Infertilità maschile: real clinical practice

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Minicorso 6:
Infertilità maschile: tra tecnologia e farmaci

16° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

9-12 novembre 2017, Roma

Quaderni del Ministero della Salute

ISSN 2038-5293

28

n. 28, maggio 2017

Prevenzione, diagnosi e cura delle patologie andrologiche dall'età pediatrica al giovane adulto

Ministero della Salute

ITALIAN CHAPTER

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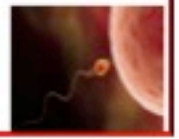
INFERTILITA'

- **Infertilità**: mancanza di concepimento dopo almeno 12 mesi di rapporti non protetti con frequenza adeguata
- **Infertilità maschile**: impossibilità di concepire dopo almeno 12 mesi di rapporti non protetti mirati al periodo ovulatorio con una partner in perfette condizioni di fertilità. Questo periodo è ridotto a 6 mesi se la partner ha > 35 anni.

Probabilità di una coppia con partner femminile < 35 aa di concepire con rapporti non protetti

- ➢25% per mese
- ➢75% entro 6 mesi
- ➢90% entro 1 anno



- ➢ **Infertilità primaria:** quando l'uomo non ha mai fecondato alcuna donna
- ➢ **Infertilità secondaria:** quando l'uomo ha già fecondato una donna (partner attuale o precedente)

- **8-15% delle coppie** non sono in grado di concepire dopo almeno 12 mesi di rapporti non protetti mirati al periodo ovulatorio
- **Il fattore maschile** è responsabile "da solo" nel **20-30%** dei casi e contribuisce in un altro 20-40% delle coppie.

Table 1. Etiology of Infertility

Factors	Percentage
Combined factors	40
Male factors	26 to 30
Ovulatory dysfunction	21 to 25
Tubal factors	14 to 20
Other (e.g., cervical factors, peritoneal factors, uterine abnormalities)	10 to 13
Unexplained	25 to 28

- **L'infertilità è un sintomo di coppia e non una malattia/diagnosi.**
- **Neanche la dispermia è una malattia/diagnosi: è un segno laboratoristico aspecifico in un paziente che ha un sintomo (infertilità, non necessariamente sua) di una possibile malattia.**

- **Il fallimento del processo riproduttivo è un evento frequente, dovuto a diverse variabili, presumibilmente molto numerose e sicuramente in parte ignote.**
- ***"The changes … are usually non specific and … with a few exceptions (Globozoospermia) … give no clue as to the cause of the male infertility"***

Human Reproduction Vol.19, No.6 pp.1245–1249, 2004 DOI: 10.1093/humrep/deh269
Advance Access publication April 22, 2004

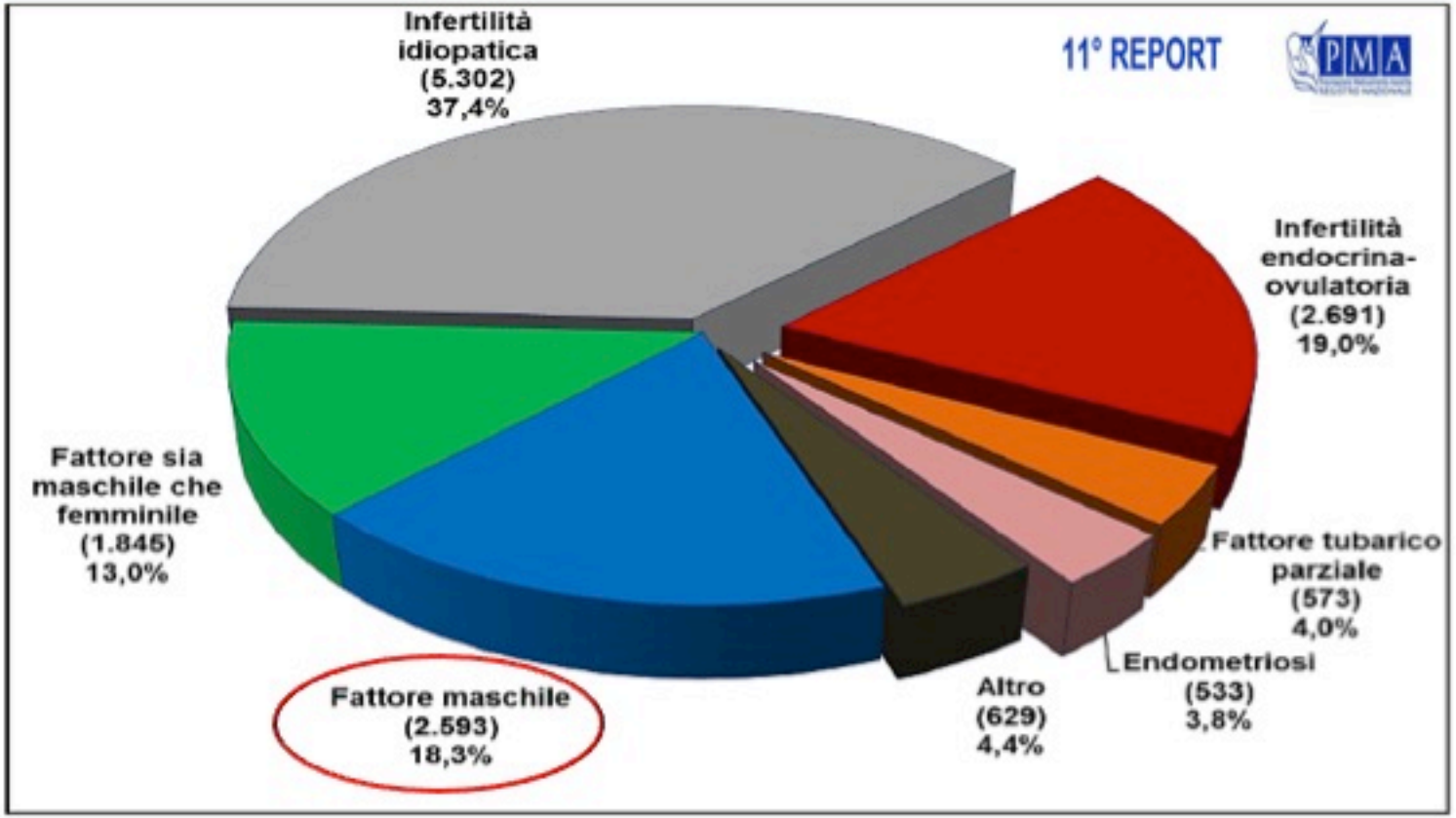
A. Jequier: Art for male infertility Praga 2006

OPINION

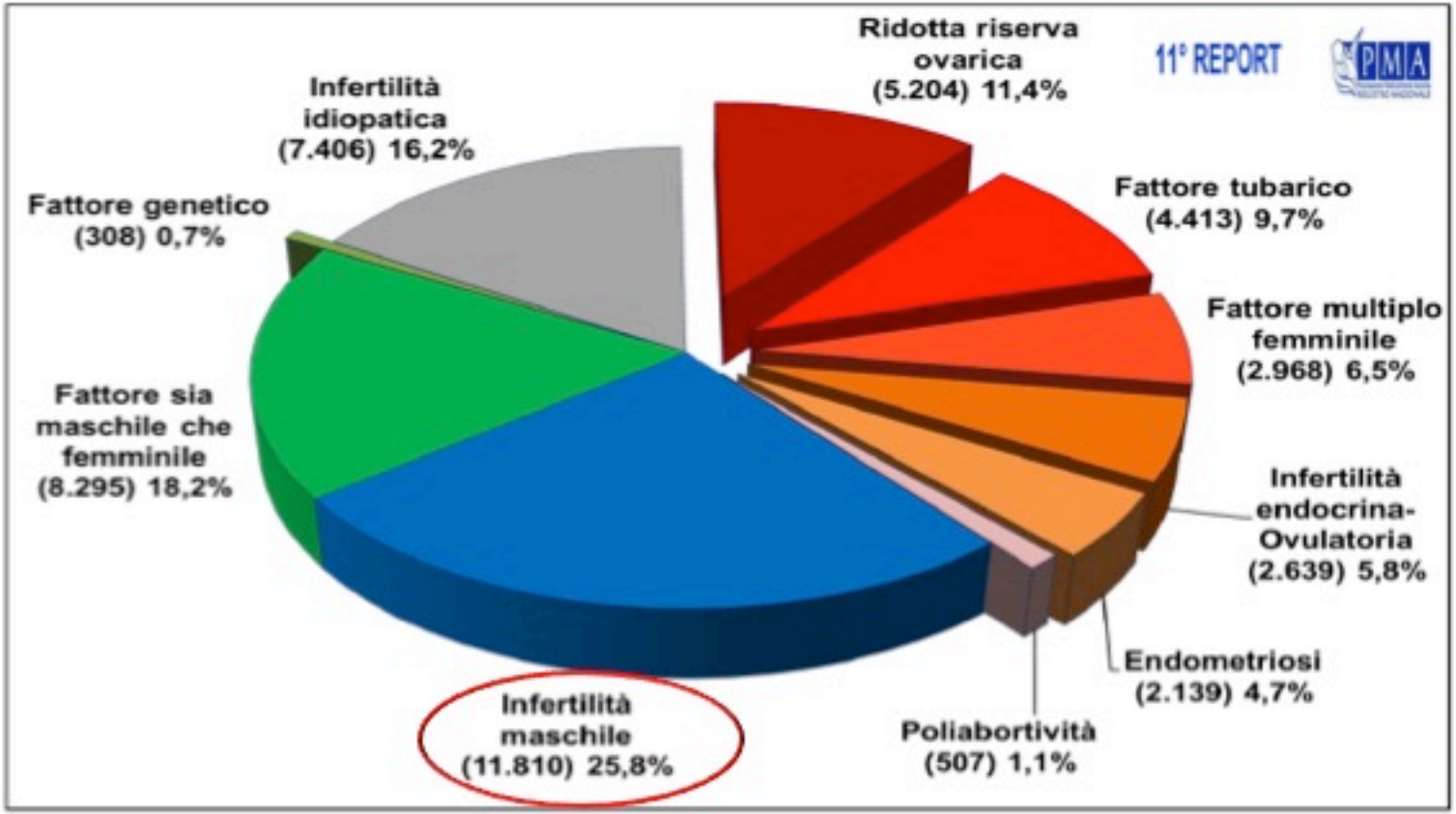
Clinical andrology—still a major problem in the treatment of infertility

Anne M. Jequier

PMA primo livello: inseminazione semplice (ISS dati 2015)



PMA secondo e terzo livello: FIVET/ICSI (ISS dati 2015)



The Epidemiology of Male Infertility

Brian R. Winters, MD, Thomas J. Walsh, MD*

Urol Clin N Am 41 (2014) 195–204

- The epidemiology of male infertility is difficult to study for well-described reasons:
  - Male infertility is not a reportable disease.
  - Male infertility is diagnosed and treated in the outpatient clinical setting.
  - Infertility care is often paid for out of pocket and, therefore, may not be noted on insurance billing.
  - Frequently, the empiric treatment of male factor infertility involves assisted reproductive technology (in vitro fertilization) that primarily treats the female partner.
- The true nature of male infertility incidence remains elusive and the prevalence has been weakly estimated in heterogeneous studies.
- Equally perplexing is the assertion of a global decline in male infertility, with many contradictory studies leading to significant debate.
- One consistency throughout this review of literature is that male infertility is variable, with a multitude of influencing factors (race, country, geography, and unique at-risk groups), many of which need further study to better characterize them.
- Future, large-scale, prospective epidemiologic studies may help physicians bridge these gaps in understanding male infertility.

