Transdermal Testosterone Pretreatment for Poor Responders

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Secretary General , HOSREM

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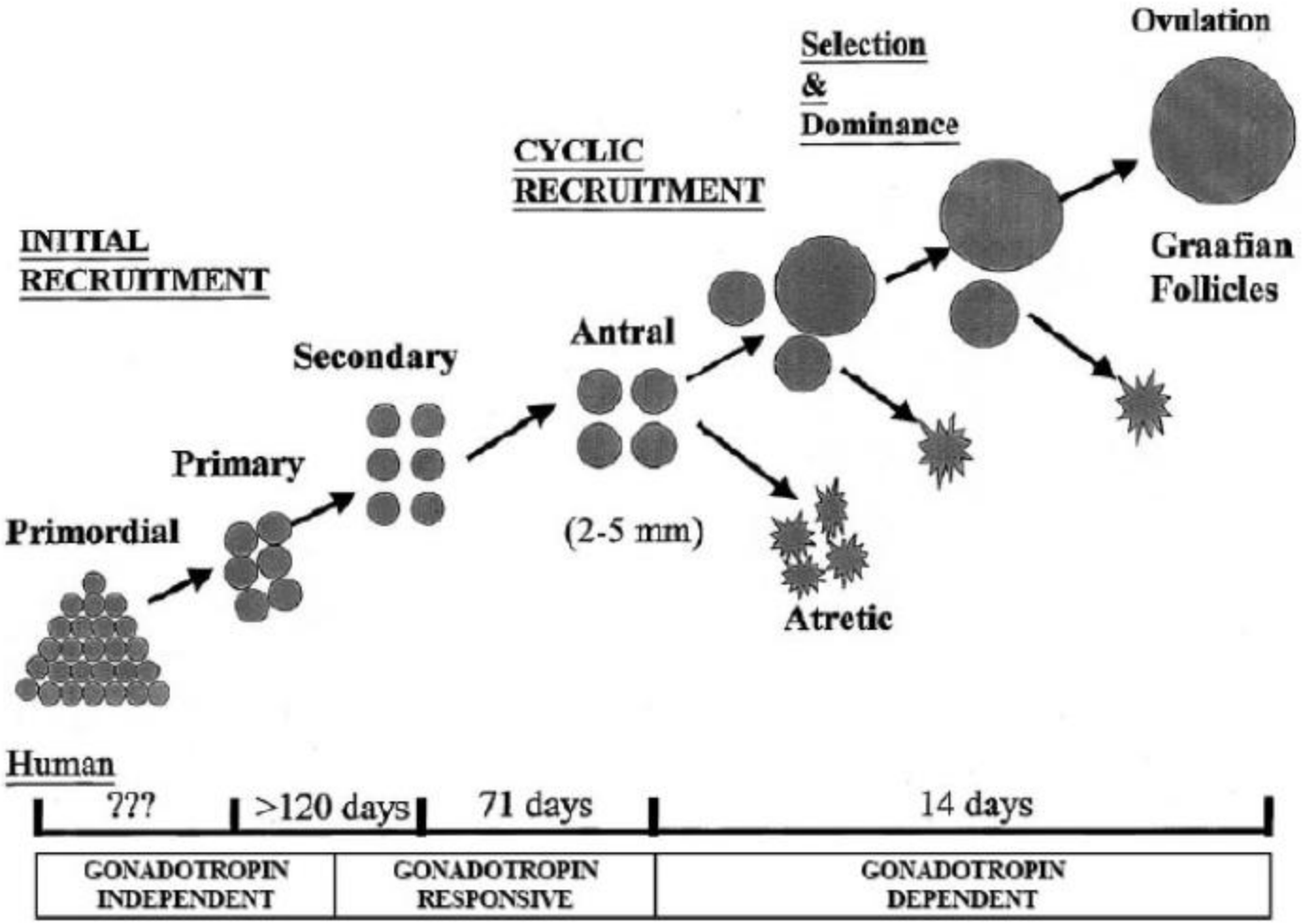
Poor responders in IVF

