POOR/SUBOPTIMAL OVARIAN RESPONSE: NEW CLASSIFICATION

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Disclosures

Declare receipt of honoraria for lectures from Merck

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Predictive factors in *in vitro* fertilization (IVF): a systematic review and meta-analysis

L.L. van Loendersloot [1,*], M. van Wely [1], J. Limpens [2], P.M.M. Bossuyt [3], S. Repping [1], and F. van der Veen [1]

- **Female age**
- **Duration of infertility**
- **Basal FSH**
- Type of infertility
- Indication
- Fertilization method
- **Number of oocytes retrieved**
- **Number of embryos transferred**
- **Embryo quality**

Predictive factors for pregnancy in ART

Negative predictors

No association

Positive predictor

ART, assisted reproductive technology;
FSH, follicle-stimulating hormone;
IVF, in vitro fertilization.

van Loendersloot LL, et al. Hum Reprod Update. 2010;16:577-89.

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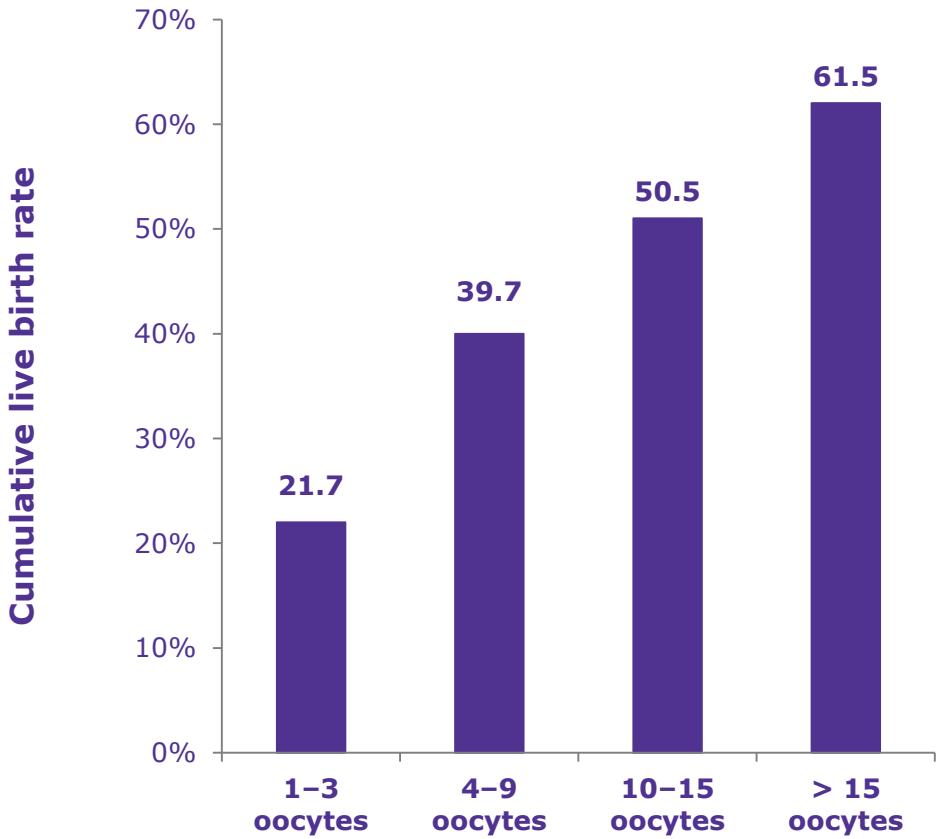
How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos?



- 1,099 patients, GnRH antagonist regimen, 150–225 rFSH daily
- Planned SET

	1–3 oocytes	4–9 oocytes	10–15 oocytes	> 15 oocytes	p value
Live birth rate, %	16.9	29.7	33.4	32.1	0.02
Cumulative live birth rate, %	21.7	39.7	50.5	61.5	< 0.001
Moderate–severe OHSS, n (%)	0	0	2 (0.6)	9 (4.1)	< 0.001

GnRH, gonadotropin-releasing hormone;
OHSS, ovarian hyperstimulation syndrome;
rFSH, recombinant FSH; SET, single embryo transfer.

Drakopoulos P, et al. Hum Reprod. 2016;31:370-6.

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Background

- Incidence of POR 6–20% of IVF cycles[1]
- Increasing incidence as women delay childbearing
- Incidence of DOR
  - **10% in 2003** and **18% in 2013**[2]

DOR, diminished ovarian reserve; POR, poor ovarian response.

1. Available from: www.IVF-Worldwide.com. Accessed April 2018.
2. Available from: www.sart.org. Accessed April 2018.

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Background (cont.)

- Wide range reflects varied demographics and definitions[1]
- Inconsistent, inconclusive evidence on POR management strategies, due to clinical heterogeneity among studies[2]
- POR remains a **therapeutic challenge** in IVF[2]

1. Badaway A, et al. Reprod Infertil. 2011;12:241-8.
2. Jirge PR. J Hum Reprod Sci. 2016;9:63-9.

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Our evidence | About us | Get involved | News and events | Cochrane Library

Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF)

Cochrane
Trusted evidence.
Informed decisions.
Better health.

Published:
20 January 2010

Authors:
Pandian Z, McTavish AR, Aucott L, Hamilton MPR, Bhattacharya S

Primary Review Group:
Menstrual Disorders and Subfertility Group

The successful end-point of IVF treatment is for a woman to give birth to a live infant. This outcome is based on various factors including adequate number of retrieved eggs, which are obtained using various treatment protocols. Failure to recruit adequate follicles, from which the eggs are retrieved, is called a 'poor response'. Various treatment protocols targeted at these women have been proposed, aiming to increase their ovarian response. This review of ten randomised controlled
any one pa
responder
outcomes
as positive
adverse ou

Conclusion:

There is insufficient evidence to support the routine use of any particular intervention for: pituitary downregulation, ovarian stimulation, or adjuvant therapy

Pandian Z, et al. Cochrane Database Syst Rev. 2010;1:CD004379.

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Risk factors for POR

- Advanced female age
- Lifestyle-related factors
  - smoking
  - obesity
- Medical causes
  - endometriosis, ovarian surgery
  - chemotherapy, radiotherapy
- Genetic
- Autoimmune
- Idiopathic

Badaway A, et al. Reprod Infertil. 2011;12:241-8.

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POR: history

- POR first described in 1983[1]

- Patients described as low responders; POR associated with
  - low serum estradiol (E2) levels
  - higher gonadotropin stimulation dose requirement[2]

1. Garcia JE, et al. Fertil Steril. 1983;39:174-9.
2. Badaway A, et al. Reprod Infertil. 2011;12:241-8.

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POR: definition

- Varied terminology
  - poor response
  - low response
  - inadequate response
  - suboptimal response ….etc.
- Numerous definitions
  - several criteria
  - different thresholds

Ferraretti AP, et al. Hum Reprod. 2011;26:1616-24.

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POR: definition (cont.)

Criteria used to define "poor responders."

Criteria	Reference
No. of mature follicles	
<2	2, 3
<3	4, 5, 6, 7
≤4	1, 8
<5	
Early follicular phase levels (mIU/mL)	
>6.5	
>9	12
>12	11
>15	3, 13, 14, 15
↑ FSH:LH ratio	17
Maximal E_2 level (pg/mL)	
<100 on day 5	10
<300	7
<400	14, 18
<500	3, 6, 21
<66	27
"E	19
	11
ay gonadotropin dose	
300 IU	2, 12, 22, 23
Total gonadotropin dose	
>25 ampules	11
>44 ampules	41
Days of gonadotropin therapy	2, 11, 13
No. of mature oocytes retrieved	
≤3	6
≤4	24
<6	25
Single dominant follicle	6
Spontaneous LH surge	7
Failed "Lupron screening test"	55, 86
Failed conception	27
Undefined	49, 51

28 different criteria[1]

Criteria related to patients' demographics	
Patients' age,	4 (9%)
>35 y	1
>38 y	1
>40 y	
Previous cycle cancellation	
Ovarian reserve markers	
Antral follicle count	
<5	
<7	
<12	
High basal FSH (cycle D	
>8.5	
>10	
>12	
>15	
M	
P	
	4
	2
	19 (40%)
	2
	8
	7
	2
s retrieved	5 (11%)
	4
	1
Lev E_2 on the final	16 (34%)
day of stimulation	
450	1
500	9
Other higher threshold	6
Good quality embryos	2 (4%)
Gonadotropin doses per day	14 (30%)
225 IU	2
300 IU	7
Other/not stated	5

47 RCTs, 41 different criteria
No more than 3 trials used the same definition
Same research group used different definitions[2]

RCT, randomized controlled trial.

1. Polyzos NP, Devroy P. Fertil Steril. 2011;96:1058-61.
2. Surrey ES, Schoolcraft WB. Fertil Steril. 2000;73:667-76.

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

A.P. Ferraretti[1,*], A. La Marca[2], B.C.J.M. Fauser[3], B. Tarlatzis[4], G. Nargund[5], and L. Gianaroli[1] on behalf of the ESHRE working group on Poor Ovarian Response Definition‡

- **At least two of the following three features must be present**
  - advanced maternal age (≥ 40 years) or any other risk factor for POR (Turner syndrome, X-fragile mutations, hystory of chemotherapy, etc.)
  - 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)

- Two episodes of POR after maximal stimulation are sufficient to define a patient as a poor responder
- Patients > 40 years with an abnormal ovarian reserve test should be more properly defined as **expected** POR patients

AFC, antral follicle count; AMH, anti-Mullerian hormone;
ESHRE, European Society of Human Reproduction and Embryology.

