

OPTIMIZE FSH STARTING DOSE AND ADAPTING COS TO IMPROVE REPRODUCTIVE OUTCOMES

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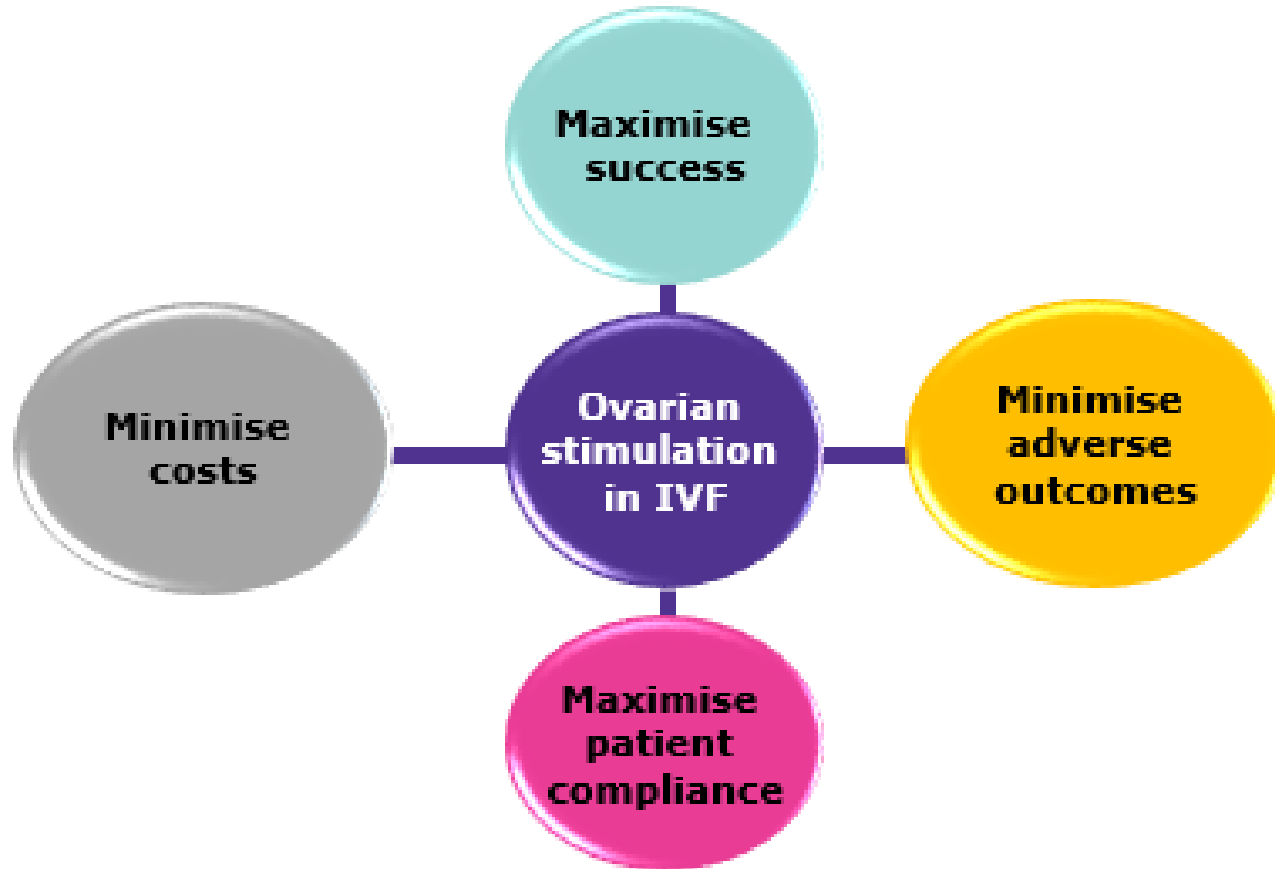
Disclosures

- Honoraria received for speaker engagements: Merck, Ferring Pharmaceuticals, MSD

Outline

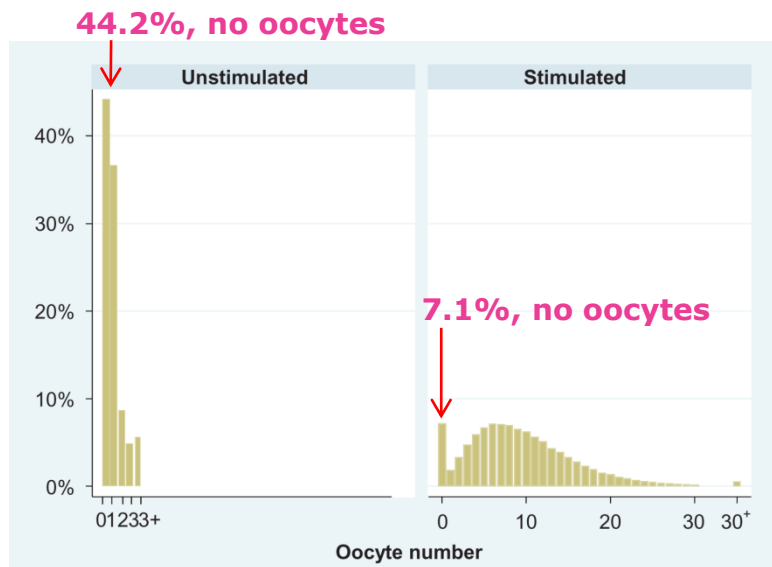
- Aim of ovarian stimulation in IVF
- Efficacy of ovarian stimulation
- Defining success in ART?
- Planning COS
- Gonadotropin dosing

Aim of ovarian stimulation

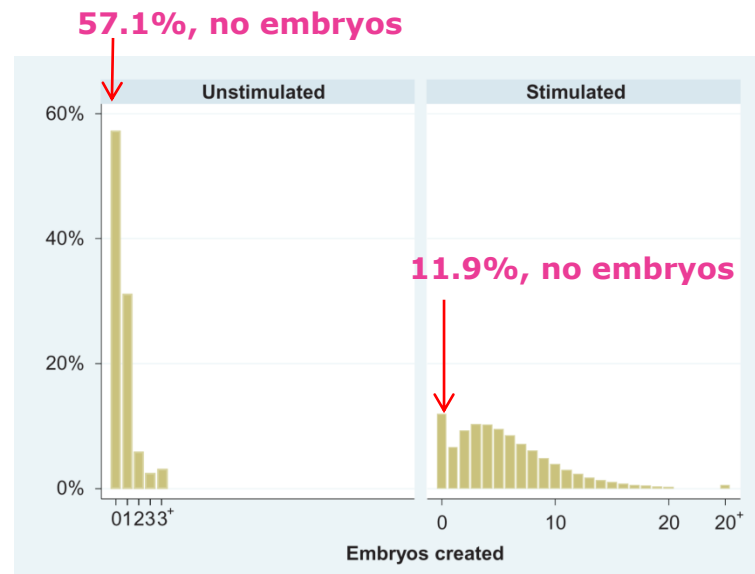


Efficacy of ovarian stimulation

- Human Fertilisation and Embryology Authority, UK ART data 1991–2011
- 6,168 unstimulated and 584,835 stimulated IVF cycles



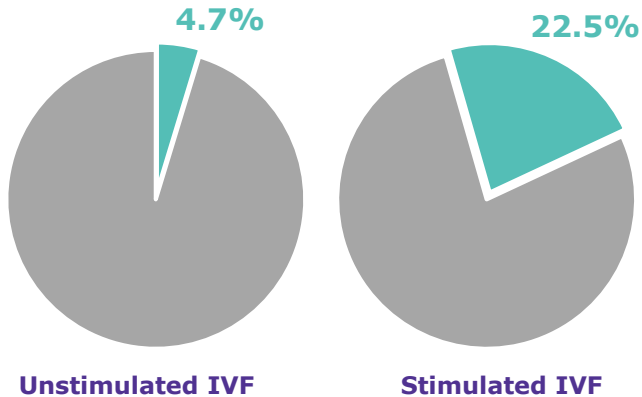
Median (IQR) = 1 (0; 1) Median (IQR) = 8 (5; 13)



Median (IQR) = 0 (0; 1) Median (IQR) = 5 (2; 8)

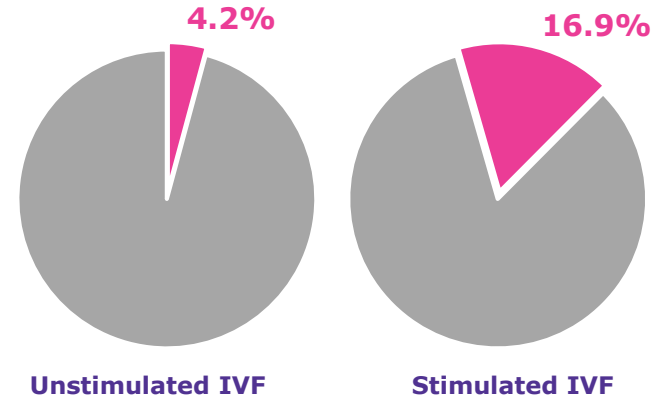
Efficacy of ovarian stimulation

Live birth per cycle



3.5 times as many unstimulated cycles to achieve a live birth compared with stimulated IVF

Singleton live birth per cycle



2.9 times as many unstimulated cycles to achieve a singleton live birth compared with stimulated IVF

What is success in ART?





