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ITALIAN CHAPTER

Iter diagnostico dell'infertilità maschile

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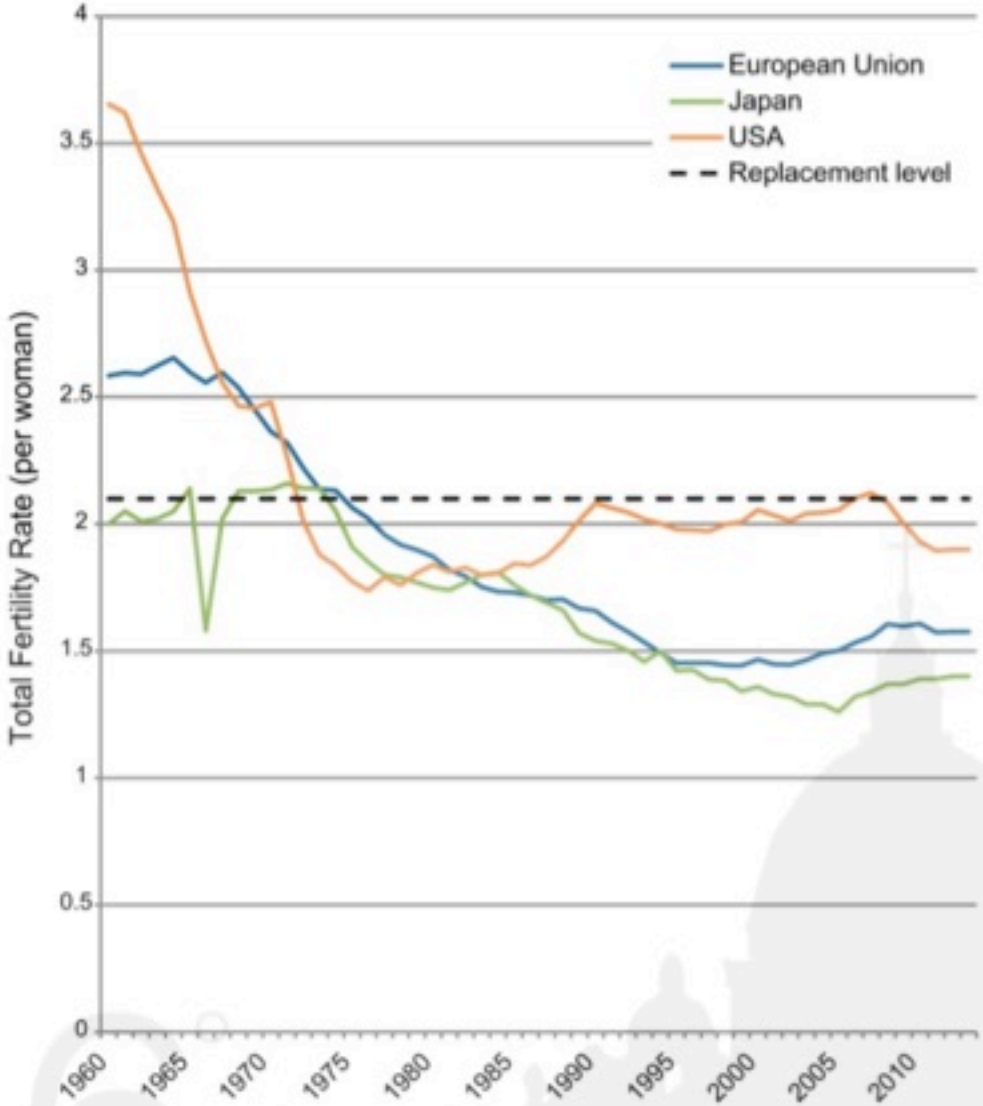
AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

"IL MONDO NASCE PER OGNUN
CHE NASCE AL MONDO"

GIOVANNI PASCOLI

Tasso di infertilità in aumento



Total Fertility Rates (TFR), European Union, Japan and United States, 1960–2013. Dotted line represents a fertility rate of 2.1, below which a population cannot be sustained. From the World Bank: http://databank.worldbank.org/data/views/variableselection/selectvariables.aspx?source=world-development-indicators

Definizione ed epidemiologia dell'infertilità


Ministero della Salute

SCHEDA

Secondo una prima definizione la sterilità, almeno nella donna, andrebbe distinta dall'infertilità, intesa come incapacità di condurre la gravidanza fino all'epoca di vitalità fetale. Nell'uomo, invece, essendo il concetto di aborto ovviamente estraneo alla patologia della riproduzione, i due termini vengono largamente utilizzati come sinonimi.

Secondo un'altra definizione una coppia è considerata infertile quando non è stata in grado di concepire e di procreare un bambino dopo un anno o più di rapporti sessuali non protetti, mentre è sterile la coppia nella quale uno o entrambi i coniugi sono affetti da una condizione fisica permanente che non rende possibile la procreazione. Secondo questa interpretazione il termine "sterilità" si riferisce, quindi, ad una condizione più grave e comunque assoluta di "infertilità" riguardante la coppia e non il singolo membro di essa.

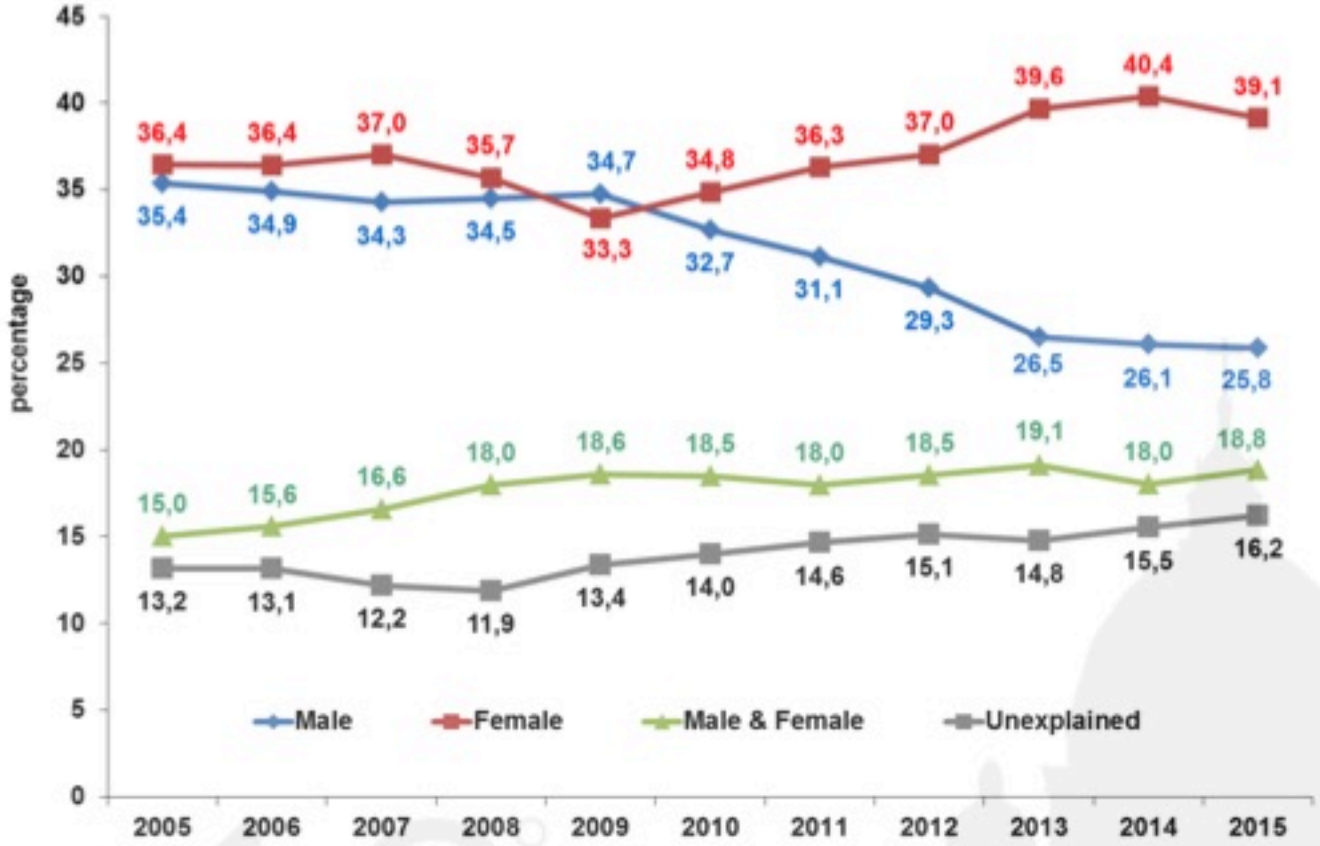
Dati infertilità

- Su 10 coppie il 20% circa (1 su 5) ha difficoltà a procreare per vie naturali
- 20 anni fa la percentuale era circa la metà
- CIRCA IL 40% delle cause di infertilità riguardano prevalentemente la componente femminile, l'altro 40% riguarda la componente maschile ed un 20%invece è di natura mista.
- Negli ultimi 50 anni il numero di spermatozoi nel maschio si è ridotto della metà
- Negli ultimi 30 anni l'età media al concepimento in ambo i sessi è aumentata di quasi 10 anni, sia per l'uomo che per la donna

Agosto 2014

Tasso di infertilità di coppia in aumento: maggior attenzione all'uomo

Figure 8: Time-trends of gender distributions of infertility causes among patients who had ART using fresh cycle, 2015. Total couples treated: 45,689



PMA
REGISTRO NAZIONALE

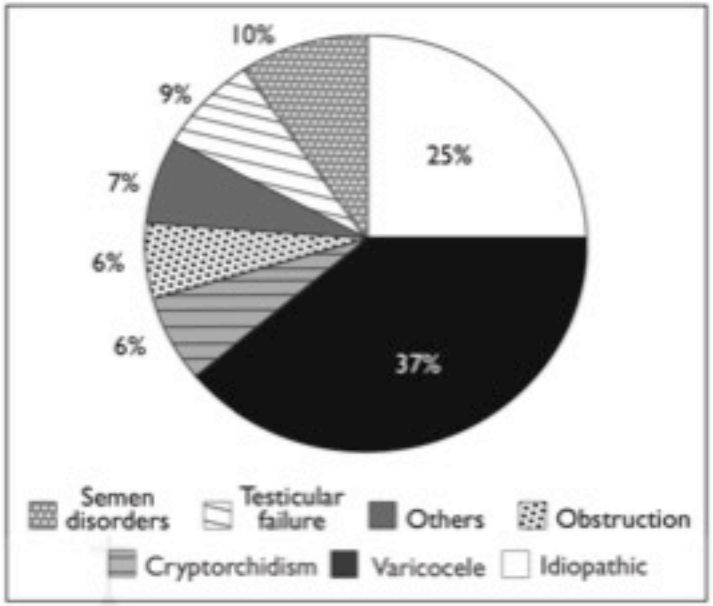
EXECUTIVE SUMMARY for 2015

IARTR – THE ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

Cause di infertilità maschile, a volte sovrapposte

TESTICOLARE

- Primary testicular defect in sperm production
  - Idiopathic
  - Chemotherapy
  - Klinefelter syndrome
  - Genetic mutations
  - Pelvic irradiation or surgery
  - Orchidectomy
  - Testicular cancer
  - Trauma
  - Large varicoceles
  - Cryptorchidism
  - Infection (eg, mumps orchitis in nonvaccinated men)
  - Autoimmune
  - Drugs



- Sexual disorders
  - Erectile dysfunction
  - Failure to have intercourse
    - Lack of libido
    - Relationship dysfunction
    - Anorgasmia

