Androgens pretreatment in advanced age women

Ayer, hoy y siempre

Dexeus mujer

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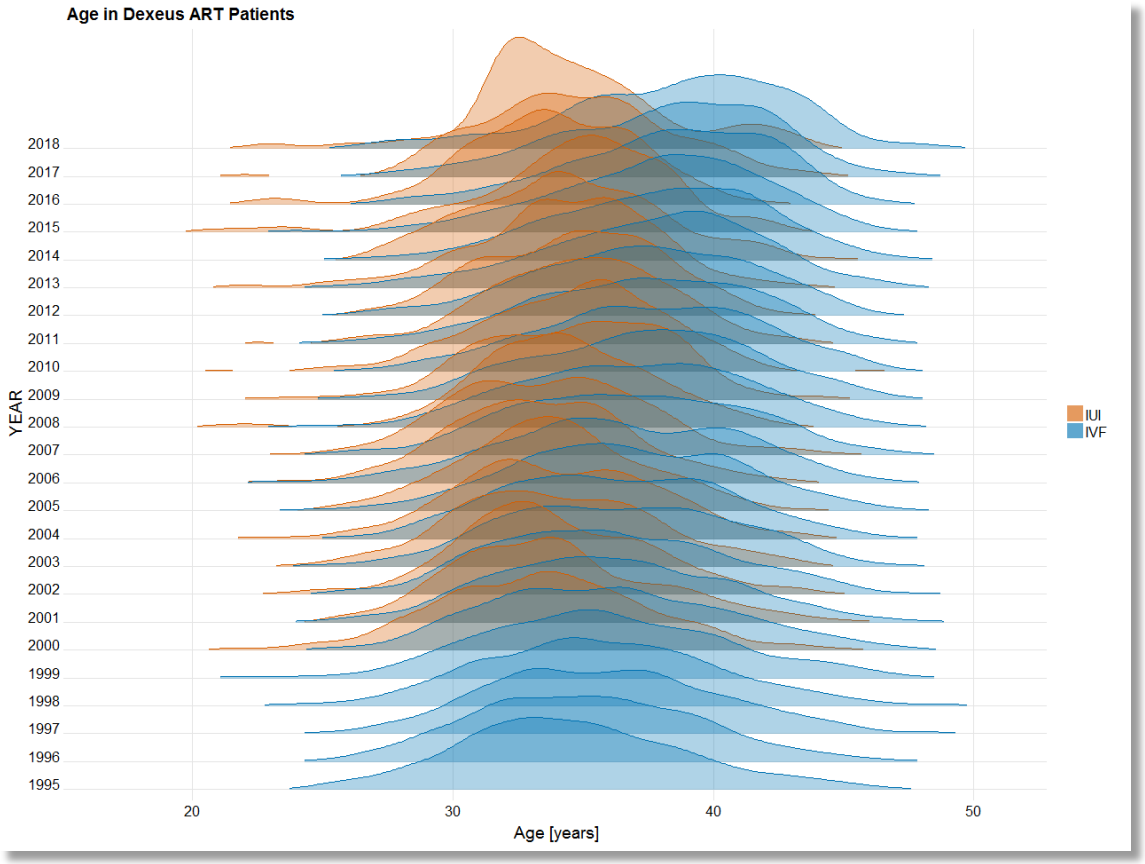
Ageing IVF population

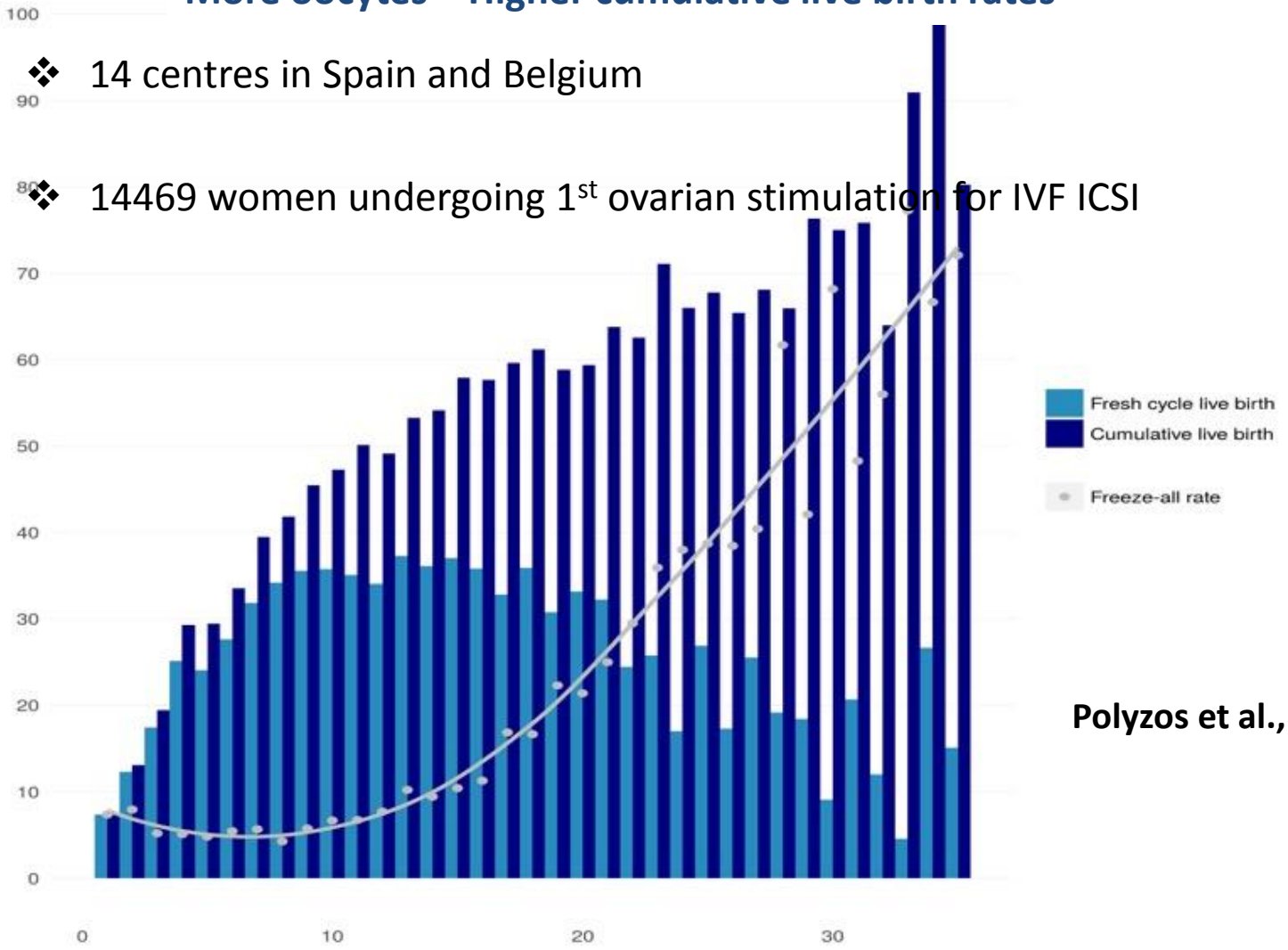
Our patients are coming to us older!



Is more oocytes better than less?