**Traditional definition: live birth
per cycle per oocyte retrieval per ET**

How do WE define success in ART?

- COS strategies
- Cryopreservation programmes

Maximising *efficacy, safety, cost-effectiveness*

Important milestones in ART

- Redefined success in ART
 - *Cumulative live birth rate (CLBR)*
 - *Time to pregnancy (TTP)*

Planning stimulation regimens

Understand key associations

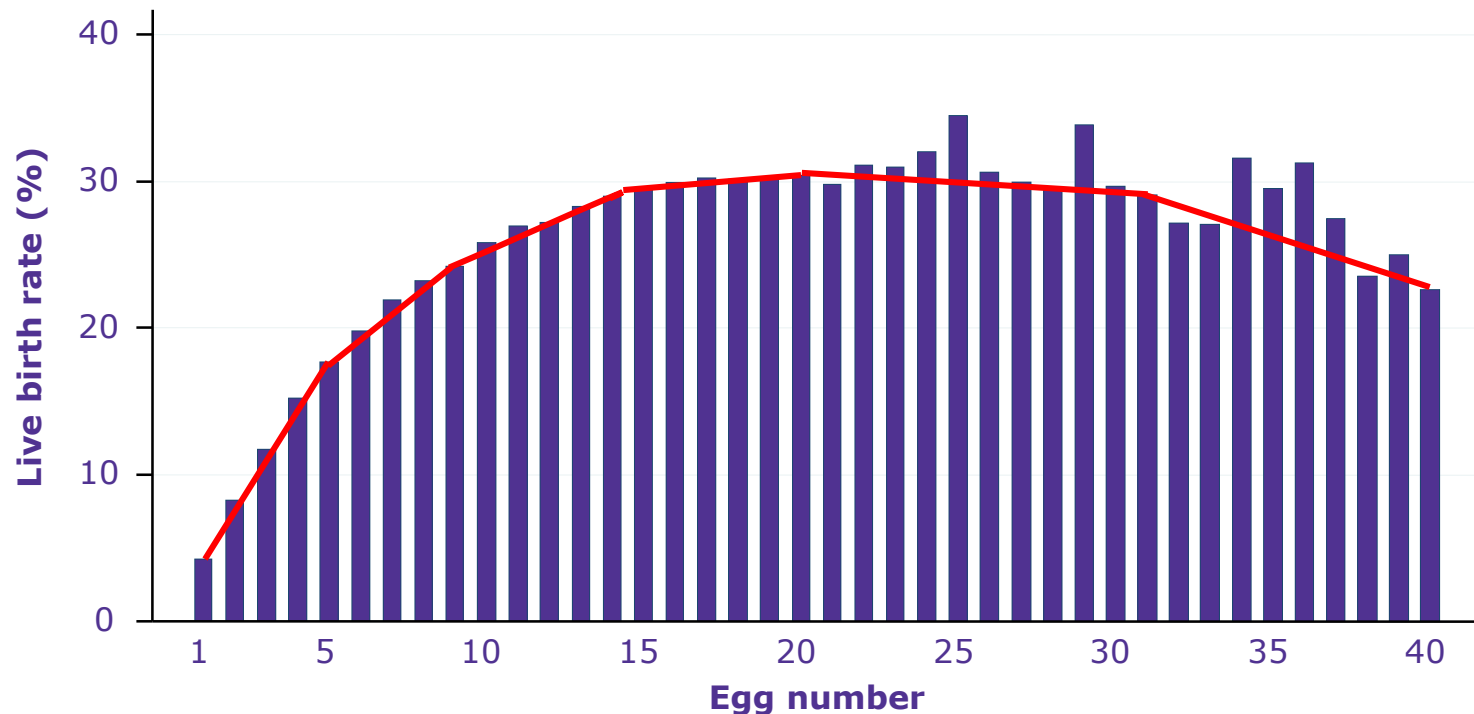
BETWEEN

Ovarian stimulation, number of oocytes

AND

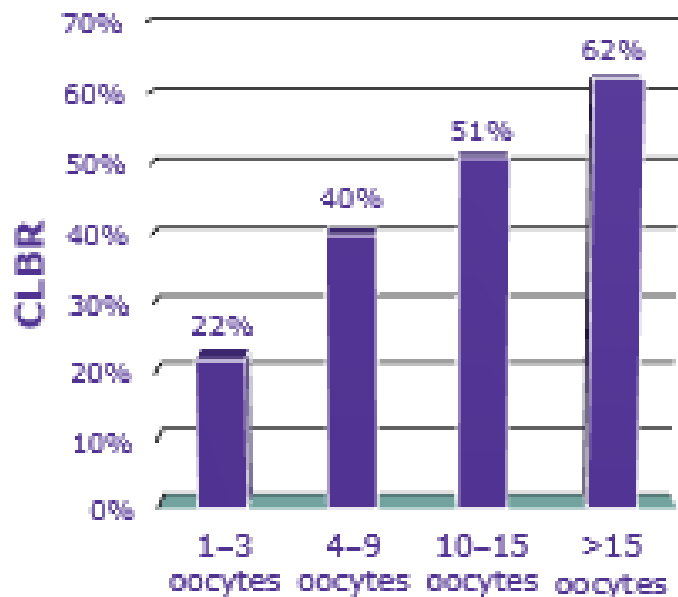
Clinical outcomes: LBR, CLBR, OHSS

Association between the number of eggs and live birth in IVF treatment: an analysis of 400,135 treatment cycles



How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos?

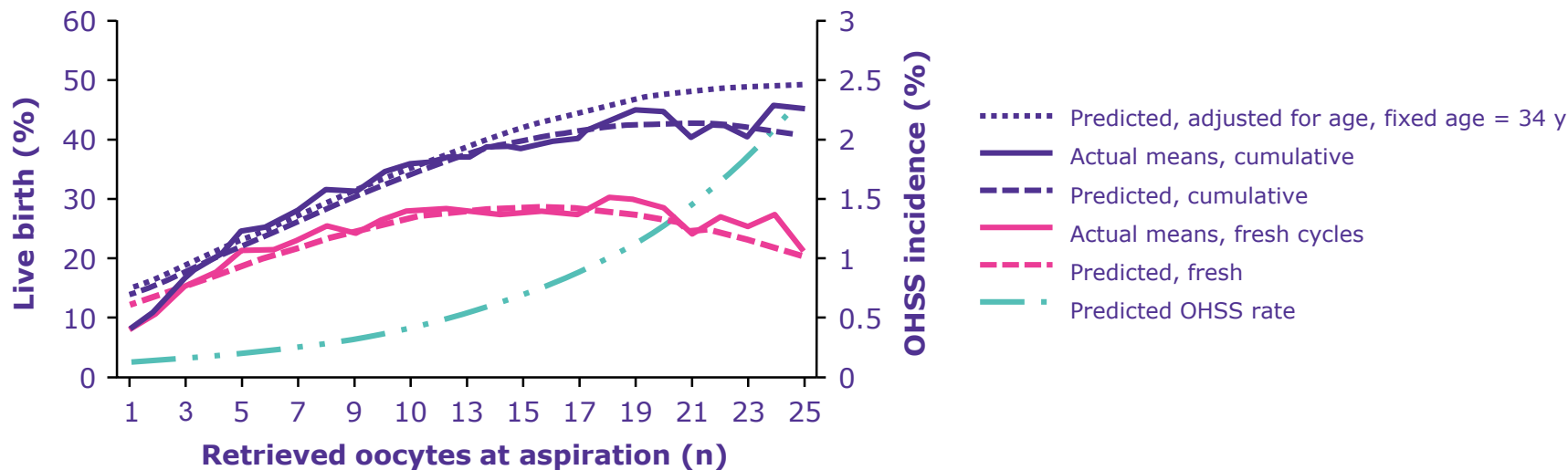
- 1,099 women, GnRH antagonist regimen, 150–225 r-FSH daily
- Planned SET



	1-3 Oocytes	4-9 Oocytes	10-15 Oocytes	>15 Oocytes	P-value
LBR	16.9%	29.7%	33.4%	32.1%	0.02
CLBR	21.7%	39.7%	50.5%	61.5%	<0.001
Moderate – severe OHSS	0	0	2 (0.6%)	9 (4.1%)	<0.001

The number of oocytes retrieved during IVF: a balance between efficacy and safety

