Terapie farmacologiche

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SAPIENZA

UNIVERSITÀ DI ROMA

Roma, 9-12 novembre 2017

The Unrecognized Challenges of the Patient-Physician Relationship

JAMA Internal Medicine November 2017 Volume 177, Number 11

Tamara L. McCarron, MBA; Manal S. Shelish, BComm; Fiona Clement, PhD

ITALIAN CHAPTER

EDITORIAL

New (Very High) Prices on Old Drugs

Saate Shakil, MD; Rita F. Redberg, MD, MSc

JAMA Internal Medicine November 2017 Volume 177, Number 11

H. P. Acthar gel, or repository corticotropin (rACTH), was ap- dosages, not placebo comparisons, of rACTH gel. There are

Predictable response:

Finding optimal drugs and doses using artificial intelligence

By Shraddha Chakradhar

VOLUME 23 | NUMBER 11 | NOVEMBER 2017 NATURE MEDICINE

Research trends and perspectives of male infertility: a bibliometric analysis of 20 years of scientific literature

[1]Y. Zhang,

Andrology, 2016, 4, 990–1001

Table 5 Top 18 most cited WOS papers [Correction added on September 21, 2016, after online publication: The author name in row 2 has been corrected.]

No.	Citations	Authors	Title	Journal	Year	Country	Institution	Subject categories
1	947	C. Barlow	Atm-deficient mice: A paradigm of ataxia telangiectasia	Cell	1996	USA	Natl Inst Health	Biochemistry & Molecular Biology; Cell Biology
2	867	R. Reijo-Pera	Diverse Spermatogenic Defects In Humans Caused By Y-Chromosome Deletions Encompassing A Novel RNA-Binding Protein Gene	Nature Genetics	1995	USA	Massachusetts Institute of Technology	Genetics & Heredity
3	669	M. Guo	Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin	Nature	2006	USA	Univ Calif Los Angeles	Science & Technology - Other Topics
4	597	G.J. Hannon	A germline-specific class of small RNAs binds mammalian Piwi proteins	Nature	2006	USA	Watson Sch Biol Sci	Science & Technology - Other Topics
5	597	M. Chillón	Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens	New England Journal Of Medicine	1995	Spain	Cancer Research Institute	General & Internal Medicine
6	569	R.A. Hess	A role for oestrogens in the male reproductive system	Nature	1997	USA	Univ Illinois	Science & Technology - Other Topics
7	532	D.P. Evenson	Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic	Human Reproduction	1999	USA	S Dakota State Univ	Obstetrics & Gynecology; Reproductive Biology
8	466	G.B. Witman	Proteomic analysis of a eukaryotic cilium	Journal Of Cell Biology	2005	USA	Univ Massachusetts, Worcester	Cell Biology
9	450	M.R. Sairam	Impairing follicle-stimulating hormone (FSH) signaling in vivo: Targeted disruption of the FSH receptor leads to aberrant gametogenesis and hormonal imbalance	PNAS	1998	Canada	Univ Montreal	Science & Technology - Other Topics
10	442	J.G. Sun	Detection of deoxyribonucleic acid fragmentation in human spermatozoa: Correlation with fertilization in vitro	Biology of Reproduction	1997	Canada	University of Toronto	Reproductive Biology

Table 1. Causes of male infertility stratified by mechanism

Pre-testicular

- Hypogonadotrophic hypogonadism – Kallmann syndrome
- Hyperprolactinaemia
- Pharmacological

Testicular

- Varicocele
- Cryptorchidism
- Testicular cancer
- Radiation
- Chemotherapy or pharmacological
- Genetic azoospermia or oligospermia
- Y-chromosome microdeletions
- Klinefelter syndrome
- Environmental
- Infection
- Injury or trauma
- Primary ciliary dyskinesia
- Sertoli cell-only syndrome
- Anti-sperm antibodies

Post-testicular

- Coital
- Pharmacological
- Retrograde ejaculation
- Congenital bilateral absence of the vas deferens
- Ejaculatory duct obstruction or seminal vesicle dysfunction
- Vasectomy or latrogenic injury to the vas deferens
- Young's syndrome
- Nerve injury
- Spinal cord injury
- Retroperitoneal lymph node dissection
- Systemic disease

Darren J Katz, Patrick Teloken, Ohad Shoshany

The World Health Organization currently defines infertility as the inability of a sexually active couple (at least three times per month), not using contraception, to achieve pregnancy within one year.

Primo Messaggio:

Rapporti sessuali congrui

A. J. Hamada *et al.*

Male infertility: a critical review of pharmacologic management

Expert Opin. Pharmacother. (2012) **13**(17)

A literature review on the relationship between infertility and sexual dysfunction: Does fun end with baby making?

The European Journal of Contraception and Reproductive Health Care, 2014; 19: 231–237

Isabella Piva, Giuseppe Lo Monte, Angela Graziano & Roberto Marci

Conclusions Appropriate measures should be designed to identify sexual disorders in infertile couples, and the medical team should be trained to deal systematically with the couple's sexuality and propose strategies to overcome sexual disturbances. This approach could preserve the quality of the couple's sexual relationship and maximise pregnancy chances in ART.

ABC of sexual health

BMJ VOLUME 329 4 SEPTEMBER 2004

Sexual problems associated with infertility, pregnancy, and ageing

Jane Read

Sexual problems often associated with infertility

Male problems

- Loss of desire, with a consequent decrease in sexual activity
- Erectile problems
- Premature ejaculation—little or no control over ejaculatory response, and ejaculation may occur before vaginal entry achieved
- Retarded ejaculation—difficulty ejaculating intravaginally, or at all

Female problems

- Loss of desire
- Vaginismus
- Dyspareunia
- Anorgasmia

Sexual function and stress level of male partners of infertile couples during the fertile period

Seung-Hun Song*, Dong Suk Kim*, Tae Ki Yoon†, Jae Yup Hong‡ and Sung Han Shim§

BJU Int 2016; 117: 173–176

Fig. 2 Prevalence of ED in male partners of infertile couples according to the IIEF-5 questionnaire.

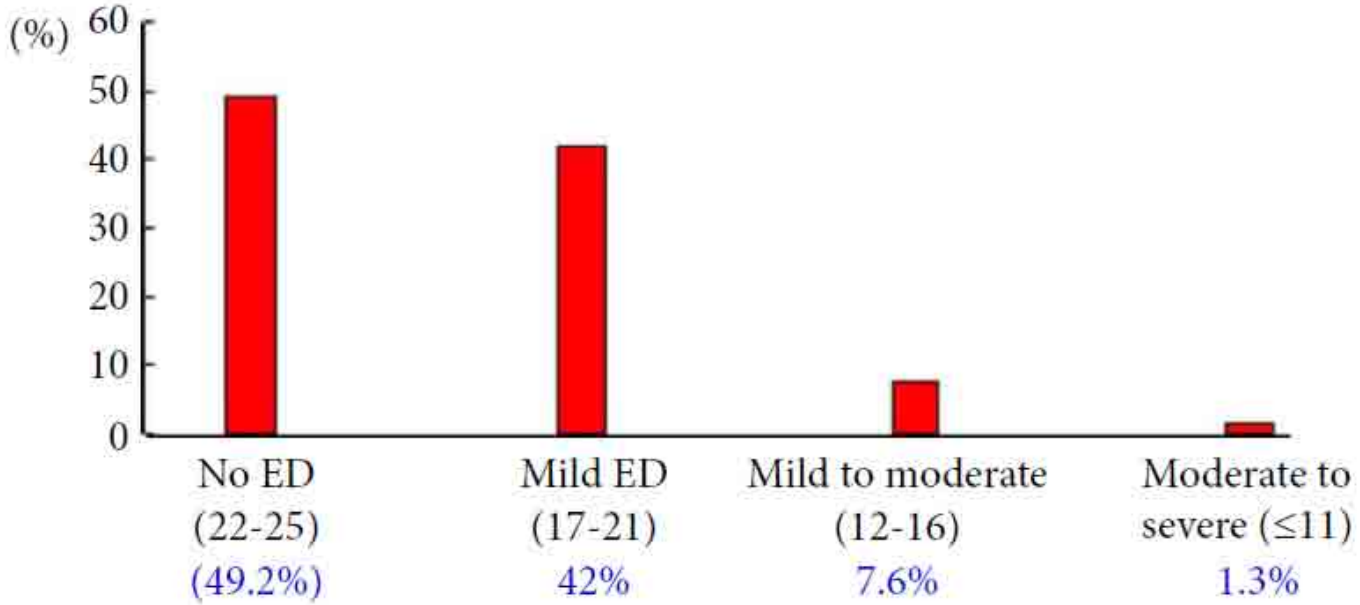


Table 5: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 h	2 h	0.9 h	0.5-0.75 h
T1/2	2.6-3.7 h	17.5 h	3.9 h	6 – 17 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; T1/2: plasma elimination halftime; AUC: area under curve or serum concentration time curve.

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.*

Table 6: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat ED*

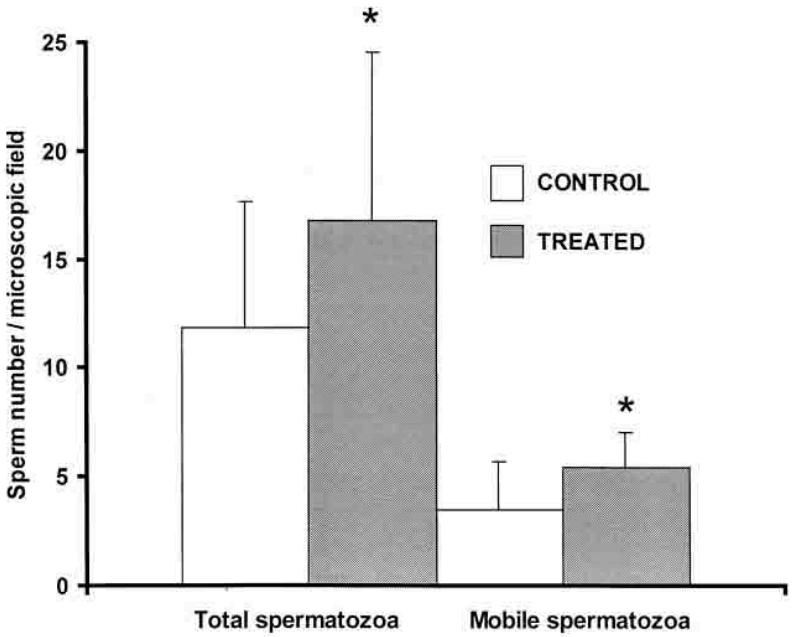
Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Treatment of sexual dysfunctions secondary to male infertility with sildenafil citrate

FERTILITY AND STERILITY®
VOL. 81, NO. 3, MARCH 2004

Emmanuele A. Jannini, M.D.[a]
Francesco Lombardo, M.D., Ph.D.[b]
Pietro Salacone, M.D.[b]
Loredana Gandini, B.Sc.[b]
Andrea Lenzi, M.D.[b]



Effetti della somministrazione di Sildenafil 50 mg un' ora prima del rapporto (post-coital test) in 12 soggetti.

European Association of Urology Guidelines on Male Infertility: The 2012 Update

EUROPEAN UROLOGY 62 (2012) 324–332

Andreas Jungwirth [a,*], *Aleksander Giwercman* [b], *Herman Tournaye* [c], *Thorsten Diemer* [d], *Zsolt Kopa* [e], *Gert Dohle* [f], *Csilla Krausz* [g],

14.2. Medical (hormonal) treatment

There is no evidence that hormonal therapies, such as human menopausal gonadotrophin (hMG)/human chorionic gonadotrophin (hCG), androgen, antioestrogens (clomiphene and tamoxifen), prolactin inhibitors (bromocriptine), and steroids improve pregnancy rates in partners of men with idiopathic OAT. However, hypogonadotrophic hypogonadism can be treated medically. The standard treatment is hCG, with the later addition of hMG or recombinant FSH, depending on initial testicular volume. In some cases of idiopathic hypogonadotrophic hypogonadism, spontaneous reversibility of reproductive function has been observed [63].

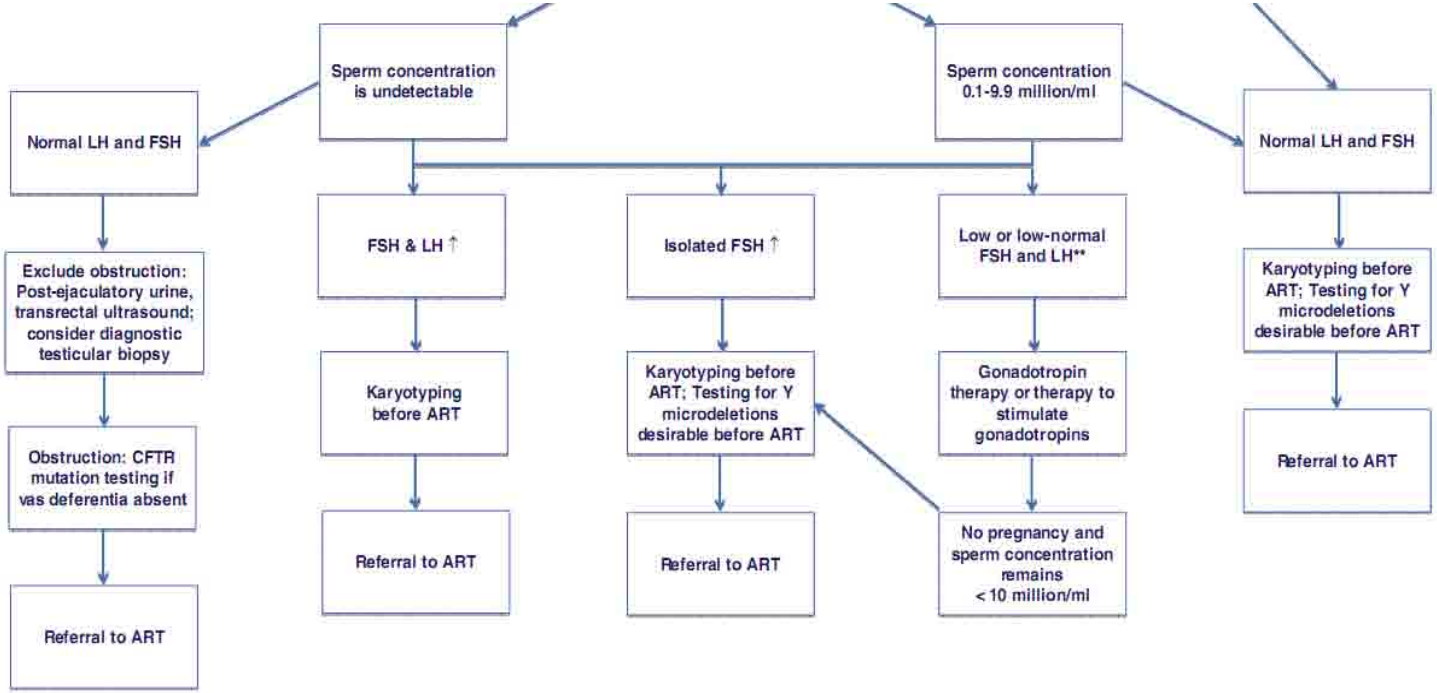
14.3. Empirical drug treatment

A wide variety of empirical drug approaches have been performed. However, the scientific evidence for such empirical approaches is low. Bromocriptine, hCG/hMG, α-blockers, systemic corticosteroids, and magnesium supplementation are not effective for the treatment of idiopathic OAT. Androgens are strictly contraindicated. Recombinant FSH, folic acid with zinc, or antioestrogens may be beneficial in some patients. Cochrane analysis has shown that men taking oral antioxidants had a significant increase in live-birth rate (pooled odds ratio: 4.85; 95% CI, 1.92–12.24; $p = 0.0008$, $I^2 = 0\%$) when compared with men taking placebo. No studies have reported evidence of harmful side effects of antioxidant therapy. The evidence suggests that antioxidant supplementation in subfertile men may improve the outcomes of live birth and pregnancy rates for subfertile couples undergoing assisted reproduction techniques (ART) cycles. This conclusion is based on only 20 live births from a total of 214 couples. Further

Approach to Male Infertility and Induction of Spermatogenesis

Bradley D. Anawalt

J Clin Endocrinol Metab, September 2013, 98(9):3532–3542



Concepts in diagnosis and therapy for male reproductive impairment

Lancet Diabetes Endocrinol 2017; 5: 554–64

Herman Tournaye, Csilla Krausz, Robert D Oates

Hormonal treatment of male infertility

Because spermatogenesis requires adequate endocrine stimulation, specific and empiric hormonal treatments have been employed since the early 1970s. Directed hormonal treatment is effective in azoospermic patients with congenital hypogonadotropic hypogonadism, (eg, Kallmann syndrome). Before FSH therapy, treatable forms of acquired hypogonadotropic hypogonadism should be ruled out, (eg, microprolactinoma), which should be treated with dopamine agonists. In a recent meta-analysis,[46] gonadotropin therapy (both recombinant FSH or urinary-derived highly purified FSH) in combination with human chorionic gonadotropin (hCG) was found to successfully stimulate testosterone synthesis and spermatogenesis. Pulsatile administration of gonadotropin-releasing hormone (GnRH) showed similar efficacy in inducing sperm production.[46] However,

Non-hormonal treatment of male infertility

After the generation of haploid spermatids, an important cyto-differentiation and maturation process converts these cells into fully functional gametes. These processes are highly influenced by external factors, such as reactive oxygen species, temperature, and lifestyle. Therefore, both non-hormonal medical treatments and food supplements are very popular to treat male infertility, even though data are extremely scarce and not generally supportive of their efficacy. Pentoxifylline is a methylxanthine known to increase intracellular cAMP levels and thereby sperm motility in vitro.[57] However, there is no good evidence that this drug enhances male

Terapie Eziologiche

Alcune tra le principali cause di infertilità ad eziologia nota, possibili obiettivi di terapia specifica, sono:

- **Immunità anti-spermatozoo**
- **Varicocele**
- **Obesità**
- **Infezioni e cause flogistiche**
- **Iperprolattinemia**
- **Acromegalia**
- **Sindrome di Cushing**
- **Sindrome Adreno-Genitale**
- **Tireopatie**
- **Criptorchidismo**
- **Ipogonadismi iper/ipogonadotropi**
- **Disordini dell'eiaculazione**

McLachlan
Approach to the Patient with Oligozoospermia
J Clin Endocrinol Metab, March 2013, 98(3):873–880

Anawalt
Approach to Management of Male Infertility
J Clin Endocrinol Metab, September 2013, 98(9):3532–3542

Terapie Eziologiche – Anticorpi anti-spermatozoo

Antisperm immunity in assisted reproduction

Francesco Lombardo*, Loredana Gandini,
Andrea Lenzi, Franco Dondero

The presence of ASA may impair in vivo sperm fertilising ability and is a serious factor which may prevent the success of various fertilisation techniques. Only ICSI seems able to overcome the problem, producing similar fertilisation and pregnancy rates in both ASA-positive and -negative patients. Due to the relativity rarity of immunological infertility, literature in this field is quite scarce and more studies need to be conducted to confirm that embryo quality is not impaired.