Ferraretti AP, et al. Hum Reprod. 2011;26:1616-24.

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Bologna criteria (ESHRE, 2011)

"Designed to select **homogeneous** groups of **patients** based on '**oocyte quantity**' for testing in prospective randomized trials for different strategies"

Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011 Jul;26(7):1616-24.

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Subgroups: Bologna ESHRE criteria

Category	Subgroups	ESHRE criteria fulfilled
No previous IVF attempt	≥ 40 years (± risk factor for POR) + abnormal ORT	1 + 3
1 previous IVF attempt with POR	≥ 40 years (± risk factor for POR)	1 + 2
	Abnormal ORT	2 + 3
	≥ 40 years (± risk factor for POR) + abnormal ORT	1 + 2 + 3
2 previous IVF attempts with POR	No risk factor for POR and normal ORT	Supplemental criterion 4
	≥ 40 years (± risk factor for POR) but normal ORT	1 + supplemental criterion 4
	Abnormal ORT but no risk factor for POR	3 + supplemental criterion 4
	≥ 40 years (± risk factor for POR) and abnormal ORT	1 + 3 + supplemental criterion 4

8 subgroups (even 13)

ORT, ovarian reserve test.

Papathanasiou A. Human Reproduction. 2014;29:1835-8.
Fischer R. Personal data.

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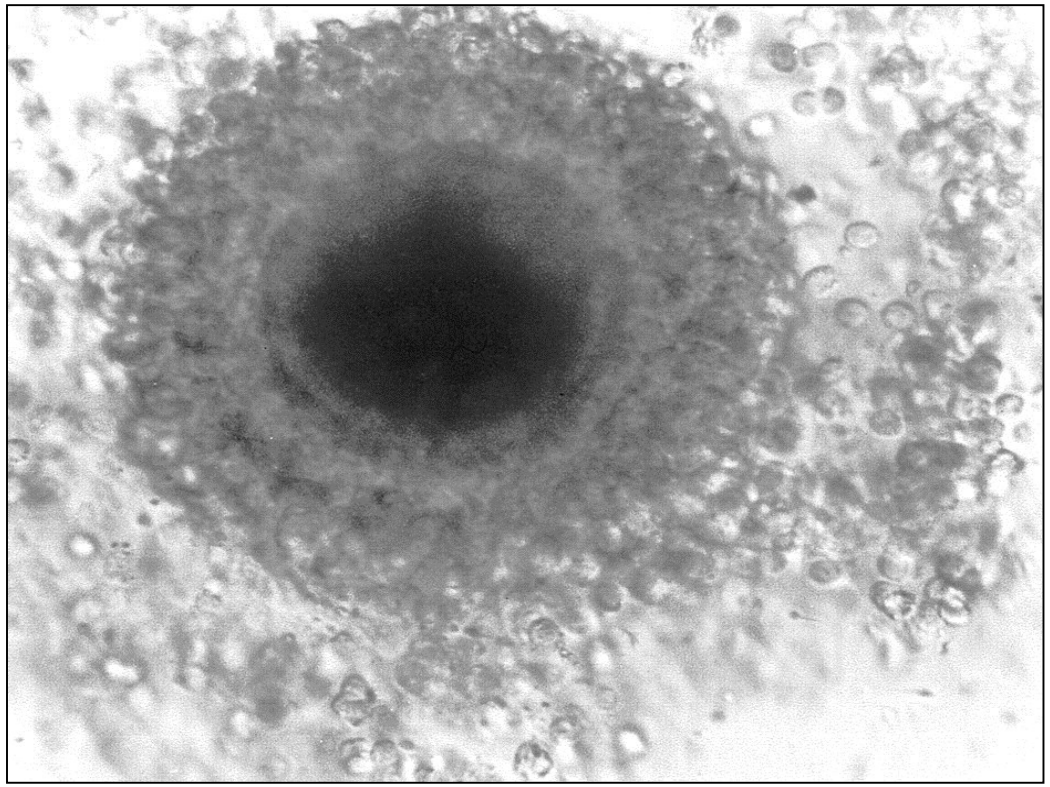
The ovarian response marker

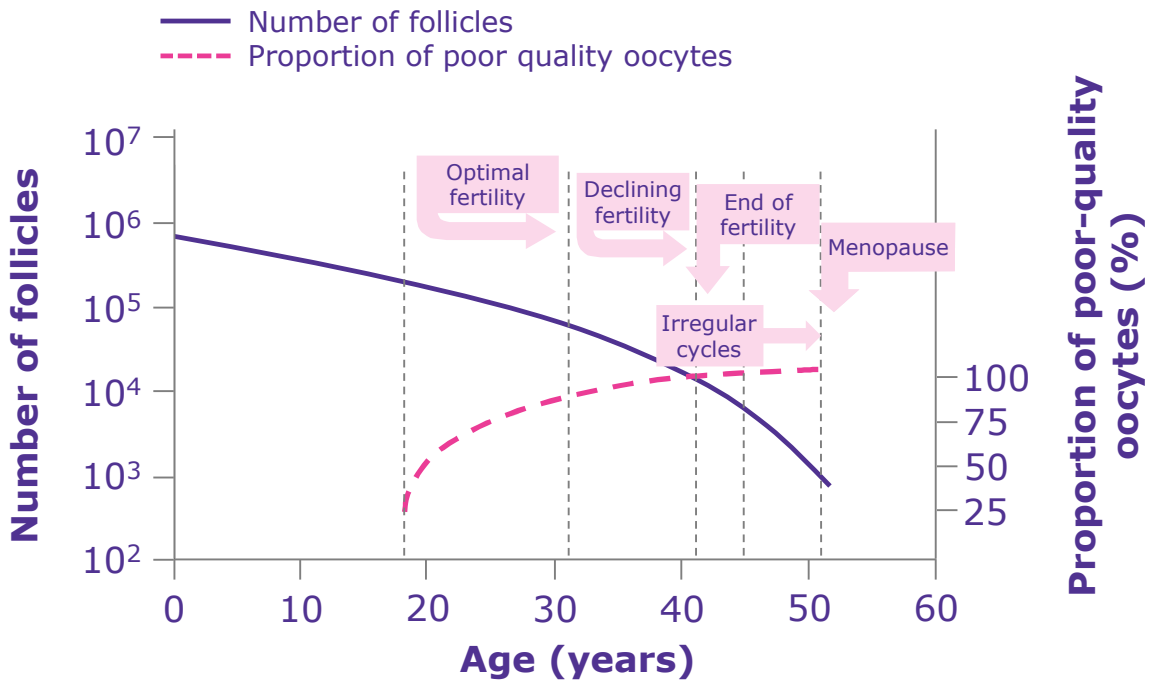
A good marker should correctly predict oocyte quality

Live birth prediction



A good marker should describe the size of the antral follicle pool

Ovarian response



Broekmans FJ, et al. Endocr Rev. 2009;30:465-93.

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What markers can we use?

Age

Markers of ovarian reserve

Hormonal biomarkers:
FSH, inhibin B, AMH

Functional markers:
AFC

Fleming R, et al. Reprod Biomed Online. 2015;31:486-96.

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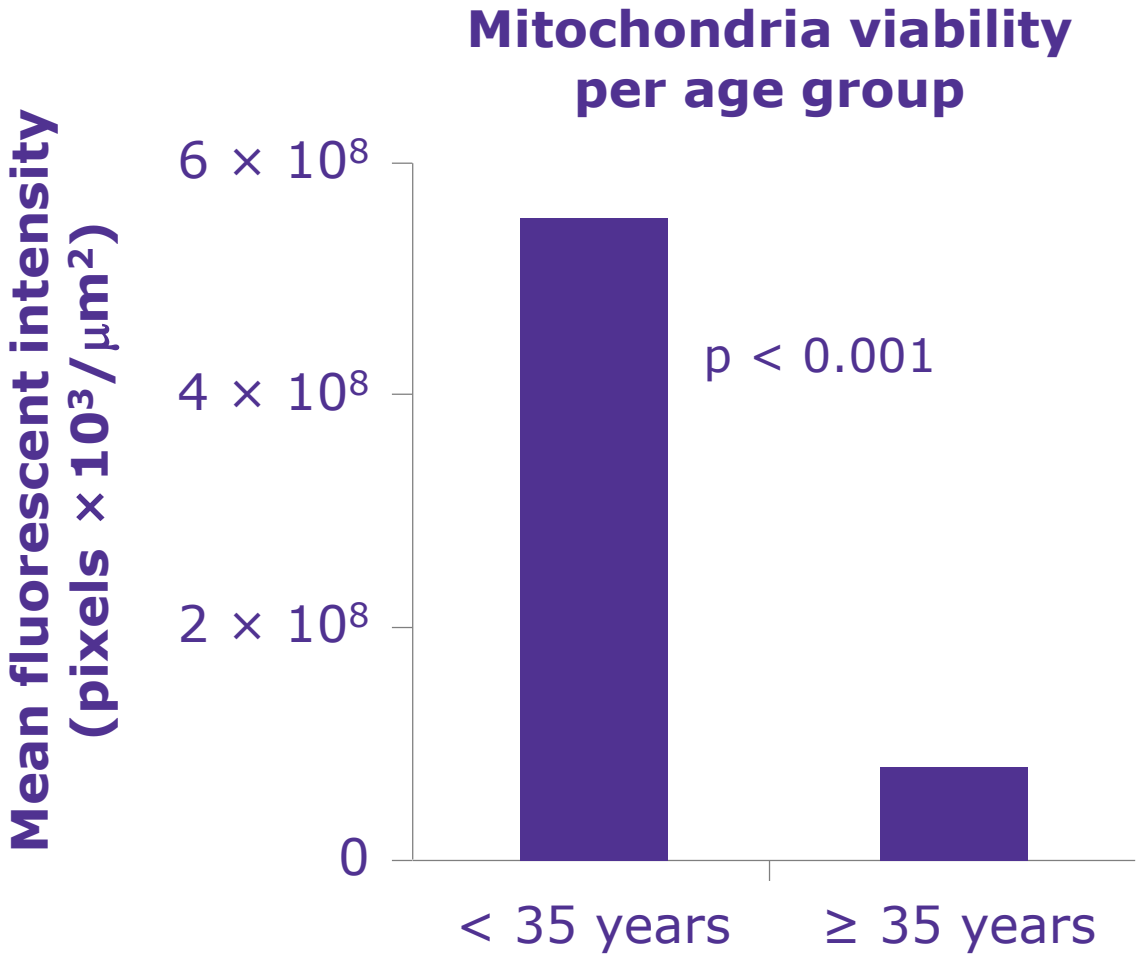
Influence of age on oocyte quality

- **M**itochondrial function impaired (less energy)
- **G**ranulosa cell number reduced (apoptosis)
- **O**xidative stress increased



Ben-Meir A, et al. Aging Cell. 2015;14:887-95.
Weall BM, et al. Reproduction. 2015;149:147-54.

