



Primo Simposio Nazionale
sulla Nutraceutica
in Urologia

ROVIGO - 16/17 FEBBRAIO 2018

*La nutraceutica in andrologia:
quasi una tradizione*

Antonio Casarico



DISFUNZIONI SESSUALI

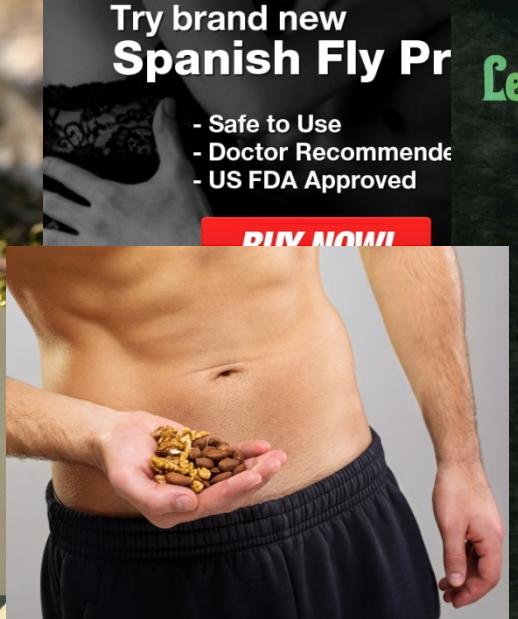
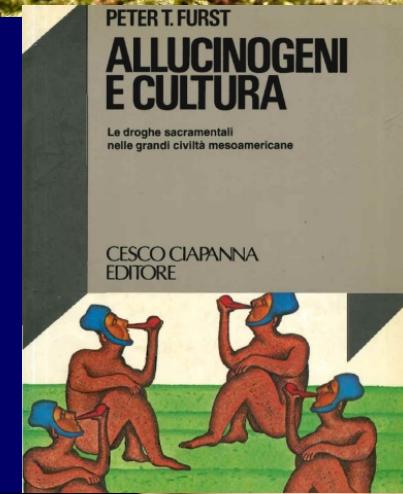
- ❖ Disturbi del desiderio ed eccitazione
- ❖ Ipogonadismo
- ❖ Disfunzione Erettile
- ❖ Eiaculazione Precoce
- ❖ Malattia di La Peyronie



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- Doctor Recommended
- US FDA Approved

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Alimenti afrodisiaci:

Sono detti **afrodisiaci** quei cibi che **aiutano a migliorare le prestazioni sessuali** incrementando la produzione di liquido seminale nell'uomo, o l'elasticità dei tessuti vaginali nella donna.

Menù:

- ❑ Asparagi avvolti in crudo e pasta sfoglia
- ❑ Linguine alle mandorle
- ❑ Pollo allo zafferano
- ❑ Avocado al lime e peperoncino
- ❑ Fonduta di cioccolato e frutta di stagione Champagne

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Natural Aphrodisiacs—A Review of Selected Sexual Enhancers

Sex Med Rev 2015;3:279–288

Elizabeth West, MD* and Michael Krychman, MD†

*Department of ObGyn, University of California at Irvine, Irvine, CA, USA; †Southern California Center for Sexual Health and Survivorship Medicine, Newport Beach, CA, USA

FDA defines an aphrodisiac drug product as

“any product that bears labeling claims that it will arouse or increase sexual desire, or that it will improve sexual performance”

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AFRODISIACI DI ORIGINE ANIMALE.

ROSPO BUFO

- ❖ Ubiquitario, pelle e veleno contengono bufotenina tossina psicoattiva (attività serotonino simile)
- ❖ allucinogeno, droga di strada e
- ❖ tradizione cinese, (chan'su) e indiana, (love stone).
- ❖ Diversi avvelenamenti e almeno una morte
- ❖ FDA: DIVIETO per la potenziale letalità.



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MIELE

- ❖ non ci sono RCT
- ❖ «Miele pazzo» dal nettare di Rhododendron ponticum prodotto in Turchia.
- ❖ Contiene Grayanotoxin (stimolazione vagale continua)
- ❖ Basse dosi causano ipotensione e bradicardia,
- ❖ alte dosi causano sincope, blocco A-V e asistolia.



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OSTRICHE

- ❖ Contengono zinco, essenziale per Te e spermatogenesi, aminoacidi e serotonina che sono fondamentali per la linea neurale del piacere
- ❖ Non vi sono RCT



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CORNO DI RINOCERONTE

- ✓ In Asia un corno costa \$ 30.000
- ✓ Composto di cheratina, contiene calcio e fosforo:
- ✓ Nessun componente con proprietà afrodisiache
- ✓ nessun dato per supportarne l'uso



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SPANISH FLY (Cantaride)

- ✓ dall'essiccazione dello Scarabeo
- ✓ inibisce PDE e proteina fosfatasi - stimola i betarecettori.
- ✓ Provoca congestione vascolare genitale e infiammazione urogenitale
- ✓ Può causare insufficienza renale, emorragie gastrointestinali e morte

California Center for Sexual Health



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AFRODISIACI VEGETALI

CHASTEBERRY (VITEX AGNUS-CASTUS)

- ❖ Dal frutto dell'albero
- ❖ influenza PRL e progesterone
- ❖ Studi clinici per sindr. premenstruale e mastodinia
- ❖ non ci sono dati
- ❖ interazione con contraccettivi orali, terapia ormonale, antagonisti della dopamina



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CIOCCOLATO (CACAO)

- ❖ Contiene tiramina, feniletilamina, metilxantina, acidi grassi simili ai cannabinoidi
- ❖ aumenta serotonina
- ❖ Nessuna differenza nella funz. sessuale

(Salonia J Sex Med 2006)



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DAMIANA (TURNERA DIFFUSA)

- ✓ estratto da arbusto Messicano.
- ✓ contiene apigenina 7-glucoside e Z-echinacina, (attività estrogenica)
- ✓ negli animali ripristina la copulazione
- ✓ mancano studi sull'uomo



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FIENO GRECO (*Trigonella foenum-graecum*)

- ✓ medicina ayurvedica come antiinfiammatorio e stimolante libido.
- ✓ contiene saponine steroidee precursori ormonali di E e Te
- ✓ piccolo CRT dimostra stimolare eccitazione sessuale maschile e orgasmo
- ✓ interazione con anticoagulanti



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GINKGO BILOBA

- ❖ Estratto dal più antico albero del mondo,
- ❖ medicina cinese: >> depress.- disf. Sess.
- ❖ rilascio di fattori di rilassamento endoteliali e prostaciclina,
- ❖ modula NO >> rilassamento vascolare e aumento ematico periferico
- ❖ RCT non beneficio nella DS da SSRI
- ❖ rischio di sanguinamento, va sospeso preoperat.
- ❖ cautela con FANS



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GINSENG

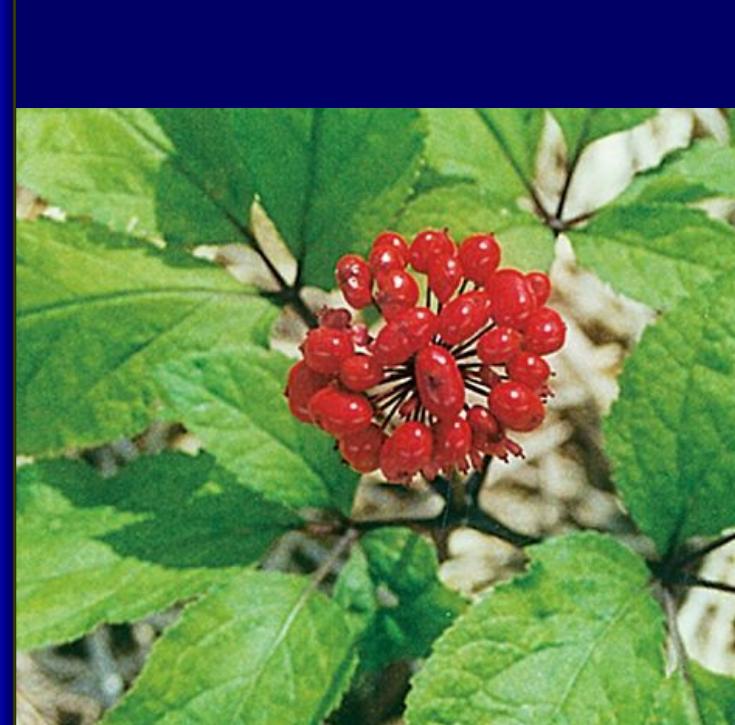
- ❖ rilascio muscol. liscia del corpo cavernoso

(de Andrade E, de Mesquita Asian J Androl 2007)

- ❖ sette CRT per DE
- ❖ revisione dei CRT >> l'efficacia complessiva

(Jang DJ Br J Clin Pharmacol 2008)

- ❖ ben tollerato (lievi eff. Coll. Gastrointestinali)
- ❖ interferenz con anticoagulanti
(interruz. 1 sett. preoperat.)



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HORNY GOAT WEED (Epimedium)

- ✓ L'erba di capra cornuta, usata nella medicina cinese per fatica, dolori articolari e DE
- ✓ contiene l'icariina (aumenta aromatasi e estrogeni), PDE5i
- ✓ non studi
- ✓ Non definiti effetti collaterali, dosaggio e tossicità



(c) Glendoick

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Sex Med R

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MACA (*Lepidium meyenii*)

- ❖ ortaggio a radice andina utilizzato per fertilità, l'eccitazione sessuale e il sollievo delle vampate di calore
- ❖ nei ratti: potenziamento di libido e funzione erettile
- ❖ tre/quattro RCT: effetto positivo su DE
(Shin, Complement Altern Med 2010).
- ❖ Bene tollerato - pochi effetti collaterali.

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MUIRA PUAMA (PotencyWood)



- ✓ erba brasiliana usata DE e deficit libidico.
- ✓ meccanismo di azione sconosciuto.
- ✓ pochi studi clinici

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SAW PALMETTO (*Serenoa repens*)



- ✓ derivato dalla bacca di una pianta nordamericana
- ✓ trattamento di LUTS/IPB e libido
- ✓ meccanismo proposto attraverso 5ARI
- ✓ non ci sono studi per DS

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TRIBULUS TERRESTRIS

- ❖ Erba (Asia, Europa e Africa)
- ❖ >> prestazioni atletiche, fertilità, libido.
- ❖ anti-infiammatorio (COX-2i)
- ❖ contiene protodioscina, (convertita in DHEA)
- ❖ ben tollerata (solo disturbi gastrointestinali minori)
- ❖ dosaggio ottimale non stabilito.



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Sex Med Rev 201

Elizabeth West, MD* and Michael Krychman, MD[†]

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YOHIMBINA

- ✓ corteccia e radici di pianta africana sempreverde.
- ✓ Antagon. recet. alfa-2-adrenergico presinaptico,
- ✓ >> colinergico e diminuito tono adrenergico.
- ✓ L'estratto usato come afrodisiaco e per DE psicogena

(Ernst J Urol 1998).

- ✓ gravi problemi di sicurezza e controindicazioni perché è adrenergico centrale
- ✓ effetti collaterali: l'ipertensione, tachicardia, broncospasmo, palpitazioni, insonnia, ansia, mania, brividi, sudorazione, nausea, e mal di testa
- ✓ NIH mette in guardia se si soffre di schizofrenia, ansia, depressione o disturbo da stress post-traumatico
- ✓ Non usare con inibitori delle monoaminossidasi (effetti additivi)

(National Center for Complementary and Alternative Medicine. Herbs at a glance: Yohimbe. 2007)

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Salute

VITAMINE AND MINERALI

Vit. B6 e B12, D, E, Mg e Zn

- ❖ coinvolti nella sintesi ormonale e spermatogenesi
- ❖ qualche studio sostiene che vitamine e minerali sono essenziali per normale funzione sessuale
- ❖ non ci sono dati su libido e DS

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Little is known about the content, consistency, and reliability of specific products that can be purchased online and in health food stores without a medical prescription unless a product is Informed-Choice certified, which is 100% guaranteed to contain exactly what is on the label, in the quantities listed, without any fillers or contaminants and are tested and verified to be effective and not damaged by heat, humidity or light

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Table 1 Natural sexual enhancers with data supporting use

Natural treatment	Dysfunction addressed	Mechanism of action	Data in support of use
Ginkgo	SSRI-associated sexual dysfunction	Release of endothelium-derived relaxing factor and prostacyclin, causing vasodilatation	Limited data to support use in males and females
Ginseng	1. Erectile dysfunction 2. Sexual arousal in menopausal women	1. Nitric oxide (NO) release from the smooth muscle of the corpus cavernosum 2. Smooth muscle relaxation on the clitoral cavernosal muscle and vaginal walls	1. Use in males supported by 7 double-blind, placebo-controlled studies 2. Limited data to support use in women
Maca	Sexual arousal in males and females	Unknown, possibly through phytoestrogen	1. 4 RTCs to support use in males and females 2. Limited data to support use in SSRI-related low libido
Tribulus	Female hypoactive sexual desire disorder	Anti-inflammatory action vs. COX-2 inhibition, and active compound, protodioscin, converted to DHEA	Limited data to support use in females
ArginMax	1. Female sexual desire and orgasm 2. Erectile dysfunction	NO pathway: smooth muscle relaxation, vascular dilatation, and vaginal wall engorgement	1. Limited data to support use in females 2. Very limited data to support use in males
Zestra	Female sexual arousal disorder	Vasodilation	Limited data to support use in females

A Urologist's Guide to Ingredients Found in Top-Selling Nutraceuticals for Men's Sexual Health

J Sex Med 2015;12:2105–2117

Tao Cui, MD, Robert C. Kovell, MD, David C. Brooks, MD, PhD, and Ryan P. Terlecki, MD

Department of Urology, Wake Forest School of Medicine, Winston Salem, NC, USA

Product name	Cost per serving/day	No. of ingredients
Biotab Nutraceuticals Inc. Extenze®	\$1.83	10*
BioXgenic BIO-HARD	\$1.33	13*
BioXgenic High Test Male Performance	\$4.00	1†
CAVALIER™ Daily Sexual Health Support	\$3.00	4*
CAVALIER™ Daily Testosterone Support	\$2.00	3*
Daily Wellness Company® FertilityBlend® for Men	\$1.33	10*
EPIQ™ TEST	\$1.33	3*
Force Factor® Test X180 ALPHA™	\$3.50	8†
Force Factor® Test X180™	\$2.33	5*
Forsta	\$5.00	5
GNC ArginMax®	\$1.23	17
GNC Horny Goat Weed	\$0.87	3
GNC Maca Man®	\$1.40	5
GNC Preventive Nutrition® Healthy Testosterone Formula	\$2.33	18
GNC Staminol™	\$0.83	13*
GNC Staminol™ Ultra	\$1.33	18
HighT® Black Caffeine Free	\$1.83	9*
Irwin Naturals Steel-Libido™	\$1.61	13*
MAGNA RX—BOGO	\$0.67	20
Maximum Human Performance T-Bomb™ II	\$1.79	24*
Now® Testo Jack 200	\$3.00	7
Nugenix™ Testosterone Booster	\$2.88	5*
PERFORMIX™ SUPER T	\$5.77	8*
PharmaFreak Test Freak™	\$1.93	17†
Progene® Daily Complex	\$1.25	33*
Prolongz™	\$4.60	3
Sera-Pharma Amidren™	\$2.33	17*
Vitalast® NewVigor®	\$2.50	4
Vitalast® NewVigor® Boost™	\$1.20	2
vitaliKoR®	\$3.00	5

*Product lists ingredients without specifying amount per dose. †Product lists a proprietary blend containing unnamed ingredients.