More oocytes = Higher cumulative live birth rates

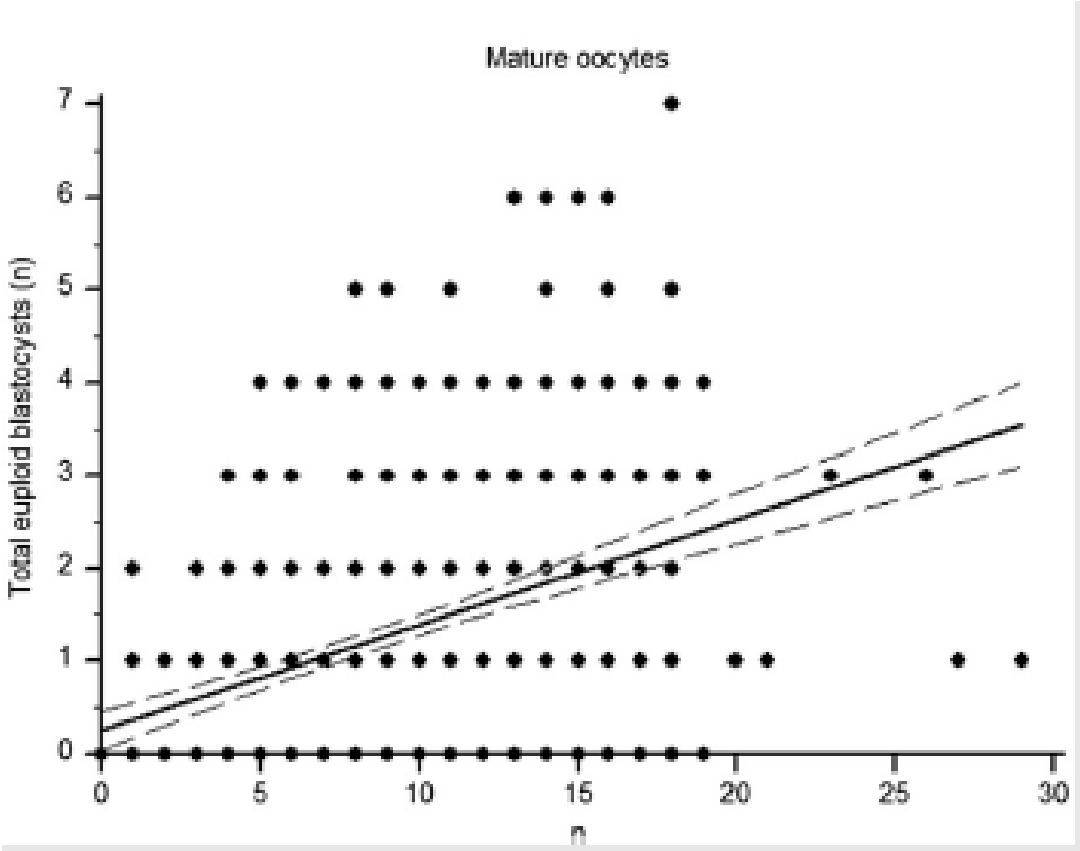
- 14 centres in Spain and Belgium
- 14469 women undergoing 1st ovarian stimulation for IVF ICSI



Polyzos et al., Fertil Steril 2018

Is more oocytes better than less?

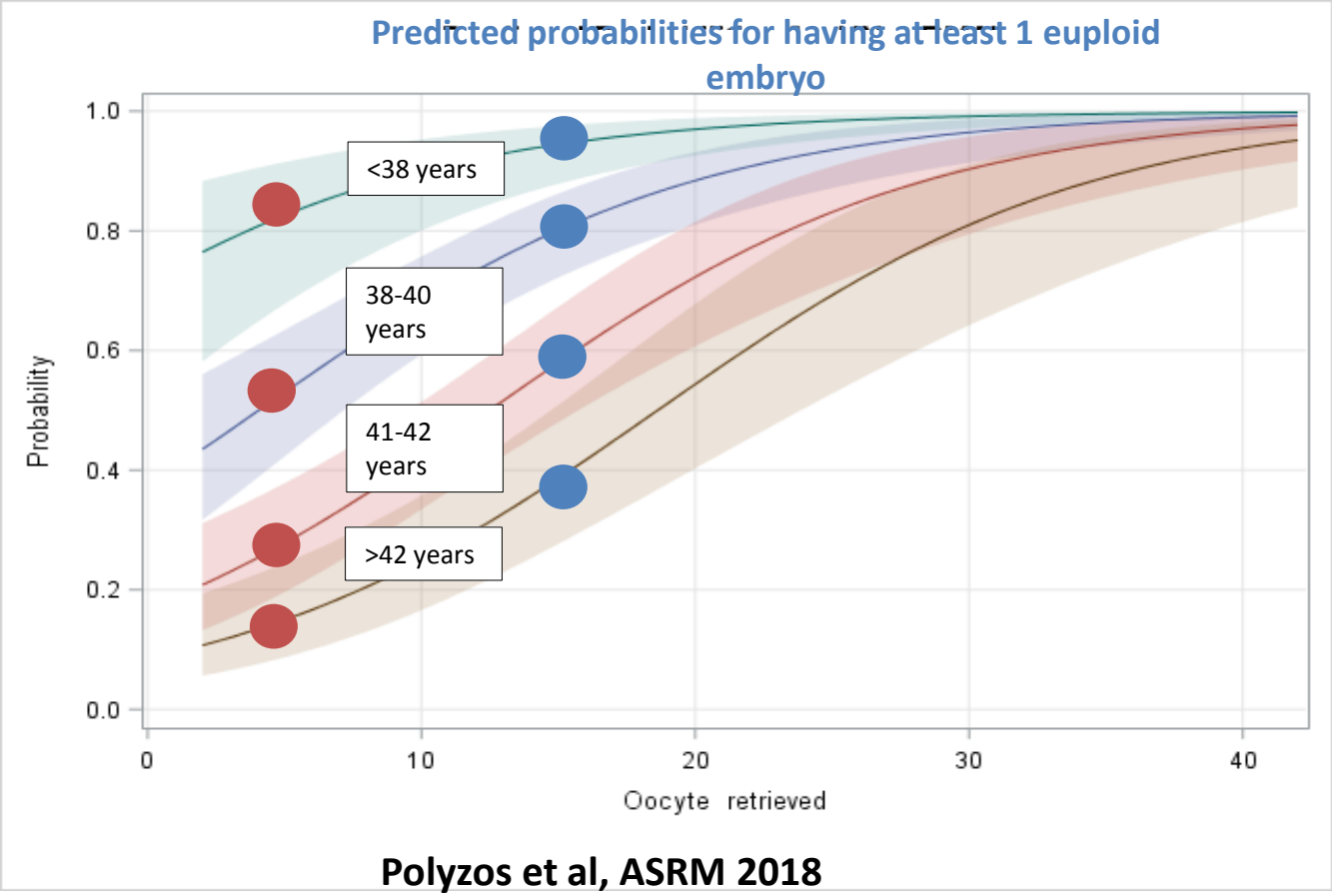
More oocytes = More euploid embryos



La Marca et al, Fertil Steril 2017

Is more oocytes better than less?

More oocytes = higher Probability of at least 1 euploid embryo

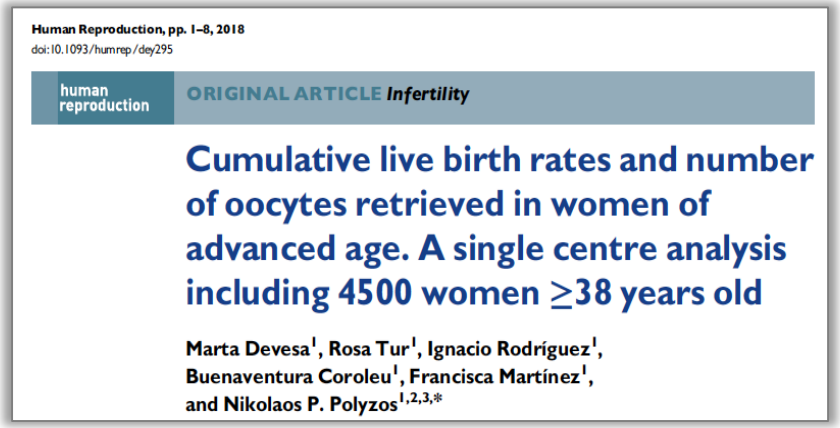


Polyzos et al, ASRM 2018

Is more oocytes better than less?