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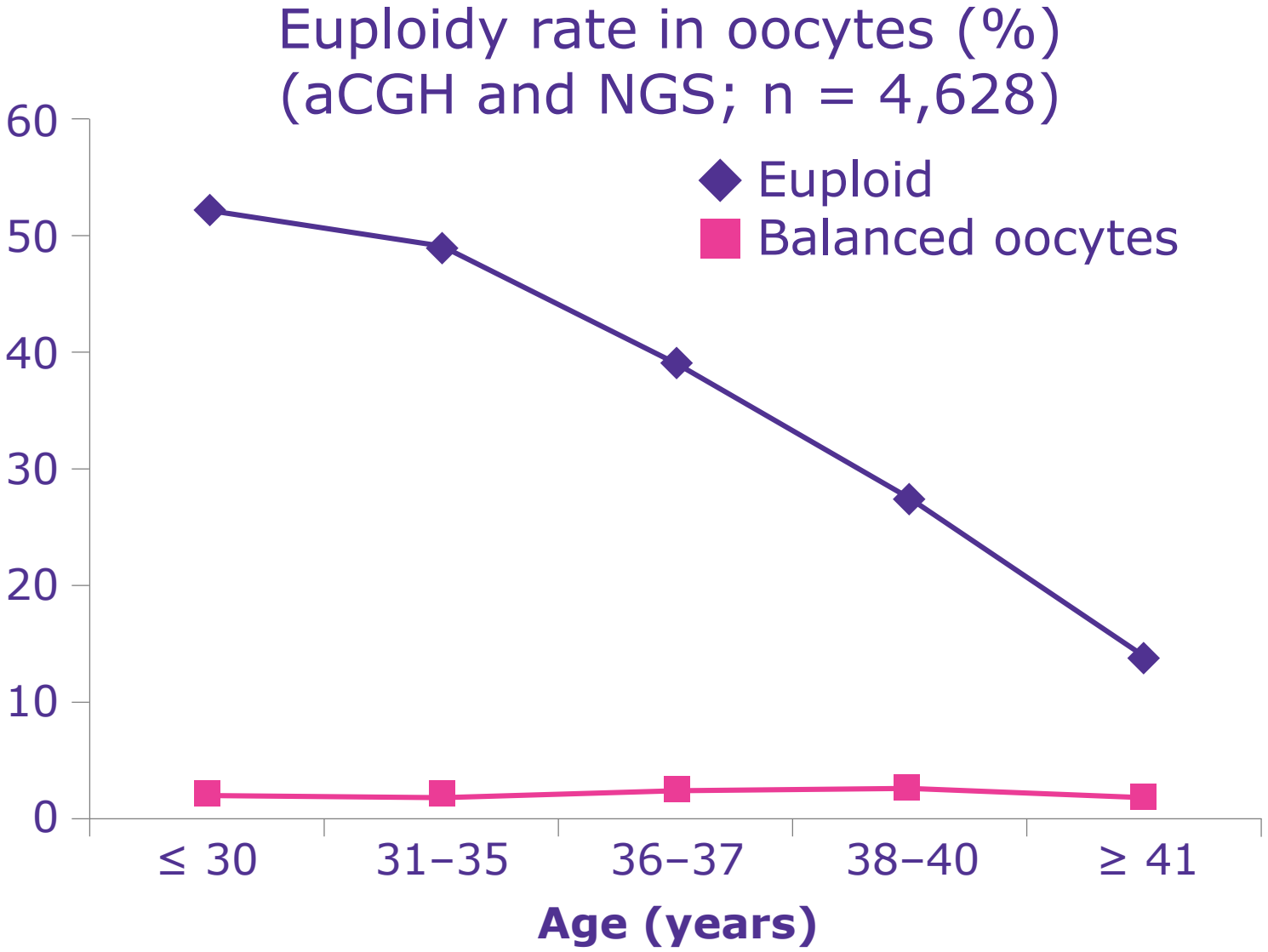
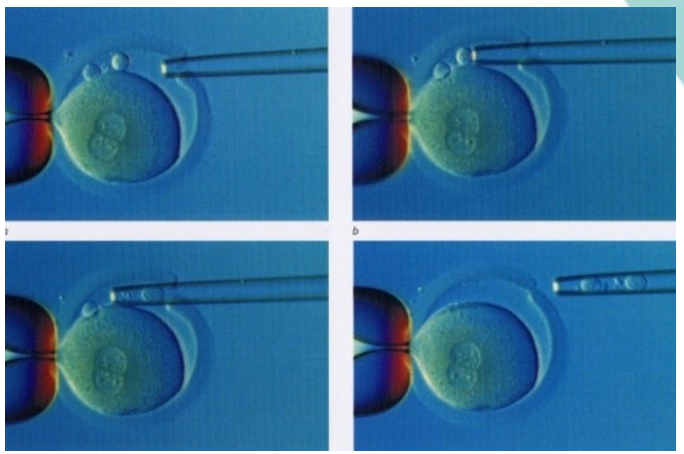
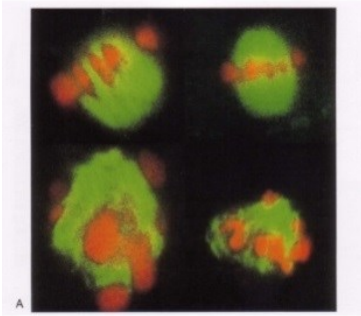
Aneuploidy and oocyte yield (FCH data)







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

Fischer R. Personal data.

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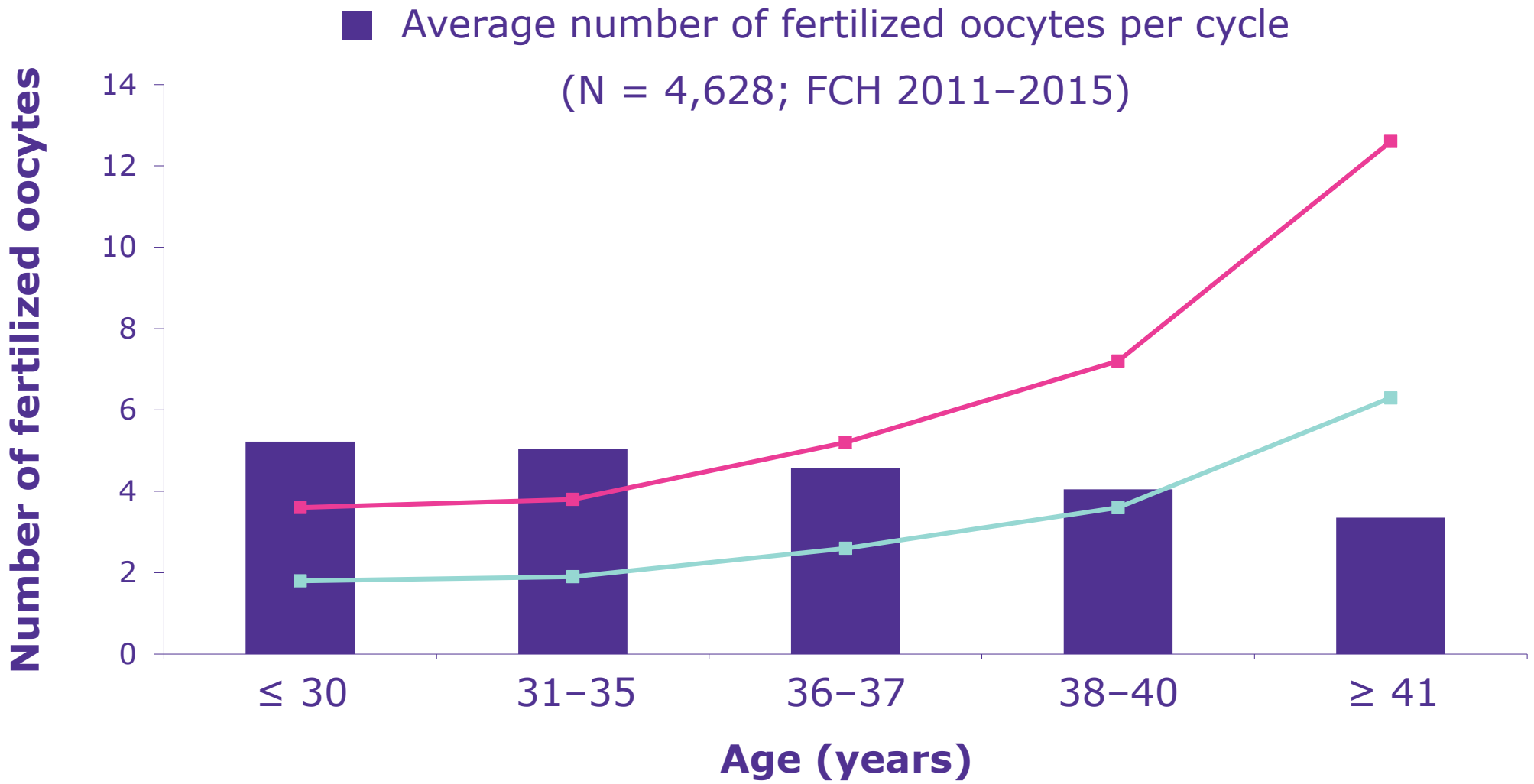
Required number of fertilized oocytes to transfer one (■) or two (■) "euploid" embryos



Fischer R. Personal data.

