

Current practice in poor responders

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Background

- Poor ovarian response (POR) remains a *therapeutic challenge* in IVF
- Increasing incidence as women delay childbearing
- Frequency of diminished ovarian reserve (DOR) –10 % *in 2003* and *18% in 2013*
(www.sart.org)

Background

- Incidence of POR 6 – 20% of IVF cycles (www.IVF-Worldwide.com)
- Wide-range reflects varied demographics and definitions
- Inconsistent, inconclusive evidence on strategies for management of PR

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria[†]

At least two of the following three features must be present:

- (i) Advanced maternal age (≥ 40 years) or any other risk factor for POR;
- (ii) A previous POR (≤ 3 oocytes with a conventional stimulation protocol);
- (iii) An abnormal ovarian reserve test (i.e. AFC $< 5-7$ follicles or AMH $< 0.5-1.1$ ng/ml).

Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT.

Implementing the ESHRE ‘poor responder’ criteria in research studies: methodological implications

Athanasios Papathanasiou

Table I A detailed presentation of distinct poor responder subpopulations, based on possible combinations of risk factors, ovarian reserve test results and number of IVF attempts.

Categories	Subpopulations	ESHRE criteria fulfilled
No previous IVF attempts (predicted poor responders)	Risk factors for POR and abnormal ovarian reserve tests (1)	Criteria I and III
One previous unsuccessful IVF attempt where POR was demonstrated	Risk factors for POR but normal ovarian reserve tests (2a)	Criteria I and II
	Abnormal ovarian reserve tests but no risk factors for POR (2b)	Criteria II and III
	Risk factors for POR and abnormal ovarian reserve tests (2c)	Criteria I, II and III
Two or more previous unsuccessful IVF attempts where POR was demonstrated	No risk factors for POR and normal ovarian reserve tests (3a)	Supplemental criterion IV
	Risk factors for POR but normal ovarian reserve tests (3b)	Criterion I and supplemental criterion IV
	Abnormal ovarian reserve tests but no risk factors for POR (3c)	Criterion III and supplemental criterion IV
	Risk factors for POR and abnormal ovarian reserve tests (3d)	Criteria I, III and supplemental criterion IV

Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: a validation study

Antonio La Marca¹ · Valentina Grisendi¹ · Simone Giulini¹ · Giovanna Sighinolfi¹Alessandra Tirelli¹ · Cindy Argento¹ · Claudia Re¹ · Daniela Tagliasacchi¹ ·Tiziana Marsella¹ · Sesh Kamal Sunkara²**Table 3** Outcome of IVF/ICSI cycles in different categories of women diagnosed as poor responders according to Bologna criteria

Variables	Poor ovarian response categories				
	1 Two cycles with <4oocytes	2 Age >40+cycle with <4oocytes	3 Age>40+abnormal markers of ovarian reserve	4 Cycle with <4oocytes+abnormal markers of ovarian reserve	5 Cycle with <4oocytes+age> 40+abnormal markers of ovarian reserve
Number of patients	76	91	76	136	73
Age (years) (mean, SD)	39±4.7	41.4±1.1	41.3±0.9	38±3.9	41.8±1.7
BMI (kg/m ²), (mean, SD)	22.1±2.2	22.3±1.8	23.0±2.3	21.9±2.7	22.1±2.4
Smokers, %	20.3	19.6	19.6	20.1	19.9
Duration of infertility, months (mean,SD)	45±21	44±22	47±26	43±24	46±20
AFC (n) (mean, SD)	4.1±0.9	3.9±1.1	3.7±0.87	3.7±1.2	3.9±1.1
AMH (ng/ml) (mean,SD)	0.6±0.29	0.5±0.32	0.65±0.29	0.5±0.3	0.57±0.31
No. of oocytes (mean, SD)	1.98±1.1	1.93±1.23	1.76±1.02	2.1±1.3	1.6±1.1
No. of embryos transferred (mean, SD)	1.3±0.15	1.1±0.2	1.2±0.13	1.2±0.17	0.9±0.2
Cycles with oocyte retrieval (%)	79.5	75.6	71.1	81.1	70.1
Cycles with embryo transfer (%)	69.1	63.2	66.3	70.6	60.4
Clinical pregnancy rate (per started cycle) (%)	13.7	12.5	14.3	13.4	12.5
Live birth rate (per started cycle)	7.4	6.6	5.9	6.7	5.5

A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria

Andrea Busnelli^{1,2,*}, Enrico Papaleo³, Diana Del Prato³,
Irene La Vecchia^{1,2}, Eleonora Iachini³, Alessio Paffoni¹,
Massimo Candiani³, and Edgardo Somigliana¹

STUDY QUESTION: Do the Bologna criteria for poor responders successfully identify women with poor IVF outcome?

SUMMARY ANSWER: The Bologna criteria effectively identify a population with a uniformly low chance of success.

WHAT IS ALREADY KNOWN: Women undergoing IVF who respond poorly to ovarian hyper-stimulation have a low chance of success. Even if improving IVF outcome in this population represents a main priority, the lack of a unique definition of the condition has hampered research in this area. To overcome this impediment, a recent expert meeting in Bologna proposed a new definition of poor responders ('Bologna criteria'). However, data supporting the relevance of this definition in clinical practice are scanty.

