ESHRE Campus Course
Reproductive Andrology:
linking laboratory to clinical practice
Thessaloniki -Greece
1-3 October 2009

NON-SURGICAL(MEDICAL) TREATMENT OF MALE INFERTILITY

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ENDOCRINE EFFECTS OF SHORT TERM COMBINED TAMOXIFEN AND TESTOSTERONE UNDECANOATE TREATMENT IN MEN.

Adamopoulos DA, Vasilopoulos P, Abrahamian A, Nicopoulou S, Kontogeorgos L et al.

IVth International Congress of Andrology, Florence, Italy, 1989.

MALE INFERTILITY IN THE ERA OF ART;
WHY TREAT ?
HOW TO TREAT ?

Goldstein M, Rosenmarks Z, Semin Reprod Med, 2009

WHY TREAT

Although Assisted Reproductive Techniques (ART) provide a realistic solution for the couple's infertility,

the clinician must face the problem of infertility with the same responsibility as in any other disturbance or disease.

That means a proper investigation of both partners.

Proper evaluation of the subfertile male is needed to:

- **Diagnose correctable pathologies:** hypogonadism, varicocele, gonadotoxin exposure etc.

(32 old man, azoospermia, candidate for TESE-ICSI → history: hypogonadotropic Hypogonadism!)

- **Detect genetic disease(s)**

- **Diagnose life-threatening disease:** cancer.
- Prognosticate success in ART (TESE) trials

The end-point of the infertile male evaluation is to find, if possible, a patho-physiologic specific treatment to :

- **Achieve spontaneous pregnancy** and reduce the need for ART
- Downgrade the level of ART needed
- Increase the pregnancy rates when ART is unavoidable

Efesoy O, 2009

HOWEVER,

- In every-day practice and at routine clinical level, the investigation of men with OTA remains extremely crude and elementary including one or two semen analyses and an estimation of basal gonadotropins and androgen concentrations
- This diagnostic approach is totally inadequate, lacks the sophistication of the relevant work-up in women and, definitely, **does not merit the distinction of a scientific approach**

Adamopoulos DA, 2001

DIAGNOSTIC CATEGORIES AS PROPOSED BY WHO AND DIFFERENT AUTHORS

	Papadimas J,1982	Bhere, 1994	WHO,2000
Accessory gland infections	31%	9%	14%
Varicocele	21%	17%	25%
Infections + varicocele	13%	-	-
Chromosome abnormalities	6%	-	3%
Cryptorchidism	3%	8%	3%
Obstractive azoospermia	3%	1%	2%
Endocrine causes	-	9%	1%
Idiopathic OTA	**20%**	**32%**	**39%**
Immuno-causes	6%	4%	6%
Acquired testicular damage (torsion, post-mump orchitis …)	3%	-	3%
Sexual dysfunction	-	6%	4%
Systemic causes	-	5%	-
Cancer	-	2%	-
Other causes	-	7%	-

MEDICAL TREATMENT OF MALE INFERTILITY

I. Etiological or specific therapy
Endocrine causes
Enviromental-Occupational
Cancer
Recent or systemic disease
II. Specific therapies in question or not established yet.
Immune causes
Infections – Oxidative stress
Varicocele
III. Not specific-empiric therapy
Idiopathic

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Cancer	-	2%	-
Other causes	-	7%	-

INCIDENSE OF DYSSPERMIA CATEGORIES IN A CONTEMPORARY DIAGNOSTIC SETTING

Adamopoulos DA, Nicopoulou SC, Michalakis C, Pappa A, Koukkou E & Venaki E.

Andrology Clinic, Endocrine Department, ELENA VENIZELOU Hospital, Athens, Greece

774 Infertile couples

Improved diagnostic armentarium

- 4th European Congress of Andrology, 2006, Toulouse, France.

- Adamopoulos DA, Mitios G, Nicopoulou S, 2009 in "Clinical Andrology", Björndahl et al (eds), Informa Healthcare, London, in press.

NEW CATEGORIES

1. Occupational – Environmental
2. Epididymal pathology

3. **Combinations**

COMBINATIONS

a	Single-factor group	n: 289 - 37.3%
b	Two-factor group	n: 263 - 34.0%
c	Three-or more factor group	n: 222 - 28.7%