More CLBR Women ≥ 38 years old

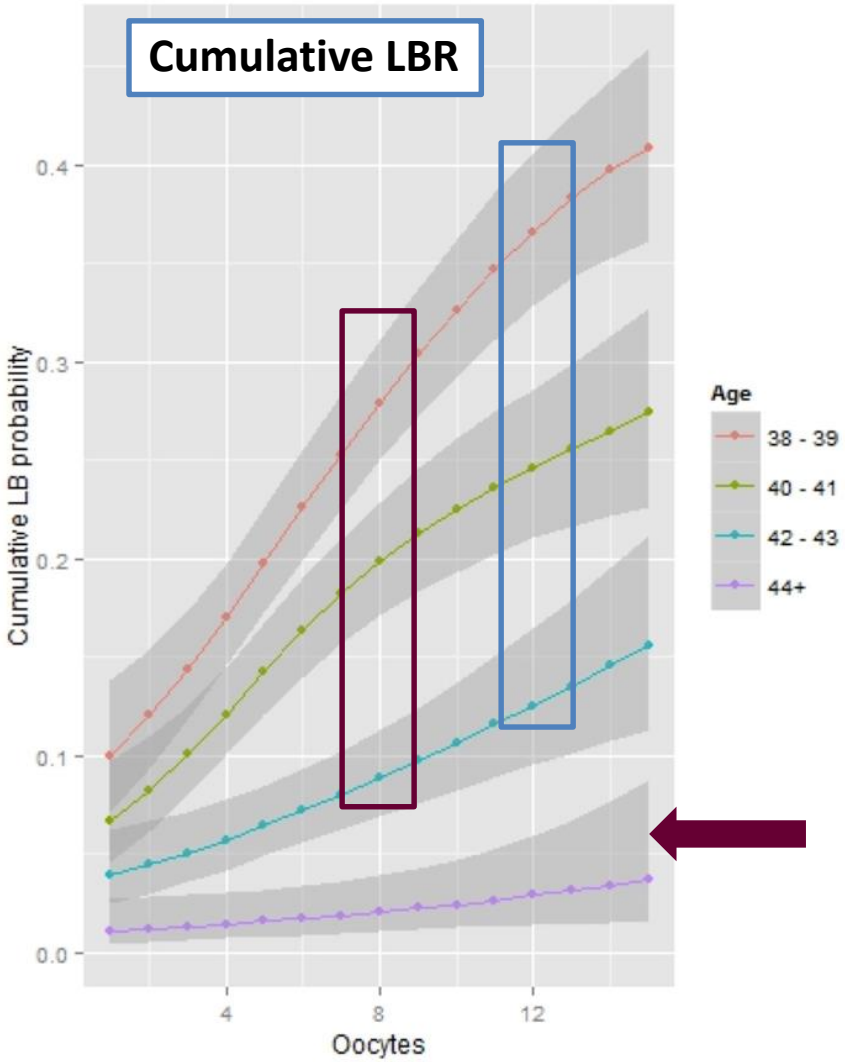
No. of oocytes	4	8	12
38-39 years	16%	27%	36%
40-41 years	12%	19%	24%
42-43 years	5%	8%	12%
≥44 years	1%	2%	2%


Human Reproduction, pp. 1–8, 2018
doi:10.1093/humrep/dey295

human reproduction ORIGINAL ARTICLE *Infertility*

Cumulative live birth rates and number of oocytes retrieved in women of advanced age. A single centre analysis including 4500 women ≥38 years old

Marta Devesa[1], Rosa Tur[1], Ignacio Rodríguez[1], Buenaventura Coroleu[1], Francisca Martínez[1], and Nikolaos P. Polyzos[1,2,3,*]



“The journey” of the advanced age patient

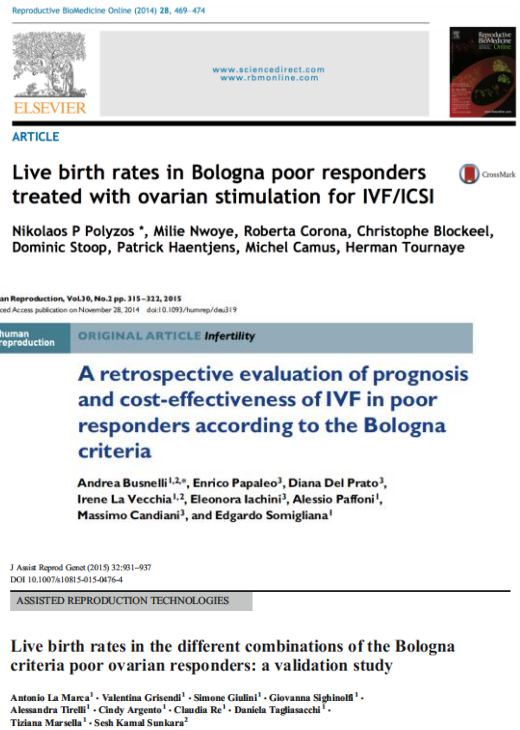
Emma

- 40 years old
- AFC 2
- AMH 0.5ng/ml

4 ovarian stimulations with 2-4 oocytes

Continuing ovarian stimulation?

Studies	Live birth /cycle
Polyzos et al., 2014	6%
Busnelli et al., 2015	6%
La Marca et al., 2015	6.3%



Reproductive BioMedicine Online (2014) 28, 469–474

www.sciencedirect.com
www.rbmonline.com

ELSEVIER

ARTICLE

Live birth rates in Bologna poor responders treated with ovarian stimulation for IVF/ICSI

Nikolaos P Polyzos *, Milie Nwoye, Roberta Corona, Christophe Blockeel, Dominic Stoop, Patrick Haentjens, Michel Camus, Herman Tournaye

Human Reproduction, Vol.30, No.2 pp. 315–322, 2015
Advanced Access publication on November 28, 2014 doi:10.1093/humrep/deu319

human reproduction ORIGINAL ARTICLE *Infertility*

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

Andrea Busnelli[1,2,*], Enrico Papaleo[3], Diana Del Prato[3], Irene La Vecchia[1,2], Eleonora Iachini[3], Alessio Paffoni[1], Massimo Candiani[3], and Edgardo Somigliana[1]

J Assist Reprod Genet (2015) 32:931–937
DOI 10.1007/s10815-015-0476-4

ASSISTED REPRODUCTION TECHNOLOGIES

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

Antonio La Marca[1] · Valentina Grisendi[1] · Simone Giulini[1] · Giovanna Sighinolfi[1] · Alessandra Tirelli[1] · Cindy Argento[1] · Claudia Re[1] · Daniela Tagliasacchi[1] · Tiziana Marsella[1] · Sesh Kamal Sunkara[2]

Consistently low live birth rates irrespective of protocol used

….ovarian stimulation?

- **No ovarian reserve** means no benefit from stimulation
- **AFC of <3** means low oocyte yield irrespective of the protocol used
- **Very high basal FSH** levels suggest limited benefit of ovarian stimulation
- **Functional ovarian reserve** is a key criterion to consider treatment

….biological clock starts ticking!

