2 administration reduces the size and improves the homogeneity of early antral follicles on day 3

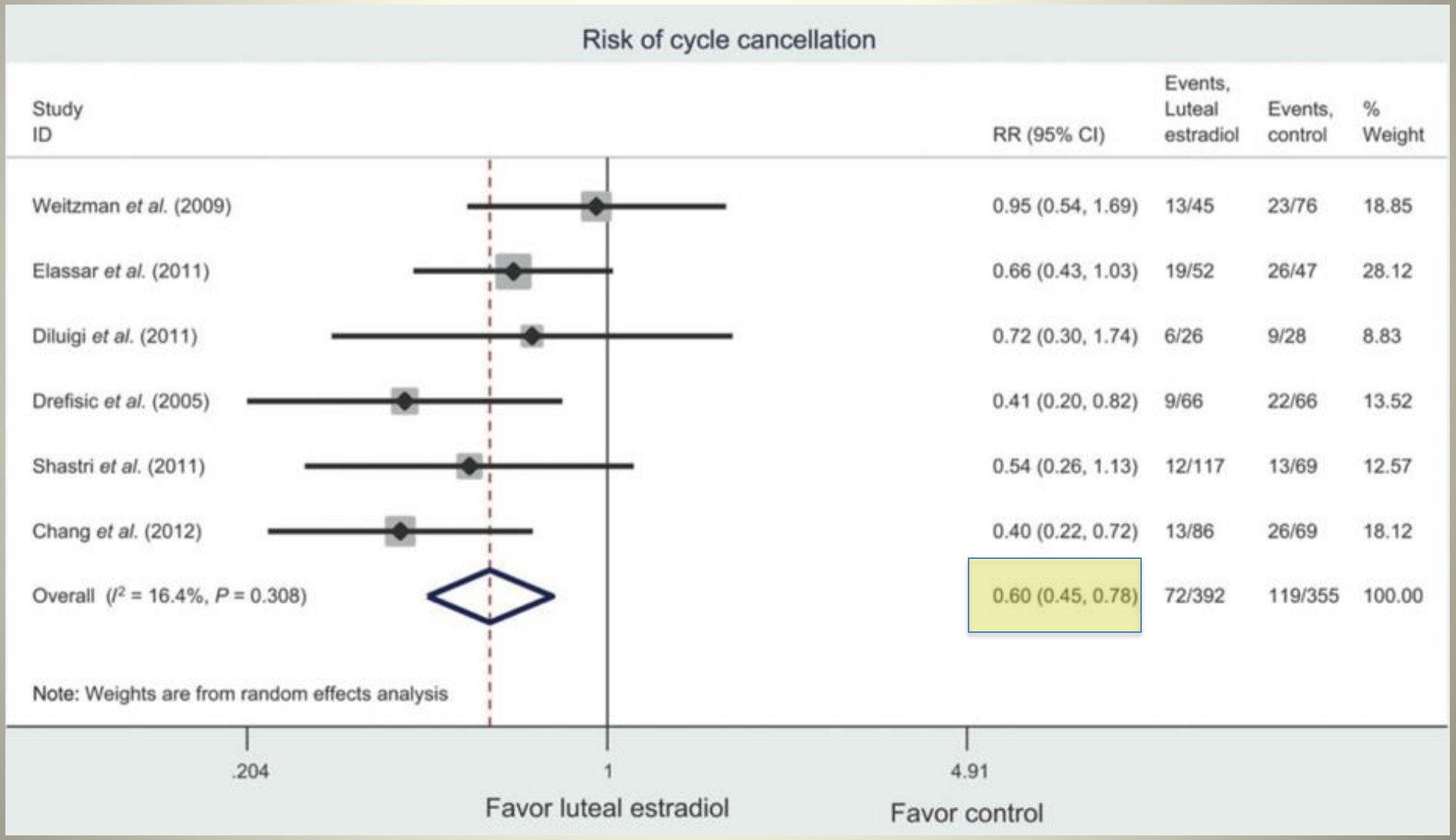


Luteal GnRH antagonist administration reduces size disparities of early antral follicles on day 2, likely through the prevention of luteal FSH elevation and early follicular development



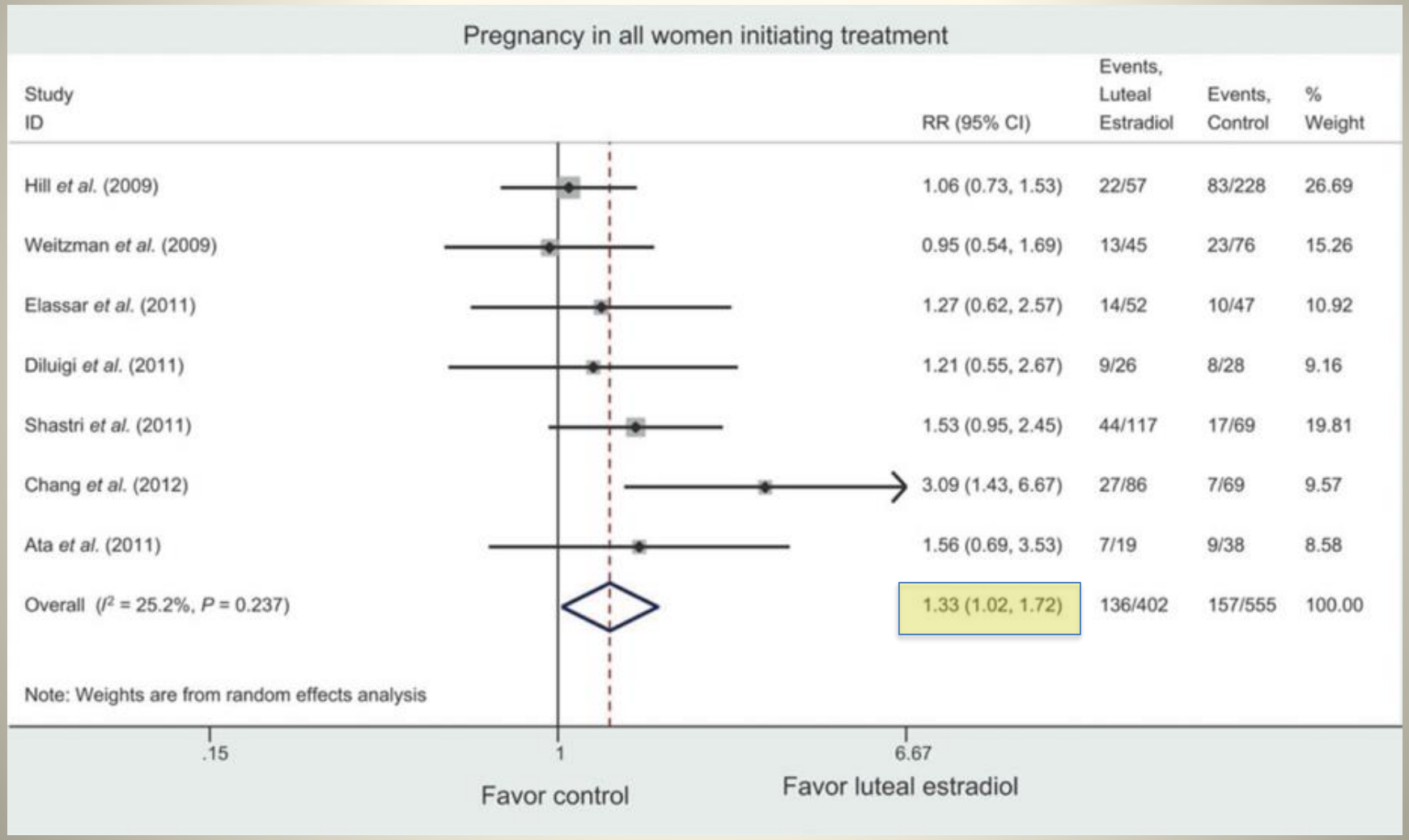
Fanchin, F&S, 2004:

Cycle cancellation and pregnancy after luteal estradiol priming in women defined as poor responders: a systematic review and meta-analysis



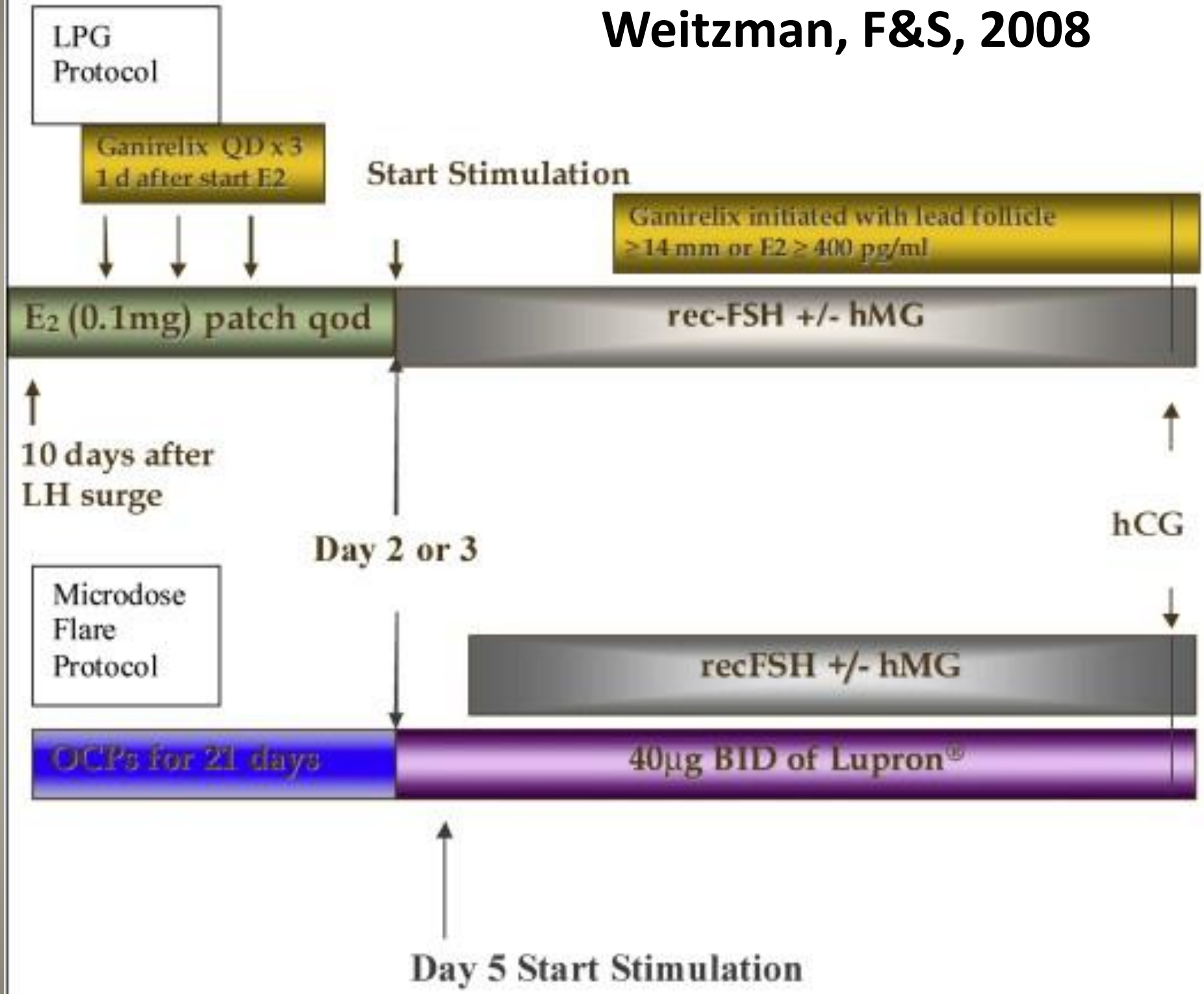
Human Reproduction, Volume 28, Issue 11, November 2013, Pages 2981–2989,

Cycle cancellation and pregnancy after luteal estradiol priming in women defined as poor responders: a systematic review and meta-analysis



Human Reproduction, Volume 28, Issue 11, November 2013, Pages 2981–2989,

Weitzman, F&S, 2008



Comparison of luteal estradiol patch and gonadotropin-releasing hormone antagonist suppression protocol before gonadotropin stimulation versus microdose gonadotropin-releasing hormone agonist protocol for patients with a history of poor in vitro fertilization outcomes

Weitzman, F&S, 2008

	LPG group	Microdose group	*P*
No. of cycles	45	76	
Peak E-2	1533	2141	<.05
Oocytes	9.1	8.9	NS
Embryos Transferred	2.5	2.7	NS
Cancellation Rate	29%	30%	NS
Implantation Rate	15%	12.5%	NS
Ongoing Pregnancy	30%	26%	NS