Journal of Reproductive Immunology
62 (2004) 101–109

Improvement in pregnancy outcomes in couples with immunologically male infertility undergoing prednisolone treatment and conventional in vitro fertilization preceded by sperm penetration assay: a randomized controlled trial

Ahmed M. Taiyeb[1] · Mundhir T. Ridha-Albarzanchi[1,2] · Shereen M. Taiyeb[1] · Zuhair A. Kanan[1,2] · Shahla K. Alatrakchi[1] · Michael E. Kjelland[1,3] ·

Endocrine

Published online: 13 October 2017

Table 5 Semen characteristics of control and treated immunologically infertile men that underwent conventional IVF and embryo transfer

Variable	Control patients	Treated patients	*P* value
Number of continued patients	46	50	–
Volume (ml)	2.5 ± 0.4	2.5 ± 0.5	NS
Sperm concentration ($\times 10^6$/ml)	25.8 ± 15.6	33.2 ± 22.5	NS
Sperm vitality (%)	35.2 ± 12.4	43.2 ± 16.9	NS
Sperm morphology (%)	3.7 ± 2.8	4.0 ± 2.1	NS
Sperm motility (%)	49.8 ± 13.6	70.1 ± 10.8	$P < 0.001$
Sperm progressive motility (%)	21.7 ± 13.6	56.7 ± 13.0	$P < 0.001$

Values are presented as mean ± SD

NS non-significant

Table 6 Fertilization outcomes of control and treated immunologically infertile men that underwent conventional IVF and embryo transfer

Variable	Control patients	Treated patients	*P* value
Number of continued patients	46	50	—
Number of mature oocytes	224	251	—
Fertilization rate	62.1 (139/224)	70.9 (178/251)	$P = 0.04$
Embryo cleavage rate	76.2 (106/139)	86.5 (154/178)	$P = 0.01$
Embryo transfer rate	77.3 (82/106)	78.6 (121/154)	NS
Average embryo transfer/patient	1.8 ± 0.7 (82/46)	2.4 ± 0.7 (121/50)	$P < 0.001$
Chemical pregnancy rate	23.9 (11/46)	46.0 (23/50)	0.02
Clinical pregnancy rate	17.4 (8/46)	36.0 (18/50)	0.04

J. Endocrinol. Invest. 24: 217-223, 2001

Lack of evidence of a genetic origin in the impaired spermatogenesis of a patient cohort with low-grade varicocele[1]

L. Foppiani*, S. Cavani**, S. Piredda*, L. Perroni**, L. Fazzuoli*, and M. Giusti*

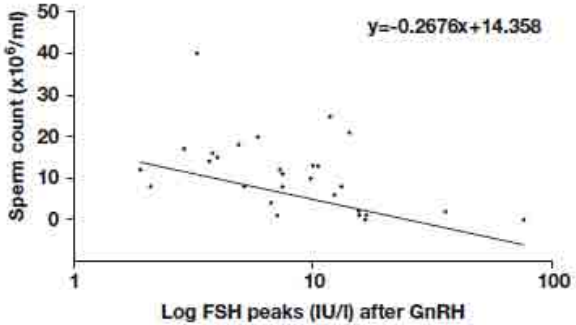


Fig. 3 - *Correlation (r=-0.50, p=0.005) between GnRH-induced FSH peaks and sperm count in patients with VAR.*

In these patients, the impaired spermatogenesis is probably due to the disease itself and/or to other unknown testicular pathologies associated to VAR. Nevertheless, Yq chromosome evaluation seems advisable in patients with VAR, especially in those with severe oligozoospermia, in order to define the aetiology of spermatogenetic failure, avoid a potentially useless varicocelectomy and inform patients about the risk of transmitting this genetic abnormality to male offspring.

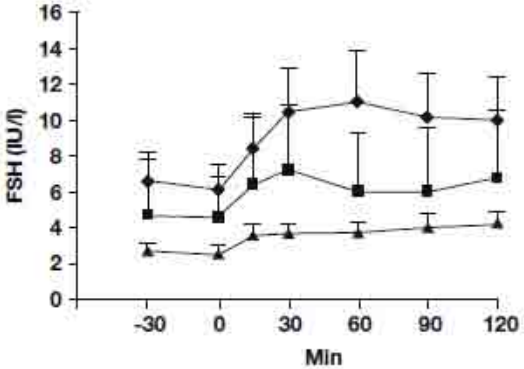


Fig. 1 - *LH (upper panel) and FSH response (lower panel) to GnRH in the three groups studied. Each time point value of the FSH VAR plot is p<0.01 vs C.*

Male accessory gland inflammation, infertility, and sexual dysfunctions: a practical approach to diagnosis and therapy

A. E. Calogero, Y. Duca, R. A. Condorelli and S. La Vignera

Andrology, 1–9

Table 1 Clinical criteria adopted for the diagnosis of MAGI (WHO, 1993)

Oligo-, astheno- and/or teratozoospermia associated with the following:

- One factor A + one factor B
- One factor A + one factor C
- One factor B + one factor C
- Two factors C

Factors	Description
A	*History:* positive for urinary infection, epididymitis, and/or sexually transmitted disease *Physical signs:* thickened or tender epididymis, tender vas deferens, and/or abnormal digital rectal examination
B	*Prostatic fluid:* abnormal prostate fluid expression and/or abnormal urine after prostatic massage
C	*Ejaculate signs:* leukocyte > 1 million per ml, culture with significant growth of pathogenic bacteria, abnormal appearance, increased viscosity, increased pH, and/or abnormal biochemistry of the seminal plasma

Current medical management of endocrine-related male infertility

Joshua D Ring, Aye A Lwin, Tobias S Köhler

Asian Journal of Andrology (2016) 18, 357

Male factor contributes to 50%–60% of overall infertility but is solely responsible in only 20% of couples. Although most male factor infertility is ascertained from an abnormal semen analysis, other male factors can be contributory especially if the sample returns normal. Male infertility can be due to identifiable hormonal or anatomical etiologies that may be reversible or irreversible. This manuscript will highlight existing guidelines and our recommendations for hormone evaluation for male infertility and empiric therapies including multivitamins, estrogen receptor modulators (clomiphene), estrogen conversion blockers (anastrozole), and hormone replacement.

CONCLUSIONS

This manuscript described existing guidelines and our recommendations for hormone evaluation for idiopathic male infertility. We utilize SHBG levels in addition to TT levels and FSH on initial patient screening given its ability to better quantify hypogonadism. Empiric therapies including multivitamins are safe and have support in the literature. Estrogen receptor modulators (clomiphene), hCG and aromatase inhibitors can be used to effectively augment and normalize low TT and potentially improve semen parameters.

Male infertility – The other side of the equation

Darren J Katz, Patrick Teloken, Ohad Shoshany

REPRINTED FROM AFP VOL.46, NO.9, SEPTEMBER 2017 641

Table 2. Hormonal profiles of different clinical scenarios

	Follicle-stimulating hormone	Luteinising hormone	Testosterone	Prolactin
Hypogonadotropic hypogonadism	Low	Low	Low	Normal or high
Abnormal spermatogenesis	High or normal	Normal	Normal	Normal
Testicular failure or hypergonadotropic hypogonadism	High	High	Low	Normal
Prolactinoma	Normal or low	Normal or low	Low	High

Terapie Eziologiche - Iperprolattinemia

Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline

Shlomo Melmed, Felipe F. Casanueva, Andrew R. Hoffman, David L. Kleinberg, Victor M. Montori, Janet A. Schlechte, and John A. H. Wass

Recommendation

4.1. We recommend dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas (1|⊕⊕⊕⊕). We recommend using cabergoline in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage (1|⊕⊕⊕⊕).

Cabergolina

Es. Dostinex, Actualene, Cabaser

Da 0,25 mg due volte a settimana separate da due giorni.

J Clin Endocrinol Metab, February 2011, 96(2):273–288

J Clin Endocrinol Metab, September 2002, 87(9):4193–4197

Short-Term Suppression of GH and IGF-I Levels Improves Gonadal Function and Sperm Parameters in Men with Acromegaly

A. COLAO, M. DE ROSA, R. PIVONELLO, A. BALESTRIERI, P. CAPPABIANCA, A. DI SARNO, V. ROCHIRA, C. CARANI, AND G. LOMBARDI

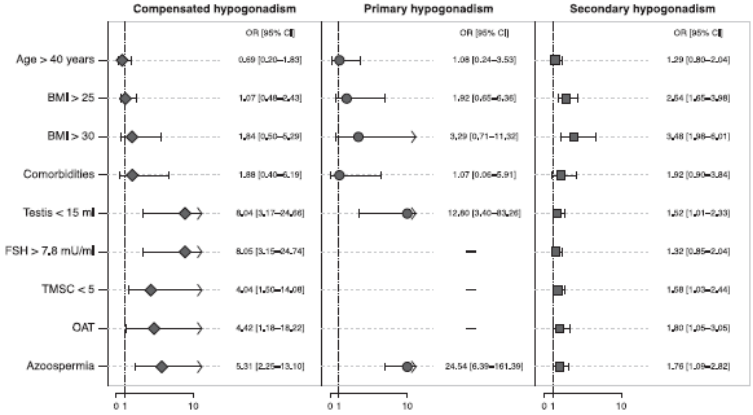
TABLE 2. Endocrine and seminal fluid parameters in men with acromegaly before and 6 months after surgery or LAN according to treatment success

	Patients cured by surgery		P	Patients controlled by LAN		P	Patients not controlled by surgery and/or LAN		P
	Basal (n = 11)	Treatment (n = 11)		Basal (n = 11)	Treatment (n = 11)		Basal (n = 13)	Treatment (n = 13)	
Age range (yr)	27–46			29–53			30–59		
Mean age (yr)	36.6 ± 2.0			40.6 ± 2.6			44.1 ± 2.7		
GH levels (μg/liter)	64.8 ± 6.6	1.5 ± 0.2	0.001	75.2 ± 12.4	1.7 ± 0.2	0.001	72.7 ± 11.0	4.6 ± 0.4	0.002
IGF-I levels (μg/liter)	908.8 ± 40.7	242.0 ± 42.3	0.001	1082 ± 221.5	428.2 ± 36.2	0.001	1204 ± 149.6	549.5 ± 52.1	0.002
FSH levels (U/liter)	3.7 ± 0.4	5.5 ± 0.8	0.03	2.5 ± 0.4	5.0 ± 0.9	0.01	4.2 ± 0.6	5.0 ± 0.9	0.4
LH levels (U/liter)	5.9 ± 0.7	7.1 ± 0.5	0.04	4.5 ± 0.3	6.2 ± 1.1	0.05	5.1 ± 0.5	5.2 ± 1.1	0.1
Testosterone levels (μg/liter)	3.1 ± 0.3	4.0 ± 0.4	0.008	3.4 ± 0.2	4.5 ± 0.3	0.002	2.5 ± 0.2	3.7 ± 0.4	0.004
DHT levels (nmol/liter)	38.4 ± 4.8	47.7 ± 4.4	0.008	32.3 ± 5.3	49.6 ± 4.7	0.001	31.2 ± 3.9	43.2 ± 5.0	0.001
17-β-Estradiol levels (ng/liter)	20.1 ± 1.2	19.1 ± 1.7	0.5	20.4 ± 1.05	17.6 ± 1.3	0.052	21.6 ± 1.7	19.6 ± 1.8	0.2
Seminal volume (ml)	2.31 ± 0.3	2.90 ± 0.3	0.01	2.92 ± 0.3	3.47 ± 0.3	0.1	2.76 ± 0.3	2.71 ± 0.3	0.8
Seminal pH	8.0 ± 0.08	8.07 ± 0.09	0.8	8.04 ± 0.06	7.96 ± 0.02	0.4	7.99 ± 0.09	8.05 ± 0.13	0.7
Sperm number/ml	37.9 ± 6.1	55.8 ± 7.2	0.001	36.7 ± 7.2	59.8 ± 7.3	0.001	42.8 ± 6.1	54.5 ± 6.2	0.002
Sperm number/ejaculate	82.5 ± 18.1	203.5 ± 31.8	0.001	109.1 ± 26.6	214.1 ± 34.2	0.001	139.2 ± 25.7	188.0 ± 31.9	0.02
Total motility (%)	23.9 ± 4.0	38.4 ± 3.9	0.007	29.6 ± 3.0	38.4 ± 4.6	0.03	27.9 ± 3.6	32.4 ± 2.5	0.5
Rapid progression (%)	14.6 ± 2.4	19.6 ± 3.1	0.2	17.8 ± 2.0	19.0 ± 3.0	0.6	21.4 ± 3.3	27.5 ± 3.2	0.2

Primary, secondary and compensated hypogonadism: a novel risk stratification for infertile men

[1,2,*]E. Ventimiglia, [1,2,*]S. Ippolito, [1,2]P. Capogrosso, [1]F. Pederzoli, [1,2]W. Cazzaniga, [1]L. Boeri, [1]I. Cavarretta, [2]M. Alfano, [3]P. Viganò, [1,2]F. Montorsi and [1,2]A. Salonia

Andrology, 2017, 5, 505–510



CONCLUSIONS

Overall, we found a high prevalence of hypogonadism among infertile patients, closely resembling epidemiological data found in cohorts of older individuals not specifically screened for infertility. Primary and compensated hypogonadism depicted the worst clinical picture in terms of impaired fertility, with primary hypogonadal men having a 24-fold increased risk of azoospermia and a 13-fold increased risk of small testicular volume compared to eugonadal men. Compensated hypogonadism emerged to be a clear condition of testicular dysfunction (fivefold increased risk of azoospermia, fourfold increased risk of low total motile sperm count, eightfold increased risk of low testicular volume), in spite of normal *T* values. Although not specifically designed for infertile men, EMAS categories might serve as a clinical stratification tool in infertile men.