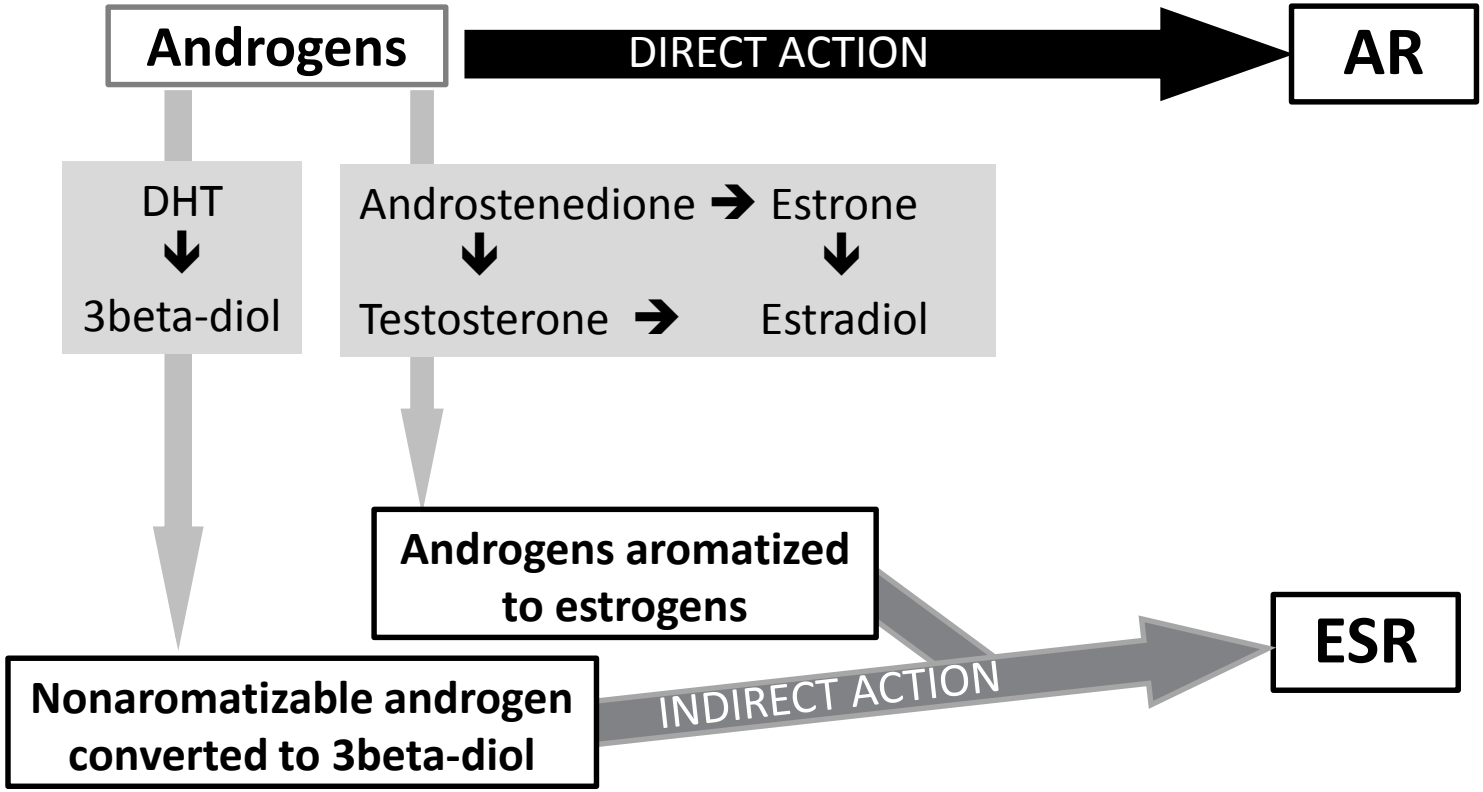
….biological clock starts ticking!

Should we wait for miracles?

Androgens to overcome ovarian ageing?

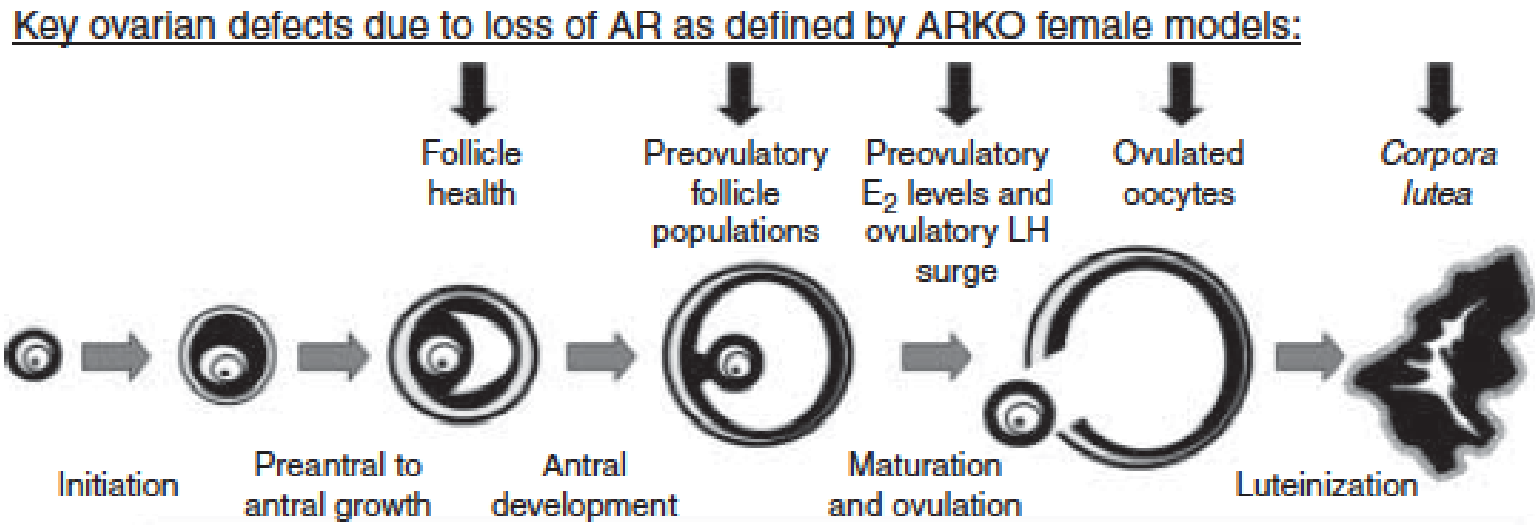
- The role of androgens in folliculogenesis and steroidogenesis
- Evidence from animal studies
- Evidence from human studies
- Need more evidence