Comparison of microdose flare-up and antagonist multiple-dose protocols for poor-responder patients: a randomized study

Parameter	Microdose flare-up (n = 45)	Multiple dose antagonist (n = 45)	*P*
Age, years	39.51 ± 2.92	40.40 ± 3.04	.161
Stimulation day	12.11 ± 2.78	11.31 ± 2.63	.166
Total gonadotropin dose, IU	3675 ± 748	4200 ± 775	.002
Mean no. of follicles	5.3 ± 2.13	6.1 ± 2.06	.074
Cancellation rate, n (%)	3/45 (6.7%)	5/45 (11.1%)	.714
Mean no. of oocytes (metaphase II) retrieved	4.3 ± 2.13	3.1 ± 1.09	.001
Fertilization rate, %	75.02	68.42	.149
Mean no. of embryos transferred	3.5 ± 2.17	2.8 ± 1.13	.058
Implantation rate, %	22.13	11.00	.017
Clinical pregnancy rate, n (%)	12/42 (28.6)	6/40 (15.0)	.204

Demirol, Fertility and Sterility, 2009-08-01,
Volume 92, Issue 2, Pages 481-485

Conventional vs. minimal ovarian stimulation in poor responder women according to the Bologna criteria.

- Poor responders(Bologna criteria) underwent both one conventional antagonist (cOS) (n=46) and one mininal stimulation (mOS) protocol (n=46)
- mOS was performed with 50mg daily clomiphene citrate and low amounts of gonadotrophins every other day from 4th day of stimulation
- Mean age was 40.4 years, FSH of 11.3, AFC: 5.3, AMH: 0.79

Labarta, F&S, September, 2015

In poor responder patients according to Bologna criteria, mOS offers a significantly greater number of good quality embryos (grades A-B) as well as higher number of total and MII oocytes, with the use of significantly lower doses of gonadotropins per oocyte and embryo obtained.

	cOS (n=46 cycles)	mOS (n= 46 cycles)	Intra-patient mean difference (95% CI)	P value
Total dose of gonadotropins (IU)	2646.72±1551.89	730.25±313.29	738.77(367.99-1109.55)	P<0.05
Oocytes retrieved	2.29±1.71	3.17±1.89	-0.88 (-0.16-(-0.18))	P<0.05
MII Oocytes retrieved	1.95±1.73	2.68±1.65	-0.86 (-1.55-(-0.7))	P<0.05
E2 levels on last day of stimulation (pg/mL)	540.31±373.44	700.23±313.29	-177.32 (-336.82-(-17.82))	P<0.05
P4 levels on last day of stimulation (ng/mL)	0.4±0.31	0.46±0.34	-0.04 (-0.22-0.15)	NS
Correctly fertilized oocytes	1.40±1.45	2.28±1.11	-0.85 (-1.51-(-0.20))	P<0.05
Fertilization rate after ICSI (%)	54.89±44.63	73.87±32.42	-21.38 (-100-(-66.67))	P<0.05
Good quality embryos	0.67±0.66	1.29±1.18	-0.79 (-1.44-(-0.14))	P<0.05
Amount of gonadotropins per MII oocyte (IU/MII oocyte)	1668.52±1350.65	297.19±183.83	1301.83(797.57-1806.09)	P<0.05
Amount of gonadotropins per good quality embryo (IU/A+B* embryo)	2578.12±2016.47	572.36±361.61	2194.37 (618.49-3770.26)	P<0.05

FSH level by Protocol

Protocol	Dose of FSH	Stim Day	E2	FSH level
Min Stim	150+CC	5	545	17.1
Antagonist	450	5	171	19.2

Modified natural IVF in patients with “genuine” poor response

- 111 patients who fulfilled two of the three Bologna criteria and also yielded a maximum of three oocytes after COH
- MNC-IVF: natural cycles with GnRH antagonist supplementation (0.25 mg/day; started when a follicle of 13 mm was present. 150-225 IU of hMG were co-administered daily during the antagonist treatment

Kedem, F&S, 2014, 101:1624

	MNC (average ± SD)	IVF (previous cycle)	*P* value
No. of cycles	111		
Age (y)	39 ± 4		
Day 3 FSH levels (IU/L)	9.3 ± 5.4		
E_2 level on hCG day (pmol/L)	299.0 ± 237.0	668.0 ± 461.0	.0001
P on hCG day (nmol/L)	0.57 ± 0.75	0.64 ± 0.51	NS
Average total dose of gonadotropins used (ampules)	14.0 ± 6.0	55.0 ± 23.0	<.001
Endometrial thickness (mm)	8.5 ± 1.8	8.9 ± 1.7	NS
Mean no. of retrieved oocytes	0.88 ± 0.96	1.65 ± 0.88	<.0001
Mean no. of 2PN	0.54 ± 0.69	0.86 ± 0.82	<.0001
Fertilization rate	0.67 ± 0.43	0.55 ± 0.44	NS
No. of cycle resulting with no oocyte at OPU	43	8	<.0001
No. of embryos transferred	0.5 ± 0.6	0.8 ± 0.8	<.002
No. of cycle resulting in ET (% of all cycles)	59 (53)	95 (85)	<.0001
Clinical PR per cycle (no. of patients)	0.9% (1)	0	
Ongoing PR per cycle (no. of patients)	0.9% (1)	0	
Delivery rate per cycle (no. of patients)	0.9% (1)	0	

Kedem, F&S, 2014, 101:1624

Alternative strategies to manage poor responders:

- Increasing follicle sensitivity to FSH
  - Testosterone
  - DHEA
  - Dexamethasone
  - Growth Hormone

Vendola in a primate model showed that an amount of systemically applied T which raised the circulating T concentration into the low male range, was capable of increasing preantral and antral follicles

Number of antral follicles, percentage staining for Ki57 (a nuclear protein associated with cellular proliferation), percentage showing apoptosis and the circulating testosterone (T) level (ng/dL) in monkeys treated with dihydrotestosterone, 20 μg/kg per day of T for 5 days, and 400 μg/kg pe day of testosterone for 10 days.

Parameter	Antral follicles (no.)	Proliferation (Ki67, %)	Apoptosis (%)	T level (ng/dL
Control	3.2	20.0	60.7	38.3
Dihydrotestosterone	8.3 (P=.038)	53.3[a]	17.7[a]	46.4
T 20 μg/kg for 5 d	8.7 (P=.018)	44.5[a]	16.8[a]	443.0[a]
T 400 μg/kg for 10 d	15.5[a]	40.0[a]	19.8[a]	1,345.0[a]

[a] $P < .001$.