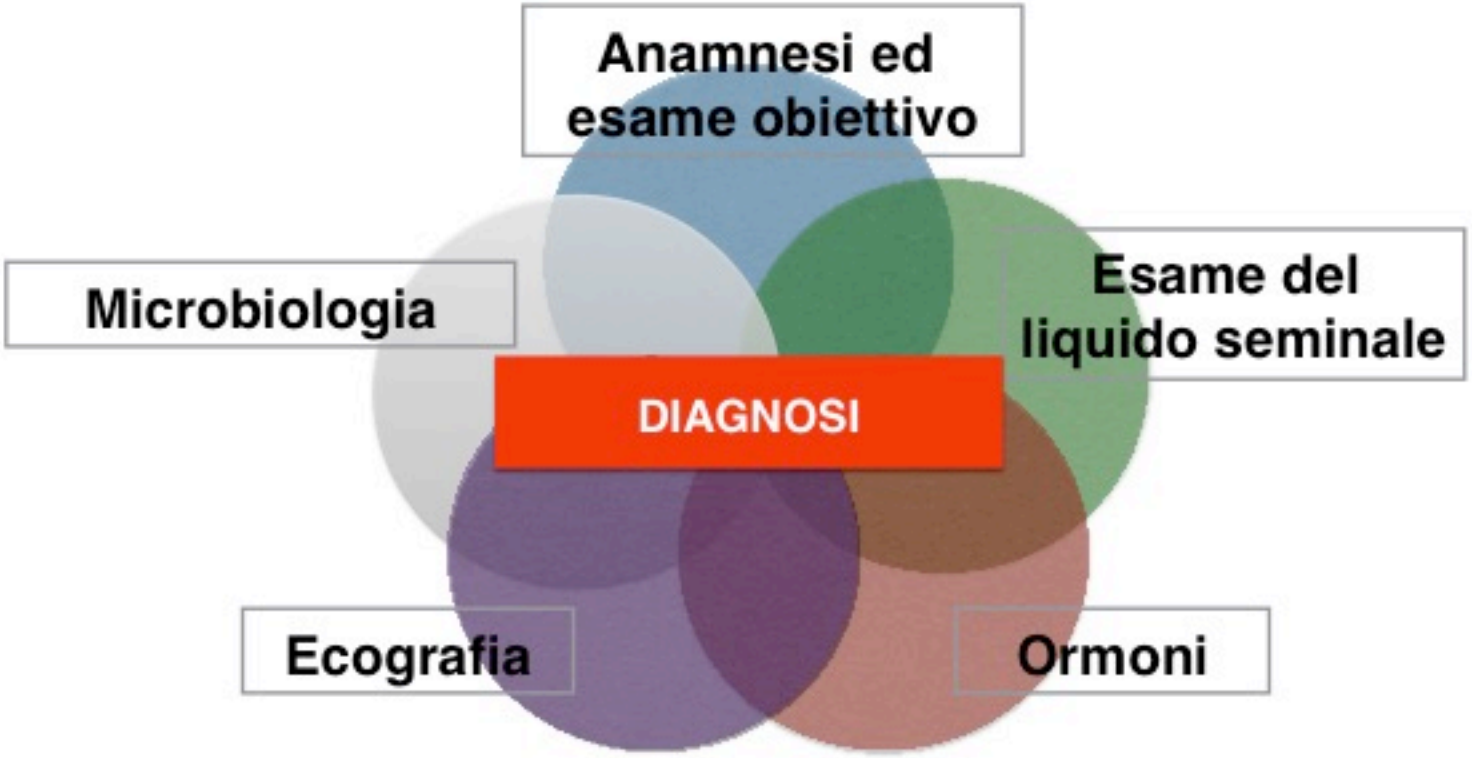
POST-TESTICOLARE

- Defects in sperm transportation
  - Obstruction
    - Congenital absence of the vasa deferens
    - Acquired ejaculatory duct obstruction (eg, recurrent infection, vasectomy)
  - Ejaculatory dysfunction
    - Anejaculation
    - Retrograde ejaculation

PRE-TESTICOLARE

- Endocrinopathies that affect spermatogenesis
  - Hypothalamopituitary disease
  - Hyperprolactinemia
  - Thyroid dysfunction
  - Obesity
  - Cushing syndrome

Infertilità maschile: diagnosi



FNA TESTIS/ biopsia

GENETICA

Infertilità maschile: anamnesi

Dati anamnestici generali	Anamnesi familiare	Anamnesi patologica remota	Malattie dell'apparato uro-genitale	Interventi chirurgici alle vie genitali	Anamnesi lavorativa e stile di vita	Anamnesi sessuale
Età	Infertilità	Febbre alta (nei mesi precedenti)	Criptorchidismo	Orchidopessi	Esposizione a fattori ambientali e occupazionali	Rapporti in periodo fertile
Razza	Aborti spontanei	Diabete mellito	Pubertà precoce o ritardata	Orchiectomia	Abitudini alimentari	Frequenza dei rapporti
Religione	Nati morti	Malattie surrenaliche	Traumi testicolari	Ernia inguinale	Sport	Libido
Professione	Malattie genetiche ed endocrine	Bronchiectasie	Torsione funicolo	Detorsione funicolo	Alcool	Erezione
Infertilità primaria o secondaria		Fibrosi cistica	Orchiti	Varicocelectomia	Fumo	Dispareunia della partner
Durata infertilità		Tubercolosi	Malattie sessualmente trasmesse	Idrocelectomia	Uso di stupefacenti	Caratteristiche della eiaculazione
		Infezioni croniche	Epididimiti	Vasectomia	Sauna	Caratteristiche dell'orgasmo
		Allergie	Prostatiti	Epididimo-vasostomia	Pantaloni stretti	
		Nefropatie	Vescicoliti	Vasovasostomia		
		Epatopatie	Uretriti	Prostatectomia		
		Neuropatie	Dermatosi dei genitali	Interventi vescicali		
		Farmaci		Ipospadia		
				Circoncisione		

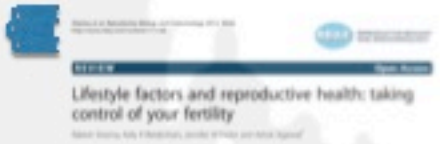
Infertilità maschile: anamnesi - farmaci

Medication	Effect on reproductive function
Anabolic Steroids	Impairment of spermatogenesis (up to one year recovery); may cause hypogonadism through pituitary–gonadal axis
	Reversible
Antiandrogens:	Impairment of spermatogenesis; erectile dysfunction
Cyproterone acetate, danazol, finasteride, ketoconazole, spironolactone	Reversible
Antibiotics:	Impairment of spermatogenesis
Ampicillin, cephalotin, cotrimoxazole, gentamycin, neomycin, nitrofurantoin, Penicillin G, spiramycin	Reversible
Antibiotics:	Impairment of sperm motility
Cotrimoxazole, dicloxacillin, erythromycin, lincomycin, neomycin, nitrofurantoin, quinolones, tetracycline, tylosin	Reversible
Antiepileptics:	Impairment of sperm motility
Phenytoin	Reversible
Antihypertensives:	Fertilization failure
Calcium channel blockers (nifedipine)	
Antihypertensives:	Erectile dysfunction
Alpha agonists (clonidine), alpha blockers (prazocin), beta blockers, hydralazine, methyldopa, thiazide diuretics	
Anti-inflammatory 5-ASA and derivatives:	Impairment of spermatogenesis and sperm motility
Mesalazine, sulfasalazine	Reversible
Antimalarials:	Impairment of sperm motility
Quinine and its derivatives	Reversible
Antimetabolites / Antimitotics:	Arrest of spermatogenesis; azoospermia
Colchicines, cyclophosphamide	Irreversible
Anti-oestrogens	Impairment of endometrial development
Clomiphene citrate	reversible
Anti-progestins:	Impairment of both implantation and tubal function
Emergency contraceptive pills, progesterone-only pills	
Antipsychotics:	Increase prolactin concentrations that can lead to sexual dysfunction
Alpha blockers, phenothiazine, antidepressants (particularly SSRIs)	
Antipsychotics:	Impairment of spermatogenesis and sperm motility
Butyrophenones	Reversible
Antischistozomal:	Impairment of spermatogenesis and sperm motility
Nindazole	Reversible
Corticosteroids	Impairment of sperm concentration and motility
	Reversible
Exogenous testosterone, GnRH analogues	Impairment of spermatogenesis
	Reversible
H2 blockers:	Increase prolactin concentrations that can lead to impairment of luteal function, loss of libido, and erectile dysfunction
Cimetidine, ranitidine	
Local anaesthetics, halothane	Impair sperm motility
Metoclopramide	Erectile dysfunction
Methadone	Suppress spermatogenesis and sperm motility
Non-steroidal anti-inflammatory drugs, Cox-2 inhibitors	Impairment of follicle rupture, ovulation, and tubal function
	Reversible

DOPING

ANTI-METABOLITI ANTI-MITOTICI

IRREVERSIBILE


Lifestyle factors and reproductive health: taking control of your fertility

Infertilità maschile: chemioterapia e radioterapia

SEOM Clinical Guideline of fertility preservation and reproduction in cancer patients (2016)

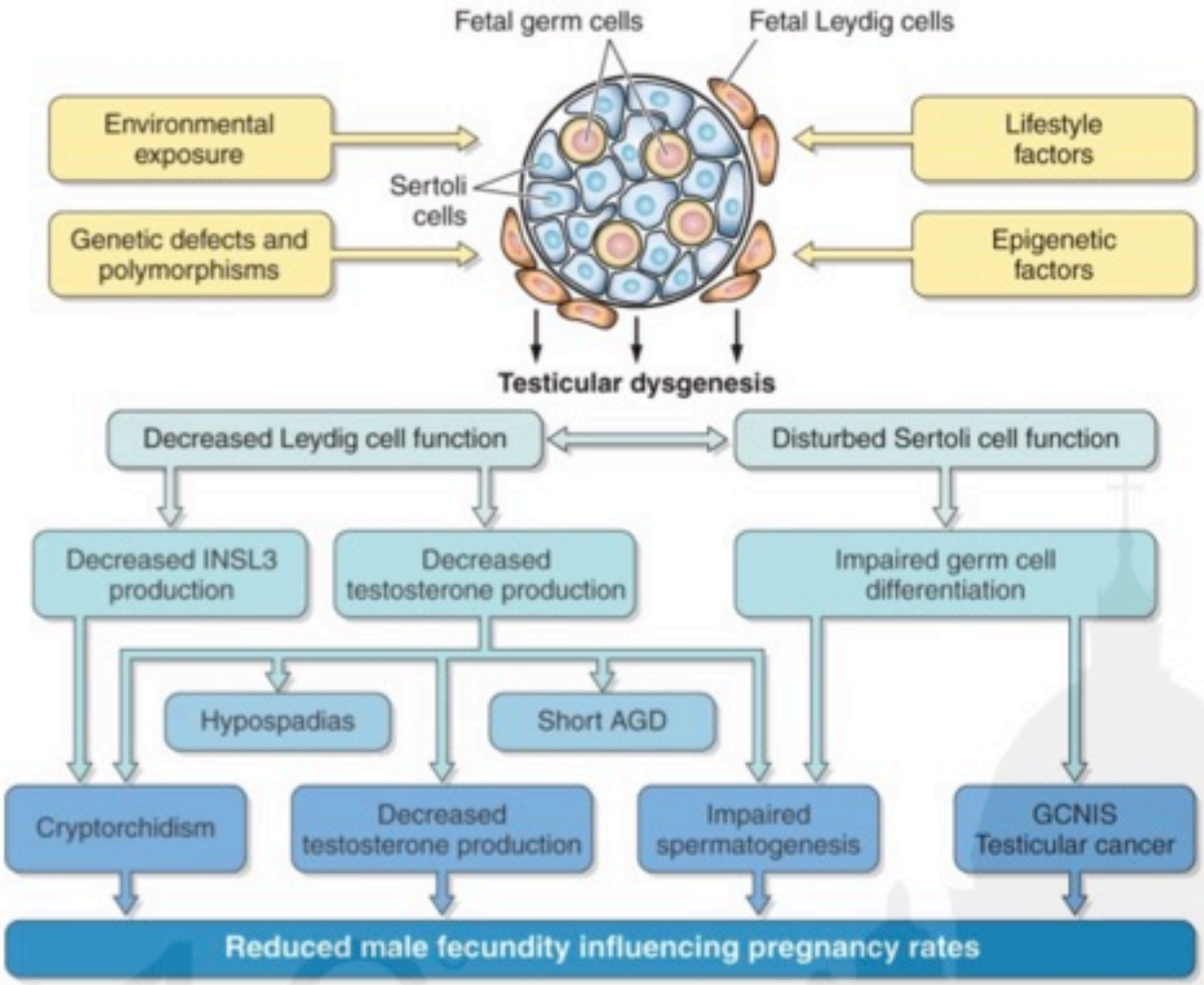
Table 1 Conditions with increased risk of infertility