- "Poor response": 9-23% *(Vollenhoven et al., 2008)*
- Low pregnancy rate
- Bologna consensus: 2 out of 3
  1) ≥ 40 or high risks of poor response
  2) Previous poor response (≤ 3 oocytes, standard hyperstimulation)
  3) AFC < 5-7 or AMH < 0.5 – 1.1 ng/ml

Ferraretti et al., Hum Reprod 2011

Fulfill your hope

Follicle Development



McGee EA, Hsueh AJ *Endocr Rev 2000*

Supplementation for poor responders

- Pretreatment with DHEA (dehydroepiandrosterone)
- Combine with aromatase inhibitor during stimulation
- Combine with growth hormone (GH) during stimulation
- Combine with luteinizing hormone (LH) during stimulation
- Pretreatment with transdermal testosterone
- …

ROLE OF ANDROGEN IN OVARIAN RESPONSE

Role of decreased androgens in the ovarian response to stimulation in older women

David R. Meldrum, M.D.,[a] R. Jeffrey Chang, M.D.,[b] Linda C. Giudice, M.D., Ph.D.,[c] Juan Balasch, M.D.,[d] and Robert L. Barbieri, M.D.[e]

Meldrum et al, Fertility and Sterility 99(1) 2013

ROLE OF ANDROGEN IN OVARIAN RESPONSE

Position Paper

Reproductive Sciences
1-3

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Testosterone for Poor Ovarian Responders: Lessons From Ovarian Physiology

Nikolaos P. Polyzos, MD, PhD[1,2], Susan R. Davis, MD, PhD[3], Panagiotis Drakopoulos, MD, MSc[1], Peter Humaidan, MD, DMSc[2], Christian De Geyter, MD[4], Antonio Gosálvez Vega, MD[5], Francisca Martinez, MD, PhD[6], Evangelos Evangelou, PhD[7,8], Arne van de Vijver, MD[1], Johan Smitz, MD, PhD[1], Herman Tournaye, MD, PhD[1], Pedro Barri, MD, PhD[6], and The T-TRANSPORT Investigators Group