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Table 2 Top 20 most commonly identified ingredients based on product nutrition labels

Ingredient name	Number of products containing ingredient
Ginseng	13
Tribulus spp.	13
Zinc	13
Epimedium spp. (Horny goat weed)	11
Vitamin B6	10
Fenugreek	10
L-Arginine	10
Vitamin B12	9
Maca	9
Vitamin B3 (also as Niacin)	6
Saw Palmetto	6
Vitamin B9 (also as Folate)	5
Dehydroepiandrosterone (DHEA)	5
Vitamin E	5
Ginkgo Biloba	5
Magnesium	5
Yohimbine	5
Vitamin B1 (also as Thiamin)	4
Vitamin B2 (also as Riboflavin)	4
Selenium	4

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- ❖ While certain natural supplements show great promise at improving mild sexual dysfunction, all substances reviewed in this article lack robust human evidence.
- ❖ concerns of contamination and adulteration are sufficiently worrisome that we would presently
- ❖ caution against routinely recommending dietary supplements for male sexual health.

Adulteration of synthetic PDE-5 inhibitors viz., sildenafil and tadalafil in marketed herbal aphrodisiacs

S.S. Agrawal Garima Mishra

2016, 6:4, 152–156

- ❖ to increase their sale herbal aphrodisiacs manufacturers adulterated formulations with PDE5is.
- ❖ 15 herbal aphrodisiac, marketed in Delhi, screened
- ❖ 5 found adulterated with sildenafil citrate
- ❖ tadalafil was detected in 14 preparations.
- ❖ a single dose of one of the adulterated sample contain 27.95 mg of tadalafil.

DISTURBI DEL DESIDERIO ED ECCITAZIONE

Standard Operational Procedures for Low Sexual Desire in Men

J Sex Med 2013;10:94–107

Eusebio Rubio-Aurioles, MD, PhD* and Trinity J. Bivalacqua, MD, PhD†

**TERAPIA ETIOLOGICA O
PSICOSESSUOLOGICA**



**NESSUN ACCENNO A
NUTRACEUTICI O
INTEGRATORI**

IPOGONADISMO



European
Association
of Urology

2017

EAU GUIDELINES ON MALE HYPOGONADISM

NESSUN ACCENNO A
TERAPIA CON
NUTRACEUTICI

Alternatives to Testosterone Therapy: A Review

Eric M. Lo,¹ Katherine M. Rodriguez,¹ Alexander W. Past Sex Med Rev 2018;6:106–113

“NATURAL TESTOSTERONE BOOSTERS.”

- ✓ not regulated by the FDA
- ✓ risks cannot be discussed because of a lack of objective studies to define efficacy and safety
- ✓ variabilities in ingredient quantities,
- ✓ ingredients might interfere with other prescribed drugs,
- ✓ supplement itself might be toxic

Lifestyle modification (aerobic exercise and diet resulting in weight loss provide a relatively risk-free approach to increase testosterone levels and should generally be recommended as a first-line, drug-free approach in overweight men.

**DISFUNZIONE
ERETTILE**



Rimedio naturale di Omeopatia Peyronie



10 Modi migliori naturale per aumentare il flusso sanguigno al pene



Erbe di Aphrodite®
VASODILATATORI NATURALI



2009

Erectile Dysfunction

3.5.1.9 Other oral agents

no place for these drugs in the treatment of ED.

- **Yohimbine** is a centrally and peripherally active alpha-2 adrenergic antagonist used as an aphrodisiac for almost a century.

Randomised trials have shown that yohimbine have a similar efficacy to placebo in patients with organic ED

- **L-arginine** is a nitric oxide donor
- **Red Korea ginseng** is a formulation with an unknown mechanism of action (though it may possibly act as a nitric oxide donor). Efficacy data on Red Korea ginseng suggested it might have a role in treatment of ED



American
Urological
Association

Erectile Dysfunction Guideline Documents

Published 2005; Reviewed and Confirmed 2011

Yohimbine

Recommendation: not recommended for the treatment of erectile dysfunction.

Other Herbal Therapies

Recommendation: not recommended for the treatment of erectile dysfunction.

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

Hartmut Porst, MD,* Arthur Burnett, MD, MBA, FACS,† Gerald Brock, MD, FRCSC,‡
Hussein Ghanem, MD,§ Francois Giuliano, MD,¶ Sidney Glina, MD,|| Wayne Hellstrom, MD, FACS,††
Antonio Martin-Morales, MD,‡‡ Andrea Salonia, MD,§§ Ira Sharlip, MD,¶¶ and the ISSM Standards
Committee for Sexual Medicine

J Sex Med 2013;10:130–171

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Oral Therapies Other than PDE5 Inhibitors

Yohimbine

- ✓ alkaloid from the bark of the tree called *Corynanthe johimbe*
- ✓ growing in Central Africa.
- ✓ first isolated in 1896. First information on its use combined with papaverine to treat ED was published in 1923.
- ✓ Until the launch of PDE5i the most prescribed substance worldwide for the treatment of ED.

sites of action :

Central: Unlike alpha1 adrenoceptors, cerebral alpha2 adrenoceptors mediate erection inhibiting impulses. Yohimbine facilitates erection in part through a central level.

Peripheral: directly blocks alpha2 adrenoceptors that dominate in the penile arteries. Counteracts the vasoconstriction induced by norepinephrine/epinephrine release and the reduction in blood flow.

Endothelium and androgen-dependent NO formation:

Experimental studies provided evidence that interferes with NO release from the endothelium:

These data indicate that yohimbine's efficacy in ED is not only due to its inhibitory effects on the presynaptic alpha1-adrenoceptor activity in the cavernous smooth muscle cells but also includes an impact on NO and cGMP formation involving endothelium and endothelial nitric oxide synthase (eNOS) activity which again is testosterone dependent.

Pharmacokinetics and Dosage orally well absorbed and has a plasma half-life of between 0.25 and 2.5 hours.

effects triggered may last for more than 13 hours. Only about 1% of yohimbine appears in the urine, indicating a predominantly hepatic clearance Doses ranged commonly from 5 to 15 mg three times a day

Efficacy: from no effect to 71% as compared with 40% for placebo in nonorganic impotence.

meta-analysis of seven large yohimbine studies, which met strict quality criteria, showed a superiority of yohimbine vs. placebo.

- ✓ The Clinical Guidelines Panel on Erectile Dysfunction of the American Urological Association (AUA) concluded that the data currently available do not allow it to be recommended as standard treatment in ED, particularly not in organic etiologies,
- ✓ this statement was not changed with the 2005 update

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

ISSM Standards Committee for Sexual Medicine

Sub-Committee Male Sexual Dysfunction

Chapter: Medical/Conservative Treatment in ED, Priapism, and Peyronie's Disease

J Sex Med 2013;10:130–171

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Side Effects and Contraindications

side effects : sympathetic activity: anxiety, nausea, restlessness, agitation, sleeplessness tachycardia, palpitations, diarrhea, and manic symptoms

increase or more infrequently decrease blood pressure,

In cases of severe CVD such as unstable angina or recent myocardial infarction, difficult to treat hypertension and severe psychiatric diseases, as well as severe hepatic impairment, should be considered contraindications for yohimbine use.

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- ❖ if yohimbine has any potential indications for use in ED management, it would be among nonorganic ED.
- ❖ In these patients, may be used for a maximum of 2 months either as a regular regimen (3 ¥ 5- 10 mg/day) and has shown in a review a superiority to placebo (Level of Evidence 1b)

L-Arginine

- ✓ precursor of NO
- ✓ A high-dose, CRT with 5 g per day for 6 weeks in 50 patients with organic, complete ED resulted in a success rate (sexual intercourse possible) of 31% (12% in the placebo arm)
- ✓ a CRT with Prelox® (commercially available L-arginine product in some European countries) in 124 patients with moderate ED over 6 months. The IIEF-EF improved from a baseline mean 15.2 (6.6) to 25.2 (2.1) after 3 months and to 27.1 (2.1) after 6 months. placebo group from baseline 15.1 (7.0) to 19.1 (3.0) and 19.0 (3.1) after 3 and 6 months, The effects were statistically significant ($P < 0.05$). these efficacy data show an increase of mean IIEF-EF score of 11.9.
- ✓ This exceeds the improvements in IIEF-EF score of about 8-10, which were achieved in clinical trials with the highest doses of PDE5 inhibitors

. Ledda. BJU Int 2010;106:1030-3.

L-Arginine

- ✓ no representative and reliable data from multicenter well-designed RCTs evidence of significant efficacy in a broad-spectrum ED population.
- ✓ The trials in ED are at best a Level of Evidence 2b that L-arginine may work in ED patients of not closely specified ED etiology.



European
Association
of Urology

Guidelines on Male Sexual Dysfunction:

Erectile dysfunction and
premature ejaculation

K. Hatzimouratidis (Chair), I. Eardley, F. Giuliano,
I. Montada, A. Salonia

eau
European
Association
of Urology

2016

Erectile Dysfunction

3A.4.5 First-line therapy

3A.4.5.1 Oral pharmacotherapy

3A.4.5.1.1 Sildenafil

3A.4.5.1.2 Tadalafil

3A.4.5.1.3 Vardenafil

3A.4.5.1.4 Avanafil

3A.4.5.1.5 Choice or preference between the different PDE5i

3A.4.5.1.6 Continuous use of PDE5i

3A.4.5.1.7 Safety issues for PDE5i

3A.4.5.1.8 Management of non- responders to PDE5i

**NON SONO CITATI
NUTRACEUTICI**

EIACULAZIONE PRECOCE

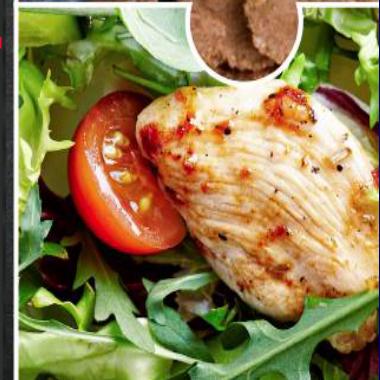


MIGLIORI ALIMENTI PER AUMENTARE
LA RESISTENZA SESSUALE



Olio di ricino per l'eiaculazione precoce

7
ALIMENTI
PER
SODDISFARE
LA TUA
RAGAZZA
A LETTO





American
Urological
Association

Pharmacologic Management of Premature Ejaculation Guideline Documents

Published 2004; Reviewed Confirmed 2010

**NESSUN ACCENNO A
NUTRACEUTICI O
INTEGRATORI**

Standard Operating Procedures in the Disorders of Orgasm and Ejaculation

J Sex Med 2013;10:204–229

Chris G. McMahon, MBBS, FACHSHM,* Emmanuele Jannini, MD,† Marcel Waldinger, MD, PhD,‡ and David Rowland, PhD§

Nutritional supplements containing L-tryptophane, other amino acids, or vitamins are not recommended for the treatment of PE (level 4)

there is not any scientific study that has investigated their use or their efficacy in the treatment of PE and they cannot be recommended.

NON SONO CITATI
NUTRACEUTICI

PREMATURE EJACULATION

3B.4 Disease management 23

3B.4.1 Psychological/behavioural strategies

3B.4.2 Dapoxetine

3B.4.3 Off-label use of antidepressants: SSRIs and clomipramine

3B.4.4 Topical anaesthetic agents

3B.4.4.1 Lidocaine-prilocaine cream

3B.4.5 Tramadol

3B.4.6 Other drugs

3B.4.6.1 Phosphodiesterase type 5is

MALATTIA DI LA PEYRONIE

The Management of Peyronie's Disease: Evidence-based 2010 Guidelines

David Ralph, MD,* Nestor Gonzalez-Cadavid, PhD,† Vincenzo Mirone, MD,‡ Sava Perovic, MD,§
Michael Sohn, MD,¶ Mustafa Usta, MD,** and Laurence Levine, MD††

*Institute of Urology, London UK; †Department Urology, UCLA, CA, USA; ‡University of Naples "Federico II", Naples, Italy; §University of Belgrade, Belgrade, Serbia; ¶University Aachen, Germany; **Akdeniz University School of Medicine, Antalya, Turkey; ††Rush Medical College, Chicago, IL, USA

ORAL THERAPY

There is evidence that there is no benefit with respect to deformity reduction with any oral therapy, including Vitamin E, potassium aminobenzoate, colchicine, tamoxifen, and carnitine

GRADE B

Standard Operating Procedures for Peyronie's Disease

J Sex Med 2013;10:230–244

Laurence A. Levine, MD* and Arthur L. Burnett, MD, MBA†

Table 1 Oral therapies

Treatment	Mechanism of action	Adverse effects	Clinical role
Vitamin E	Antioxidant effect; immune modulation	Possible cerebrovascular events, nausea, vomiting, diarrhea, headache, dizziness	No benefit
Colchicine	Inhibition of fibrosis and collagen deposition	Myelosuppression, diarrhea, nausea, vomiting	No benefit
Potassium aminobenzoate	Stabilization of tissue serotonin monoamine oxidase activity; antifibrotic effect (direct inhibitory effect on fibroblast glycosaminoglycan secretion)	Anorexia, nausea, fever, skin rash, hypoglycemia	No benefit
Tamoxifen	Modulation of TGF release from fibroblasts	Alopecia, retinopathy, thromboembolism, pancytopenia	No benefit
Carnitine	Attenuation of collagen fiber deposition and elastogenesis	Seizure, diarrhea, nausea, stomach cramps, vomiting	No benefit
Pentoxifylline	Nonspecific phosphodiesterase inhibition; attenuation of collagen fiber deposition and elastogenesis	Indigestion, nausea, vomiting, dizziness, headache, angina, aplastic anemia, leucopenia, thrombocytopenia	Uncertain benefit

Standard Operating Procedures for Peyronie's Disease

J Sex Med 2013;10:230–244

Laurence A. Levine, MD* and Arthur L. Burnett, MD, MBA†

- ✓ incomplete knowledge of the pathophysiology
- ✓ rational mechanism-based therapy is restricted.
- ✓ therapies plausible, often not supported by rigorous clinical trials
- ✓ clinical trials compromised by study design limitations (small numbers, brief follow-up, and lack of a standardized approach for the evaluation and inclusion of patients)

The International Consultation on Sexual Medicine has taken a stance in recently published guidelines that **oral therapy is not currently proven to be beneficial in PD**; therefore, does not support their clinical use for this condition at the present time

Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M, Levine L. The medical management of Peyronie's disease: Evidence-based 2010 guidelines. J Sex Med 2010;7:2359–74.