- Retrospective registry-based study
- 39,387 women undergoing 77,956 fresh IVF cycles and 36,270 frozen transfers



Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice

Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice

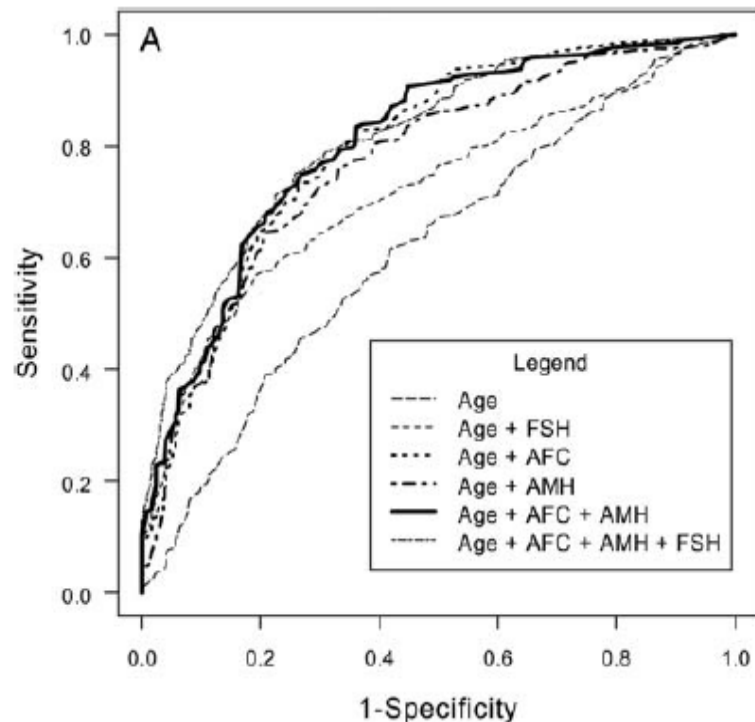
Antonio La Marca^{1,*} and Sesh Kamal Sunkara²

¹Mother-Infant Department, Institute of Obstetrics and Gynaecology, University of Modena and Reggio Emilia, 41100 Modena, Italy ²King's College London, London, UK

- AFC or AMH to categorise women:
 - *Normal, poor, hyper response*
- Choose treatment protocols tailored to the prediction
- Fine tuning at the different stages of COS:
 - Pituitary suppression, **ovarian stimulation**, oocyte maturation trigger

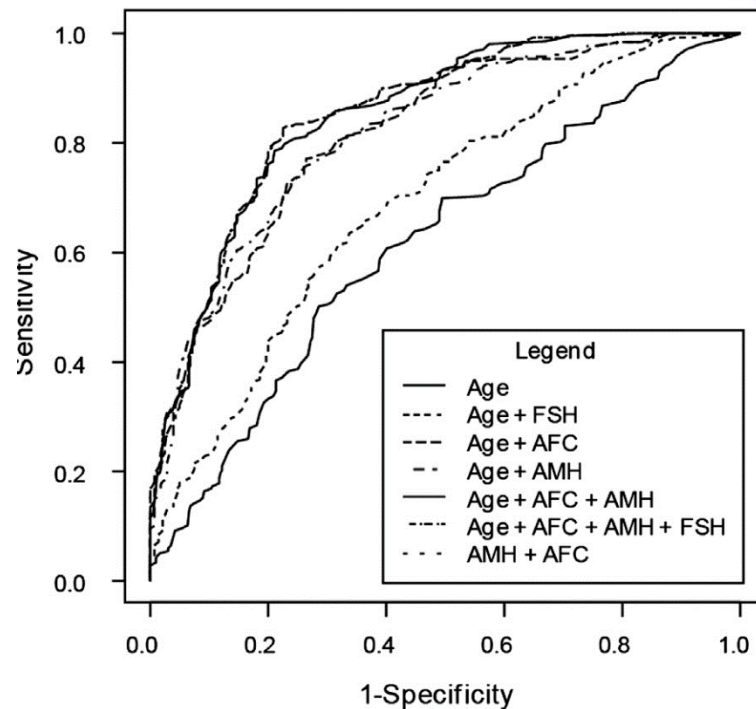
ORTs and prediction of poor ovarian response

	AUC	95% CI	P-value
Univariable models			
Age	0.61	0.54–0.68	NA
FSH	0.68	0.61–0.74	0.051
AFC ✓	0.76	0.70–0.82	<0.001
AMH ✓	0.78	0.72–0.84	<0.001
Multivariable models			
Age and FSH	0.71	0.65–0.78	<0.001
Age and AFC	0.79	0.73–0.85	<0.001
Age and AMH	0.77	0.70–0.83	<0.001
Age and AMH and AFC	0.80	0.74–0.86	<0.001
Age and AMH and AFC and FSH	0.81	0.75–0.86	<0.001



ORTs and prediction of hyper response

	AUC	95% CI	P-value
Univariable models			
Age	0.61	0.54–0.68	NA
FSH	0.66	0.60–0.73	0.071
AFC ✓	0.79	0.74–0.85	<0.001
AMH ✓	0.81	0.76–0.87	<0.001
Multivariable models			
Age and FSH	0.68	0.62–0.75	<0.001
Age and AFC	0.81	0.76–0.87	<0.001
Age and AMH	0.81	0.76–0.87	<0.001
Age and AMH and AFC	0.85	0.80–0.90	<0.001
Age and AMH and AFC and FSH	0.81	0.75–0.86	<0.001
AMH and AFC	0.85	0.80–0.90	<0.001



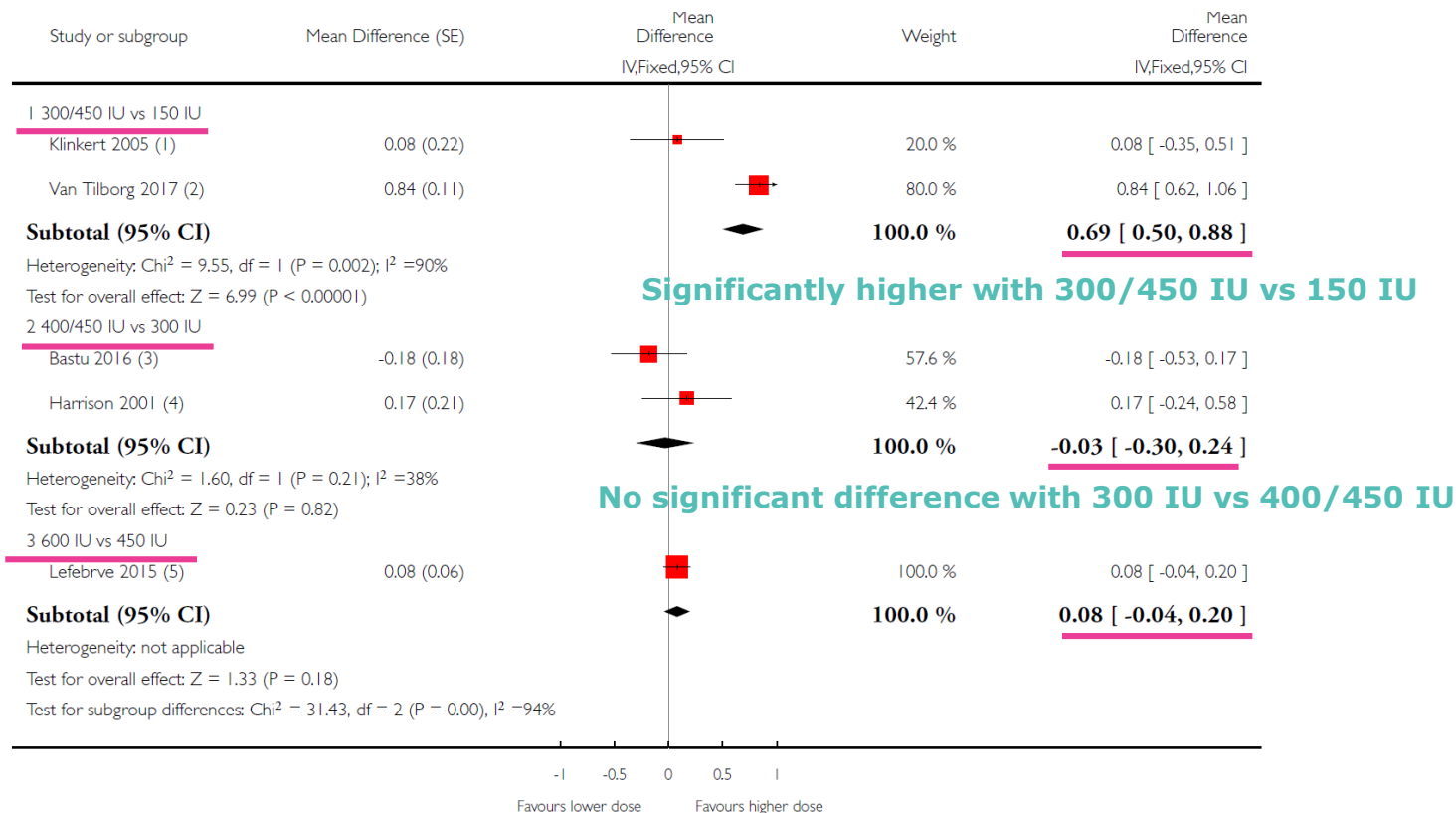


Poor responder

Poor response: individualised vs standard dose

- 5 RCTs in predicted low responders
 - 300/ 400/ 450 IU vs 150 IU
(Klinkert et al. Fertil Steril 2005; Van Tilborg et al. Hum Reprod 2017)
 - 400/ 450 IU vs 300 IU
(Harrison et al. Fertil Steril 2001, Batsu et al. EJOG 2016)
 - 600 IU vs 450 IU
(Lefebvre et al. Fertil Steril 2015)
- Overall pooling of studies not possible due to variation of gonadotropin dose in study and control arms