Meldrum. Androgens in ovarian response to aging. Fertil Steril 2013.

Transdermal Testosterone for Poor Responders

- Androderm patch 2.5 mg) (20 mcg/kg per day for 5 days(Fábregues et al, Hum Reprod 2009 24:349-359)
  - Percentage of cycles with poor response was lower in T group (32.2% vs. 71%, $p<.05$)
  - Trend towards lower cancellation rate (19.4% vs. 41.9%, $p=.09$)
- Androgel(12.5 mg daily x 21 days(Kim et al, Fertil Steril 2011;95:679-83)
  - Significant ↑ in mature and fertilized oocytes, good quality embryos, implantation and clinical pregnancy rates with TTG

DHEA Meta-analysis

Kolibianakis, O-084,Eshre abstract, 2016

- Seven eligible RCTs evaluating a total of 576 patients were meta-analyzed
- No significant differences were observed in the number of oocytes retrieved, the number of 2-pronuclei oocytes and in the number of embryos transferred
- DHEA did not improve the probability of clinical pregnancy (RR: 1.10; 95% CI: 0.81–1.50) or live birth (RR: 1.18; 95% CI: 0.36–3.88) as compared to no DHEA treatment

Growth Hormone for Poor Responders

- Poor responders have low IFG-1 levels
- GH stimulates granulosa cell proliferation and ovarian response to FSH through IFG-1 synthesis
- Higher intrafollicular GH levels have been correlated with oocyte and embryo competence

GH and Poor Responders: Meta-Analysis

Kolibianakis et al, Hum Reprod Update 2009; 15:613-22

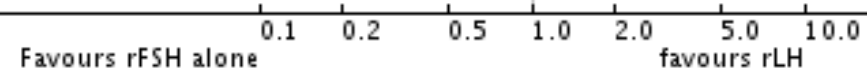
- 6 RCTs including 169 patients
- 17% ↑ live birth rate (95% CI: 5-30)
  22% ↑ % in patients undergoing ET (95% CI: 7-30)
- High degree of heterogeneity makes interpretation difficult: Definition of poor responders, GH dose, duration, and ovarian stimulation protocol

Comparison of rLH and rFSH versus rFSH alone for COH in GnRH agonist dowregulated IVF/CSI cycles in poor responders, Outcome: Ongoing pregnancy per woman randomized.

Review: Recombinant Luteinizing Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles
Comparison: 3 rLH and rFSH versus rFSH alone for COH in GnRH agonist dowregulated IVF/CSI cycles in poor responders
Outcome: 1 Ongoing pregnancy per woman randomised

Study or subgroup	rLH and rFSH n/N	rFSH alone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Barrenetxea 2006	8/36	7/36		25.7 %	1.18 [0.38, 3.70]
De Placido 2005	19/65	13/65		43.5 %	1.65 [0.74, 3.71]
Ferraretti 2004	22/54	11/54		30.8 %	2.69 [1.14, 6.33]
Total (95% CI)	**155**	**155**		**100.0 %**	**1.85 [1.10, 3.11]**

Total events: 49 (rLH and rFSH), 31 (rFSH alone)
Heterogeneity: Chi² = 1.40, df = 2 (P = 0.50); I² =0.0%
Test for overall effect: Z = 2.32 (P = 0.020)



Lower apoptosis rate in human cumulus cells after administration of recombinant luteinizing hormone to women undergoing ovarian stimulation for in vitro fertilization procedures

Ruvolo F&S, 2007

TdT assay and caspase-3 immunoassay in cumulus cells.

Study group	Cells (n)	Positive TdT (%)	Positive caspase-3 immunoassay (%)
Control group ± SD	568 ± 72	18.2	17.0
LH group ± SD	612 ± 76.5	12.1	11.0

Note: TdT, terminal deoxynucleotidyl transferase

Ruvolo. Apoptosis in human cumulus cells. Fertil Steril 2007.

Patients with poor oocytes yield, (<50%) number of oocytes retrieved per number of follicles > 14 mm in diameter on day of hCG administration
Given double trigger(hcg and agonist) in subsequent cycle

Comparison between IVF cycles with hCG versus double trigger (GnRH-ag + hCG)

	hCG	Double trigger	p values
Number of gonadotropin ampoules used	38.5 ± 24.5	49.8 ± 15.4	ns
Length of stimulation (days)	10.7 ± 2.5	10.7 ± 2.2	ns
Total number of gonadotropin used	39 ± 25	49 ± 15	ns
Peak E2 levels on day of hCG administration (pmol/l)	5402 ± 1983	4642 ± 2483	ns
Progesterone levels on day of hCG administration (nmol/l)	1.7 ± 0.9	1,5 ± 0.7	ns
Number of follicles of >14 mm on day of hCG administration	8.0 ± 3.5	6.4 ± 4.3	ns
Number of follicles of >10 mm on day of hCG administration	10.6 ± 5.8	8.2 ± 4.3	ns
Number of oocytes retrieved	2.3 ± 2.5	7.0 ± 4.6	p < 0.02
Number of 2PN embryos	1.7 ± 1.2	6.0 ± 4.6	p < 0.002
Number of top quality embryos	0.4 ± 0.5	3.7 ± 0.8	p = 0.06
Number of embryos transferred	0.85 ± 0.9	2.2 ± 0.7	p < 0.002
Number of oocytes retrieved per number follicles of >14 mm on day of hCG administration (%)	23.7 ± 21.5	118.0 ± 71.2	p < 0.01
Number of oocytes retrieved per number follicles of >10 mm on day of hCG administration (%)	18.5 ± 16.6	80.3 ± 31.1	p < <0.001
Positive hCG (%)	0 (0/8)	62.5% (5/8)	p < 0.001
Clinical ongoing pregnancy (%)	0 (0/8)	37.5% (3/8)	p < 0.03