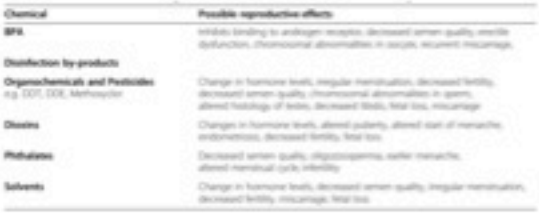
Risk of infertility	Males	Females
High risk (>80% risk of permanent amenorrhea in women; prolonged azoospermia in men)	Radiation >2.5 Gy to testis	Hematopoietic stem cell transplantation with cyclophosphamide
	Chlorambucil (1.4 g/m^2)	Total-body irradiation or cyclophosphamide/busulfan
	Cyclophosphamide (19 g/m^2)	External beam radiation to a field that includes the ovaries
	Procarbazine (4 g/m^2)	CMF, CEF, CAF, TAC × 6 cycles in women ≥40 years
	Melphalan (140 mg/m^2)	
	Cisplatin (500 mg/m^2)	
	BCNU (1 g/m^2) and CCNU (500 mg/m^2)	
Intermediate risk (40– 60% risk of permanent amenorrhea in women; likelihood of azoospermia in men)	Busulfan (600 mg/kg)	BEACOPP
	Ifosfamide (42 g/m^2)	CMF, CEF, CAF, TAC × 6 cycles in women age 30–39
	BCNU (300 mg/m^2)	AC × 4 cycles in women ≥40 years
	Nitrogen mustard	AC or EC × 4 → Taxanes
	Actinomycin D	

AC adriamycin, cyclophosphamide, *BEACOPP* Bleomycin, Etoposide , Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisona, *CAF* Cyclophosphamide , Adriamycin, 5-fluoruracil, *CEF* Cyclophosphamide, Epirrubicin, 5-fluoruracil, *CMF* cyclophosphamide, Methotrexate, 5-fluoruracil, *TAC* Docetaxel, Adriamycin, Cyclophosphamide

CRIO-CONSERVAZIONE GAMETI

Infertilità maschile: ruolo dell'esposizione intra-uterina





The hypothesis of testicular dysgenesis syndrome (TDS) and signs that might be linked to it: poor spermatogenesis, testicular cancer, hypospadias, cryptorchidism, and short ano-genital distance (AGD). The single symptoms and combinations thereof are risk factors for reduced fecundity. [Upd from Skakkebaek et al. (387).]

Ci sono dati sulla relazione tra dieta e Infertilità maschile?

GOOD

Linear regression analysis of eating and social habits that may affect the sperm concentration, sperm motility, and sperm morphology.

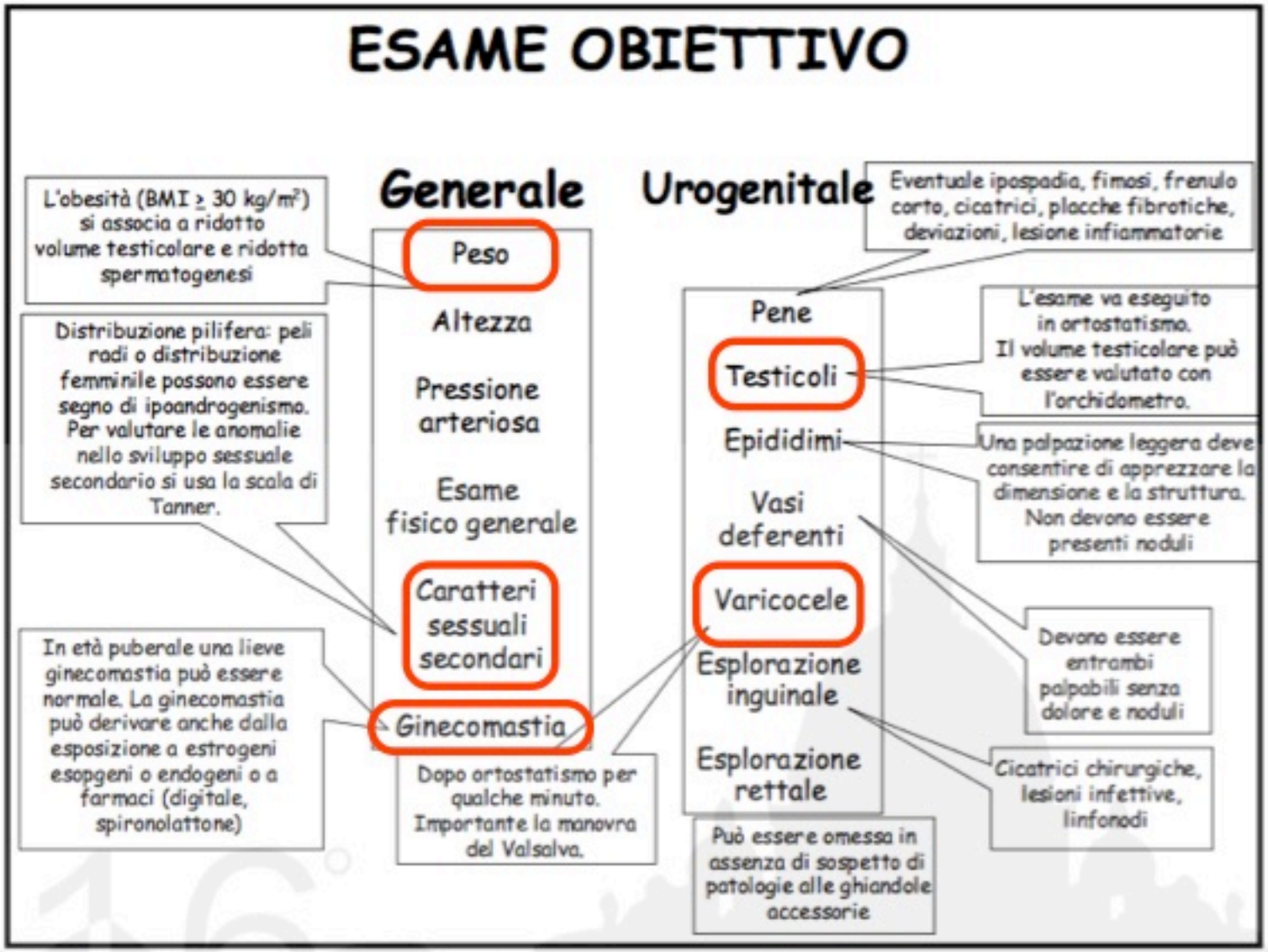
Response variable	Predictor variable	RC	*P* value
Sperm concentration	Cereals	15.293	<.01
	Vegetables	5.380	.104
	Legumes	7.983	.035
	Fruits	5.541	.129
	Meat	−7.776	.310
	Fish	2.764	.441
	Dairy products	2.834	.440
	Sweet foods	−4.046	.089
	Alcoholic drinks	−5.003	<.01
	Soft drinks	−0.233	.897
	Coffee	2.749	.138
	Exercising	7.888	.074
	Weight loss diet	9.487	.045
	Smoking	−0.238	.945
	Meals/d	5.836	.046
	BMI	−2.3331	<.01
Sperm motility	Cereals	10.974	<.01
	Vegetables	9.602	.436
	Legumes	2.861	.444
	Fruits	7.453	.028
	Meat	−0.078	.991
	Fish	4.091	.217
	Dairy products	2.579	.445
	Sweet foods	2.568	.239
	Alcoholic drinks	−8.5592	<.01
	Soft drinks	0.595	.721
	Coffee	−0.109	.949
	Exercising	2.861	.444
	Weight loss diet	−3.848	.374
	Smoking	−8.003	.013
	Meals/d	4.295	.110
	BMI	−2.7780	<.01
Sperm morphology	Cereals	0.749	.327
	Vegetables	6.029	.643
	Legumes	6.823	.326
	Fruits	5.760	.609
	Meat	−5.829	.878
	Fish	6.456	.564
	Dairy products	3.765	.604
	Sweet foods	1.963	.421
	Alcoholic drinks	−8.865	.974
	Soft drinks	0.934	.612
	Coffee	−0.312	.906
	Exercising	3.164	.231
	Weight loss diet	−2.484	.984
	Smoking	−8.003	.567
	Meals/d	3.457	.476
	BMI	−0.876	.573

Note: BMI = body mass index; RC = regression coefficient.

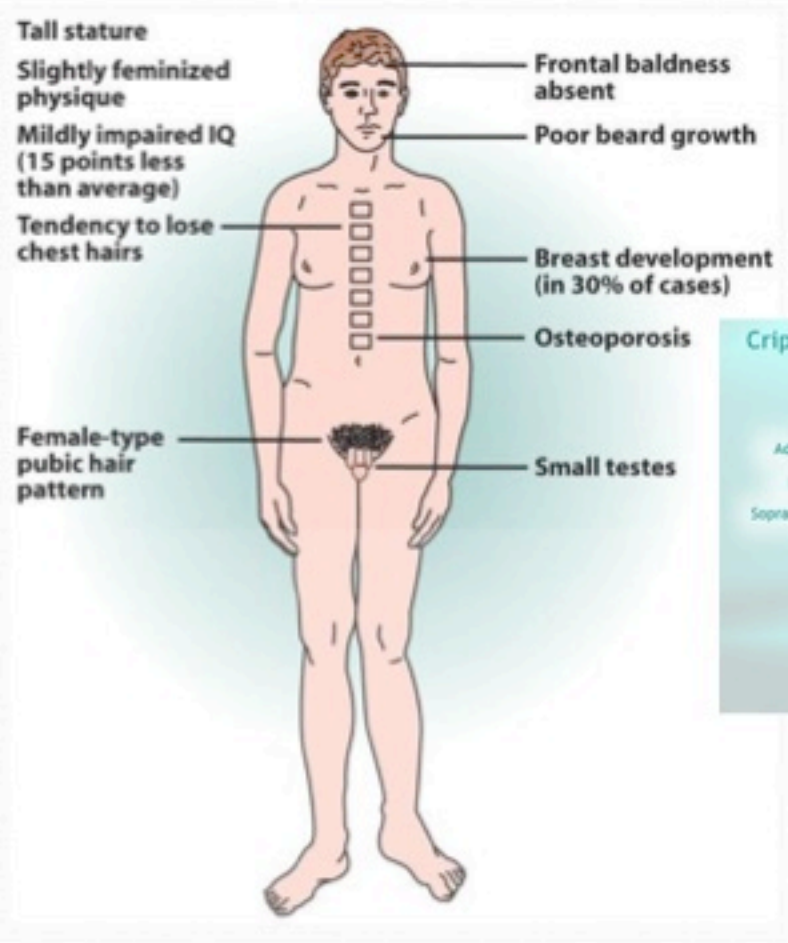
Braga. Lifestyle and assisted reproduction. Fertil Steril 2012.