Oocytes retrieved



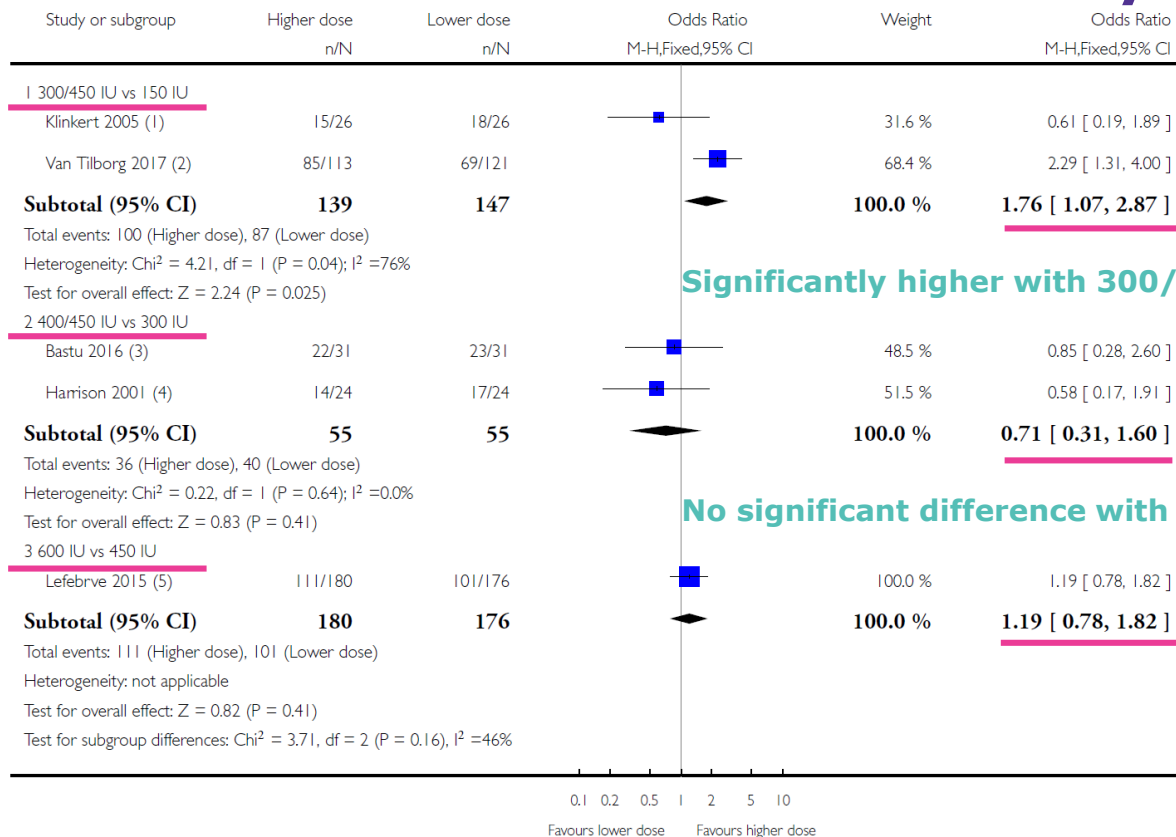
Cycles cancelled due to poor ovarian response



Significantly lower with 300/450 IU vs 150 IU

No significant difference with 300 IU vs 400/450 IU

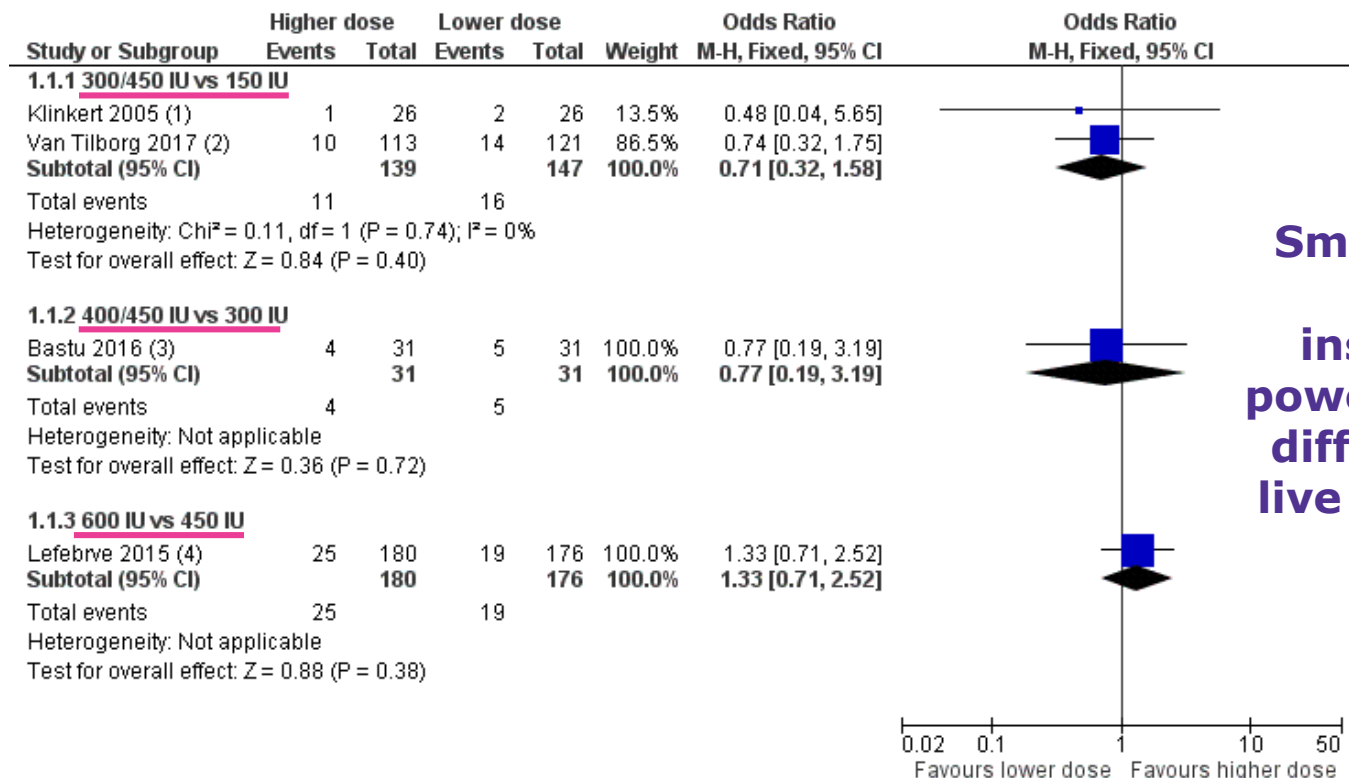
Women with at least one transferrable embryo