Haas J, J Ovarian Res. 2014 Aug 2;7:77. doi: 10.1186/1757-2215-7-77

Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates

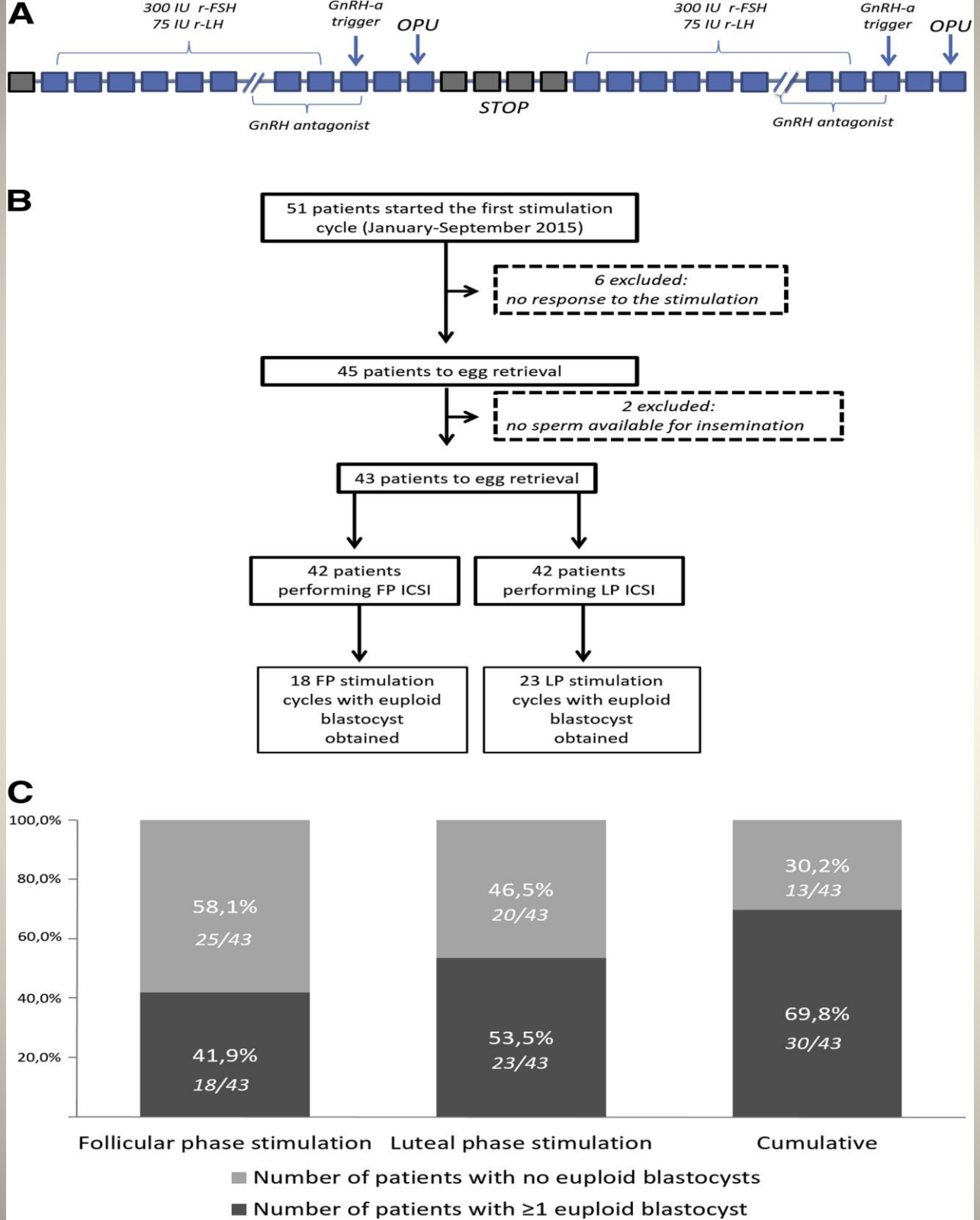
Griffin, Fertility and Sterility, Vol. 102, Issue 2, p405–409

Variable	Prior cycle (n = 27)	Dual trigger (n = 27)	*P* value
Outcome of ovarian stimulation			
Total days of stimulation	10 (8–11)	10 (9–11)	NS
Total dose of gonadotropins (IU)	4,200 (2,575–6,000)	5,400 (3,300–6,750)	.02
Oocytes retrieved (n)	9 (4–14)	11 (5–16)	.02
Mature oocytes (n)	3 (1–5)	7 (4–9)	<.01
% of mature oocytes	38.5 (16.7–55.6)	75.0 (55.6–80.0)	<.01
Fertilization rate (%)	66.7 (40.0–100.0)	83.3 (72.4–93.8)	NS
Embryos transferred (n)	1 (0–2)	2 (2–3)	NS
Endocrine profile			
Peak E_2 (pg/mL)	1,490 (1,142–2,752)	1,661 (1,163–2,162)	NS
E_2, day after trigger (pg/mL)	2,032 (1,140–3,827)	1,904 (1,176–2,592)	.01
P, day after trigger (ng/mL)	2.6 (1.9–4.0)	4.0 (2.9–5.2)	<.01
LH, day after trigger (IU/L)	NA	54.2 (36.0–81.4)	NA
hCG, day after trigger (IU/L)	135 (96–190)	203 (128–297)	<.01

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

- Patients with reduced ovarian reserve—AMH level of ≤1.5 ng/mL, AFC ≤6 follicles, and/or ≤5 oocytes retrieved in a previous cycle
- Blastocyst stage CCS
- Mean age: 39.2
- Mean FSH: 12.3 Mean
- AMH 0.7
- Mean antral follicle count: 5.2

Ubaldi, F&S, 2016



The number of patients who could cumulatively obtain a euploid blastocyst increased from 18 of 43 (41.9%) to 30 of 43 (69.8%) when including the luteal phase-derived blastocysts. Twelve patients (27.9%) had euploid blastocysts exclusively after the luteal phase stimulation.

Ubaldi, F&S, June 2016, 105, 6, 1488–1495

Data according to follicular and luteal phase stimulation.

	Follicular	Luteal	P value
Days of stimulation	9.6	10.3	NS
Oocytes	5.1	5.7	NS
Blastocysts	1.2	1.4	NS
Euploid Blastocyst	0.6	0.7	NS
Euploid Blast/M-2 oocyte	16.2%	15%	NS
Implantation Rate	71.4%	62.5%	

Ubaldi, F&S, June 2016, 105, 6, 1488–1495

Optimal embryo transfer strategy in poor response:cleavage vs blastocyst

Berkkanoglu M, J Assist Reprod Genet. 2016 Nov 10.