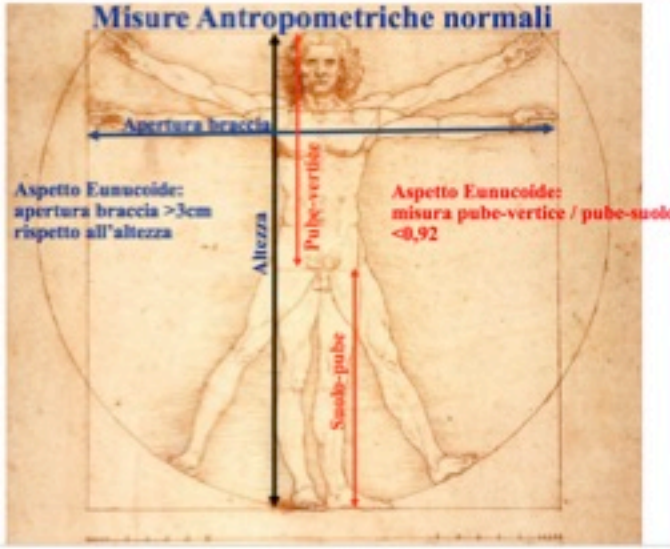
BAD

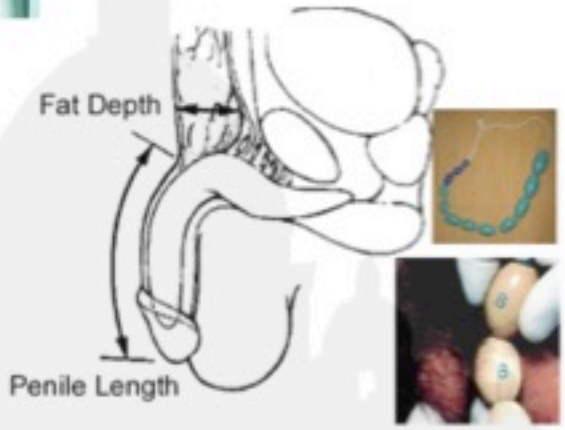
Paes de Almeida Ferreira Braga D 2014 Fertil Steril 97(1)


ESAME OBIETTIVO
Generale
Peso
Altezza
Pressione arteriosa
Esame fisico generale
Caratteri sessuali secondari
Ginecomastia
L'obesità (BMI ≥ 30 kg/m²) si associa a ridotto volume testicolare e ridotta spermatogenesi
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.
In età puberale una lieve ginecomastia può essere normale. La ginecomastia può derivare anche dalla esposizione a estrogeni esopgeni o endogeni o a farmaci (digitale, spironolattone)
Dopo ortostatismo per qualche minuto. Importante la manovra del Valsalva.
Urogenitale
Pene
Testicoli
Epididimi
Vasi deferenti
Varicocele
Esplorazione inguinale
Esplorazione rettale
Eventuale ipospadia, fimosi, frenulo corto, cicatrici, placche fibrotiche, deviazioni, lesione infiammatorie
L'esame va eseguito in ortostatismo. Il volume testicolare può essere valutato con l'orchidometro.
Una palpazione leggera deve consentire di apprezzare la dimensione e la struttura. Non devono essere presenti noduli
Devono essere entrambi palpabili senza dolore e noduli
Cicatrici chirurgiche, lesioni infettive, linfonodi
Può essere omessa in assenza di sospetto di patologie alle ghiandole accessorie

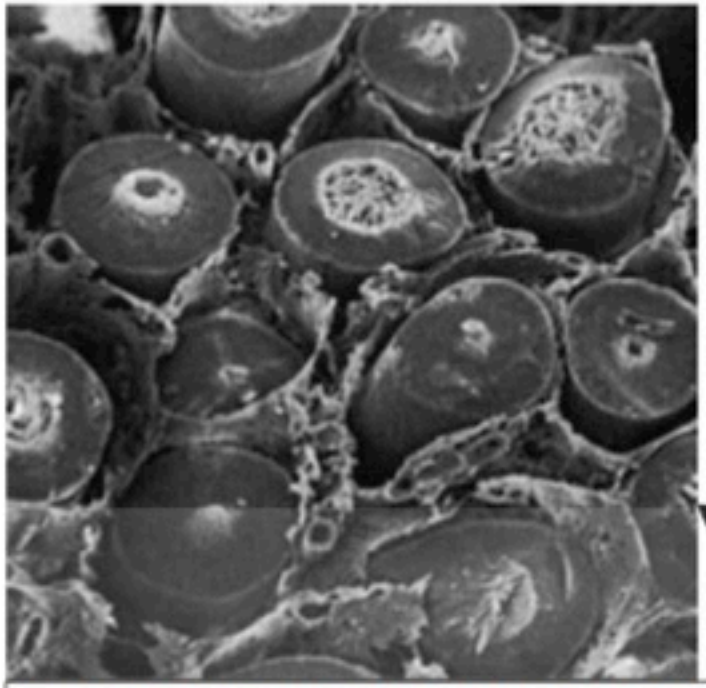
Infertilità maschile: esame obiettivo - ginecomastia e caratteri sessuali secondari

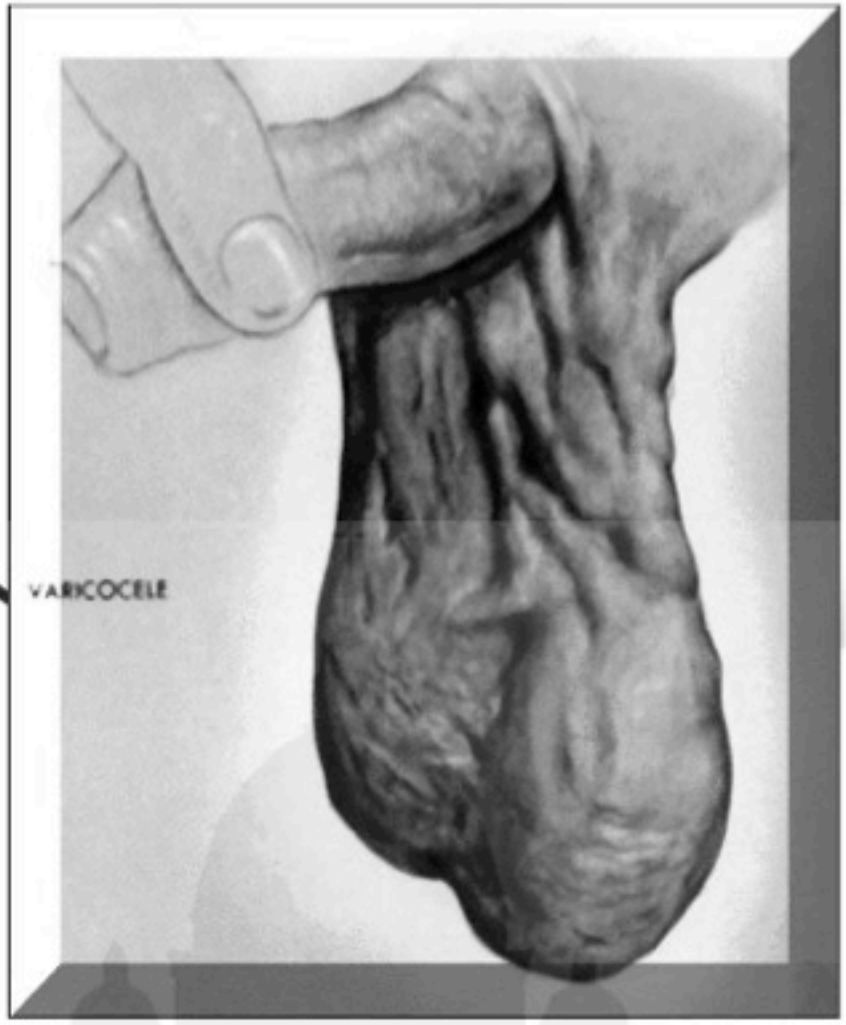






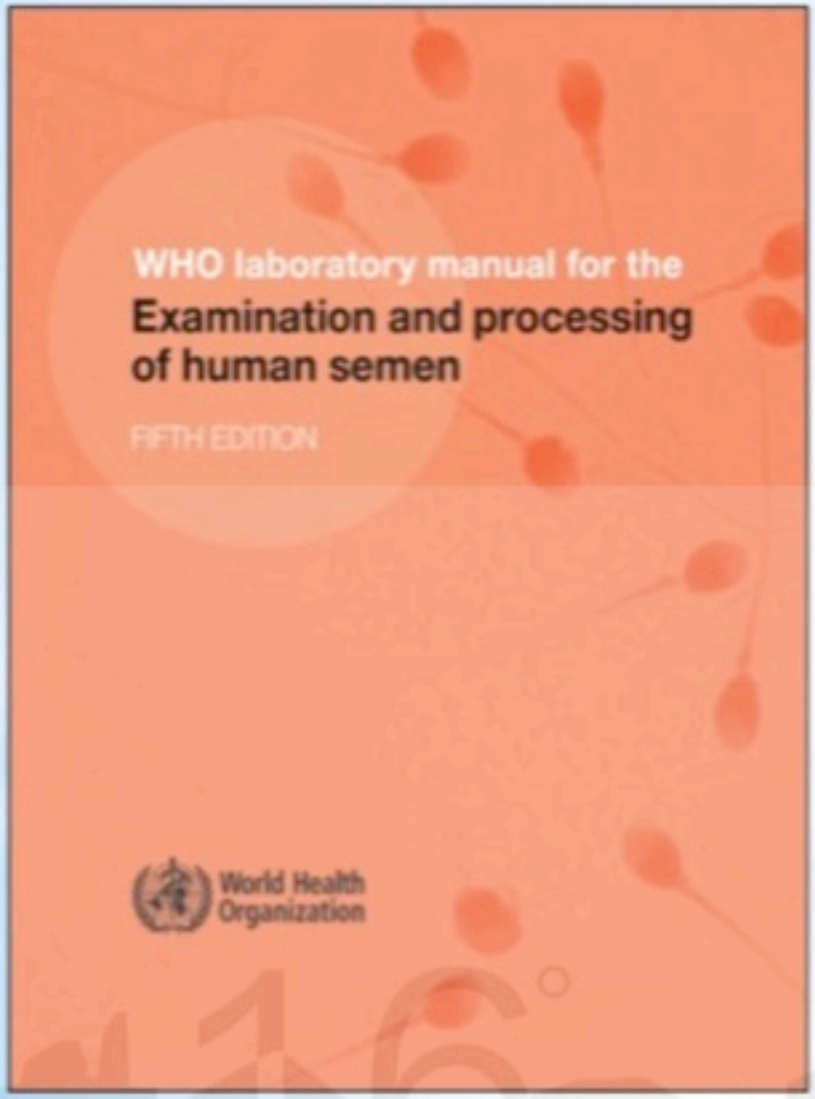
Infertilità maschile: esame obiettivo - varicocele





La dilatazione delle vene del testicolo induce un danno per:
- **Aumento della temperatura**
- **Stasi venosa ed edema**