Standard Operating Procedures for Peyronie's Disease

J Sex Med 2013;10:230–244

Laurence A. Levine, MD* and Arthur L. Burnett, MD, MBA†

Vitamin E

Vitamin E, a fat-soluble vitamin metabolized in the liver, The most common nonsurgical prescription therapy to limit oxidative stress in tissues and reduce the actions of reactive oxygen species increased during the acute and proliferative phases of wound-healing characteristic of PD double-blinded, randomized, placebo-controlled trials showed **nonsignificant improvements in pain, curvature, and plaque size**

Pryor, Prog Reprod Biol 1983;9:41-5.
Safarinejad, J Urol 2007;178:1398-403. [22, 23].

Carnitine

metabolic intermediate, facilitates entry of long-chain fatty acids into muscle mitochondria. to inhibit acetyl coenzyme-A linked with the repair of damaged cells. A doubleblinded, randomized, controlled trial evaluating alone or with Vitamin E **failed to demonstrate improvement in pain, curvature, or plaque size**



American
Urological
Association

PEYRONIE'S DISEASE: AUA GUIDELINE 2015

Guideline Statement 6.

Clinicians should not offer oral therapy with vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or vitamin E + Lcarnitine.

[Moderate Recommendation; Evidence Strength Grade B(vitamin E)/
B(omega-3 fatty acids)/
B (Vitamin E + propionyl-L-carnitine)
C (tamoxifen)/ C(procarbazine)]

PEYRONIE'S DISEASE

Vitamin E

- ❖ *(tocopherol, fat-soluble, natural antioxidant to reduce oxygen-free radicals produced in energy metabolism)*
- ❖ *wide availability, low cost and safety*
- ❖ *A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size*
- ❖ *conflicting evidence as to the long-term cardiovascular effects at the large doses*



European
Association
of Urology

Guidelines on Male Sexual Dysfunction:

Erectile dysfunction and
premature ejaculation

K. Hatzimouratidis (Chair), I. Eardley, F. Giuliano,
I. Moncada, A. Salonia



European
Association
of Urology

2016

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Guidelines on
Male Sexual
Dysfunction:

Erectile dysfunction and
premature ejaculation

K. Hatzimouratidis (Chair), I. Eardley, F. Giuliano,
L. Montada, A. Salonia

© European Association of Urology 2015

2016



PEYRONIE'S DISEASE

Acetyl-L-carnitine and propionyl-L-carnitine

- ❖ *to inhibit acetyl coenzyme-A*
- ❖ *anti-proliferative effect on
human endothelial cells*
- ❖ *suppress fibroblast
proliferation and collagen
production*

Evidence-Based Management Guidelines on Peyronie's Disease

Eric Chung, FRACS,^{1,2} David Ralph, FRCS,³ Ates Kagioglu, MD,⁴ Giulio Garaffa, FRCS,³ Ahmed Shamsodini,¹ Trinity Bivalacqua, MD,⁶ Sidney Glina, MD,⁷ Lawrence Hakim, MD,⁸ Hossein Sadeghi-Nejad, MD,⁹ and Gregory Broderick, MD¹⁰

J Sex Med 2016;13:905–923

Vitamin E

low cost and wide availability
double-blinded, placebo-controlled studies
have shown no significant difference
between vitamin E and placebo in resolving
penile curvature, plaque, or pain.

Pryor, Prog Reprod Biol Med 1983.

Safarinejad, J Urol 2007

Evidence-Based Management Guidelines on Peyronie's Disease

Eric Chung, FRACS,^{1,2} David Ralph, FRCS,³ Ates Kagioglu, MD,⁴ Giulio Garaffa, FRCS,³ Ahmed Shamsodini,¹ Trinity Bivalacqua, MD,⁶ Sidney Glina, MD,⁷ Lawrence Hakim, MD,⁸ Hossein Sadeghi-Nejad, MD,⁹ and Gregory Broderick, MD¹⁰

J Sex Med 2016;13:905–923

Acetyl Ester of Carnitine

a comparative study vs tamoxifen is more effective and safer

Biagiotti, BJU Int 2001

follow-up study showed that propionyl-L-carnitine and verapamil significantly decreased penile curvature, plaque size, and the need for surgery and increased the erectile function compared with a combination of tamoxifen and intraplaque verapamil injection.

Cavallini BJU Int 2002

Another study reported the combined use of propionyl-L-carnitine and vitamin E had a minimal outcome.

Safarinejad, J Urol 2007

Evidence-Based Management Guidelines on Peyronie's Disease

Eric Chung, FRACS,^{1,2} David Ralph, FRCS,³ Ates Kagioglu, MD,⁴ Giulio Garaffa, FRCS,³ Ahmed Shamsodini,¹ Trinity Bivalacqua, MD,⁶ Sidney Glina, MD,⁷ Lawrence Hakim, MD,⁸ Hossein Sadeghi-Nejad, MD,⁹ and Gregory Broderick, MD¹⁰

J Sex Med 2016;13:905–923

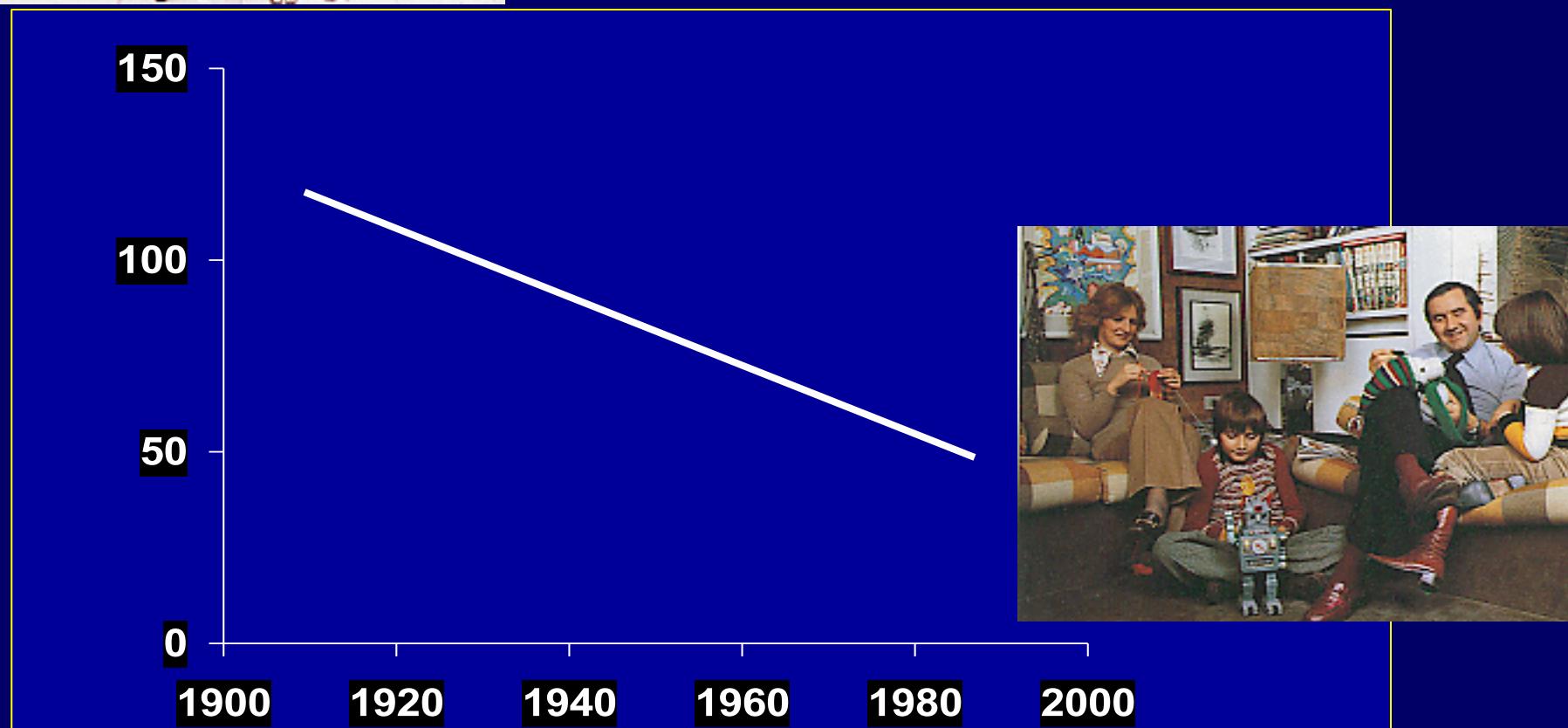
ORAL THERAPY (GRADE B, LEVEL 2)

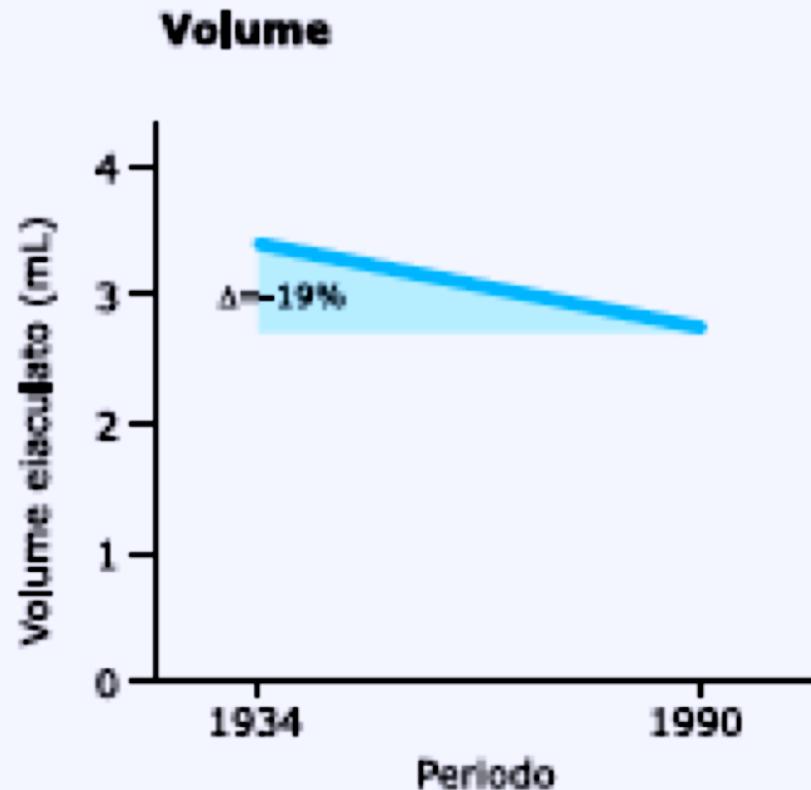
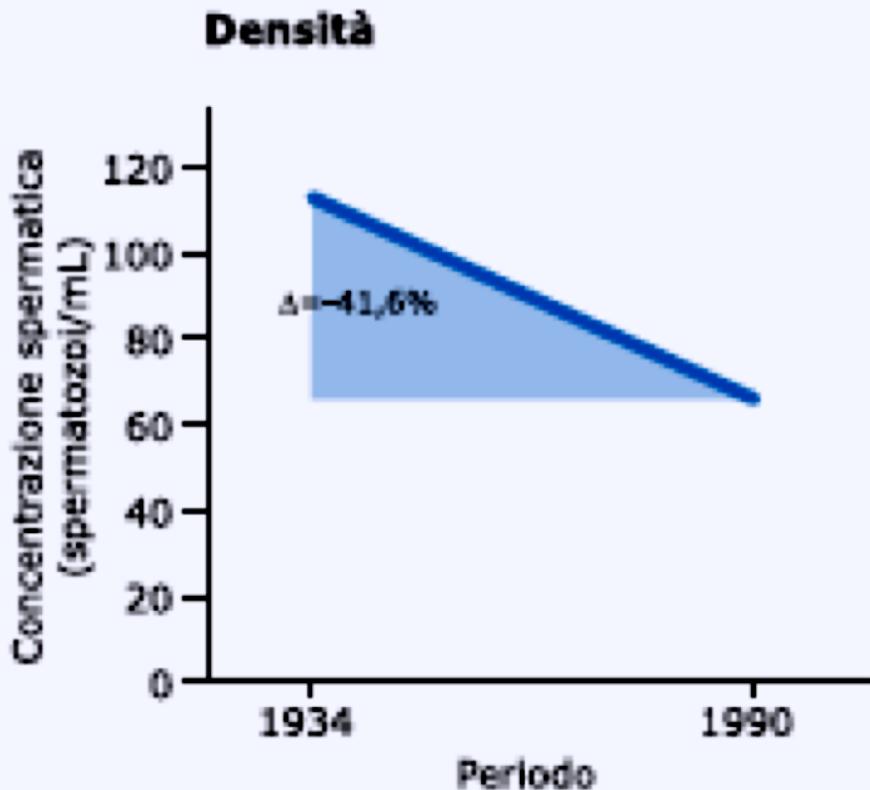
The published literature shows minimal or no benefit with respect to a significant decrease in deformity with any oral therapy

INFERTILITA' MASCHILE



Calo della concentrazione spermatozoaria negli ultimi 50 anni in Europa





Variazioni storiche delle caratteristiche del liquido seminale registrate i differenti paesi Europei tra il 1934 ed il 1990

Carlsen E, 1992

Temporal trends in sperm count: a systematic review and meta-regression analysis.

Levine H et al. Hum Reprod Update. 2017 Nov 1;23(6):646-659.

185 studies of 42 935 men in 1973-2011

- ✓ SC declined significantly (slope in unadjusted simple regression models -0.70 million/ml/year; 95% CI: -0.72 to -0.69; P < 0.001; slope in adjusted meta-regression models = -0.64; -1.06 to -0.22; P = 0.003).
- ✓ significant decline in SC among Unselected and among Fertile (North America, Europe, Australia and New Zealand)
 - ✓ On average, 1.4% per year
 - ✓ Overall decline 52.4%
- ✓ average decline in mean TSC of 1.6% per year and overall decline of 59.3%.

no significant trends were seen among Other Countries (South America, Asia and Africa)

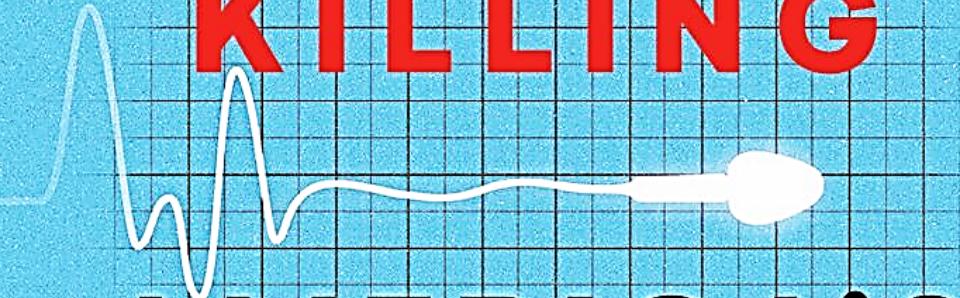
Inside Trump's Haunted House / Death of the Keyboard

Newsweek

WHO'S

08.22.2017

The sudden rise in male infertility is a scary national crisis.