Live birth rates of poor responders according to the to the chosen embryo transfer strategy

	Poor response group A ≤4 oocytes(cleavage stage)	Poor response group B ≤4 oocytes(blastocyst stage)	*p* value
Number of OPU	645	234	
Total ET	482 (74.7 %)	146 (62.3 %)	<0.001
Day 3 LBR per ET	30 (21.7 %)	NA	
Day 5 LBR per ET	NA	18 (30.5 %)	
Day 5 FET LBR per ET	NA	42 (48.2 %)	
Total LBR per OPU	16.1 %	25.6 %	0.002

In the subgroups, the PR, clinical PR, and LBR increased from the lowest in subgroup A1 (day 2 cleavage stage) to the highest in subgroup B2 (blastocyst FET). In that subgroup, the IR was 47.0 % and the LBR per ET was 48.2 %

Patient Preparation

- Poor nutrition, obesity, stress, smoking, alcohol, and caffeine all negatively impact IVF
- Pre-cycle life-style modification can improve cycle outcome
- Antioxidants may improve outcome

Oxidative Stress and IVF

- Follicular fluid reactive oxygen species(ROS) negatively impact IVF*
- Total antioxidant capacity(TAC) positively impact IVF*
- ROS induce granulosa cell apoptosis**

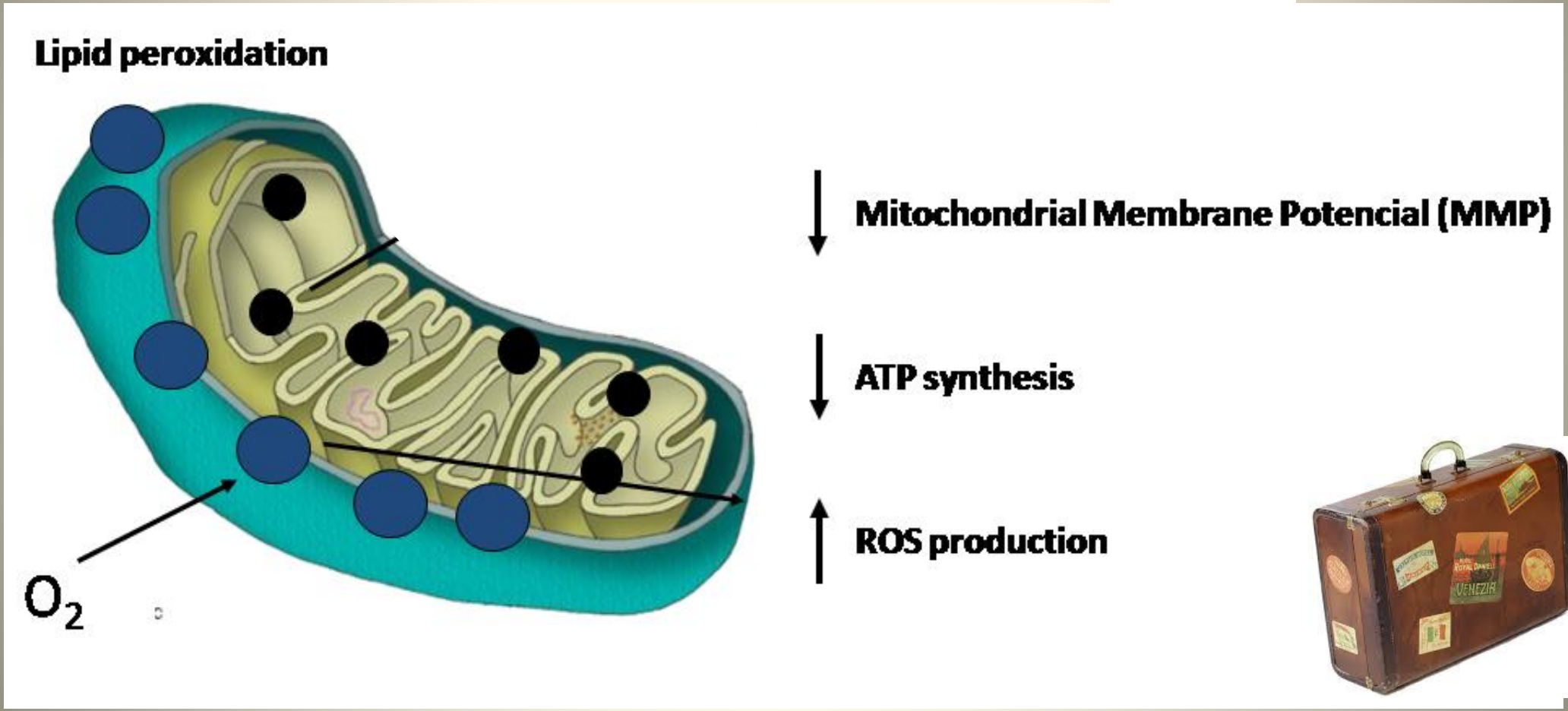
*Bedaiwy, Gyncol Endocrinol 2012;28:51

**Devine, Biol Reprod 2012;86:27

ACAI Study CCRM
n=93 FETs:

- 54% overall blastocyst euploid rate
- 35% more oocytes vs prior non-acai cycle; P=0.0001)
- 40% more fertilized zygotes vs prior non-acai cycle; P=0.0003)
- 84.9% clinical pregnancy with fetal heart tone
- 6.3% miscarriage rate
- 79.6% ongoing pregnancy/live birth rate

With age mitochondria in cells becomes dysfunctional, partly as a result of accumulating mtDNA mutations