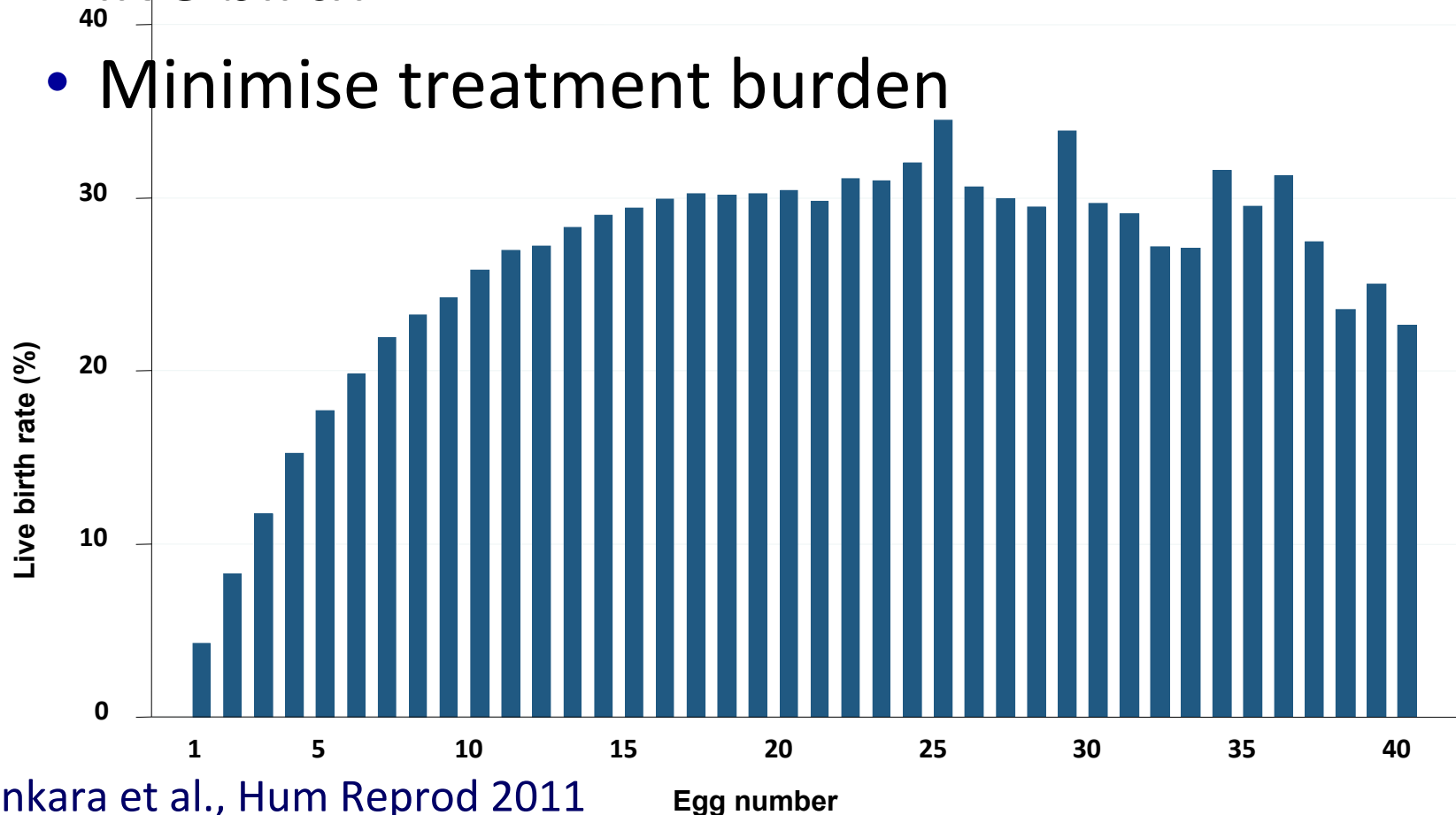
STUDY DESIGN, SIZE, DURATION: Retrospective study of women undergoing IVF-ICSI between January 2010 and December 2012 in two independent infertility units. Women could be included if they fulfilled the definition of poor ovarian response (POR) according to Bologna criteria prior to initiation of the cycle. Women were included only for one cycle. The main outcome was the live birth rate per started cycle. The perspective of the cost analysis was the one of the health provider.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Three-hundred sixty-two women from two independent Infertility Units were selected. A binomial distribution model was used to calculate the 95% CI of the rate of success. Characteristics of women who did and did not obtain a live birth were compared. A logistic regression model was used to adjust for confounders. The economic analysis included costs for pharmacological compounds and for the IVF procedure. The benefits were estimated on quality-adjusted life years (QALY). To develop the model, we used the local life-expectancy tables, we applied a 3% discount of life years gained and we used a 0.07 improvement in quality of life associated with parenthood. Sensitivity analyses were performed varying the improvement of the quality of life and including/excluding the male partner. The reference values for cost-effectiveness were the Italian and the local (Lombardy) gross domestic product (GDP) pro capita per year in the studied period and the upper and lower limits suggested by NICE.

MAIN RESULTS AND THE ROLE OF CHANCE: Overall, 23 women had a live birth (6%, 95% CI: 4–9%), in line with the previous evidence. This proportion did not significantly differ in the different subgroups of poor responders. Positive predictive factors of success were previous deliveries (adjusted OR = 3.0, 95% CI: 1.1–8.7, $P = 0.039$) and previous chemotherapy (adjusted OR = 13.9, 95% CI: 2.5–77.2, $P = 0.003$). Age, serum AMH, serum FSH and antral follicle count were not significantly associated with live birth. The total cost per live birth was 87 748 Euros, corresponding to 49 919 Euros per QALY. This is above both the limits suggested by NICE for cost-effectiveness and the Italian and local GDP pro capita. Sensitivity analyses mainly support the robustness of the conclusion.