KILLING AMERICA'S

And we can't blame it on Trump—or can we?

SPERM?

"Something is very wrong with men."

Motivi dell'incremento nella frequenza di infertilità/sterilità

- ✓ maggior età alla 1° gravidanza
- ✓ maggior accesso alla diagnosi e trattamento
- ✓ cambiamento nella esposizione a fattori di rischio.

FATTORI AMBIENTALI ED INFERTILITA' MASCHILE

PATOLOGIE GENITALI CORRELATE al DECLINO SEMINALE

NEOPLASIE TESTICOLARI

- aumento annuo: 2,3 (Svezia) 5,2% (Germania Est)
- incidenza raddoppia ogni 15-20 anni
- maggiore nei paesi in cui lo sperma è maggiormente peggiorato - familiarità (genetica/ambientale?)

Oesterlind, Br J Cancer, 1986 - Adami, Int J Cancer, 1994

CRYPTORCHIDISMO

- aumento del 65-77% in Europa

IPOSPADIA

- incidenza minore nei paesi più fertili

tutte queste patologie individuano una unica

“Sindrome Disgenetica Testicolare” ,

che troverebbe origine nell'alterato sviluppo gonadico embrionale.

Skakkebaek NE Hum Reprod 2001

queste anomalie legate alla presenza
ubiquitaria nell'ambiente di
sostanze chimiche ad attività
ormonale estrogenica
o antiandrogenica

“endocrine
disrupters”

I composti chimici sospetti hanno in comune:

- debole azione estrogenica (DDT, bifenili policlorinati, prodotti di combustione del petrolio) o androgeno inibitrice (p,p'-DDE, principale e più persistente metabolita del DDT)

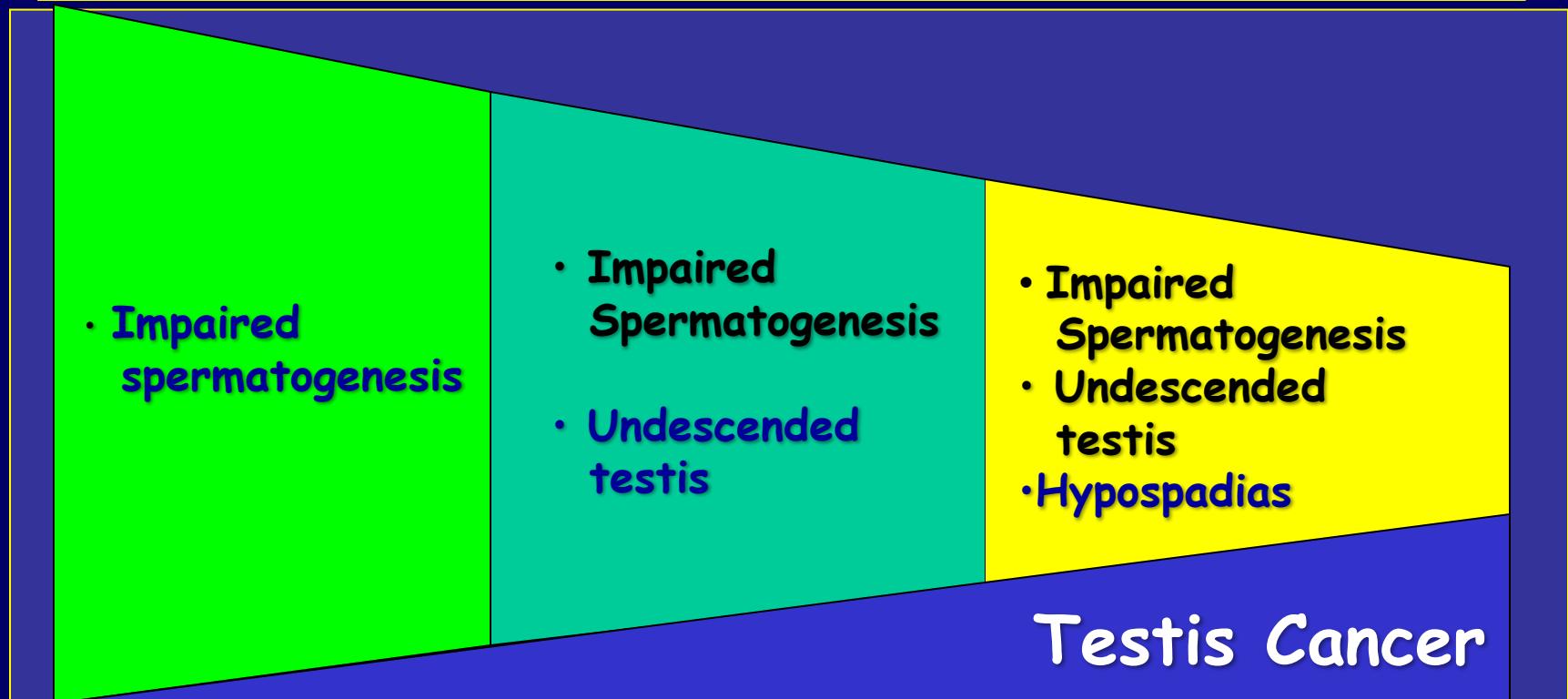
Kelce WR, Nature 1995

- legame con il recettore degli estrogeni è debole, ma la combinazione di due di questi estrogeni deboli (dieldrin, endosulfan, toxafene) è 1.000 volte più potente nella attivazione recettoriale di quanto lo siano i singoli composti

Arnold SF, Science 1996

- ubiquitarietà (dai pesticidi ai plastificanti), resistenza alla biodegradazione, presenza nella catena alimentare, tendenza all'accumulo nel tessuto adiposo.

ILLUSTRATION OF THE RELATIONSHIP BETWEEN THE RELATIVE FREQUENCY OF VARIOUS SYMPTOMS OF THE TESTICULAR DYSGENESIS SYNDROME (TDS).

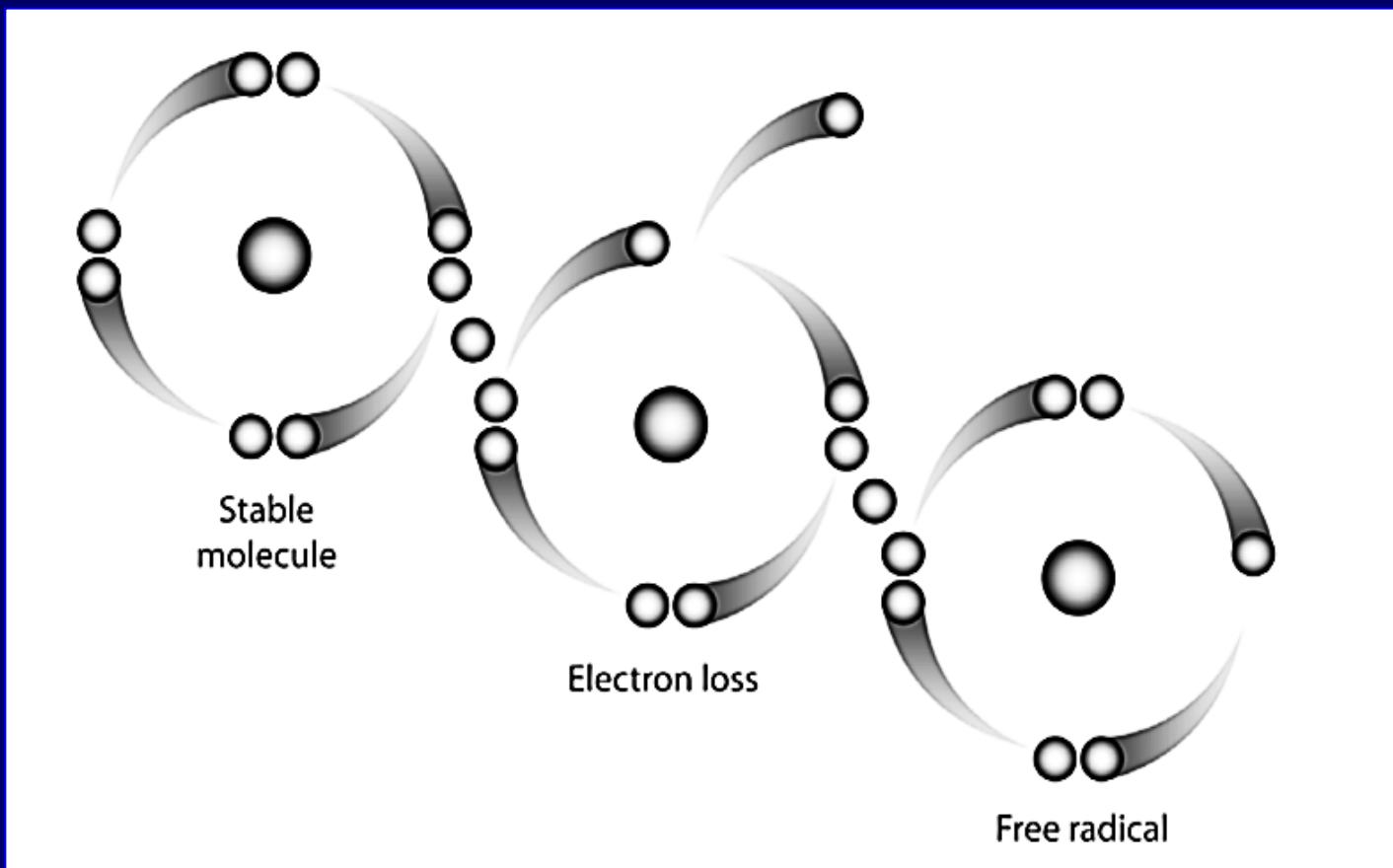


Note that while the overall incidence of TDS decreases with the degree of severity, the relative incidence of testicular cancer increases.

STRESS OSSIDATIVO ED INFERTILITA' MASCHILE

Radicali Liberi

L'ossigeno si combina con l'idrogeno formando molecole instabili "affamate" di elettroni: i RADICALI LIBERI, o "ROS" (*Reactive Oxygen Species*)



- l'ossigeno (O_2), è citotossico sia direttamente, sia indirettamente attraverso la produzione nei processi biochimici di sostanze contenenti specie dell'ossigeno altamente reattive (Reactive Oxygen Species -ROS-).
- i tessuti maggiormente coinvolti nella produzione di energia sono anche i maggiori produttori di ROS.
- tali tessuti devono essere dotati, più degli altri, di un efficace sistema di neutralizzazione dei ROS, la cosiddetta *barriera antiossidante*.
- La quota di ROS che sfugge alla barriera antiossidante contribuisce ad alterare la bilancia ossidativa, determinando una *condizione di insulto biochimico nota come stress ossidativo (SOx)*.

- Lo spermatozoo è un grande utilizzatore di O₂ e, conseguentemente, un forte produttore di ROS
 - il liquido seminale è un sistema ad intenso metabolismo ossidativo, caratterizzato da elevata produzione di H₂O₂
 - spermatozoo la fonte primaria di questo prodotto metabolico nocivo.

MacLeod J Am J Physiol 1943

• L'altra fonte di ROS sono gli spermatozoi, soprattutto immaturi.

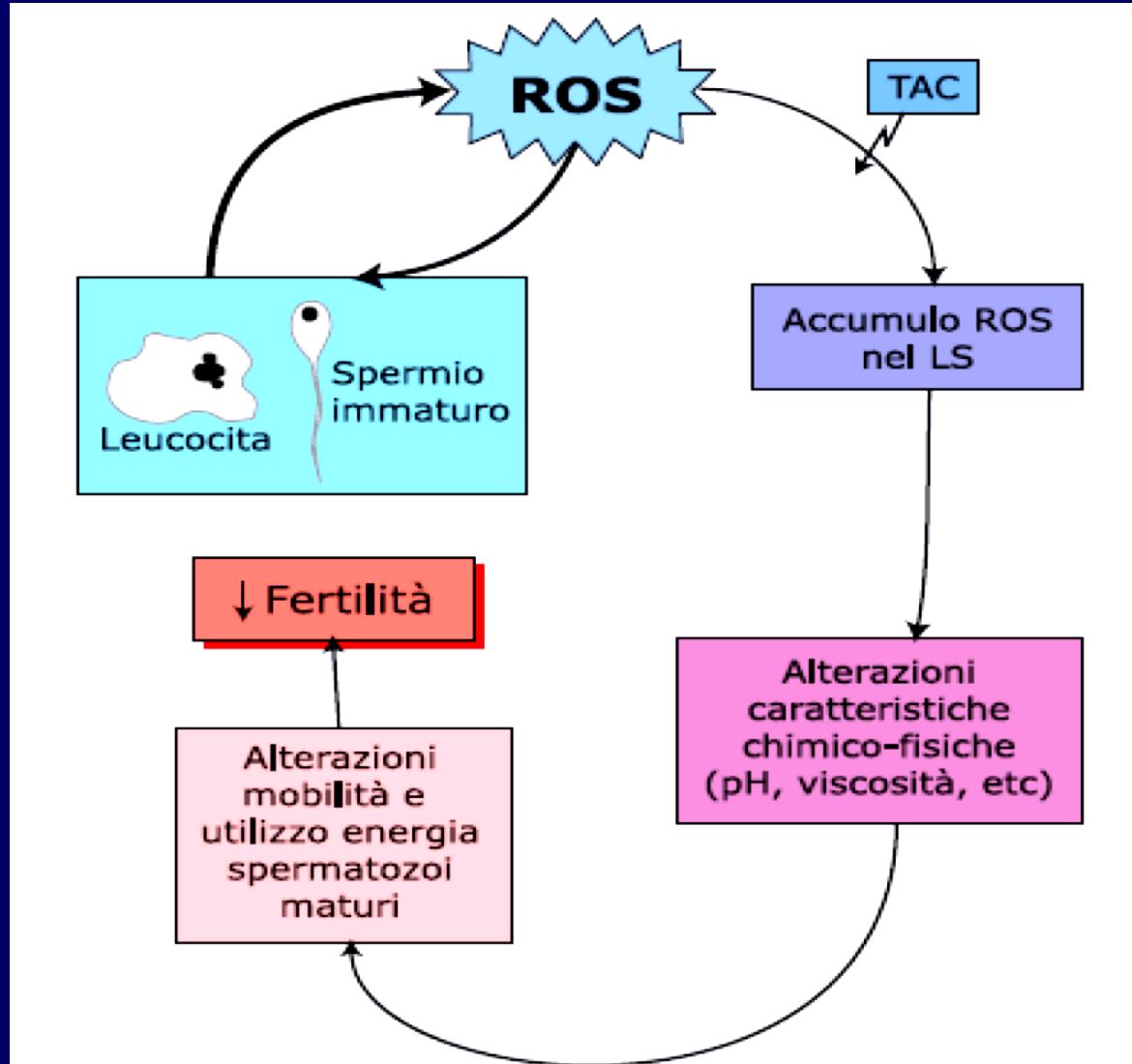
Gomez E J Androl 1996

- correlazione forte fra numero di spermatozoi immaturi e produzione di ROS.
- circolo vizioso attraverso il quale lo stress ossidativo causato dai gameti immaturi altera le caratteristiche anche degli spermatozoi sani e maturi, che sono quindi allo stesso tempo fonte (accessoria) e target indesiderato dei ROS

