Συχνοί φαρμακευτικοί χειρισμοί στην υπογονιμότητα που κάνουμε λάθη

Sofikitis Nikolaos MD, PhD, DMSci
Professor and Chairman
Department of Urology
Ioannina University

Pharmaceutical treatment of OAT is indicated

a) In males in whom there is no definite cause of their diminished fertility potential
b) In males in whom the treatment of a specific pathophysiology has been proven to be unsuccessful.

Targets of the pharmaceutical treatment of OAT

a) To assist the couple to achieve natural conception
b) To result in the employment of less invasive methods of assisted reproduction technology such as artificial insemination or IVF instead of ICSI.
c) To improve the live birth rate after ART methods.

Hormonal treatment
1. GnRH analogues 2. GnRH antagonists 3. Gonadotrophins 4. Testosterone 5. Testosterone rebound therapy 6. Antiestrogens (Clomiphene, Tamoxifen) 7. Testolactone-Anastrazole (aromatase inhibitors) 8. Bromocryptine
Non-hormonal treatment
1. PDE5 inhibitors 2. Kallikrein 3. Indomethacin 4. ACE inhibitors 5. Arginine 6. Pentoxyphyline 7. Antioxidants

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GnRH Analogues

- In Hypogonadotropic Hypogonadism Only.

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GnRH Antagonists

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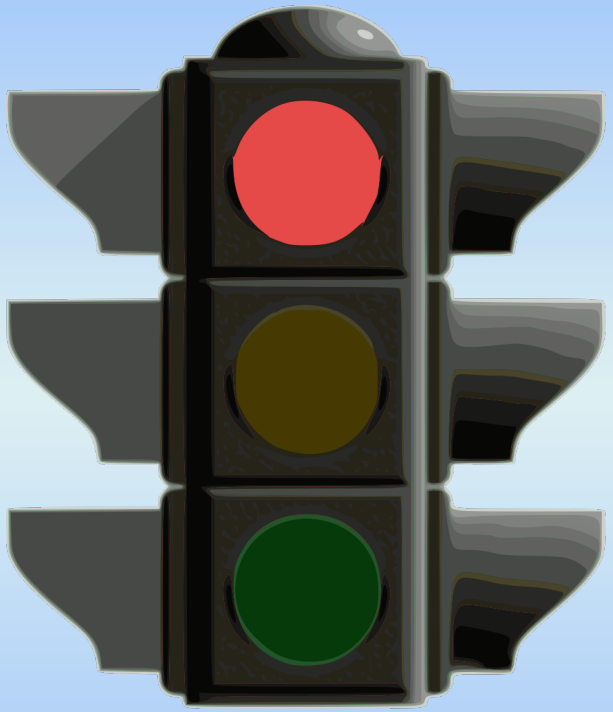
Gonadotrophins



- In Hypogonadotropic Hypogonadism Only

BUT

- The efficiency of FSH treatment has been studied in two metanalyses published in Cohrane Database.
- Significantly larger pregnancy rate was demonstrated after three-month-treatment (13.4% versus 4.4%).

(Attia et al., 2006; Attia et al., 2007)

International Journal of Andrology

international journal of andrology ISSN 0105-6263

ORIGINAL ARTICLE

The response to FSH treatment in oligozoospermic men depends on FSH receptor gene polymorphisms

R. Selice, A. Garolla, M. Pengo, N. Caretta, A. Ferlin and C. Foresta

Department of Histology, Microbiology and Medical Biotechnologies, Section of Clinical Pathology & Centre for Male Gamete Cryopreservation, University of Padova, Padova, Italy

Conclusions

This study suggests that the analysis of this gene represents a valid pharmacogenetic approach to the treatment of male infertility, confirming also the importance of strict criteria for the selection of patients to be treated with FSH

Treatment of male idiopathic infertility with recombinant human FSH: a prospective, controlled randomized clinical study

- FSH therapy does not improve sperm concentration or pregnancy rate when infertile male patients are chosen solely by the clinical criteria of idiopathic oligospermia and normal FSH concentration. Subgroup analysis, however, does indicate that patients without maturation arrest in addition to the clinical scenario do benefit from medical therapy.