Ovarian action of androgens



Walters Reproduction 2015

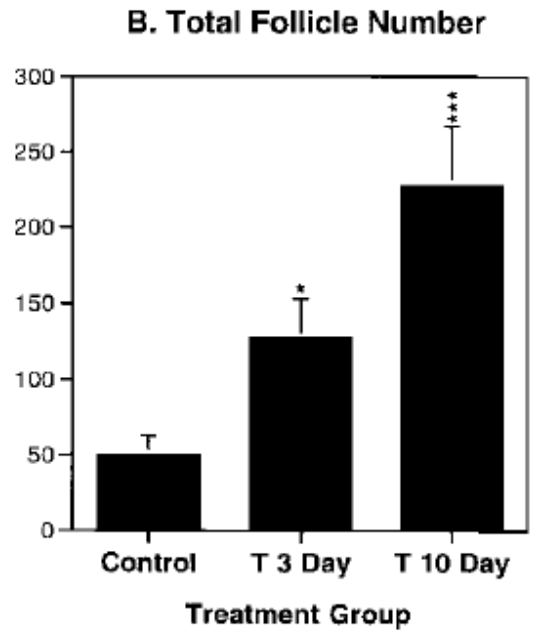
Androgens and folliculogenesis



Walters Reproduction 2015

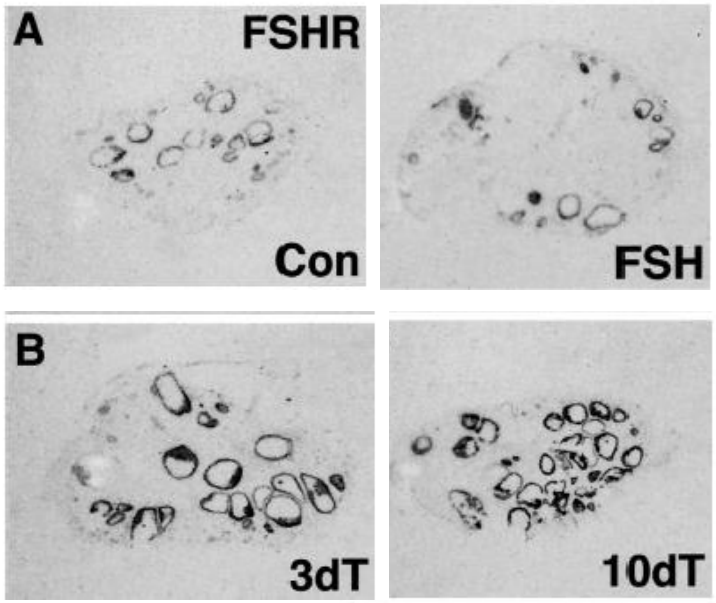
Evidence from animal studies

Number of follicles



Vendola et al., J Clin Invest 1998

FSHR expression

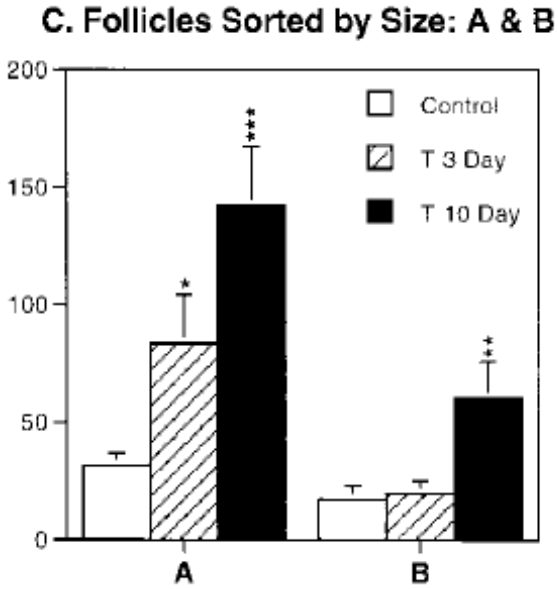


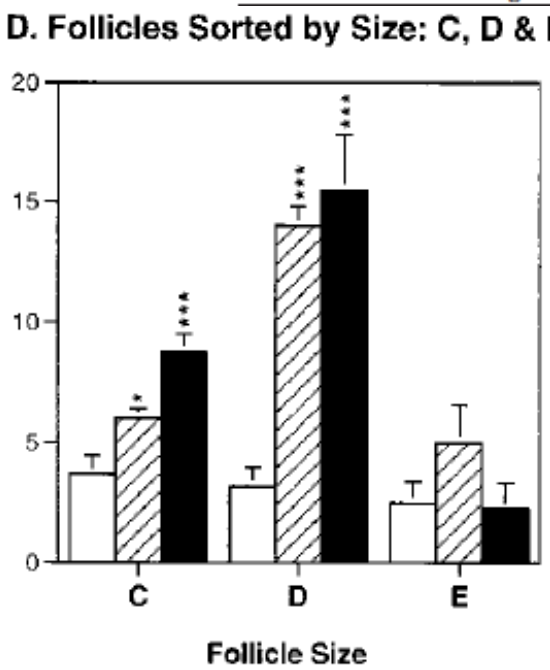
Weil et al., JCEM 1999

Evidence from animal studies

Effect on pre-antral follicles

Follicle class	Name	Diameter (μm)
A	Primary	50–100
B	Preantral	101–380
C	Periantral	381–620
D	Small antral	621–1000
E	Large antral	>1000





Vendola et al., J Clin Invest 1998

Weak evidence from human studies

- Preliminary uncontrolled and small RCTs

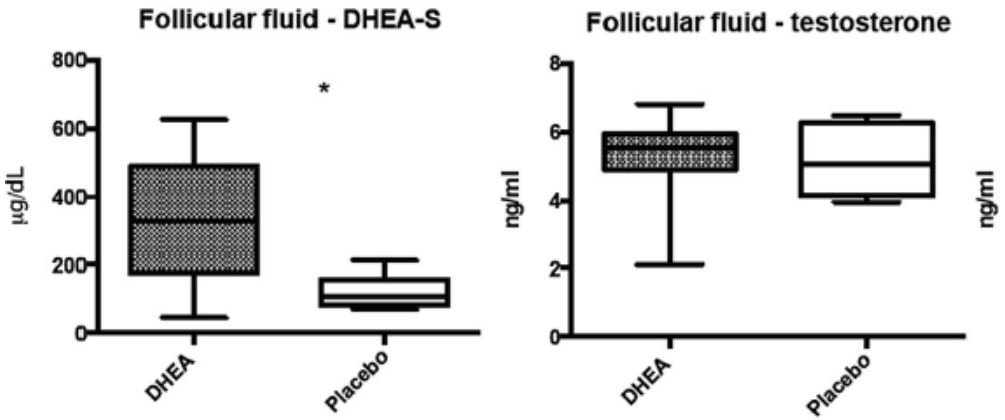
- Treatment with DHEA or testosterone
    1. May increase AFC
    2. May increase the number of growing follicles
    3. May increase pregnancy rates

Balasch et al., Hum Reprod 2006; Fabregues et al., Hum Reprod 2009

Should it be DHEA or Testosterone?

- DHEA is binding through **androgen receptors** after converting to **testosterone**

- DHEA effect on intrafollicular **testosterone levels**



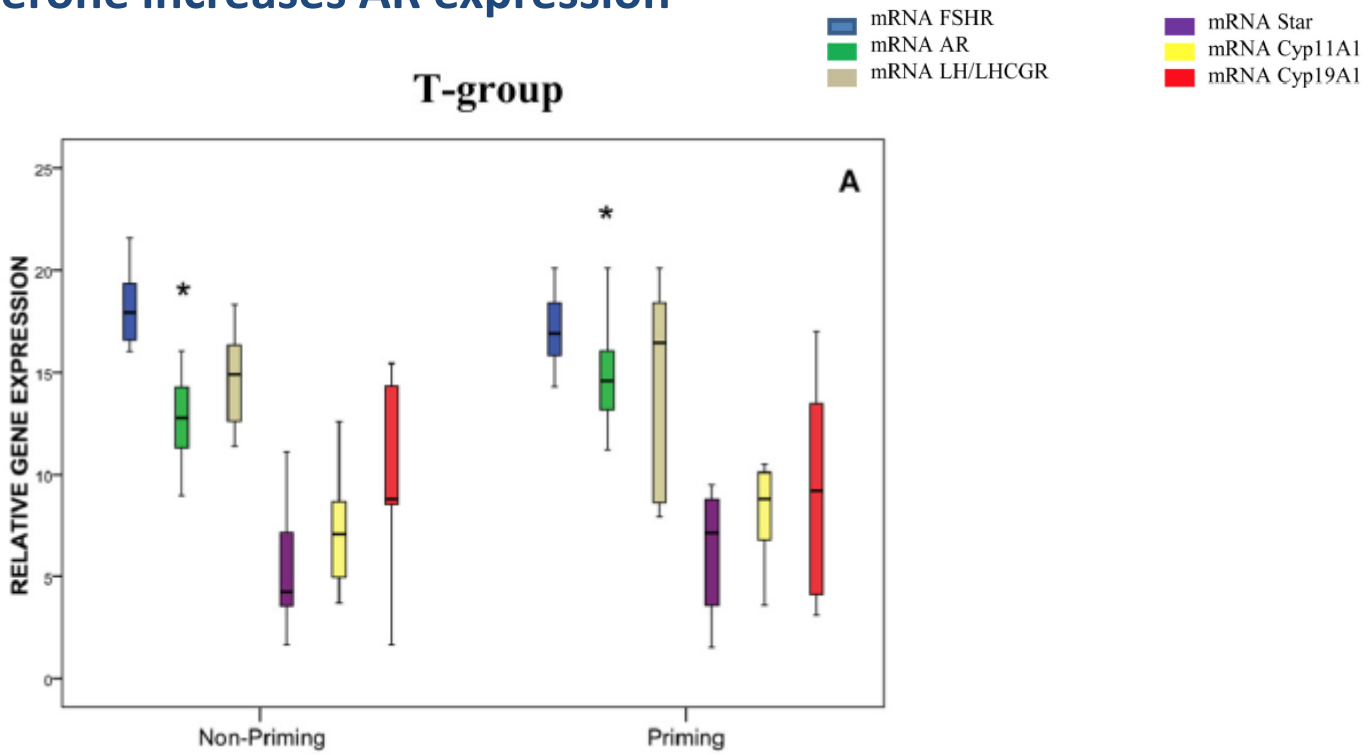
Yeung et al., Fertil Steril 2014

- DHEA **did not increase** ovarian reserve markers, ovarian response in poor responders, normal responders of POI women