Table 1
Examples of population-based studies focused on describing the scope of infertility in men and women

Title	Author, Year	Population	Female Factor? (%	Male Factor? (%)	Both? (%)
Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989)	Thonneau et al,[16] 1991	1686 Couples	30	20	39
Infertility prevalence, needs assessment and purchasing	Gunnell & Ewings,[5] 1994	3141 Surveyed women	26.4	N/A	N/A
Estimation of the prevalence and causes of infertility in Western Siberia	Philippov et al,[6] 1998	2000 Married women surveyed, 186 couples	52.7	6.4	38.7
High prevalence of male infertility in southeastern Nigeria	Ikechebelu et al,[18] 2003	314 Couples	25.8	42.4	20.7
Clinical patterns and major causes of infertility in Mongolia	Bayasgalan et al,[19] 2004	430 Couples	45.8	25.6	18.8

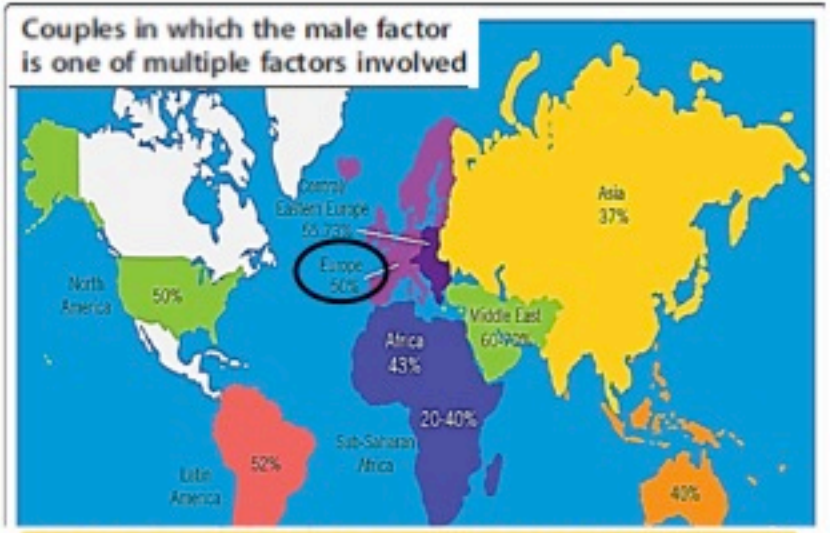
A unique view on male infertility around the globe

Ashok Agarwal[1*], Aditi Mulgund[1,3], Alaa Hamada[2] and Michelle Renee Chyatte[3]

Reproductive Biology and Endocrinology (2015) 13:37

Roma, 9-12 novembre 2017

ITALIAN CHAPTER



In summary, we strongly recommend, owing to the very low quality of evidence, that it is not currently possible to determine an unbiased prevalence of male infertility within the global, regional or national populations, including neglected individual populations. Additionally, it is not currently possible to determine what proportion of infertility in heterosexual couples is attributable to the male partner (Table I)

Barratt C.L. Hum Reprod Update 19: 1-21, 2017

Table 5 Infertility around the world[a], [12] reported from previous studies examining male infertility to summarize previous research

	Population	Author, year	Female factor	Male factor	Combination
French Regions (1988-1989)	1686 Couples	Thonneau et al. 1991 [13]	38%	20%	39%
Western Siberia	2000 Married women; 186 couples	Philippov et al. 1998 [27]	52.70%	6-40%	38.70%
Southeastern Nigeria	314 couples	Ikechebelu et al. 2003 [19]	25.80%	42-40%	20.70%
Mongolia	430 Couples	Bayasgalan et al. 2004 [28]	45.80%	25.60%	18.80%
Poland/Eastern Europe	Unreported	Sanocka and Kurpisz 2003 [14]; Bablok et al. 2011 [6]	Unreported	40-60%[b] [14]; 56% [6]	Unreported
Egypt	190 Women	Inhorn, Buss 1994 [7]	82%	13%[c]; 48%[d] [7]	Unreported
Yazd Province of Iran	5200 Couples	Aflatoonian et al. 2009 [8]	57.5%	25.3% [8]	8%
Sudan	710 couples	Elussein et al. 2008 [9]	49.3%	36.2% [9]	Unreported

Novel concepts in the aetiology of male reproductive impairment

Herman Tournaye, Csilla Krausz, Robert D Oates

Lancet Diabetes Endocrinol 2016

Panel 1: Epidemiology of infertility

- Primary infertility: after 5 years of trying, 48·5 million women worldwide aged 20–44 years were unable to have any livebirth (prevalence 1·9%, 95% CI 1·7–2·2)[2]
- Secondary infertility: 10·5% (95% CI 9·5–11·7) of women worldwide aged 20–44 years were unable to have another child after at least one previous livebirth[2]
- In 2002, 186 million married couples in developing countries (ie, ≥25%) were unable to have any livebirth after 2 years of trying[3]
- Worldwide infertility rates have been stable for the past 20 years[2]
- >30 million men worldwide are estimated to be infertile[4]
- Data on decrease in sperm count over time remain controversial

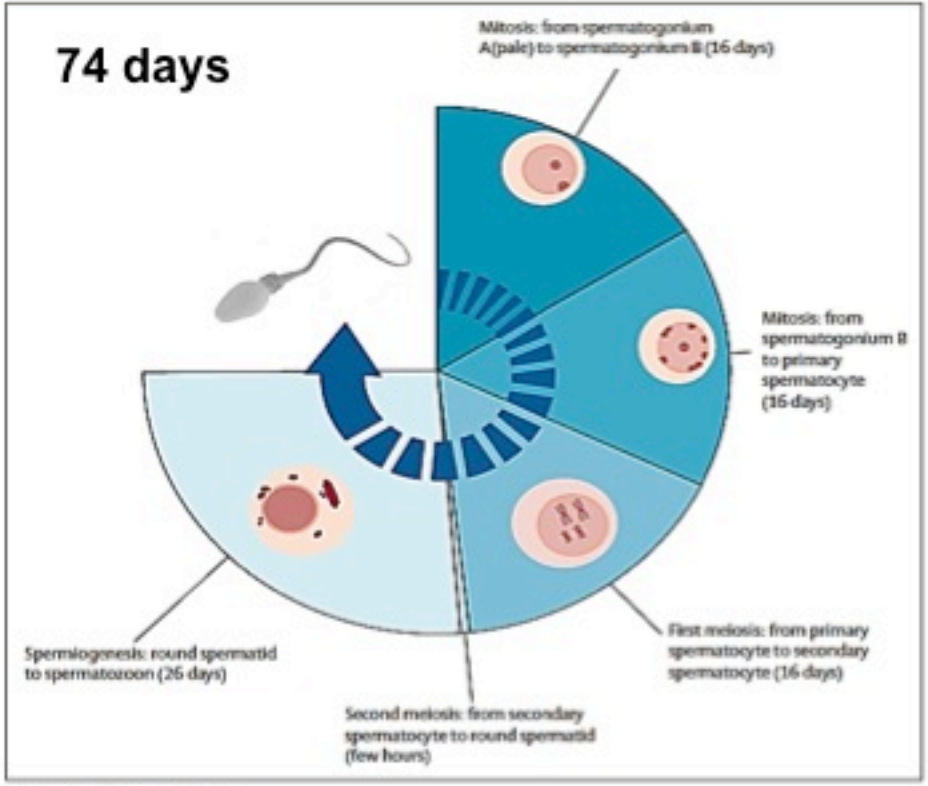


Figure: Spermatogenic cycle
Production of a mature spermatozoon from a testicular stem cell takes around 74 days (95% CI 69–80).

Evidence for decreasing quality of semen during past 50 years

BMJ 1992;305:609-13

Elisabeth Carlsen, Aleksander Giwercman, Niels Keiding, Niels E Skakkebæk

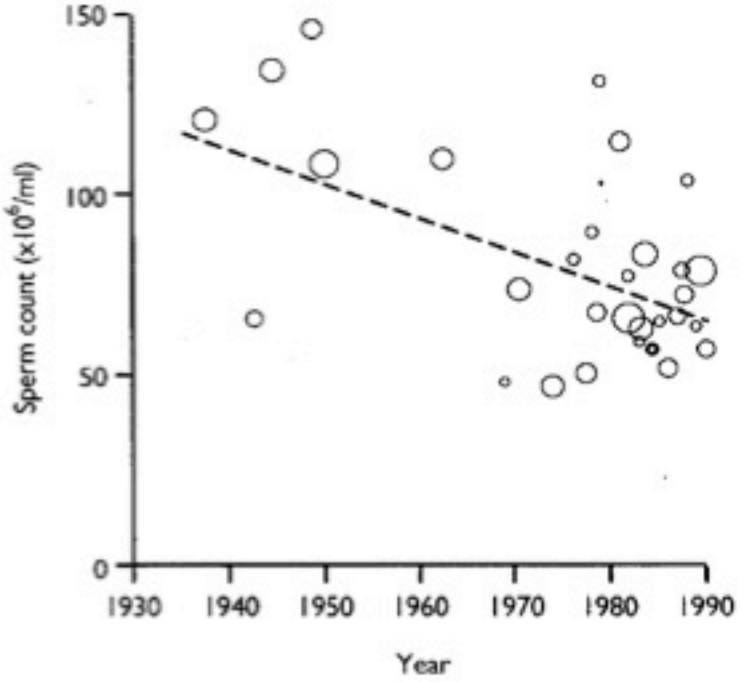
***Subjects*—14 947 men included in a total of 61 papers published between 1938 and 1991.**

***Main outcome measures*—Mean sperm density and mean seminal volume.**

***Results*—Linear regression of data weighted by number of men in each study showed a significant decrease in mean sperm count from 113×10^6/ml in 1940 to 66×10^6/ml in 1990 ($p<0{\cdot}0001$) and in seminal volume from 3·40 ml to 2·75 ml ($p=0{\cdot}027$), indicating an even more pronounced decrease in sperm production than expressed by the decline in sperm density.**

***Conclusions*—There has been a genuine decline in semen quality over the past 50 years. As male fertility is to some extent correlated with sperm count the results may reflect an overall reduction in male fertility. The biological significance of these changes is emphasised by a concomitant increase in the incidence of genitourinary abnormalities such as testicular cancer and possibly also cryptorchidism and hypospadias, suggesting a growing impact of factors with serious effects on male gonadal function.**

The analysis was based on a total of 61 papers published between 1938 and 1990, which included data on 14 947 men.