Polyzos et al, 2016

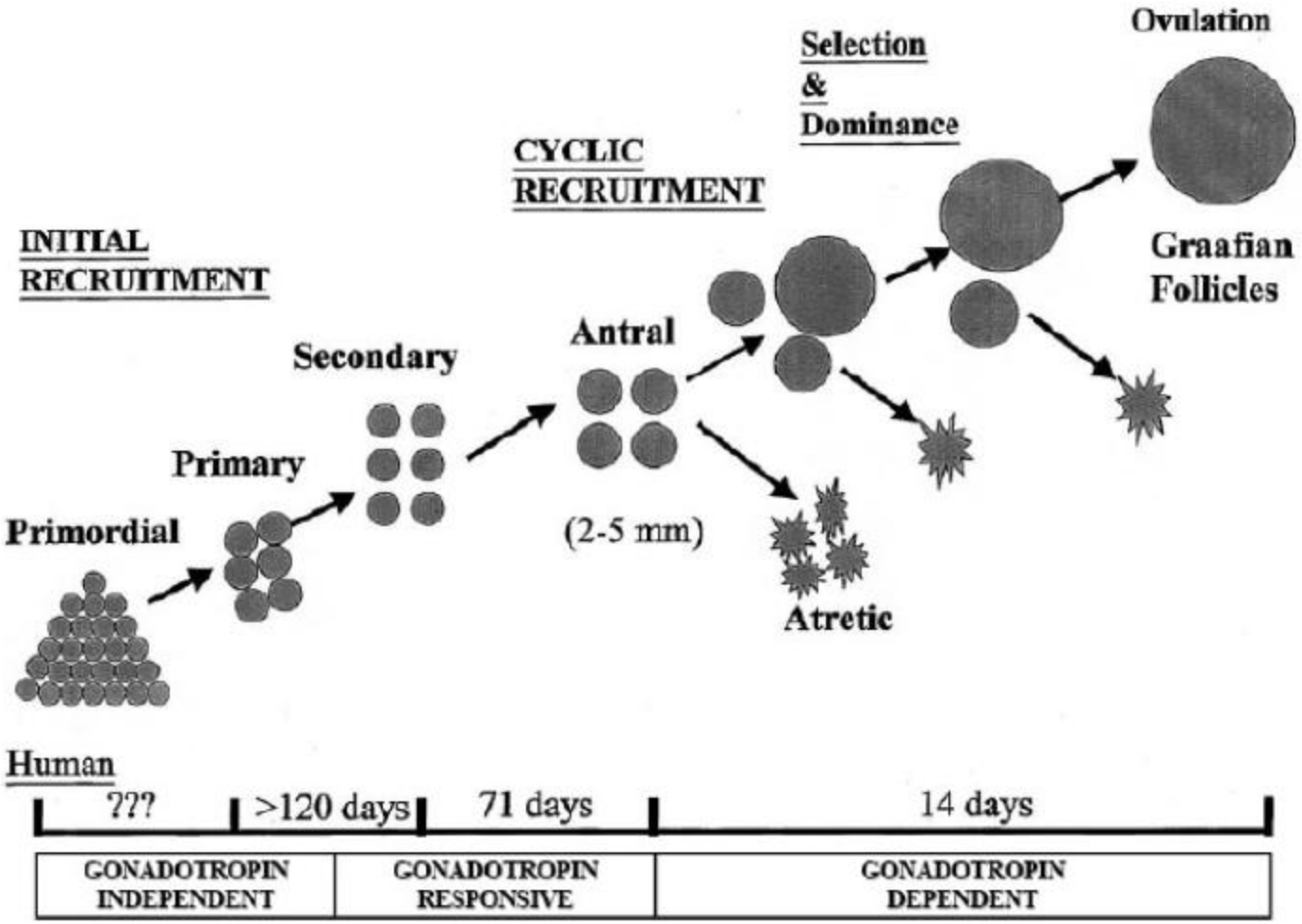
Fulfill your hope

Testosterone and Ovarian Response

- Increasing the pool of follicles up to the preantral stage
- Reduce apoptosis of the originally recruited follicles
- Improve responsiveness of the ovaries to gonadotropins and amplify the effects of FSH on the ovary
- Proliferation of granulosa and theca cells, reduce apoptosis of granulosa cells
- Testosterone decreases as age advances in premenopausal women

Meldrum et al, F&S 2013; Polyzos et al, 2016

Follicle Development



McGee EA, Hsueh AJ *Endocr Rev 2000*

Human Reproduction Update, Vol.18, No.2 pp. 127–145, 2012
Advanced Access publication on February 3, 2012 doi:10.1093/humupd/dmr051

human reproduction update

Conclusions:

- Transdermal testosterone pretreatment increase clinical pregnancy and live birth rates in poor responders.
- Insufficient data to support a beneficial role of rLH, hCG, DHEA or letrozole

CONCLUSIONS: Based on the limited available evidence, transdermal testosterone pretreatment seems to increase clinical pregnancy and live birth rates in poor responders undergoing ovarian stimulation for IVF. There is insufficient data to support a beneficial role of rLH, hCG, DHEA or letrozole administration in the probability of pregnancy in poor responders undergoing ovarian stimulation for IVF.

Transdermal Testosterone

- Testosterone Gel
- Testosterone Patch

Massin et al, 2006

- Testosterone gel (T)
- 1g gel (10 mg testosterone) / day
- 15-20 days, before stimulation
- RCT, Placebo control. Matched, cross-over. N=49
- Serum testosterone increased in treatment group, compared with control 1.55 ± 0.89 ng/ml and 0.58 ± 0.16 ($p < 0.0001$)
- No statistical difference in ovarian response. Small sample ?
- Yet, there were trends of increasing number of eggs retrieved, embryos and pregnancy rate in treatment group.