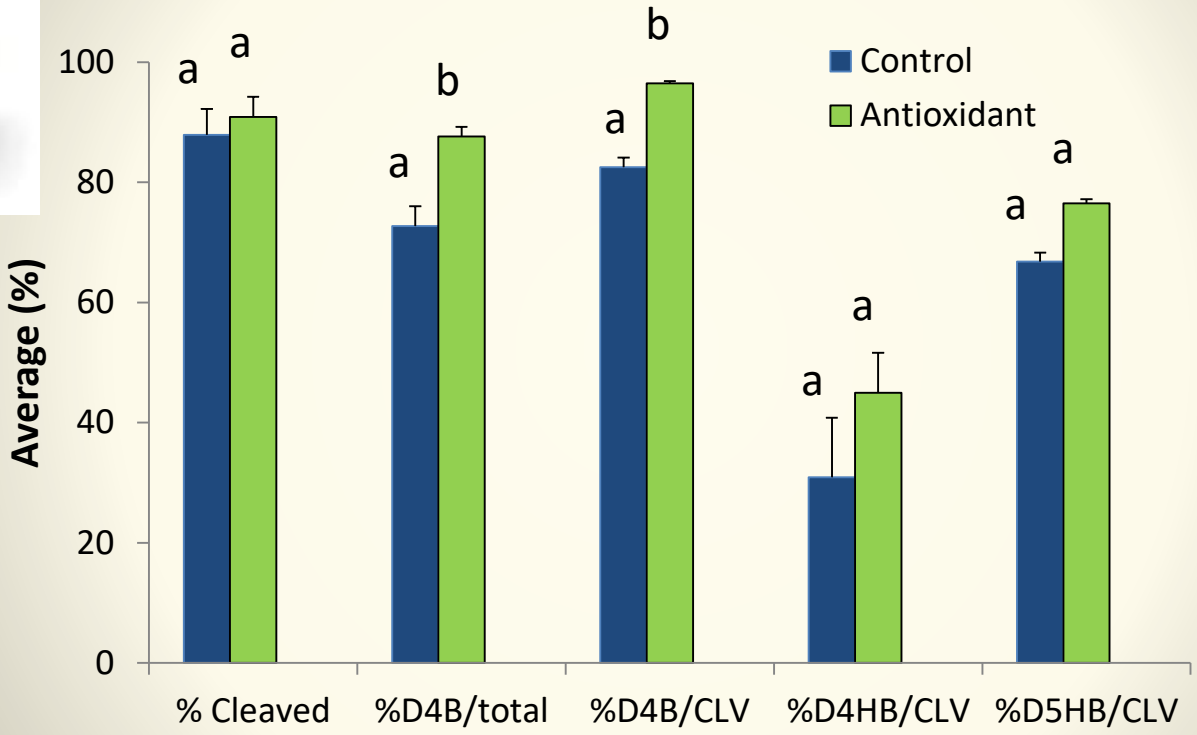
Mitochondria have to become more active to make enough ATP in a less efficient way, which results in a large increase in ROS production

Mitochondrial Support

- Challenge-improve ART outcomes for women of AMA
- Can we improve mitochondrial function in these embryos through culture media supplementation?
- Mitochondrial Modification

  - Antioxidant cocktail

Aged Mouse Embryo Development



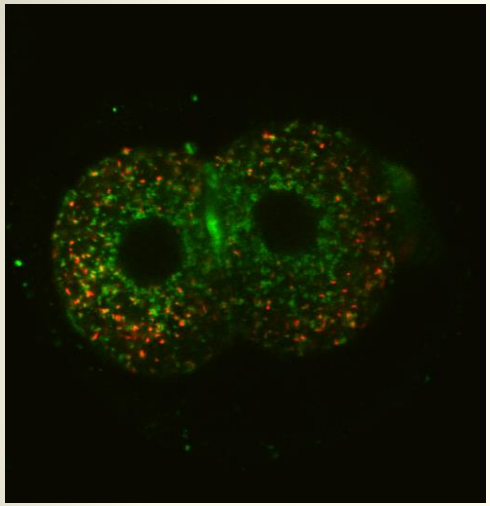
Control n=142
Antioxidant n=145

RFD, http://dx.doi.org/10.1071/RD14474

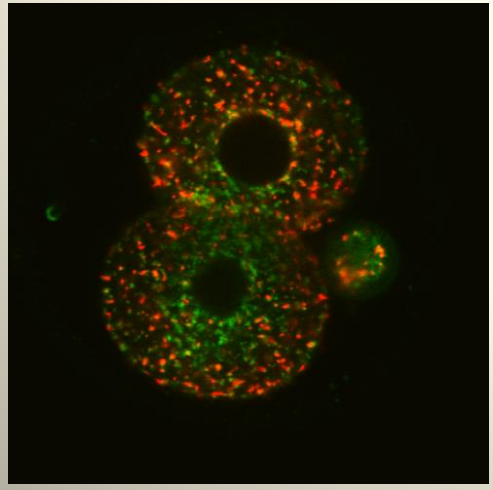
Affect of Antioxidant cocktail
Mitochondrial Function in aged mice