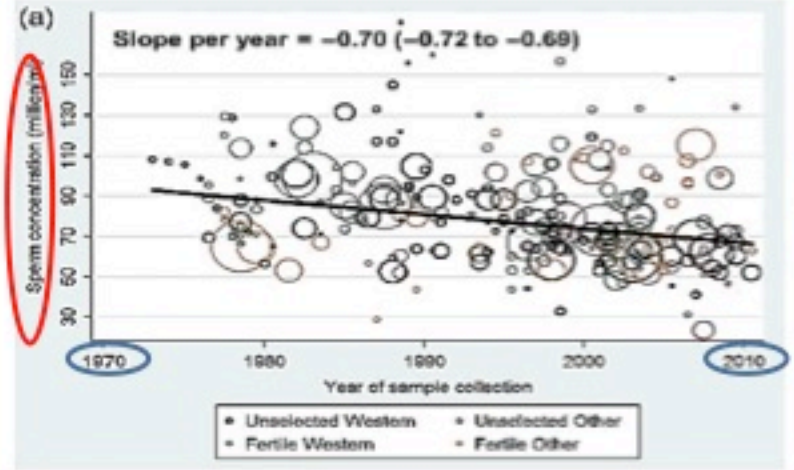


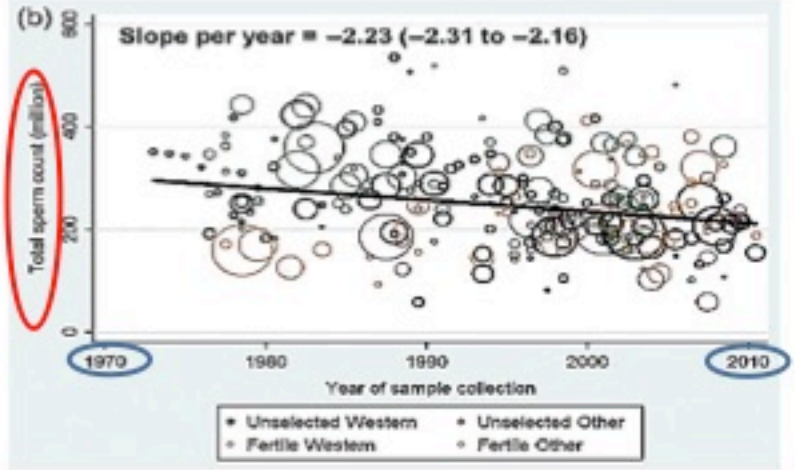
Temporal trends in sperm count: a systematic review and meta-regression analysis

Human Reproduction Update, pp. 1–14, 2017

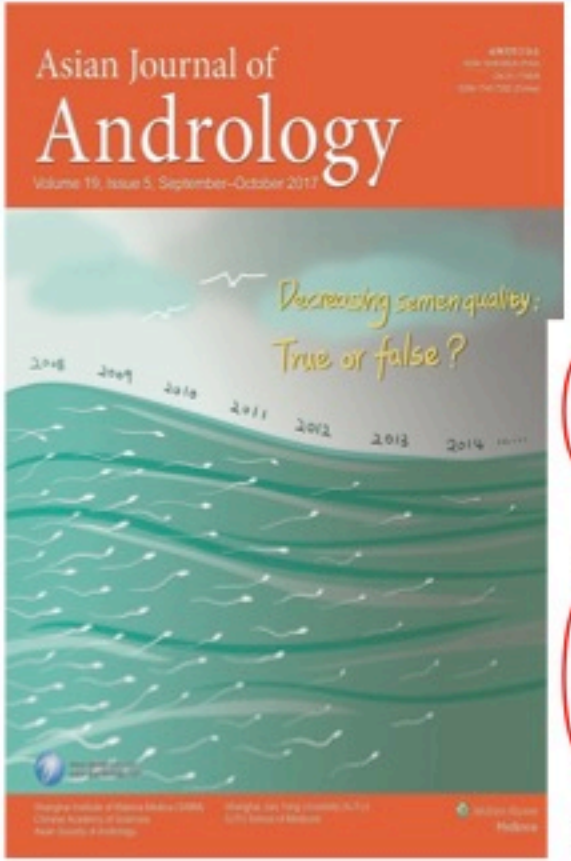
Hagai Levine [1,2,*], Niels Jørgensen [3], Anderson Martino-Andrade [2,4], Jaime Mendiola [5], Dan Weksler-Derri [6], Irina Mindlis [2], Rachel Pinotti [7], and Shanna H. Swan [2]

244 estimates from 42935 men who provided semen sample from 1973-2011





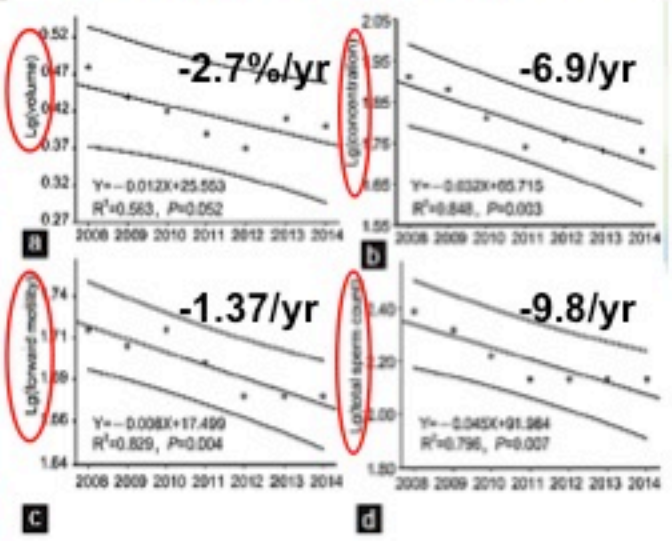
WIDER IMPLICATIONS: This comprehensive meta-regression analysis reports a significant decline in sperm counts (as measured by SC and TSC) between 1973 and 2011, driven by a 50–60% decline among men unselected by fertility from North America, Europe, Australia and New Zealand. Because of the significant public health implications of these results, research on the causes of this continuing decline is urgently needed.



Decline of semen quality among Chinese sperm bank donors within 7 years (2008–2014)

Li Wang[1,2,3,4], Lin Zhang[2,3,4], Xiao-Hui Song[2,3,4], Hao-Bo Zhang[2,3,4], Cheng-Yan Xu[1,2,3,4], Zi-Jiang Chen[1,2,3,4]

Asian Journal of Andrology (2017) 19, 521–525



Declining sperm counts — the never-ending story

Jens Peter Bonde and Egbert te Velde NATURE REVIEWS | UROLOGY 2017

A recent systematic review on worldwide declining trends in sperm counts has fuelled alarming reports in national and international news media. However, methodological issues exist with data gathering and analysis precluding any conclusion and no solid data exist to indicate increasing frequency of couple infertility during past decades.

> "Whether sperm counts are actually declining in some regions and across time periods is still unknown..."

The recent review by Levine and co-authors[1] updates the 1992 meta-analysis, covering the period 1973–2011 (REF. 1), and amends the applied methodologies. A rigorous literature search identified 185 papers published in English from 50 countries with data on sperm counts from 42,935 men who were not recruited from infertility clin-

in their conclusions, the authors ignore the severe methodological limitations that apply to all retrospective sperm trend studies using antecedent data collected for other purposes, such as high nonresponse in semen studies, large variation in sperm counting between laboratories, and geographical variation.

studies of sperm counts is the lack of comparability of study populations across space and time — a violation of the main principle of any trend analysis[5]. In fact, more valid data are

European Journal of Obstetrics & Gynecology and Reproductive Biology 214 (2017) 204–208

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Editorial

Ever growing demand for in vitro fertilization despite stable biological fertility—A European paradox

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Dik Habbema
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before [28]. The 1-year "infertility-is-a-disease" definition has become the standard in clinical practice, and is endorsed by influential organizations like the American Society for Reproductive Medicine (ASRM), the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and WHO [27,28].

In addition, three studies using 2-years- [10], 5-years- [11] and lifelong- primary infertility rates [12] also found no decreasing trend in infertility rates.

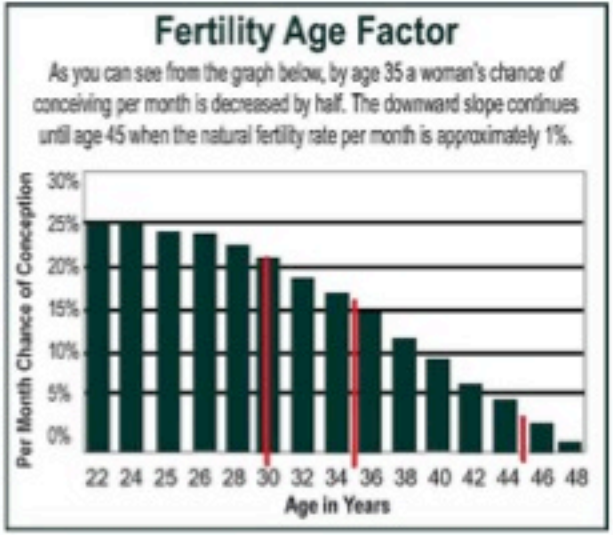
However, so called tailored expectant management (TEM) [49] is a realistic and successful alternative for couples who do not yet require IVF because their chances for a natural conception are still good. To find out for whom such an approach is suitable, the couples' chance of a natural pregnancy is assessed by applying a prediction rule (e.g. the Hunault's model [50]). Those couples who still have a (fairly) good chances of achieving a natural pregnancy, are then encouraged to continue trying for some time while making use of the fertile period and adapt intercourse frequency.

We conclude that the combined evidence indicates that the prevalence of infertility in high-income countries did not increase, thus refuting the hypothesis that the growing demand for IVF is caused by an infertility epidemic in high-income countries.

3A.1.2 *Recommendations on epidemiology and aetiology*

EAU 2015

Recommendations	GR
To categorise infertility, both partners should be investigated simultaneously.	C
In the diagnosis and management of male subfertility, the fertility status of the female partner must also be considered, because this might determine the final outcome [5].	B
The urologist/andrologist should examine any man with fertility problems for urogenital abnormalities. This applies to all men diagnosed with abnormal semen parameters. A diagnosis (even if idiopathic) is mandatory to start appropriate therapy (drugs, surgery, or assisted reproduction).	C



Frequency of the Male Infertility Evaluation: Data from the National Survey of Family Growth

Michael L. Eisenberg,* Ruth B. Lathi, Valerie L. Baker, Lynn M. Westphal, Amin A. Milki and Ajay K. Nangia

From the Departments of Urology (MLE), and Obstetrics and Gynecology (MLE, RBL, VLB, LMW, AAM), Stanford, California, and Department of Urology, Kansas University School of Medicine (AKN), Kansas City, Kansas

Abbreviations and Acronyms

IVF = in vitro fertilization

NSFG = National Survey of Family Growth

Accepted for publication August 13, 2012.

* Correspondence: Department of Urol... Stanford University School of Medi... teur Dr., Stanford, Calif... phone: 650-72... eis...

Purpose: An estimated 7 million American couples ne... re in the United States. A male factor contribute... is unclear what proportion of infertile couples ... on.