Fabregues et al., 2009

- RCT, N=62, cancelled in previous cycles due to poor response
- Pretreatment: Testosterone patch, 2.5mg/day, 5 days, before stimulation, down-regulation protocol
- Control: high dose FSH, mini-dose GnRHa flare-up
- Results: reduced days of stimulation, total dose of FSH used, and rate of cancellation due to poor response.
- No difference in number of oocytes retrieved

Table II Gonadotrophin treatment, ovarian response, ovum retrieval and IVF/ICSI outcome in Groups 1 and 2

Variable	Group 1 (n = 31)	Group 2 (n = 31)	P-value
Days to ovarian arrest	15.1 ± 2.4	14.1 ± 2.1	0.66
Days of ovarian stimulation	10.3 ± 2.2	11.1 ± 1.9	<0.001
Total IU of FSH	3154 ± 1168	3950 ± 1870	<0.01
No. of follicles on hCG day			
10 to <14 mm	1.8 ± 0.7	1.9 ± 0.8	0.60
14 to <18 mm	1.9 ± 0.9	1.6 ± 1	0.22
≥18 mm	4 ± 0.6	3.1 ± 0.7	0.15
E_2 on hCG day (pg/ml)	1171 ± 389	1427 ± 660	0.23
Endometrial thickness on hCG day (mm)	10.8 ± 1.1	10.9 ± 0.7	0.67
Patients with hCG and ovum retrieval (n, %)	25 (80.6)	18 (58.1)	0.09[b]
Low responders (n, %)	10 (32.2)	22 (71)	<0.05[c]
No. of oocytes retrieved[a]	5.1 ± 1.9	4.3 ± 2.3	0.25

Fabregues et al., 2009

Kim et al., 2011

- RCT, 110 poor responders
- Testosterone gel, 12.5 mg / day, 21 days, before stimulation.

  GnRH antagonist protocol.
- Results: Increase in
  - Number of oocytes, number of good embryos
  - Implantation rate
  - Clinical pregnancy rate
- No adverse effect recorded

Comparison of controlled ovarian stimulation results and IVF/ICSI outcome.

	TTG pretreatment	Control	*P* value
No. of cycles initiated	55	55	
No. of cycles retrieved	55	54	
No. of ET cycles	54	53	
No. of cycles canceled	1 (1.8%)	2 (3.6%)	NS[a]
No. of cycles with ICSI	17 (42.5%)	16 (41.0%)	NS[a]
On stimulation day 1			
Serum T (ng/mL)	1.9 ± 0.4	0.3 ± 0.2	<.001[b]
Serum free T (pg/mL)	1.0 ± 0.3	0.4 ± 0.2	<.001[b]
AFC	5.0 ± 1.1	4.3 ± 1.1	.026[b]
Days of rhFSH	9.6 ± 1.1	10.5 ± 1.6	<.001[b]
Total dose of rhFSH	2,552.3 ± 397.2	3,000.8 ± 449.8	<.001[b]
Days of GnRH antagonist	4.5 ± 0.8	5.3 ± 1.5	.001[b]
No. of follicles on hCG day			
14 to <17 mm	2.7 ± 1.4	1.4 ± 0.7	<.001[b]
≥17 mm	4.2 ± 1.4	2.7 ± 1.0	<.001[b]
EMT on hCG day (mm)	9.8 ± 1.2	9.9 ± 1.4	NS[b]
No. of oocytes retrieved	5.4 ± 1.9	3.8 ± 1.4	<.001[b]
No. of mature oocytes	4.6 ± 1.7	3.2 ± 1.2	<.001[b]
No. of fertilized oocytes	4.3 ± 1.7	3.0 ± 1.2	<.001[b]
No. of grade I, II embryos	1.9 ± 1.0	1.3 ± 0.8	.001[b]
No. of embryos transfered	2.6 ± 0.9	2.6 ± 0.7	NS[b]
Embryo implantation rate (%)	14.3 (20/140)	7.2 (8/138)	.019[a]
Clinical PR per cycle initiated (%)	30.9 (17/55)	14.5 (8/55)	.041[a]

Kim et al., 2011

Transdermal Testosterone

(Gonzalez-Comadran et al., RBMO 2012)

Reproductive BioMedicine Online (2012) 25, 450–459

ELSEVIER

www.sciencedirect.com
www.rbmonline.com

REVIEW

Effects of transdermal testosterone in poor responders undergoing IVF: systematic review and meta-analysis