Significantly higher with 300/450 IU vs 150 IU

No significant difference with 300 IU vs 400/450 IU

Live birth/ongoing pregnancy rate

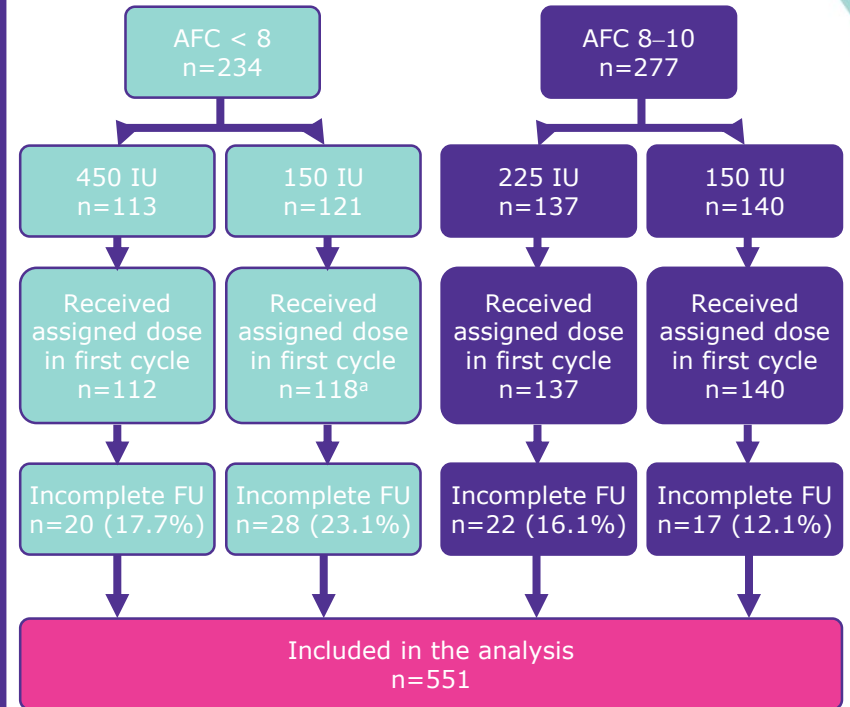


**Small sample
sizes,
insufficient
power to detect
differences in
live birth rates**

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

Theodora C. van Tilborg^{1,*}, Helen L. Torrance¹, Simone C. Oudshoorn¹, Marinus J.C. Eijkemans², Carolien A.M. Koks³, Harold R. Verhoeve⁴, Annemiek W. Nap⁵, Gabrielle J. Scheffer⁶, A. Petra Manger⁷, Benedictus C. Schoot^{8,9}, Alexander V. Sluijmer¹⁰, Arie Verhoeff¹, Henk Groen¹², Joop S.E. Laven¹³, Ben Willem J. Mol^{14,15}, and Frank J.M. Broekmans¹, on behalf of the OPTIMIST study group[†]

¹Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, The Netherlands ²Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, The Netherlands ³Department of Obstetrics and Gynaecology, Maxima Medical Centre Veldhoven, PO Box 7777, 5500 MB Veldhoven, The Netherlands ⁴Department of Obstetrics and Gynaecology, Onze Lieve Vrouwe Gasthuis Oost, PO Box 95500, 1190 HM Amsterdam, The Netherlands ⁵Department of Reproductive Medicine, Rijnstate Hospital, PO Box 9555, 6800 TA Arnhem, The Netherlands ⁶Department of Obstetrics and Gynaecology, Gelre Hospital, PO Box 9014, 7300 DS Apeldoorn, The Netherlands ⁷Department of Obstetrics and Gynaecology, Diaconessenhuis, PO Box 80250, 3508 TG Utrecht, The Netherlands ⁸Department of Obstetrics and Gynaecology, Catharina Ziekenhuis, PO Box 1350, 5602 ZA Eindhoven, The Netherlands ⁹Department of Obstetrics and Gynaecology, University Hospital Gent, 9000 Gent, Belgium ¹⁰Department of Gynaecology, Wilhelmina Hospital, PO Box 30001, 9400 RA Assen, The Netherlands ¹¹Department of Gynaecology, Maastricht Hospital, PO Box 9100, 3007 AC Rotterdam, The Netherlands ¹²Department of Epidemiology, University of Groningen, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands ¹³Department of Obstetrics and Gynaecology, Erasmus Medical Centre, Postbus 2040, 3000 CA Rotterdam, The Netherlands ¹⁴The Robinson Research Institute, School of Paediatrics and Reproductive Health, University of Adelaide, SA 5006 Adelaide, Australia ¹⁵The South Australian Health and Medical Research Unit, PO Box 11060, SA 5001 Adelaide, Australia



AFC 0–10			
Results 18 months follow-up	450/225 IU (n=250)	150 IU (n=260)	P-value
Number of fresh cycles per woman	2.1 (0.9)	2.1 (1.1)	0.29
Total number of fresh cycles started	513	558	
First cycle	250 (100%)	260/261 (99.6%)	
Second cycle	165 (66.0%)	176 (67.7%)	
Third cycle		87 (33.3%)	
Fourth cycle		27 (10.3%)	
Fifth cycle		6 (2.3%)	
Sixth cycle	0	2 (0.8%)	
Cancellation classification			<0.001 ^c
No cancellation	464 (90.4%)	444/557 (79.7%)	<0.001^{c,d}
Insufficient growth	36 (7.0%)	99/557 (17.8%)	<0.001 ^{c,d}
Excessive response	3 (0.6%)	1/557 (0.2%)	0.34 ^{c,d}
Other	10 (1.9%)	13/557 (2.3%)	0.67 ^{c,d}
Number of oocytes^a	7.6 (5.0)	6.4 (4.3)	0.002^c
Poor response	178/510 (34.9%)	275/556 (49.5%)	<0.001^c
Hyper response	44/510 (8.6%)	19/556 (3.4%)	0.003 ^c
Number of fresh embryos for transfer^a	3.6 (3.1)	3.1 (2.7)	0.04^c
Number of fresh embryo transfers	399 (77.8%)	385/557 (69.1%)	0.005^c
Number of fresh embryos/transfer	1.3 (0.5)	1.3 (0.5)	0.60 ^c
Number of frozen embryos^b	3.0 (2.2)	2.6 (1.7)	0.11^c



**Based on the women who had an ovum pick-up
Based on the women who had frozen embryos**

ITT analysis



**9.6% cycle
cancellation**

**21.3% cycle
cancellation**

^aBased on the women who had an ovum pick-up; ^bBased on the women who had frozen embryos; ^cP-value calculated by using a generalized estimating equation model; ^dPost hoc testing. P-value is considered to be significant when <0.013 (Bonferroni correction [0.05/4])

Results 18 months follow-up	AFC 0–7			AFC 8–10		
	450 IU (n=113)	150 IU (n=120)	P-value	225 IU (n=137)	150 IU (n=140)	P-value
Number of fresh cycles per woman	2.1 (0.9)	2.1 (1.0)	0.77	2.0 (1.0)	2.2 (1.1)	0.26
Total number of fresh cycles started	236	255		277	303	
First cycle	113 (47.9%)	120 (47.1%)		137 (49.5%)	140 (46.2%)	
Second cycle	80 (33.9%)	84 (32.9%)		85 (30.7%)	92 (30.4%)	
Third cycle	37 (15.7%)	36 (14.1%)		42 (15.2%)	51 (16.8%)	
Fourth cycle	6 (2.5%)	12 (4.7%)		12 (4.3%)	15 (5.0%)	
Fifth cycle	0	2 (0.8%)		1 (0.4%)	4 (1.3%)	
Sixth cycle	0	1 (0.4%)		0	1 (0.3%)	
Dose increase between first and second cycle	0/78	61/84 (72.6%)	<0.001	3/84 (3.6%)	52/91 (57.1%)	<0.001

AFC 0–10				
Pregnancy data per woman	450/225 IU (n=250)	150 IU (n=260)	RR (95% CI)	P-value
Ongoing pregnancy resulting in live birth within 18 months of FU	106 (42.4%)	117 (44.8%)	0.95 (0.78–1.15)	0.29

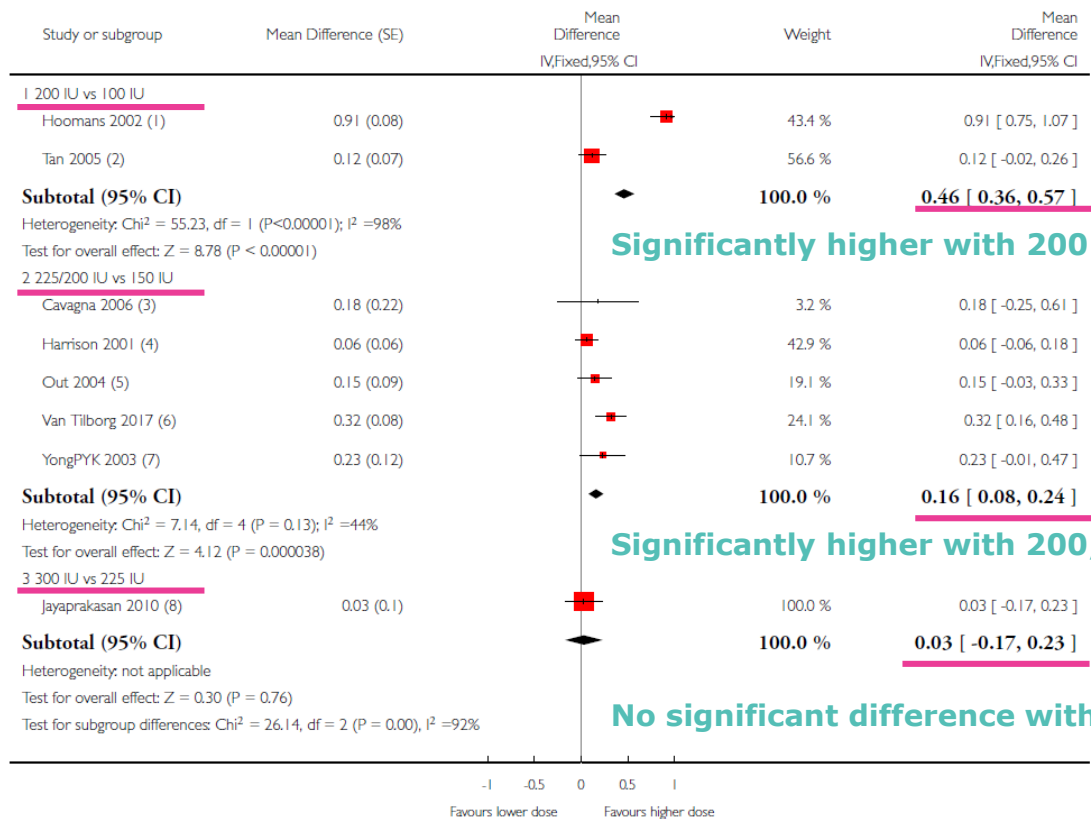
STUDY QUESTION: Does an increased FSH dose result in higher cumulative live birth rates in women with a predicted poor ovarian response, apparent from a low antral follicle count (AFC), scheduled for IVF or ICSI?