Materials and Methods: We ... es 5 to 7 of the National Survey of Family G... Centers for Disease Control to determine the ... fertility evaluation, and associated reproductiv... rs.

...,546 women and 11,067 men were surveyed. Male evaluation was completed in 18% of couples when the male partner was asked vs 30% when female partners were asked. This corresponds to approximately 370,000 to 860,000 men in the population who were not evaluated at the time of infertility evaluation. Longer infertility duration and white race were associated with increased odds of male infertility evaluation. The male and female samples showed no change in the receipt of male examination with time.

Conclusions: Many men from infertile couples do not undergo male evaluation in the United States. Given the potential implications to reproductive goals and male health, further examination of this pattern is warranted.

Key Words: testes; ovary; infertility, male; infertility, female; questionnaires

0022-5347/13/1893-1030/0
THE JOURNAL OF UROLOGY®

Vol. 189, 1030-1034, March 2013

DEI 7 MILIONI DI COPPIE AMERICANE CANDIDATE A PMA OGNI ANNO, CIRCA 1.3 MILIONI (18%) DI MASCHI NON ESEGUE UNA VALUTAZIONE ANDROLOGICA

ANAMNESI DEL MASCHIO INFERTILE

Dati anamnestici generali

- Età
- Etnia
- Religione
- Professione
- Infertilità primaria o secondaria
- Durata infertilità

Anamnesi familiare

- Infertilità
- Aborti spontanei
- Nati morti
- Malattie genetiche ed endocrine

Anamnesi patologica remota

- Febbre > 38° (nei 3 mesi precedenti)
- Diabete mellito
- Malattie surrenaliche
- Bronchiectasie
- Fibrosi cistica
- Tubercolosi
- Infezioni croniche
- Allergie
- BPCO
- Nefropatie/ Epatopatie
- Neuropatie
- Farmaci

Malattie dell'apparato uro-genitale

- Criptorchidismo
- Pubertà precoce o ritardata
- Traumi testicolari
- Torsione funicolo
- Orchiti
- Epididimiti
- Prostatiti
- Vescicoliti
- Uretriti
- Malattie sessualmente trasmesse
- Dermatosi dei genitali

Interventi chirurgici alle vie genitali

- Orchidopessi
- Orchiectomia
- Ernia inguinale
- Detorsione funicolo
- Varicocelectomia
- Idrocelectomia
- Vasectomia
- Epididimo-vasostomia
- Vasovasostomia
- Prostatectomia
- Interventi vescicali
- Ipospadia
- Circoncisione

Anamnesi lavorativa e stile di vita

- Esposizione a fattori ambientali e occupazionali
- Abitudini alimentari
- Sport
- Alcool
- Fumo
- Stupefacenti
- Sauna
- Pantaloni stretti

Anamnesi sessuale

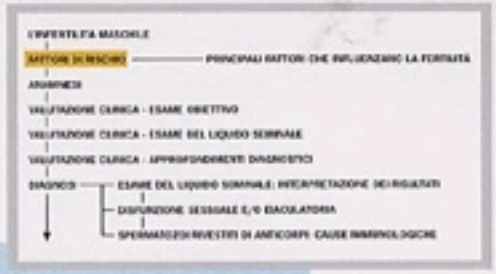
- Rapporti nel periodo fertile
- Frequenza dei rapporti
- Libido
- Disfunzione erettile
- Dispareunia della partner
- Caratteristiche della eiaculazione
- Caratteristiche dell'orgasmo

Da Infertilità maschile
A. Lenzi e L. Gandini,
Neolibro 2004 (modificato)

Fattori di rischio

Da Infertilità maschile
A. Lenzi e L. Gandini, Neolibro 2004

Per tutto l'arco della vita di un uomo, numerosi fattori possono influenzare negativamente la sua capacità riproduttiva, determinando situazioni di infertilità transitorie o meno.



Fattori principali nel determinismo dell'infertilità maschile anche transitori la cui rimozione o trattamento può ricondurre alla normalità

- Febbre
- Patologie quali: diabete, infezioni urinarie, orchite etc.
- Terapie mediche
- Trattamenti chirurgici
- Fattori ambientali e occupazionali
- Abuso di sostanze voluttuarie

Principali fattori che influenzano la fertilità

I fattori che possono influenzare negativamente la fertilità maschile sono molti: alcuni agiscono più frequentemente in età particolari.

PRIMA DEL CONCEPIMENTO
Uso di farmaci da parte della madre

FINO AI 10 ANNI
Criptorchidismo, chirurgia erniaria

FINO AI 20 ANNI
Torsioni funicolo, traumi, orchite postparotitica, steroidi anabolizzanti

FINO AI 30 ANNI
Infezioni genitali, varicocele, orchiepididimite

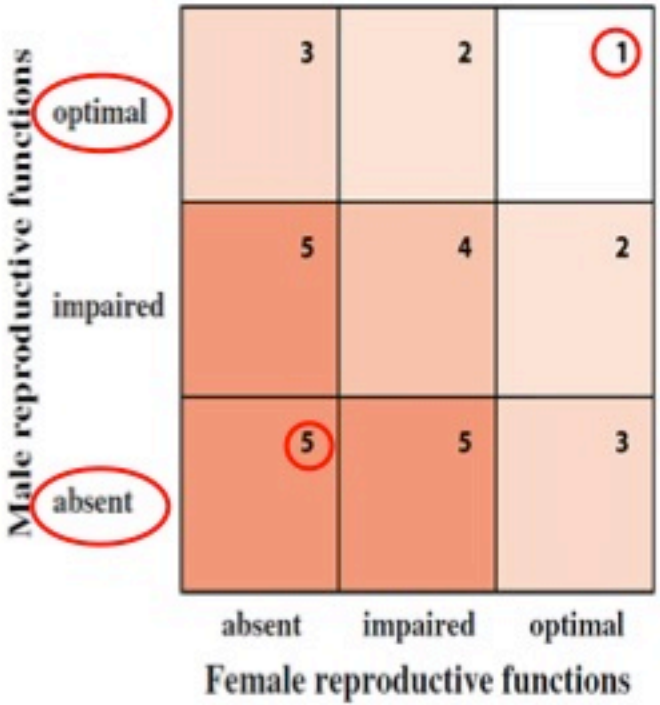
FINO AI 50 ANNI
Uso di farmaci, patologie professionali, abusi di alcol e fumo

DOPO I 50 ANNI
Patologie prostatiche, infezioni urinarie

The conventional management of male infertility

Eberhard Nieschlag [a,c,*], Andrea Lenzi [b]

International Journal of Gynecology and Obstetrics 123 (2013) S31–S35



- La spermatogenesi continua fino in età avanzata
- Comunque, la motilità nemaspermica si riduce con l'età
- TTP e aborti spontanei aumentano significativamente quando l'età del partner maschile è > 40 anni
- Il rate di anomalie cromosomiche e malattie genetiche autosomiche dominanti è più elevato tra i figli/figlie di padri di età "avanzata"

Prior fertility in the male partner does not predict a normal semen analysis

R. Scott Lucidi, M.D.
J. David Pierce, B.S.
Shahryar K. Kavoussi, M.D.
Craig A. Witz, M.D.

TABLE 1

Semen parameters in men of proven and unproven fertility.

	n	Mean concentration (million/mL)	Mean motility (%)	Mean normal morphology (%)	No. of normal concentration	No. of normal motility	No. of normal morphology	No. of normal semen analysis
Proven fertility	73	65.9	54.8	60.6	58 (79%)	53 (73%)	69 (95%)	44 (60%)
Unproven fertility	96	61.7	57.2	61.3	66 (69%)	74 (77%)	91 (95%)	57 (59%)

Note: No comparison is statistically significant.

Lucidi. Prior fertility and semen analysis. Fertil Steril 2005.

A history of male fertility is not an accurate predictor of a normal semen analysis result. The semen analysis should remain part of the evaluation of the infertile couple even in cases where a history of male fertility is reported. (Fertil Steril® 2005;84:793–4. ©2005 by American Society for Reproductive Medicine.)

ANAMNESI DEL MASCHIO INFERTILE (II)

orientata per patologie ambientali, occupazionali e chimici

Ipogonadismo ipogonadotropo

- Chirurgia ipotalamo-ipofisaria
- RT encefalo
- Androgeni
- Progesterone
- MAP

IperPRL

- Amitriptilina
- Anti-depressivi
- Anfetamine
- Fenotiazine
- MetilDOPA
- Metoclopramide
- Sulpiride
- Domperidone
- Risperidone
- Estrogeni

Ipogonadismo iper/normogonadotropo

- Traumi
- Chirurgia testicolare
- Chemioterapia/RT
- Anestetici
- Calore
- Bario/Cadmio
- Piombo/Mercurio
- Solventi organici (metanolo, etanolo, toluene, acetone)
- Pesticidi (DDT) Fungicidi
- Ftalati/Bisfenolo A

Ipocinesi nemaspermica

- Anti-depressivi
- Antibiotici (eritromicina, cotrimoxazolo, tetracicline)
- Clorpromazina
- Diazepam
- Propranololo
- 5-ASA derivati (mesalazina)
- Anti-epilettici

Patologie ostruttive

- Chirurgia epididimo/deferente
- Ernioplastica inguinale
- Orchidopessi
- Chirurgia prostata/vescica
- Mercurio

Da Infertilità maschile
A. Lenzi e L. Gandini,
Neolibro 2004 (modificato)

Endocrine disruptors and estrogenic effects on male reproductive axis

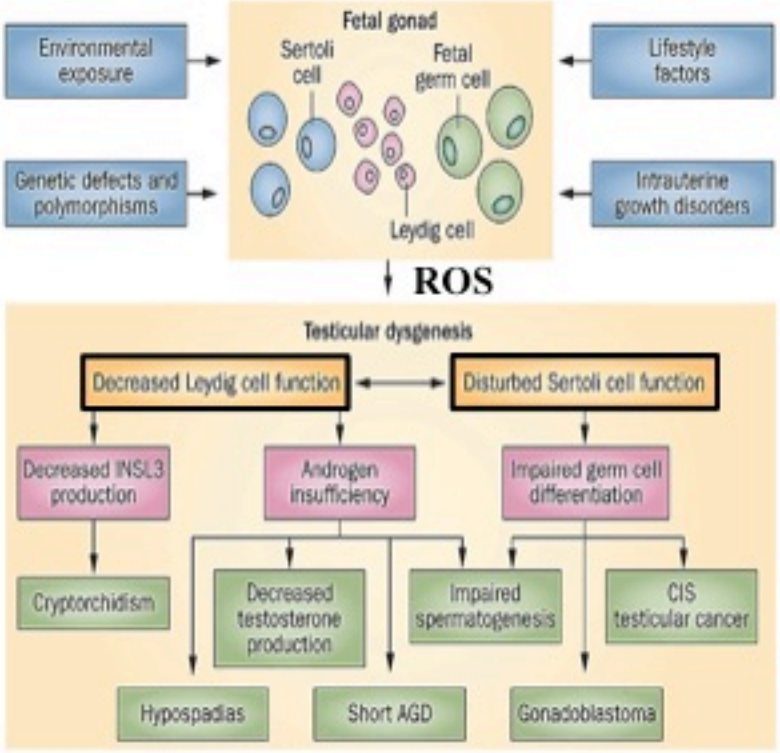
Suresh C. Sikka, Run Wang

Asian Journal of Andrology,
2008 Jan; 10: 134–145,

Table 1. Endocrine disruptors that affect male reproduction. CNS, central nervous system; DBCP, dibromochloropropane; DDT, dichlorodiphenyl-trichloroethane; HPG, hypothalamic-pituitary-gonadal; KTZ, ketoconazole; ROS, reactive oxygen species; LPO, lipid peroxidation; T, testosterone.