POR: treatment objective

- Optimise number of oocytes and maximise live birth
- Minimise treatment burden



Treatment strategies

➤ Pituitary suppression regimens

➤ Stimulation approaches

- Conventional stimulation: gonadotrophin dose
- Mild stimulation, natural cycle
- Double stimulation

➤ Adjuvant therapies

- DHEA, testosterone, luteinising hormone (LH)
- Growth hormone (GH)
- E2 priming

➤ Oocyte/ embryo accumulation

Evidence

- Bologna criteria poor responder
- Level 1



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

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

Characteristics	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
Fertilisation 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				Bologna criteria ✓
							Level 1 ✓

Sunkara et al., Fertil Steril 2014

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

Jessica Lefebvre, M.D.,^{a,b} Roland Antaki, M.D.,^{a,b} Jacques I. Kadoch, M.D.,^{a,b} Nicola L. Dean, Ph.D.,^b Camille Sylvestre, M.D.,^a François Bissonnette, M.D.,^{a,b} Joanne Benoit, M.D.,^a Sylvain Ménard, M.D.,^{a,b} and Louise Lapensée, M.D.^{a,b}

- POR definition: previous cancelled IVF cycle, < 8 follicles or < 5 oocytes following stimulation with gonadotrophin ≥ 300 IU/ day **OR**
- Basal FSH > 10, AFC ≤ 8 , AMH < 1ng/L

Maximal gonadotrophin dose

Cycle outcomes.

Characteristic	450 IU/d FSH (n = 171)	600 IU/d FSH (n = 175)	P value
Cancelled before egg retrieval, n (%) ^b	45 (26.3)	34 (19.4)	.16
No. of cancelled cycles, n (%) ^b	32 (18.7)	29 (16.5)	.70
No. of cycles converted to IUI, n (%) ^b	13 (7.6)	5 (2.9)	.08
No. of cycles with no egg retrieved, n (%) ^b	1 (0.6)	1 (0.6)	NA
Stimulation characteristics ^a			
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 (MI) 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
Implantation rate ^d	29.8	30.4	1.00

**Bologna
criteria**



Level 1



Optimal maximal dose

- RCT: 300 vs 450 vs 600 IU rec-FSH

	300 IU rFSH (n = 38)	450 IU rFSH (n = 39)	600 IU rFSH (n = 39)	P value
Total oocytes	5.2 ± 0.4	6.7 ± 0.7	6.6 ± 0.7	0.21
Mature oocytes	3.7 ± 0.4	4.9 ± 0.6	4.8 ± 0.6	0.24
Embryos transferred	2.3 ± 0.2	2.3 ± 0.3	2.4 ± 0.2	0.94
Live birth rate (%)	10.5	7.7	9.5	0.81

- POR definition: AFC < 12, 1st IVF cycle

Bologna
criteria



Level 1



Mild stimulation regimens

- Clomiphene citrate (CC) vs conventional (Ragni et al., 2012 Reprod Biol Endocrinol 2012)
- Letrozole/ 150 IU FSH/ GnRH antagonist vs conventional (Mohsen et al., Gynecol Endocrinol 2013)
- CC/ 150 IU FSH/ GnRH ant vs conventional (Revelli et al., J Assist Reprod Genet 2014)

Clomiphene citrate versus high doses of gonadotropins for *in vitro* fertilisation in women with compromised ovarian reserve: a randomised controlled non-inferiority trial

Ragni et al. *Reproductive Biology and Endocrinology* 2012, **10**:114

Characteristics	Clomiphene (n=145)	High dose rFSH (n=146)	p
Cancelled cycles	21 (14%)	21 (14%)	1.00
Number of follicles > 15 mm ^a	1.7 ± 1.1	2.8 ± 1.9	<0.00
Total number of follicles > 10 mm ^a	2.5 ± 1.4	4.1 ± 2.6	<0.00
Number of oocytes retrieved ^a	1.1 ± 1.1	2.0 ± 1.8	<0.00
0	52 (42%)	29 (23%)	
1-2	58 (47%)	57 (46%)	<0.00
≥ 3	14 (11%)	39 (31%)	
Fertilisation rate ^b	75% (93/124)	70% (164/236)	0.33
Women performing Embryo Transfer	56 (39%)	79 (54%)	0.008
Number of embryos transferred ^c	1.5 ± 0.7	1.7 ± 0.7	0.06
1	33 (59%)	33 (42%)	
2	18 (32%)	35 (44%)	0.14
3	5 (9%)	11 (14%)	
Number of pregnant women	8	9	
PR per started cycle	5% (8/145)	6% (9/146)	
PR per retrieval	6% (8/124)	7% (9/125)	
PR per embryo transfer	14% (8/56)	11% (9/79)	
Embryos implanted (implantation rate)	11% (9/84)	9% (12/136)	
Number of live birth deliveries	5	7	
DR per started cycle	3% (5/145)	5% (7/146)	

**Bologna
criteria**



Level 1



Minimal stimulation protocol using letrozole versus microdose flare up GnRH agonist protocol in women with poor ovarian response undergoing ICSI