Diagnosis and treatment of infertility-related male hormonal dysfunction

Martin Kathrins[1] and Craig Niederberger[2]

NATURE REVIEWS | UROLOGY 2016

Box 2 | Hormonal therapy

Selective oestrogen receptor modulators

- Clomiphene citrate
- Tamoxifen citrate
- Enclomiphene citrate

Aromatase inhibitors

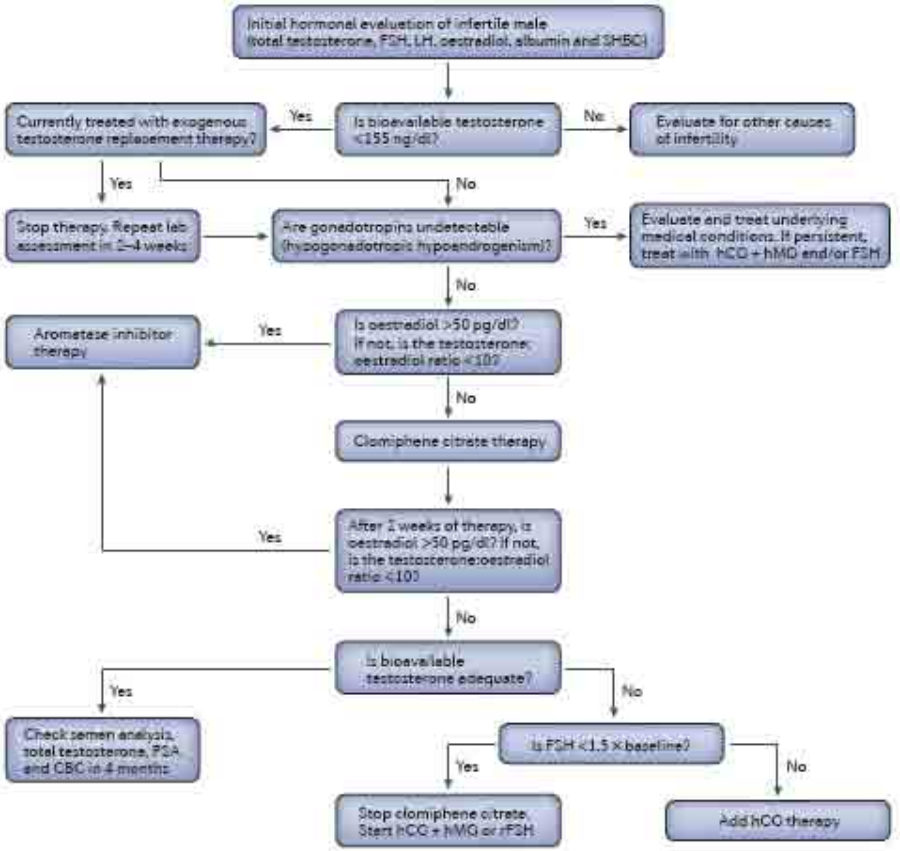
- Anastrozole
- Testolactone
- Letrozole

Gonadotropin therapy: recombinant or purified urine-derived

- Follicle stimulating hormone
- Human chorionic gonadotropic (luteinizing hormone-analogue)

Urine-derived

- Human menopausal gonadotropin



ANDROLOGIA 23, 285–289 (1991) ACCEPTED: JULY 20, 1990

Achievement of spermatogenesis and genital tract maturation in hypogonadotropic hypogonadic subjects during long term treatment with gonadotropins or LHRH

I. Mastrogiacomo, R. G. Motta, S. Botteon, G. Bonanni and M. Schiesaro

Key words. Spermatogenesis – hypogonadism – gonadotropin therapy – human.

Summary. 15 subjects with Hypogonadotropic Hypogonadism (HH) were treated with either gonadotropins (13 cases) or pulsatile subcutaneous Luteinizing Hormone Releasing Hormone (LHRH) (2 cases) for up to 42 months, to study the effects of therapy step by step. The following results were obtained: (A) In postpubertal HH (5 cases = Group A), therapy brought about onset of spermatogenesis within 3 months and its normalization

Introduction

Treatment of male Hypogonadotropic Hypogonadism (HH) is satisfactory for improving blood hormone levels, but in many cases normal spermatogenesis is not obtained (Stanhope *et al.*, 1985; Spratt *et al.*, 1986; Liu *et al.*, 1988; Finkel *et al.*, 1985; Crowley & Spratt, 1985). This is true not only for conventional treatment with gonadotropins, but al-

ARTICLE IN PRESS

FERTILITY AND STERILITY: 50 YEARS AGO TODAY

Use of gonadotropins in infertile patients

Daniela Galliano, M.D., Ph.D.

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Gonadotrophin replacement for induction of fertility in hypogonadal men

Andrew A. Dwyer,

Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 91–103

Author (year)	Treatment regimen (duration)	Cases[a] (# CHH)	Sperm positive	TV < 4 mL sperm +	TV > 4 mL sperm +	Negative predictor	Comments
Burris et al. (1988)	hCG: 2'000 U 3×/wkly (24 months)	22 (22 CHH)	15/22 (68%)	6/11 (55%)	9/11 (82%)	TV < 4 mL	• hCG mono-therapy – outcomes better for larger initial TV
Pitteloud et al. (2002)	Pulsatile GnRH: 25–600 ng/kg every 2 h (12–24 months)	76 (70 CHH)	51/70 (87%)	43/52 (83%)	18/18 (100%)	TV < 4 mL cryptorchidism IB < 60 pg/mL	• Cryptorchidism more common in CHH men with TV < 4 mL • 3/6 bilateral cryptorchidism remained azoospermic • 24/31 (77%) have sperm by 12 mos, 42/51 (82%) by 24mos
Miyagawa et al. (2005)	hCG: 3'000 U 2× weekly FSH: 75 IU 2× weekly (12–24 months)	36 (29 CHH)	9/18 (50%)	4/11 (36%)	5/7 (71%)	TV < 4 mL	• Cryptorchidism more common in CHH men with TV < 4 mL • Positive correlation between initial TV and sperm count
Liu et al. (2009)	hCG: 1'500–2'000 U 2×/wk FSH (post 6 mos hCG): 75–150 IU 3×/wk (23 ± 2 months)	75 (51 CHH)	85–90%	n/a	n/a	TV < 4 mL priorT	• Time to response effected by initial TV • Positive effect of prior cycles
Warne et al. (2009)	hCG: 1'000 U 3×/wk or 2'000 U 2×/wk FSH (post 3–6 mos hCG): 150–300 3×X/wk (18 months)	81 (77 CHH)	68/81 (84%)	n/a	n/a	TV < 4 mL BMI > 30	• Time to response effected by initial TV • No effect of prior treatment • All non-responders were CHH men with initial TV < 4 mL

Terapie Eziologiche – Ipogonadismo

ITALIAN CHAPTER

Efficacy of recombinant human follicle stimulating hormone at low doses in inducing spermatogenesis and fertility in hypogonadotropic hypogonadism

A.A. Sinisi[1], D. Esposito[1], G. Bellastella[1], L. Maione[1], V. Palumbo[1], L. Gandini[2], F. Lombardo[2], A. De Bellis[1], A. Lenzi[2], and A. Bellastella[1]

In conclusion, the present study demonstrates that administration of 150 IU rFSH weekly, added to hCG, is effective in inducing spermatogenesis and fertility in HH men. In our experience, rFSH gave satisfactory outcome also shortening the time to achieve potential fertilizing SC with respect to hpFSH.

SC: Sperm concentration;

rFSH: Recombinant FSH

Es. : Follitropina beta (Puregon 100-150-200), Follitropina alfa (Gonal F 150-1050; Bemfola 150-225-300-450; Ovaleap 300-450-900)

hpFSH: Highly purified urinary FSH

Es. : Urofollitropina (Fostimon 150-225-300)

J. Endocrinol. Invest. 33: 618-623, 2010

Terapie Eziologiche – Ipogonadismo

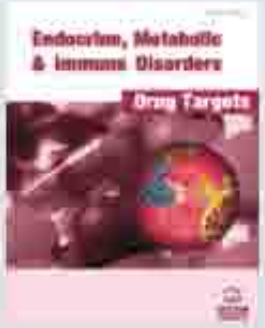
A combined analysis of data to identify predictive factors for spermatogenesis in men with hypogonadotropic hypogonadism treated with recombinant human follicle-stimulating hormone and human chorionic gonadotropin

David W. Warne, Ph.D.,[a] Genevieve Decosterd, Pharm D.,[a] Hiroshi Okada, M.D.,[b] Yumiko Yano, B.A.,[c] Nakako Koide,[c] and Colin M. Howles, Ph.D.[a]

Intervention(s): Pretreatment with hCG for 3–6 months, followed by combination therapy with hCG and r-hFSH (150 IU three times weekly) for up to 18 months. Doses of r-hFSH were adjusted according to spermatozoa count until the maximum dose was reached.

In summary, this metabase of data from four worldwide clinical trials confirms the efficacy and safety of hCG and r-hFSH in a large number of men with HH. Combination therapy with r-hFSH and hCG is effective in the restoration of fertility in the majority of men with this rare condition. In this combined data analysis, spermatogenesis was induced in 84% of men with HH. Similar treatment responses were observed among Caucasian and Japanese men. However, obese patients may require hCG and r-hFSH dose titration to achieve adequate treatment responses.

Fertility and Sterility® Vol. 92, No. 2, August 2009



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Effectiveness of Gonadotropin Administration for Spermatogenesis Induction in Hypogonadotropic Hypogonadism: A Possible Role of Androgen Receptor CAG Repeat Polymorphism and Therapeutic Measures

Author(s): V. A. Giagulli, V. Triggiani, G. Corona, M. D. Carbone, E. Tafaro, B. Licchelli, F. Resta, C. Sabba Maggi, E. Guastamacchia.

Journal Name: Endocrine, Metabolic & Immune Disorders - Drug Targets

Volume 12 , Issue 3 , 2012 **DOI** 10.2174/187153012802002866

Journal Home

Abstract:

Prepuberal-onset (PRHH) and postpuberal-onset (PSHH) Hypogonadotropic Hypogondism (HH) refer to a heterogeneous group of patients, showing a broad spectrum of clinical signs and symptoms of androgen deficiency in consideration of the different possible aetiologies and the ag at onset. These patients, though, required Gonadotropin treatment (GnTh) by means of administration of both the β Human Chorionic Gonodadotropin (β HCG) and the Follicle Stimulating Hormone (FSH) to obtain mature sperms in the ejaculate aiming to reach fertility levels. However, the response to GnTh is always unpredictable concerning either the effectiveness or the duration of the therapy. Consequently, differen

An open-label clinical trial to investigate the efficacy and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotropic hypogonadism

Eberhard Nieschlag[1*], Pierre-Marc G. [illegible]
Anjela Tzontcheva[3], Christine McCran

Reproductive Biology and Endocrinology (2017) 15:17

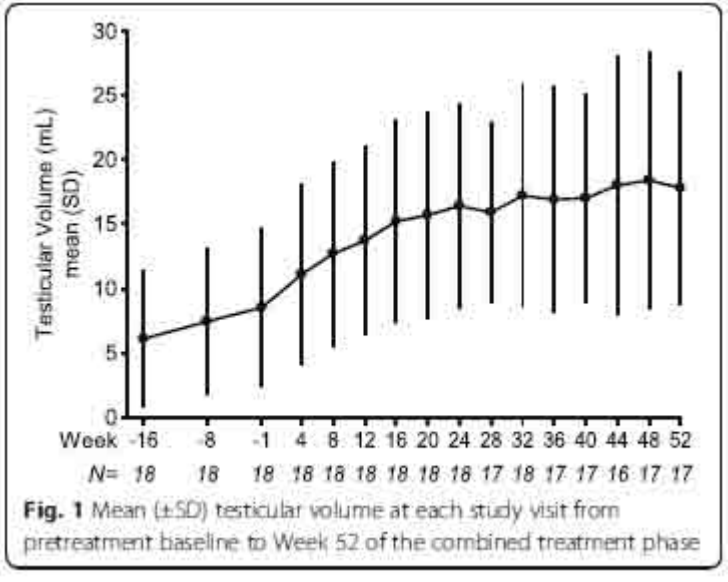
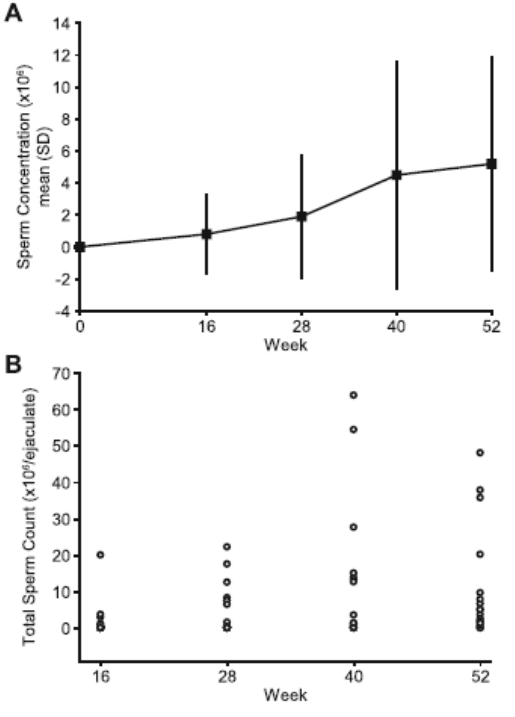
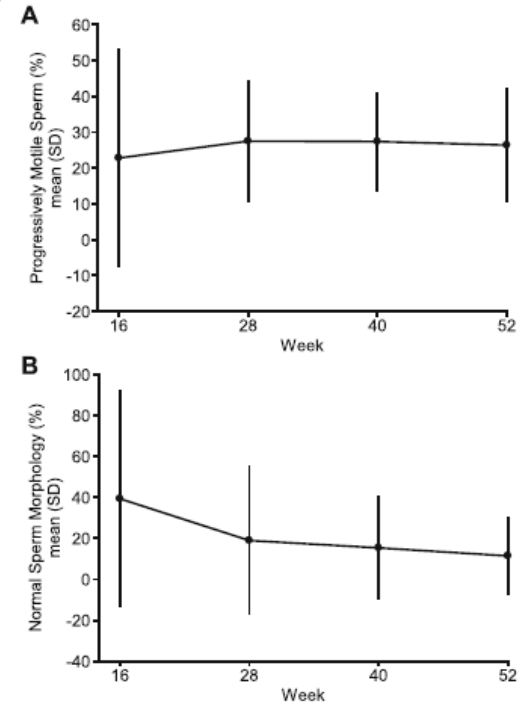


Fig. 1 Mean (±SD) testicular volume at each study visit from pretreatment baseline to Week 52 of the combined treatment phase





Gonadotoropin actions on spermatogenesis and hormonal therapies for spermatogenic disorders

Koji Shiraishi and Hideyasu Matsuyama

Endocrine Journal 2017, **64** (2), 123-131

Abstract. Microdissection testicular sperm extraction and intracytoplasmic sperm injection have made it possible for men with non-obstructive azoospermia (NOA) to conceive a child. A majority of men cannot produce sperm because spermatogenesis *per se* is believed to be "irreversibly" disturbed. For these men, it has been thought that any hormonal therapy will be ineffective. Further understandings of endocrinological regulation of spermatogenesis are needed and LH or FSH receptor knock out (KO) mice have revealed the roles of gonadotropin separately. Spermatogenesis has been shown to shift during evolution from FSH to LH dominance because LH receptor KO causes infertility while FSH receptor KO does not. High concentrations of intratesticular testosterone secreted from Leydig cells, ranging from 100- to 1,000-fold higher than in the systemic circulation, has pivotal roles during spermatogenesis. This is especially important during spermiogenesis, a post-meiotic step for progression from round to elongating spermatids. Sertoli cells are the target of FSH and have numerous androgen receptors, indicating that Sertoli cells are regulated by FSH and the paracrine functions of testosterone. In combination with Leydig cell-derived growth factors, particularly epidermal growth factor-like growth factors, Sertoli cells support spermatogenesis, especially at proximal levels of spermatogenesis (*e.g.*, spermatogonial proliferation). Taken together, the current knowledge from human studies indicating that testosterone optimization by clomiphene, hCG and/or aromatase inhibitors and high dose hCG/FSH treatment can, at least in part, improve spermatogenesis in NOA. Accordingly hormonal therapy may open a therapeutic window for sperm production in selected patients.

Terapie Eziologiche – Ipogonadismo

29-8-2016 Nota 74 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA *Serie generale* - n. **201**

Farmaci per l'infertilità femminile e maschile: - Corifollitropina alfa - Coriogonadotropina alfa - Follitropina alfa - Follitropina alfa/ Lutropina alfa - Follitropina beta - Lutropina alfa - Menotropina - Urofollitropina	La prescrizione a carico del SSN, su diagnosi e piano terapeutico di strutture specialistiche, secondo modalità adottate dalle Regioni e dalle Province Autonome di Trento e Bolzano, è limitata alle seguenti condizioni: • trattamento dell'infertilità femminile: in donne di età non superiore ai 45 anni con valori di FSH, al 3° giorno del ciclo, non superiori a 30 mUI/ml • trattamento dell'infertilità maschile: in maschi con ipogonadismo-ipogonadotropo con livelli di gonadotropine bassi o normali e comunque con FSH non superiore a 8 mUI/ml • preservazione della fertilità femminile: in donne di età non superiore ai 45 anni affette da patologie neoplastiche che debbano sottoporsi a terapie oncologiche in grado di causare sterilità transitoria o permanente. - Corifollitropina alfa - Coriogonadotropina alfa - Follitropina alfa - Follitropina beta - Menotropina - Urofollitropina

Terapie Eziologiche – Ipogonadismo

29-8-2016 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA *Serie generale* - n. **201**

Nell'uomo l'uso delle gonadotropine ha un fondamento razionale nella terapia sostitutiva dell'ipogonadismo ipogonadotropo, dove il deficit di gonadotropine è il responsabile dell'assenza di spermatogenesi e la somministrazione di preparati ad azione LH e FSH-simile avvia la maturazione tubulare e porta alla comparsa di spermatozoi nell'eiaculato.