62.7% Combined causes

Adamopoulos DA, Nicopoulou S et al Toulouse 2006

SINGLE FACTOR INCIDENSE PER DIAGNOSTIC CATEGORY

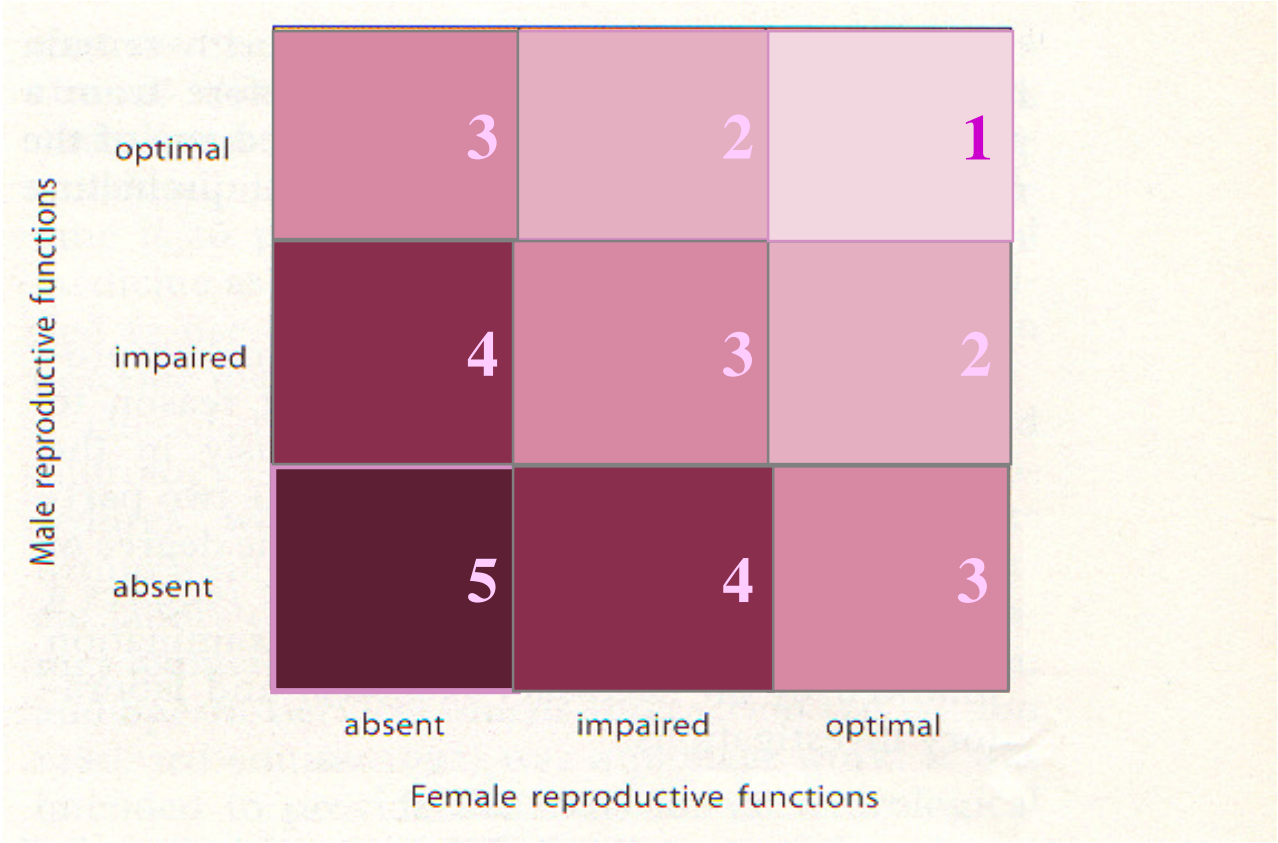
	Causative Factor	No	% of the single-factor	% of the total
1	**Idiopathic**	117	40.6%	**15.2%**
2	Varicocele	55	18.7%	7.0%
3	Epididymopathy	37	12.8%	4.8%
4	Envir/al-Occup/al	23	8.%	3.0%
5	Infections	15	5.3%	1.9%
6	Aquired test. damage	14	4.8%	1.8%
7	Congen. Anomalies	8	3.2%	1.1%
8	Systemic causes	6	2.1%	0.8%
9	Endocrine causes	5	1.6%	0.6%
10	Sexual dysfunction	4	1.3%	0.5%
11	Various <1% each	5	1.6%	0.6%
	Total	289	100.0%	**37.3% (n:774)**

TWO AND ≥ 3-FACTOR INCIDENSE PER DIAGNOSTIC CATEGORY

Most frequent component	2-factor group	≥ 3 factor group
Epididymopathy	31.3%	19.0%
Varicocele-hydrocele	26.5%	19.2%
Enviromental – Occupational	20.6%	24.8%
Other combinations	21.6%	37.0%
Total	100.0%	100.0%

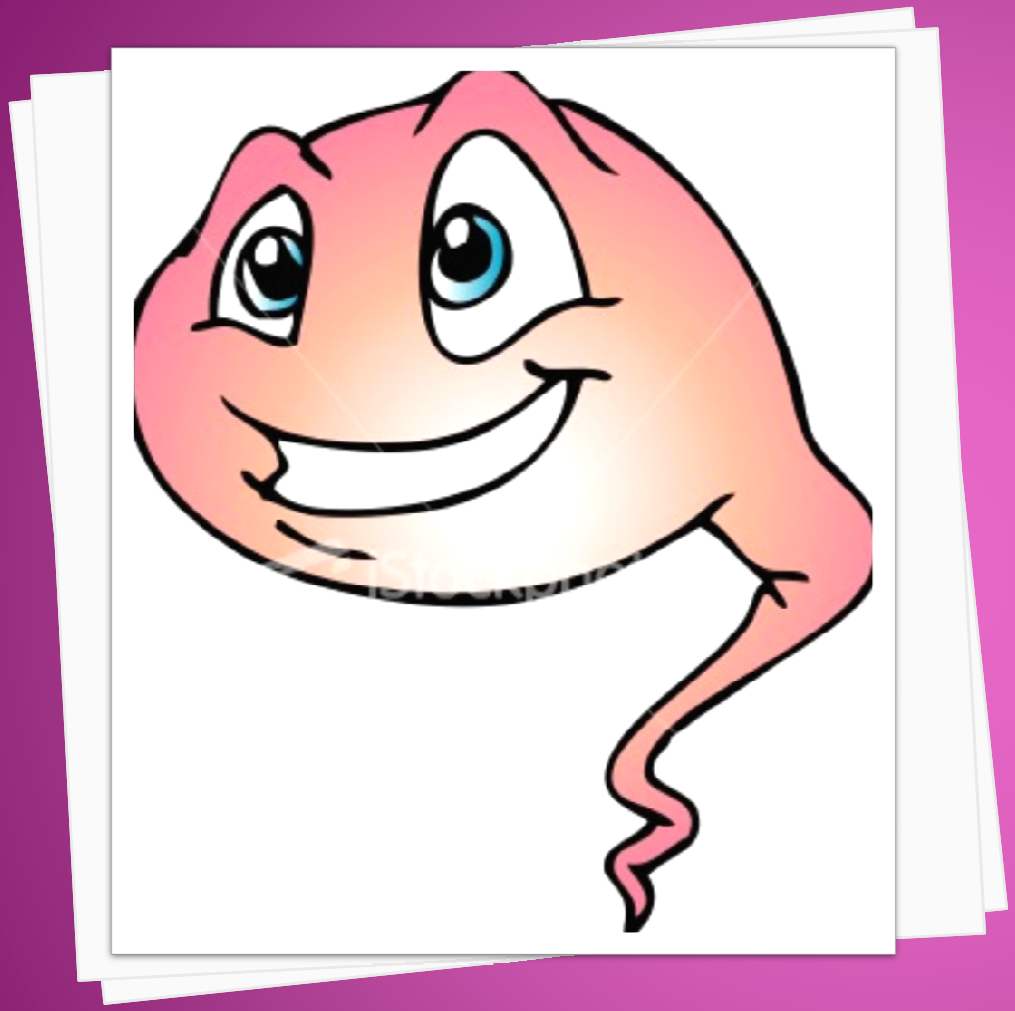
Adamopoulos DA, Nicopoulou S, et al
Toulouse 2006