Infertilità maschile: esame del liquido seminale

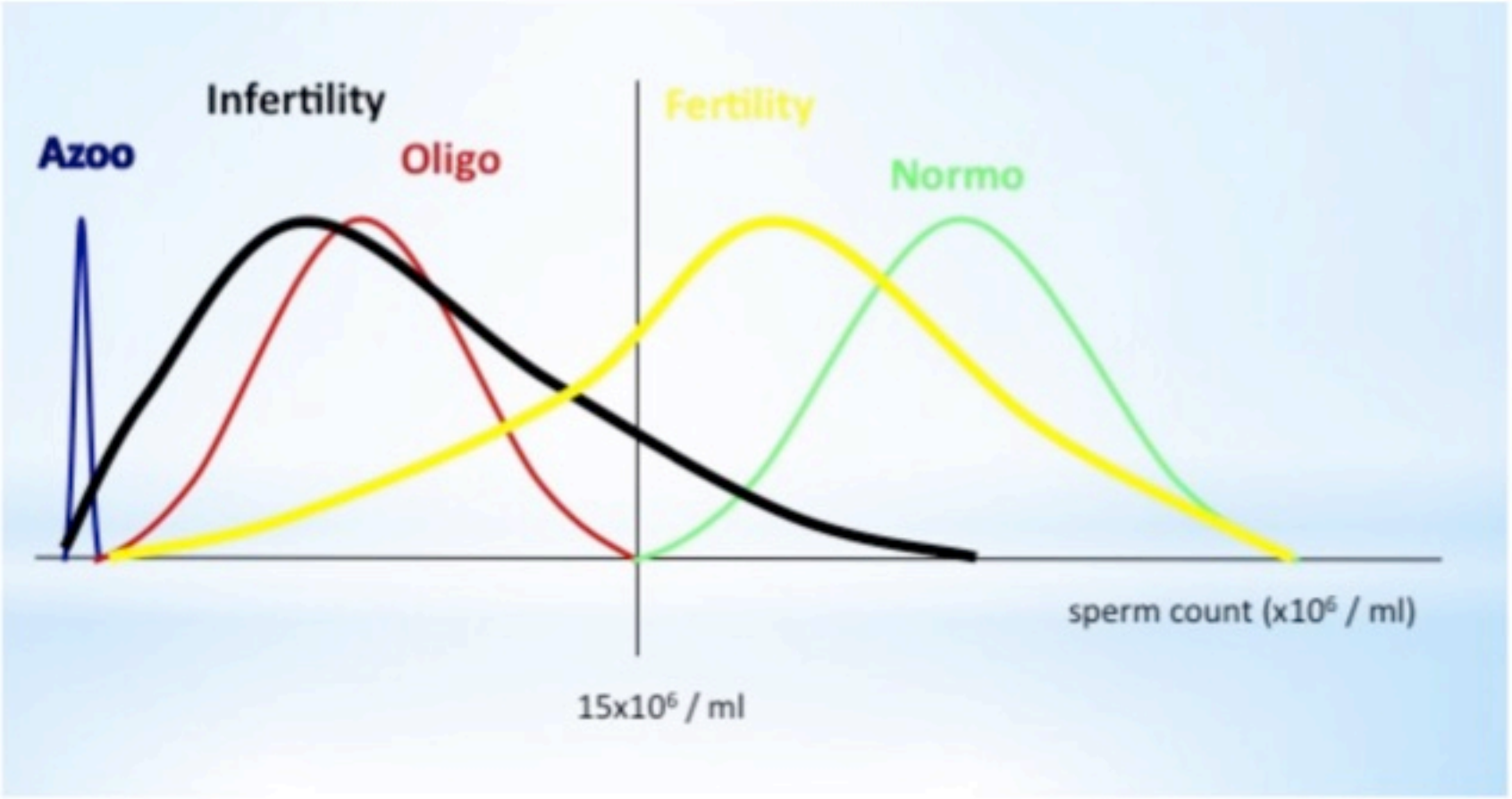


Limite minimo di riferimento WHO 2010

Volume	1.5 (1.4-1.7) mL
Concentrazione	15 (12-16) x 10^6/mL
Numero totale di spermatozoi	39 (33-46) x 10^6/ eiac
Motilità progressiva	32 (31-34) %
Morfologia (forme normali)	4 (3.0-4.0) %
Vitalità	58 (55-63) %

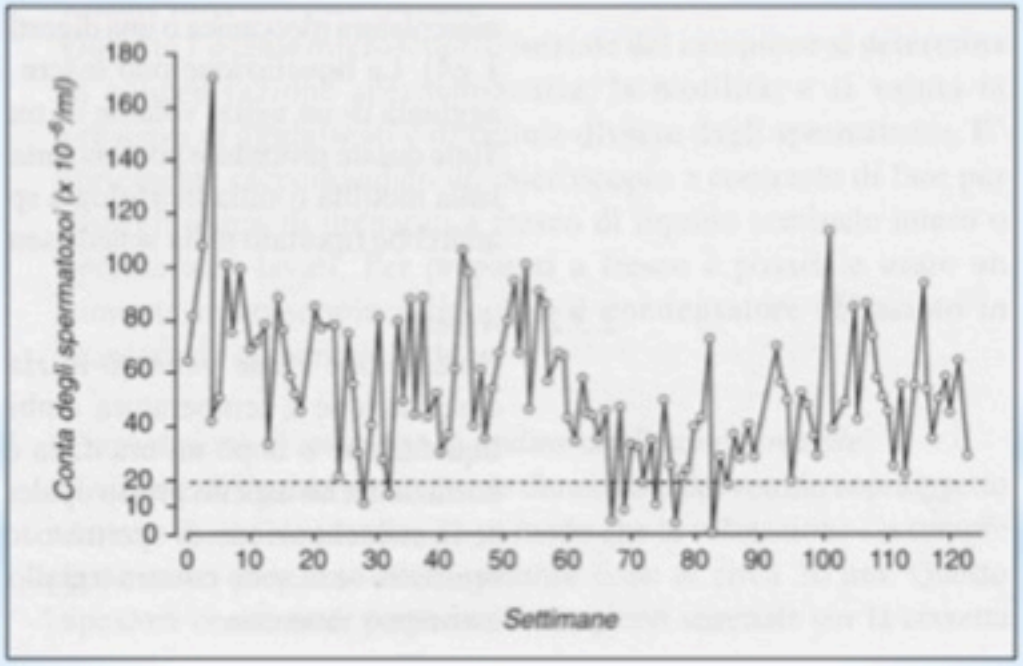
NB: Valori corrispondenti al 5 per centile rispetto alla distribuzione Gaussiana

Infertilità maschile: esame del liquido seminale



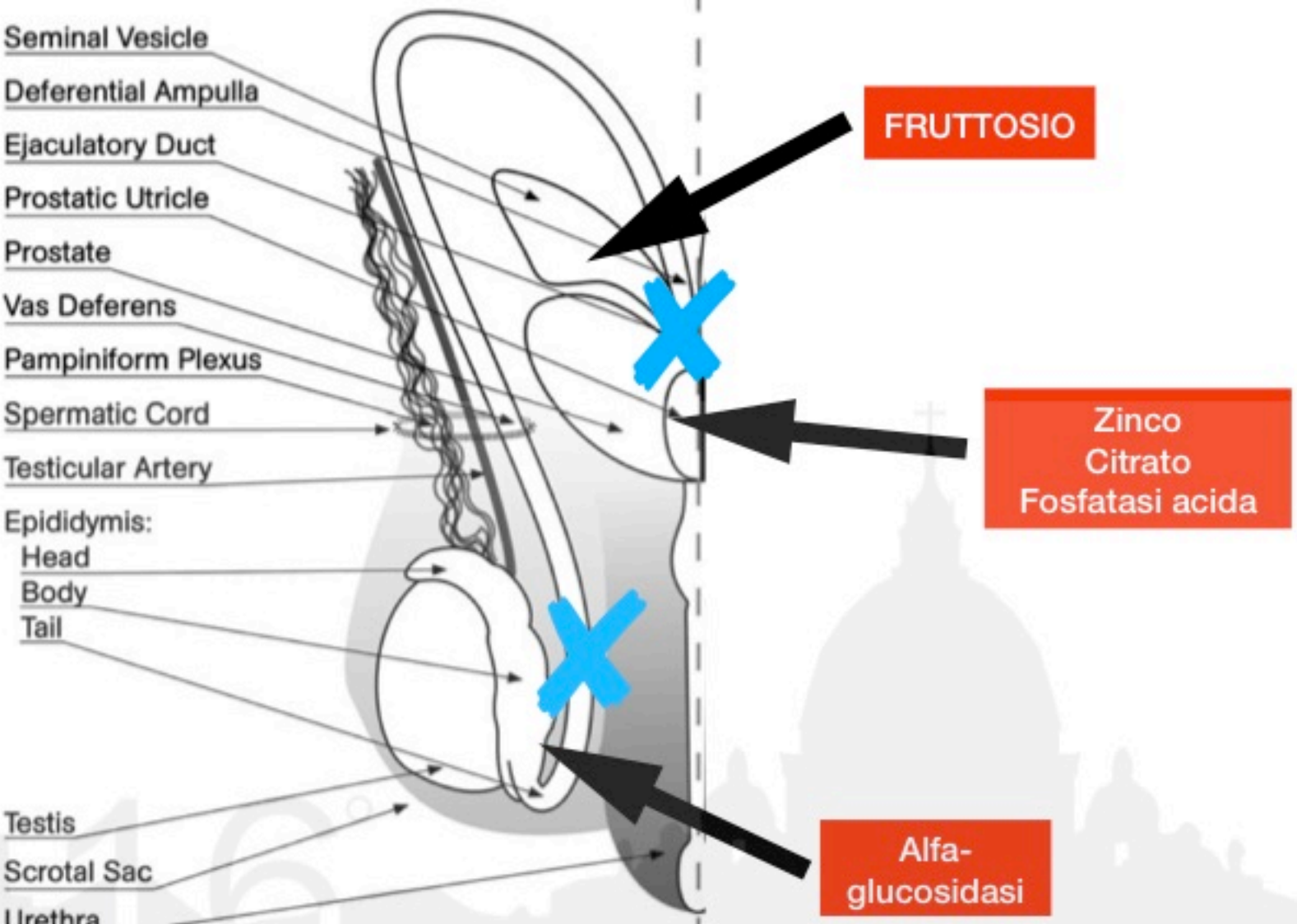
Variazioni fisiologiche seminali

Concentrazioni in un soggetto sano nell'arco di 120 settimane



Normo

Infertilità maschile: esame del liquido seminale - biochimica e pH



Infertilità maschile: esame del liquido seminale - biochimica e pH

	Function	Percentage of total ejaculate volume (%)	Biochemical markers in seminal plasma	pH of ejaculate fractions	Duration of germ cell/sperm exposure
Testis	Spermatogenesis	–	–	–	74 days
Epididymis	Sperm maturation	5	α-glucosidase (L-carnitine)	–	7–14 days
Seminal vesicles	Accessory secretion	50–80	Fructose	7.2–7.5	Seconds
Prostate	Accessory secretion	15–30	Zinc (PSA; citrate; acid phosphatase)	6.4	Seconds

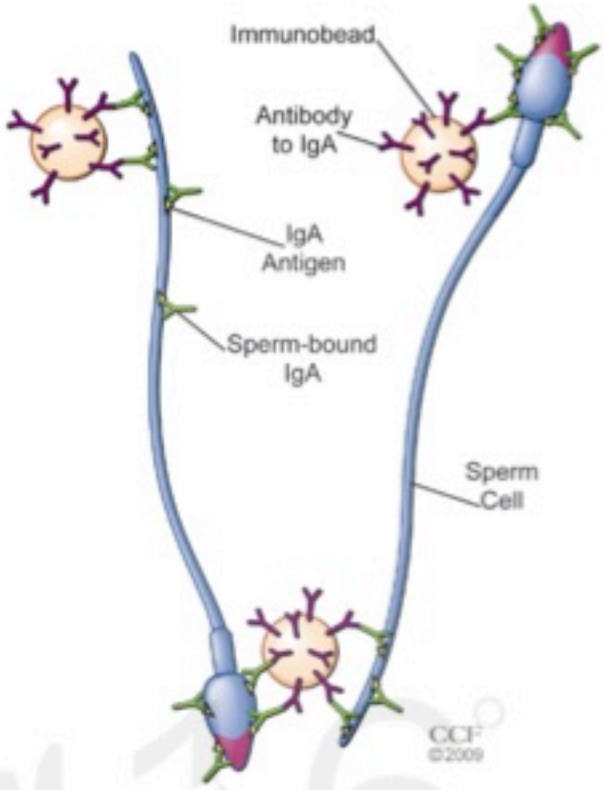
	pH	Indici biochimici		
		Carnitina	Fruttosio	Acido citrico
Azoospermia secretiva con normale testosteronemia	Normale	Normale	Normale	Normale
Azoospermia secretiva con ipotestosteronemia	Normale	Ridotta	Normale/Ridotto	Ridotto
Azoospermia ostruttiva intra-epididimaria o dei dotti deferenti	Normale	Ridotta	Normale	Normale
Azoospermia ostruttiva dei dotti eiaculatori	Acido	Ridotta/indosabile	Ridotto/indosabile	Aumentato