Nell'uomo l'efficacia dell'utilizzo delle gonadotropine come terapia sostitutiva dell'ipogonadismo ipogonadotropo, sia primitivo che secondario, è ampiamente riconosciuta (3). Il ruolo delle gonadotropine nell'infertilità maschile idiopatica è invece ancora dibattuto in letteratura e i differenti studi condotti in merito non offrono sufficienti ed inequivocabili evidenze di un miglioramento significativo della percentuale di fecondazione e di gravidanze e dei parametri nemaspermici convenzionali nei pazienti trattati con differenti formulazioni di FSH. Sebbene una recente revisione della Cochrane sull'impiego delle gonadotropine nell'infertilità maschile idiopatica abbia mostrato una differenza statisticamente significativa nella percentuale globale di gravidanze per coppia a favore del gruppo in trattamento con gonadotropine con un 16% di gravidanze nel gruppo trattato rispetto al 7% nel gruppo di controllo (4), le più recenti linee guida europee non consigliano il trattamento con gonadotropine nell'infertilità maschile idiopatica.

Le gonadotropine sono una famiglia di ormoni di origine ipofisaria che esercitano un effetto stimolante sulle gonadi maschili e femminili e includono l'ormone follicolo-stimolante (FSH), l'ormone luteinizzante (LH) e la gonadotropina corionica (HCG). Le gonadotropine utilizzate a scopo farmacologico si possono ottenere per estrazione da urina umana o mediante tecnologia del DNA ricombinante, prodotte tramite transfezione della linea cellulare ovarica di criceto cinese con plasmidi contenenti le due sub unità geniche che codificano per l'FSH. Recentemente è stata messa a punto una nuova forma di FSH ricombinante, la coriofollitropina alfa, che presenta una lunga durata di azione e richiede quindi una sola somministrazione invece delle somministrazioni giornaliere degli altri tipi d FSH.

sivo di 12.600 UI/paziente diviso in due o più cicli non superando comunque il dosaggio massimo di 6.300 UI/ciclo nella donna. Nell'infertilità maschile si suggerisce di non superare il dosaggio massimo, per singola prescrizione, di 150 UI di FSH 3 volte alla settimana per 4 mesi. Se dopo

Nell'uomo, la somministrazione di gonadotropine provoca ginecomastia, dolore al seno, mastite, nausea, anormalità delle frazioni lipoproteiche, aumento nel sangue degli enzimi epatici, eritrocitosi

Terapie Eziologiche – Ipogonadismo

The treatment of hypogonadism in men of reproductive age

Edward D. Kim, M.D.,[a] Lindsey Crosnoe, B.S.,[a] Natan Bar-Chama, M.D.,[b] Mohit Khera, M.D.,[c] and Larry I. Lipshultz, M.D.[c]

Recovery of Spermatogenesis after Exogenous T Use

Rates of success in recovering spermatogenesis after use of exogenous T are generally quite favorable. The first strategy

For those hypogonadal men who desire to protect their future fertility, exogenous T should be discouraged.

strated in the contraceptive trials, cessation of T therapy may result in the restoration of baseline serum T levels.

Fertility and Sterility® Vol. 99, No. 3, March 1, 2013

Title: Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline

Short Title: Guidelines for Testosterone Therapy in Men

Authors: Shalender Bhasin (chair), Juan P Brito, Glenn R. Cunningham, Frances J. Hayes, Howard N. Hodis, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, Hubert W. Vesper, Frederick C. Wu, Maria A. Yialamas (The authors are listed in alphabetical order)

Affiliations: (To be Completed by Staff)

Cosponsoring Associations: (Co-sponsors to be Added Once Confirmed).

Fertility and Sterility® Vol. 94, No. 6, November 2010

Anabolic steroids purchased on the Internet as a cause of prolonged hypogonadotropic hypogonadism

Ilenia Pirola, M.D.,[a] Carlo Cappelli, M.D.,[a] Andrea Delbarba, M.D.,[a] Tiziano Scalvini, M.D.,[a] Barbara Agosti, M.D.,[a] Deodato Assanelli, M.D.,[a] Antonio Bonetti, M.D.,[b] and Maurizio Castellano, M.D.[a]

Objective: To report a case of hypogonadotropic hypogonadism due to the chronic abuse of anabolic steroids purchased over the Internet.
Design: Case report.
Setting: Endocrinology unit of the University of Brescia.
Patient(s): A 34-year-old man.
Intervention(s): A single dose (100 μg) of triptorelin (triptorelin test).
Main Outcome Measure(s): Clinical symptoms, androgen normalization, levels of serum testosterone, follicle-stimulating hormone, and luteinizing hormone.
Result(s): Within 1 month, the patient's serum testosterone was in the normal range, and he reported a return to normal energy and libido.
Conclusion(s): The World Anti-Doping Code has proved to be a very powerful and effective tool in the harmonization of antidoping efforts worldwide, but it is insufficient to combat this illegal phenomenon. To tackle the serious side effects caused by doping we believe that it is necessary to increase monitoring and adopt severe sanctions, particularly with regard to Internet sites. (Fertil Steril® 2010;94:2331.e1–e3. ©2010 by American Society for

Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy

Taylor P. Kohn, M.Phil.,[a] Matthew R. Louis, B.S.,[a] Stephen M. Pickett, B.B.A.,[b] Mark C. Lindgren, M.D.,[c] Jaden R. Kohn, B.S.,[a] Alexander W. Pastuszak, M.D. Ph.D.,[d,e] and Larry I. Lipshultz, M.D.[d,e]

Conclusion(s): Increasing age and duration of T use significantly reduce the likelihood of recovery of sperm in the ejaculate, based on a criterion of a TMC of 5 million sperm, at 6 and 12 months. Physicians should be cautious in pursuing long-term T therapy, particularly in men who still desire fertility. Using these findings, physicians can counsel men regarding the likelihood of recovery of sperm at 6 and 12 months. (Fertil Steril® 2017;107:351–7. ©2016 by American Society for Reproductive Medicine.)

J Abram McBride, Robert M Coward

Asian Journal of Andrology (2016) 18, 373–380

Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use

Table 2: Commonly used pharmacologic agents for maintenance or restoration of spermatogenesis after anabolic-androgenic steroid or exogenous testosterone use

Medication	*Maintenance dose*	*Restoration dose*	*Combination therapy*	*Dosing considerations*
Gonadotropin analogs				
hCG	500–2500 IU 2x/wk[57] 500 IU every other day[58]	3000 IU every other day[59] 10 000 IU 3x/wk[52] 1000–3000 IU 3x/wk[34]	Yes, with FSH[57,59,62] SERM[59,60] AI[59]	Titrate dose based upon response of testosterone levels
Recombinant FSH	-	75 IU daily[62] 150 IU 3x/wk[57] 75–150 IU 3x/wk[59]	Yes, with hCG	Typically initiate with or add to hCG regimen and titrate dose every 3 months based upon semen analysis
SERM				
Clomiphene citrate	25 mg daily or 50 mg every other day *Note no data exist to support this indication*	50 mg 3x/wk[80] 25–50 mg every other day[59,60] 100 mg daily[78,79]	Yes, with hCG[59]	Titrate dose based upon response of testosterone levels Monitor semen parameters
Enclomiphene	12.5–25 mg daily[84]	25 mg daily[82]	-	Phase III data and FDA approval pending
AI				
Anastrozole	-	1 mg daily[59,86–88]	Yes, with hCG[59]	Useful as an adjunctive therapy in scenarios of T: E <10:1
Letrozole	-	2.5 mg daily[89]	-	Beware of possible hepatotoxicity and pulmonary embolism risk

Terapie Eziologiche – Ipogonadismo

Selective Estrogen Receptor Modulators: Clomiphene Citrate

Common dosing starts at 25 mg orally every other day with upward titration to 50 mg daily, as needed. It is not as effective in increasing serum T levels when LH and FSH levels are already elevated, as seen in primary testis failure.

Es. : Clomid (50 mg compresse), (Serofene, Omifin)

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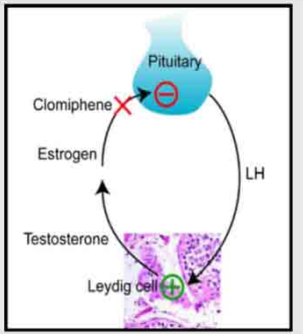


Clomiphene citrate (CC) works by blocking estrogen (E) at the pituitary. The pituitary sees less E, and makes more LH. More LH means that the Leydig cells in the testis make more T. (Adapted from Craig Neiderberger, M.D. http://urol.uic.edu/dept/niederberger.php and used with permission.)

Kim. Hypogonadism therapy in reproductive age men. Fertil Steril 2013.

Human Chorionic Gonadotropin

For men with hypogonadotropic hypogonadism from anabolic steroid abuse, administration of IM injections two to three times per week at doses of 2,000–3,000 units for 4 months can initiate spermatogenesis (25).

Es. : Gonasi Hp (1000-10000), Pregnyl (5000)

The effect of clomiphene citrate on serum hormone profiles.

	Baseline, mean (±SD)	After treatment, mean (±SD)	*P* value
Total T (ng/dL)	192 (87)	485 (165)	<.01
Free T (pg/mL)	22 (16)	95 (35)	<.01
SHBG (nM/L)	30 (12)	32 (15)	.72
E_2 (pg/mL)	26 (22)	39 (19)	<.05
LH (IU/mL)	2.6 (2.2)	6.8 (2.9)	<.01
FSH (IU/mL)	1.9 (1.7)	7.6 (1.9)	<.01

Note: Adapted from Katz DJ et al. British Journal of Urology 2012;110:573–8. SHBG = sex hormone-binding globulin.

Kim. Hypogonadism therapy in reproductive age men. Fertil Steril 2013.

Terapie Eziologiche – Ipogonadismo

If at all possible, exogenous T use should be avoided in men desiring future fertility given the potential for long-term effects on spermatogenesis. Clomiphene citrate, an oral selective ER modulator, is an off-label, but safe and effective therapy for men who desire to maintain future potential fertility. Although less frequently used in the general population, hCG therapy with or without T supplementation represents an alternative treatment. At present, routine use of aromatase inhibitors is not recommended based on a lack of long-term data.

Fertility and Sterility® Vol. 99, No. 3, March 1, 2013

Terapie Eziologiche – Disordini dell'eiaculazione

The management of retrograde ejaculation: a systematic review and update

Amanda Jefferys, B.M., B.S., Dimitrios Siassakos, M.Sc., and Peter Wardle, M.D.

Medical Management

Six studies used sympathomimetic medications, 4 studies employed anticholinergics, 2 used a combination of sympathomimetics and anticholinergics, and 1 study used a combination of acupuncture and traditional Chinese medicines.

Urinary Sperm Retrieval

There are three different methods: centrifugation and resuspension of postejaculatory urine specimens, the Hotchkiss (7) or modified Hotchkiss technique, and ejaculation on a full bladder (Tables 1 and 2).

Fertility and Sterility® Vol. 97, No. 2, February 2012

Terapie Eziologiche – Disordini dell'eiaculazione

Management of ejaculatory disorders in infertile men

Yagil Barazani[1], Peter J Stahl[2], Harris M Nagler[1] and Doron S Stember[1]

ANEJACULATION (AE)

AE is a relatively rare condition but represents an important causative factor of male subfertility. The causes of AE can be categorized as organic, pharmacological and psychogenic. Any disease, surgical procedure, or trauma that interferes with the afferent or efferent innervation of the seminal vesicles, vasa deferentia, bladder neck, or posterior urethra can potentially result in AE. Organic etiologies of AE include diabetes mellitus (DM), spinal cord injury (SCI), transverse myelitis, multiple sclerosis and surgical injury of the autonomic nervous system.[8]

In addition to the medical and surgical causes of ejaculatory dysfunction, a number of medications have been shown to interfere with ejaculation. At the forefront are psychotropic drugs, which have some of the highest reported rates of associated sexual dysfunction.

Asian Journal of Andrology (2012) 14, 525–529

Terapie Eziologiche – Disordini dell'eiaculazione

- ***Imipramina***
  Es. : Tofranil
  25 mg per 4 giorni, seguito da 50 mg al giorno
- ***Midodrina***
  Es. : Gutron, Rodom
  7,5 (tre cp da 2,5 mg) al giorno, aumentando di 2,5 mg a settimana fino a raggiungere la dose di 15 mg al giorno

Midodrine for treating of organic anejaculation
MR Safarinejad
International Journal of Impotence Research (2009) **21**, 213–220

- ***Pseudoefedrina ed Efedrina***
  In Italia solo in formulazioni combinate per riniti e patologie ORL

OFF-LABEL

Asian Journal of Andrology (2012) **14**, 525–529

Sine causa

- Nel 30% dei pazienti la OAT (OligoAstenoTeratozoospermia) non è riconducibile ad alcuna causa organica al momento evidenziabile.
- L'infertilità maschile idiopatica rappresenta una sfida per il clinico, poichè molte delle terapie disponibili producono solo parziali benefici, o addirittura nessuno.
- La difficoltà di trattamento è spesso fonte di frustrazione sia per il clinico quanto per il paziente.

A. J. Hamada *et al.*
Male infertility: a critical review of pharmacologic management
Expert Opin. Pharmacother. (2012) **13**(17)

Fertility: assessment and treatment for people with fertility problems

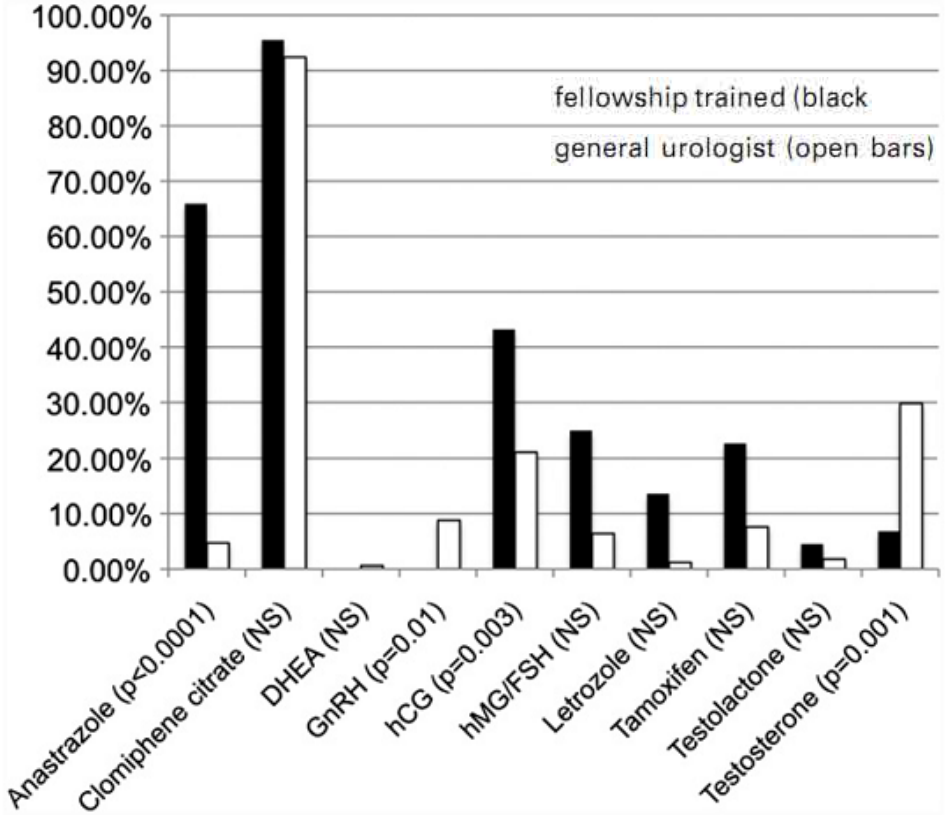
NHS Evidence
accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

Royal College of Obstetricians and Gynaecologists
Bringing to life the best in women's health care

Empirical Medical Therapy for Idiopathic Male Infertility: A Survey of the American Urological Association

Vol. 187, 973-978, March 2012
THE JOURNAL OF UROLOGY®

Edmund Y. Ko, Kashif Siddiqi, Robert E. Brannigan and Edmund S. Sabanegh, Jr.*



Terapie Eziologiche – Ipogonadismo

Curr Urol Rep (2016) 17: 56
DOI 10.1007/s11934-016-0612-4

MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Hormone-Based Treatments in Subfertile Males

Darshan P. Patel[1] · Jason C. Chandrapal[1] · James M. Hotaling[1]

There is variable evidence for the use of hormone-based therapies for specific and nonspecific infertility diagnoses in men. Although there is potential for some treatments, specific diagnostic indications, safe and effective dosing, and improvement in semen analysis parameters or pregnancy rates are unknown or inconsistent. Of specific interest is the role of hormone based therapies in subtle alterations in the androgenic axis and impact on fertility. Large, multi-centered randomized controlled trials with consistent inclusion and exclusion criteria are needed to evaluate safety and efficacy of hormone-based therapies for male infertility.