INTERDEPENDENSE OF MALE AND FEMALE REPRODUCTIVE FUNCTIONS



"Andrology" (2000) Nieschlag,Behre

Fertility, as many other things, does not only need the single perfect
But, often, a good collaboration is enough.



HOW TO TREAT

MEDICAL TREATMENT OF MALE INFERTILITY

I. Etiological or specific therapy
Endocrine causes !
Enviromental-Occupational
Cancer
Recent or systemic disease
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III. Not specific-empiric therapy
Idiopathic !

ENDOCRINE CAUSES
Treatment of male Hypogonadotropic Hypogonadism or Isolated FSH Deficiency

Change the T substitution therapy with gonadotropins.

- **Human chorionic gonadotropin (hCG)1500 IU 2-3 times/week for 2-3 months and then add**
- **rhFSH 100-150 IU 3 times /week continuously for 12-18 months.**

Initial testicular volume may provide a measure of severity and predict response

First spermatozoa appear in the ejaculate after a median of 7 months

EFESOY O. J Andrology 2009

OTHER ENDOCRINOPATHIES OR SYSTEMIC DISEASES

- Treat the underlying disease, if possible. Wait the proper time-period for restoration of testicular function and spermatogenesis.
- Sperm cryopreservation: spermatogenesis restoration not possible or worse prospects (pollution – chemotherapy)

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OXIDATIVE STRESS

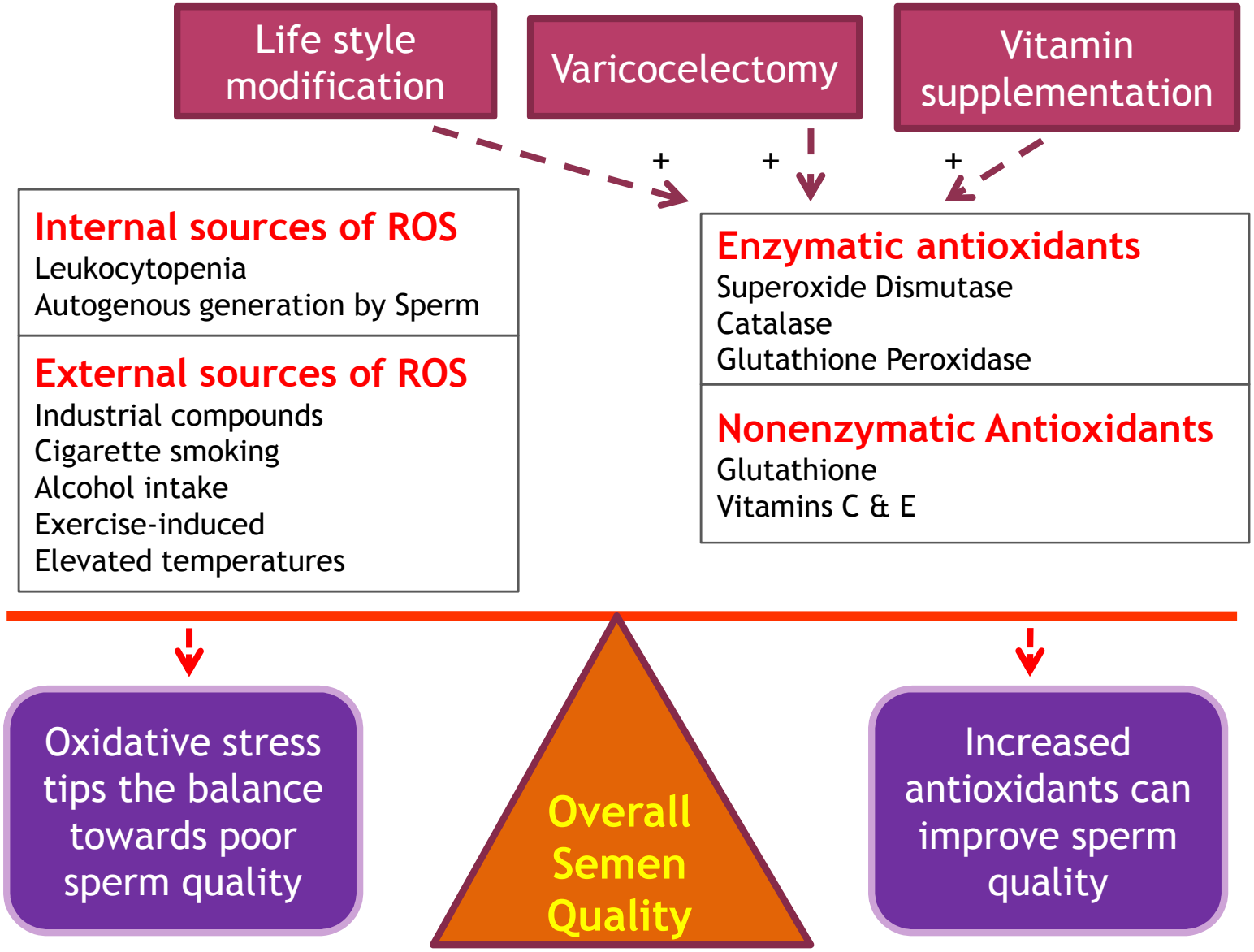
It is induced by excessive levels of Reactive Oxygen Species (ROS), or free radicals.