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Aneuploidy rates increase with age

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

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

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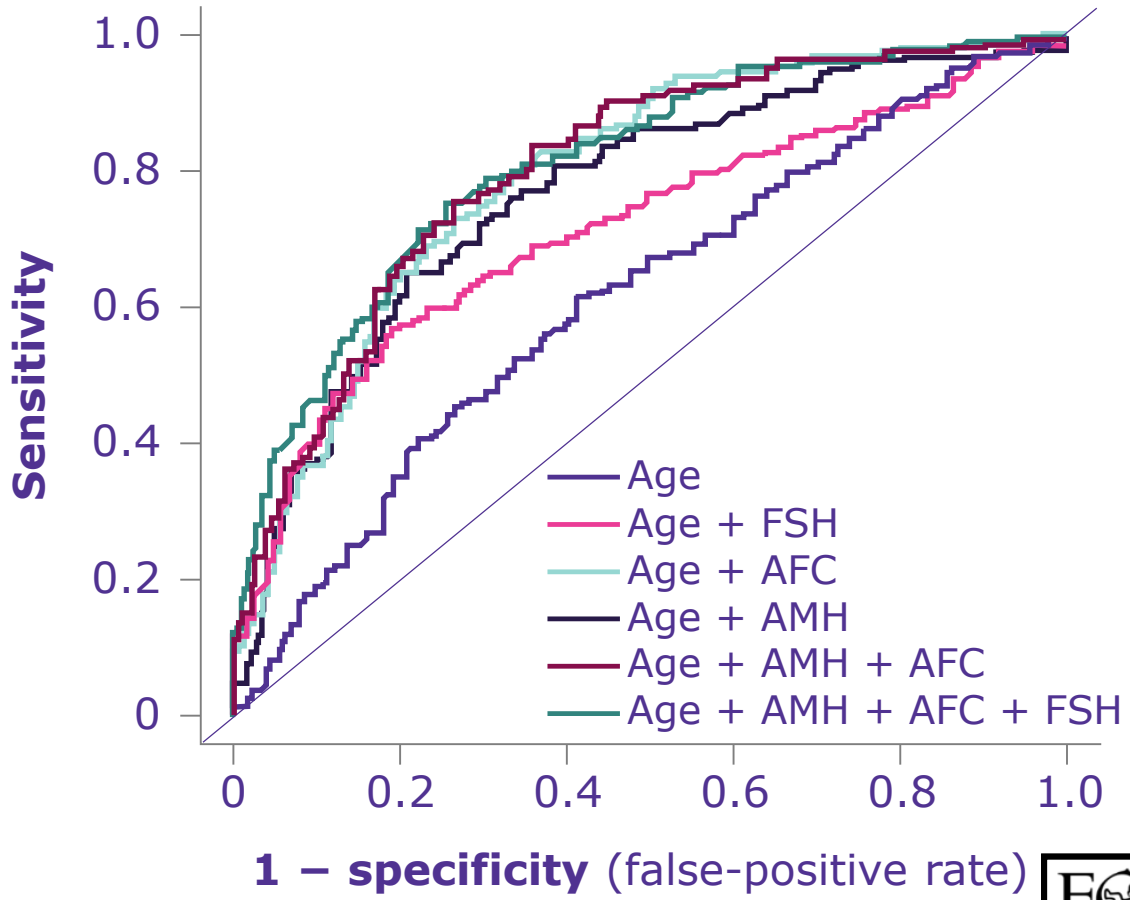
Prediction of POR (< 5 oocytes)
Agonists; N = 5,705

	AUC	95% CI	p value
Poor response prediction			
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



AUC, area under the curve; CI, confidence interval; NA, not applicable.

Broer SL, et al. Hum Reprod Update. 2013;20:688-701.

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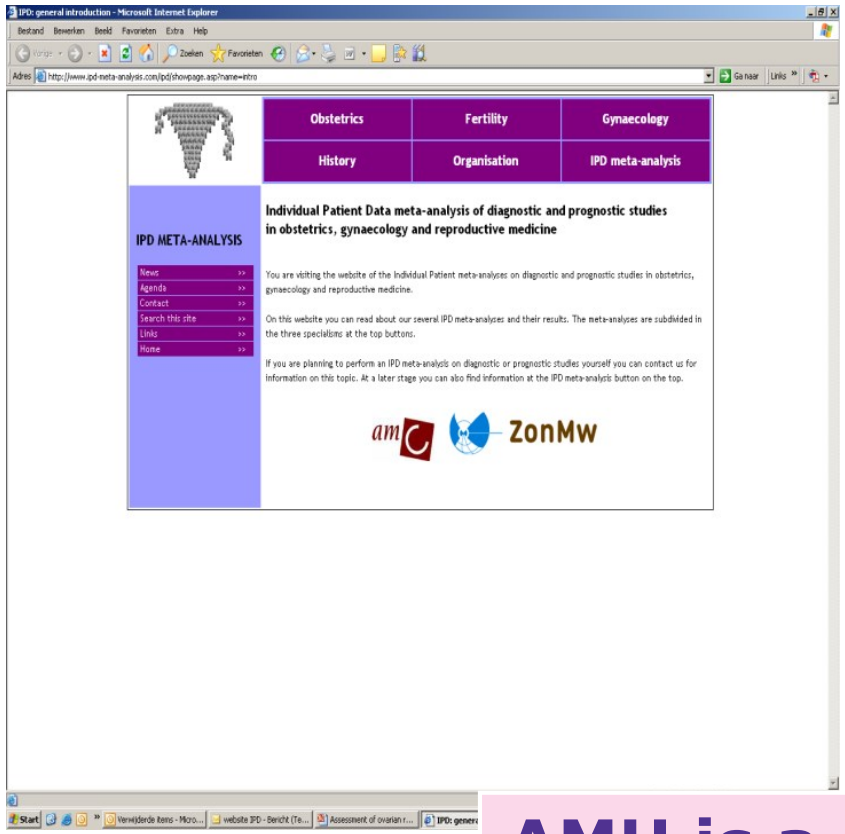
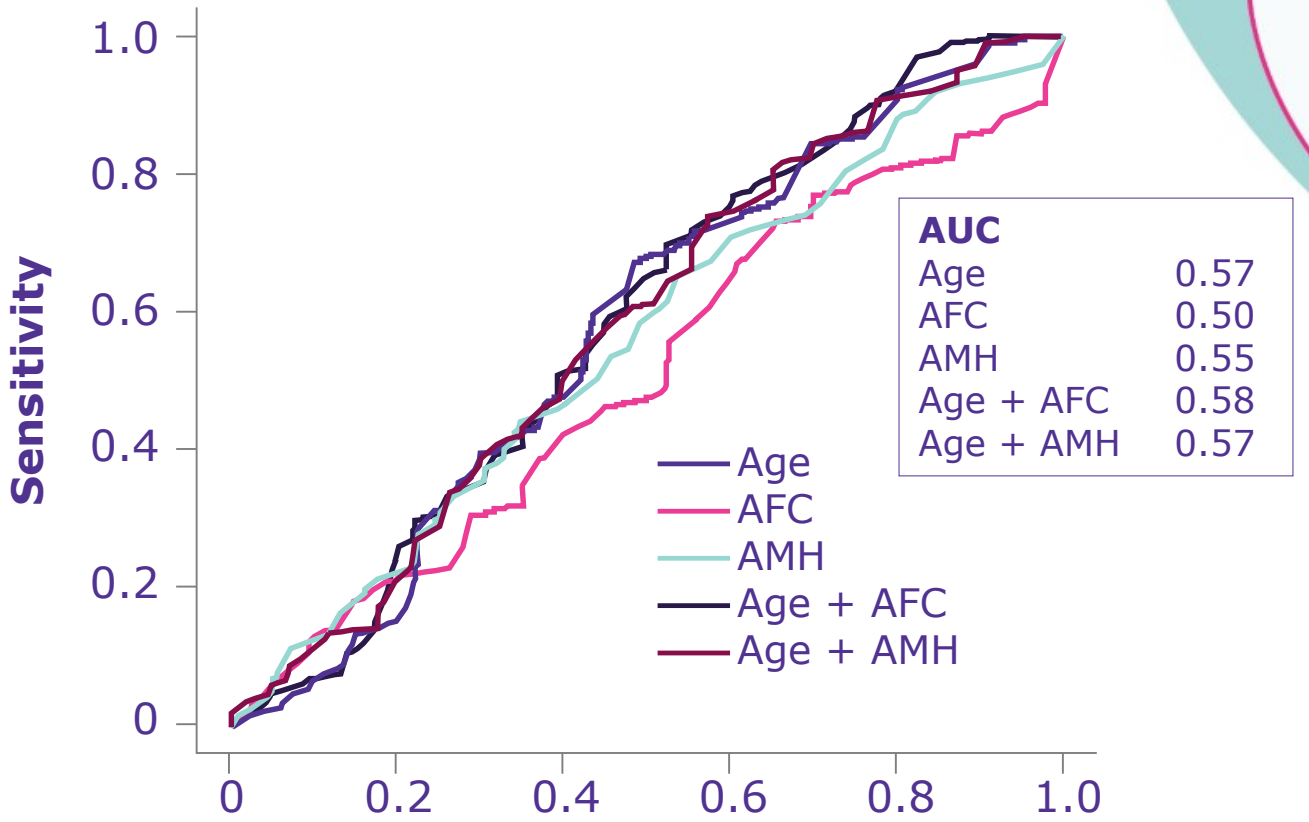
Prediction of ongoing pregnancy





N = 5,705

AMH is a quantity marker
NOT a quality marker
Same for AFC!