Sine causa – Altri farmaci

Pic Source: http://homeimprovementbasics.com/

Use of recombinant human follicle-stimulating hormone in the treatment of male factor infertility

Fertil Steril® 2002;77:238–44.

Seminal parameters evaluated before and after treatment at different doses of r-hFSH.

	Nontreated patients (n = 15)		Treated patients r-hFSH 50 IU (n = 15)		Treated patients r-hFSH 100 IU (n = 15)	
	Basal	After 3 months	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Spermatozoa ($\times 10^6$/mL)	4.3 ± 2.1	5.6 ± 2.9	3.7 ± 1.8	5.8 ± 2.6	5.1 ± 2.2	9.6 ± 3.6[a]
Normal morphology (%)	35.6 ± 8.8	36.8 ± 10.3	34.2 ± 10.1	33.5 ± 9.3	37.8 ± 9.4	43.2 ± 7.4
Forward motility (%)	28.6 ± 6.7	27.6 ± 8.5	30.4 ± 7.5	32.2 ± 9.6	35.5 ± 11.6	37.2 ± 8.8

[a] $P<.05$ vs. pretreatment.

Conclusion(s): The findings of this study demonstrate that r-hFSH at a dose of 100 IU, as previously seen with highly purified FSH, increases the spermatogonial population and sperm production in idiopathic patients with oligozoospermia with normal FSH and inhibin B plasma levels and a cytological picture of

Sine causa – FSH in normogonadici

Table 1 | Effects of FSH treatment on conventional sperm parameters

Study	Cohort	FSH intervention	Outcomes
Acosta *et al.*[39] (1992)	*n*=24 men with OAT who had prior IVF failure versus 26 men with OAT who had not had prior IVF attempts	pFSH (150 IU three times per week for 3 months)	No significant change in sperm concentration, motility and morphology in both groups
Bartoov *et al.*[47] (1994)	*n*=31 men with teratozoospermia	pFSH (75 IU daily for 1 month)	No significant change in sperm concentration, motility and morphology
Iacono *et al.*[32] (1996)	*n*=33 men with idiopoathic oligozoospermia versus 28 men with testicular conditions*	pFSH (150 IU three times per week for 3 months) for low-dose group (*n*=17) and controls; pFSH (150 IU daily for 3 months) for high-dose group (*n*=16)	Significant improvement in sperm motility ($P<0.0001$) and morphology ($P<0.007$) in high-dose group
Baccetti *et al.*[31] (1997)	*n*=81 men idiopathic infertility	pFSH (150 IU three times per week for 3 months) for test group (*n*=66); saline for placebo group (*n*=15)	No significant change in sperm concentration, motility and morphology
Strehler *et al.*[58] (1997)	*n*=46 men with OAT	hpFSH (150 IU three times per week for 3 months)	Significant improvement in sperm morphology ($P<0.001$)
Kamischke *et al.*[43] (1998)	*n*=67 men with OAT	pFSH (150 IU three times per week for 3 months) and saccharose (30 mg three times per week for 3 months) for test group (*n*=34); saccharose (30 mg three times per week for 3 months) for control group (*n*=33)	Slight improvement in progressive sperm motility in saccarose-only group ($P>0.05$)
Radicioni *et al.*[53] (1999)	*n*=20 young adults (15–20 years old) with left-sided varicocele	hpFSH (150 IU three times per week for 3 months)	Significant improvement in sperm concentration, progressive motility and morphology ($P<0.05$)
Dimfeld *et al.*[52] (2000)	*n*=76 infertile men with OAT versus 102 matched controls	pFSH (75 IU daily for 3 months) for treatment group; no treatment for controls	Significant increase in sperm motility ($P<0.05$)
Foresta *et al.*[33] (1998)	*n*=90 men with oligozoospermia	pFSH (75 IU three times per week for 3 months) for test group (*n*=60); saline for placebo group (*n*=30)	Increase in spermatogonial population and sperm concentration in responding patients (*n*=20; $P<0.01$)

Nat. Rev. Urol. **10**, 55–62 (2013)

Gonadotrophins for idiopathic male factor subfertility (Review)

Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD005071.

Attia AM, Abou-Setta AM, Al-Inany HG

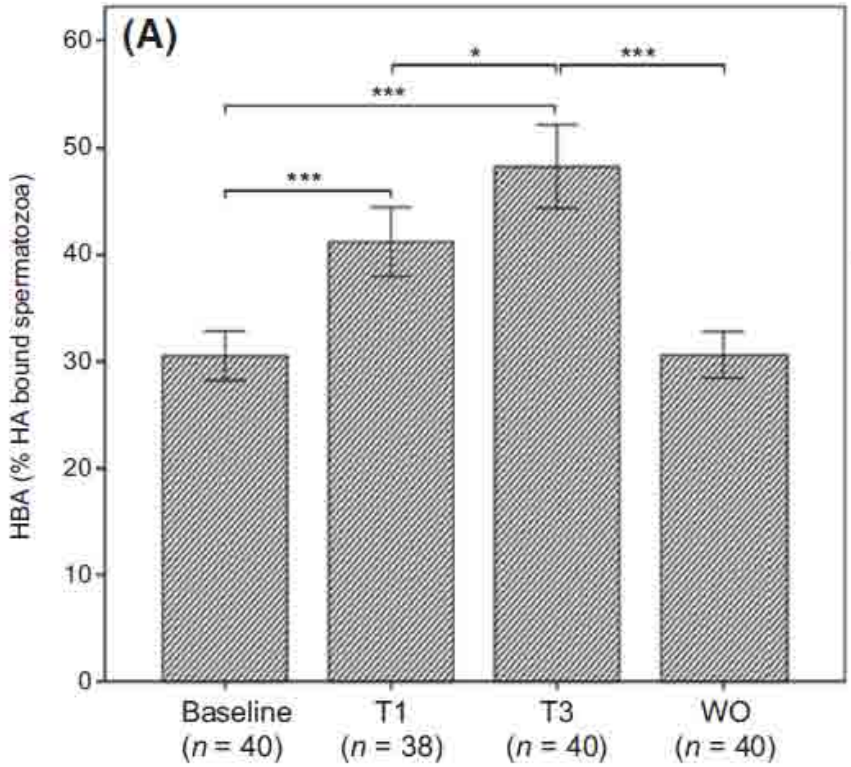
Encouraging preliminary data suggest a beneficial effect on live birth and pregnancy of gonadotrophin treatment formen with idiopathic male factor subfertility, but because the numbers of trials and participants are small, evidence is insufficient to allow final conclusions.

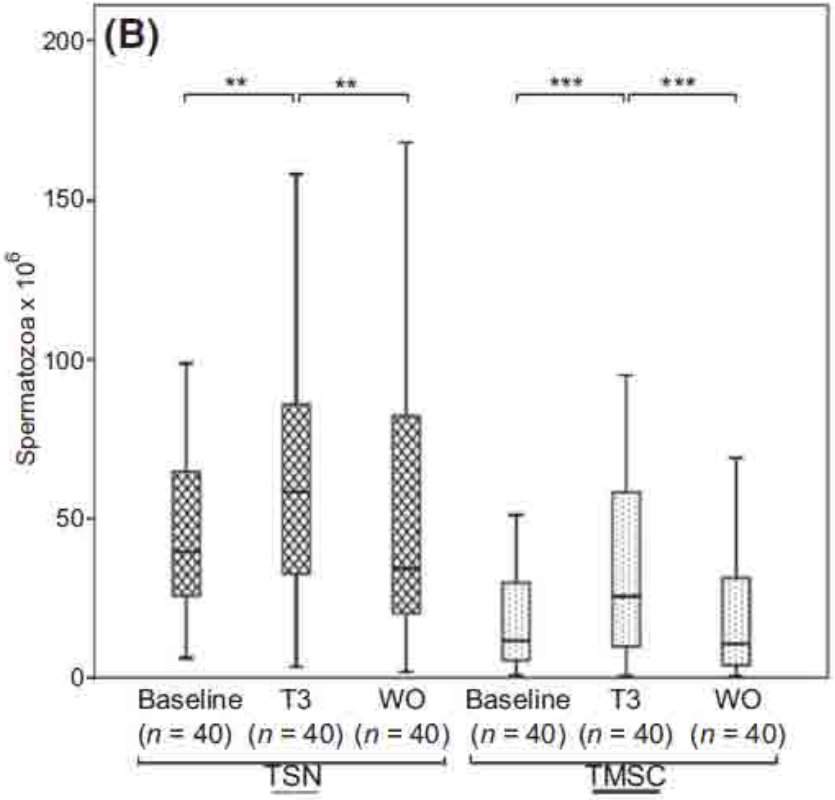
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo/no treatment for the treatment of idiopathic male subfertility	Gonadotrophins			
Live birth rate per couple randomly assigned	0 per 1000	0 per 1000 (0 to 0)	OR 9.31 (1.17 to 73.75)	30 (1 study)	⊕◯◯◯ very low[1,2]
Spontaneous pregnancy rate per couple randomly assigned	14 per 1000	67 per 1000 (30 to 142)	OR 4.94 (2.13 to 11.44)	412 (5 studies)	⊕⊕⊕◯ moderate[3]

Short-term FSH treatment and sperm maturation: a prospective study in idiopathic infertile men

[1]E. Casamonti, [1]S. Vinci, [1]E. Serra, [1]M. G. Fino, [1]S. Brilli, [1]F. Lotti, [1]M. Maggi, [2]M. E. Coccia, [1]G. Forti and [1]C. Krausz

Andrology, 2017, 5, 414–422





FSH treatment in infertile males candidate to assisted reproduction improved sperm DNA fragmentation and pregnancy rate

Andrea Garolla[1] · Marco Ghezzi[1] · Ilaria Cosci[1] · Barbara Sartini[1] · Alberto Bottacin[1] · Bruno Engl[2] · Andrea Di Nisio[1] · Carlo Foresta[1]

Endocrine (2017) 56:416–425

In this observational study, we showed that follicle-stimulating hormone treatment improves sperm DNA fragmentation, which in turn leads to increased pregnancy rates in infertile males undergoing in-vitro fertilization. In particular, double strand breaks (measured with γH2AX test) emerged as the most sensible parameter to follicle-stimulating hormone treatment in predicting reproductive outcome.

Patients characteristics	Treated patients (Cases $n = 84$)	
	T0	T1
Semen volume, mL	2.9 ± 1.8	2.9 ± 1.5
Sperm concentration, $\times 10^6$/mL	3.4 ± 2.8	7.5 ± 5.5^a
Sperm count, $\times 10^6$	8.5 ± 7.5	19.9 ± 16.1^a
Progressive motility, %	19.8 ± 13.1	26.0 ± 14.4^a
Normal morphology, %	6.9 ± 4.9	7.9 ± 4.5
Sperm aneuploidies, %	2.3 ± 1.1	2.0 ± 1.1
Acridine Orange, %	31.4 ± 6.0	25.3 ± 6.1
TUNEL, %	26.7 ± 7.9	23.4 ± 7.4^a
γH2AX, %	17.8 ± 4.7	14.9 ± 2.1^a
MFI γH2AX, *n*	470.3 ± 192.1	382.7 ± 191.8^b

Sine causa – Altri farmaci

Nome

- Inibitori dell'aromatasi

Razionale

- Presenza in uomini infertili di un'eccessiva attività aromatasica.

Efficacia

- I dati al momento presenti in letteratura incoraggiano quest'opzione terapeutica.

Sine causa – Inibitori dell'aromatasi

Aromatase inhibitors for male infertility

OFF-LABEL

Peter N. Schlegel, M.D.

Men with impaired sperm concentration appear to commonly have excess aromatase activity, reflected by relatively increased serum T/E ratio, especially in men with nonobstructive azoospermia.

Treatment of infertile men with low serum testosterone levels using aromatase inhibitors is rational, and has been associated with improved semen parameters as well as increased total serum testosterone levels as well as suppressed estradiol.

Letrozolo

Es. Calantha, Femara, Letrix

2,5 mg al giorno per 4-6 mesi

Anastrozolo

Es. Arimidex, Eristrol, Extroplex, Ibistrazolo, Iniben, Keyfen, Renazole

1 mg al giorno per 4-6 mesi

Fertility and Sterility® Vol. 98, No. 6, December 2012

Aromatase inhibitors in the treatment of oligozoospermic or azoospermic men: a systematic review of randomized controlled trials

JBRA Assisted Reproduction 2016;**20**(2):82-88 Mariana A. Ribeiro

Table 2. Study characteristics related to number of participants, inclusion and exclusion criteria, type of interventions, type of outcomes, and follow-up.

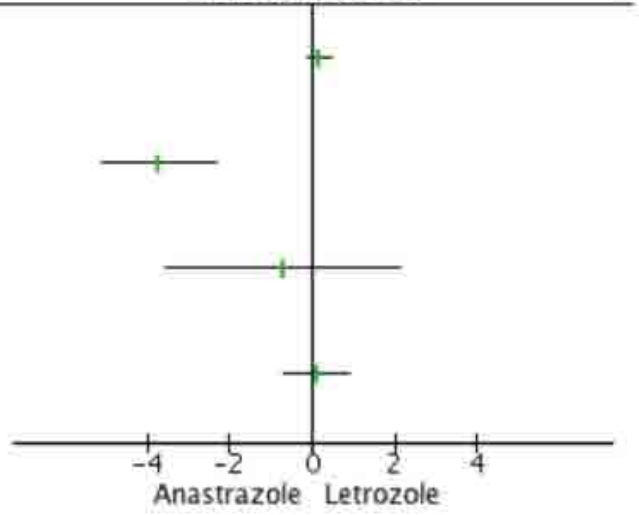
	Author, year		
	Clark & Sherins, 1989	**Gregoriou *et al.*, 2012**	**Cavallini, 2013**
Location	Atlanta, USA	Athens, Greece	Andros, Italy
No. participants	25	29	46
Inclusion criteria	Men that were partners in infertile marriages in which there was failure to conceive for at least two years prior to consideration of entry into the protocol	Men with low T/E2 ratio (<10)	Non-smoker non- obstructive azoospermic (NOA) patients who yielded no spermatozoa with fine needle and cryptozoospermic patients with T/E2 ratio < 10

Aromatase inhibitors in the treatment of oligozoospermic or azoospermic men: a systematic review of randomized controlled trials

JBRA Assisted Reproduction 2016;**20**(2):82-88 Mariana A. Ribeiro

Figure 5. Representation of meta-analysis with a single study comparing letrozole versus anastrozole with regards sperm quality at six months

Study or Subgroup	Letrozole Mean	SD	Total	Anastrazole Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.3.7 Ejaculate volume (mL)							
Gregoriou 2012	3.35	0.2	15	3.18	0.52	14	0.17 [-0.12, 0.46]
2.3.8 Sperm count ($x10^6$)							
Gregoriou 2012	5.19	1.62	15	8.9	2.11	14	-3.71 [-5.09, -2.33]
2.3.9 Motility (%)							
Gregoriou 2012	22.13	4.37	15	22.85	3.38	14	-0.72 [-3.55, 2.11]
2.3.10 TFSF (total sperm count ($x10^6$) by motility (%) and by morphology (%)							
Gregoriou 2012	2.51	1.09	15	2.41	1.06	14	0.10 [-0.68, 0.88]



Outcomes of anastrozole in oligozoospermic hypoandrogenic subfertile men

Fertility and Sterility® Vol. 107, No. 3, March 2017

Ohad Shoshany, M.D.,[a] Nikita Abhyankar, M.D.,[a] Naem Mufarreh, M.S.,[b] Garvey Daniel, M.D.,[a]

Patient(s): The study group consisted of 86 subfertile hypoandrogenic men with low T/estradiol (E_2) ratio (n = 78) or a prior aversive reaction to clomiphene citrate (n = 8).