ROS are:

- Products of normal cellular metabolism
- While their presence is necessary for sperm capacitation, hyperactivation and sperm-oocyte fusion, excessive levels have a negative impact on sperm quality as they result in the oxidation of cell membrane lipids, amino acids in proteins or within nucleic acids.

Kefer JC, 2009

OXIDATIVE STRESS



OXIDATIVE STRESS CONCLUSIONS

Despite the increasing knowledge on ROS production and action in the male genital tract offering new openings for potential therapies,

further well-designed trials are required to test the treatments proposed for best efficacy

MEDICAL TREATMENT OF MALE INFERTILITY

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Infections –
Varicocele Oxidative stress !
III. Not specific-empiric therapy
Idiopathic !

IDIOPATHIC OTA

- Impaired sperm quantity and quality not related to any of known or detectable causes of spermatogenic disturbances.

- **Empiric therapy is necessary.**

MEDICAL TREATMENT OF IDIOPATHIC OTA

I. **Medical treatment:** enhance the spermatogenic process in order to:

- substitute, set at a higher level or lower pace or re-arrange the endocrine activity, or
- Support, through different mechanisms, sperm capability for fertilization.

II. ART

MEDICAL TREATMENT OF IDIOPATHIC OTA IN THE ERA OF ART

Re-arrange the endocrine activity

- Gonadotropins : FSH
- Antioestrogens : Clomiphene-Tamoxifen citrate
- Combination: tamoxifen +testosterone undecanoate.

GONADOTROPINS

Given the important role of these hormones in the growing economy of assisted reproduction with ovarian hyperstimulation,

as well as the crucial role of **FSH** in inducing and maintaining spermatogenesis

one cannot miss the irony of the marginal role that these hormones played in the treatment of infertile men.

GONADOTROPINS

The landmark study of Acosta et al in 1992 although uncontrolled, reporting an impressive improvement of fertilization and pregnancy rates, gave the spark for a number of new relevant trials that continue till today.

1. FSH TREATMENT IN IDIOPATHIC OTA

Study/Author	Outcome	
Acosta A et al, 1992 (uncontrolled)	Increase 2-54% in sperm parameters and fertilization rate in IVF	
CONTROLLED STUDIES		
Ben Rafael Z et al, 1995 (n=40)	Fertilization after IVF	Control: 5.8% FSH: 20.0%
Comodo et al, 1996 (n=26)	Fertilization after IVF	Control: 10.6% FSH: 18.9%
Matorras et al 1997 (n=148)	Pregnancy after IUI	↑ In a subset of FSH
Foresta et al, 1998 (n=90)	Number of spermatids	↑ In a subset of FSH
Kamischke et al, 1998 (n=67)	Testicular volume Sperm parameters DNA condensation	Increase No change Increase
Loumaye et al 1998 (n=122)	Fertilization after IVF	Control: 24% FSH: 23%

FSH TREATMENT IN IDIOPATHIC OTA

Study/Author	Outcome	
Foresta et al 2002 (n=15)	Sperm aspiration in hypospermato-genic men (FNA)	Positive in 11 out of 15
Caroppo et al, 2003 (n=33)	Fertilization in ICSI Pregnancy	Control: 30.4% FSH : 62.3% Control: 0.0% FSH :47.2%
Attia AM et al, 2006 (n=278) a Cochrane meta-analysis	Pregnancy rates (spontaneous-ART)	Control: 4.4% FSH : 13.4%

FSH IN MATURATION ARREST

Study/Author	Outcome	
Aydos et al, 2003	quantity of retrieved spermatozoa	Control: 33.0% FSH: 64.0%
Selman et al , 2004 Case report	sperm in the ejaculate in an azoospermic patient with Y chromosome microdeletion	
Selman et al , 2006 (n=49)	sperm in the ejaculate or in TESE	22 .4% in FSH group (11/49)
Efesoy et al, 2009 (n=11)	>>	36.3% (4/11)

FSH IN OTA - CONCLUSIONS

Apart from its use as a specific treatment in hypogonadotropic hypogonadism and isolated FSH deficiency,

FSH is a safe, well tolerated and effective therapeutic option but in a **subset** of men with idiopathic OTA or even non-obstructive azoospermia by

- either increasing ICSI success or
- providing sperm in ejaculate in azoospermics.

Foresta C, 2009 – Efesoy O, 2009

2. ANTIOESTROGENS: CLOMIPHENE CITRATE & TAMOXIFEN CITRATE

ANTIOESTROGENS: CLOMIPHENE CITRATE & TAMOXIFEN CITRATE

- Nonsteroidal selective estrogen receptor modulators
- They block the estrogen receptor preventing inhibition of gonadotropin secretion.
- **Tamoxifen** is prefered than clomiphene because it exerts a weaker estrogenic action.

ANTIOESTROGENS: CLOMIPHENE CITRATE & TAMOXIFEN CITRATE

- First results published by Comhaire et al in 1976. Since then many studies were published, with varying results due to the different etiologies included in idiopathic OTA.
- *However, in almost every study published there was a subgroup of men with a satisfactory response.*
- If this subgroup could be identified, it would change our position to the proposed treatment.

3. ANTIOESTROGENS IN COMBINATION WITH A WEAK ANDROGEN (TESTOSTERONE UNDECANOATE)

ANTIOESTROGENS IN COMBINATION WITH A WEAK ANDROGEN (TESTOSTERONE UNDECANOATE)

Adamopoulos et al:

- IVth International Congress of Andrology,1989 (short)
- Fertil Steril, 1995 (long)
- Fertil Steril, 1997
- Fertil Steril, 2003
- J Androl, 2005

Why add the weak androgen?