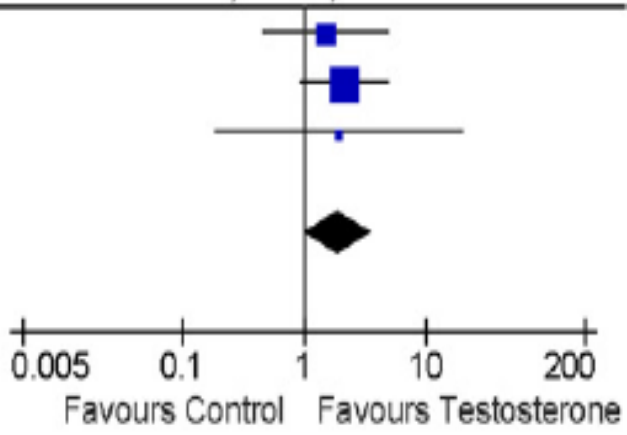
Mireia González-Comadran [a,b], Montserrat Durán [b], Ivan Solà [c,d], Francisco Fábregues [e], Ramón Carreras [a,f], Miguel A Checa [a,f,g,*]

(a) Live birth

Study or Subgroup	Testosterone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fábregues et al., 2009	6	31	4	31	33.3%	1.50 [0.47, 4.80]
Kim et al., 2011	15	55	7	55	58.2%	2.14 [0.95, 4.84]
Massin et al., 2006	2	27	1	26	8.5%	1.93 [0.19, 19.98]
Total (95% CI)		**113**		**112**	**100.0%**	**1.91 [1.01, 3.63]**
Total events	23		12			

Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%

Test for overall effect: Z = 1.98 (P = 0.05)

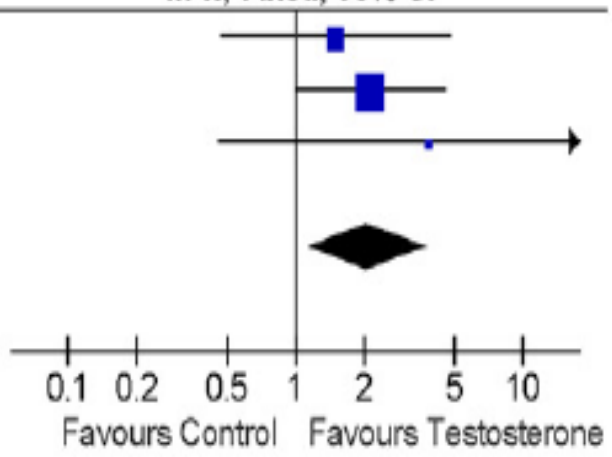


(b) Clinical pregnancy

Study or Subgroup	Testosterone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fábregues et al., 2009	6	31	4	31	30.7%	1.50 [0.47, 4.80]
Kim et al., 2011	17	55	8	55	61.4%	2.13 [1.00, 4.51]
Massin et al., 2006	4	27	1	26	7.8%	3.85 [0.46, 32.22]
Total (95% CI)		**113**		**112**	**100.0%**	**2.07 [1.13, 3.78]**
Total events	27		13			

Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%

Test for overall effect: Z = 2.36 (P = 0.02)

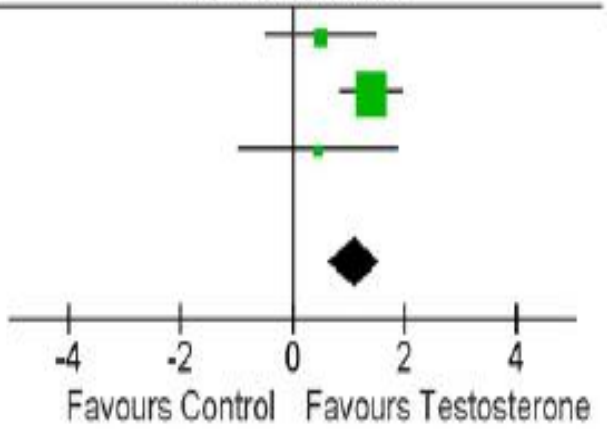


(d) Number of metaphase II oocytes

Study or Subgroup	Testosterone Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fábregues et al., 2009	4.1	1.8	31	3.6	2.1	31	21.7%	0.50 [-0.47, 1.47]
Kim et al., 2011	4.6	1.7	55	3.2	1.2	55	67.9%	1.40 [0.85, 1.95]
Massin et al., 2006	3.75	3.34	27	3.3	1.6	26	10.4%	0.45 [-0.95, 1.85]
Total (95% CI)			**113**			**112**	**100.0%**	**1.11 [0.65, 1.56]**