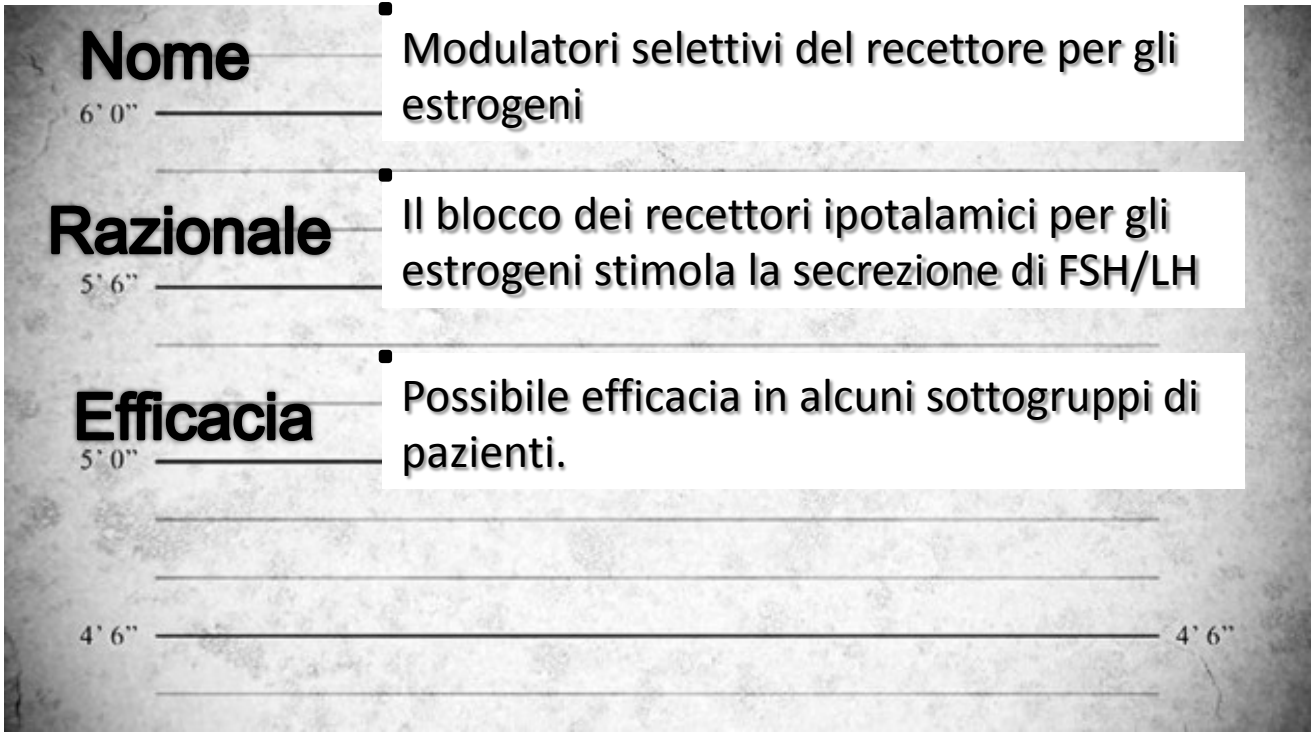
Intervention(s): All patients were treated with 1 mg anastrozole daily, administered orally.

Semen parameters in 21 men with hypoandrogenism and oligozoospermia treated with anastrozole.

	Baseline		At 4 mo		
Parameter	**Mean ± SE**	**Median (IQR)**	**Mean ± SE**	**Median (IQR)**	***P* value**
Volume (mL)	2.56 ± 0.22	2.5 (1.7–3.3)	2.32 ± 0.25	2.2 (1.6–3)	NS
Concentration (×10^6/mL)	4.7 ± 1.2	2 (1.5–7.3)	13.1 ± 2.9	7 (4.4–19.5)	.001
Motility (%)	39.9 ± 5	41.5 (24–55)	40.5 ± 4.8	38.5 (29–54)	NS
Total motile count (×10^6)	4.6 ± 1.3	2.8 (0.7–6.6)	8 ± 3.4	8.1 (3.3–12.1)	< .01

Parameter	**Baseline**	**At 3 wk**	**At 4 mo**	***P* value**
Total T (ng/dL)	258.4 ± 10.8	509.2 ± 20.4	449.9 ± 19.5	< .000
Bioavailable T (ng/dL)	128.8 ± 4.7	297.5 ± 12.7	N/A	< .000
E_2 (pg/mL)	40.8 ± 1.9	24.6 ± 2.1	23.2 ± 2.2	< .000
T/E_2 ratio	6.98 ± 0.33	34.5 ± 6.5	24.2 ± 3	< .000
SHBG (nmol/L)	25.6 ± 1.1	24.9 ± 1.2	N/A	NS
LH (IU/L)	6.41 ± 0.89	10.7 ± 1.1	N/A	< .000
FSH (IU/L)	12.4 ± 2	19.4 ± 2.3	N/A	< .000

Sine causa – Altri farmaci



"Cherchez La Femme": Modulation of Estrogen Receptor Function With Selective Modulators: Clinical Implications in the Field of Urology

Sevann Helo, MD,[1] Blake Wynia, MD,[1] and Andrew McCullough, MD[2]

Sex Med Rev 2017;5:365–386

Results: Few prospective rigorously controlled trials have been undertaken on the use of SERMs in men. Most existing trials are largely retrospective anecdotal studies with inconsistent inclusion and end-point measurements. The SERMs are complex and at times can produce paradoxical results. Their action likely depends on the genetics of the individual, his tissue-specific composition of estrogen receptors, the molecular structure and pharmacodynamics of the SERMs, and their metabolism.

Conclusion: Rigorously controlled trials of the use of SERMs in men are needed to better identify their clinical benefit and long-term safety in infertile and hypogonadal men. Recent placebo-controlled pharmaceutical industry SERM trials have demonstrated short-term safety and efficacy in men with secondary hypogonadism and eventually might provide an alternative to exogenous testosterone replacement therapy in men with secondary hypogonadism. **Helo S, Wynia B, McCullough A. "Cherchez La Femme": Modulation of**

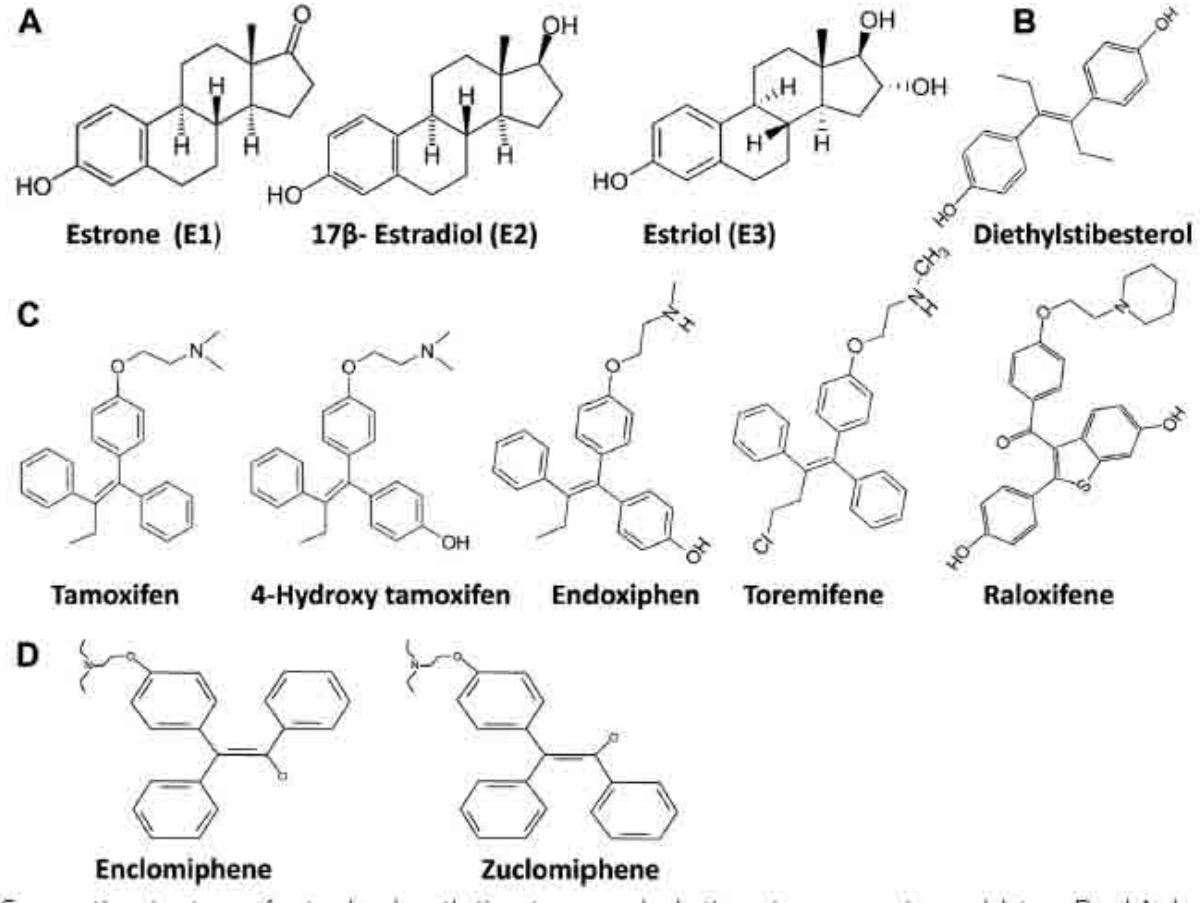


Figure 3. Comparative structures of natural and synthetic estrogen and selective estrogen receptor modulators. Panel A shows naturally occurring estrogens. Panel B shows the synthetic estrogen diethylstilbestrol. Panel C shows selective estrogen receptor modulators. Panel D shows cis- and trans-stereoisomers of clomiphene citrate (enclomiphene and zuclomiphene).

Sine causa – Selective Estrogen Receptor Modulators

Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis

Andrology, 2013, 1, 749–757

OFF-LABEL

Tamoxifene

Es. : Kessar, Nolvadex, Nomafen, Tamoxene, tamoxifene 10-20 mg cp

20 mg al giorno per 3-6 mesi

[1,2]M. E. Chua, [3]K. G. Escusa, [1]S. Luna, [3]L. C. Tapia, [4,5]B. Dofitas and [1,6]M. [illegible]

In summary, oestrogen antagonists with a good safety profile seem to be effective as empiric medical therapy in a subset of idiopathic infertile males. The authors suggest the use of Clomiphene citrate 50 mg or Tamoxifen citrate 20–30 mg daily for 3–6 months not reaching 12 months. If no consequential pregnancy occurred after the proposed treatment period, it could then become an indication to proceed with ART.

Expert Opin Pharmacother. 2016 August ; 17(11): 1561–1567. doi:10.1080/14656566.2016.1204294.

Enclomiphene Citrate for the Treatment of Secondary Male Hypogonadism

Katherine M. Rodriguez[1], **Alexander W. Pastuszak**[2,3], and **Larry I. Lipshultz**[2,3]

[1]Baylor College of Medicine, Houston, TX

[2]Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX

[3]Scott Department of Urology, Baylor College of Medicine, Houston, TX

Abstract

Introduction—Hypogonadism is a growing concern in an aging male population. Historically treated using exogenous testosterone, concerns about possible adverse effects of testosterone have led physicians to seek alternative treatment approaches.

Areas Covered—Enclomiphene citrate is the *trans* isomer of clomiphene citrate, a non-steroidal estrogen receptor antagonist that is FDA-approved for the treatment of ovarian dysfunction in women. Clomiphene citrate has also been used off-label for many years to treat secondary male hypogonadism, particularly in the setting of male infertility. Here we review the literature examining the efficacy and safety of enclomiphene citrate in the setting of androgen deficiency.

Expert Opinion—Initial results support the conclusion that enclomiphene citrate increases serum testosterone levels by raising luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, without negatively impacting semen parameters. The ability to treat testosterone deficiency in men while maintaining fertility supports a role for enclomiphene citrate in the treatment of men in whom testosterone therapy is not a suitable option.

Terapia non ormonale

Conservative Nonhormonal Options for the Treatment of Male Infertility: Antibiotics, Anti-Inflammatory Drugs, and Antioxidants

BioMed Research International
Volume 2017, Article ID 4650182, 17 pages

Aldo E. Calogero,[1] Rosita A. Condorelli,[1] Giorgio Ivan Russo,[2] and Sandro La Vignera[1]

TABLE 2: List of all available treatments.

Antibiotics	Quinolones, trimethoprim, tetracyclines, macrolides, β-lactam antibiotics
NSAIDs	Salicylates, profens, sulfonanilides
Steroidal anti-inflammatory drugs	Docosanoic acid (DHA), eicosanoid acid (EPA)
Fibrinolytic treatment	Serratiopeptidase, bromelain, escin
Antioxidants	Superoxide dismutases, catalase, glutathione peroxidase, glutathione, N-acetyl-cysteine, vitamin A, vitamin C (ascorbic acid), vitamin E, coenzyme Q10, carnitine, myoinositol, lycopene, astaxanthin, *Serenoa repens*
Micronutrients	Selenium, zinc, copper

Terapia non ormonale

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Aldo E. Calogero,[1] Rosita A. Condorelli,[1] Giorgio Ivan Russo,[2] and Sandro La Vignera[1]

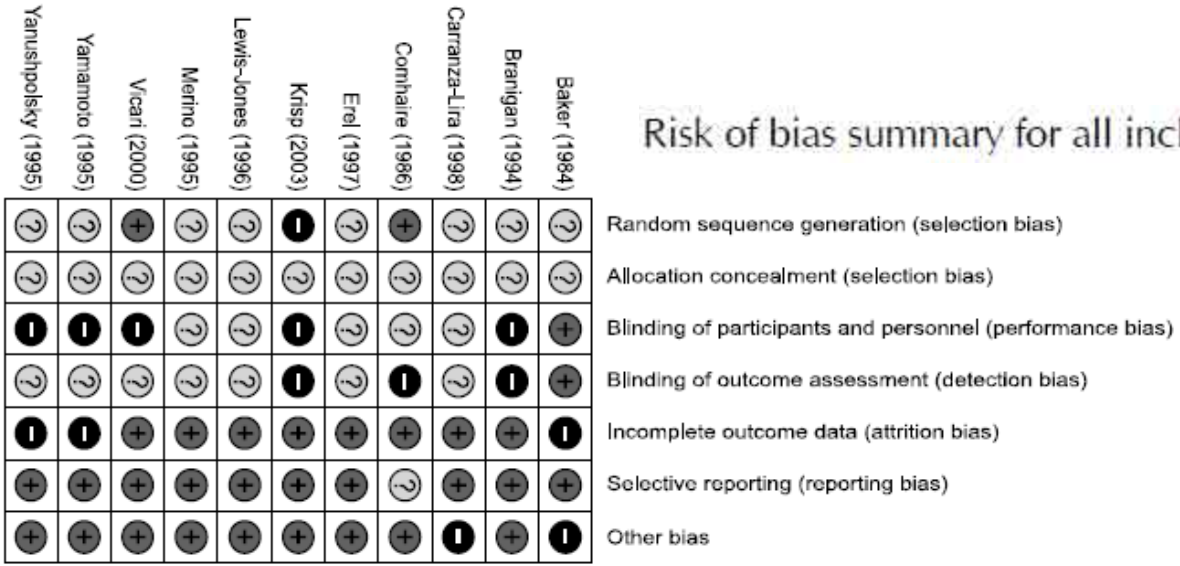
TABLE 3: Other antioxidants.

Amino acids	Arginine, taurine, ornithine, citrulline
Vitamins	Vitamins of group B complex, niacin (vitamin PP), pantothenic Acid, folic acid
Omega-3 fatty acids	Docosanoic acid (DHA), eicosanoid acid (EPA)
Others	Magnesium, flavonoid, *Curcuma longa*, *Camellia sinensis*, *Urtica dioica*, *Lepidium meyenii* Walp., Muira Puama(*Ptychopetalum olacoides* Benth), *Ginkgo biloba*, *Scutellaria baicalensis*, *Georgi radix*, *Pinus massoniana*, *Cucurbita maxima*, *Aesculus hippocastanum*, *Crocus sativus*, *Epilobium* (*angustifolium* and *parviflorum*), *Citrus bergamia*, *Orthosiphon*, etc.

Jae Hung Jung

World J Mens Health 2016 December 34(3): 165-172

Treatment of Leukocytospermia in Male Infertility: A Systematic Review



The present review reveals that antibiotics might improve sperm parameters, the rate of resolution of leukocytospermia, the bacteriologic cure rate, and even the pregnancy rate, although some reports conflict. Antioxidants might also have clinical benefits for sperm function as shown by *in vitro studies.* However, the data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia are effective or not.