Iman Abdel Mohsen¹ & Rasha Ezz El Din² *Gynecological Endocrinology*, 2013; 29(2): 105–108

	Group 1 (n = 30) Letrozole/antagonist	Group 2 (n = 30) Flare up GnRHa	p value
No. of HP hMG ampoules	23.53 ± 7.33	71.97 ± 9.35	0.000
Days of stimulation	8.60 ± 1.63	12.03 ± 2.86	0.000
E2 day hCG (pg/ml)	998.87 ± 222.43	1039.07 ± 189.91	0.455
Endometrial thickness day of hCG (mm)	10.92 ± 2.31	11.30 ± 1.90	0.489
No. of retrieved oocytes	5.14 ± 2.45	5.11 ± 1.29	0.953
No. of fertilized oocytes	3.31 ± 1.35	3.52 ± 1.01	0.498
No. of transferred embryos	2.03 ± 0.8	2.09 ± 1.05	0.804
Cycle cancellation (n, %)	(6) 20%	(5) 16.6%	0.739
Clinical pregnancy rate/cycle (n, %)	(4) 13.3%	(5) 16.6%	

**Bologna
criteria**



Level 1



- RCT but no *a priori* sample size calculation

“Mild” vs. “long” protocol for controlled ovarian hyperstimulation in patients with expected poor ovarian responsiveness undergoing in vitro fertilization (IVF): a large prospective randomized trial

Alberto Revelli • Alessandra Chiadò • Paola Dalmaso
Veronica Stabile • Francesca Evangelista Gemma Basso • Chiara Benedetto

	Mild protocol (n=309)	Long protocol (n=331)	<i>p</i>		Mild protocol (n=309)	Long protocol (n=331)	<i>p</i>
Started cycles	355	340		hCG positive tests	55	70	
Cycle cancellation rate (%)	13	2.7	<0.01	Clinical pregnancies	47	52	
Completed cycles	309	331		n. of gestational sacs	52	60	
Stimulation length (days)	10.9±1.6	12.1±2.0	<0.05	CPR/started cycle (%)	13.2	15.3	ns
Total amount of Gn (IU)	2237±1215	5265±2083	<0.001	CPR/OPU (%)	15.2	15.7	ns
Peak E2 level (ng/ml)	1088±661	1562±879	<0.01	CPR/ET (%)	23.2	19.9	ns
Endometrial thickness at OPU (mm)	7.6±2.1	10.4±2.1	<0.01	Implantation Rate (%)	15.2	12.3	ns
OPUs	309	331		abortions	11	8	
Cycles without retrieved oocytes (%)	9.4	1.6	ns	Abortion Rate (%)	23.4	15.3	ns
Retrieved oocytes/OPU	2.7±2.3	4.8±3.3	<0.01	ongoing pregnancies >12 w	36	44	
MII oocytes/OPU	2.2±1.9	4.0±2.8	<0.01	OPR/ET (%)	17.8	16.8	ns
Fertilization Rate (%)	66.5	63.5	ns				
Transferred embryos	1.8±1.7	2.7±2.3	<0.01				
Embryos scored ≥8 points (%)	57.6	54.8	ns				
ETs	202	261					

**Bologna
criteria**



Level 1



Live birth rates after modified natural cycle compared with high-dose FSH stimulation using GnRH antagonists in poor responders

Lainas et al. **Human Reproduction** 2015

STUDY DESIGN, SIZE, DURATION: The present retrospective study included 161 MNCs (106 women in the MNC group) and 164 HDFSHT antagonist cycles (136 women in the HDFSHT group) performed between January 2008 and December 2013 at Eugonia Assisted Reproduction Unit. The patients included in the study had to fulfill the Bologna criteria for the definition of poor ovarian response.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Irrespective of their age, poor responder patients should have a diminished ovarian reserve as shown by low antral follicle count (≤ 5) and increased basal FSH (> 12 IU/l), and one or more previous failed IVF cycles in which ≤ 3 oocytes were retrieved using a high gonadotrophin dose. Analysis was performed by adjusting for the non-independence of the data.

MAIN RESULTS AND THE ROLE OF CHANCE: The probability of live birth was significantly higher in the MNC when compared with the HDFSHT group (OR: 4.01, 95% CI: 1.14–14.09), after adjusting for basal FSH, female age and cause of infertility, variables which were shown to be associated with the probability of live birth in univariable analysis. MNCs were characterized by significantly lower total gonadotrophin dose (490.0 ± 35.2 IU versus 2826.1 ± 93.4 IU, $P < 0.001$), lower estradiol concentrations (237.5 ± 12.3 pg/ml versus 487.3 ± 29.8 pg/ml, $P < 0.001$), fewer follicles present on the day of hCG (1.9 ± 0.1 versus 3.2 ± 0.2 , $P < 0.001$), fewer oocytes retrieved (1.1 ± 0.01 versus 2.4 ± 0.1 , $P < 0.001$), fewer oocytes fertilized (0.7 ± 0.1 versus 1.4 ± 0.1 , $P < 0.001$), fewer embryos transferred (0.7 ± 0.1 versus 1.4 ± 0.1 , $P < 0.001$), fewer good-quality embryos available (0.5 ± 0.1 versus 0.8 ± 0.1 , $P < 0.001$) and fewer good-quality embryos transferred (0.5 ± 0.05 versus 0.8 ± 0.1 , $P < 0.001$) compared with the HDFSHT group. However, the proportion of cycles with at least one good-quality embryo transferred per started cycle was similar between the two groups compared (62.5, 95% CI: 52.7–72.3 versus 62.7, 95% CI: 53.0–72.5, respectively).