Said TM Fertil Steril 2004 - Gil-Guzman E Hum Reprod 2001

i leucociti sembrano i maggiori produttori di ROS, con un rilascio fino a 1000 volte maggiore di quello di origine gametica

Plante M, Fertil Steril 1994



relazione positiva e forte fra numero di neutrofili presenti nel LS e stress ossidativo

Whittington K, Int J Androl 1999 - Sharma RK J Androl 2001
affinché i neutrofili rilascino ROS devono trovarsi in stato di attivazione e evidenziabile dal rilascio di citochine infiammatorie (IL-6, IL-8, TNF- α , etc)

Martinez P Asian J Androl 2007 - Nandipati KC, Andrologia 2005
L'attivazione leucocitaria è correlata ai processi infettivi e/o infiammatori del tratto urogenitale

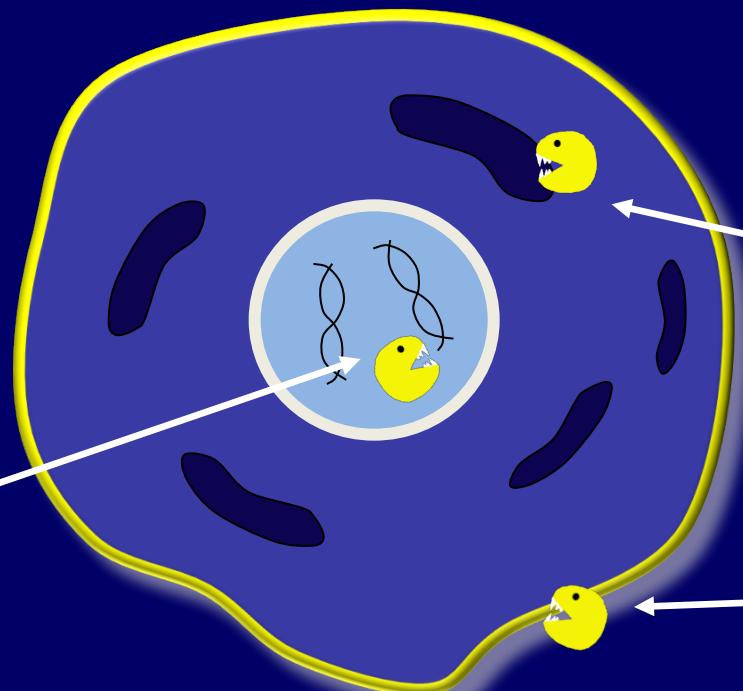
il gamete maschile è insolitamente sensibile all'insulto di queste sostanze, divenendo la vittima sacrificale primaria dello stress ossidativo

Jedrzejczak P Int J Androl 2005 - Saleh RA Fertil Steril 2002

I danni dei radicali liberi ("ROS")



- ✓ attacco alla membrana cellulare -> patologie degenerative;
- ✓ attacco al DNA -> inefficienza dello spermatozoo.



■ Danno
al
DNA

■ Danno ai
mitocondri

■ Danno a membr.
cellulare

**squilibrio tra produzione e rimozione
dei ROS → stress ossidativo**

**sistemi di difesa cellulare endogeni per
prevenire il danno ossidativo**

- ❖ **Enzimi:** proteine complesse che disattivano i radicali dell'ossigeno
(superossido \leftrightarrow superossido dismutasi)
- ❖ **Nutrienti:** vitamine, betacarotene, bioflavonoidi forniscono elettroni per saturare i radicali liberi

Aumentate concentrazioni di ROS determinano alterazioni meccaniche e funzionali dello spermatozoo, ed anche di alcune proprietà chimico-fisiche del plasma seminale,

Per quanto riguarda le alterazioni a carico dello spermatozoo le alterazioni di tre parametri:

1)mobilità;

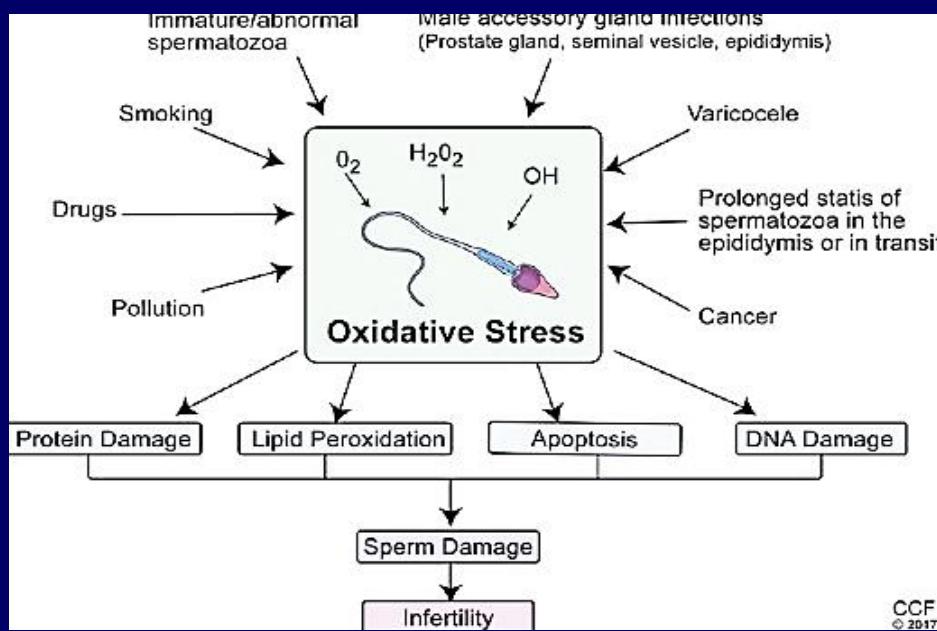
2)capacità di fertilizzazione;

3) corredo genomico.

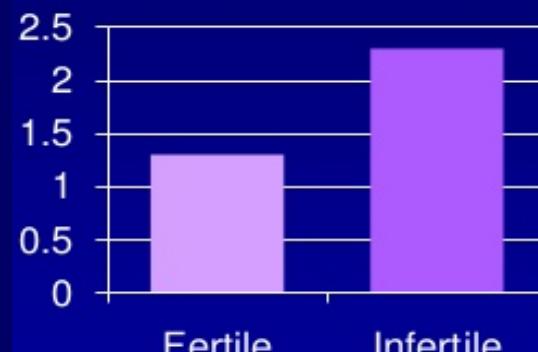


I TEST FUNZIONALI: QUANDO E PERCHE'

- infertilità idiopatica
- ripetuti fallimenti di cicli di PMA
- sviluppi embrionali anomali
- poliabortività



**Seminal
Reactive Oxygen
Species (ROS)
(Log ROS + 1; cpm)**



Pasqualotto et al., Fertil Steril 2000

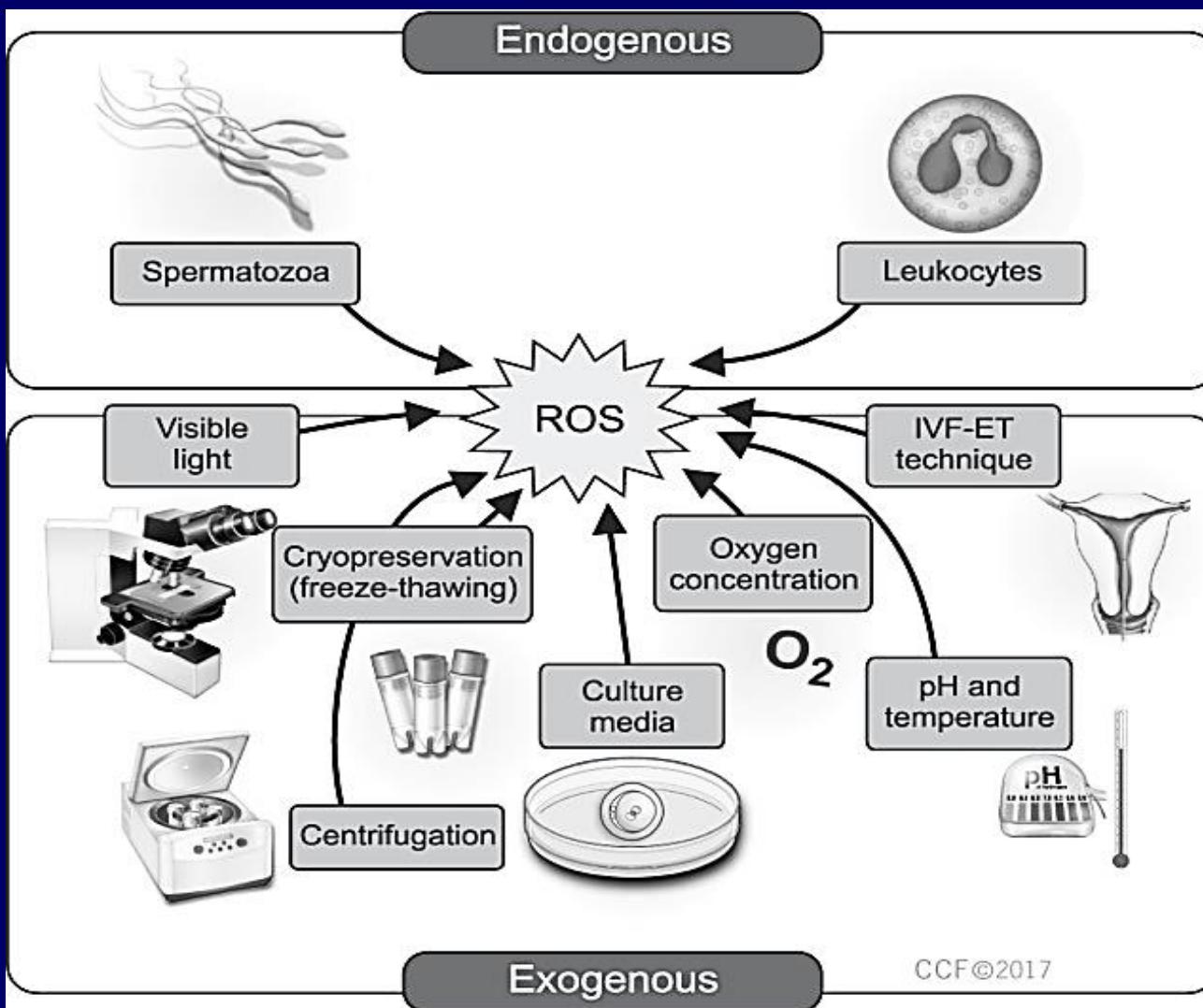
World J Mens Health. 2017 Aug; 35(2): 77–93.

Published online 2017 Apr 30. doi: [10.5534/wjmh.2017.35.2.77](https://doi.org/10.5534/wjmh.2017.35.2.77)

PMCID: PMC5583374

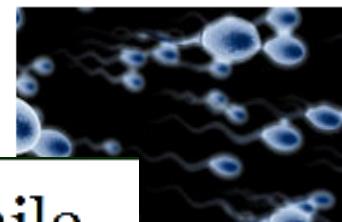
Role of Antioxidants in Assisted Reproductive Techniques

Ashok Agarwal¹ and Ahmad Majzoub²



LA SETTIMANA DELLA PREVENZIONE ANDROLOGICA È DEDICATA QUEST'ANNO ALL'ALIMENTAZIONE

**La dieta mediterranea
è alleata di fertilità e sessualità**



**Fertilità maschile,
per migliorarla bastano
sport e cibi sani**

Stilato il menù della fertilità maschile

KEYWORDS |



NEWS | DAILY LIFE | REGIONI | AKI ITALIANO | AKI ENGLISH | LAVORO | SPECIALI | SECONDO MESE | MEDIACENTER

portale del Gruppo **Adnkronos**

seguici su: newsletter:

**Un'alimentazione buona, sana e sostenibile fa
bene alla sessualità maschile**

MERCATO • LIBERA VENDITA

Integratori, Italia al top dei consumi

Con 1,6 miliardi di euro su un totale di 7,5, l'Italia è il paese dell'Europa occidentale che registra i consumi maggiori di integratori e vitamine. Farmacie e parafarmacie primo canale nel continente, con una c

**Salute: integratori alimentari, 141 mln
confezioni vendute in 1 anno, +3%**

Consumo di integratori Gli italiani ne vanno
matti: +6%

Fermenti lattici, seguiti da multivitaminici e dimagranti, integratori sportivi e ginseng & pappa reale. Chi più ne sa più ne metta. Agli italiani piace farne uso e lo dimostrano i dati della federazione di categoria relativi alle vendite



ARTICOLI RECENTI

*Straus Seet al.. Evidence-based medicine:
how to practice and teach EBM 3d ed 2005*

Popolazione bersaglio



Razionale



Evidenze

*Popolazione
bersaglio*

Guidelines on Male Infertility

A. Jungwirth (chair), T. Diemer, G.R. Dohle, A. Giwercman,
Z. Kopa, H. Tournaye, C. Krausz



European
Association
of Urology

2016

Recommendation	GR
Effective drug therapy is available to achieve fertility in men with hypogonadotropic hypogonadism (4).	A*
Testosterone replacement is strictly contraindicated for the treatment of male infertility (13).	A*

2016



European
Association
of Urology

Guidelines on Male Infertility

A. Jungwirth (chair), T. Diemer, G.R. Dohle, A. Giwercman,
Z. Kopa, H. Tournaye, C. Krausz

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
<i>Infertility of known (possible) cause</i>	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm autoantibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
<i>Idiopathic infertility</i>	30.0	13.3
<i>Hypogonadism</i>	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	<0.1	0.3
Others	0.8	0.8
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
<i>General/systemic disease</i>	2.2	0.5
<i>Cryopreservation due to malignant disease</i>	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
<i>Disturbance of erection/ejaculation</i>	2.4	-
<i>Obstruction</i>	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CFTRΔF508)	0.5	2.1

Ma quali sottopopolazioni ?