SUMMARY ANSWER: In women with a predicted poor ovarian response (AFC <11) undergoing IVF/ICSI, an increased FSH dose (225/450 IU/day) does not improve cumulative live birth rates as compared to a standard dose (150 IU/day)



Normal responder

Oocytes retrieved

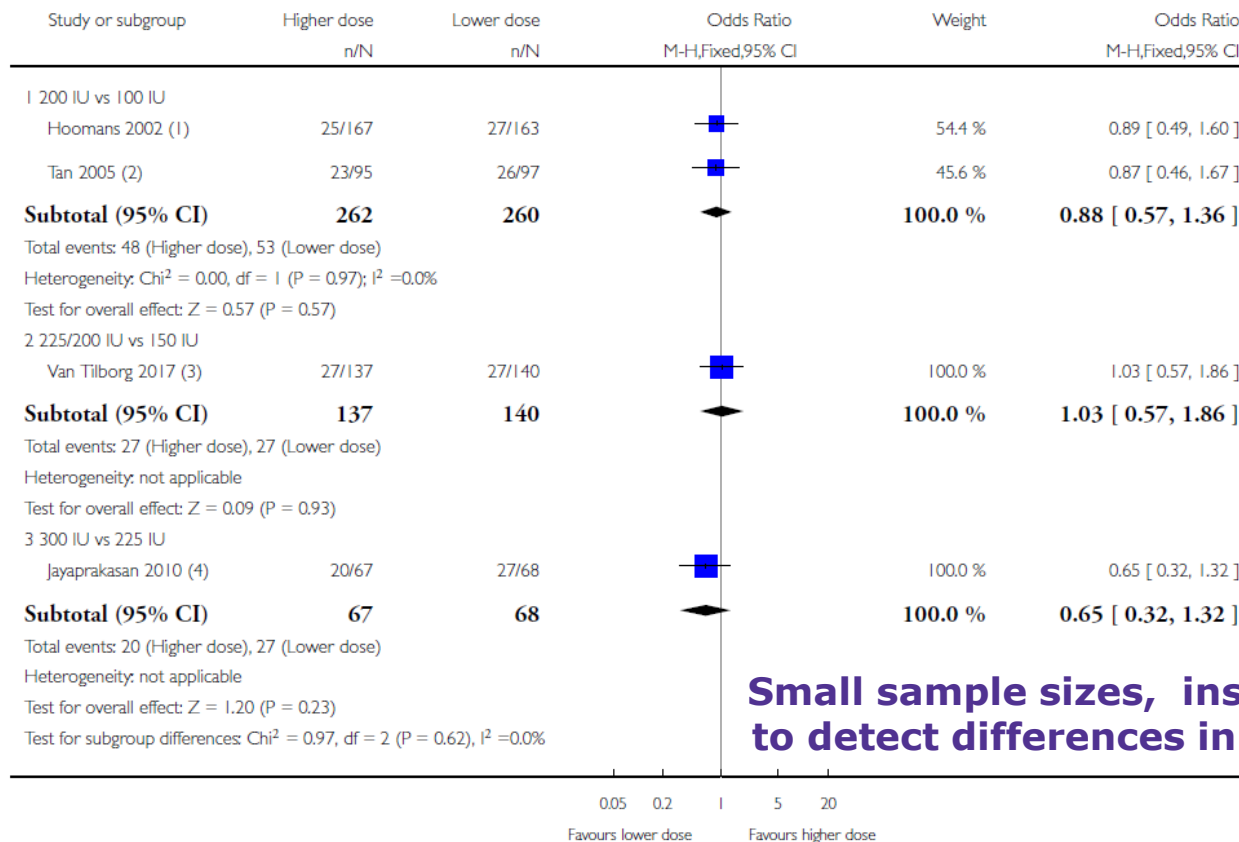


Significantly higher with 200 IU vs 100 IU

Significantly higher with 200/ 225 IU vs 150 IU

No significant difference with 225 IU vs 300 IU

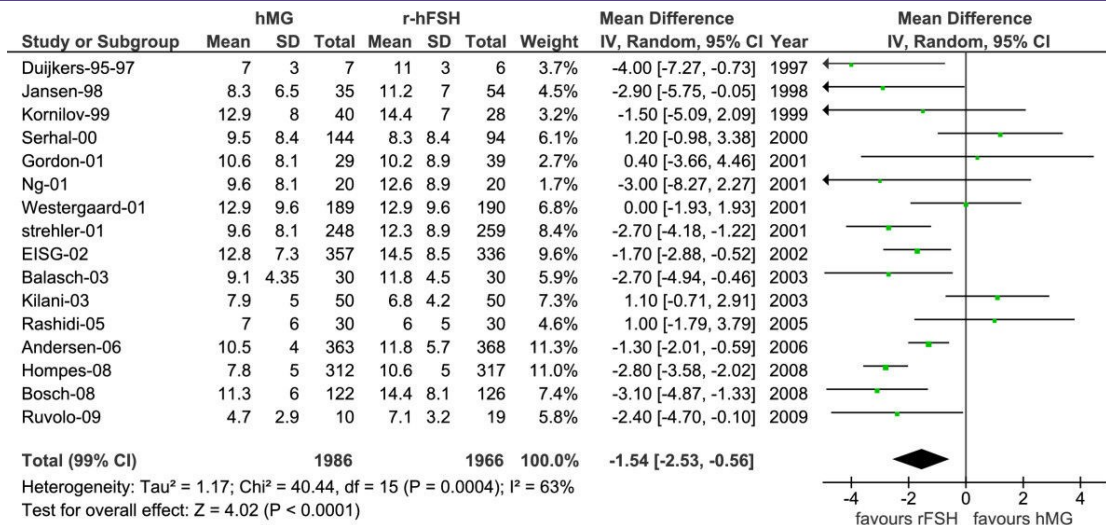
Live birth/ongoing pregnancy rate



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

Recombinant human follicle-stimulating hormone produces more oocytes with a lower total dose per cycle in assisted reproductive technologies compared with highly purified human menopausal gonadotrophin: a meta-analysis

Philippe Leher¹, Joan C Schertz², Diego Ezcurra^{3*}



Number of oocytes. Number of oocytes for hMG versus r-hFSH in 16 studies (main analysis population, data reported by study authors for 3,952 patients). Forest tree with mean difference using the random effects model

*Ratio number of oocytes/
1000 IU of gonadotropin dose*

4.39 for hMG vs 5.10 for r-FSH

Mean difference
0.70 oocytes/1,000 IU
(p=0.021)