Class	Agent	Adverse effects
Environmental		
Organochemicals and pesticides	DBCP DDT PCBs Dioxins Methyl chloride	[↓ fertility, ↓ libido, embryo fetal loss, birth defects, cancer, estrogenic effects, poor semen quality]
Heavy metals	Lead Mercury Cadmium Cobalt Chromium	[↓ HPG axis, ↓ spermatogenesis, CNS effects, testicular damage]
Ionizing radiations	α- and β-rays	[direct/indirect effect on gonads]
Biological		
	Hyperthermia	[↑ ROS, ↓ T biosynthesis, ↓ spermatogenesis, testicular damage, poor sperm morphology]
	Superoxide, and Nitric oxide radicals	[↑ ROS, ↓ antioxidants, ↓ sperm function]
	Oxidative Stress	[↑ ROS, ↑ LPO, ↑ cytokines, ↓ T, ↓ sperm function]
Pharmacological		
Radiation therapy	X-rays, γ-rays	[germ cell and Leydig cell damage]
Drugs/Phytoestrogens	GnRH-analogs KTZ, Leuprolide Cyclosporine Lithium, Narcotics Anabolic steroids Ethanol, Nicotine Flutamide, Gossypol Marijuana	[↓ HPG-axis, ↓ sperm, ↓ libido, ↓ steroidogenesis]

Possible fetal determinants of male infertility
Juul et al. Nat Rev Endocrinol 10: 553-562, 2014.



Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium

Lancet Oncol 2017; 18: e75-90

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant or discordant
Who needs impaired spermatogenesis surveillance?					
At risk		All survivors			
Alkylating agents*	Yes	Not specified	Yes	Yes	Discordant
Procarbazine	Yes	Not specified	Yes	Not specified	Discordant
Temozolamide, dacarbazine	Yes	Not specified	Yes	Not specified	Discordant
Carboplatin, cisplatin	Yes	Not specified	Yes	Not specified	Discordant
Cytarabine	Not specified	Not specified	Yes	Not specified	Discordant
Radiotherapy exposing testes†	Yes	Not specified	Yes	Yes	Discordant
Unilateral orchiectomy	Yes	Not specified	Not specified	Not specified	Discordant
Highest risk					
Higher doses alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Alkylating agent dose	MOPP ≥3 cycles or more Busulfan (≥600 mg/m²) Cyclophosphamide (≥7·5 g/m²) Cyclophosphamide for HSCT Ifosfamide (≥60 g/m²)	Not specified	Not specified	Not specified	Discordant
Combination alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Higher dose radiotherapy exposing testes	Yes	Not specified	Not specified	Not specified	Discordant
Radiotherapy dose	1–3 Gy: azoospermia possibly reversible 3–6 Gy: azoospermia possibly reversible (but unlikely) 6 Gy or more: azoospermia probably permanent	Not specified	Not specified	Not specified	Discordant
Alkylating agents and radiotherapy exposing testes	Yes	Not specified	Not specified	Not specified	Discordant
Unilateral orchiectomy and radiotherapy exposing testes or alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Bilateral orchiectomy†	Yes	Not specified	Not specified	Not specified	Discordant
Which surveillance modality should be used?					
Tanner staging	Yes	Yes	Yes	Yes	Concordant
Testicular volume	Yes	Yes	Yes	Yes	Concordant
FSH	Yes	Yes	Yes	Yes	Concordant
Inhibin B	Not specified	Not specified	Yes	Not specified	Discordant
Semen analysis	Yes	Yes	Yes	Yes	Concordant
At what frequency should impaired spermatogenesis surveillance be performed?					
Tanner staging	Every 1 year (until sexually mature)	Every visit	Every 0·5 year (all survivors, until sexually mature)	Not specified	Discordant
Testicular volume	Every 1 year	Every visit	Every 0·5 year (all survivors)	Not specified	Discordant
FSH	In sexually mature patients if unable to obtain semen analysis	As clinically indicated	Every 0·5–1 years	Not specified	Discordant
Inhibin B	N/A	N/A	Every 0·5–1 years (if available)	N/A	N/A
Semen analysis	As requested by patient	As clinically indicated	When appropriate	Not specified	Partly concordant

ciclofosfamide

Low-risk: vincristine, vinblastine, methotrexate

> 0.35 Gy

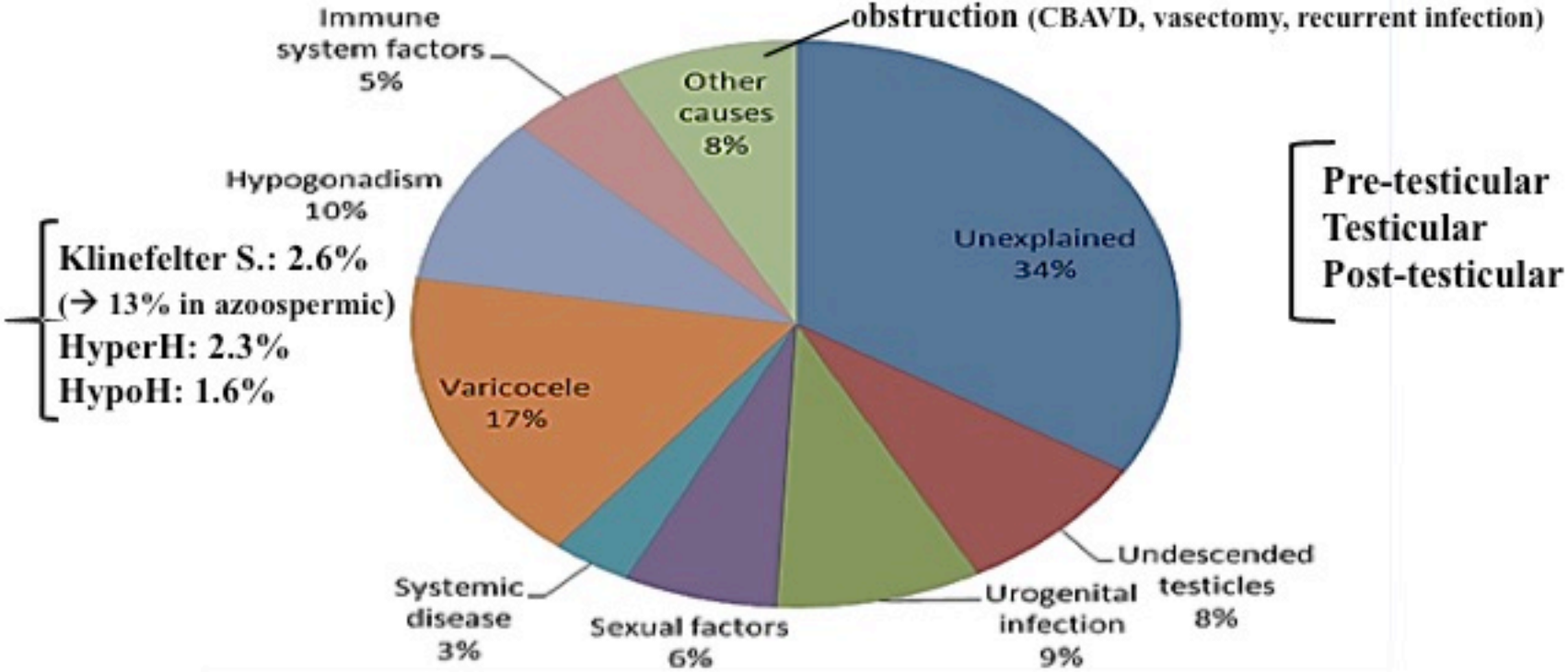
	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant or discordant
Who needs testosterone deficiency surveillance?					
At risk		All survivors			
Alkylating agents*	Yes	Not specified	Yes	Yes	Discordant
Procarbazine	Yes	Not specified	Yes	Not specified	Discordant
Temozolamide, dacarbazine	Yes	Not specified	Yes	Not specified	Discordant
Carboplatin, cisplatin	Yes	Not specified	Yes	Not specified	Discordant
Cytarabine	Not specified	Not specified	Yes	Not specified	Discordant
Radiotherapy exposing testes†	Yes if 20 Gy or more	Not specified	Yes	Yes	Discordant
Unilateral orchiectomy	Yes	Not specified	Not specified	Not specified	Discordant
Highest risk					
Higher doses alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Alkylating agent dose	MOPP Cyclophosphamide (≥ 20 g/m²) Cyclophosphamide for HSCT Ifosfamide (≥ 60 g/m²)	Not specified	Not specified	Not specified	Discordant
Combination alkylating agents	Yes	Not specified	Not specified	Not specified	Discordant
Higher doses radiotherapy exposing testes	Yes	Not specified	Not specified	Not specified	Discordant
Radiotherapy dose	20 Gy or more	Not specified	Not specified	Not specified	Discordant
Radiotherapy exposing testis	Yes	Not specified	Not specified	Not specified	Discordant
Alkylating agents and radiotherapy exposing testes	Yes	Not specified	Not specified	Not specified	Discordant
Bilateral orchiectomy‡	Yes	Not specified	Not specified	Not specified	Discordant
Which surveillance modality should be used?					
Height and weight	Not specified	Yes	Yes	Yes	Discordant
Testicular volume	Yes	Yes	Yes	Yes	Concordant
LH	Not specified	Yes	Yes	Yes	Discordant
Testosterone	Yes	Yes	Yes	Yes	Concordant
At what frequency should testosterone deficiency surveillance be performed?					
Tanner staging	Every 1 year (until sexually mature)	Every visit	Every 0-5 year (all survivors, until sexually mature)	Not specified	Discordant
Testicular volume	Every 1 year	Every visit	Every 0-5 year (all survivors)	Not specified	Discordant
LH	N/A	As clinically indicated	Every 0-5–1 years	Not specified	Discordant
Testosterone	Baseline at age 14 years and as clinically indicated (ideally morning)	As clinically indicated	Every 0-5–1 years	Not specified	Discordant

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

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

EUROPEAN UROLOGY 62 (2012) 324–332

Causes of male infertility



Klinefelter S.: 2.6%
(→ 13% in azoospermic)
HyperH: 2.3%
HypoH: 1.6%

Pre-testicular
Testicular
Post-testicular

ESAME OBIETTIVO

Da Infertilità maschile
A. Lenzi e L. Gandini, Neolibro 2004

Generale

- Peso
- Altezza
- Pressione arteriosa
- Esame fisico generale
- Caratteri sessuali secondari
- Ginecomastia

Urogenitale

- Pene
- Testicoli
- Epididimi
- Vasi deferenti
- Varicocele
- Esplorazione inguinale
- Esplorazione rettale

L'obesità (BMI ≥ 30 kg/m2) si associa a VT ridotto e ridotta spermatogenesi

Eventuale ipospadia, fimosi, frenulo corto, cicatrici, placche fibrotiche, deviazioni, lesione infiammatorie

Distribuzione pilifera: peli radi o distribuzione femminile possono essere segno di ipoandrogenismo. Per valutare le anomalie nello sviluppo sessuale secondario si usa la scala di Tanner

L'esame va eseguito in ortostatismo. Il VT può essere valutato con l'orchidometro.