LIMITATIONS, REASONS FOR CAUTION: This is a retrospective comparison between MNC and HDFSHT GnRH antagonist protocols in a large group of poor responder patients according to the Bologna criteria. Although the two groups compared were not imbalanced for all basic characteristics and multivariate analysis were performed to adjust for all known confounders, it cannot be excluded that non-apparent sources of bias might still be present. Future randomized controlled trials are necessary to verify the present findings.

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

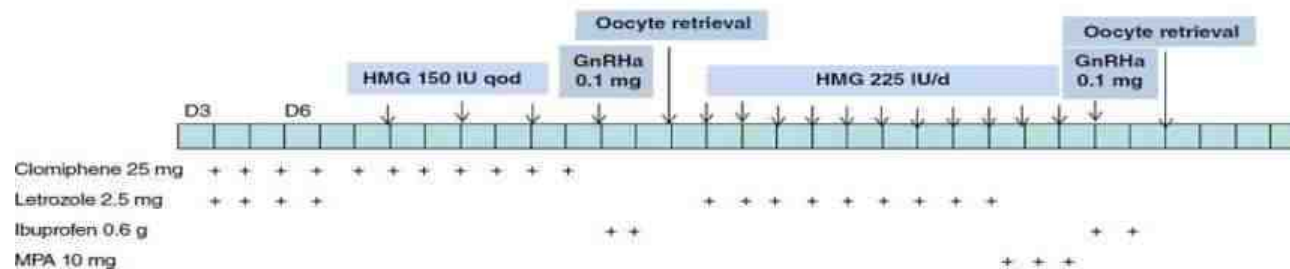
N.P. Polyzos*, C. Blockeel, W. Verpoest, M. De Vos, D. Stoop, V. Vloeberghs, M. Camus, P. Devroey, and H. Tournaye

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 (≤ 35 years, 36–39 years and ≥ 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.

Y-P Kuang et al.



Women screened ($n = 178$)

Poor responders according to Bologna criteria enrolled ($n = 38$)

Stage 1
First oocyte retrieval using mild stimulation during the follicular phase ($n = 38$)

20 women with no viable embryos

Stage 2
Second oocyte retrieval using
luteal-phase stimulation ($n = 30$)

13 women with no viable embryos

26 women retrieved 72 viable embryos from double stimulations (n = 26)

21 women completed 23 cryopreserved embryo transfer cycles, resulting in 13 clinical pregnancies ($n = 21$)

Cancel second oocyte retrieval:

- patient requirement $n = 2$
- Low antral follicle count $n = 3$
- Poor response $n = 3$

Five women did not perform cryopreserved embryo transfer until end of research

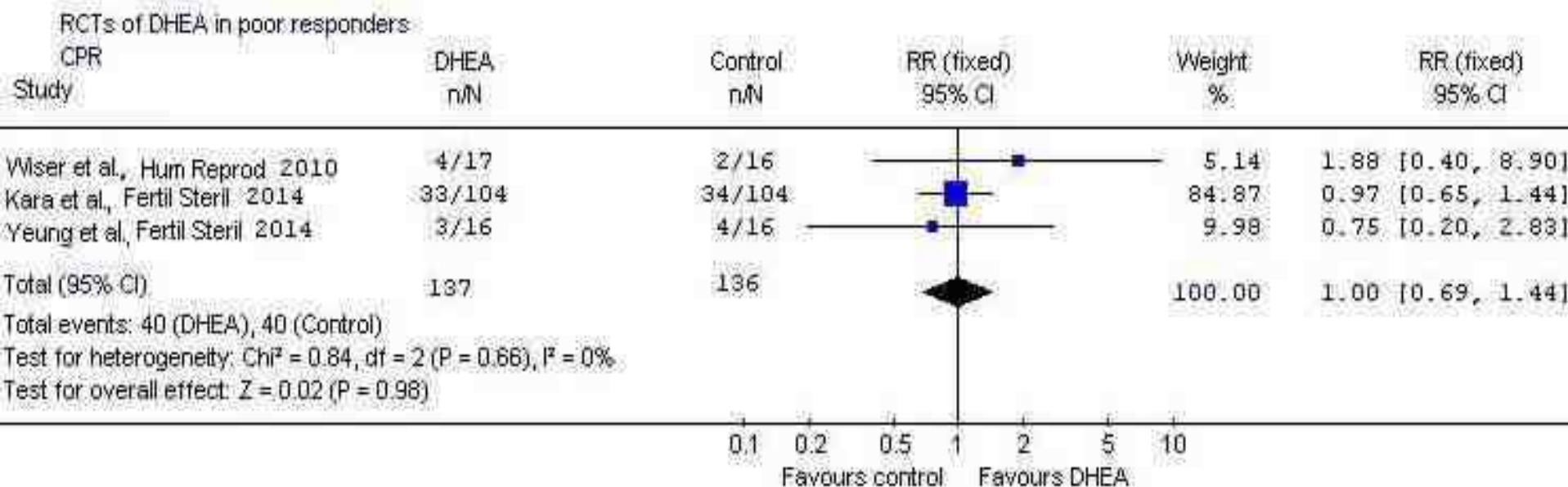
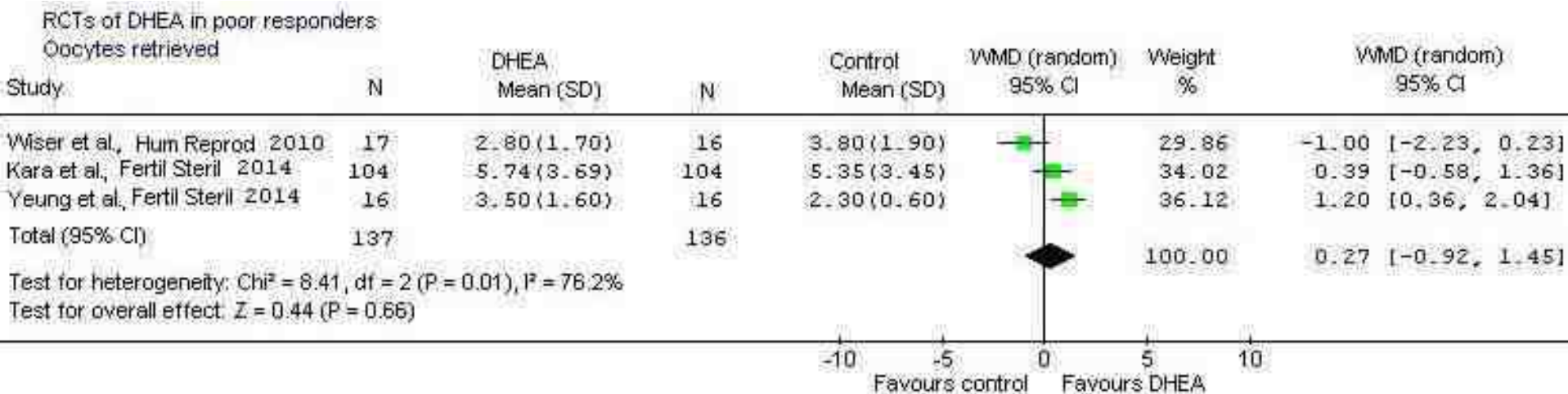
	Total
Number of patients	21
Cryopreserved embryo transfer cycles	23
Embryos warmed	43
Embryo transferred	41
Embryo survival rate (%)	41/43 (95.3)
Clinical pregnancy rate (%)	13/23 (56.5)
Implantation rate (%)	15/41 (36.6)
Spontaneous abortion rate (%)	2/13 (15.4)
Ongoing pregnancy rate (%)	11/23 (47.8)