Higher drug efficiency
with r-FSH

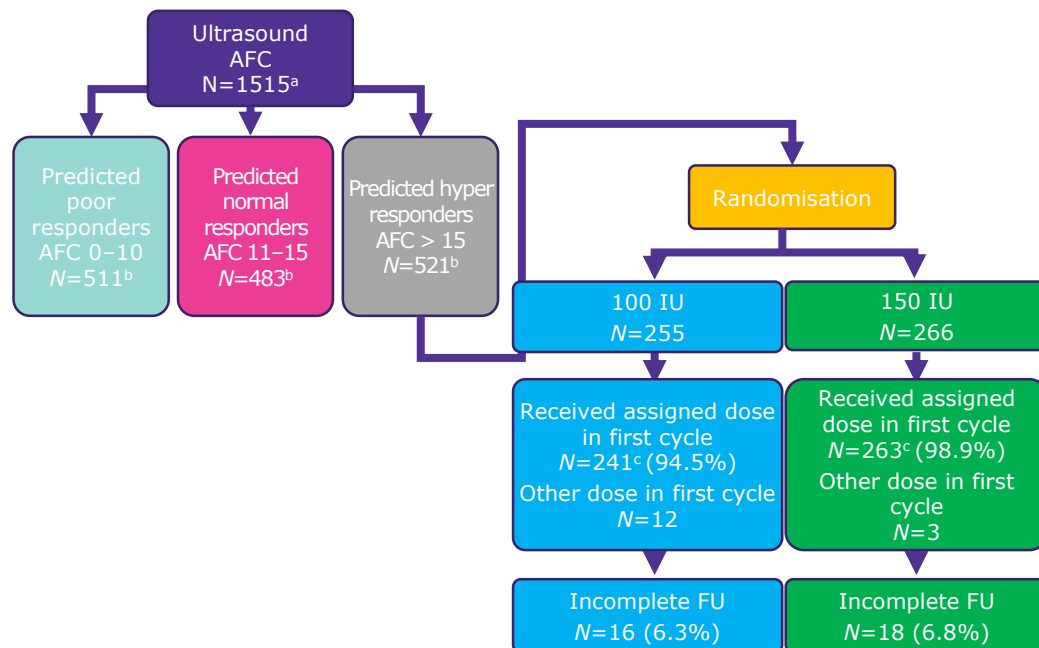


Hyper responder

Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 2: The predicted hyper responder

Simone C. Oudshoorn^{1,*}, Theodora C. van Tilborg¹,
 Marinus J.C. Eijkemans², G. Jur E. Oosterhuis³, Jaap Friederich⁴,
 Marcel H.A. van Hooff⁵, Evert J.P. van Santbrink⁶, Egbert
 A. Brinkhuis⁷, Jesper M.J. Smeenk⁸, Janet Kwee⁹, Corry H. de
 Koning¹⁰, Henk Groen¹¹, Cornelis B. Lambalk¹², Ben Willem
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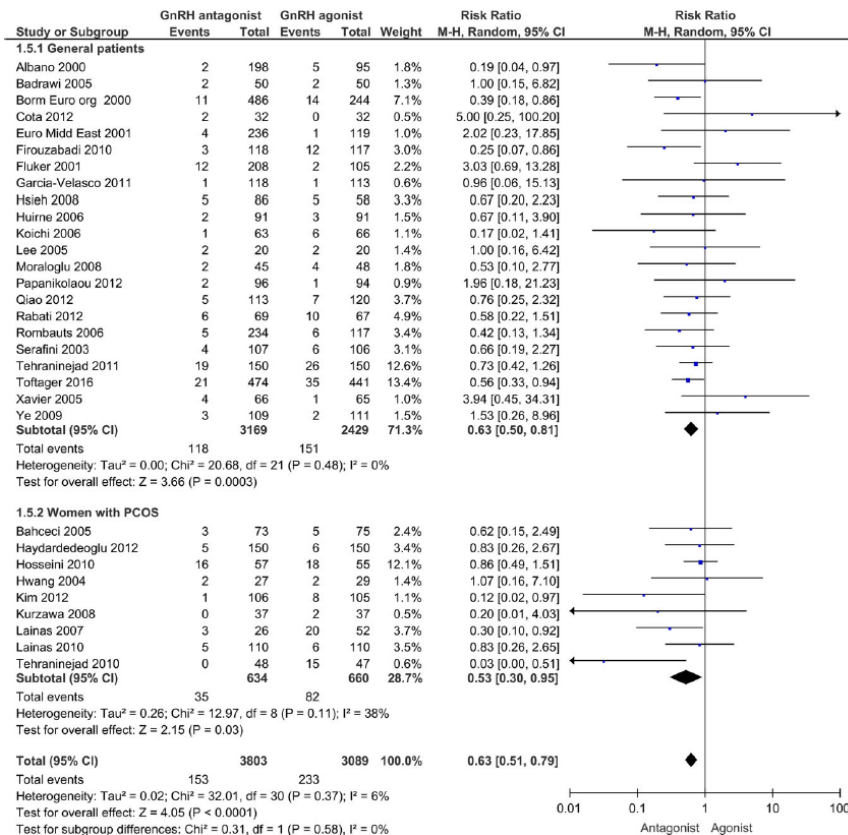
Results 18 months follow-up	100 IU (n=253)	150 IU (n=266)	P-value
Number of oocytes	9.0 (4.9)	11.9 (6.0)	<0.001
Poor response	133/459 (29.0%)	68/474 (14.3%)	<0.001
Hyper response	48/459 (10.5%)	144/474 (30.4%)	<0.001
Number of embryo transfers	349/461 (75.7%)	376/475 (79.2%)	0.219
Number of OHSS events	24/456 (5.2%)	56/474 (11.8%)	0.001
Classification OHSS			
Mild	18/456 (3.9%)	40/474 (8.4%)	0.008
Moderate	0/456	11/474 (2.3%)	0.001
Severe	6/456 (1.3%)	5/474 (1.1%)	0.712

	100 IU (n=255)	150 IU (n=266)	RR (95%CI)	P-value
Ongoing pregnancy within 18 months of FU resulting in live birth	169 (66.3%)	185 (69.5%)	0.953 (0.85–1.07)	0.423

Baseline characteristics FSH dose	100 IU (n=255)	150 IU (n=266)
Age, years	32.0 (4.3)	31.6 (4.5)
AFC, median (IQR)	20.0 (7.0)	21.0 (8.0)
AMH (ng/ml), median (IQR)	3.26 (1.98)	3.00 (1.89)

Would you use the GnRH agonist or the GnRH antagonist regimen?

GnRH agonist vs antagonist: OHSS



Mild stimulation

ISMAAR definition¹

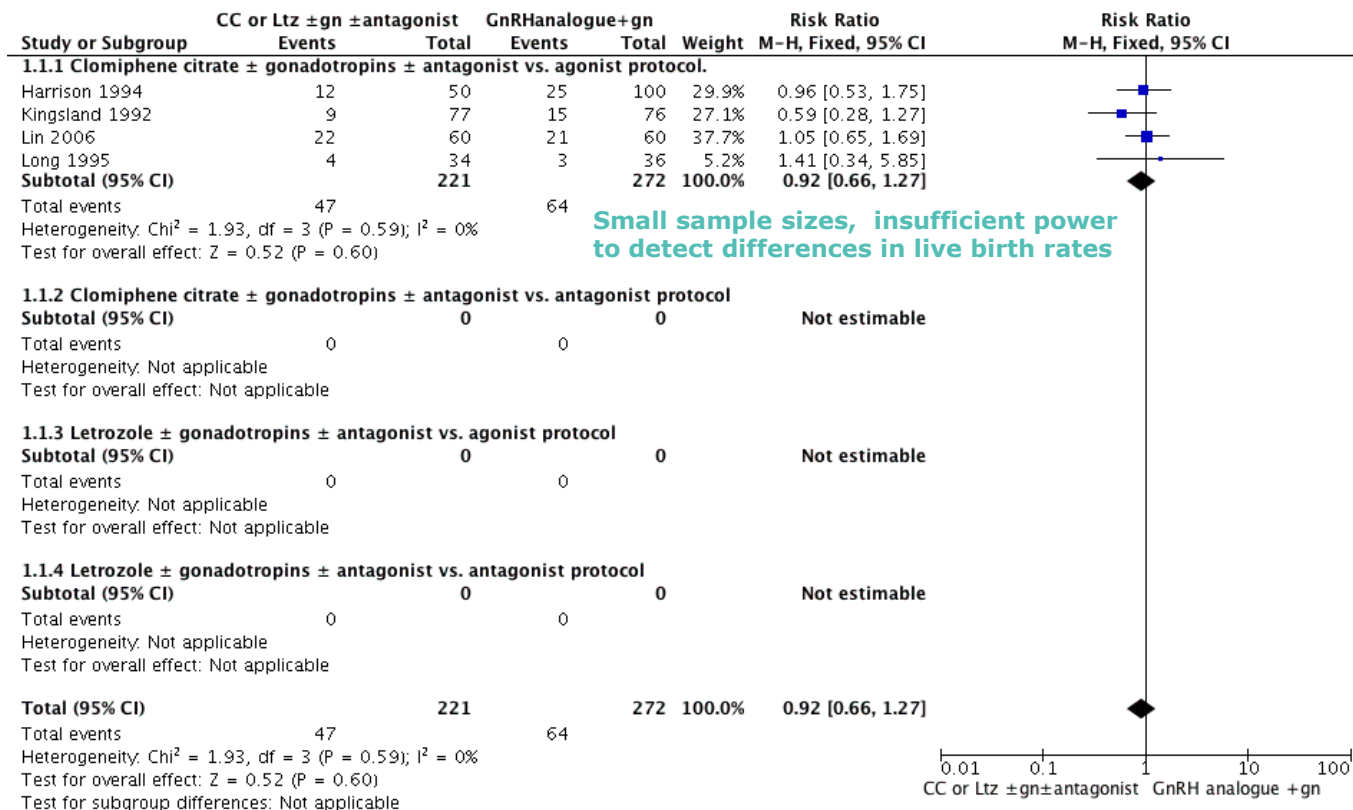
- Use of lower doses and/or a shorter duration of gonadotropin OR
- Use of oral anti-oestrogens or aromatase inhibitors alone or in combination with gonadotropin AND
- GnRH antagonist
- Aiming for 2–7 oocytes