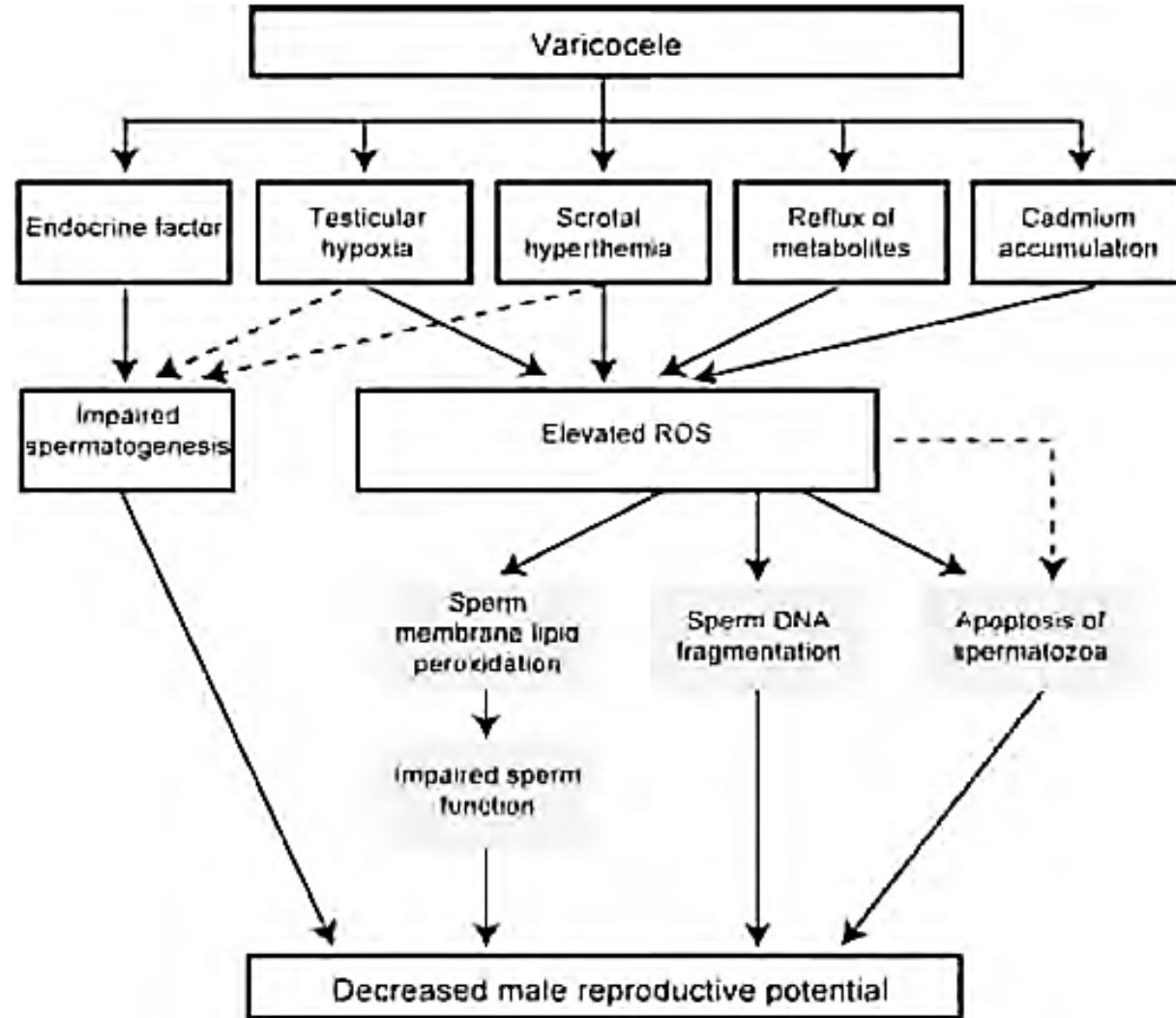
Open Access

INVITED REVIEW

Male Fertility

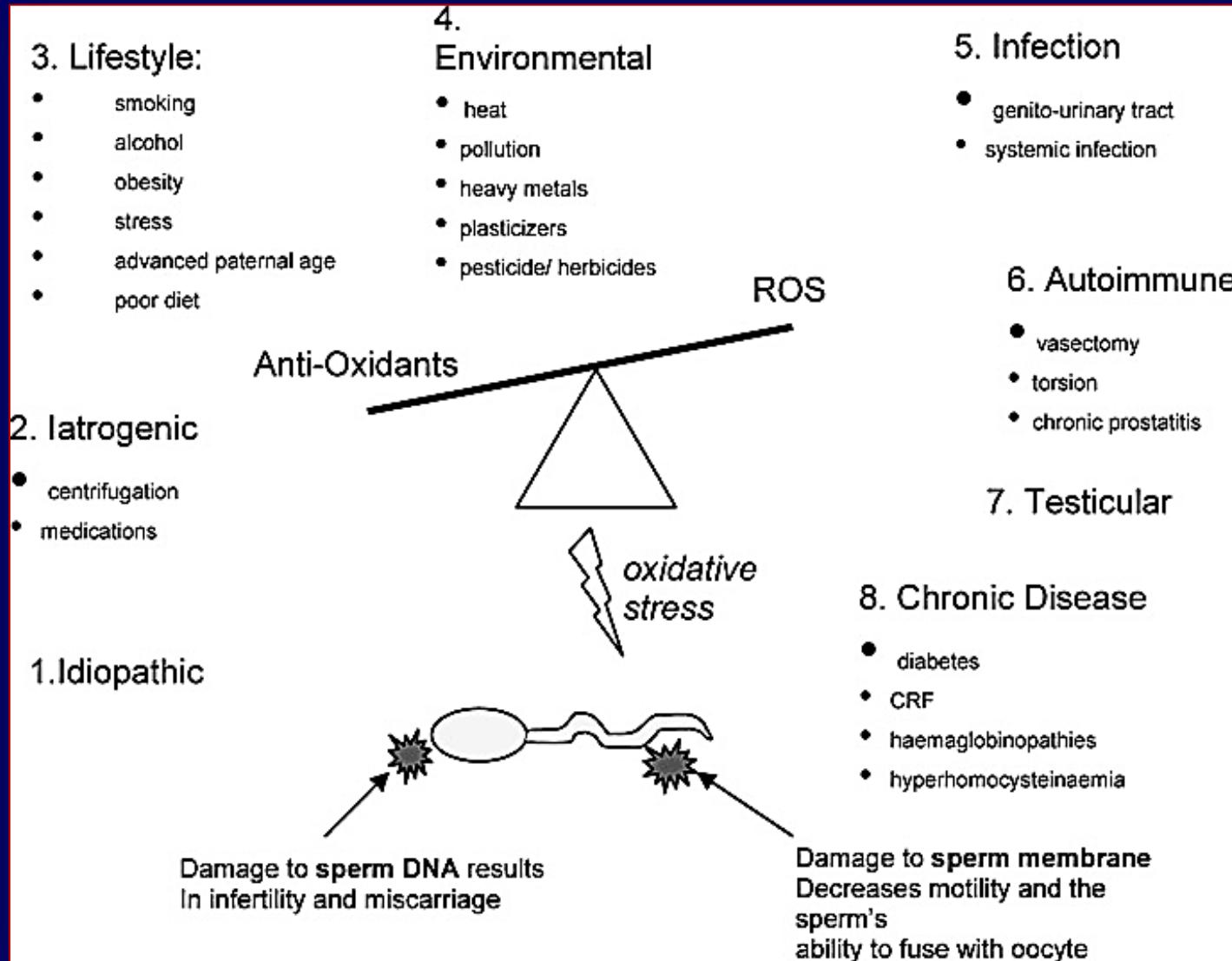
Novel insights into the pathophysiology of varicocele and its association with reactive oxygen species and sperm DNA fragmentation

Chak-Lam Cho¹, Sandro C Esteves², Ashok Agarwal³



Razionale

STRESS OSSIDATIVO NELL'INFERTILITÀ MASCHILE



Review

Investigating ROS sources in male infertility: A common end for numerous pathways

G. Lavranos, M. Balla, A. Tzortzopoulou, V. Syriou, R. Angelopoulou*

Department of Histology-Embryology, Medical School, Athens University, Greece

- Calore
- Radiazioni
- Farmaci
- Tossine
- Metalli
- Tabacco
- Iperglycemia
- Agenti biologici



- Apoptosi testicolare
- Frammentazione del DNA
- Difetto nelle protamine
- Bassa conta spermatica
- Alterazioni strutturali

ANTIOSSIDANTI

Sono enzimi e sostanze nonenzimatiche che riducono il danno ossidativo.

Le sostanze nonenzimatiche sono sia naturali che sintetiche, e sono utilizzabili sia tramite assunzione di alimenti specifici che come integratori.

PRINCIPALI ANTISSIDANTI nella Subfertilità Maschile:

- ❖ Vitamine E, B12, C
- ❖ Carotenoidi *carotene, astaxantina, licopene*
- ❖ Ubiquinolo *Coenzima Q10*
- ❖ Micronutrienti *Folato, Zinco*
- ❖ PUFAs *Omega 3, Omega 6, Omega 9*
- ❖ Carnitine *L-acetilcarnitina, L-Carnitina*
- ❖ Pentossifillina
- ❖ Inositolo
- ❖ Arginina
- ❖

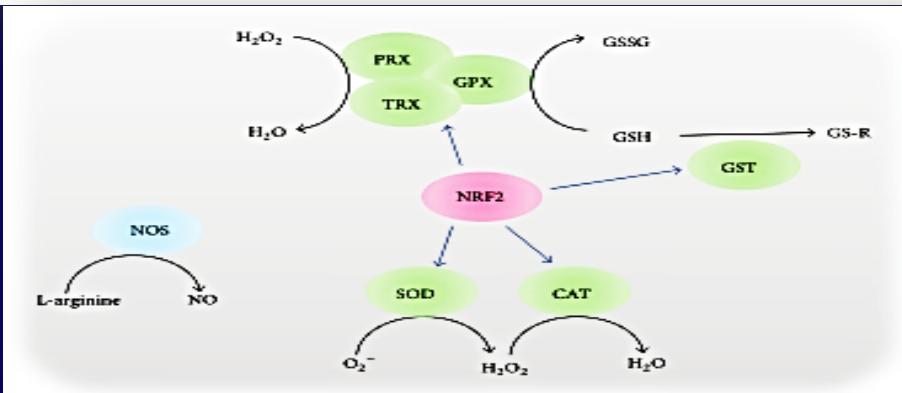
Variations in Antioxidant Genes and Male Infertility

Bolan Yu^{1,2} and Zhaofeng Huang^{3,4,5}

Biomed Res Int. 2015

TABLE 2: Reported antioxidant genetic variations associated with male infertility.

Gene	Variation	Official description	Trait/effect	Species	Reference
NRF2	Deletion	—	Subfertility	Mice	[7]
	rs6721961 G>T	NC_000002.11:g.178130037 T>G	Oligoasthenozoospermia	Human	[20]
	rs35652124T>C	NC_000002.11:g.178130073 T>C	Oligoasthenozoospermia	Human	[20]
	rs6721961 G>T + smoking	NC_000002.11:g.178130037 T>G	Sperm concentration and count	Human	[12]
GST	GSTM1-null	Deletion	Male infertility, oligozoospermia, male infertility with varicocele	Human	[21–28]
	GSTT1-null	Deletion	Male infertility, male infertility with varicocele	Human	[24, 26–32]
	GSTM1 rs135955605 C/G	—	Sperm motility after cryopreservation	Bulls	[33]
	GSTPI (Ile105Val)	NC_0000011.10:g.67585218 A>G	Male infertility, oligospermia, oligoasthenoteratozoospermia, azoospermia	Human	[26, 31, 34]
	GSTPI (Ala14Val)	NC_0000011.10:g.67586108 C>T	Male infertility with varicocele, oligoasthenoteratozoospermia	Human	[27, 34]
SOD	GSTM1-null + PAH exposure	Deletion	PAH-DNA adducts	Human	[35]
	GSTM1-null/GSTT1-null + smoking	Deletion	Idiopathic male infertility	Human	[36]
	GSTM1-null + CYP1A1	Deletion	Male infertility	Human	[37]
	SOD2 rs4880 CC	NC_000006.11:g.16013872 A>G	Idiopathic infertility, male infertility, pregnancy rates in IVE, sperm concentration, sperm motility, and sperm DNA fragmentation	Human	[38–41]
	SOD1 knockout	—	Male infertility	Drosophila	[42]
CAT	SOD1 knockout	—	Spermatogenic cell damage during heat stress	Mice	[43]
	C-262T	NC_0000011.10:g.34438684 C>T	Idiopathic male infertility	Human	[44]
	eNOS T786C	NC_000007.13:g.150690079 C>T	Male infertility, oligoasthenoteratozoospermia, idiopathic male infertility	Human	[45–47]
	eNOS G894T	NC_000007.13:g.150696111 T>G, NP_001153582.1:p.Asp298Glu,	Oligoasthenoteratozoospermia, asthenozoospermia, idiopathic male infertility	Human	[46–50]
	eNOS 4a/b	NC_000007.14:g.150997188_150997214-AGGGGTGAGGAAGTCTAGACCTGCTGC(2)(3)	Idiopathic male infertility, sperm morphology	Human	[45, 47, 51]
GPX	GPX4 deletion	—	Male infertility, sperm chromatin condensation	Mice	[52, 53]
	GPX5 deletion	—	Sperm DNA integrity	Mice	[54]



*Non esiste un momento ottimale
per una terapia "empirica".*

*1. Alla
prima
diagnosi di
dispermia*

*3.
associata a
tecniche di
PMA*

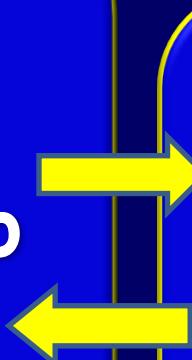
*2. Al primo
fallimento
di rapporti
mirati*

TRATTAMENTO DELL'INFERTILITÀ MEDIATA DALLO STRESS OSSIDATIVO

1. Terapia specifica

- ✓ Terapia antibiotica: per infezioni del tratto genitale
- ✓ Chirurgia del varicocele
- ✓ Cambiamenti dello stile di vita:
ridurre gli ossidanti

2. Terapia antiossidante



Evidenze Scientifiche

Table 2 Lifestyle factors modifiable without risk.