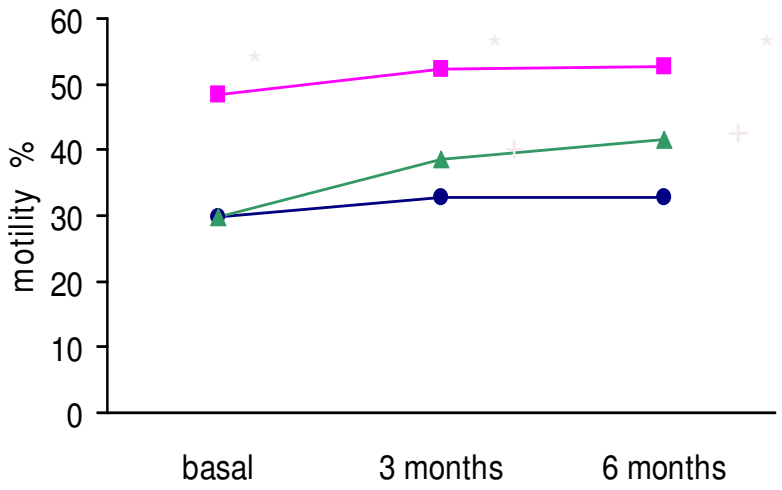
To promote androgen bioactivity in epididymis and in accessory glands.

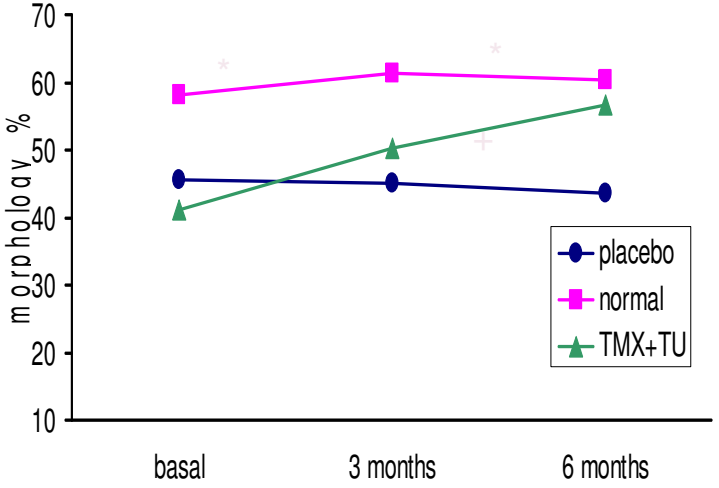
"Testosterone undecanoate in the functional compartements of the male reproductive tract."

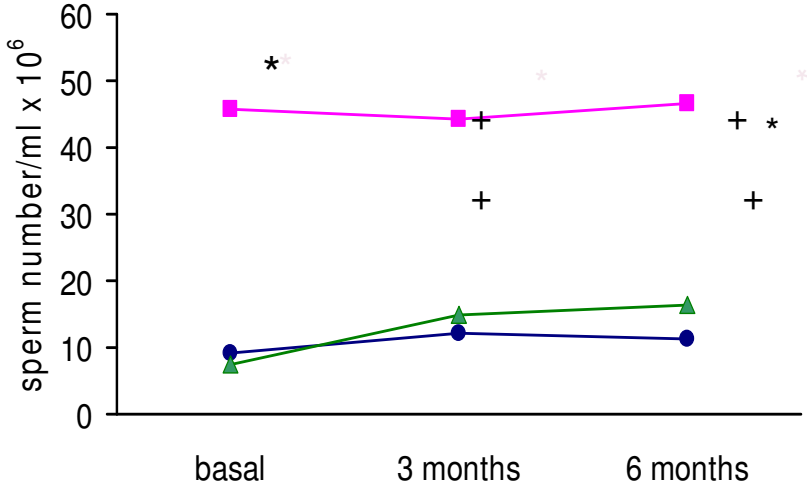
E. Koukkou et al 2009 in press

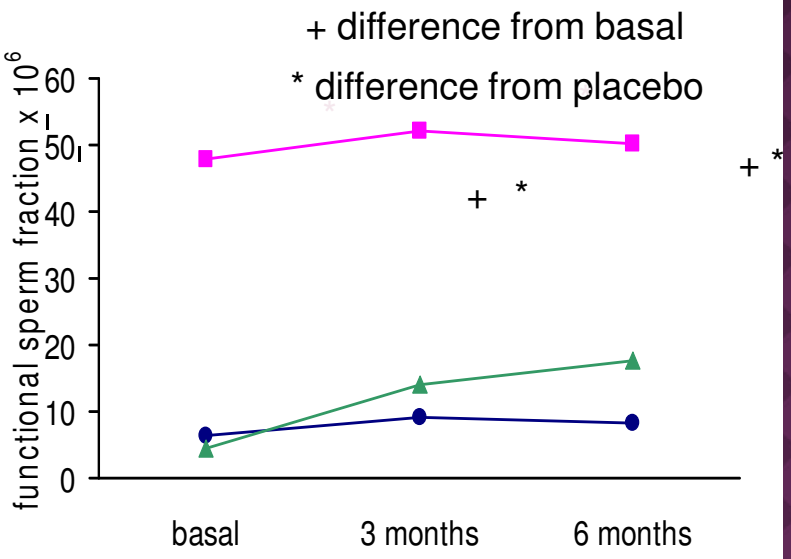
1. There is an active transfer mechanism of TU from circulation to seminal plasma as its concentration was 87% of that in preripheral blood, and
2. A marked rise in blood DHT was found (147.8%) showing a probable amplification in the bioavailability of DHT in peripheral blood and probably in accessory glands too.