Yeung et al., Fertil steril 2014
Yeung eal JCEM 2013
Yeung et al., BJOG 2015

Transdermal testosterone

Testosterone increases AR expression



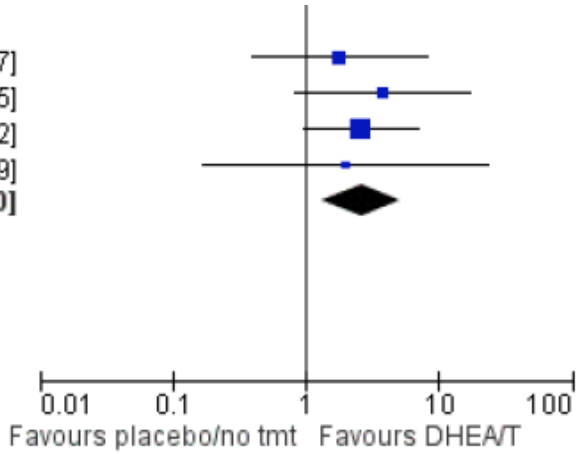
Marzal Escriva et al., JCEM 2015

Transdermal testosterone

1.1.2 Testosterone						
Fábregues 2009 (9)	5	31	3	31	23.0%	1.79 [0.39, 8.27]
Kim 2010 (10)	19	90	2	30	21.7%	3.75 [0.82, 17.15]
Kim 2011 (11)	15	55	7	55	46.6%	2.57 [0.96, 6.92]
Massin 2006 (12)	2	27	1	26	8.6%	2.00 [0.17, 23.49]
Subtotal (95% CI)		**203**		**142**	**100.0%**	**2.60 [1.30, 5.20]**
Total events	41		13			

Heterogeneity: Chi² = 0.49, df = 3 (P = 0.92); I² = 0%

Test for overall effect: Z = 2.69 (P = 0.007)



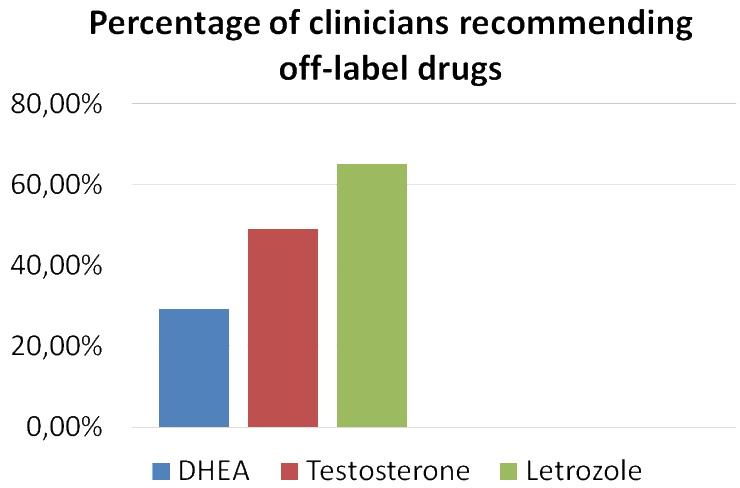
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%

1. Duration of administration
2. Daily dose of testosterone

Nagels et al., Cochrane 2015

Do we need a testosterone RCT in poor responders?

We are using it without any evidence or safety profile!!!



AARHUS UNIVERSITY

Off-label use of androgens and letrozole in infertile women – a multinational survey in Europe and Australia

Andersen MF[1], Drakopoulos P[2], Humaidan P[1], Gomes JL[3], Bruna I[4], Rombauts L[5], Santos-Ribeiro S[6], Dosouto C[7], Coroleu B[7], Barri PN[7], Polyzos NP[7]

[1]Department of Clinical Medicine- Aarhus University, The Fertility Clinic- Skive Regional Hospital, Skive, Denmark, [2]Vrije Universiteit Brussel, Department of Reproductive Medicine, Brussel, Belgium, [3]FIVMadrid, Department of Reproductive Medicine, Madrid, Spain, [4]Director Médico de HM Fertility Centers, Hospital Universitario Madrid-Montepríncipe, Madrid, Spain, [5]Monash University, Reproductive Medicine-Monash Health, Clayton Victoria, Australia, [6]Universitair Ziekenhuis Brussel, Reproductive Medicine- Genetics and Immunology, Brussel, Belgium, [7]Dexeus University Hospital, Department of Reproductive Medicine, Barcelona, Spain

Andersen et al, ESHRE 2018

Do we need a testosterone RCT in poor responders?

Duration and dose of testosterone?

Study	Sample Size	Duration, days	Dose (per day)
Bosdou et al[7]	50	21	10 mg
Kim et al[4]	110	21	12.5 mg
Fábregues et al[5]	62	5	0.02 mg/kg
Massin et al[6]	49	15	10 mg

Polyzos et al., Reprod Sciences 2016

TTRANSPORT trial

Testosterone TRANSdermal gel for
Poor Ovarian Responders Trial

Double blind placebo controlled RCT examining the value of testosterone pre-treatment in women with poor ovarian response.