Broer SL, et al. Hum Reprod Update. 2013;20:688-701.

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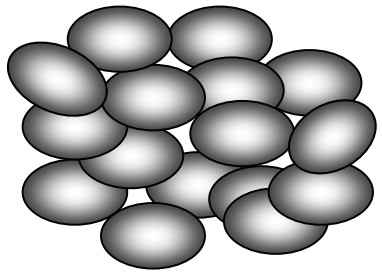
"FORT – Follicle Output RaTe": an index of ovarian sensitivity to FSH

Ratio preovulatory/small antral follicles

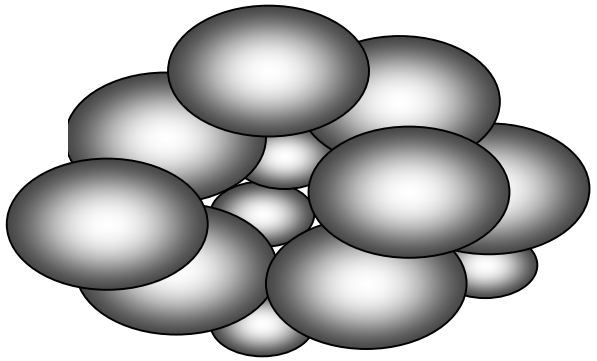
15



Small antral follicles

Normo-responder

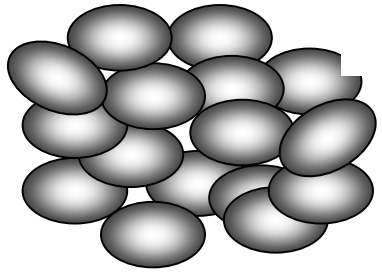
70%



Preovulatory follicles

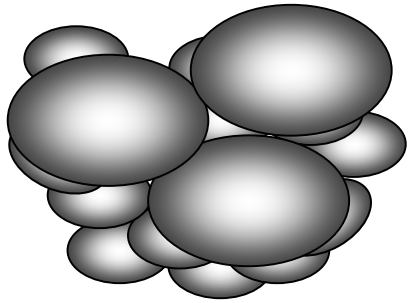
11

15



Hyporesponder

20%



3

Gallot V, et al. Hum Reprod. 2012;27:1066-72.

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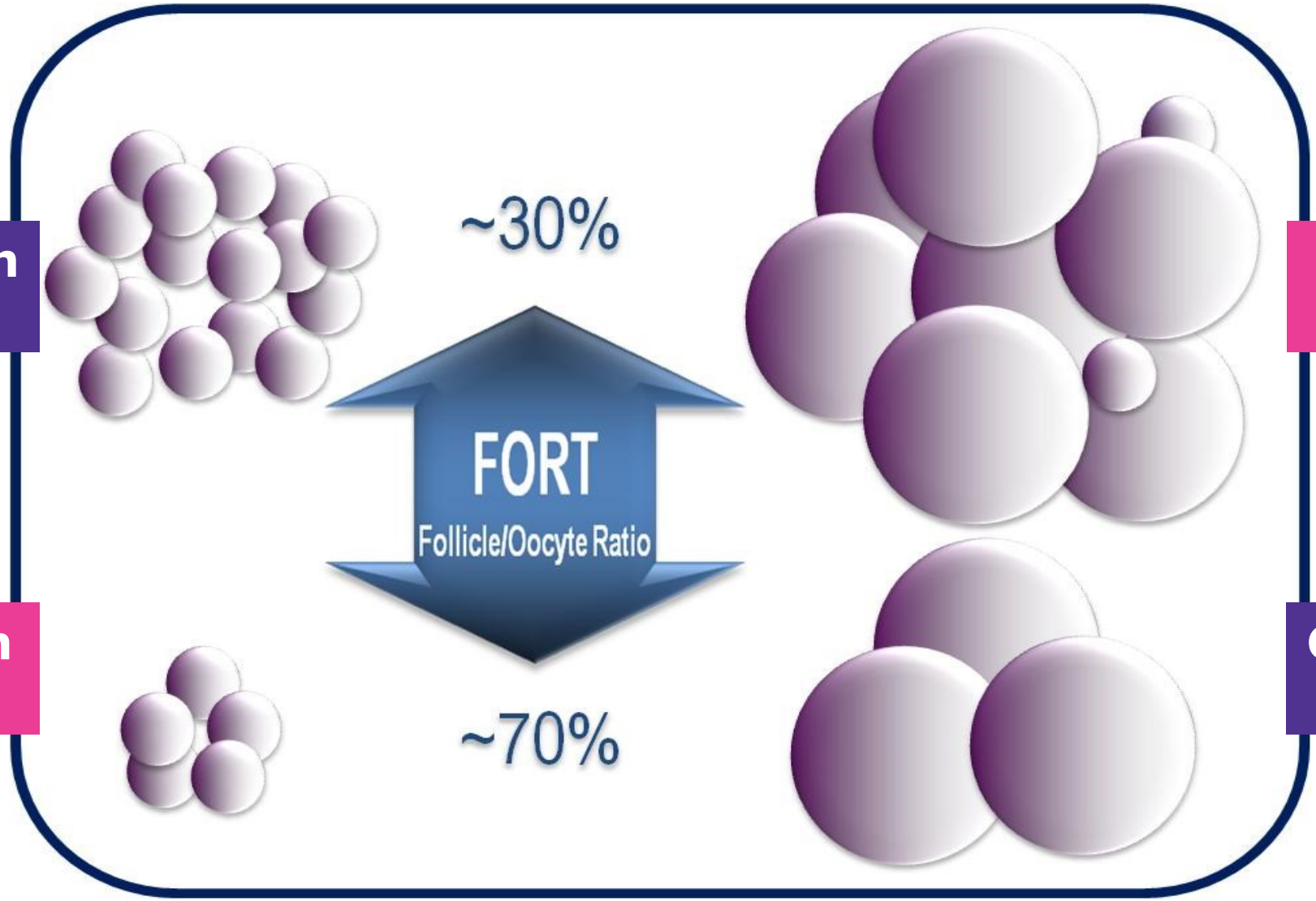
"FORT – Follicle Output RaTe"



Gallot V, et al. Hum Reprod. 2012;27:1066-72.

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What is a hyporesponse to FSH?

Hyporesponders are women with normal ovarian reserve who can achieve an "adequate" number of oocytes retrieved and estradiol production

BUT…

There is an increase in the cumulative FSH dose (i.e. > 3,000 IU) and in the stimulation length

Same reserve – different sensitivity to FSH/LH

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

LH, luteinizing hormone.

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What markers can we use?

Age

Markers of ovarian reserve

Hormonal biomarkers:
FSH, inhibin B, AMH

Functional markers:
AFC

Polymorphism

Genetic markers:
FSHR, LHCGR, V-βLH

FSHR, FSH receptor;
LHCGR: luteinizing hormone/choriogonadotropin receptor;
V-βLH, variant-beta LH.

Alviggi C, et al. Reprod Biomed Online. 2009;18:9-14.
Fleming R, et al. Reprod Biomed Online.2015;31:486-96.

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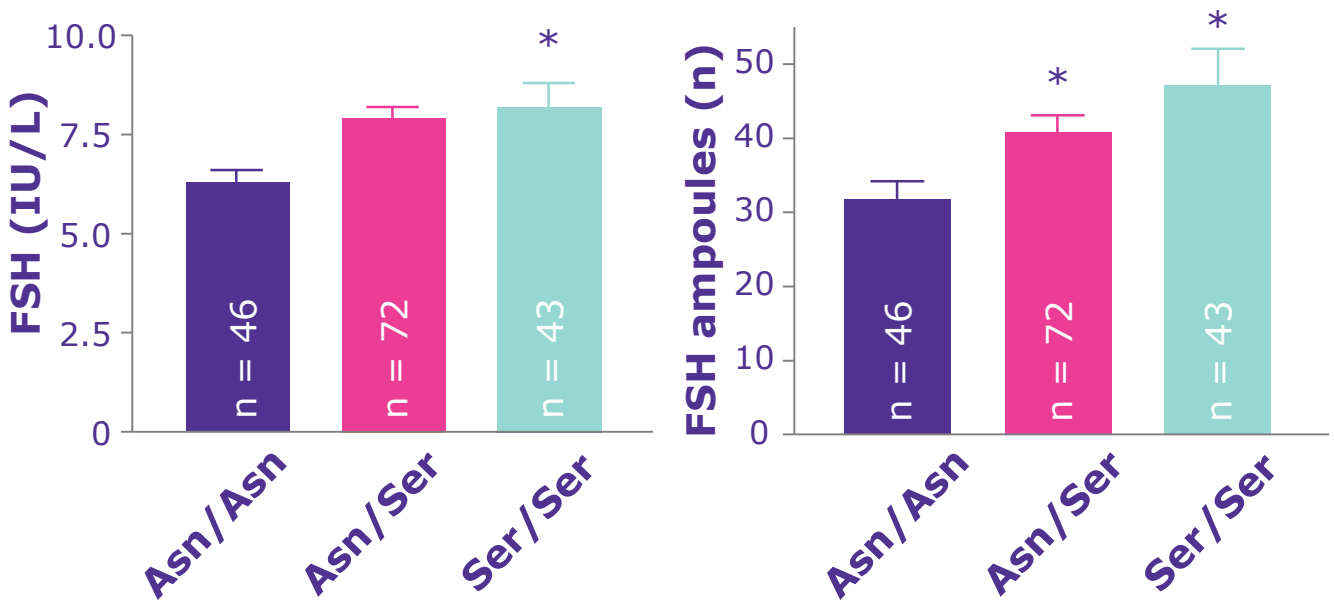
FSH consumption is higher in carriers of FSHR Ser^{680} and V-βLH variants