MAIN SPERM CHARACTERISTICS IN THE 3 GROUPS DURING THE STUDY (Fertil Steril, 1997) *









ANALYSIS OF OWN DATA (1997-2000)

- ***Clinical material***

  a) oligozoospermic men, aged 25 to 46

  b) normozoospermic men, aged 28 to 43

- ***Treatment prescribed***

  oligozoospermic men : n=212

  subgroup 1: active treatment, n:106

  subgroup 2: placebo treatment, n:106

  normozoospermic men: n=82

  follow-up: 3, 6 and 9 months

Adamopoulos et al, Fertil Steril 2003

Mean ±SD values of functional sperm fraction in the 3 groups

	basal	3 months	6 months	3+6 average
TMX/TU group	4.57±	14.05±*+	17.68±*+	15.86±*+
n:106	5.11	11.60	14.91	13.20
placebo group	6.11±	4.72±	8.41±**	6.27±
n:106	6.31	6.41	7.93	7.10
normo-	47.80±^{x}	52.11±^{x}	50.23±^{x}	51.17±^{x}
n:82	35.62	43.31	33.50	38.63

differences from (a) own basal: * P<0.001, ** P<0.05 (b) placebo: $^{+}$P<0.001
(c) from TMX/TU or placebo: ^{x}P<0.001

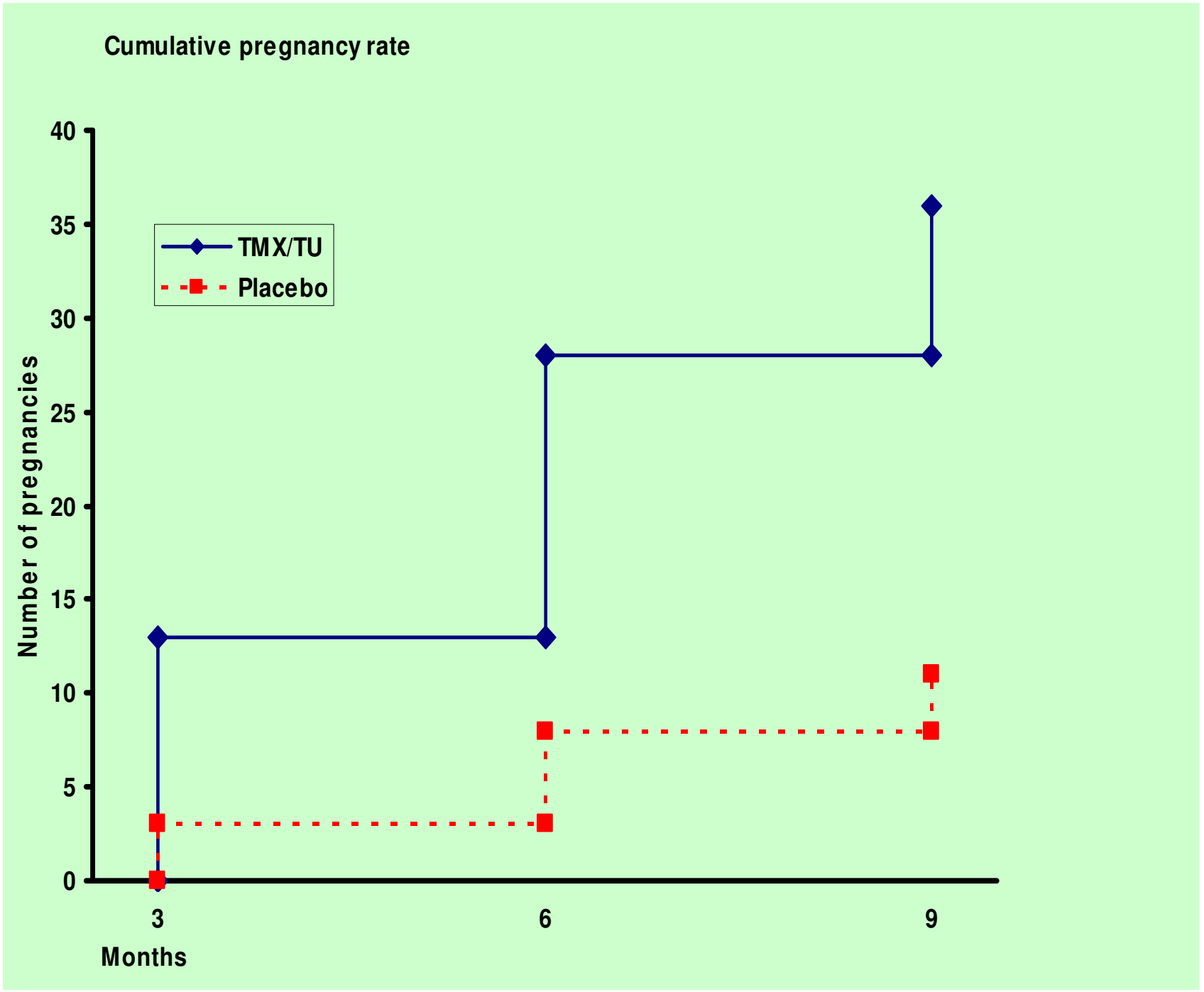
Incidence of pregnancy in the 3 groups

group	no of pregnancies	%	relative risk
TMX/TU*	36/88	40.9**	3.195
placebo	11/87	12.6	2.615 - 3.765[+]
normo-	17/48	37.0	