TTRANSPORT study details

- **Eligible patients**

  Poor responders fulfilling the “Bologna criteria” 18-43y old

- **Number of patients**

  400 → Interim analysis at 280 women → 700 women

- **Study design**

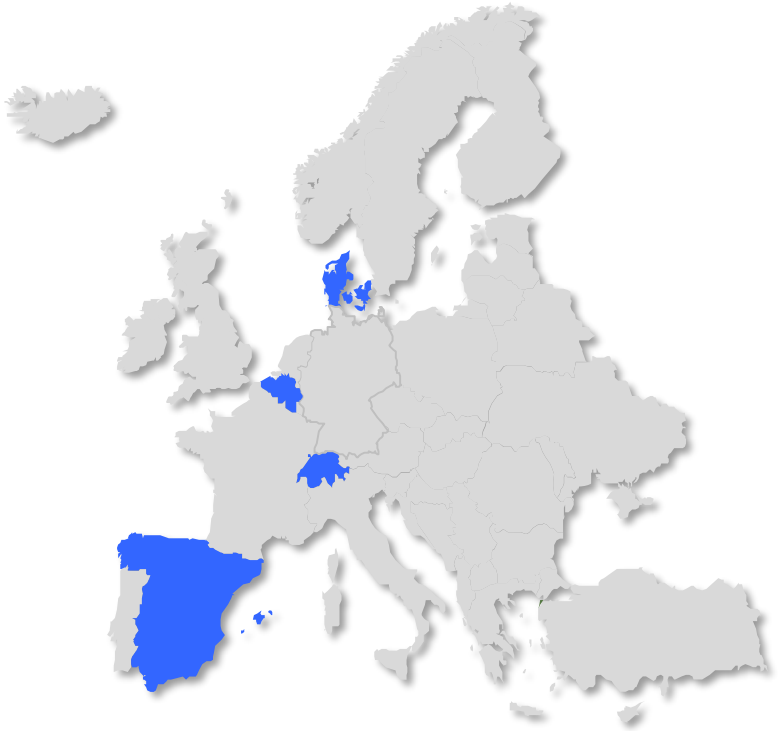
  Double blind placebo controlled

- **Sample size calculation**

  T-gel may increase pregnancy rates from 14.5% to 26%

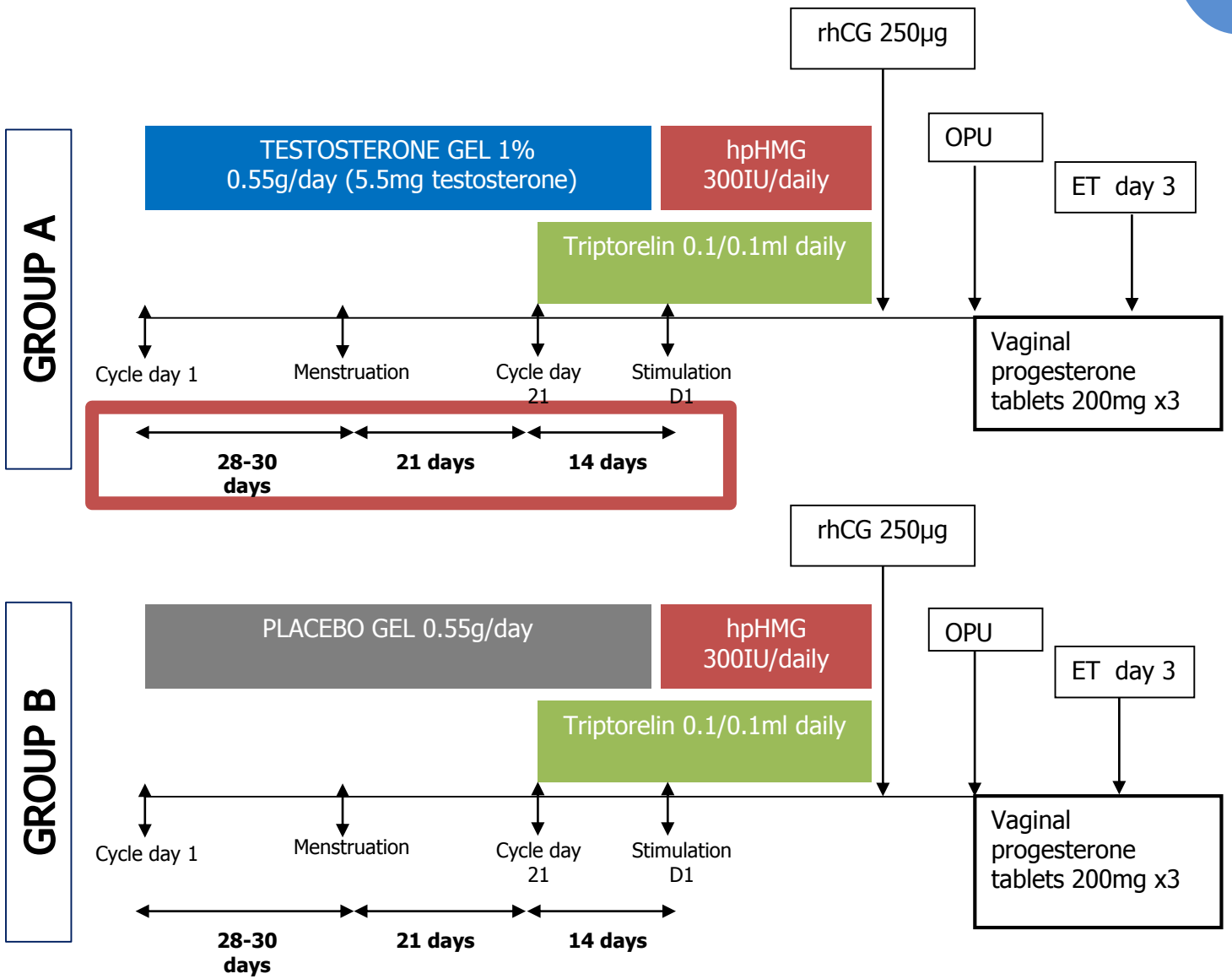
TTRANSPORT trial

Testosterone TRANSdermal gel for
Poor Ovarian Responders Trial

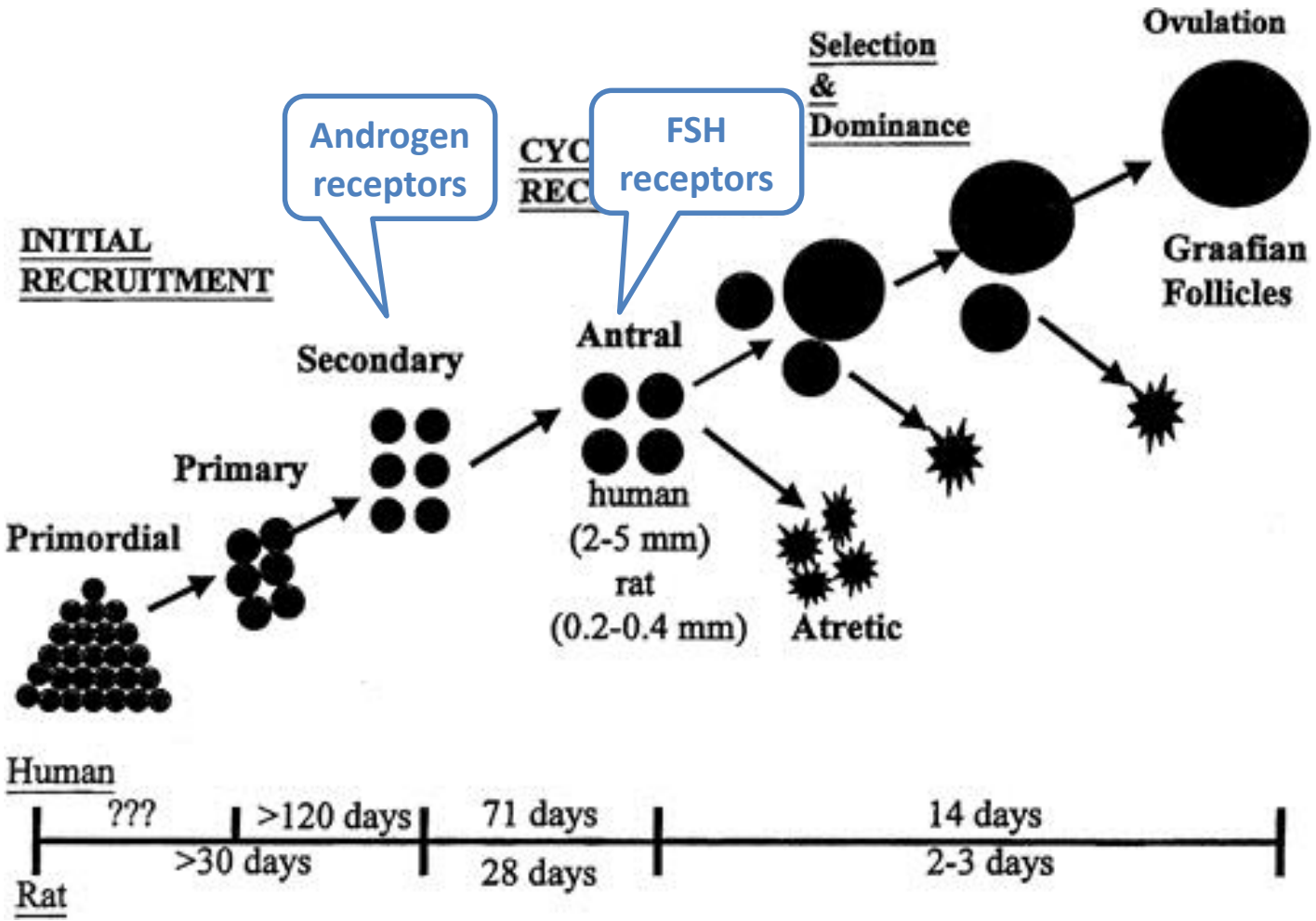


- Dexeus Barcelona
- UZ Brussel
- Skive Denmark
- Quiron Madrid
- University hospital of Basel
- UZ Antwerp