Foresta et al., 2005. Fertil Steril. 84: 654-61.

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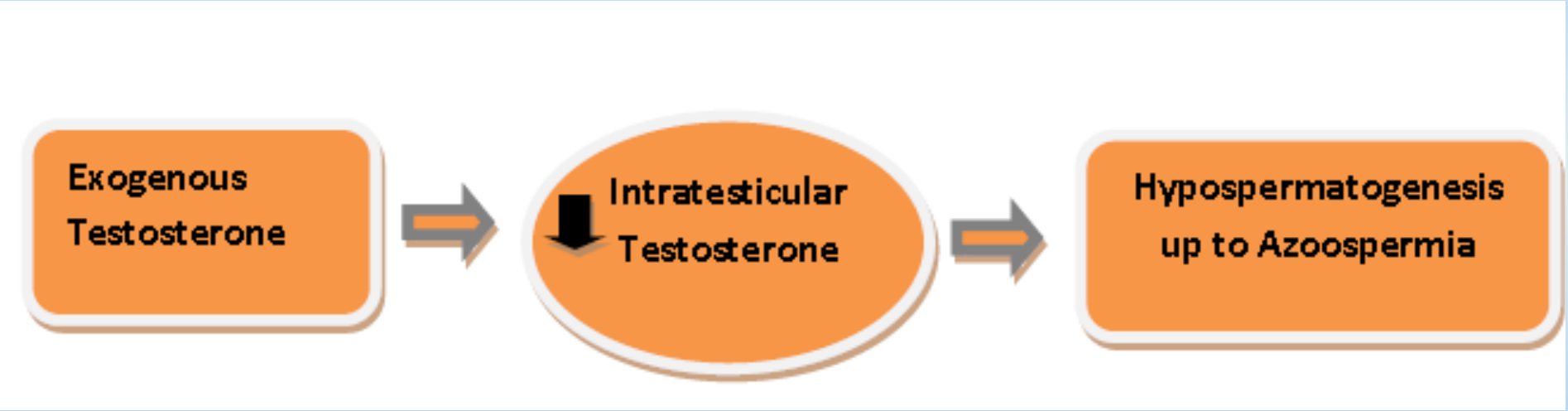
TRT AND MALE FERTILITY POTENTIAL



Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis

Peter Y Liu, Ronald S Swerdloff, Peter D Christenson, David J Handelsman, Christina Wang, and the Hormonal Male Contraception Summit group*

Lancet 2006; 367: 1412–20

- These data represented about 90% of all published data from individuals using androgen or androgen-progestagen regimens. Multivariate Cox's analysis showed higher rates of recovery with older age, Asian origin, shorter treatment duration, shorter-acting testosterone preparations, higher sperm concentrations at baseline, faster suppression of spermatogenesis, and lower blood concentrations of luteinising hormone at baseline.