Heterogeneity: Chi² = 3.43, df = 2 (P = 0.18); I² = 42%

Test for overall effect: Z = 4.78 (P < 0.00001)

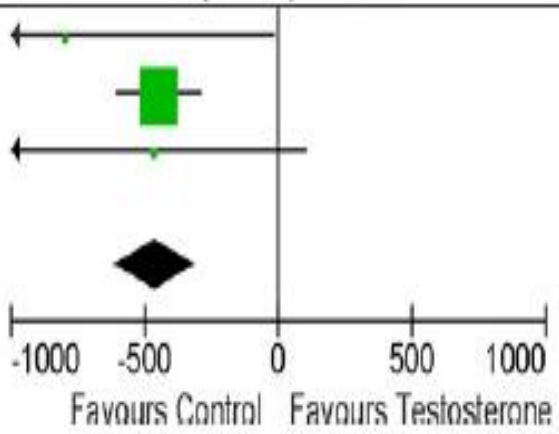


(e) Total dose of FSH administered

Study or Subgroup	Testosterone Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fábregues et al., 2009	3,154	1,168	31	3,950	1,870	31	3.7%	-796.00 [-1572.13, -19.87]
Kim et al., 2011	2,552.3	397.1	55	3,000	449.8	55	89.3%	-447.70 [-606.27, -289.13]
Massin et al., 2006	3,539	965	27	4,005	1,136	26	6.9%	-466.00 [-1034.47, 102.47]
Total (95% CI)			**113**			**112**	**100.0%**	**-461.96 [-611.82, -312.09]**

Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 6.04 (P < 0.00001)



Kim et al., 2014

- RCT, 120 por responders
- RCT, 3 groups. GnRH ant. Protocol
  - Testosterone gel, **12.5 mg** / day, **2 weeks**
  - Testosterone gel, **12.5 mg** / day, **3 weeks**
  - Testosterone gel, **12.5 mg** / day, **4 weeks**
- 3-week and 4-week groups: increased AFC, increased blood flow to ovaries, increased number of oocytes
- 4-week group: increased clinical pregnancy and live birth rates

Table 2. Comparison of controlled ovarian stimulation results and IVF-ET outcome

	Control	2 wks treatment	3 wks treatment	4 wks treatment
No. of cycles initiated	30	30	30	30
No. of cycles retrieved	28	29	30	30
No. of ET cycles	27	28	30	30
No. of cycles cancelled	3 (10.0%)	2 (6.7%)	0	0
On stimulation day 1				
AFC	4.0 ± 1.3	4.1 ± 1.2	4.9 ± 1.1[a]	5.2 ± 1.0[b]
MFD	5.9 ± 0.6	5.7 ± 0.5	5.2 ± 0.4[c]	4.7 ± 0.4[c]
RI of OSA	0.95 ± 0.03	0.94 ± 0.03	0.92 ± 0.03[d]	0.89 ± 0.03[e]
Total dose of rhFSH (IU)	3,025.0±425.9	2,765.7±567.8	2,596.7±335.3[e]	2,643.5±389.0[e]
Days of rhFSH administered	10.6±1.5	10.2±1.7	9.6±1.1[e]	9.8±1.0[e]
No. of oocytes retrieved	3.9±1.3	4.3±1.6	5.3±2.0[e]	5.8±1.9[e]
No. of mature oocytes	3.1±1.1	3.6±1.3	4.5±1.8[e]	4.9±1.6[e]
No. of fertilized oocytes	3.1±1.1	3.5±1.3	4.2±1.7[e]	4.6±1.6[e]
No. of grade I, II embryos	1.5±0.6	1.6±0.6	2.2±0.6[a]	2.1±0.7[a]
No. of embryos transferred	2.9±0.9	2.7±0.7	2.9±0.9	2.9±0.8
CPR per cycle initiated (%)	10.0 (3/30)	16.7 (5/30)	30.0 (9/30)	36.7 (11/30)[e]
Miscarriage rate per clinical pregnancy (%)	33.3 (1/3)	20.0 (1/5)	22.2 (2/9)	18.2 (2/11)
Live birth rate per cycle initiated (%)	6.7 (2/30)	13.4 (4/30)	20.0 (6/30)	30.0 (9/30)[f]