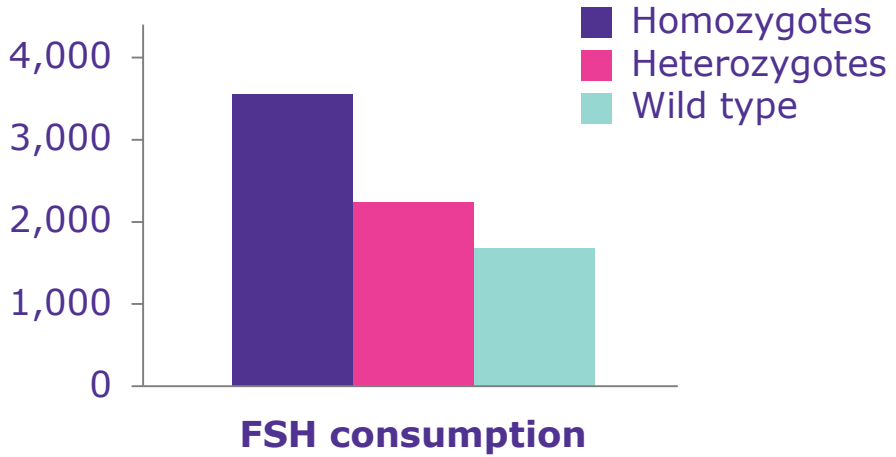
FSH receptor Ser^{680} genotype and ovarian response to FSH



* $p < 0.05$.
Asn, asparagine; Ser, serine; V-LH, variant LH.

V-βLH genotype and ovarian response to FSH

- 11.6% V-LH carriers found
- 10.2% heterozygotes
- 1.4% homozygotes



Alviggi C, et al. Reprod Biomed Online. 2009;18:9-14.
Alviggi C, et al. Reprod Biol Endocr. 2012;10:9.
Falconer H, et al. Acta Obstet Gynecol Scand. 2005 Aug;84:806-11.
Greb RR, et al. J Clin Endocrinol Metab. 2005;90:4866-72.
Gromoll J, Simoni M. Trends Endocrinol Metab. 2005;16:368-73.
Perez Mayorga M, et al. Clin Endocrinol Metab. 2000;85:3365-9.
Sudo S, et al. Mol Hum Reprod. 2002;8:893-9.

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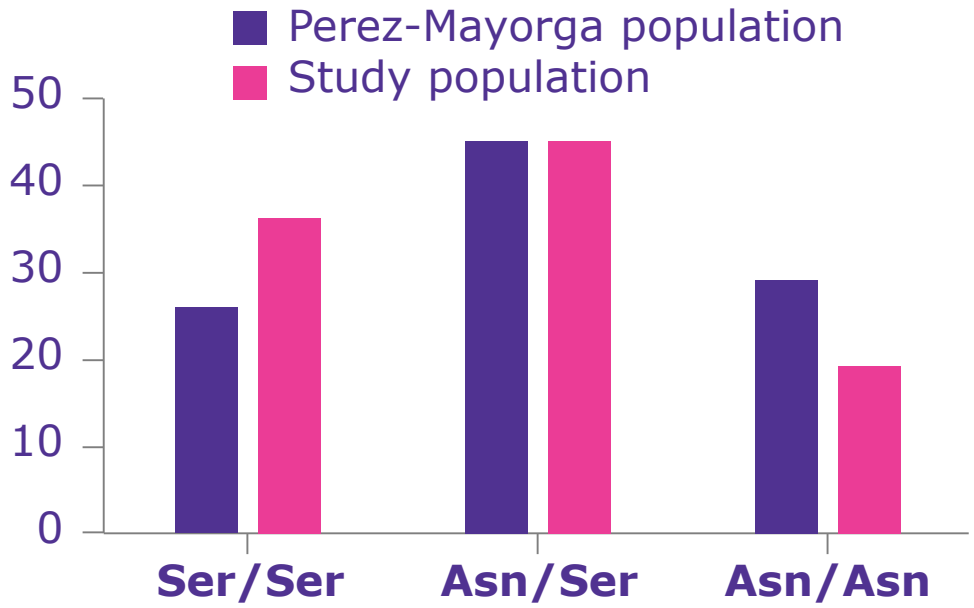
Frequency of FSH-R Ser^{680} is higher in patients selected as hyporesponders

Background

- 17 hyporesponder young patients who required a cumulative dose of rFSH > 2,500 UI (Group A) were compared with a control group of randomly selected patients who required a cumulative dose of rFSH < 2,500 UI (Group B)



Prevalence of FSHR polymorphisms: comparison between population study and data reported by Perez-Mayorga, et al.

Characteristics	Group A: Hyporesponders (n = 17)	Group B: Controls (n = 25)	p value
Distribution of the FSHR genotypes			
Ser/Ser, n (%)	10 (58.8)	5 (20)	0.02
Asn/Ser, n (%)	4 (23.5)	15 (60)	0.04
Asn/Asn, n(%)	3 (17.6)	5 (20)	NS

NS, not significant.

Alviggi C, et al. Reprod Sci. 2016;23:1103-8.
Perez Mayorga M, et al. J Clin Endocrinol Metab. 2000;85:3365-9.

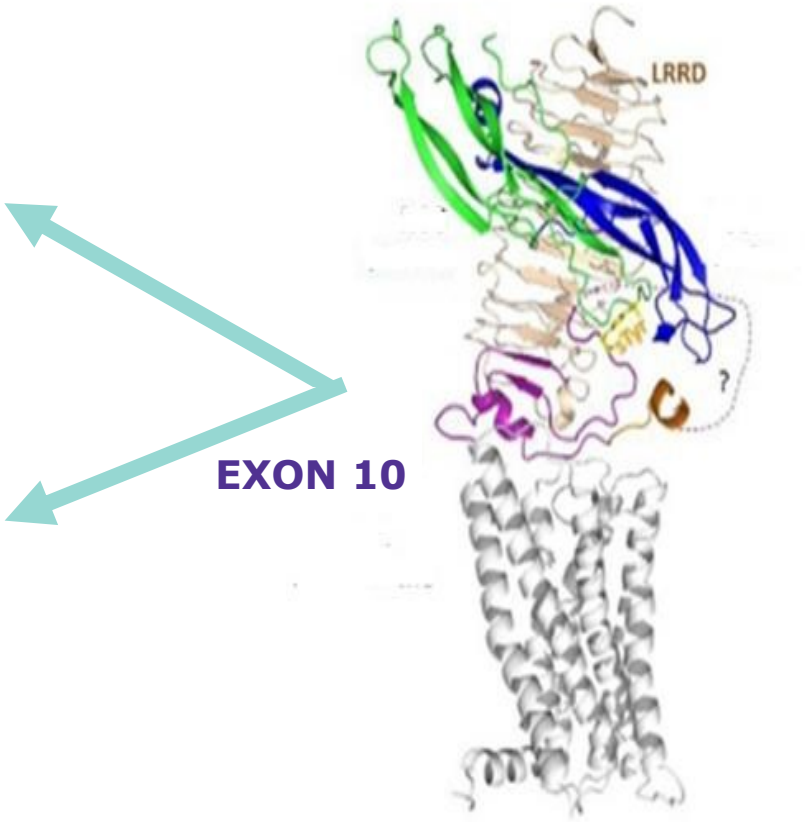
Two single nucleotide polymorphisms of LHCR affect sensitivity to exogenous gonadotropins

LHCGR 291Asn/Ser (rs12470652)

Preliminary data suggest that it could affect the number of oocytes/FSH consumption during COS[1]

LHCGR 312 Ser/Asn (rs2293275)

A few cohort studies have proposed that the N variant may render LHCGR more sensitive to the ligand[2]



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

Full length article

Role of Lh polymorphisms and r-hLh supplementation in GnRh agonist treated ART cycles: A cross sectional study

Ramaraju G.A.*, Ravikrishna Cheemakurthi, Kavitha Prathigudupu, Kavitha Lakshmi Balabomma, Madan Kalagara, Sivanarayana Thota, Muralikrishna Kota

Center for Assisted Reproduction, Krishna IVF Clinic, Maharanipeta, Visakhapatnam 530002, Andhra Pradesh, India

1. Alviggi C, et al. Hum Repod. 2016;32 (Suppl).
2. Lindgren I, et al. Hum Reprod 2016;31:672-83.
Ramaraju GA, et al. Eur J Obstet Gynecol Reprod Biol. 2018;222:119-25.

COS, controlled ovarian stimulation.