Lifestyle factor	Results	Recommendations	References
Smoking	Strong correlation with % DFI, DFI markedly higher in infertile smokers	Cessation of smoking	Elshal et al. (2009)
POP/PCB	Positive correlation between exposure and % DFI	PCB accumulate in food chain: avoid fatty fish, particularly farmed	Rignell-Hydbom et al. (2005), Spano et al. (2005), Stronati et al. (2006)
Organophosphorus	Marked increase in % DFI (>30%) in exposed workers	Avoid pesticide exposure	Sanchez-Pena et al. (2004)
Lead	Increase in percentage of spermatozoa with DNA fragmentation	Avoid occupational exposure and smoking or exposure to cigarette smoke	Hsu et al. (2009), Vani et al. (2012)
Bisphenol A	Significant trend of increased DNA damage with increased urinary bisphenol A concentrations	Avoid plastic packaging, tinned foods, heating or storing foods in plastic	Meeker et al. (2010)
Testicular heat	Increase in DNA fragmentation with 2–3°C temperature increase	Avoid cycling with tight pants, avoid sauna use, avoid using laptop on closed legs	Southorn (2002), Ahmad et al. (2012), Sheynkin et al. (2011), Garolla et al. (2013)
Mobile phone radiation	No specific studies on DNA fragmentation, increased ROS and decreased antioxidants	Do not store mobile phone in trouser pocket	Desai et al. (2009)
Obesity	Positive correlation of body mass index and DNA fragmentation, higher incidence in obese males	Weight loss through diet and moderate exercise	Kort et al. (2006), Chavarro et al. (2010), Fariello et al. (2012a), La Vignera et al. (2012), Dupont et al. (2013)

DFI = DNA fragmentation index; PCB = polychlorinated biphenyls; ROS = reactive oxygen species.

Effect of modifiable lifestyle factors and antioxidant treatment on semen parameters of men with severe oligoasthenoteratozoospermia

Y. Magdi¹ | E. Darwish² | S. Elbashir³ | A. Majzoub⁴ | A. Agarwal⁵

TABLE 2 Data for the semen parameters of patients before and after the therapy

Variables assessed	Before therapy	After therapy	Paired t test	p-Value
Volume (ml)	3.45 ± 1.73	3.43 ± 1.64	1.77	.079
Count ($\times 10^6$ /ml)	0.215 ± 0.15	0.237 ± 0.17	2.75	.006**
Motility (%)	24.03 ± 14.5	29.77 ± 15.43	11.18	.001**
Progressive motility (%)	2.27 ± 2.48	6.17 ± 4.14	Z = 11.35	.001**
Abnormal forms (%)	99.93 ± 0.36	99.53 ± 0.67	7.23	.001**
Total count ($\times 10^6$)	0.71 ± 0.61	0.77 ± 0.64	1.97	.05*
Total motile count ($\times 10^6$)	0.2 ± 0.24	0.25 ± 0.27	Z = 8.35	.001**
Total progressive motile count ($\times 10^6$)	0.019 ± 0.028	0.051 ± 0.059	Z = 11.36	.001**

Values are a mean ± SD. P < 0.05 was considered to be significant when compared with the fresh ET control group.

**Highly significant.

Antiossidanti

Gli antiossidanti rimuovono i ROS

proteggono dallo stress e
danno ossidativo

[Ross et al, 2010].

Aiutano il metabolismo
spermatico

[Agarwal et al 2004].

sorgenti antiossidanti: sia
fisiologiche sia dietetiche.

Gli antiossidanti fisiologici sono presenti nel plasma seminale e spermatozoi.
[Tremellen, 2008].

ANTIOSSIDANTI ENZIMATICI FISIOLOGICI:

*superossido dismutasi,
glutazione, perossidasi e
catalasi.*

ANTIOSSIDANTI NON FISIOLOGICI:

*vit. C e E, carnitina,
carotenoidi, taurine, e
ipotaurine [Agarwal et al, 2007
(AUA Update)].*

Male Infertility: Nutritional and Environmental Considerations

by Steven Sinclair, ND, LAc



Carnitina

Coenzima
Q10

Arginina

Inositolo

Zinco

Vitamina
B12

Astaxantina

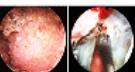
Vitamina E

Glutatione

Vitamina C

Meccanismo d'azione comune

Kumar et al, J Urol, 2006



Drug Therapy for Idiopathic Male Infertility: Rationale Versus Evidence

Rajeev Kumar,* Gagan Gautam and Narmada P. Gupta

From the Department of Urology, All India Institute of Medical Sciences, New Delhi, India

10

*Mancanza di
studi
metodologicamen-
te validi e di
metanalisi (grado
di
raccomandazione
A)*

*Solo pochi studi
considerano il
pregnancy rate
come outcome
primario*

*Difficoltà ad
individuare
sottopopolazioni
omogenee di
pazienti da
trattare*

*Differenze nel
dosaggio dei
principi utilizzati*



European
Association
of Urology

Guidelines on Male Infertility

G.R. Dohle, A. Jungwirth, Z. Kopa,
A. Giwercman, T. Diemer, T.B. Hargreave

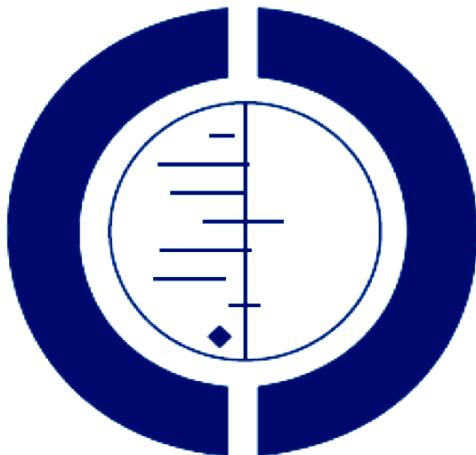
2011

"A wide variety of empirical drug treatments of idiopathic male infertility have been used; however, there is little scientific evidence for an empirical approach"

The Cochrane Library 2011, Issue 8

Antioxidants for male subfertility (Review)

Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ



THE COCHRANE
COLLABORATION®

Conclusioni

Le evidenze suggeriscono che la supplementazione con antiossidanti nella subfertilità maschile potrebbe migliorare la percentuale di bambini e di gravidanza nelle coppie sub-fertili che si sottopongono a cicli ART.

Ulteriori studi di comparazione diretta sono necessari per identificare la superiorità di un antiossidante vs l'altro.



2011

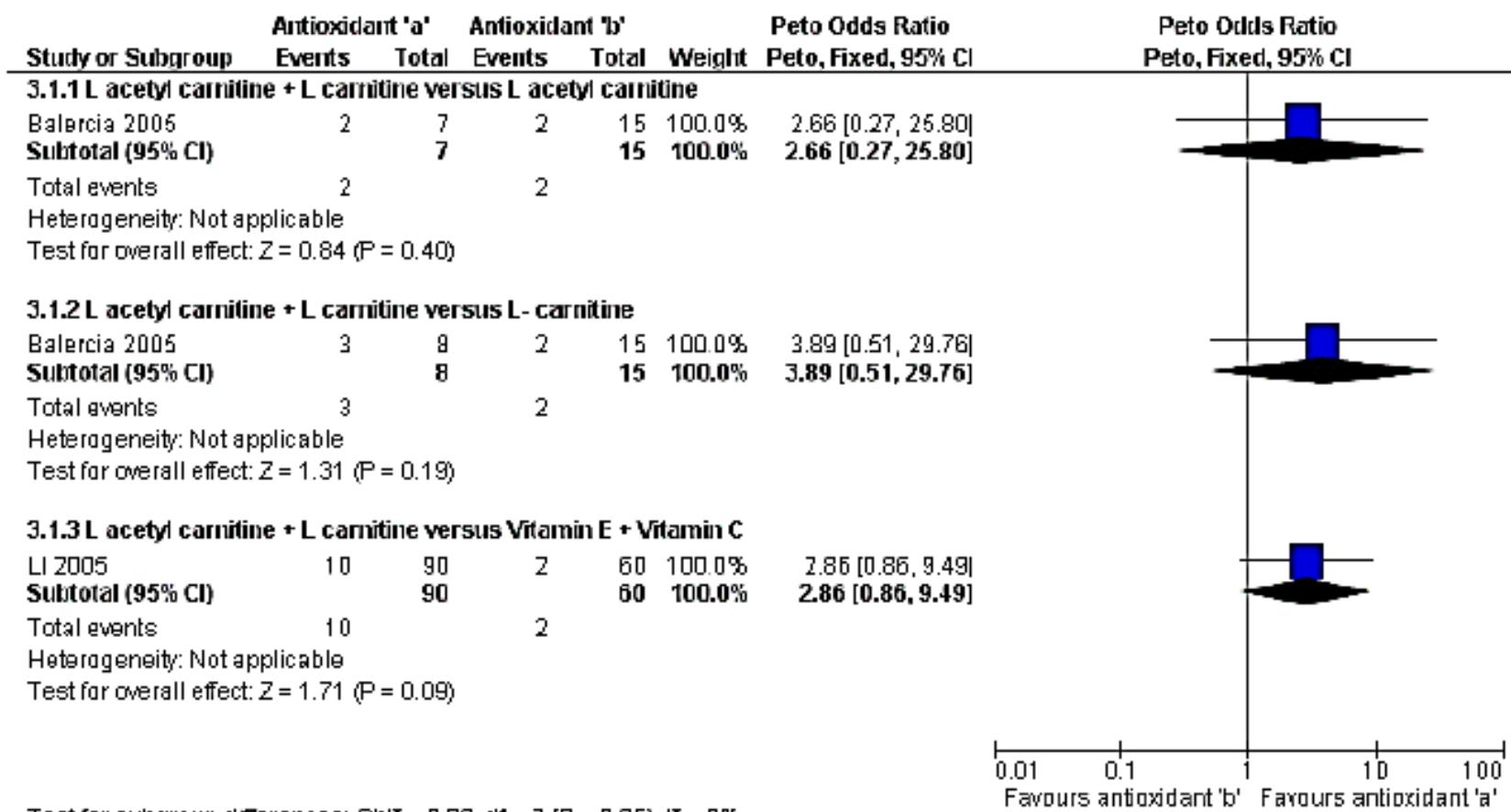
Metodologia: inclusi tutti i trials randomizzati che prevedono l'utilizzo di antiossidanti (da soli o in combinazione), vs placebo o vs altro antiossidante, in coppie che decidono di intraprendere un percorso di fecondazione assistita

Bambini nati vivi: I pazienti che assumono antiossidanti hanno un significativo aumento del tasso di bimbi nati vivi rispetto ai controlli (dati su solo 3 studi)

Pregnancy Rate: La terapia con antiossidanti è associata ad un pregnancy rate significativamente aumentato rispetto ai controlli.



Figure 17. Forest plot of comparison: 3 Antioxidant(s) versus antioxidant(s), outcome: 3.1 Pregnancy per couple randomised.



I TRATTAMENTI CON ANTISSIDANTI

Cochrane Review 2011

Outcome	N studies	N participants	Effect size (OR; 95% CI)
Live birth	3	214	4.85 [1.92, 12.24]
Pregnancy rate	15	964	4.18 [2.65, 6.59]
DNA fragmentation	1	64	-13.80 [-17.50, -10.10]
Miscarriage, sperm count, sperm motility	6-16	242-700	No effect
Adverse effects	6	426	No effect

Showell MG, Brown J, Yazdani A, Stankiewicz, Hart RJ. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2011

2011

Guidelines on Male Infertility

G.R. Dohle, A. Jungwirth, Z. Kopa,
A. Giwercman, T. Diemer, T.B. Hargreave

2015

Guidelines on Male Infertility

A. Jungwirth (chair), T. Diemer, G.R. Dohle, A. Giwercman,
Z. Kopa, H. Tournaye, C. Krausz

"A wide variety of empirical drug treatments of idiopathic male infertility have been used; however, there is little scientific evidence for an empirical approach"

"The evidence suggests that antioxidant supplementation in subfertile men may improve the outcomes of live birth and pregnancy rate for subfertile couples undergoing assisted reproduction technique (ART) cycles."

The Cochrane Library 2014



Cochrane Database of Systematic Reviews

Antioxidants for male subfertility (Review)

Showell MG, Mackenzie-Proctor R, Brown J, Yazdani A, Stankiewicz MT, Hart R.

evidenze di bassa
qualità suggeriscono
che la terapia
antiossidante possa
migliorare il tasso
di bambini nati vivi
ed il pregnancy
rate per coppie che
cercano aiuto per
la fertilità presso
centri di
riferimento.

*Ulteriori studi sono
necessari*

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antioxidants versus placebo or no treatment for male subfertility

Patient or population: patients with male subfertility

Settings:

Intervention: Antioxidants versus placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antioxidants versus placebo or no treatment				
Live Birth per couple randomised Follow-up: 3 - 24 months	50 per 1000	181 per 1000 (99 to 309)	OR 4.21 (2.08 to 8.51)	277 (4 studies)	⊕⊕○○ low ^{1,2}	
Clinical Pregnancy rate per couple randomised Follow-up: 3-24 months	59 per 1000	177 per 1000 (108 to 277)	OR 3.43 (1.92 to 6.11)	522 (7 studies)	⊕⊕○○ low ^{1,3}	
Adverse event: Miscarriage rate per couple randomised Follow-up: 3-18 months	19 per 1000	33 per 1000 (8 to 129)	OR 1.74 (0.40 to 7.60)	247 (3 studies)	⊕○○○ very low ^{1,4}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

Key results: antioxidants may have been effective in treating subfertile men but the reporting of studies was too inconsistent to be confident in these findings. The live birth results suggest that we would expect a live birth of a baby for 5 out of 100 subfertile men who did not take any antioxidants, compared to between 10 and 31 out of 100 men who were taking antioxidants. The results for the clinical pregnancy rate showed an expected clinical pregnancy for 6 out of 100 subfertile men who did not take any antioxidants, compared to between 11 and 28 out of 100 men who were taking antioxidants. Adverse events were poorly reported and we could not make conclusions on any harmful effects. More high quality, larger placebo-controlled trials reporting on these outcomes and adverse events are needed to draw definite conclusions.

Figure 4. Forest plot of comparison: I Antioxidant(s) versus placebo or no treatment, outcome: 1.1 Live birth; type of antioxidant.