Kim et al., 2014

Human Reproduction, Vol.31, No.5 pp. 977–985, 2016
Advanced Access publication on March 7, 2016 doi:10.1093/humrep/dew028

human reproduction

ORIGINAL ARTICLE *Endocrinology*

Transdermal testosterone pretreatment in poor responders undergoing ICSI: a randomized clinical trial

J.K. Bosdou[1], C.A. Venetis[2], K. Dafopoulos[3], L. Zepiridis[1], K. Chatzimeletiou[1], G. Anifandis[3], A. Mitsoli[1], A. Makedos[1], I.E. Messinis[3], B.C. Tarlatzis[1], and E.M. Kolibianakis[1,*]

[1]Unit for Human Reproduction, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece [2]School of Women's and Children's Health, UNSW Medicine, University of New South Wales, Sydney, Australia [3]Unit for Human Reproduction, Department of Obstetrics and Gynecology, Medical School, University of Thessaly, Larissa, Greece

Bosdou et al., 2016

- Testosterone Gel - transdermal
- 10mg / day
- 21 days
- N = 39 (started: study 26 – control 24)
- No difference in number of oocytes retrieved (3.5 vs 3.0; p 0.76)
- No difference in clinical pregnancy and live birth rates

Adverse effects
Transdermal Testosterone

- Long-term use for menopausal women. No significant adverse effect were identified.
- *Goldstat et al., 2003*: testosterone gel 10 mg / day for 3 months, menopausal women. No significant adverse effect were identified.
- *Gelfand & Wiita, 1997*: recommended, testosterone gel: ≤ 10 mg/day, for 6 months

Clinical application at IVFMD

- Testosterone Gel
- 10mg / day
- 4 – 8 weeks
- Dosage: 1/5 sachet / day (50mg sachet)
    - preparation and storage

Current issues of transdermal T for poor responders

- Transdermal Testosterone pretreatment may improve IVF results for poor responders
- Inconsistent results, different dosages, treatment courses and studied populations.
- To be considered:
  - Which group of patients most benefit ?
  - How long of treatment course ?
  - RCT with larger sample size ?

Need for further study

- Longer treatment course, more than 4 weeks ?
- Testosterone dose: max 10mg/day
- RCT with larger sample size