Una palpazione leggera deve consentire di apprezzare la dimensione e la struttura. Non devono essere presenti noduli

In età puberale una lieve ginecomastia può essere normale. La ginecomastia può derivare anche dalla esposizione ad estrogeni esogeni o endogeni o a farmaci (digitale, spironolattone)

Dopo ortostatismo per qualche minuto. Importante la temperatura ambientale (> 20°C) e la manovra del Valsalva.

Devono essere entrambi palpabili senza dolore e noduli

Può essere omessa in assenza di sospetto di patologie alle ghiandole accessorie

Cicatrici chirurgiche, lesioni infettive, linfonodi

The significance of clinical practice guidelines on adult varicocele detection and management

Anand Shridharani[1], Ryan C Owen[2], Osama O Elkelany[2], Edward D Kim[2]

Asian Journal of Andrology (2016) 18, 269–275

Table 1: Summary of report recommendations

	AUA[11]	ASRM/SMRU[8]	EAU[10]
Guideline title	The optimal evaluation of the infertile male: AUA best practice statement	Report on varicocele and infertility: a committee opinion	Guidelines on male infertility
Objective	To offer recommendations for the optimal diagnostic evaluation of the male partner of an infertile couple	To provide clinicians with principles and strategies for the evaluation of couples with male infertility problems	To assist urologists and healthcare
Infertile male evaluation	A complete medical history, physical examination by a urologist or other specialist in male reproduction and at least two semen analyses	A careful medical and reproductive history, a physical examination, and at least two semen analyses	
Optimal method to detect varicoceles	Physical exam. Varicoceles graded from 1 to 3	Physical exam. Varicoceles graded from 1 to 3	
Role of scrotal ultrasonography	Indicated in those patients in whom physical examination of the scrotum is difficult or inadequate or in whom a testicular mass is suspected	For inconclusive physical exam	
Role of additional testing	Not stated	Ancillary diagnostic measures, thermography, Doppler	
Indications for treatment of varicocele	Not stated		
Contraindications to treatment	Not stated	Varicocele treatment is not indicated in patients with either normal semen quality, isolated teratozoospermia, or a subclinical varicocele. Also it is not indicated when IVF or IVF-ICSI is otherwise required for the treatment of a female factor infertility	

Present in 25% of pts with abnormal semen analysis

When the male partner of a couple attempting to conceive has a varicocele, treatment of the varicocele should be considered when most or all of the following conditions are met

- The varicocele is palpable on physical examination
- The couple has known infertility
- The female partner has normal fertility or a potentially treatable cause of infertility, and time to conception is not a concern
- The male partner has abnormal semen parameters

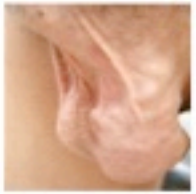
An adult male who is not currently attempting to achieve conception but has a palpable varicocele, abnormal semen analyses and a desire for future fertility, and/or pain related to the varicocele is also a candidate for varicocele repair

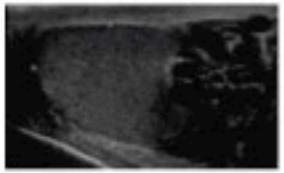
3E.5 Conclusions and recommendations for varicocele

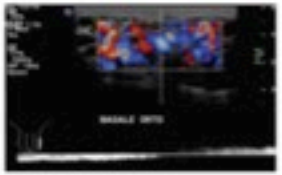
EAU 2015

Conclusions	LE
Current information supports the hypothesis that the presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment.	3
Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility.	1a

Recommendations	GR
Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination.	B
No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended.	A
Varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of ≥ 2 years and otherwise unexplained infertility in the couple.	A







3A.2.2 *Recommendations for the diagnostic evaluation of male infertility*

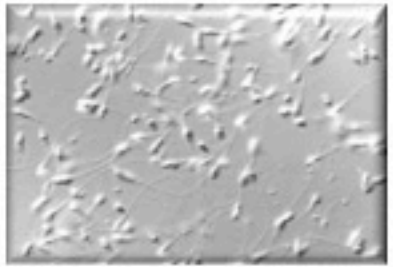
Recommendations	GR
According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests to define a diagnosis.	A*
Diagnosis and evaluation of male subfertility according to the WHO Manual for the standardised investigation, diagnosis and management of the infertile male is recommended [10].	C
Semen analysis must follow the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) [9].	A*
The WHO laboratory manual proposes reference values based on fertility, hence, these reference values do not allow to classify a man as being infertile.	A

WORK-UP PER L'INFERTILITA' MASCHILE (I°LIVELLO)

I. ESAME OBIETTIVO

- ❑ internistico
- ❑ andrologico

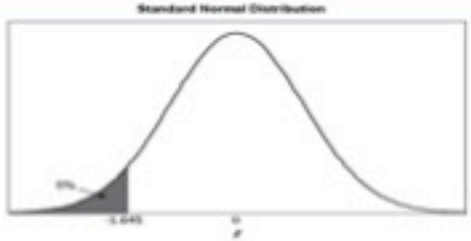
II. ESAME STANDARD DEL LIQUIDO SEMINALE (WHO 2010) +ASA (anti-sperm antibodies, MAR test (IgG, IgA), immunobead test) (fattori di rischio: orchiti, biopsie, varicocele, tumore testicolare, trauma, vasectomia)



WHO 2010 - 5°percentile

Parametri	Valori di riferimento minimi
Volume (ml)	1.5 (1.4-1.7)
Numero spermatozoi/eiaculato (10^6/eiaculato)	39 (33-46)
Numero spermatozoi/ml (10^6/ml)	15 (12-16)
Motilità totale (PR + NP,%)	40 (38-42)
Motilità progressiva (PR,%)	32 (31-34)
Vitalità (spermatozoi vitali,%)	58 (55-63)
Morfologia (forme normali,%)	4 (3.0-4.0)
Altri valori di riferimento	
pH	≥7.2
Leucociti perossidasi-positivi (10^6/ml)	<1.0
MAR test (% di spermatozoi mobili con particelle adese)	<50
Immunobead test (% di spermatozoi mobili con sferule adese)	<50
Zinco seminale (µmol/eiaculato)	≥2.4
Fruttosio seminale (µmol/eiaculato)	≥13
Glucosidasi neutra seminale (mU/eiaculato)	≥20

Valori di riferimento minimi delle caratteristiche seminali (5° percentile e intervallo di confidenza del 95%)



Il 5°percentile **NON** discrimina la popolazione fertile da quella infertile, ma vuole identificare i **VALORI MINIMI** sotto quali i maschi, con maggiore probabilità, contribuiscono alla infertilità in una coppia.

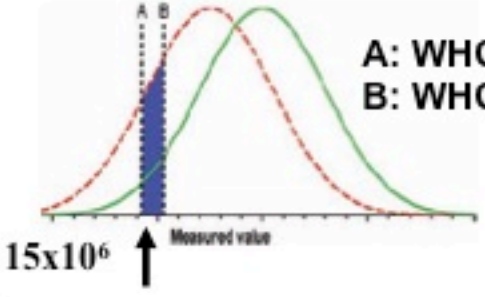


Table 1. Cutoff reference values for semen characteristics as published in consecutive WHO manuals

Semen Characteristics	WHO 1980	WHO 1987	WHO 1992	WHO 1999	WHO 2010*
Volume (mL)	ND	≥2	≥2	≥2	1.5
Sperm count (10^6/mL)	20-200	≥20	≥20	≥20	15
Total sperm count (10^6)	ND	≥40	≥40	≥40	39
Total motility (% motile)	≥60	≥50	≥50	≥50	40
Progressive motility† (%)	≥2†	≥25	≥25 (grade a)	≥25% (grade a)	32 (grade a + b)
Vitality (% alive)	ND	≥50	≥75	≥75	58
Morphology (% normal forms)	80.5	≥50	≥30§	14¶	4‖
Leukocyte count (10^6/mL)	<4.7	<1.0	<1.0	<1.0	<1.0

Table 3. Distribution of semen characteristics of fertile men whose partners had a time-to-pregnancy of ≤12 months, used to establish 2010 WHO manual reference limits, according to percentiles **1800 recent fathers, TTP≤ 1yr**

	Percentile		
Characteristic	5%	50%	95%
Volume (mL)	1.5	3.7	6.8
Sperm count (×10^6/mL)	15.0	73.0	213.0
Sperm count (×10^6/ejaculate)	39.0	255.0	802.0
Motility (%)			
Total	40	61	78
Progressive	32	55	72
Normal*	4	15	44
Alive†	58	79	91

It is important to stress that the reference semen values proposed by the new WHO manual are not suitable to indicate a treatment modality. They merely represent the distribution of the semen profile of a small group of fertile individuals. The choice of assisted reproductive technol-

important, not only to compare patient results with the lower reference limit, but also with the 50th percentile, which represents a value into which 50% of the reference population of "fertile" men falls. This strategy might be more realistic and can help in understanding a patient's seminal profile in relation to the reference group.

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ORIGINAL ARTICLE

Interpretation of semen analysis using WHO 1999 and WHO 2010 reference values: Abnormal becoming normal

S. Alshahrani, K. Aldossari, J. Al-Zahrani, A. H. Gabr, R. Henkel, G. Ahmad

First published: 3 August 2017 Full publication history

DOI: 10.1111/and.12838 View/save citation

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Summary

Reference values of WHO 1999 manual were used for the interpretation of semen analysis until 2010 when new reference values were introduced which have lower cut-off compared to WHO 1999. Therefore, several men who previously were diagnosed abnormal based on their semen analysis have now become normal using new reference values. This study was conducted on semen analyses of 661 men from Middle East region and Pakistan. All semen analyses were reviewed using WHO 1999 and WHO 2010 criteria. Results showed that based on new criteria, 19% of the population changed classification from abnormal to normal when all normal semen parameters were considered. When at least one or more abnormal semen parameters were considered, of the total 661, 44% (288) of the population changed its classification from abnormal to normal with shift from WHO 1999 to 2010 criteria. These findings show that using new cut-off

Normal reference ranges for semen quality and their relations to fecundity

Niels E. Skakkebaek Asian Journal of Andrology (2010) 12: 95–98

However, I have some concerns. The most important problem is that the new WHO guidelines may be less useful for practising physicians working on infertile couples. In our daily work we need a demarcation line between semen quality with 'full reproductive competence' and that of subfertile men who should be referred for andrological work-up. Several recent publications show that a sperm concentration of 15 million spermatozoa per mL is far too low in general to be associated with normal fertility, although some will be able to achieve a conception. Even the previous WHO cut-off value of 20 million spermatozoa per mL was probably too low to identify a significant group of males who need to be referred to andrology experts [7]. We have suggested a higher cut-off value of 40 million spermatozoa per mL, on the basis of a prospective study of first time pregnancy planners (Figure 1) [8]. Similarly, Slama [9], Guzick [10]

the guidelines may do more harm than good. Two cut-off values for sperm counts seem needed. One of them should be much higher than the proposed, probably in the range of 40 million spermatozoa per mL, as previously suggested [12]. It is common knowledge that unless a man has azoospermia, conception may occur. Therefore it is not surprising that the WHO databases on semen quality of men whose partners were pregnant contained some very low values. Nevertheless, the fecundity of a man decreases progressively with sperm concentrations below 40 million per mL. The other cut-off value could be 15 million spermatozoa per mL as suggested. Thus, the area between 15 and 40 million spermatozoa per mL would delineate a grey subfertility zone.