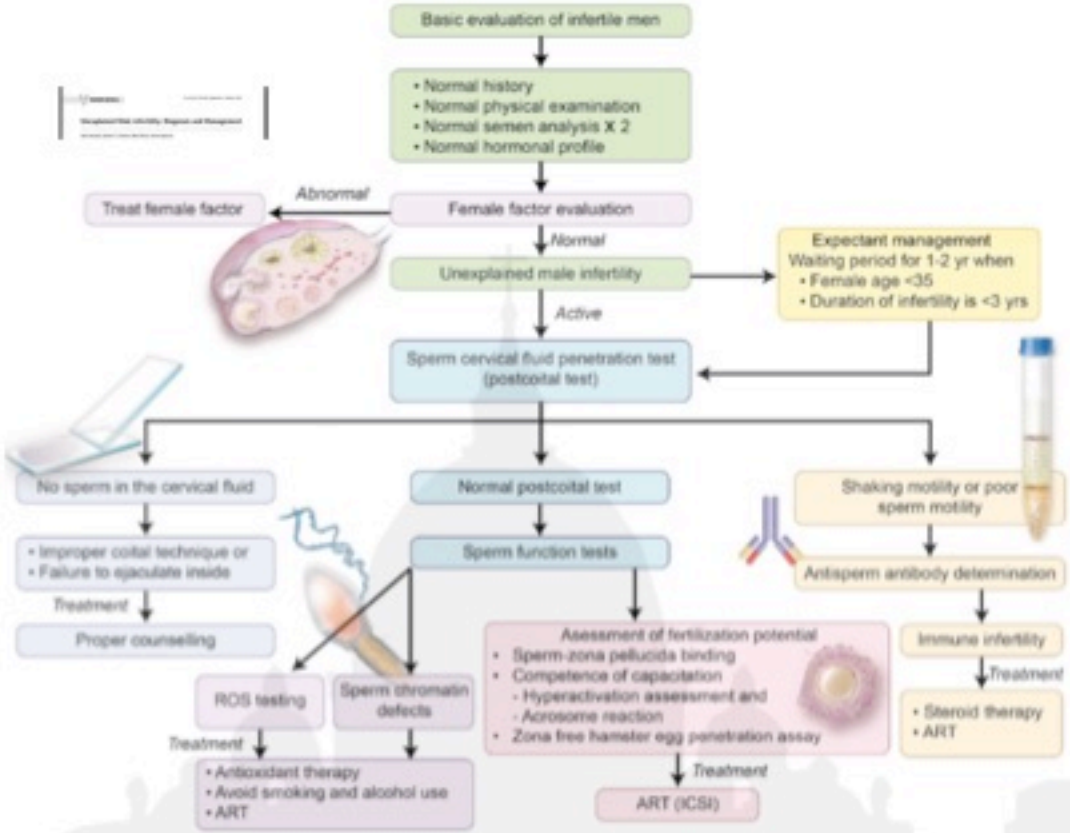
Infertilità maschile: esame del liquido seminale - anticorpi anti-spermatozoo

Test immunologici

La ricerca di anticorpi anti-spermatozoo può essere eseguita mediante:

- metodiche indirette, atte a valutare l'attività biologica degli anticorpi circolanti. Tra queste: *Gelatin Agglutination* Test (GAT) e *Tray Aggl*
- metodiche dirette, in grado di valutare la presenza di anticorpi direttamente adesi alla superficie dello spermatozoo. Tra queste: *Mixed A*

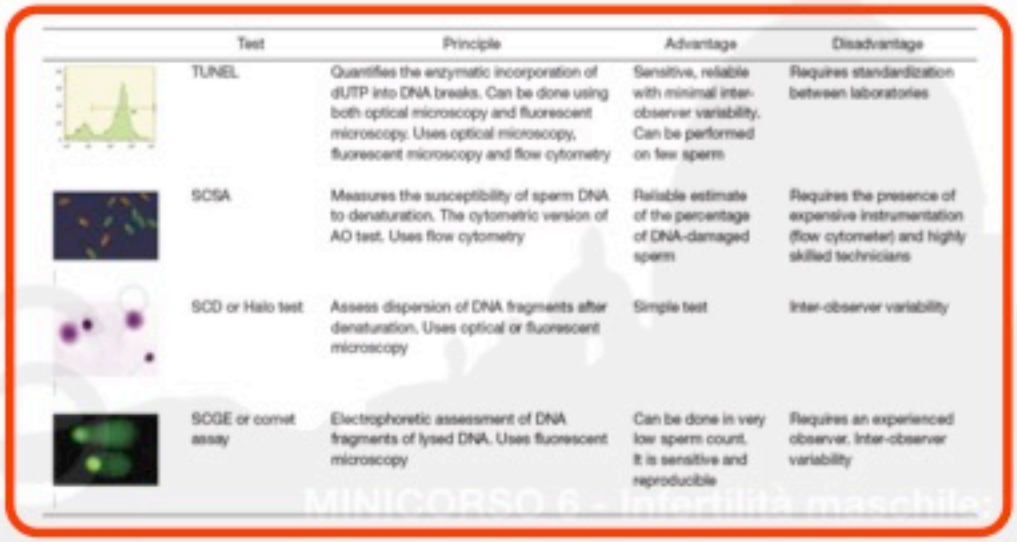




Infertilità maschile: esame del liquido seminale - studi funzionali

Test	Oggetto di valutazione	Significato clinico
Annessina V	Esternalizzazione fosfatidilserina	Apoptosi fasi iniziali
JC-1	Potenziale di membrana mitocondriale	Apoptosi fasi iniziali
Arancio di acridina	Integrità cromatinica	Stress ossidativo e alterazione dei meccanismi di riparazione del DNA
TUNEL	Frammentazione del DNA nucleare	Necrosi e apoptosi in fase avanzata
Anilina	Protaminazione del DNA nucleare	Alterazione dei processi di maturazione nucleare
Decondensazione nucleare	Condensazione nucleare	Alterazione dei processi di condensazione nucleare
FISH	Aneuploidie spermatiche	Alterazione del numero dei cromosomi spermatici

Fonte percorso andrologico



	Test	Principle	Advantage	Disadvantage
	TUNEL	Quantifies the enzymatic incorporation of dUTP into DNA breaks. Can be done using both optical microscopy and fluorescent microscopy. Uses optical microscopy, fluorescent microscopy and flow cytometry	Sensitive, reliable with minimal inter-observer variability. Can be performed on few sperm	Requires standardization between laboratories
	SCSA	Measures the susceptibility of sperm DNA to denaturation. The cytometric version of AO test. Uses flow cytometry	Reliable estimate of the percentage of DNA-damaged sperm	Requires the presence of expensive instrumentation (flow cytometer) and highly skilled technicians
	SCD or Halo test	Assess dispersion of DNA fragments after denaturation. Uses optical or fluorescent microscopy	Simple test	Inter-observer variability
	SCGE or comet assay	Electrophoretic assessment of DNA fragments of lysed DNA. Uses fluorescent microscopy	Can be done in very low sperm count. It is sensitive and reproducible	Requires an experienced observer. Inter-observer variability

Infertilità maschile: microbiologia

Infezione da Papillomavirus (HPV) e condilomatosi
Gonorrea
Herpes
Chlamydia
Mycoplasma – Ureaplasma urealyticum
Candida Albicans
Mollusco contagioso
Uretriti
HIV/AIDS

Fattori favorenti l'aumentata incidenza delle infezioni sessualmente trasmissibili

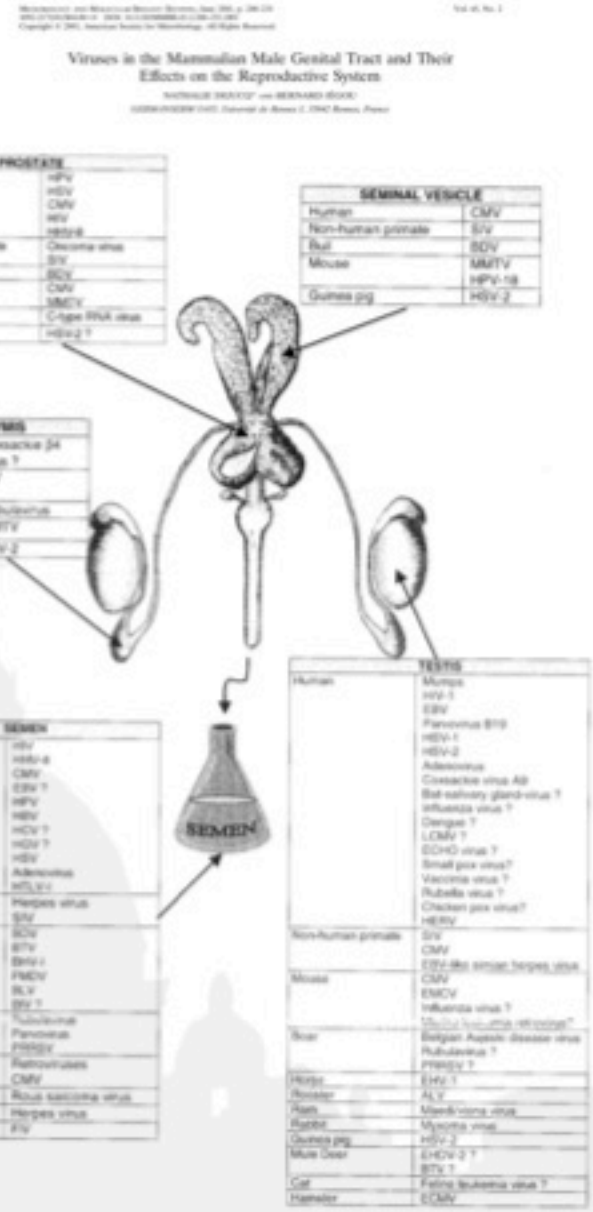
- Rapporti sessuali non protetti
- Rapporti sessuali con partner diversi
- Scarsa conoscenza delle stesse da parte dei giovani
- Difficoltà di accesso ai contraccettivi meccanici
- Precocità del primo rapporto sessuale
- Scarsa igiene intima
- Frequentazione di ambienti non adeguatamente igienizzati
- Promiscuità degli asciugamani utilizzati per l'igiene intima
- Tendenza all'autodiagnosi e all'autoterapia
- Uso di droga
- Fumo
- Abuso di alcol

Tabella 10. Comportamenti a rischio per la diffusione delle MST

Strategie di prevenzione e controllo della trasmissione delle infezioni sessualmente trasmesse

- campagne di informazione e sensibilizzazione rivolte alla popolazione generale e alle categorie a rischio;
- informazione e counseling dei soggetti con comportamenti sessuali "a rischio"
- identificazione delle persone infette asintomatiche e sintomatiche
- diagnosi, trattamento e counselling delle persone infette
- valutazione, trattamento e counseling dei partner sessuali di soggetti con MST
- mezzi di profilassi pre-esposizione e post-esposizione

Tabella 11. Strategie di prevenzione e controllo delle MST



Infertilità maschile: infezioni/infiammazioni

REVIEW ARTICLE

Male accessory gland infection and sperm parameters (review)

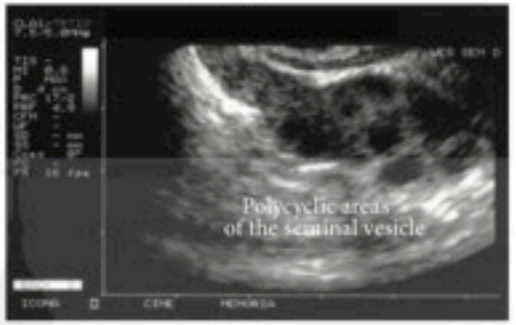
S. La Vignera, E. Vicari, R. A. Condorelli, R. D'Agata and A. E. Calogero

International Journal of Andrology © 2011 European Academy of Andrology, **34**, e330–e347

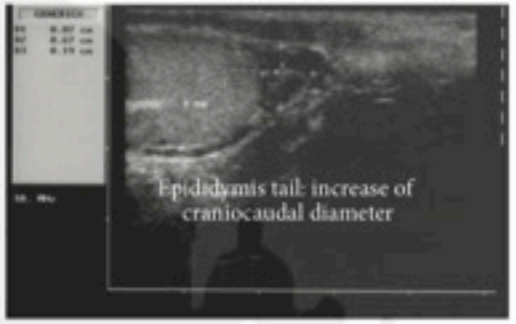
- Viscosità aumentata
- Presenza di leucocitospermia (v.n. leucociti < 1 x 10^6/ml)
- Presenza di emospermia micro/macroscopica
- Variazioni del pH (acido / basico) (v.n. pH 7.2 - 8.0)
- Agglutinazioni presenti
- Poliposia - Ipoposia (v.n. 1.5 - 7 cc)

NB: la componente prostatica è principalmente acida (fruttosio e acido citrici, zinco), quella a carico delle vescicole seminali prevalentemente alcaline (plasma seminale, fruttosio).

(a)



(b)



(c)

Infertilità maschile: microbiologia - HPV

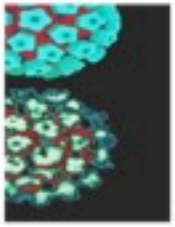
The HPV DNA virion iceberg

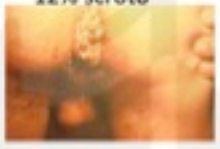
Fig. 1. — The HPV DNA virion iceberg. Green: Largest HPV DNA fraction inside L1-L2 protein capsid, free outside cells and infectious; Blue: HPV DNA present in transient virion producing infections inside non-dividing desquamating cells, limited in time, infectious; Red: Smallest HPV DNA fraction comprising of integrated HPV DNA inside dividing cells, HPV transforming pathway can lead to cancer but is non-infectious; Orange: HPV DNA present in both non-dividing virion producing cells and in transformed dividing cells, both the virion producing and clonal HPV transforming pathways occur simultaneously, can lead to cancer and is infectious.

