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 Hypogonadotrophic Hypogonadism Only.
Hormonal treatment

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GnRH Antagonists

- In Hypogonadotropin
- Hypogonadism **Only**.
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Gonadotrophins

- In Hypogonadotropin Hypogonadism Only
• The efficiency of FSH treatment has been studied in two metanlysises published in Cochrane Database.

• Significantly larger pregnancy rate was demonstrated after three-month-treatment (13.4% versus 4.4%).

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

Exogenous Testosterone \rightarrow Intratesticular Testosterone \rightarrow Hypospermatogenesis up to Azoospermia
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*

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.

<table>
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<th>Probability of Recovery to 20 million per mL</th>
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<td>67% (61-72)</td>
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<tr>
<td>90% (85-93)</td>
<td>12</td>
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<td>96% (92-98)</td>
<td>16</td>
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<td>100%</td>
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*Lancet 2006; 367:1412-20*
Influence of the male reproductive tract on the reproductive potential of round spermatids abnormally released from the seminiferous epithelium*

N. Sofikitis¹, K. Ono¹, Y. Yamamoto¹, H. Papadopoulos² and I. Miyagawa¹
Administration of Testosterone to Infertile Men

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

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.

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.

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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.

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.

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.

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.

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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.

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

Because 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 17α-hydroxyprogesterone and depressed SHBG binding capacity with elevation of free testosterone. Testolactone is not efficacious in the treatment of idiopathic oligozoospermic infertility.

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STOP to Bromocryptine

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

PDE5 Inhibitors AND Indiopathic Oligozoospermia

for PDE5 Inhibitors that do not Interact with the PDE11
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For Idiopathic OAT
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• Arginine in Micronutrient Supplements
• A Nitric Oxide Donor
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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.

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.


- 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