In addition to revising reference limits for sperm counts the committee should perhaps look again at other cut-off values for semen quality parameters, including 'normal forms'. Here the proposed new lower reference limit of 4% normal forms (using strict criteria) seems to be rather low, neglecting results from recent studies suggesting that values up to 9%–12% normal forms may be associated with subfertility or infertility [10].

In conclusion, a high proportion of subfertile men in involuntary childless relationships have parameters of semen quality above the new WHO proposed cut-off values. If the new guidelines are left unchanged, a large group of subfertile men all over the world may not receive appropriate andrological help in the future. In addition,

Abbassare la soglia

- **riduce la sensibilità**

(identificare correttamente gli infertili)

- **aumenta la specificità**

(identificare correttamente i fertili)

Methods We evaluated two semen specimens from each of the male partners in 765 infertile couples and 696 fertile couples at nine sites. The female partners in the infertile couples had normal results on fertility evaluation. The sperm concentration and motility were

Results The subfertile ranges were a sperm concentration of less than 13.5×10^6 per milliliter, less than 32 percent of sperm with motility, and less than 9 percent with normal morphologic features. The fertile ranges were a concentration of more than 48.0×10^6 per milliliter, greater than 63 percent motility, and greater than 12 percent normal morphologic features. Values between these ranges indicated indeterminate fertility. There was extensive overlap between the fertile and the infertile men within both the subfertile and the fertile ranges for all three measurements. Although each of the sperm measurements helped to distinguish between fertile and infertile men, none was a powerful discriminator. The percentage of sperm with normal morphologic features had the greatest discriminatory power.

Conclusions Threshold values for sperm concentration, motility, and morphology can be used to classify men as subfertile, of indeterminate fertility, or fertile. None of the measures, however, are diagnostic of infertility. (N Engl J Med 2001;345:1388-93.)

Sperm Measurement	Sensitivity	Specificity
	percent	
Concentration		
10.0×10^6/ml	10.2	96.8
13.5×10^6/ml*	14.8	96.1
48.0×10^6/ml†	57.1	58.0
60.0×10^6/ml	67.7	45.0
Percentage of motile sperm		
25	8.1	97.7
32*	15.3	95.1
63†	84.6	26.2
75	98.6	2.7
Percentage with normal morphologic features		
5	18.6	93.8
9*	43.3	81.4
11†	60.8	65.3
15	75.6	41.0

, M.D.,

345:1388-93.)

R COMBINATIONS

F SPERM MEASUREMENTS.*

UREMENT RANGE		ODDS RATIO (95% CI)
ILITY	CONCENTRATION	
ile	Fertile	1.0
ile	Fertile	2.9 (2.2–3.7)
fertile	Fertile	2.5 (1.6–4.2)
ile	Subfertile	2.2 (1.3–3.6)
fertile	Fertile	7.2 (4.3–12.2)
ile	Subfertile	6.3 (3.8–10.3)
fertile	Subfertile	5.5 (3.0–10.2)
fertile	Subfertile	15.8 (8.7–29.0)

New WHO-reference limits—revolution or storm in a teapot?

Gerhard Haidl

Asian Journal of Andrology (2011) 13, 208–211

- Routine semen analysis provides useful information concerning sperm production by the testes, sperm motility and viability, the patency of the male genital tract, the secretions of the accessory organs, as well as ejaculation and emission. Hence, the information obtained by this procedure is obviously useful for the initial evaluation of the infertile male.

- During andrological work-up, reductions in a single semen parameter has only limited prognostic value. In a comprehensive approach, the results of physical examination as well as the cumulative importance of various laboratory findings including hormone analysis, etc., have to be considered.

- The investigation and treatment should not focus on unspecific symptoms but on any potential underlying disorder, thus reducing or even eliminating the contribution of the male partner to couple subfertility.

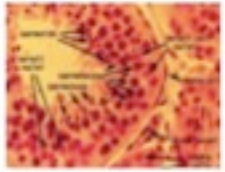
- However, as far as the diagnosis of sub- or infertility is concerned, **semen analysis does not represent a definitive test of male fertility.**

WORK-UP PER L'INFERTILITA' MASCHILE (II°LIVELLO)

III. VALUTAZIONE ORMONALE (conta nemaspemica < 10 mil/ml, reperti clinici suggestivi di endocrinopatie, alterazione della funzione sessuale)

- **LH, FSH (v.n. < 7-8 U/L), PRL, testosterone totale (h. 7-11, v.n. > 350 ng/dL)**

- **I livelli di FSH correlano in maniera inversa con il numero di spermatogoni**
- **I livelli di FSH sono normali se l'arresto maturativo avviene a livello di spermatociti o spermatidi e nelle azoospermie ostruttive**



IV. VALUTAZIONE MICROBIOLOGICA

- **Spermiocoltura/Tampone uretrale: Mycoplasma hominis, Ureaplasma Urealyticum, Clamidia Trachomatis, Gram +, Gram-**

Table 3 Characteristic endocrine profiles of infertile men.

Condition	T	FSH	LH	PRL
Normal	Normal	Normal	Normal	Normal
Primary testis failure	Low	High	Normal/high	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Hyperprolactinemia	Low	Low/normal	Low	High
Androgen resistance	High	High	High	Normal

FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone.

Turek PJ. Practical approaches to the diagnosis and management of male infertility. *Nat Clin Pract Urol* 2: 226–238, 2005.

WORK-UP PER L'INFERTILITA' MASCHILE (II° LIVELLO)

V. TEST GENETICI

- **Cariotipo** (aneuploidia, inversioni, translocazioni): da eseguire nell'azoospermia non ostruttiva (NOA): 10-15% e nell'oligozoospermia severa: < 5 mil/ml: ~5%

- **Microdelezioni del cromosoma Y**: da ricercare nell'azoospermia non ostruttiva (NOA): 8-16% e nell'oligozoospermia severa < 5 mil/ml: 3-7%.
  Rare (< 1%) se conta nemaspermica > 5 mil/ml.
  AZFc (65-70%, azoospermia→ oligozoospermia, TESE+), AZFa (5%)→ SCO

- **Mutazioni del gene CFTR (cystic fibrosis conductance regulator)**: da ricercare se almeno un vaso deferente è assente alla palpazione + azoospermia (ostruttiva) + volume seminale < 1.5 ml e pH < 7. Mutazioni trovate nel 80% pts (max ΔF508)

Recommendations	GR
From a diagnostic view point, standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa < 5-10 million/mL) who are seeking fertility treatment by IVF.	B
Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A
All men with Klinefelter's syndrome need long-term endocrine follow-up and usually require androgen replacement therapy.	A
Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.	A
Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling.	A
If complete AZFa or AZFb microdeletions are detected, micro-TESE should not be performed because it is extremely unlikely that any sperm will be found.	A
If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.	A
When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.	A

Guidelines on

Male Infertility

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

Genetic infertility

WORK-UP PER L'INFERTILITA' MASCHILE (2°LIVELLO)

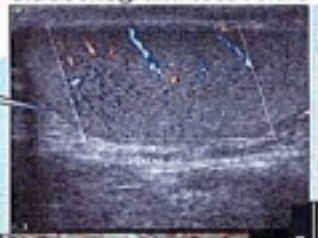
Valutazione clinica - Approfondimenti diagnostici

Per completare la diagnosi può essere opportuno approfondire le indagini con tecniche di imaging (ultrasonografia e u. Doppler) e biopsia testicolare.

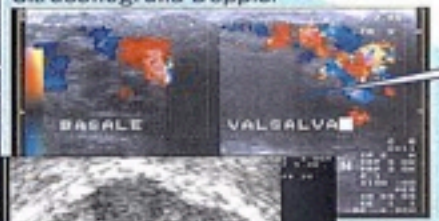
Eco-doppler testicolare

«Deve essere eseguita con sonda lineare 7,5 Mhz; devono essere descritte le dimensioni testicolari, l'eventuale presenza di idrocele, una accurata descrizione dei didimi (posizione, forma, struttura, ecogenicità parenchimale, lesioni focali) e fornita una accurata descrizione degli epididimi nelle varie parti (testa, corpo, coda) e dei deferenti.»

Ultrasonografia testicolare



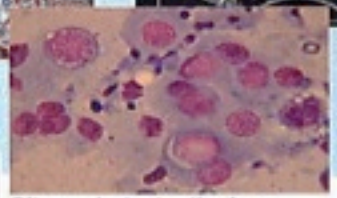
Ultrasonografia Doppler



«Devono essere descritti i parametri velocimetrici arteriosi e venosi con rilievo di eventuali reflussi da varicocele. Una valutazione accurata intratesticolare può identificare focolai di ipermatogenesi attiva.»

Valutazione clinica
- Esame obiettivo

Biopsia testicolare



Citoaspirato testicolare

Ultrasonografia prostato-vescicolare

«Deve essere eseguita con sonda transrettale e deve descrivere con accuratezza anche piccole lesioni, depositi calcifici, ipodensità che denuncino una flogosi prostatica o dilatazioni, fibrosi o concamerazioni vescicolari che siano suggestive di un ristagno seminale.»

«Si può eseguire un citoaspirato con ago sottile o una biopsia a cielo aperto. La prima indagine citologica dovrebbe essere di routine nei centri andrologici; la seconda, istologica, dà informazioni sull'architettura tissutale.»