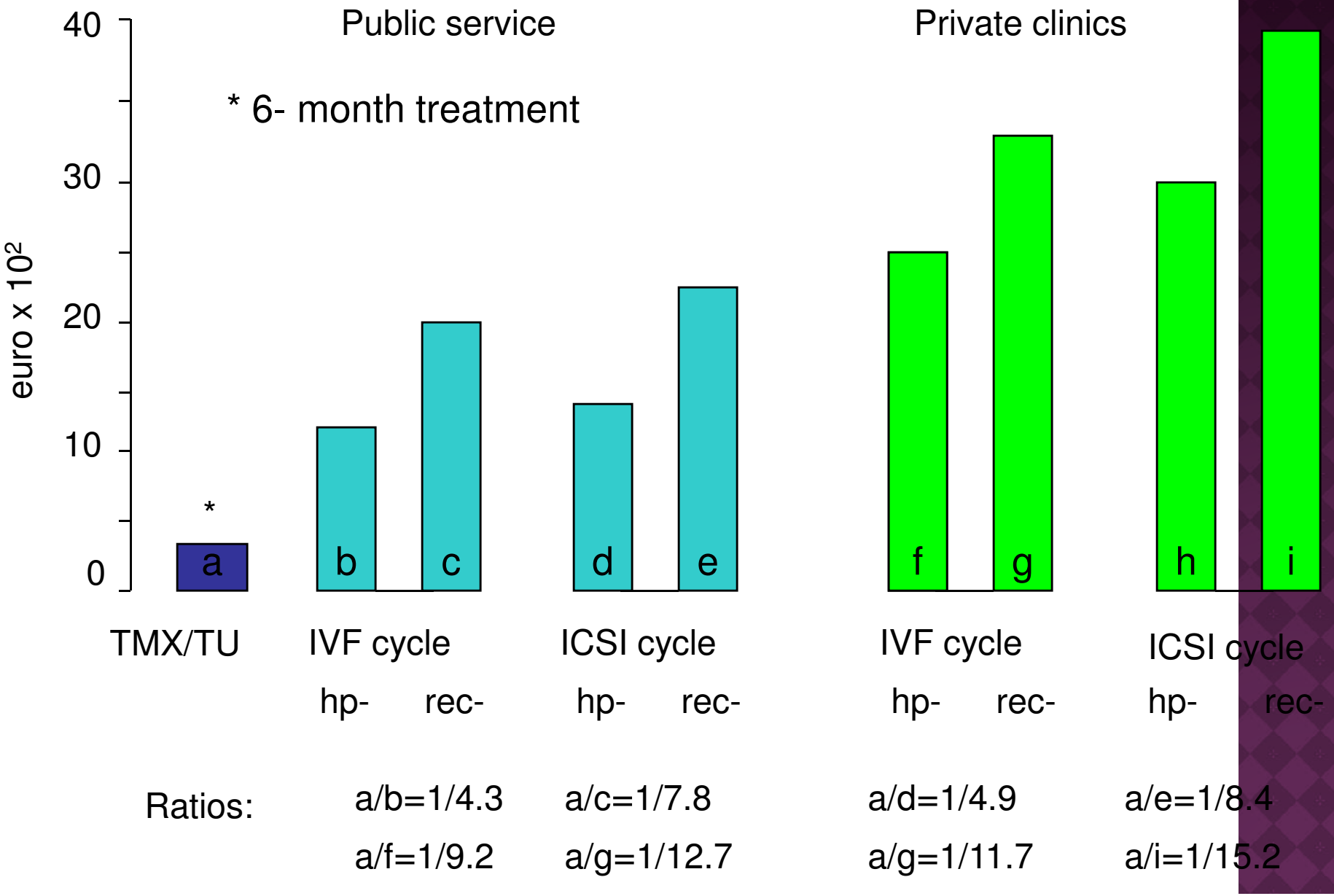
* in 3 cases additional pregnancy occurred with a new course

** P<0.001 from placebo

.[+] 95% confidence intervals


Cumulative pregnancy rate
40
35
30
25
20
15
10
5
0
Number of pregnancies
TMX/TU
Placebo
3
6
9
Months

Comparison of this type of treatment cost to that of ART



ANTIOESTROGENS IN OTA (ALONE OR IN COMBINATION WITH A WEAK ANDROGEN) - CONCLUSIONS

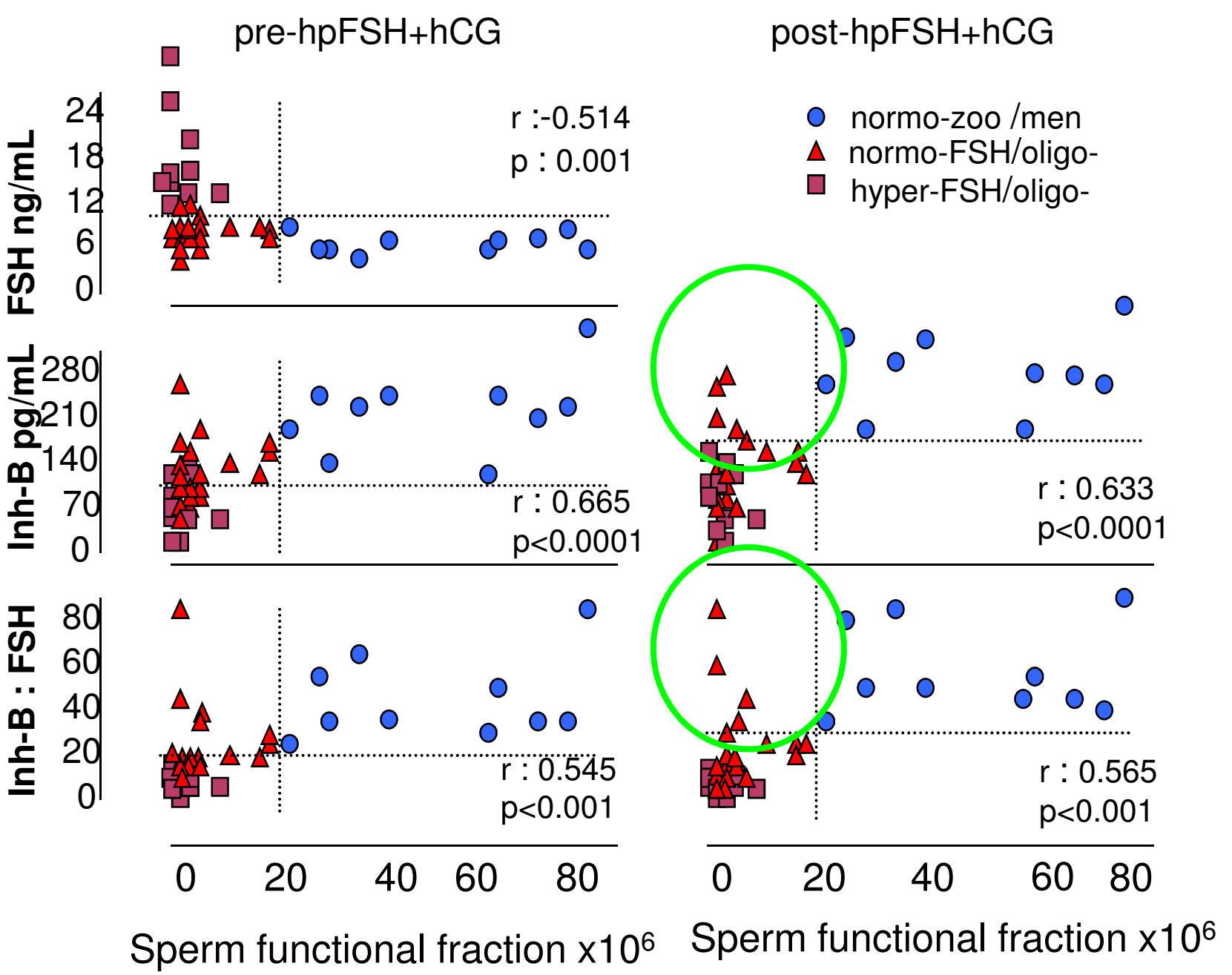
1. Even though treatment of idiopathic OTA with antiestrogens gave marginal results, it seems that, a not yet defined, subgroup of men respond reasonably well to this kind of treatment.
2. On the basis of the existing evidence from well-designed trials, tamoxifen was proposed by a WHO 2000 working committee as the first line of treatment for idiopathic OTA.