ICMART definition²

- A protocol by which ovaries are stimulated with the intention of limiting the number of oocytes

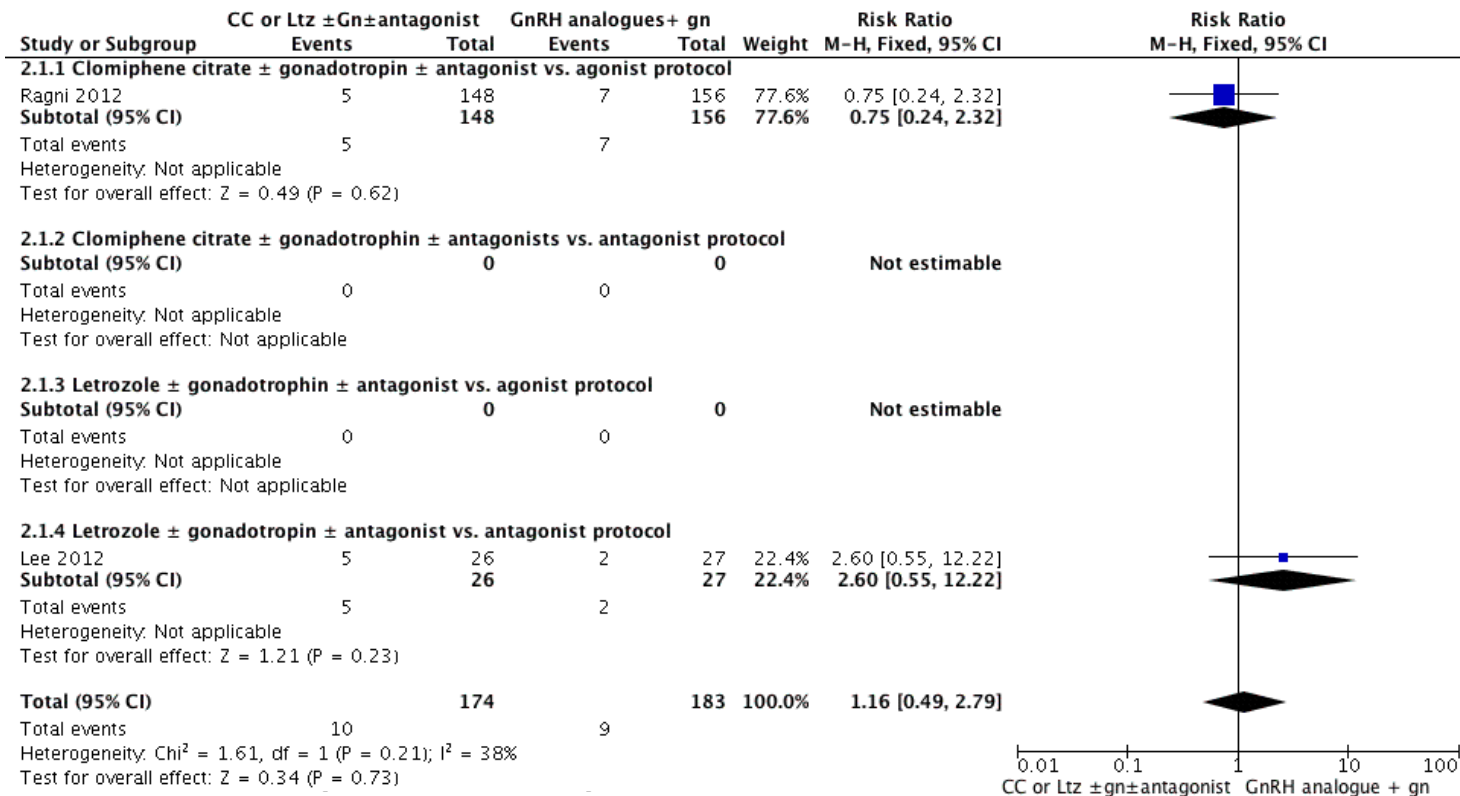
Mild stimulation: general patients

Live birth

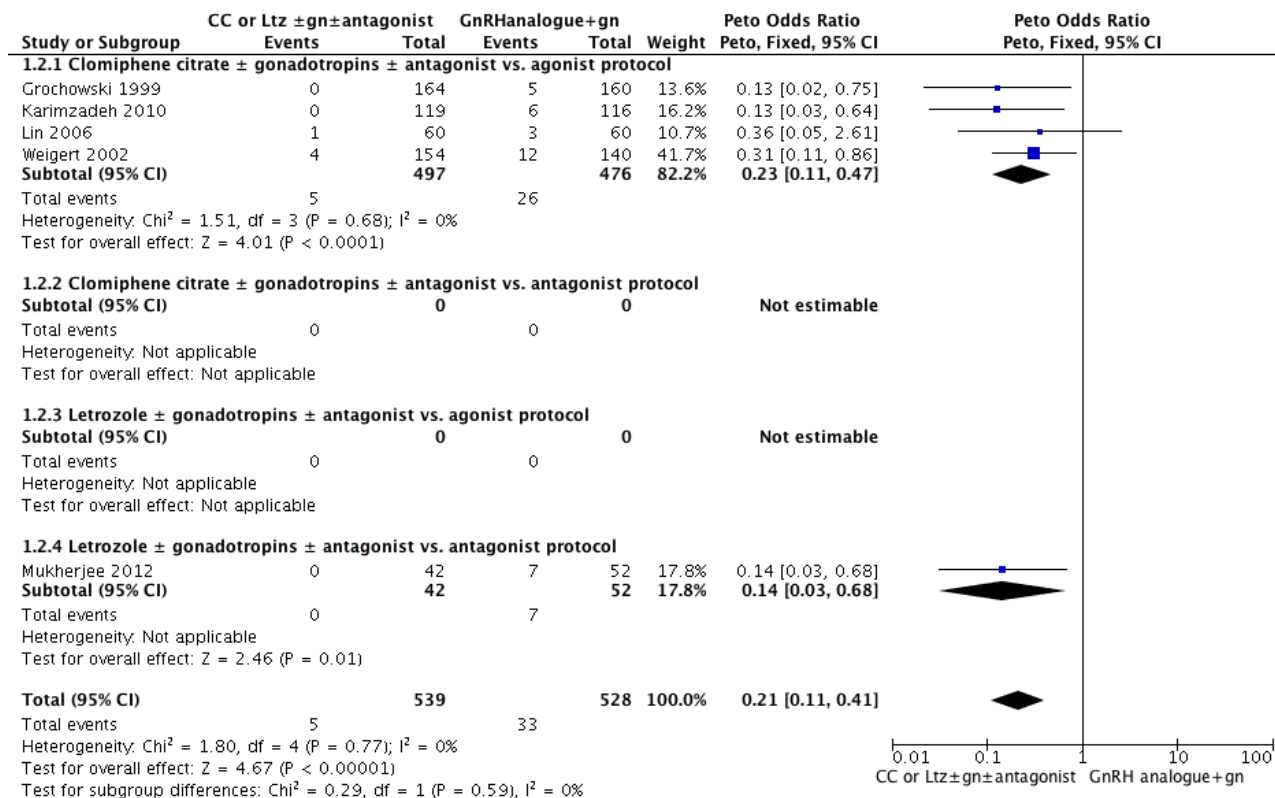


Mild stimulation: poor responders

Live birth



Mild stimulation: OHSS



Conclusions (1)

- **Number of oocytes retrieved is an important prognostic variable in IVF**
 - non-linear association between oocyte number and live birth following FRESH IVF
 - higher cumulative live birth rates with increasing oocyte numbers
- **Increased risk of OHSS with >20 oocytes; higher threshold with GnRH antagonist $\pm$ GnRH agonist trigger $\pm$ freeze all strategy**
- **Understanding important associations between *ovarian response, oocytes retrieved* and IVF outcomes is useful for planning ovarian stimulation regimens**

Conclusions (2)

- **Gonadotropin dose: 225 IU daily for normal responders; ≤ 150 IU daily for hyper responders**
- **No benefit from gonadotropin dose >300 IU/ day**
- **No standardised regimen for mild stimulation**
 - not an outcomes-based definition
 - lack of evidence for oocyte numbers 2–7
 - no cost-effectiveness studies for collective clinical end points – LBR, CLBR, OHSS
- **Individualised FSH dosing ensures safety and efficacy in ART**

Thank you