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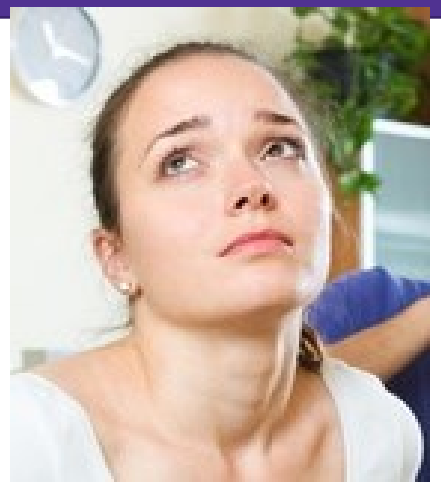
Problems with Bologna criteria: would you manage these patients the same way?

Young woman (< 35 years) with low OR with a previous episode of POR



Young woman (< 35 years) with normal OR with two episodes of POR

Older woman (≥ 40 years) with normal OR and previous POR

OR, ovarian reserve.

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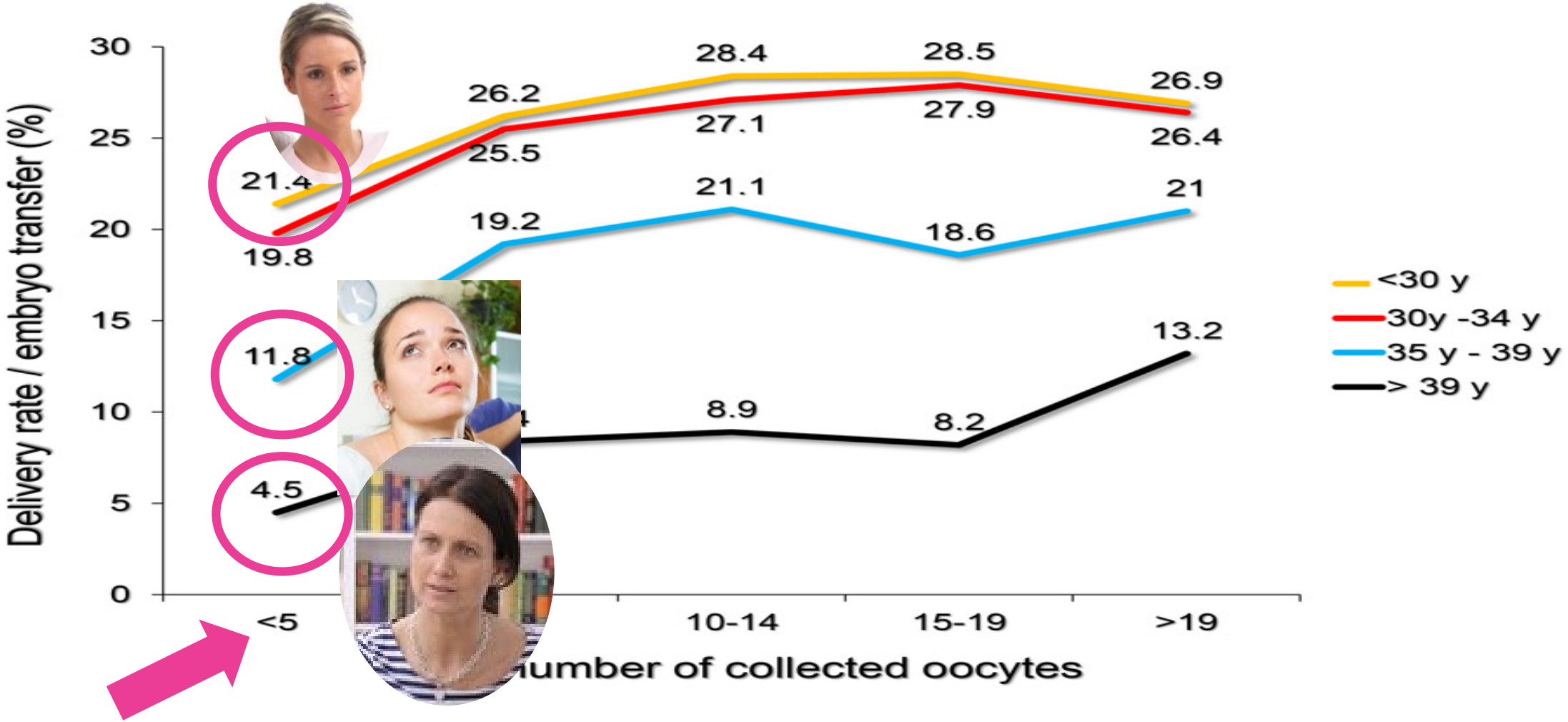
Same prognosis?

Same oocyte number but different oocyte quality, which is related to age



De Geyter C, et al. Swiss Med Wkly. 2015;145:w14087 (Swiss data registry for ART).

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Problems with Bologna criteria

- Bologna POR are classified as a single population of patients, although they are a **heterogeneous group of patients**
- Confusion exists between real poor response to the treatment and the cause of the poor response
- Bologna POR (mathematical model) does not take the age-related effect on oocyte quality into consideration
- No clinical recommendations

Courtesy of P. Humaidan.

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A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept

Fertility and Sterility

Proposes a new definition of POR based on the concept of "low prognosis" to guide patient management

- Carlo Alviggi
- Claus Y. Andersen
- Klaus Buhler, Alessandro Conforti
- Giuseppe De Placido
- Sandro Esteves
- Robert Fischer
- Daniela Galliano
- Nikolaos Polyzos
- Sesh Sunkara
- Filippo Ubaldi
- Peter Humaidan

POSEIDON working group
October 2015, Ischia

POSEIDON: **P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualize**D** **O**ocyte **N**umber

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

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POSEIDON working group

New measure for successful treatment

"The ability to retrieve the number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient"

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

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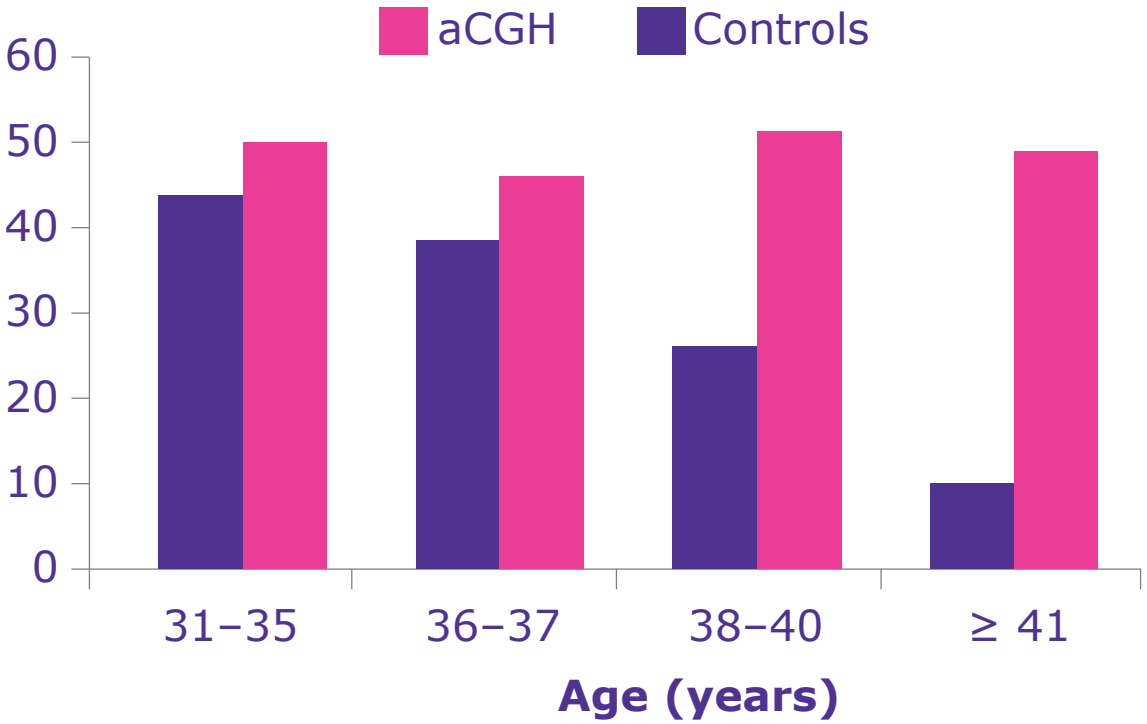
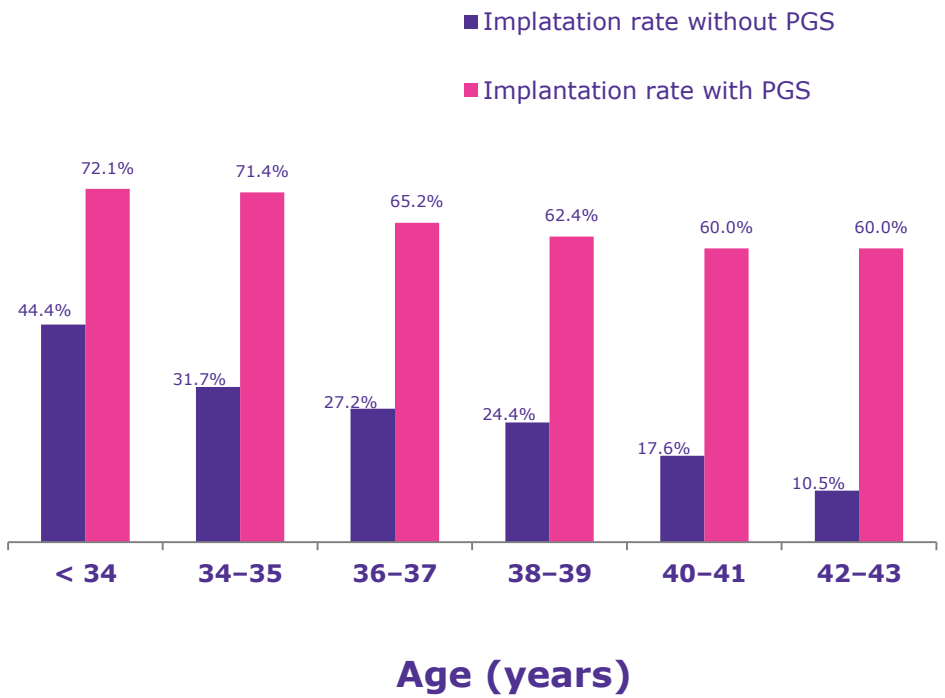
Transfer of euploid embryos eliminates the age-related decrease in implantation

AMA: age-related implantation rates (%) using aCGH (N = 258) vs controls



FCH data: Polar Bodies Aneuploidy Testing



AMA, advanced maternal age; PGS, preimplantation genetic screening.