On-label and off-label drugs used in the treatment of male infertility

Fertil Steril® 2015;103:595–604

Mahmoud Chehab, M.D., Alosh Mada

Drug	Mechanism of action	Excretion; half life	FDA indication	Main side effects	Pertinent drug interactions	FDA (pregnancy) category	Contraindications
CC; clomid	Nonsteroidal estrogen agonist/antagonist. Disrupts negative feedback of estrogen on the hypothalamus and pituitary	Feces via biliary tract; 5 d	Female infertility, ovulation induction	Headache, nausea, visual disturbances, dizziness, abdominal discomfort, mouth sores, cataract formation	None known	Human teratogen; X	Pregnancy, liver disease, uncontrolled thyroid or adrenal dysfunction, presence of an organic intracranial lesion (e.g., pituitary tumor)
AI; femara, letrozole, anastrozole	Down-regulate production of estrogen by reversibly inhibiting cytochrome P450 isoenzymes CYP19 and 2C19 of the aromatase enzyme complex	Renal; 2 d	Breast cancer, female infertility	Loss of libido, cutaneous rash, osteoporosis, hypercholesterolemia, fatigue, dizziness, drowsiness	Tamoxifen coadministration reduces letrozole plasma level by 78%	Human teratogen; X	Pregnant females
Androgens, testosterone T undecanoate	Responsible for promoting the growth and development of the male sex organs and maintaining secondary sex characteristics in androgen-deficient males	Hepatic, urine Variable 10–100 min	Androgen-deficient, delayed male puberty	Erythrocytosis, acne, prostate cancer progression, decreased fertility	None known	Masculinization of the female fetus; X	Pregnant females, breast/prostate cancer, erythrocytosis (HCT > 52%–54%), obstructive sleep apnea, heart failure, severe BPH, desire for fertility
PF; trental	Methylxanthine derivative, competitive nonselective phosphodiesterase inhibitor, increases blood flood to the affected microcirculation. Blood viscosity is lowered, erythrocyte flexibility is increased, leukocyte deformability is increased, and neutrophil adhesion and activation are decreased	Hepatic; urine drug: 24–48 mn; metabolites: 60–96 mn	Intermittent claudication	Gastrointestinal nausea, vomiting, indigestion	Increased anticoagulation effect of heparin, nonsteroidal anti-inflammatory drugs. Keflex ac enhances anticoagulation effect. Enhances hypotensive effect of antihypertensives. Increases effect of theophylline	C	Xanthine intolerance (caffeine, theophylline), recent cerebral/retinal hemorrhage

Sine causa – Altri farmaci

Nome

- Anti-ossidanti

Razionale

- Ridurre lo stress ossidativo.

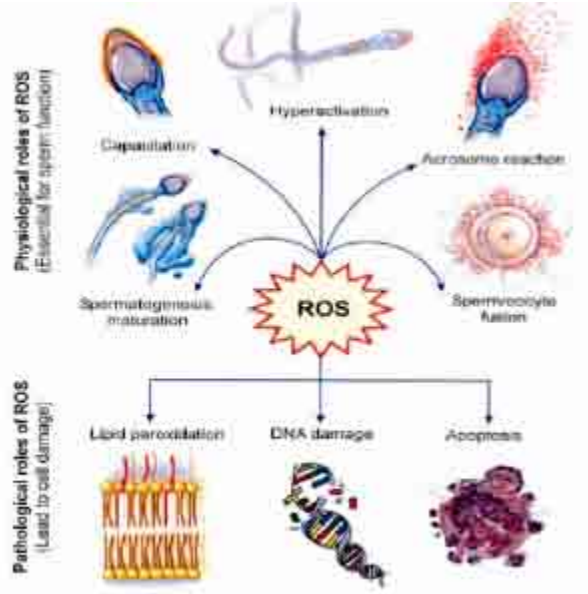
Efficacia

- Sempre più studi confermano un miglioramento nei parametri seminali, ma restano ancora dubbi da sciogliere.

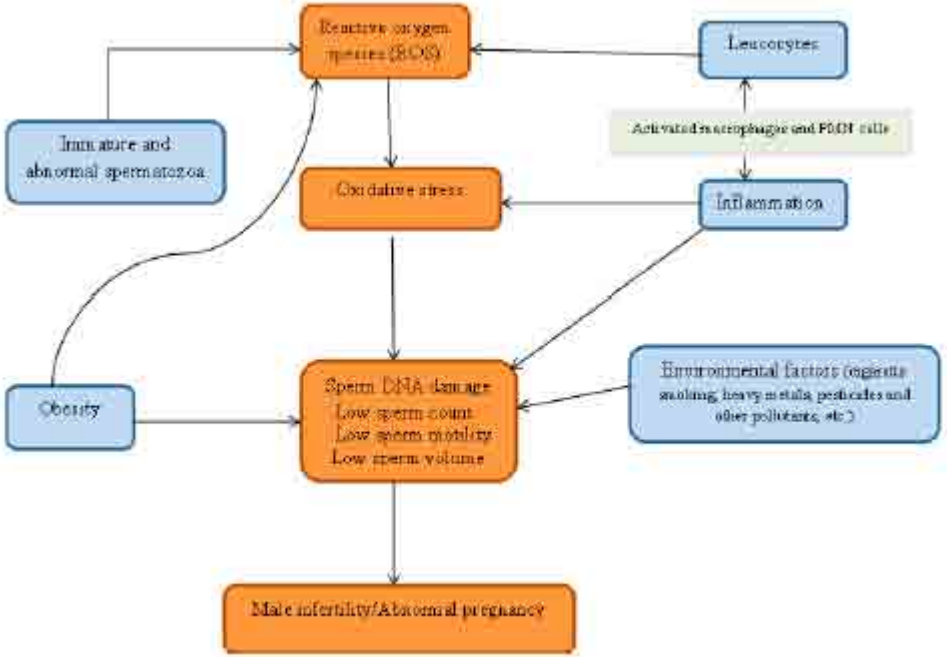
Male Infertility: The Effect of Natural Antioxidants and Phytocompounds on Seminal Oxidative Stress

Diseases **2017**, 5, 9; doi:10.3390

Malik Adewoyin [1], Muhammad Ibrahim [1,*], Ramli Roszaman [2], Muhammad Lokman Md Isa [3], Nur Aizura Mat Alewi [1], Ainin Azwani Abdul Rafa [1] and Mohd Nur Nasyriq Anuar [1]



ROS – In Male Infertility



Sine causa – Anti-ossidanti

The role of antioxidant therapy in the treatment of male infertility: an overview

Francesco Lombardo, Andrea Sansone, Francesco Romanelli, Donatella Paoli, Loredana Gandini and Andrea Lenzi

The clinical heterogeneity of the results, the different drugs used and the doses administered, together with the small numbers of subjects recruited, all contribute to the lack of concrete evidence. The improvement in sperm parameters resulting from antioxidant therapy may result in a higher pregnancy rate, but this is not consistent and the possibility of negative effects on sperm DNA, capacitation and the acrosome reaction should be carefully evaluated. Furthermore, not all individuals are equally eligible for antioxidant therapy, and not all are likely to benefit in the same way from the same treatment.

Asian Journal of Andrology (2011) 13, 690–697

Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD007411.

Antioxidants for male subfertility (Review)

Showell MG,

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	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]

Authors' conclusions

There is low quality evidence from only four small randomised controlled trials suggesting that antioxidant supplementation in subfertile males may improve live birth rates for couples attending fertility clinics. Low quality evidence suggests that clinical pregnancy rates may increase. There is no evidence of increased risk of miscarriage but this is uncertain as the evidence is of very low quality. Data were lacking on other adverse effects. Further large well-designed randomised placebo-controlled trials are needed to clarify these results.

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

Andrologia. 2017;49:e12694.

Y. Magdi[1] | E. Darwish[2] | S. Elbashir[3] | A. Majzoub[4] | A. Agarwal[5]

Lifestyle factors such as dietary habits, exposure to chemicals and testicular hyperthermia are proven to have a significant influence on sperm production. In this study, a treatment protocol of oral antioxidants, frequent ejaculation and control of lifestyle factors was associated with documented improvement in sperm concentration, motility and morphology in a group of patients with severe OAT.

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**

Sine causa – Coenzima Q10

Coenzyme Q_{10} in male infertility: Physiopathology and therapy

*Antonio Mancini[1] and Giancarlo Balercia[2]**

Endogenous CoQ_{10} is significantly related to sperm count and motility, as one could expect considering its important [illegible] compartmentalization; furthermore it appears to be [illegible] the most important antioxidants in seminal plasma. Its pres-

Improved sperm motility upon exogenous CoQ_{10} administration could be explained on the basis of the well known involvement of CoQ_{10} in mitochondrial bioene[illegible] and of its widely recognized antioxidant properties. The increased

BioFactors

Published online 11 October 2011 in Wiley Online Library (wileyonlinelibrary.com)

Sine causa – Altre sostanze

Carnitines (L-acetyl carnitine and L-carnitine)

there is good evidence to suggest carnitines are mildly effective at improving the fertility rates of men with idiopathic infertility.

Selenium

A randomized, placebo-controlled trial (n = 468) found selenium (200 µg daily for 6 months) significantly increases sperm motility, concentration, and normal morphology in men with idiopathic infertility when compared to placebo [117].

Expert Opin. Pharmacother. (2012) **13**(17)

Sine causa – Carnitina

A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetyl-carnitine treatment in men with asthenozoospermia

Andrea Lenzi, M.D.,[a] Paolo Sgrò, M.D.,[a] Pietro Salacone, M.D.,[a] Donatella Paoli, B.Sc.,[a] Barbara Gilio, M.D.,[a] Francesco Lombardo, Ph.D.,[a] Maria Santulli, B.Sc.,[b] Ashok Agarwal, Ph.D.,[c] and Loredana Gandini, B.Sc.[a]

In conclusion, the combined L-carnitine and L-acetyl-carnitine treatment in a controlled study of efficacy was effective in increasing sperm motility, especially in groups with lower baseline levels. Further studies should concentrate on the sperm-fertilizing ability of patients with very low numbers of motile sperm who are undergoing assisted reproduction. Also needed are biological studies of the effect of carnitine on the metabolism of the male gamete, using molecular and cellular studies on single intracellular functions or organelles.

FERTILITY AND STERILITY®
VOL. 81, NO. 6, JUNE 2004

Sine causa – Altre sostanze

Magnesium Larger studies are needed.

Zinc The complete activity spectrum and specific indications of zinc therapy for male infertility are unclear.

N-acetyl cysteine (NAC)

data on pregnancy rates are absent, but needed to fully assess the impact of NAC on idiopathic male infertility.

Carotenoids (e.g., astaxanthin and lycopene)

Larger, randomized, placebo-controlled trials are needed to truly assess the impact of carotenoids on idiopathic male infertility.

Expert Opin. Pharmacother. (2012) **13**(17)

Sine causa – Altre integrazioni alimentari

Folate

This large study demonstrates that folate shows little promise as a treatment option for idiopathic male infertility.

Omega-3 fatty acids

Statistically significant improvement in sperm concentration, motility, and morphology was seen in the treatment group.

Expert Opin. Pharmacother. (2012) **13**(17)

Sine causa – Altri farmaci

Non-steroidal anti-inflammatories (NSAIDs)

Leukocytes are a common finding in seminal plasma of infertile males and have been shown to negatively affect sperm function [63], but the link between abacterial leukocytospermia and male infertility is not completely clear [64,65].

COX-2 inhibitors (rofecoxib) daily for 30 days significantly reduced leukocytospermia and improved sperm parameters

Mast-cell stabilizers/blockers

Increased numbers of mast cells in seminal fluid have been associated with idiopathic male infertility [158,159].

There is convincing evidence suggesting mast cell blockers are a good treatment option, but more studies are needed.

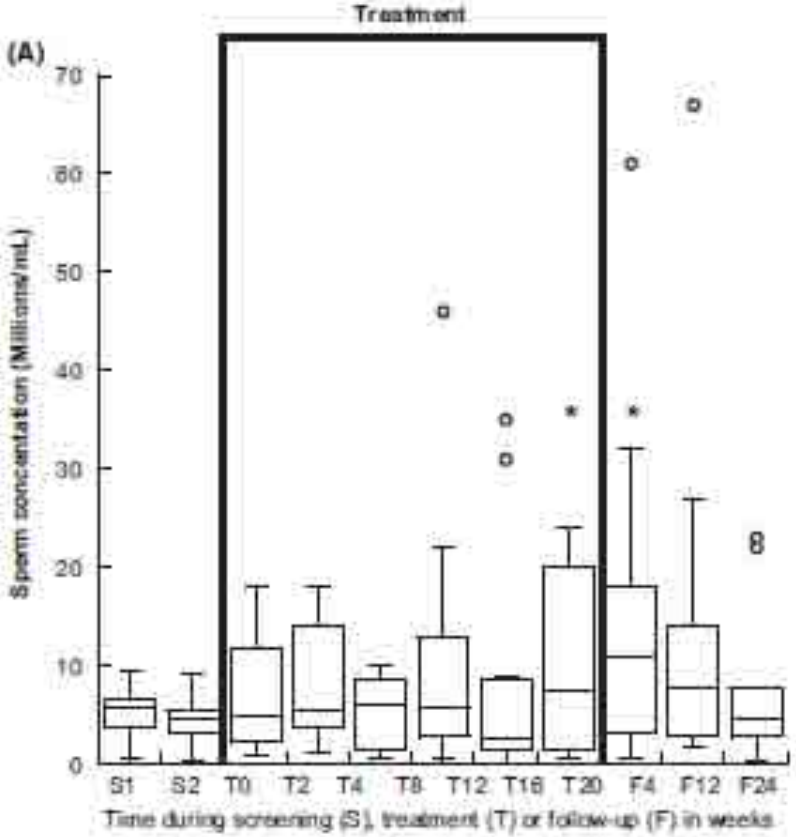
Expert Opin. Pharmacother. (2012) **13**(17)

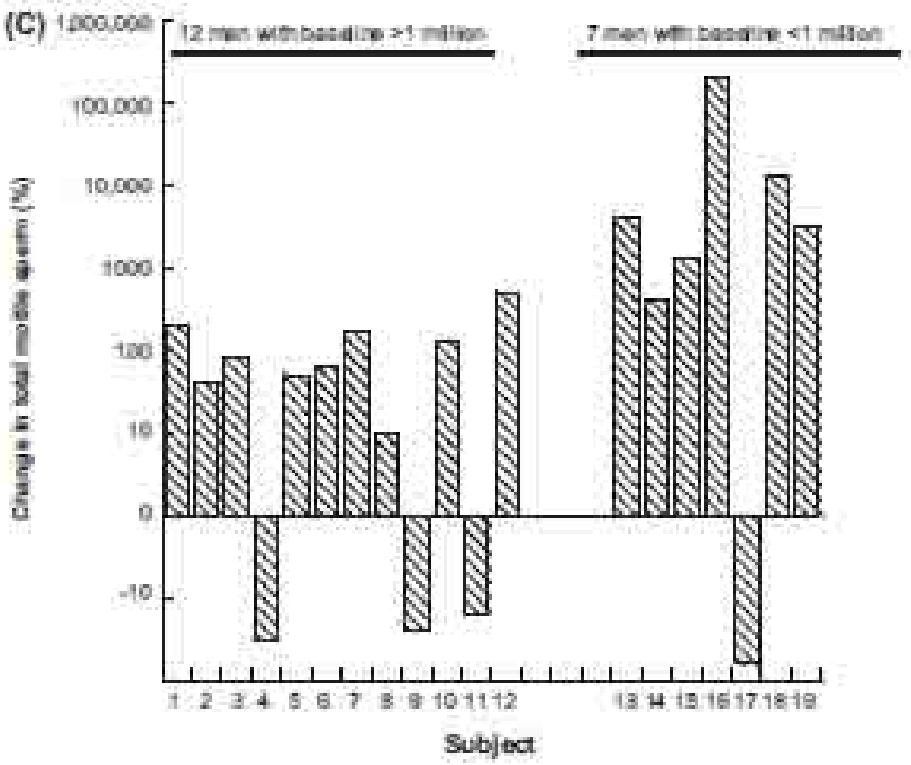
Isotretinoin administration improves sperm production in men with infertility from oligoasthenozoospermia: a pilot study

[1]J. K. Amory, [2]K. A. Ostrowski, [3]J. R. Gannon, [1]K. Berkseth, [4]F. Stevison, [4]N. Isoherranen, [2]C. H. Muller and [2]T. Walsh

Andrology, 1–9

ITALIAN CHAPTER





The association of a probiotic with a prebiotic (Flortec, Bracco) to improve the quality/quantity of spermatozoa in infertile patients with idiopathic oligoasthenoteratospermia: a pilot study

[1]C. Maretti and [2]G. Cavallini

Andrology, 2017, 5, 439–444

Table 2 Comparisons between sperm concentration, motility, morphology, volume of the ejaculate, and blood levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), prolactin (PRL), and 17-beta-2-estradiol (E2) at the beginning of the study and after a 6-month administration of Flortec (Bracco), one sachet per day (*Lactobacillus paracasei* B21060 5 × 10^9 cells + arabinogalactan 1243 mg + oligo-fructosaccharides 700 mg + L-glutamine 500 mg) (Group 1), or a control substance (alimentary starch) (Group 2)