Should androgen supplementation be used for poor ovarian response in IVF?

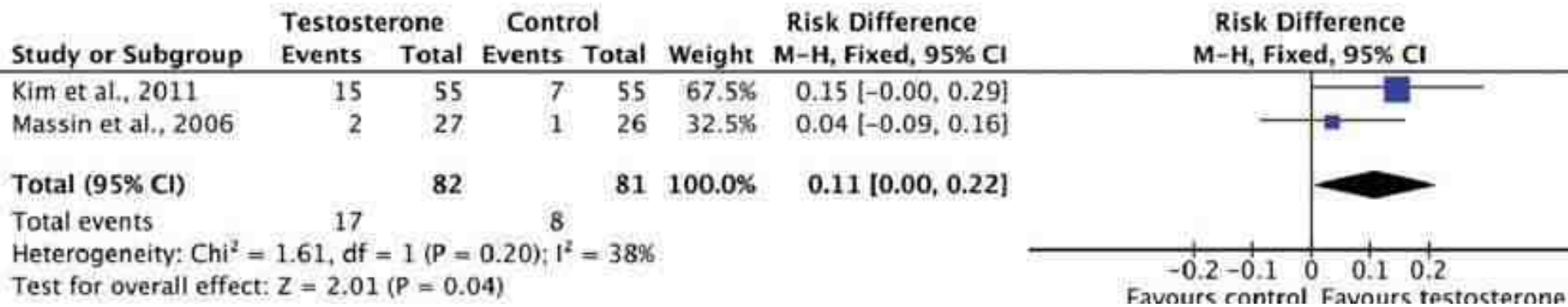
Sesh Kamal Sunkara^{1,*}, Arri Coomarasamy², Wiebke Arlt²,
and Siladitya Bhattacharya³

- LH stimulates production of androgens from theca cells
- Androgens exert ovarian autocrine/ paracrine effect
 - Androgen receptor mRNA and androgen levels in follicular fluid correlate with FSH receptor mRNA in granulosa cells (Nielsen et al., Mol Hum Reprod 2011)
 - Increase of FSH receptors in granulosa cells enhances FSH responsiveness and follicle recruitment