Nghiên cứu T-TRANSPORT

T. Dose 5,5mg/ngày.

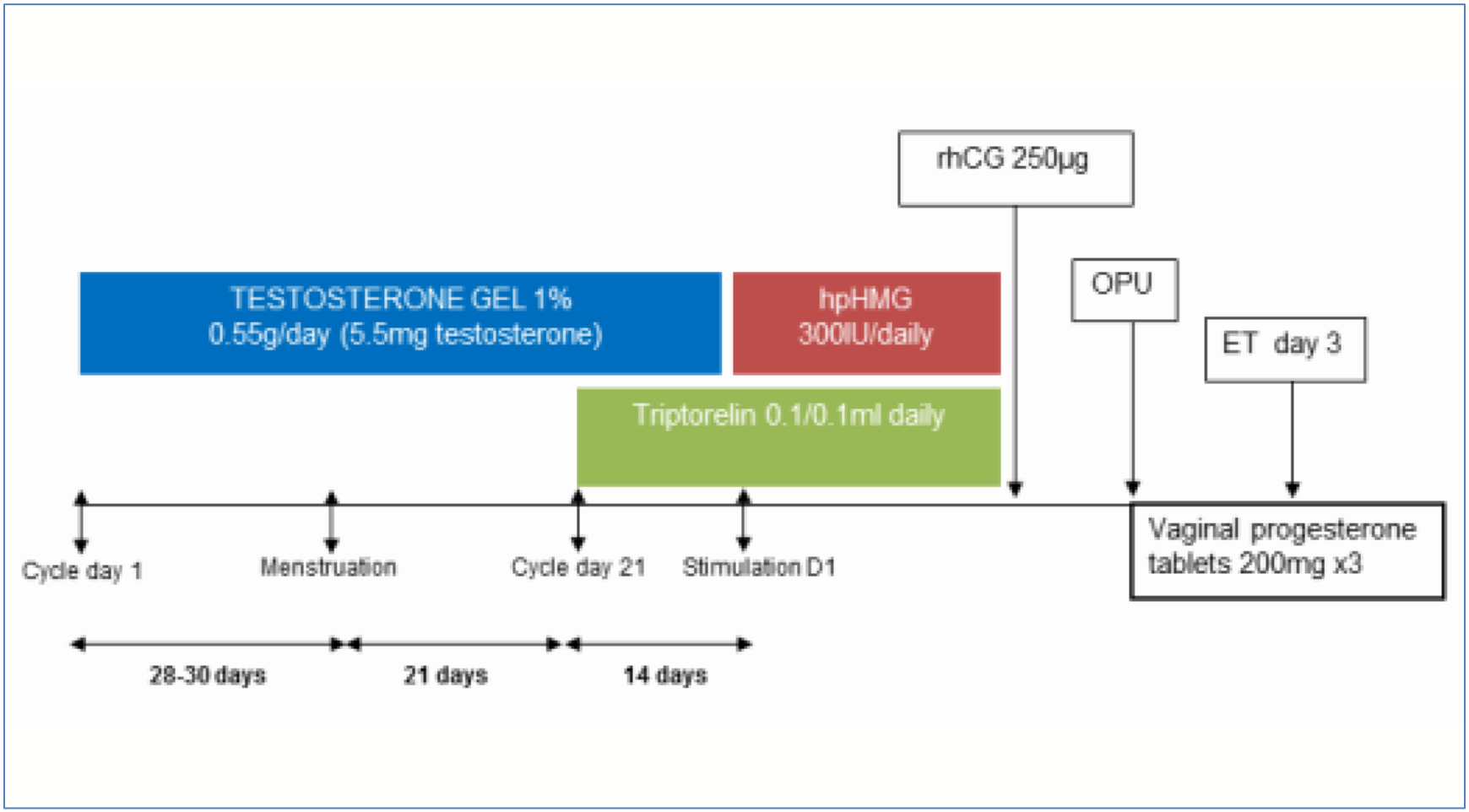
Treatment course: > 60 days

Sample size: 400

TITLE PAGE

Abbreviated Title	**Testosterone TRANSdermal gel for Poor Ovarian Responders Trial (T-TRANSPORT)**
Title	**Transdermal testosterone gel for poor ovarian responders. A multicentre double-blind placebo controlled randomized trial.**
Clinical Phase	**III**
Protocol Code	**2014.TTRANSPORT**
Study Sponsor	**Universitair Ziekenhuis Brussel**
EudraCT No.	**2014-001835-35**
Clinicaltrials.gov No.	**NCT02418572**
Chief investigator	**Nikolaos P. Polyzos MD PhD** MEDICAL DIRECTOR Centre for Reproductive Medicine UNIVERSITAIR ZIEKENHUIS BRUSSEL 1090, BRUSSELS, BELGIUM

Nghiên cứu **T-TRANSPORT**



Fulfill your hope

Conclusions

- Transdermal Testosterone pretreatment might improve IVF results in poor resonders.
- Two forms: ***gel*** or ***patch***
- Dose < 10mg/day. Duration: > 4 weeks
- Safe, inexpensive, simple
- Applied in Vietnam, limited data

IVFMD

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THANK YOU