TTRANSPORT trial

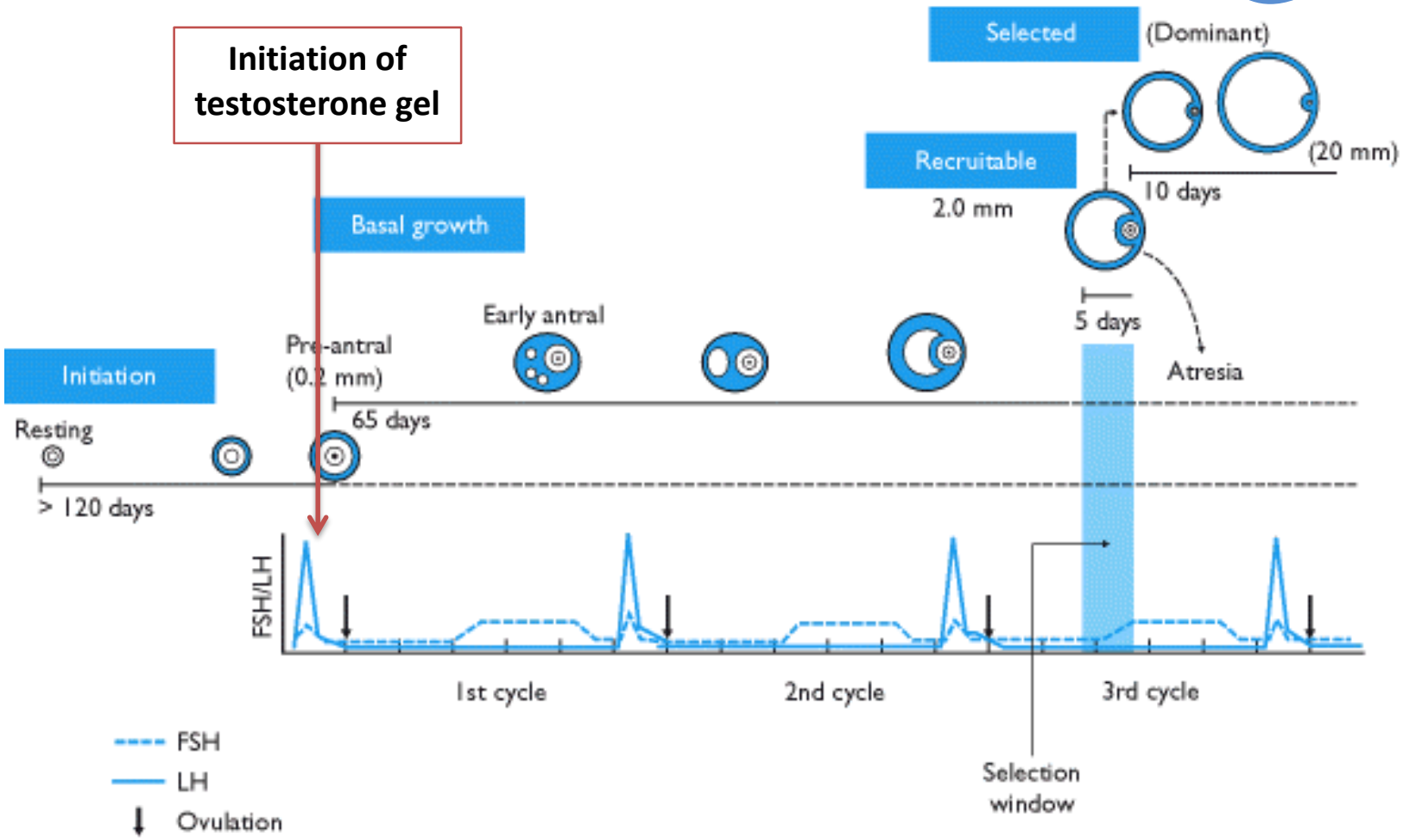


Why ~ 2 months of administration?



Polyzos et al., Reprod Sciences 2016

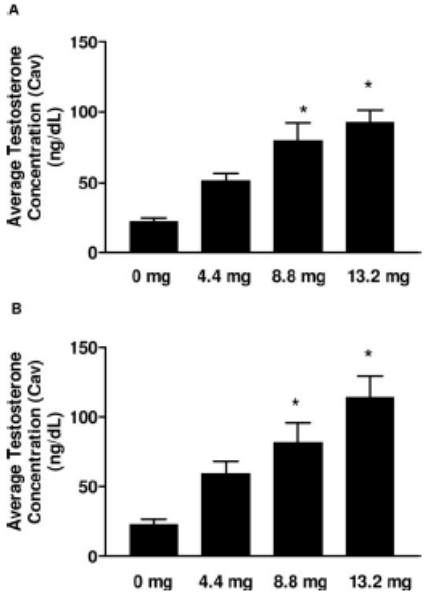
Why ~ 2 months of administration?



Polyzos et al., Reprod Sciences 2016

Why 5.5mg of testosterone/day?

- Pharmacokinetics and testosterone serum levels in postmenopausal women



Singh et al., JCEM 2006

- Testosterone levels above 100ng/ml are at the level of male testosterone levels!

Polyzos et al., Reprod Sciences 2016

Why 5.5mg of testosterone/day?

More might be worse..

Female to male transsexuals

- Very high T levels negatively affects ovarian reserve

	Before treatment	After treatment	P value
Testosterone nmol/L, mean (SD)	1.4 (0.24)	17.8 (9.6)	.000
AMH ng/dl, mean (SD)	4.4 (4.4)	1.4 (2.1)	.000

Caenen et al., Fertil Steril 2015

- Very high T levels do not induce PCO morphology

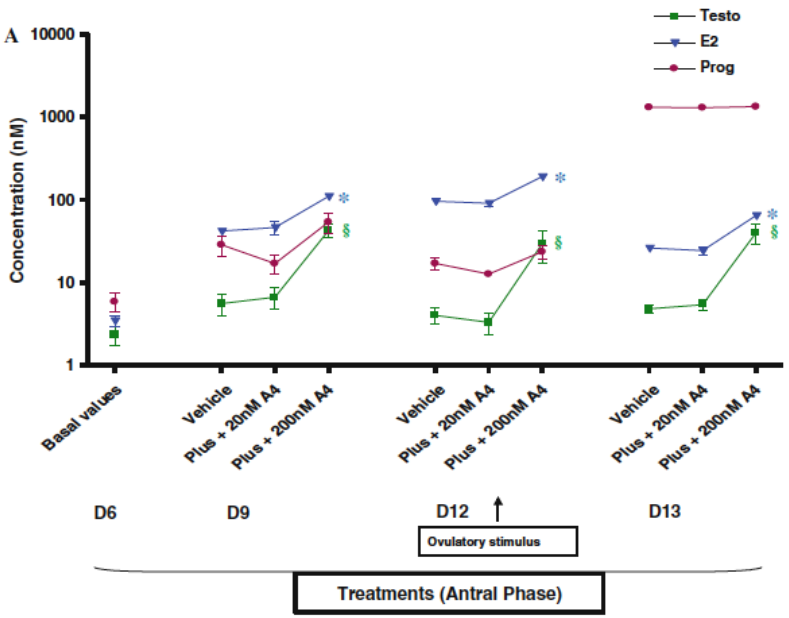
Ikeda et al., Hum Reprod 2013

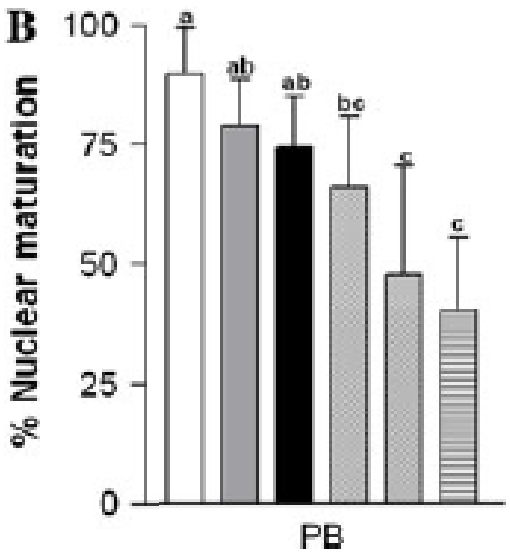
Caenen et al., Hum Reprod 2017

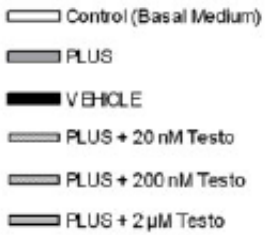
Why 5.5mg of testosterone/day?

More might be worse..

High testosterone concentration reduces oocyte meiotic capacity







Romero, S., & Smitz, J. Endocrine 2010

T-TRANSPORT trial major analysis

Clinical study

- Live births and pregnancy rates
- Number of oocytes, embryos etc
- Results concerning neonatal health

Nested substudies within TTRANSPORT

1. **Follicular fluid and cumulus cell analysis** on day of OPU
2. Effect of testosterone on **ovarian reserve markers**
3. **Endocrine profile** during androgen supplementation
4. **Endocrine profile** during ovarian stimulation
5. Effect of testosterone of **female libido (FSFI, FSDS-R)**
6. Effect of testosterone **quality of life (Fertiquol)**
7. Assessment of **hirsutism**

Conclusions

❖Ovarian physiology and animal experiments suggest that **testosterone may benefit** poor responders

❖Evidence from **clinical trials is weak**

❖**Duration and dose of testosterone** much follow ovarian physiology and pharmacokinetics

What our patients perceive as a little miracle?

Ayer, hoy y siempre

Dexeus mujer

Thank you for your attention

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