Siti d'infezione

Da studio condotto su 436 infetti

- 44% superficie interna del prepuzio
- 33% Liquido seminale
- 30% uretra
- 24% superficie esterna del prepuzio
- 24% glande
- 12% scroto





CONDILOMI

Human Papilloma Virus - HPV

Escrescenze di consistenza più o meno dura e di colorito variabile

→ **infertilità, tumori** del pene, dell'ano o dell'orofaringe

→ accurata visita medica
tampone uretrale e balanoprepuziale
peniscopia

Nella donna alcuni ceppi virali contribuiscono alla patogenesi del carcinoma della cervice uterina

Facts Views Vis Obgyn, 2016, 8 (4): 211-222

Review

Human Papillomavirus (HPV) virion induced cancer and subfertility, two sides of the same coin

C.E. Depuydt[1], J. Beert[1,2], E. Bosmans[3], G. Salembier[3]

HPV induced processes: infectious virion producing pathway in non-dividing HPV DNA harboring cells and the clonal transforming pathway in dividing HPV DNA harboring cells

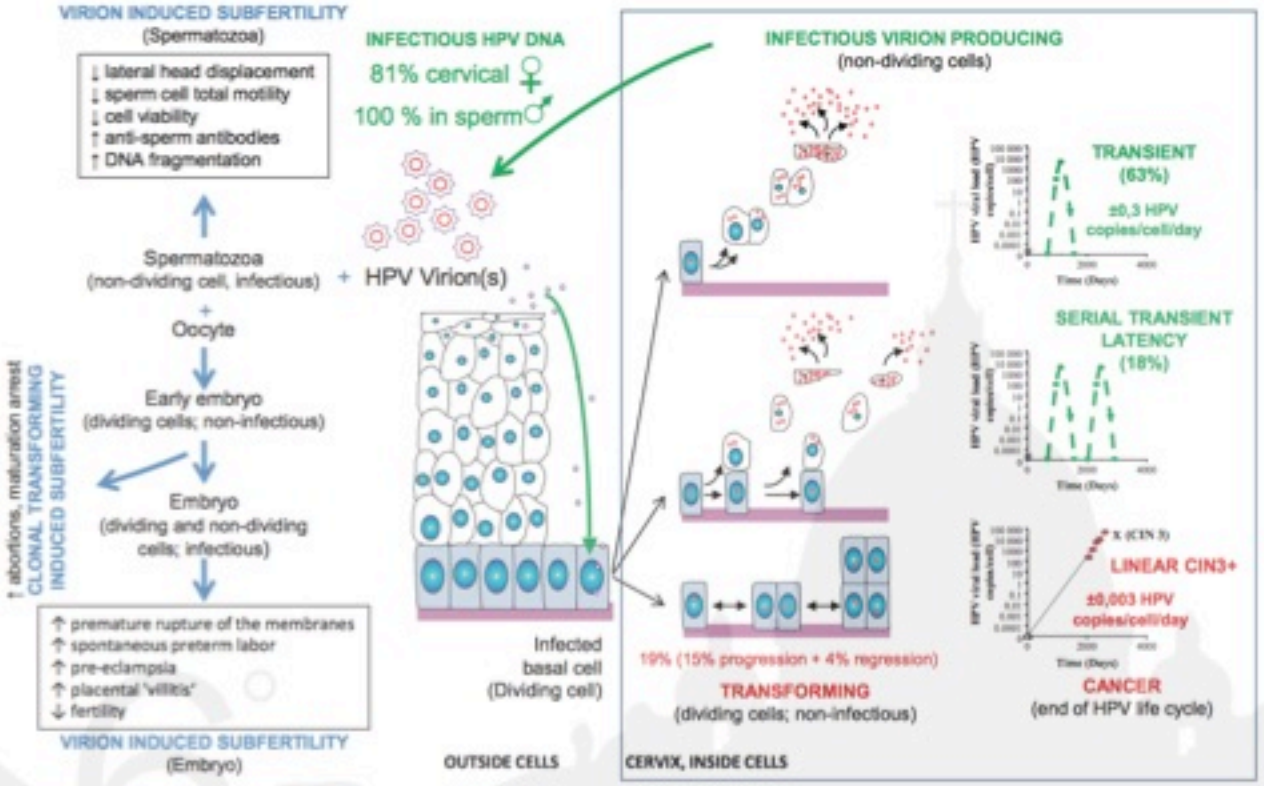
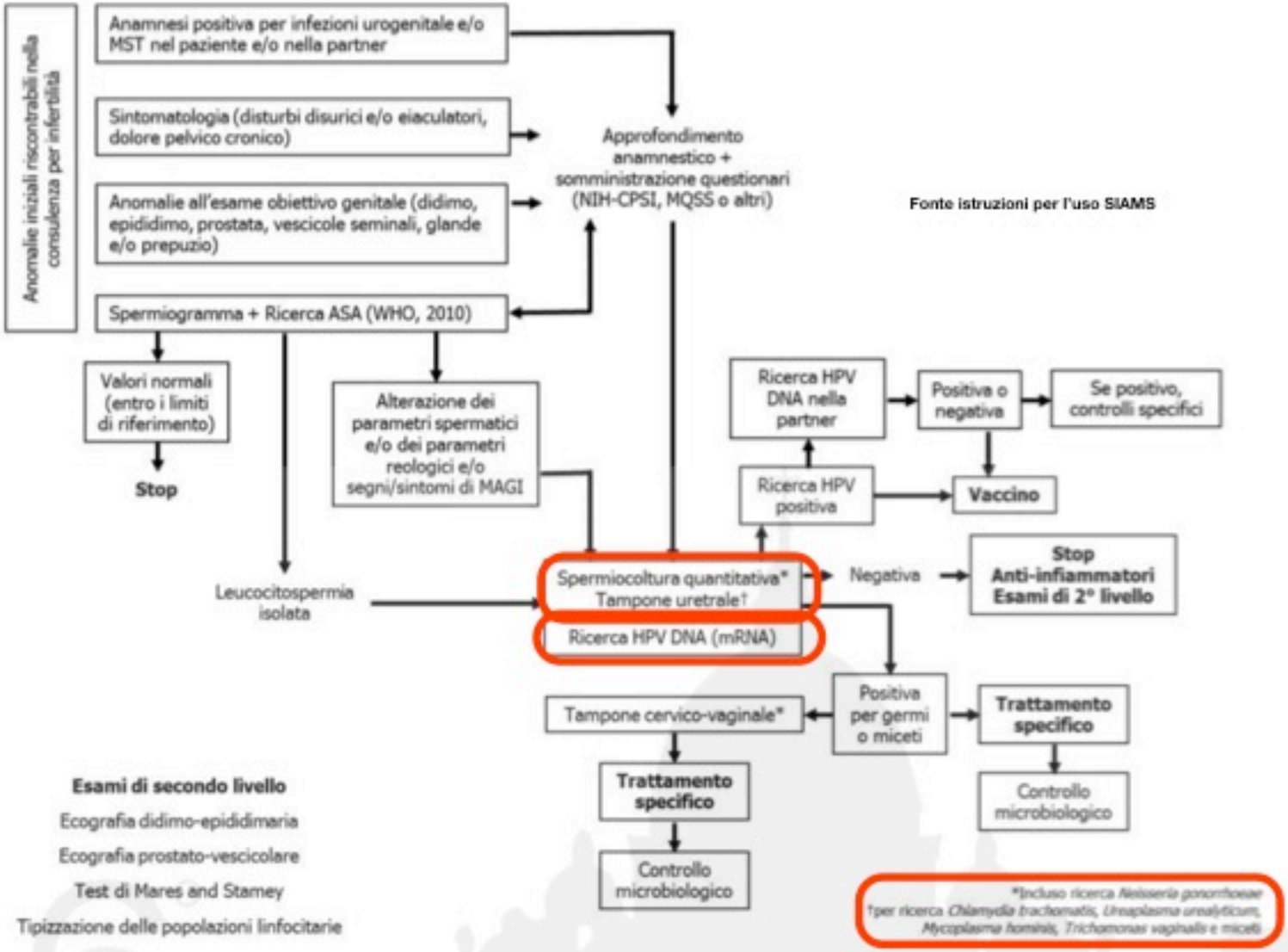
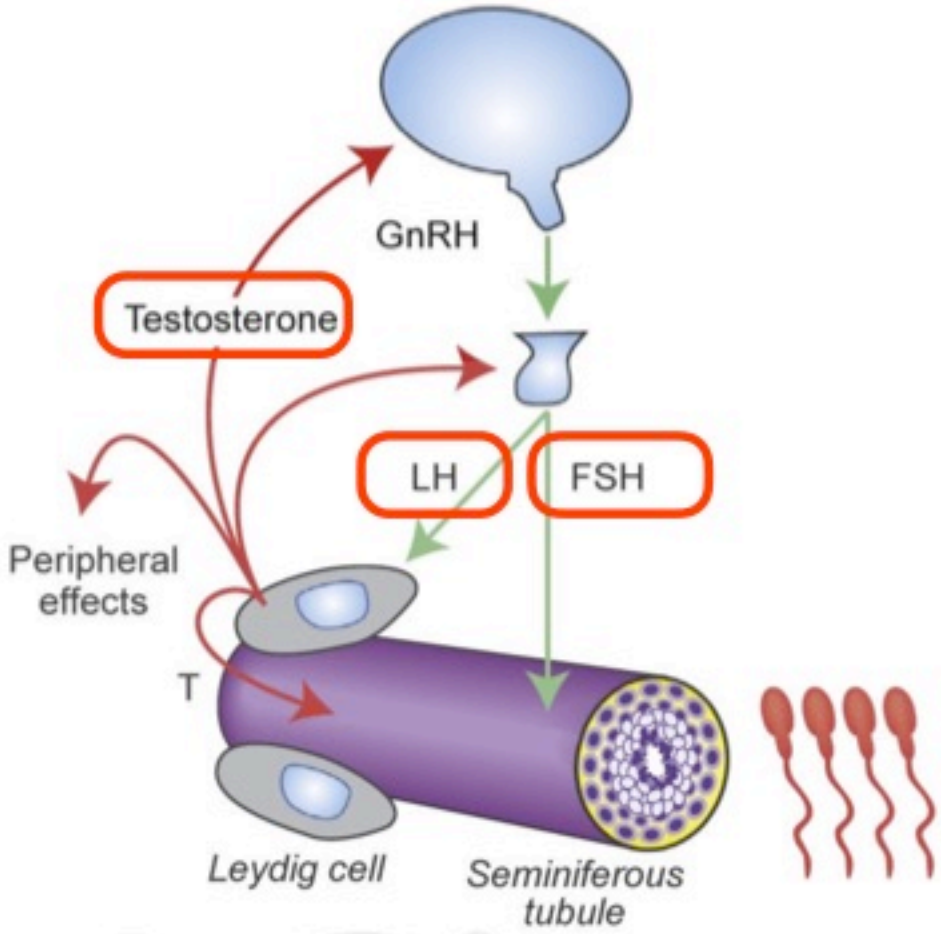


Fig. 2. — Overview of HPV induced processes defined on the basis of dividing and non-dividing HPV DNA harbouring cells.

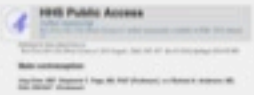
Infertilità maschile: microbiologia - flow chart



Infertilità maschile: ormoni



TSH (soprattutto se motivazioni cliniche), prolattina, 17BEstradiolo



Hum Reprod. 2016 Mar;31(3):518-29. doi: 10.1093/humrep/dev338. Epub 2016 Jan 11.

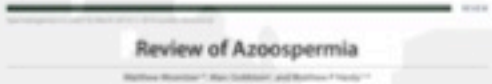
Is thyroid hormones evaluation of clinical value in the work-up of males of infertile couples?