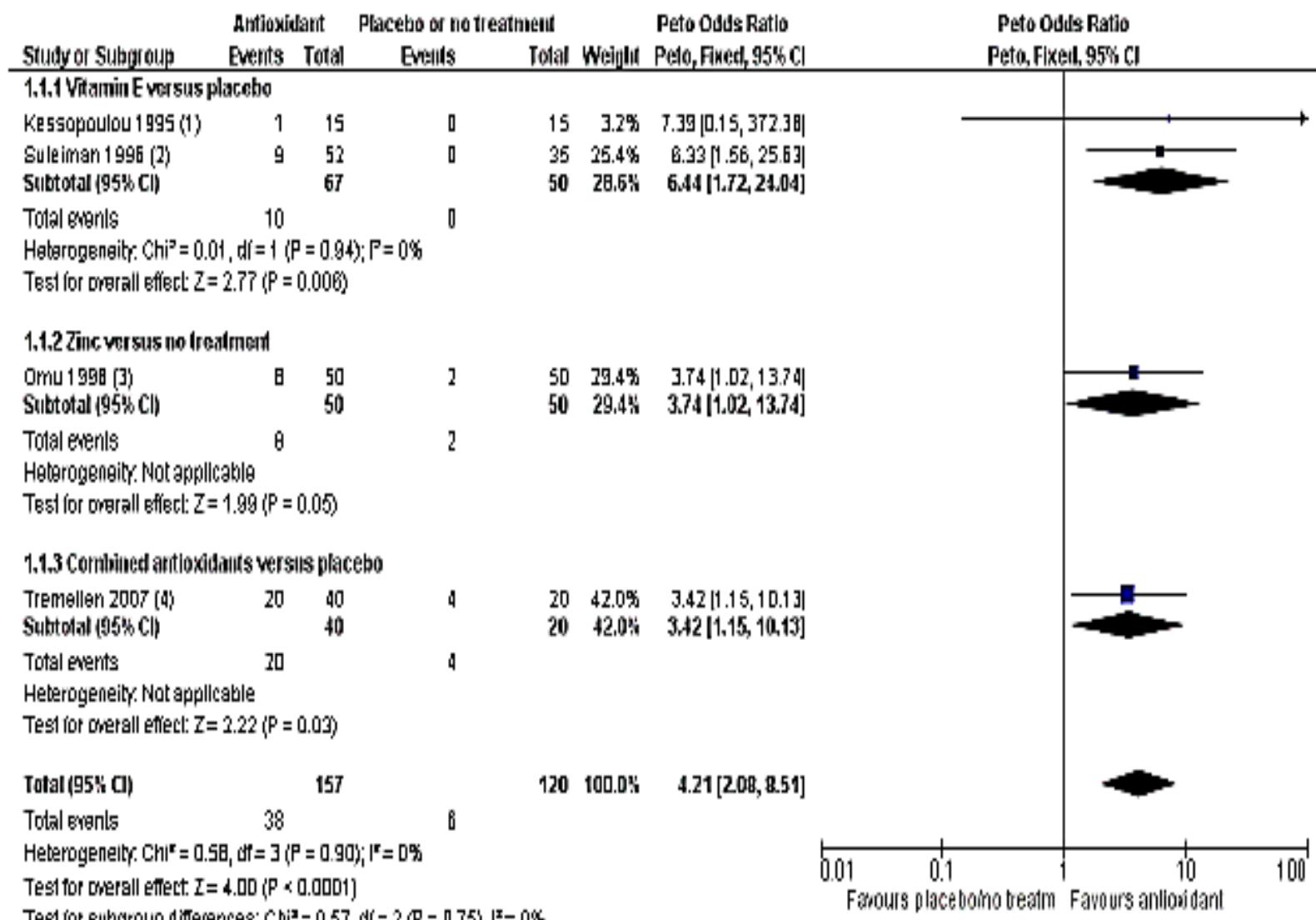
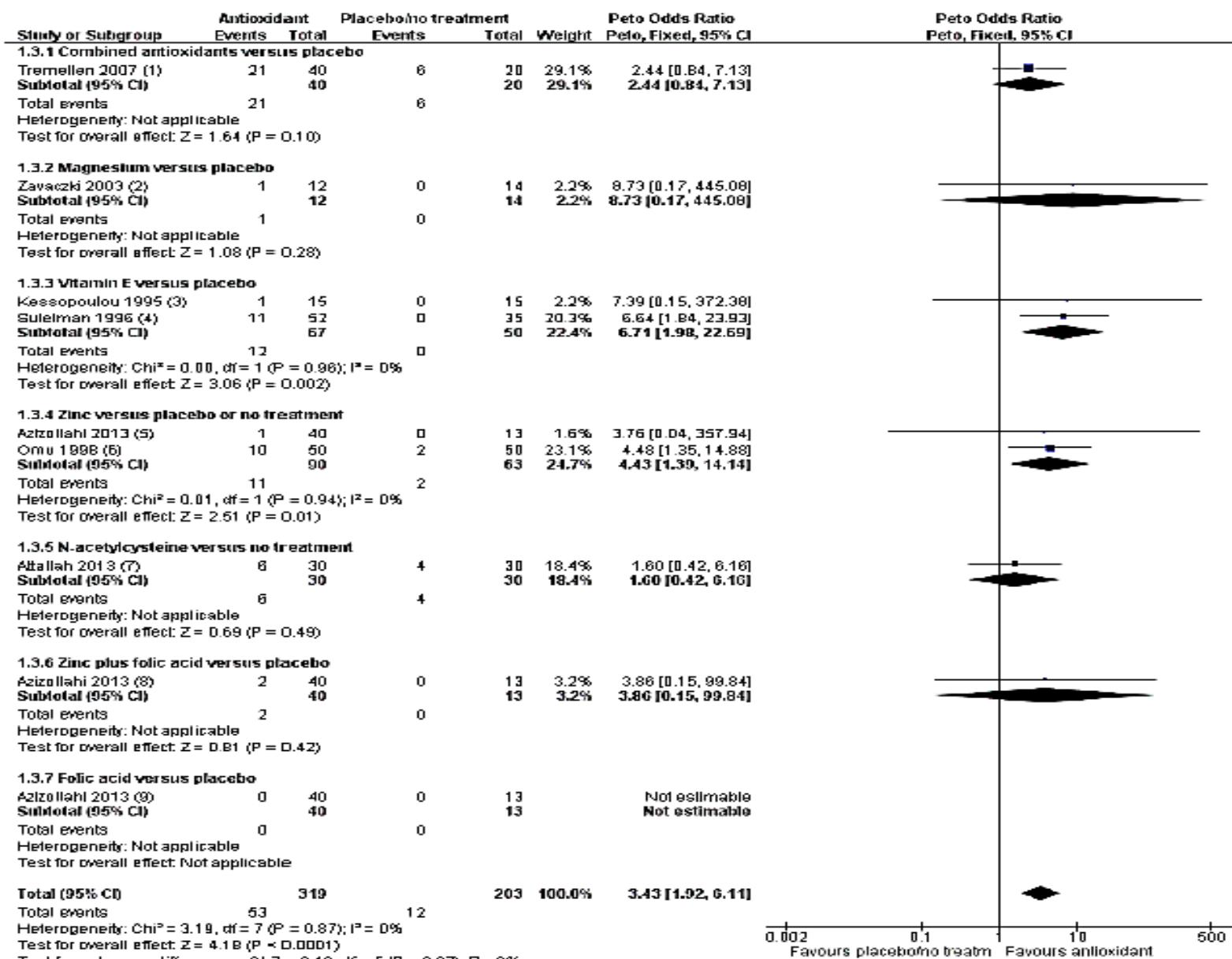
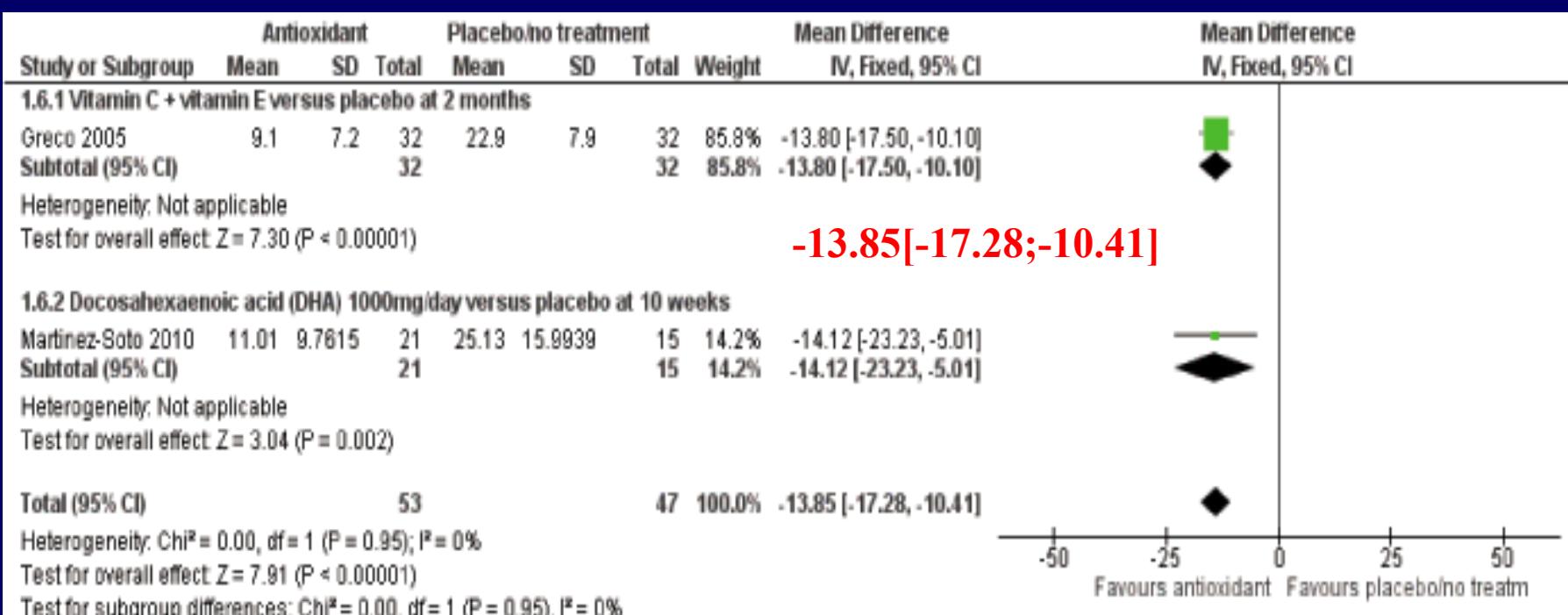


Figure 5. Forest plot of comparison: I Antioxidant(s) versus placebo or no treatment, outcome: 1.3 Clinical pregnancy; type of antioxidant.



Antioxidants for male subfertility (Review)

Showell MG, Mackenzie-Proctor R, Brown J, Yazdani A, Stankiewicz MT, Hart RJ

**Antioxidant(s) versus placebo or no treatment, outcome:
Sperm DNA fragmentation**



European
Association
of Urology

Guidelines on Male Infertility

A. Jungwirth (chair), T. Diemer, G.R. Dohle, A. Giwercman,
Z. Kopa, H. Tournaye, C. Krausz

2016

"Men taking oral antioxidants had an associated significant increase in sperm parameters and in live birth rates in IVF patients in a Cochrane analysis. Concerning natural conception the role of antioxidants needs further investigations".

Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study

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^bInstitute of Population Health, University of Ottawa, Ottawa, Ontario, Canada

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^dToronto Health Economics & Technology Assessment Centre, Toronto, Ontario, Canada

^eClinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada

Accepted 29 August 2008

Abstract

Objectives: To determine which factors predict favorable results and positive conclusions in systematic reviews (SRs) and to assess the level of agreement between SR results and conclusions.

Study Design and Setting: A sample of 296 English SRs indexed in MEDLINE (November, 2004) was obtained. Two investigators independently categorized SR characteristics, results, and conclusions. Descriptive analyses and logistic regression predicting favorable results (nonstatistically significant and statistically significant positive) and positive conclusions were conducted. The level of concordance between results and conclusions was assessed using a weighted-kappa statistic.

Results: Overall, 36.5% of the SRs had favorable results, increasing to 57.7% for Cochrane and 64.3% for non-Cochrane reviews with a meta-analysis of the primary outcome. Non-Cochrane reviews with a meta-analysis of the primary outcome were twice as likely to have positive conclusions as Cochrane reviews with such an analysis (P -value <0.05). The weighted kappa for agreement between SR results and conclusions was 0.55. It was lower for Cochrane (0.41) vs. non-Cochrane (0.67) reviews.

Conclusion: SRs including a meta-analysis of the primary outcome may be affected by indirect publication bias in our sample. Differences between the results and conclusions of Cochrane and non-Cochrane reviews were apparent. Further research on publication-related issues of SRs is warranted. © 2009 Elsevier Inc. All rights reserved.

Keywords: Systematic review; Meta-analysis; Research methodology; Bias; Publication bias; Cross-sectional study

TERAPIA ANTISSIDANTE POST-VARICOCELE

Int J Fertil Steril. 2016 Apr-Jun;10(1):120-6. Epub 2016 Apr 5.

A Preliminary Study: N-acetyl-L-cysteine Improves Semen Quality following Varicocelectomy.

Barekat F¹, Tavalaee M², Deemeh MR², Bahreinian M², Azadi L², Abbasi H³, Rozbahani S⁴, Nasr-Esfahani MH⁵.

Int Braz J Urol. 2015 Mar-Apr;41(2):230-8. doi: 10.1590/S1677-5538.IBJU.2015.02.07.

The effect of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile men: a double blind placebo controlled clinical trial.

Cyrus A¹, Kabir A², Goodarzi D¹, Moghimi M³.

Andrologia. 2014 Apr;46(3):240-5. doi: 10.1111/and.12067. Epub 2013 Jan 28.

Effect of folic acid and zinc sulphate on endocrine parameters and seminal antioxidant level after varicocelectomy.

Nematollahi-Mahani SN¹, Azizollahi GH, Baneshi MR, Safari Z, Azizollahi S.

Horm Metab Res. 2005 Jul;37(7):428-32.

Semenal antioxidants in humans: preoperative and postoperative evaluation of coenzyme Q10 in varicocele patients.

Mancini A¹, Miliardi D, Conte G, Festa R, De Marinis L, Littarru GP.

ORIGINAL ARTICLE

Comparing the effectiveness of infertility treatments by numbers needed to treat (NNT)F. Comhaire¹ & W. Decler²

Significance of the difference in success rate between the controls and the treated cases

Treatment	Total number	% pregnancy controls	% pregnancy treated	NNT	95% CI
Endometriosis	341	17.2	29.1**	8.4	3.1–20.8
Clomid	133	3.2	20.0**	5.9	3.6–16.7
Varicocele multicentre	350	14.3	30.3**	6.3	4.1–13.4
Varicocele single-centre	308	18.1	32.6**	6.8	4.1–19.9
Tamoxifen + testosterone undecanoate	128	10.4	35.8***	3.9	2.9–7.8
Antioxidant	1053	4.4	17.2***	7.8	6.1–11.0
Varicocele + nutriceutical	64	5.0	44.0**	2.6	1.6–5.3
IVF historical	1741	23	35***	8.3	6.1–13.2
IVF + nutriceutical	25	20	45*	4.0	

NNT, numbers needed to treat.

***P ≤ 0.0001.

**P < 0.01.

*Not significant.

✓ NNT di vari approcci terapeutici per le coppie infertili può aiutare a selezionare l'approccio più efficace, considerando anche il rapporto costo beneficio.

✓ ha senso ipotizzare l'utilizzo dei nutraceutici nel migliorare il tasso di successo in pazienti con varicocele ed in coppie che si apprestano ad effettuare IVF

Aree grigie della letteratura scientifica

numerose ed ampie zone grigie dove esiste incertezza sull'efficacia di un intervento diagnostico-terapeutico e/o delle sue alternative.

Evitare la paralisi decisionale - EBM richiede "migliori evidenze disponibili" e non sulle "migliori evidenze possibili" (potrebbero non essere mai disponibili)

delimitazione delle aree grigie riferimento assoluto per la pianificazione della ricerca, per ampliare progressivamente le evidenze necessarie alla pratica clinica ed alla sanità pubblica.