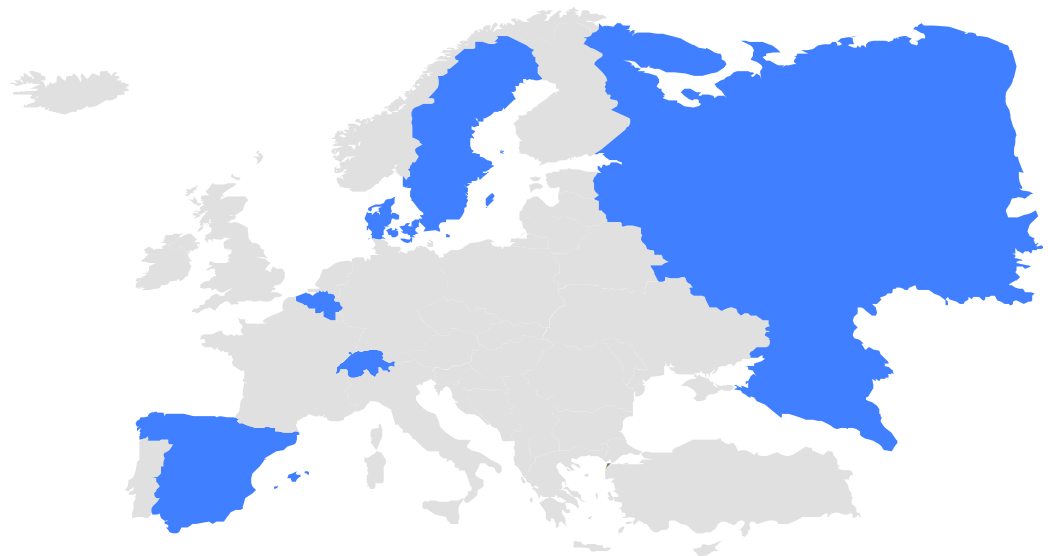
DHEA supplementation



Testosterone pre-treatment



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



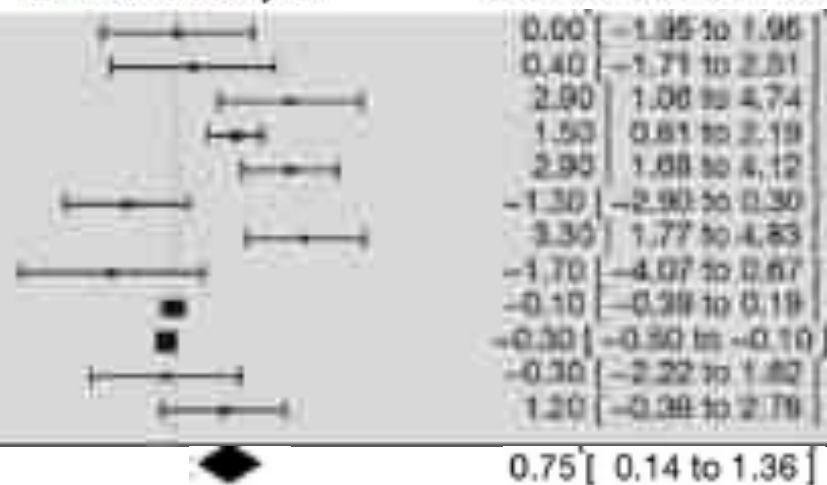
recombinant-LH supplementation

Lehert et al. *Reproductive Biology and Endocrinology* 2014,

MSGO29	5	18	5	23
Lihi 2002a	5.8	9	8	13
Ferraretti 2004	8.2	54	11.1	54
Demirci 2005	2.8	53	4.3	53
DeFranco 2005	6.1	65	9	65
Ramirez 2006b	5.8	16	4.5	16
Aytac 2006	8.7	17	12	18
Rivolo 2007	7	16	5.5	24
Polidoropoulos 2007	3.5	68	3.4	68
Banerjee 2008	5.7	42	5.4	42
Brunet 2009	8.8	45	6.5	40
Muham 2012	7.4	128	6.8	110

Number of oocytes

Mean difference (95% CI)

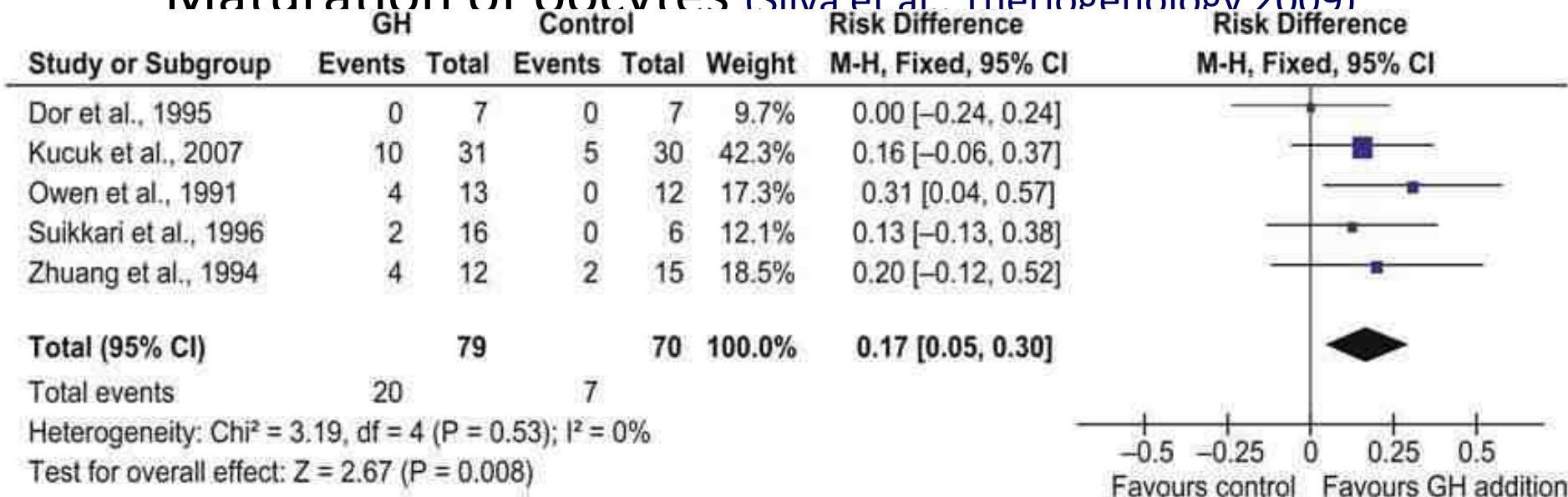


BMJ Open Efficacy and Safety of Pergoveris in Assisted Reproductive Technology – ESPART: rationale and design of a randomised controlled trial in poor ovarian responders undergoing IVF/ICSI treatment