Da Infertilità maschile
A. Lenzi e L. Gandini, Neolibro 2004

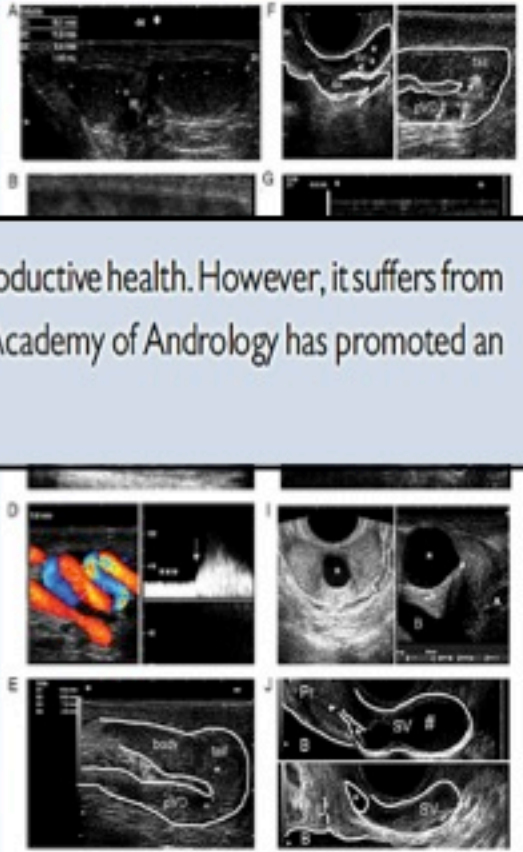
Ultrasound of the male genital tract in relation to male reproductive health

Francesco Lotti and Mario Maggi*

Human Reproduction Update, Vol.21, No.1 pp. 56–83, 2015

Table IV Schematic summary of seminal, ultrasound and hormonal abnormalities in different etiological causes of male infertility.

	Primary hypogonadism*	Secondary hypogonadism*	Complete bilateral EDO	CBAVD§	Proximal bilateral (sub)obstruction	Maturation arrest and SCOS
Semen parameters						
Sperm concentration	Oligo/azoospermia	Oligo/azoospermia	Azoospermia	Azoospermia	Oligo/azoospermia	Azoospermia
Ejaculate volume^	~Reduced	~Reduced	Low	Normal. Reduced if SV	Normal	Normal
Proximal vas deferens°	Normal width	Normal width	Normal/increased	Normal/increased	Normal	Normal width
Deferential ampulla°	Normal width	Normal width	Normal/increased	Normal/increased	Normal	Normal width
Prostate volume°	Reduced	Reduced	Normal	Normal	Normal	Normal
Ejaculatory ducts°	Normal	Normal	Dilated and/or cysts and/or calcifications	Possible abnormalities	Normal	Normal
SV°	Reduced (?)	Reduced (?)	Dilated. No modification with ejaculation#	Possible abnormalities	Normal	Normal
Kidneys	Present	Present	Present	Usually present	Present	Present
Hormones						
T♣	Low	Low	Normal	Normal	Normal	Normal
FSH♣	Elevated	Normal/low	Normal	Normal	Normal	– Maturation arrest: normal; – SCOS: normal/high
LH♣	Elevated	Normal/low	Normal	Normal	Normal	Normal



CONCLUSIONS: MGT-CDUS is a useful tool in detecting abnormalities related to impaired male reproductive health. However, it suffers from a lack of standardization and often produces subjective/vague diagnoses. To fill this gap, the European Academy of Andrology has promoted an ongoing multicenter study aimed at defining the MGT-CDUS characteristics of healthy, fertile men.

WORK-UP PER L'INFERTILITA' MASCHILE (2°LIVELLO)

Limitations of semen analysis as a test of male fertility and anticipated needs from newer tests

Christina Wang, M.D.[a,b] and Ronald S. Swerdloff, M.D.[a]

Fertility and Sterility® Vol. 102, No. 6, December 2014

There are a number of biochemical tests to measure functions of the accessory gland including zinc and acid phosphatase (prostate), fructose (seminal vesicle), and carnitine and alpha-glucosidase (epididymis) (1). These biochemical tests are not routinely performed and are of rare clinical usefulness as biomarkers of male factor infertility.

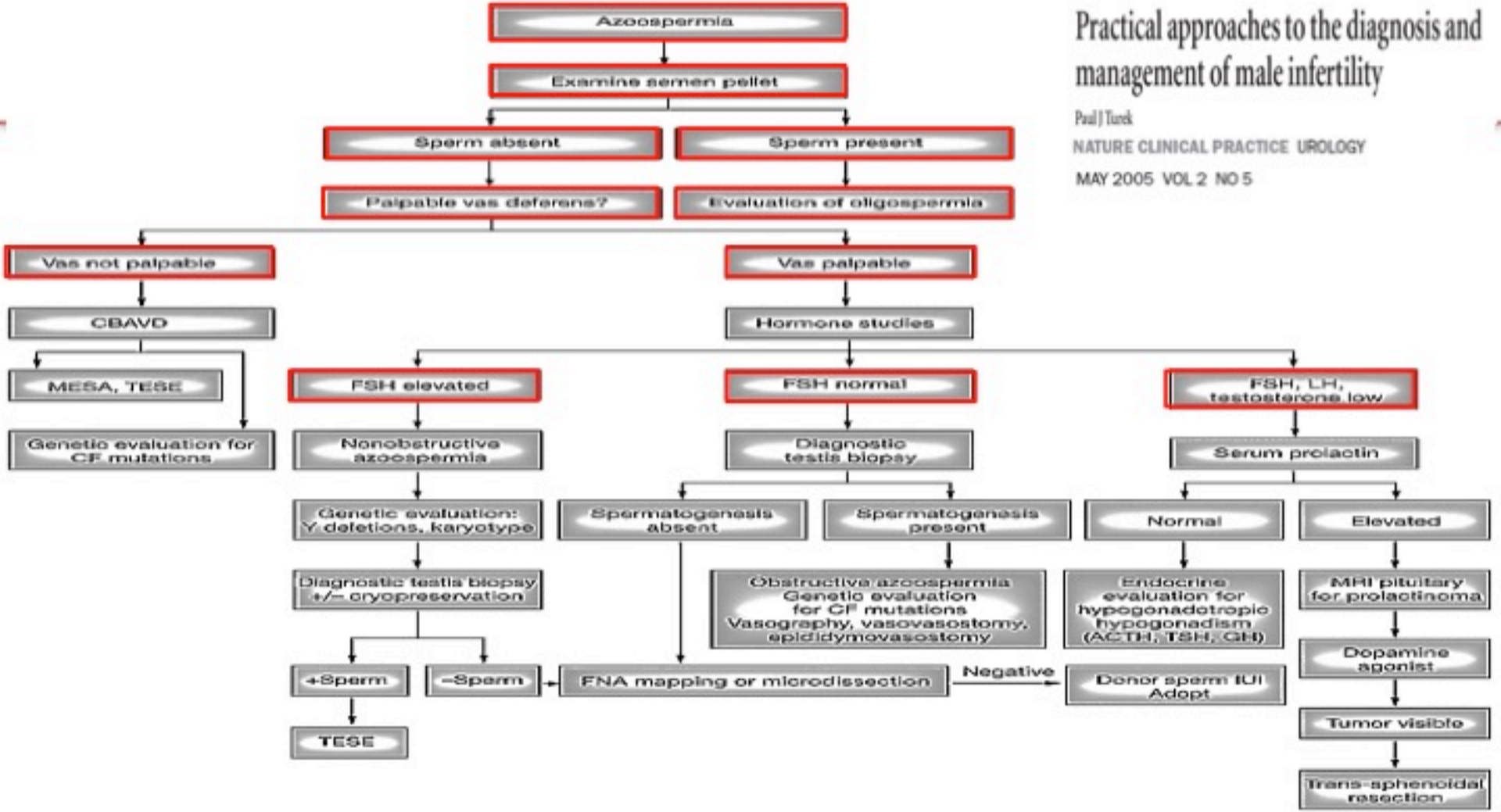
IV. TEST BIOCHIMICI E DI FUNZIONE SPERMATICA

- **Fruttosio seminale (vescichette seminali)**
- **Test di funzione spermatica: CASA, Sperm DNA fragmentation (TUNEL, COMET assay)**

Practical approaches to the diagnosis and management of male infertility

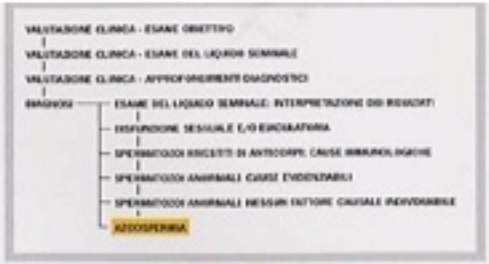
Paul J Turek

NATURE CLINICAL PRACTICE UROLOGY
MAY 2005 VOL 2 NO 5



Azoospermia

Indica la carenza di spermatozoi maturi nel seme, possono essere presenti cellule germinali immature se non vi è ostruzione.



Spermatozoi anormali: cause evidenziabili

Azoospermia

alto — FSH — basso

Danno testicolare primitivo ← **Azoospermia non ostruttiva** → Ipogonadismo Ipogonadotropo

normale

CARIOTIPO - MICRODELEZIONI CROSOMA Y

- Sindrome di Klinefelter classica (47,XXY)
- Sindrome di Klinefelter a mosaico
- 46,XX maschile
- Alterazioni autosomiche

- Sindrome a sole cellule del Sertoli
- Criptorchidismo
- Orchite
- Tumori del testicolo
- Varicocele
- Traumi testicolari
- Torsione funicolo
- Cause iatrogene
- Cause occupazionali
- Cause ambientali

- Infezioni
- Anomalie congenite
- Tumori epididimari
- Traumi
- Fibrosi cistica
- Sindrome di Young
- Cause post-chirurgiche
- Esposizione al mercurio

LH
TESTOSTERONE — alto → Resistenza agli androgeni

normale

ESAME OBIETTIVO — causa evidente di → **Intratesticolare**, **Epididimaria (30-67%)**, **Vasi deferenti**, **Dotti eiaculatori**

causa non evidente

Esplorazione scrotale

Cariotipo
Microdelezioni cr. Y
Citoaspirato
Biopsia testicolare

anormale

VT normale (almeno un didimo>15 ml)
Epididimo con > volume
Noduli epididimo/deferenti
Assenza/atresia parziale dei deferenti

Azoospermia ostruttiva

Valutazione clinica - Approfondimenti diagnostici

anormale

Danno testicolare

Azoospermia ostruttiva

Biochimica seminale

Mutazioni gene CFTR

- Deficit isolato di gonadotropine e/o GnRH
- Sindromi genetiche
- Tumori soprasellari
- Traumi
- Infezioni al SNC
- Deficit vascolare del SNC
- Tumori ipofisari
- Malattie croniche
- Cause iatrogene

Anamnesi

Da Infertilità maschile
A. Lenzi e L. Gandini,
Neolibro 2004

CONCLUSIONI

- **L'infertilità maschile è presente in una significativa percentuale (20-30%) di coppie infertili**
- **Comprende cause :**
  - **che possono essere corrette (modifica dello stile di vita, farmaci, chirurgia)**
  - **irreversibili possibilmente risolvibili con la PMA**
  - **irreversibili: sperm donation o adozione**
- **Richiede un work-up accurato che comprenda una accurata anamnesi, l'esame obiettivo, la valutazione ormonale, genetica (quando indicata) e microbiologica, l'imaging ultrasonografico**
- **Un work-up in centri dedicati permette la risoluzione del problema in una percentuale significativa di soggetti**