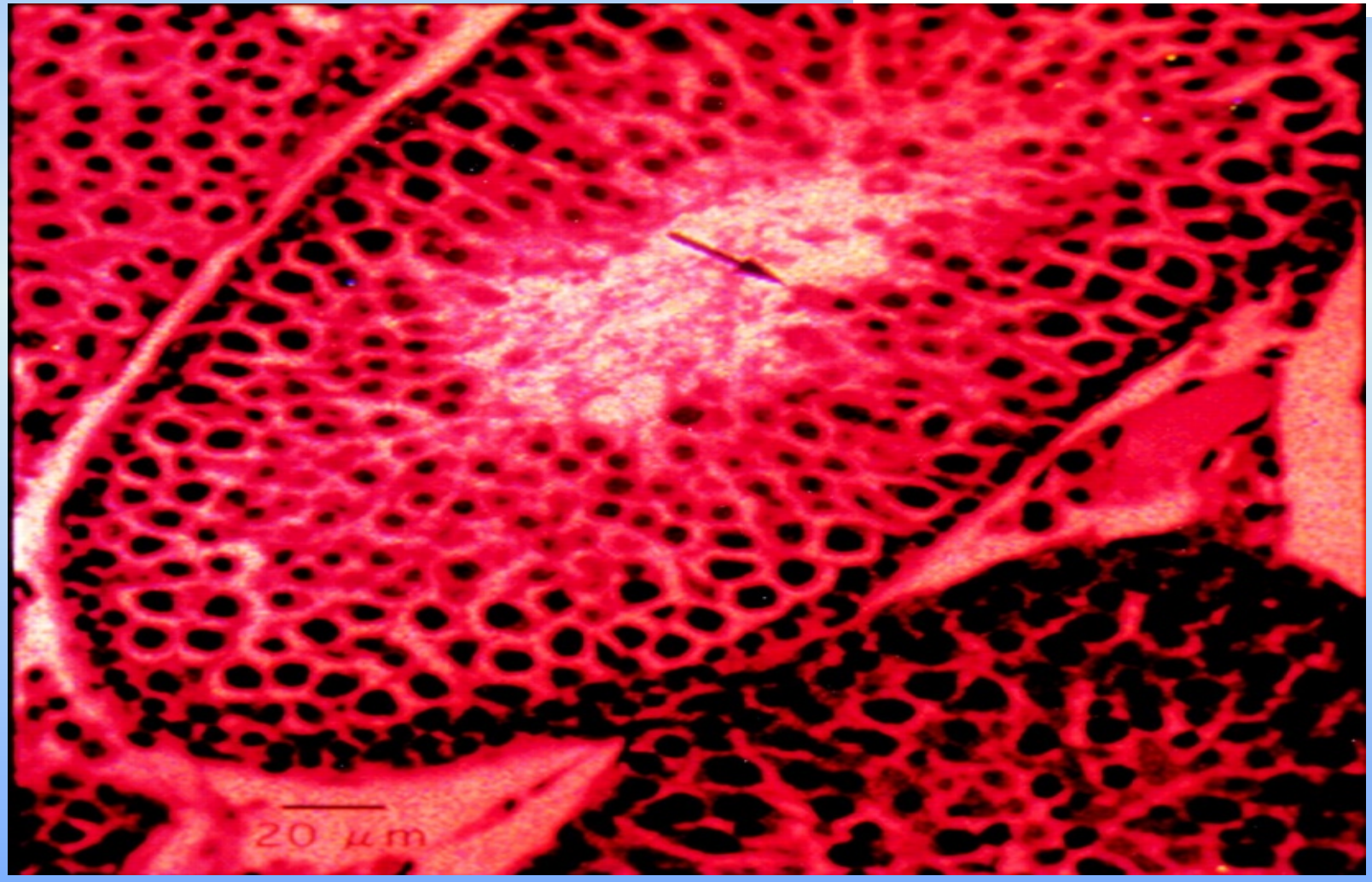
Probability of Recovery to 20 million per mL	Duration (months)
67% (61-72)	6
90% (85-93)	12
96% (92-98)	16
100%	24

Lancet 2006; 367:1412-20

Human Reproduction vol.14 no.8 pp.1998–2006, 1999

Influence of the male reproductive tract on the reproductive potential of round spermatids abnormally released from the seminiferous epithelium*

N.Sofikitis[1,3], K.Ono[1], Y.Yamamoto[1], H.Papadopoulos[2] and I.Miyagawa[1]



Administration of Testosterone to Infertile Men

- Do Not Administer Contraceptive Agents to the Individuals who want to Father their Own Children.

BUT

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Vol. 67, No. 4, April 1997
Printed on acid-free paper in U. S. A.

The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia*

Dimitrios A. Adamopoulos, M.D.†
Stamatina Nicopoulou, M.D.
Niki Kapolla, B.S.,
Maria Karamertzanis, M.D.
Evangelia Andreou, M.D.

FERTILITY AND STERILITY®
VOL. 80, NO. 4, OCTOBER 2003

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia

Dimitrios A. Adamopoulos, M.D., Athina Pappa, M.Sc., Evangelia Billa, M.D., Stamatina Nicopoulou, M.D., Eftychia Koukkou, M.D., and John Michopoulos, M.D.