Methods and analysis: Phase III, randomised, single-blind, parallel-group trial in women undergoing *in vitro* fertilisation and/or intracytoplasmic sperm injection. Approximately 946 women aged 18–<41 years from 18 countries will be randomised (1:1) to receive a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio (Pergoveris) or r-hFSH monotherapy (GONAL-f). The primary end point is the total number of retrieved oocytes per participant.

GH supplementation

- GH exerts its action directly and mediated through IGF
 - Development of small antral follicles to gonadotrophin-dependent stages
 - Maturation of oocytes (Silva et al. Theriogenology 2009)



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

Kasey A. Reynolds^{1,*}, Kenan R. Omurtag¹, Patricia T. Jimenez¹, Julie S. Rhee¹, Method G. Tuuli¹, and Emily S. Jungheim¹

Study	Country of origin	Study period	Study type	Average study quality score	Number of patients (LE/control)
Hill et al. (2009)	USA	1/2004–8/2006	Retrospective cohort	17/22	285 (57/228)
DiLuigi et al. (2011)	USA	7/2006–7/2009	RCT	18/26	54 (26/28)
Ellassar et al. (2011a,b)	USA	1/2009–8/2010	Retrospective cohort	15/22	99 (52/47)
Weitzman et al. (2009)	USA	5/2005–4/2006	Retrospective cohort	16/22	121 (45/76)
Shastri et al. (2011)	USA	1/2004–1/2008	Retrospective cohort	16/22	186 (117/69)
Chang et al. (2012)	Korea	1/2009–5/2010	Retrospective cohort	18/22	155 (86/69)
Dragisic et al. (2005)	USA	1/2003–6/2004	Retrospective paired cohort	16/22	132 (66/66)
Ata et al. (2011)	Canada	2/2007–7/2009	Retrospective cohort	18/22	57 (19/38)

Women exposed to LE priming had a lower risk of cycle cancellation RR 0.60; 95% CI: 0.45-0.78

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A randomized trial of microdose leuprolide acetate protocol versus luteal phase ganirelix protocol in predicted poor responders

DiLuigi J, Engmann L, Schmidt D, Benadiva C, Nulsen J

Accumulation of oocytes: a new strategy for managing low-responder patients

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242 low responders (LR), MII oocytes accumulated by vitrification with later insemination vs 482 LR patients with standard stimulation and fresh insemination

	LR-Accu-Vit	LR-fresh
Embryo transfers (n)	220	318
Transfer cancellations/patient (%; 95% CI)	9.1 (6.8–11.4) ^a	34.0 (29.8–38.2) ^a
Implantation rate		
n/total	110/440	138/540
% (95% CI)	25.0 (20.7–30.0)	25.6 (21.9–29.3)
Embryos transferred (mean, 95% CI)	2.0 (1.9–2.1) ^b	1.7 (1.6–1.8) ^b
Live-birth rate/embryo transfer		
n/total	73/220	108/318
% (95% CI)	33.2 (25.7–38.0)	34.0 (28.7–39.1)
Live-birth rate/patient		
n/total	73/242	108/482
% (95% CI)	30.2 (24.3–35.9)	22.4 (18.7–26.1)
Cumulative live-birth rate/patient ^c		
n/total	88/242	114/482
% (95% CI)	36.4 (30.3–42.4) ^d	23.7 (19.9–27.4) ^d

Prognosis

- Low success rates in Bologna criteria poor responders
 - Influenced by age and oocyte number (Sunkara et al., 2011; Oudendijk et al., Hum Reprod Update 2012)
 - LBR: 7% - 10% per cycle (Polyzos et al., RBMO 2014; La Marca et al., J Assis Reprod Genet 2015; Busnelli et al., Hum Rep 2015)
 - Cumulative LBR (Ke et al., J Huazhong Univ Sci Technol 2012)

	Total	≤35 years	36—39 years	≥40 years
Three-cycle cumulative live birth per patient				
Optimistic	98 (20.5)	37 (24.5)	29 (27.4)	33 (14.9)
Pessimistic	61 (12.7)	28 (18.5)	14 (13.2)	19 (8.6)

- Cost-implications: mean cost/ live birth € 87748 (Busnelli et al., Hum Rep 2015)

Conclusion

- Prediction, counselling, individualization
- Bologna criteria
- *GnRH agonist long and antagonist regimens* are suitable choice for poor responders
- GnRH agonist short “flare” regimen is *less* effective
- Unlikely benefit from gonadotrophin dose >300 IU/ day

Conclusion

- Some evidence to suggest adjuvant testosterone, growth hormone could be beneficial
- Robust RCTs needed to further determine potential benefit
- How much can any intervention improve live birth outcome?
- Perhaps the stringent definition of Bologna criteria POR precludes significant benefit!

Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment

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Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency

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