JC-1 Staining

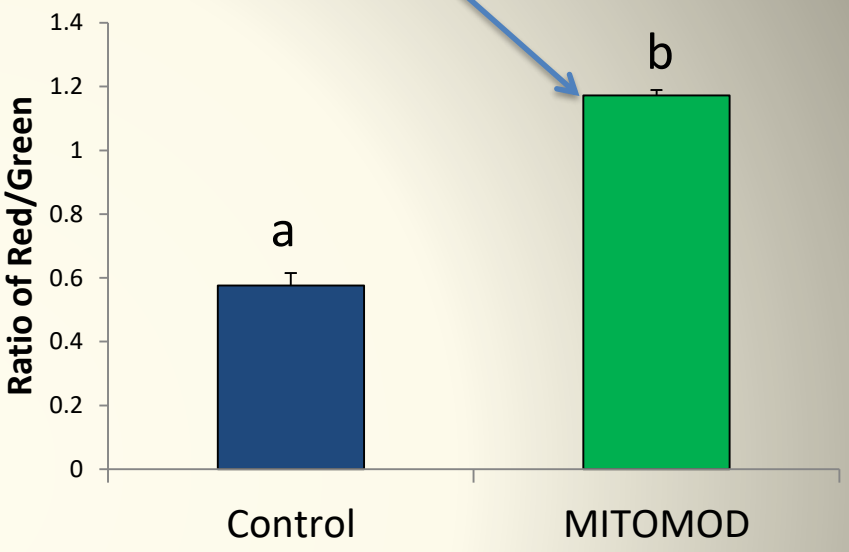
Control



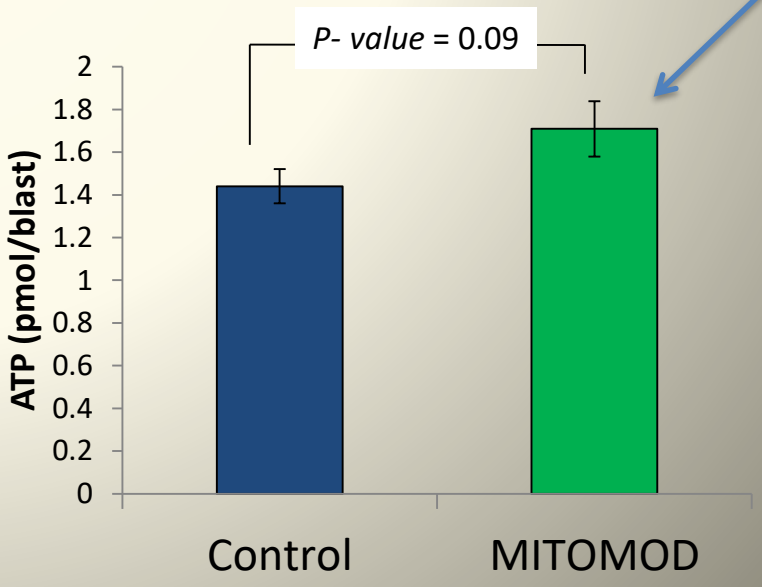
MITOMOD



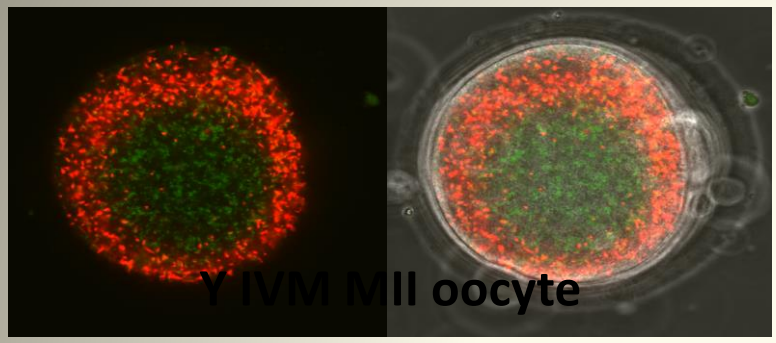
Increase in mitochondrial membrane potential

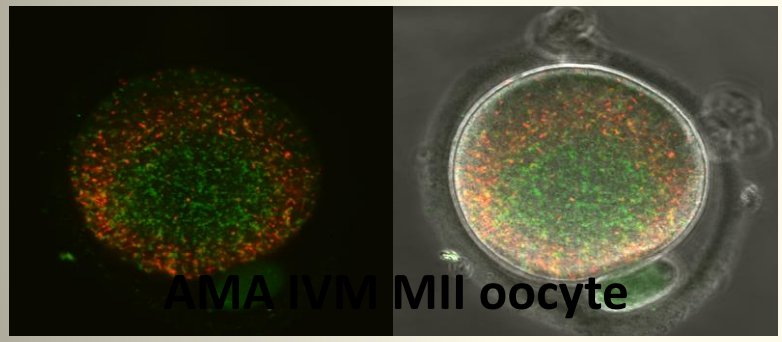


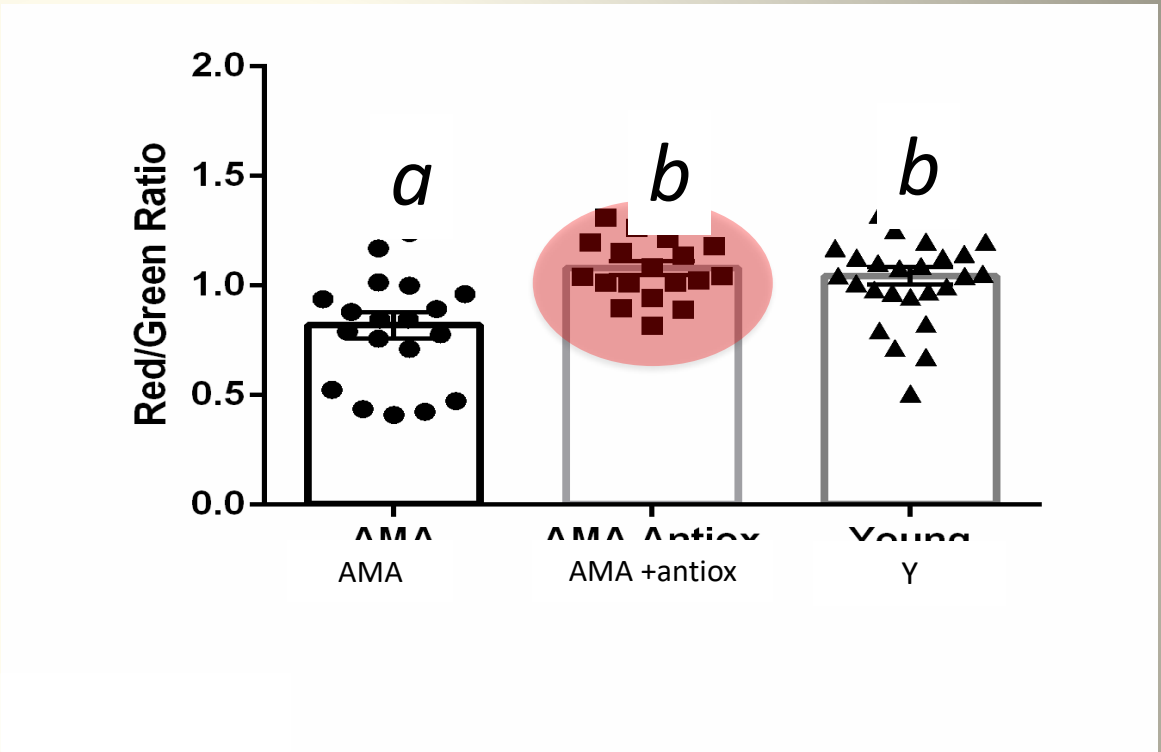
increase ATP production in blastocysts



Outbred CF1







- Lower MMP in AMA oocytes
- MMP is restored after *in vitro* maturation supplemented with antioxidants
- Could IVM with ”mitochondria therapy” be option for AMA oocytes?

Future approaches to DOR

- Bone marrow autologous stem cell ovarian transplant
- Autologous mitochondrial transfer
- In vitro activation
- ESCs/iPSCs to reconstitute oogenesis

Poor Responders: Conclusions

- The lack of a uniform definition of the poor responder makes comparison of results from trials difficult
- Among GnRH agonist protocols, microdose agonist flare with brief OC pre-treatment seem most effective
- Whether microdose flare protocols are more effective than antagonist protocols is unclear
- Growth hormone appears to improve outcomes although the ideal patient population has not been defined
- More data are needed on the role of androgen pre-treatment (DHEA, T)

Conclusions

- Clomid protocols may hold promise in the era of vitrification/embryo banking
- Dual Trigger may improve the number of oocytes retrieved/follicle as well as oocyte maturity
- Duo-stim may shorten time to pregnancy in predicted poor responders(Poseidon type 3,4)

Conclusions

- Life-style optimization is critical for poor responders
- Acai(or other anti-oxidants) may improve oocyte quantity and quality
- Culture media modifications may help embryo development in poor responders
- IVM may offer access to oocytes at an early enough stage to improve mitochondrial function

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