	Flortec (20 patients)		Control substance (alimentary starch)		*p*			
	Before administration (a)	After administration (b)	Before administration (c)	After administration (d)	Wilcoxon signed rank test		Mann-Whitney rank test	
					(a) vs. (b)	(c) vs. (d)	(a) vs. (c)	(b) vs. (d)
Sperm concentration Number of spermatozoa per mL × 10^6	15.2 (5.0–19.3)	28.3 (20.4–41.6)	15.3 (6.0–18.8)	16.3 (7.0–19.8)	0.003	0.431	0.342	0.003
Progressive motile spermatozoa (%)	16.2 (5.3–28.2)	42.0 (36.0–51.3)	17.4 (6.4–29.3)	19.4 (7.4–29.6)	0.001	0.234	0.443	0.003
Typical forms (%) (strict criteria)	7 (5–11)	16. 3 (12.2–18.4)	6 (4–11)	7 (5–12)	0.007	0.367	0.338	0.002
Volume of the ejaculate (mL)	2.4 (2–3.5)	3.1 (2–4)	2.4 (2–3.5)	2.5 (2–3.5)	0.009	0.354	0.332	0.006
Number of ejaculated sperm × 10^6	37.0 (10.3–57.9)	90.0 (41.7–118.6)	36.2 (11.1–58.0)	37.5 (10.9 – 58.9)	0.004	0.437	0.654	0.005
FSH (reference range: 2–10 IU/L)	5.1 (2–9.4)	7.6 (4.1–12)	4.9 (2.5–8.2)	5.0 (2.4–8.3)	0.007	0.431	0.334	0.008
LH (reference range: 2–10 UI/L)	4.4 (2.4–6.3)	5.7 (3.3–7.3)	4.6 (2.3–6.2)	4.5 (2.3–6.4)	0.009	0.432	0.541	0.008
T (reference range: 12–34 nmol/L)	25.3 (20.9–32.3)	30 (25.4–36.4)	24.8 (21.2–33.2)	25.4 (22.3–22.5)	0.005	0.175	0.149	0.007
PRL (reference range: 2–15 mcg/L)	8.3 (4.1–14.7)	7.7 (3.6–14.1)	8.9 (4.6–15)	8.5 (5.7–13.9	0.145	0.218	0.117	0.118
E2 (reference range: 10–40 pg/mL)	16.3 (12.3–25.6)	17.4 (13.2–30.4)	17.2 (12.6–22.49	16.4 (13.2–20.9)	0.116	0.231	0.318	0.319

Future studies will also need to assess the potential for commercially available pharmacological compounds targeting the availability of AG and DAG to remedy stress-induced infertility. Encouragingly, recently developed bioactive DAG analog, AZP-531 (Alizé Pharma, France), is a potent inhibitor of circulating AG (574, 580). This compound is currently undergoing clinical trials in patients with type 2 diabetes and in patients with Prader-Willi syndrome, who suffer from elevated AG and dysregulation of the ghrelin system. Thus far, AZP-531 has been shown to be safe, well tolerated, and its improved pharmacokinetic profile differentiates it from existing ghrelin antagonists (581). This compound may therefore provide a useful therapeutic in the context chronic stress-induced infertility. However, due to the involvement of ghrelin in multiple functions, extensive research is required to address the possibility of safely utilizing this compound in improving fertility. Nonetheless, the clear evidence of ghrelin's role in stress and fertility suggest targeting its action may provide a useful therapeutic to remedy infertility in some stress-susceptible couples.

Association between vitamin D and sperm parameters: Clinical evidence

Endocrine (2017) 58:194–198

Giacomo Tirabassi[1] · Melissa Cutini[1] · Giovanna Muscogiuri[2] · Nicola delli Muti[1] · Giovanni Corona[3] · Mariano Galdiero[2] · Rosario Pivonello[4] · Annamaria Colao[4] · Giancarlo Balercia[1]

Table 1 General, clinical, biochemical and sperm characteristics in the total sample and in vitamin D quartiles

	Total sample ($n = 104$)	I quartile 25-OH vitamin D ($n = 26$)	II quartile 25-OH vitamin D ($n = 25$)	III quartile 25-OH vitamin D ($n = 27$)	IV quartile 25-OH vitamin D ($n = 26$)
Age (years)	33.1 ± 4.78	33.1 ± 6.14	32 ± 3.37	32.7 ± 2.85	34.6 ± 5.76
Varicocele (yes/no)	(24/80)	(5/21)	(7/18)	(5/22)	(7/19)
BMI	23.9 ± 1.71	23.8 ± 2.17	24.2 ± 1.15	23.6 ± 1.58	24.1 ± 1.81
Weight (Kg)	75.6 ± 6.39	75.5 (69.7–82.7)	74 (73–79.5)	75 (73–78)	75.5 (70.7–79)
FSH (IU/l)	4.5 (3.5–6.4)	4.2 (3.5–6.5)	3.7 (3.3–5.5)	5.8 (3.8–10.4)	4.2 (3.3–5.9)
LH (IU/l)	5.4 (3.8–7.1)	5.8 (3.8–7.5)	4.1 (3.7–5.5)	5.5 (3.9–5.8)	5.3 (3.5–8.1)
Total testosterone (ng/ml)	5.09 ± 0.88	5.16 ± 1.05	4.92 ± 0.75	5.31 ± 0.83	4.94 ± 0.87
Free testosterone (pg/ml)	98.3 ± 22	99.5 ± 29.4	95.6 ± 18.7	104.1 ± 16.8	93.6 ± 20.7
Estradiol (pg/ml)	28 ± 6.02	26.3 (23.4–32.6)	29.9 (27.9–31.7)	28.3 (25.7–29.6)	26.8 (22.6–31.4)
SHBG (nmol/l)	39 ± 6.13	40.2 ± 8.23	38.1 ± 4.45	38 ± 4.76	39.8 ± 6.36
Sperm volume (ml)	3.2 ± 0.63	3.3 ± 0.73	3.1 ± 0.51	3.2 ± 0.51	3.2 ± 0.75
Sperm concentration ($\times 10^6$ spermatozoa/ml)	36.1 ± 13.1	37.4 ± 14.4	36.1 ± 13.1	32.8 ± 13.5	38.4 ± 11.1
Progressive sperm motility (%)	23.5 ± 3.46	19.2 ± 2.34	22.7 ± 0.97[a]	24.5 ± 1.57[a,b]	27.3 ± 2.09[a,b,c]
Total sperm motility (%)	37.1 ± 3.69	33.1 ± 2.60	35.8 ± 1.73[a]	38.3 ± 2.12[a,b]	41.2 ± 2.16[a,b,c]
Typical sperm cells (%)	13.3 ± 2.59	13.4 ± 2.45	12.6 ± 2.30	14.1 ± 2.59	13.2 ± 2.89
Creatinine (mg/dl)	0.56 ± 0.08	0.57 (0.48–0.69)	0.56 (0.54–0.59)	0.56 (0.54–0.59)	0.58 (0.52–0.65)
PTH (pg/ml)	53.6 ± 11.23	65.8 ± 10.38	48.8 ± 5.75[a]	48 ± 9.75[a]	51.7 ± 8.08[a]
Calcemia (mg/dl)	9.4 ± 0.22	9.46 ± 0.21	9.49 ± 0.20	9.46 ± 0.22	9.37 ± 0.25
25-OH vitamin D (ng/ml)	30.8 ± 8.06	20.8 ± 4.76	28.7 ± 1.21[a]	32.7 ± 1.08[a,b]	40.8 ± 5.09[a,b,c]
Albumin (g/dl)	4.67 ± 0.22	4.75 (4.5–4.9)	4.7 (4.6–4.7)	4.6 (4.5–4.7)	4.65 (4.47–4.9)

Data are reported as mean and standard deviation for variables normally distributed or as median and interquartile range for variables non-normally distributed

The role of vitamin D in male fertility: A focus on the testis

Cristina de Angelis[1] · Mariano Galdiero[1] · Claudia Pivonello[2] · Francesco Garifalos[2] · Davide Menafra[2] · Federica Cariati[3,4] · Ciro Salzano[2] · Giacomo Galdiero[2] · Mariangela Piscopo[2] · Alfonso Vece[2] · Annamaria Colao[2] · Rosario Pivonello[2]

Rev Endocr Metab Disord (2017) 18:285–305

REF.	SPECIES	REPRODUCTION		SEMINAL PARAMETERS		
		Mating Ratio	*Fertility Ratio*	*Sperm Count*	*Sperm Motility*	*Sperm Morphology*
Kwiecinski G.G. 1989	*Rat*	+	+	NA	NA	NA
Uhland A.M. 1992	*Rat*	+	+	NA	NA	NA
Sood S. 1992	*Rat*	NA	NA	+	NA	NA
Sood S. 1995	*Rat*	NA	NA	+	NA	NA
Kinuta K. 2000	*Mouse*	NA	NA	+	+	NA
Sun W. 2015	*Mouse*	NA	NA	+	+	NA

SPECIES	HORMONE PRODUCTION — *Testosterone*		
	Action	*Mechanism of action*	*Effect*
Animals	Direct	G, ↑ calbindin-D_{28k}	NA, ↑*
	Indirect	G, ↑ osteocalcin	NA, ↑*
Humans	Direct	G, ↑ steroidogenesis enzymes	↑
	Indirect	G, ↑ osteocalcin	NA, ↑*

SPECIES	SEMEN QUALITY		
	Action	*Mechanism of action*	*Effect*
Animals	Direct	modulation of calcium homeostasis	↑ sperm motility
	Direct	NG, ↑ cell proliferation, ↓ apoptosis	↑ sperm count
Humans	Direct	NG, ↑ intracellular calcium	↑ sperm motility
	Direct	NG, ↑ activation of intracellular pathways	↑ sperm motility

Male infertility: lifestyle factors and holistic, complementary, and alternative therapies

Asian Journal of Andrology (2016) 18, 410–418

David F Yao,

Nonprescription medication and supplements	Balercia, 2009 Clifton, 2009 Fang, 2010 Hunt, 1992 Kolahdooz, 2014 Lenzi, 1993 Lenzi, 2003 Park, 2015 Rolf, 1999 Safarinejad, 2009 Safarinejad, 2009 Safarinejad, 2011 Safarinejad, 2011 Safarinejad, 2012 Scott, 1998 Showell, 2014 Tremellen, 2007 Wong, 2002	Healthy young men (n=11) Abnormal semen parameters (n=1371) Abnormal sperm parameters associated with germ-free genital tract inflammation (n=10) Subfertile men (n=94) Subfertile men with varicocele (n=309) Couples with isolated male infertility undergoing IVF-ICSI treatment (n=60)	Improvement of sperm concentration, motility, and morphology Increased seminal volume Improvement of testosterone, LH, and FSH Decreased varicocele diameter Higher pregnancy rate with IVF-ICSI	Antioxidant Anti-apoptotic Anti-edematous Anti-inflammatory	+ Aescin, coenzyme Q_{10}, glutathione, Korean red ginseng, L-carnitine, nigella sativa, omega-3, selenium±NAC, zinc + folate, and Menevit improved seminal parameters, improved gonadotropins and testosterone, decreased varicocele size, and/or increased pregnancy rate with IVF-ICSI
Chinese herbal medication	Yang, 2011 Yang, 2002	Asthenospermia or oligospermia (n=70) Isolated male infertility associated with antisperm antibodies (n=90)	Wuzi Yanzong Wan and Sheng Jing Zhong Zi Tang improved sperm concentration and motility Sheng Jing Zhong Zi Tang improved pregnancy rates by men with antisperm antibodies compared to prednisone and clomiphene	Anti-estrogenic Antioxidant	– No RCT to judge true efficacy

Nutraceutica e riproduzione: cosa piace realmente allo spermatozoo?

SAPIENZA UNIVERSITÀ DI ROMA

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Il Bridge selfie!

ORIGINAL PAPER

Archivio Italiano di Urologia e Andrologia 2013; 85, 1

Impact of long-term and short-term therapies on seminal parameters

Jlenia Elia, Norina Imbrogno, Michele Delfino, Rossella Mazzilli, Vincenzo Spinosa, Fernando Mazzilli

Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, Unit of Andrology, University of Rome "Sapienza", Rome, Italy.

Summary

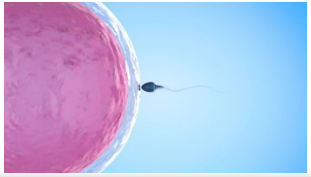
Aim: The aim of this work was: i) to evaluate the prevalence of male partners of subfertile couples being treated with long/short term therapies for non andrological diseases; ii) to study their seminal profile for the possible effects of their treatments on spermatogenesis and/or epididymal maturation.

Methods: The study group was made up of 723 subjects, aged between 25 and 47 years. Semen analysis was performed according to World Health Organization (WHO) guidelines (1999). The Superimposed Image Analysis System (SIAS), which is based on the computerized superimposition of spermatozoa images, was used to assess sperm motility parameters.

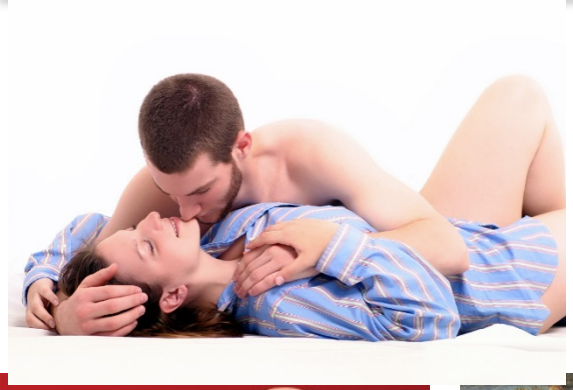
Results: The prevalence of subjects taking pharmacological treatments was 22.7% (164/723). The prevalence was 3.7% (27/723) for the Short-Term Group and 18.9% (137/723) for the Long-Term Group. The subjects of each group were also subdivided into subgroups according to the treatments being received. Regarding the seminal profile, we did not observe a significant difference between the Long-Term, Short-Term or the Control Group. However, regarding the subgroups, we found a significant decrease in sperm number and progressive motility percentage in the subjects receiving treatment with antihypertensive drugs compared with the other subgroups and the Control Group.

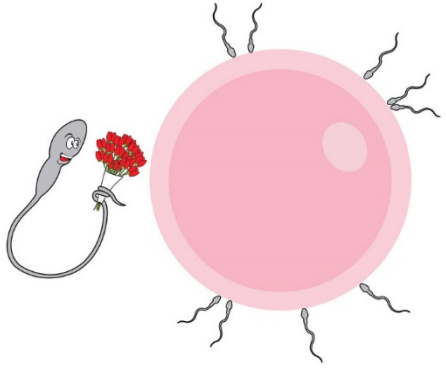
Conclusions: In the management of infertile couples, the potential negative impact on seminal parameters of any drugs being taken as Long-Term Therapy should be considered. The pathogenic mechanism needs to be clarified.

Roma, 9-12 novembre 2017



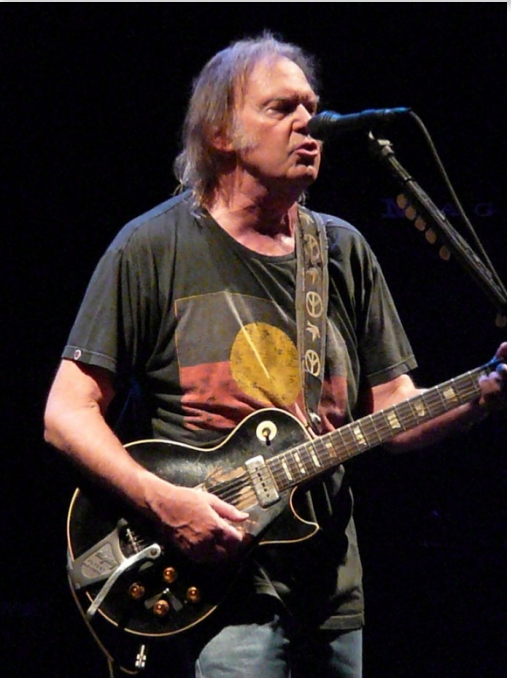
ITALIAN CHAPTER





Abbiamo imparato a gestire la nostra fertilità, facendo scivolare la maternità in coda alle priorità della nostra vita, salvo poi farla diventare un'imperiosa necessità quando ci rendiamo conto che l'orologio del tempo ha accelerato i suoi battiti. Susanna Tamaro

La differenza tra l'amore e il sesso, è che il sesso allevia le tensioni e l'amore le provoca. **Woody Allen**



Neil Young 72 **Anne Hathaway 35** **Mietta 48** **Dario Simic 42**

Buon Compleanno per oggi 12 novembre

Grazie per l'attenzione!