The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia

- The combination of tamoxifen citrate with Testosterone undecanoate not only improves significantly important seminal parameters but also compares favorably with the single treatments used. Therefore, this combination deserves a place as a first line of treatment in idiopathic oligozoospermia.

Adamopoulos et al., 1997.Fertil. Steril. 67:756-62.

Hormonal treatment
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Testosterone rebound therapy

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Outcomes of clomiphene citrate treatment in young hypogonadal men

- Long-term follow-up of CC treatment for HG shows that it appears to be an effective and safe alternative to testosterone supplementation in men wishing to preserve their fertility.

Katz et al., 2011. BJUI. doi:10.1111/j.1464-410X.2011.10702.x

Changes in the endocrinological milieu after clomiphene citrate treatment for oligozoospermia: the clinical significance of the estradiol/testosterone ratio as a prognostic value.

- The rate of increase in the E_2/T ratio during clomiphene citrate treatment has prognostic value, and performing the hCG test before this treatment may be helpful in predicting the endocrinological milieu after It. If the rate of increase In the E_2/T ratio following hCG injection Is high, treatment should consist of a combination of clomiphene citrate and an aromatase inhibitor to decrease the E_2/T ratio.

Itoh et al., 1994. J Androl.15: 449-55.

Clomiphene Administration for Cases of Nonobstructive Azoospermia: A Multicenter Study

- Clomiphene citrate administration may result in sperm in the ejaculate of patients with nonobstructive azoospermia or the simplification of testis sperm retrieval. Surgeons may consider a course of clomiphene citrate administration prior to surgical sperm retrieval in patients with nonobstructive azoospermia.

Hussein et al., 2005. J Androl. 26: 787–791

Azoospermia after treatment with clomiphene citrate in patients with oligospermia

- The benefits of empiric treatment with CC must be balanced with the possible undesirable effects, such as azoospermia.

Pasqualotto et al., 2008. Fertil. Steril. 90:2014.e11–e12.

Hormonal treatment
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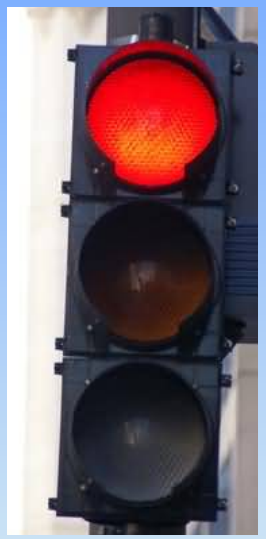
EVIDENCE OF A TREATABLE ENDOCRINOPATHY IN INFERTILE MEN

- An endocrinopathy was identified in men with severe male factor infertility that was characterized by a decreased serum testosterone-to-estradiol ratio. This ratio can be corrected by aromatase inhibition, resulting in a significant improvement in semen parameters in oligospermic patients.

Pavlovich et al., 2001. J. Urol. 165: 837-841.



Because

Treatment of men with idiopathic oligozoospermic infertility using the aromatase inhibitor, testolactone. Results of a double-blinded, randomized, placebo-controlled trial with crossover.

- It may be suggested that chronic administration of testolactone at this dose fails to maintain aromatase inhibition despite depression of 17,20-desmolase activity with elevated 17a-hydroxyprogesterone and depressed SHBG binding capacity with elevation of free testosterone. Testolactone is not efficacious in the treatment of idiopathic oligozoospermic infertility.

Clark and Sherins 1989. J. Androl. 10: 240-247

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to Bromocryptine

- Chronic Renal Failure
- Pituitary Adenoma

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BJUI
BJU INTERNATIONAL

Effects of phosphodiesterase-5 inhibitors on Leydig cell secretory function in oligoasthenospermic infertile men: a randomized trial

Fotios Dimitriadis*†, Stavros Tsambalas†, Panagiota Tsounapi*, Hiroshi Kawamura†, Evlalia Vlachopoulou†, Nikolaos Haliasos†, Stavros Gratsias†, Takeshi Watanabe*, Motoaki Saito‡, Ikuo Miyagawa* and Nikolaos Sofikitis†