ANTIOESTROGENS IN OTA (ALONE OR IN COMBINATION WITH A WEAK ANDROGEN) - CONCLUSIONS-2

3. Some of the groups working in the field tried to create a kind of selection criteria as: the FSH level (Kadioglu, 2009), or the responsiveness of Sertoli cell to stimulation with gonadotropins

"Assessment of Sertoli cell funcional reserve and its reelationship to sperm parameters"

Adamopoulos DA, Nicopoulou S, Intern J Androl, 2003



Adamopoulos DA, Nicopoulou S, Intern J Androl, 2003

ANTIOESTROGENS IN OTA-
FINAL CONCLUSION

The continuing interest is justified by the fact that antiestrogen treatment is a safe, easy, economical and, on some occasions (due to ethnic, religious economical reasons or lack of access to the ART), this treatment remains the only feasible therapeutic approach for idiopathic male infertility .

MEDICAL TREATMENT OF IDIOPATHIC OTA IN THE ERA OF ART

Support sperm capability for fertilization.

- Vitalizers: l-carnitine, CoQ10
- Aromatase inhibitors
- Oxytocin

SPERM VITALIZERS: CARNITINE

It has been proposed to have a role in sperm maturation and energy production in epididymis and therefore enhances, sperm motility. Recently it was found to have also an antioxidant capacity.

Its use came up again recently by the two randomized controlled trials of **Lenzi et al (2003-2004)** using carnitine or its acetyl- compound in men with asthenozoospermia and noted improvements in all sperm parameters with significant increases only in motility.

SPERM VITALIZERS – CoQ10

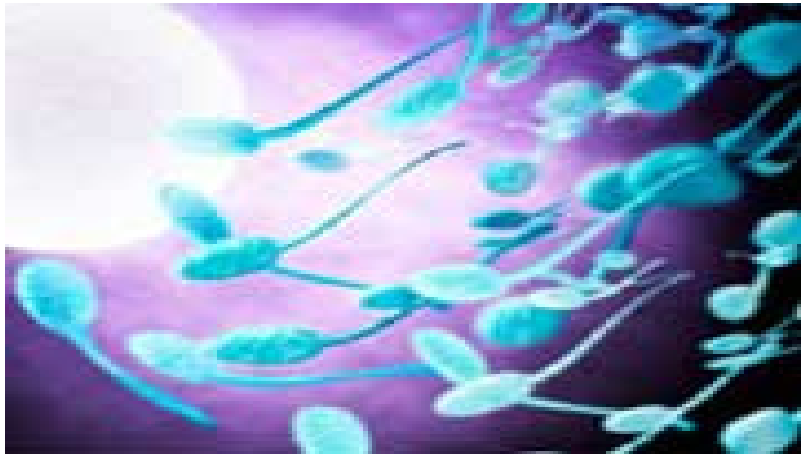
- It is involved in cellular respiration, improving motility and preventing oxidative stress. Its presence in seminal plasma shows a linear correlation with sperm count and motility.
- Two uncontrolled studies, (Balercia et al 2004, 2009) showed an improvement in sperm motility.

5. AROMATASE INHIBITORS

- They inhibit the conversion of testosterone to estrogens, resulting in an increase in gonadotropin secretion.
- The most known inhibitors are: **testolactone, anastrosole and letrozole.**
- Their historical use (a number of uncontrolled studies), came up again with the case report of Patry G et al. (2009) showing restoration of active spermatogenesis in FNA, after treatment with **letrozol** for 4 months.

6. OXYTOCIN

- Oxytocin is a neurohypophysial hormone which promotes sperm progression and increases sperm retrieval in oligospermic men. Its use by Byrne et al (2003) as a single dose before sperm collection, had no effect.
- Nevertheless, it is considered a relative newcomer to the hormonal arsenal of male infertility treatment.
- It's therapeutic use must be further explored



All andrologists in their every day practice are presented with the challenge to find the proper way to treat their infertile patient, using the existing knowledge and experience and at the same time trying to create new perspectives in the field.

- **Dimitri Adamopoulos**
- Stamatina Nicopoulou
- Niki Kapolla
- Efi Koukkou
- Athina Pappa
- Evi Venaki
- Lili Andreou
- Litsa Billa
- George Mitios
- Others

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ESHRE Campus Course
Reproductive Andrology:
linking laboratory to clinical practice
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1-3 October 2009

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THANK YOU !

HELLENIC SOCIETY OF ANDROLOGY

EUROPEAN ACADEMY OF ANDROLOGY

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6th European Congress of Andrology

29 September - 1 October 2010

Athens - Greece

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