Courtesy of Ubaldi & Rienzi (GENERA Group). Jan 2012–Dec 2013.
Fischer R. Personal data.

Define strategy according to age and ovarian reserve

Age
=
oocyte quality

Ovarian reserve
=
oocyte quantity

Good ovarian reserve

Poor responder
Young

Poor responder
Old

Poor responder
Young

Poor responder
Old

POR

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

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Four groups of patients with lower prognosis

Group 1

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

Subgroup 1a: < 4 oocytes[a]

Subgroup 1b: 4–9 oocytes retrieved[a]

Group 2

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

Subgroup 2a: < 4 oocytes[a]

Subgroup 2b: 4–9 oocytes retrieved[a]

Group 3

Young patients (< 35 years) with poor ovarian reserve prestimulation parameters (AFC < 5; AMH < 1.2 ng/mL)

Group 4

Older patients (≥ 35 years) with poor ovarian reserve prestimulation parameters (AFC < 5; AMH < 1.2 ng/mL)

[a] After standard ovarian stimulation.

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

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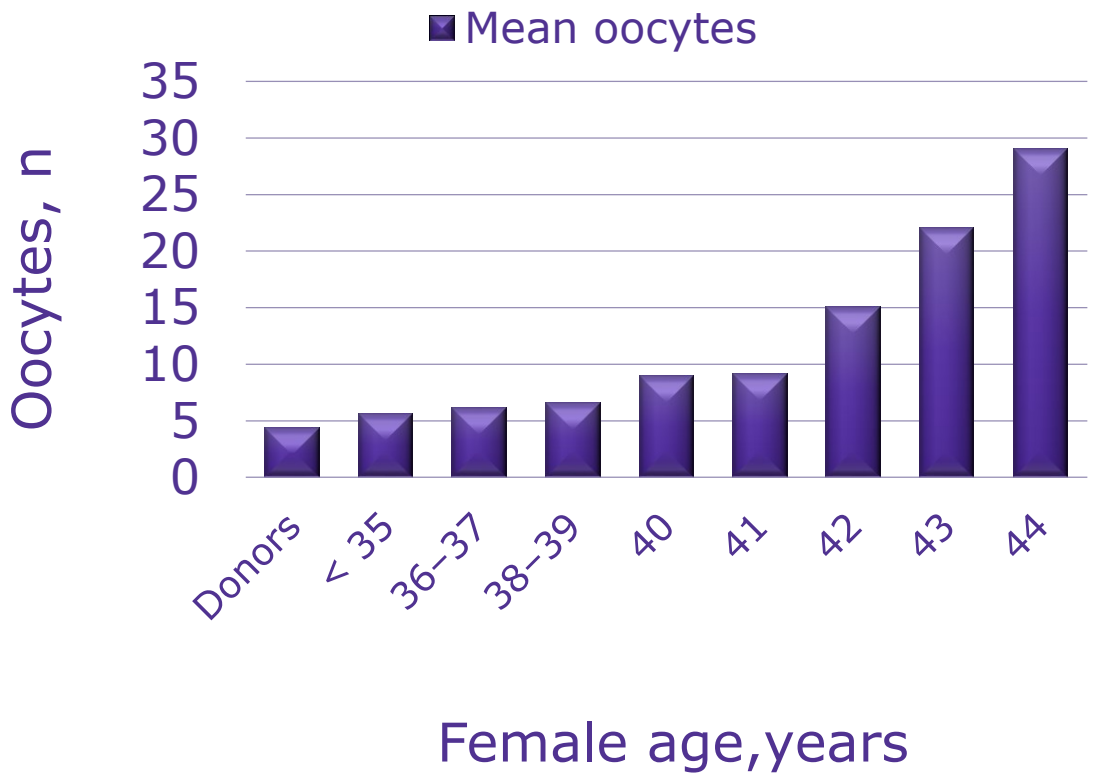
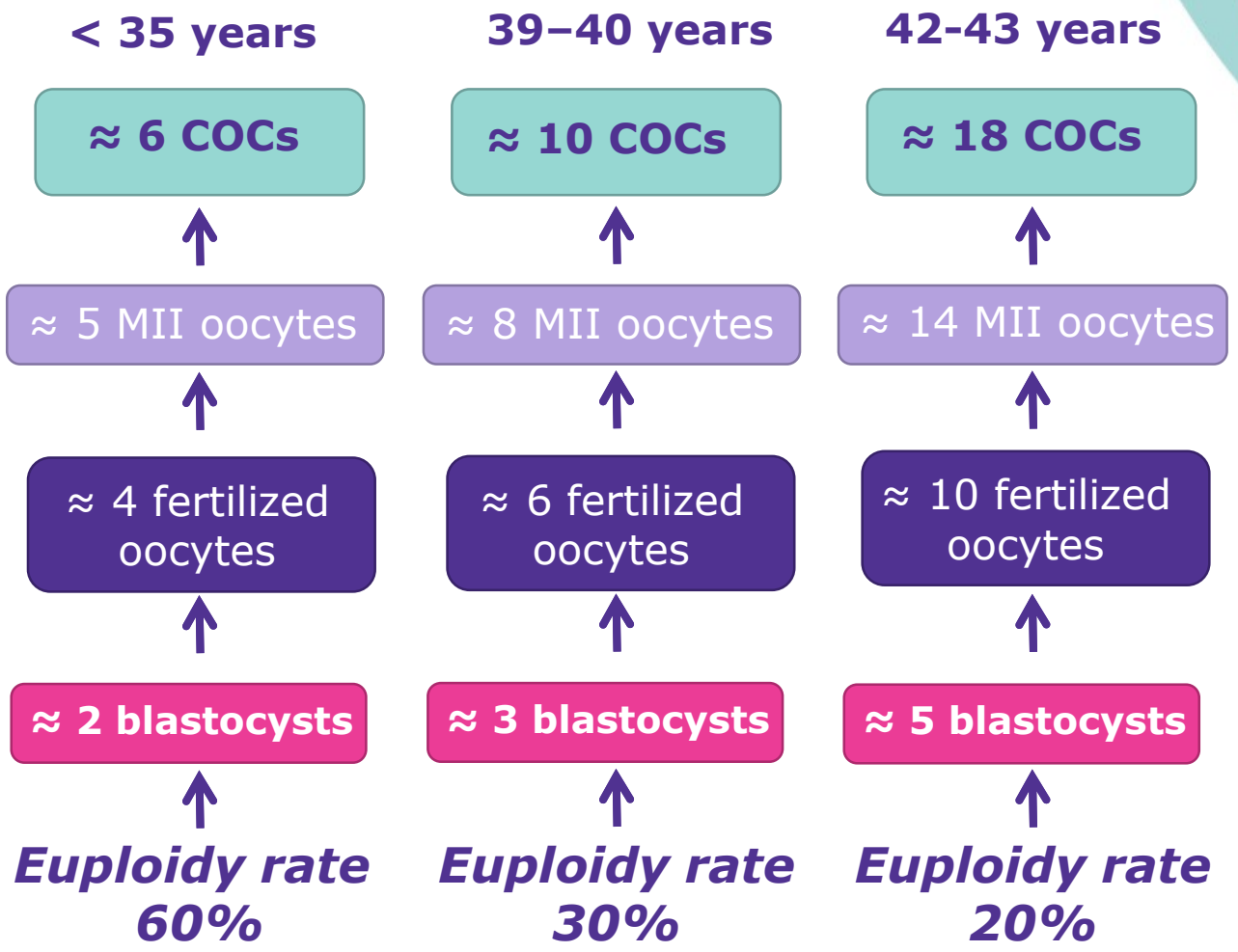
Number of oocytes needed to obtain an euploid blastocyst relative to female age





Preimplantation genetic testing for aneuploidy (PGT-A) cycles 2016 (n=1,145).

COC, cumulus-oocyte-complexes; MII, metaphase II.

Courtesy of E. Bosch, IVI Valencia (left graph).
Courtesy of P. Ubaldi. GENERA Group. Unpublished data (right figure).

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Conclusions

- Hyporesponse is different to POR
- Hyposensitivity to standard FSH dose (low FORT) is a polygenic trait and can cause unexpected poor or suboptimal response
- There is evidence that the FSHR polymorphism Ser^{680} plays a crucial role in determining sensitivity to standard doses of FSH
- Polymorphisms of LH and LHCGR also seem to be involved in determining hyporesponse
- The concept of "low prognosis" should be developed by considering new categories of abnormal ovarian response (i.e. hypo- and suboptimal responders) and ovarian "quality" (age-related aneuploidies)
- Practical endpoints (i.e. the number of eggs to retrieve to have one euploid embryo) should be considered in clinical practice

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Thank you for your time

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