*Department of Urology, Tottori University School of Medicine, †Department of Pathophysiological and Therapeutic Science, Division of Molecular Pharmacology, Faculty of Medicine, Tottori University, Yonago, Japan, and †Laboratory of Molecular Urology and Genetics of Human Reproduction, Department of Urology, Ioannina University School of Medicine, Ioannina, Greece

First International Journal of Andrology
ANDROLOGIA

ORIGINAL ARTICLE

Effects of phosphodiesterase-5 inhibitor vardenafil on testicular androgen-binding protein secretion, the maintenance of foci of advanced spermatogenesis and the sperm fertilising capacity in azoospermic men

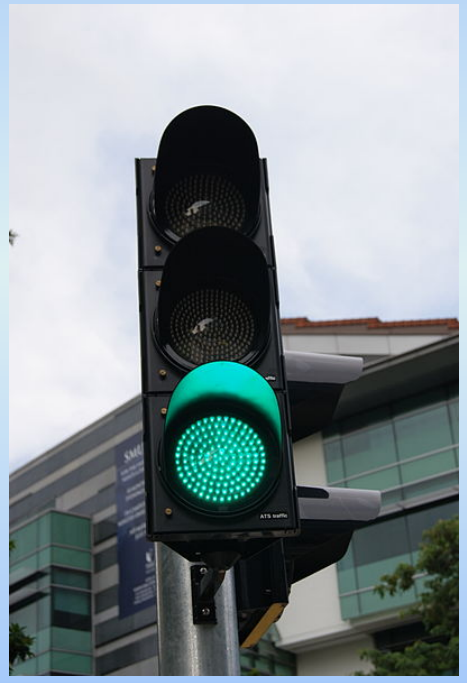
F. Dimitriadis[1,2,3], S. Tsampalas[2], P. Tsounapi[1,2,3], D Giannakis[2], N.Chaliasos[2], D. Baltogiannis[2], I. Miyagawa[3], M. Saito[1], A. Takenaka[3] & N. Sofikitis[1,2,3]

1 Department of Molecular Pharmacology, Tottori University School of Medicine, Yonago, Japan;
2 Laboratory of Molecular Urology and Genetics of Human Reproduction, Department of Urology, Ioannina University School of Medicine, Ioannina, Greece;
3 Department of Urology, Tottori University School of Medicine, Yonago, Japan

Vardenafil administration in NOA-men increased ABP secretion and did not affect detrimentally the presence of testicular foci of advanced spermatogenesis.

Dimitridis et al., 2011. Andrologia, 44 Suppl 1: 144-53.

PDE5 Inhibitors AND Indiopathic Oligozoospermia



for

PDE5 Inhibitors that **do not Interact** with the PDE11

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Indomethacin For Idiopathic OAT

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ACE inhibitors
For Idiopathic OAT

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- Arginine in Micronutrient Supplements
- A Nitric Oxide Donor

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Mol Cell Biochem
DOI 10.1007/s11010-012-1382-z

Antioxidant treatment with edaravone or taurine ameliorates diabetes-induced testicular dysfunction in the rat

Panagiota Tsounapi · Motoaki Saito · Fotios Dimitriadis · Sotirios Koukos · Shogo Shimizu · Keisuke Satoh · Atsushi Takenaka · Nikolaos Sofikitis

- The morphological damage, increased lipid peroxidation, and apoptosis in testicular tissue can be significantly relieved by edaravone or taurine treatment through suppressing the increased oxidative stress in the rat testis.

Tsounapi et al., 2012. Mol. Cell. Biochem.

Administration of Antioxidants in Men with OAT

- Did you quantify ROS generation?

ROS ARE IMPORTANT

- Human spermatozoa appear to use reactive oxygen species for a physiological purpose and have the difficult task of ensuring the balanced generation of these potentially harmful, but biologically important, modulators of cellular function.
- Bioessays. 1994 Apr;16(4):259-67.
- Aitken J, Fisher H.

- Spermatozoa of fertile men produce extremely low levels of ROS and yet, paradoxically, these molecules appear to be important mediators of normal sperm function.

Respect ROS

Do not administer large amounts of antioxidants