Lotti F1, Maseroli E1, Fralassi N1, Degl'Innocenti S1, Boni L2, Baldi E1, Maggi M3.

STUDY QUESTION:
Is thyroid hormones (TH) evaluation of clinical value in the work-up of males of infertile couples?
STUDY ANSWER:
Our results suggest that TH evaluation is not mandatory in the work-up of male infertility.
WHAT IS KNOWN ALREADY:
A few previous studies performed on a limited series of subjects reported a negative impact of hyper- and hypo-thyroidism on semen volume, sperm concentration, progressive motility and normal morphology. No previous study has systematically evaluated associations between TH variation, semen parameters and ultrasound characteristics of the male genital tract.
STUDY DESIGN, SIZE AND DURATION:
Cross-sectional analysis of a consecutive series of 172 subjects seeking medical care for couple infertility from September 2010 to November 2014.
PARTICIPANTS/MATERIALS, SETTING, METHODS:
Of the entire cohort, 163 men (age 38.9 ± 8.0 years) free of genetic abnormalities were studied. All subjects underwent a complete andrological and physical examination, biochemical and hormonal assessment, scrotal and transrectal colour-Doppler ultrasound (CDUS) and semen analysis (including seminal interleukin 8 levels, sIL-8) evaluation within the same day.
MAIN RESULTS AND THE ROLE OF CHANCE:
Among the patients studied, 145 (88.9%) showed euthyroidism, 6 (3.7%) subclinical hyper- and 12 (7.4%) subclinical hypo-thyroidism. No subjects showed overt hyper- or hypo-thyroidism. At univariate analysis, no associations among thyroid-stimulating hormone (TSH) or TH levels and sperm parameters were observed. Conversely, we observed positive associations among free triiodothyronine (fT3) and free thyroxine (fT4) levels, ejaculate volume and seminal fructose levels. In a multivariate model, after adjusting for confounders such as age, body mass index, smoking habit, sexual abstinence, calculated free testosterone, prolactin and sIL-8 levels, only the associations found for fT3 levels were confirmed. When CDUS features were investigated, using the same multivariate model, we found positive associations between fT3 levels and seminal vesicles (SV) volume, both before and after ejaculation (adj. $r = 0.354$ and adj. $r = 0.318$, both $P < 0.0001$), as well as with SV emptying (ΔSV volume; adj. $r = 0.346$, $P < 0.0001$) and echo-texture inhomogeneity. In addition, after adjusting for confounders, negative associations between fT4 levels and epididymal body and tail diameters were found. No significant associations between TSH or TH levels and CDUS features of other organs of the male genital tract, including testis and prostate, were found. Finally, when the features of subjects with euthyroidism, subclinical hypo- and hyper-thyroidism were compared, no significant differences in seminal or hormonal parameters were found. Conversely, evaluating CDUS parameters, subjects with subclinical hyperthyroidism showed a higher difference between the SV longitudinal diameters measured before and after ejaculation when compared with that of subclinical hypothyroid men, even after adjusting for confounders ($P < 0.007$). All the other male genital tract CDUS characteristics did not differ among groups.
LIMITATIONS, REASONS FOR CAUTION:
First, the number of patients investigated is relatively small and those with (subclinical) thyroid dysfunctions are an even smaller number; hence, it is therefore difficult to draw firm conclusions. Moreover, the present results are derived from patients consulting an Italian Andrology Clinic for couple infertility, and could have different characteristics from the male general population or from those males consulting general practitioners for reasons other than couple infertility. Finally, due to the cross-sectional nature of the study, neither a causality hypothesis nor mechanistic models can be inferred.
WIDER IMPLICATIONS OF THE FINDINGS:
Although no associations between TH and sperm parameters were observed, present data support a positive effect of TH on SV size and a permissive role on the ejaculatory machinery, likely through an action on SV and epididymal contractility. This is the first study reporting such evidence. However, in contrast with the view that TH assessment is important for female fertility, our results do not support a systematic evaluation of thyroid function in males of infertile couples. How TH abnormalities impact male fertility needs to be addressed by further studies

Infertilità maschile: ormoni nelle azoospermie ostruttive e secretive

Etiology	Subtype	FSH	LH	Testosterone	Testis Volume
Obstructive Azoospermia		↔	↔	↔	↔
Non-obstructive Azoospermia	Primary Testicular Failure	↑	↑	↓	↓
	Hypogonadotropic Hypogonadism	↓	↓	↓	↓



Cause di azoospermia

Azoospermia ostrutiva

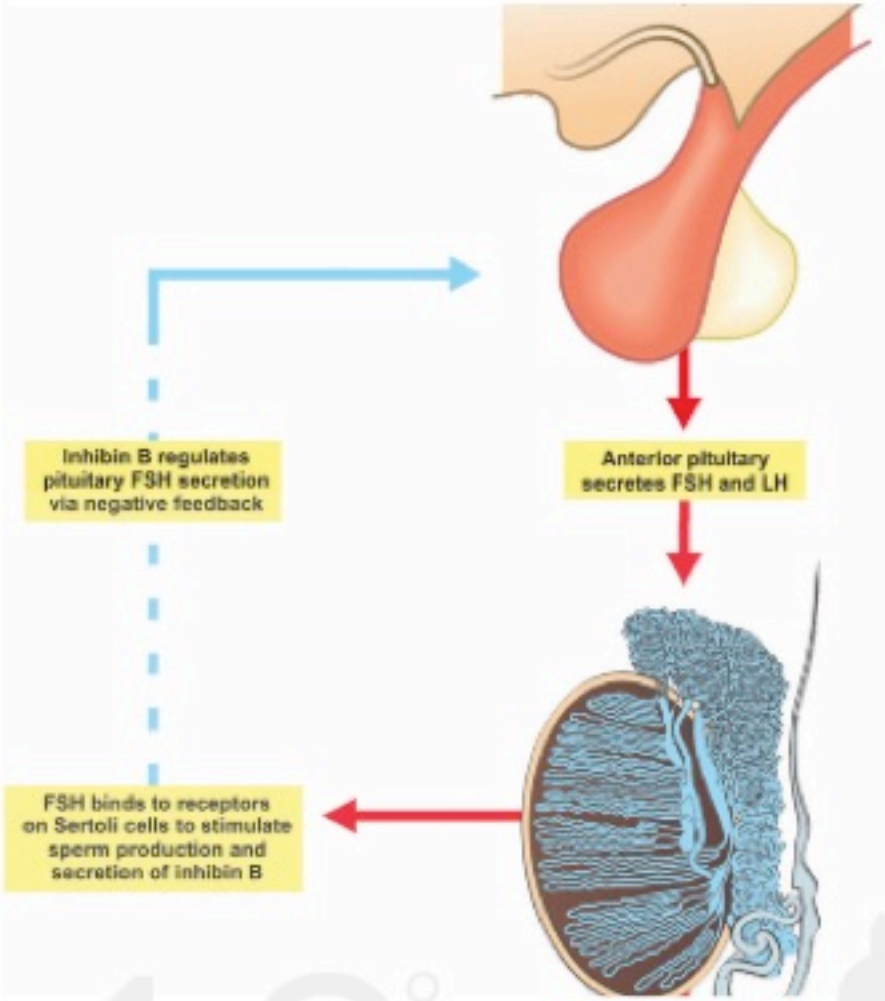
Azoospermia secretiva

Obstructive Azoospermia	Non-obstructive Azoospermia (Testicular Failure)
Congenital Ductal Obstructions: Congenital bilateral absence of the vas deferens Young's syndrome (clinical triad of chronic sinusitis, bronchiectasis, and obstructive azoospermia) Stenosis or atresia of the ejaculatory ducts Midline prostatic cysts (utricular and Müllerian cysts) Ejaculatory duct cysts Seminal vesicle cysts	*Congenital Testicular Failure:* Testicular dysgenesis/cryptorchidism Genetic abnormalities (Klinefelter syndrome, Y chromosome microdeletions*) Germ cell aplasia (Sertoli cell-only syndrome) Spermatogenic (maturation) arrest
Acquired Ductal Obstructions: Post-infection (epididymitis, prostatitis, seminal vesiculitis) Post-vasectomy Post-surgical (epididymal cysts, hernia repair, scrotal surgery, bladder neck surgery, prostatectomy) Iatrogenic (urologic endoscopic instrumentation)	*Acquired Testicular Failure:* Testicular trauma Testicular torsion Post-inflammatory (*e.g.*, mumps orchitis) Exogenous factors (steroid medications, cytotoxic drugs, irradiation, heat) Systemic diseases (liver cirrhosis, renal failure) Testicular tumor Varicocele Post-surgical (surgeries that may compromise testicular vascularization, resulting in testicular atrophy)
Idiopathic: Idiopathic epididymal obstruction	*Idiopathic (unknown etiology)*

*The likelihood of obtaining sperm at sperm retrieval is virtually zero when complete AZFa and/or AZFb Yq microdeletions are found.

CLINICS review
An update on sperm retrieval techniques for azoospermic males

Infertilità maschile: altri ormoni - inibina B



Utile nella ricerca.
In clinica nella valutazione delle testicolopatie e nella diagnosi differenziale tra azoospermia ostruttiva e secretiva

Infertilità maschile: altri ormoni - AMH

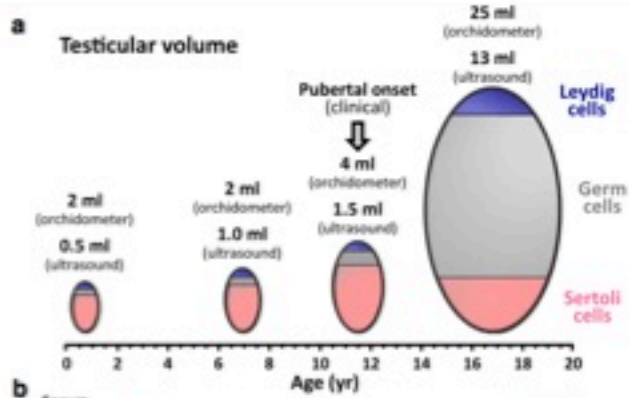


Fig. 1 Developmental physiology of the testis in postnatal life. **a**: Testicular volume increases slightly during infancy and childhood (from birth to the age of 8–10 yr), as measured by ultrasonography, mainly due to the increase of the Sertoli cell population. After pubertal onset, clinically defined by a testicular volume of 4 ml as measured by comparison with the orchidometer, testicular volume increases drastically due to the onset of pubertal spermatogenesis, which requires androgen-dependent Sertoli cell maturation. **b**: Schematic serum levels of gonadotropins (FSH and LH), testosterone (T), inhibin B (Inh B) and AMH from birth through adulthood (left axis) and percentage of Sertoli cells expressing the androgen receptor (AR, right axis). *Reprinted, with permission, from Rey et al. [85], copyright 2009 Wiley-Liss, Inc.*

Utile nella ricerca.
In clinica nella valutazione dell'asse ipofisi-gonadi in bambini ed adolescenti

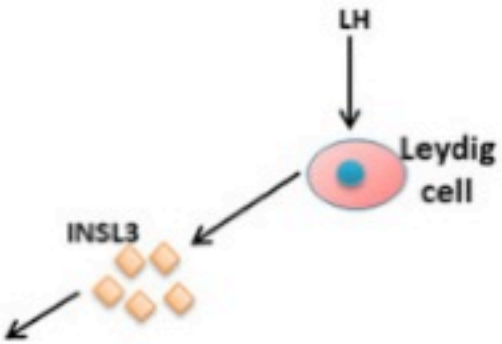
Table 2 Serum AMH levels according to clinical presentation

	Serum AMH			
Clinical sign	Undetectable	Low	Normal	High
Cryptorchidism	Anorchidism (Testicular regression, bilateral gonadectomy) PMDS - AMH mutation	Primary hypogonadism (testicular dysgenesis syndrome) Central hypogonadism	Rules out testicular dysgenesis PMDS - AMHR mutation	–
Micropenis	Fetal testicular regression	Primary hypogonadism Central hypogonadism	Malformative micropenis	–
Absence of puberty	Testicular regression Bilateral gonadectomy	Primary hypogonadism Central hypogonadism	Constitutional delay of puberty	–
Precocious pubertal signs	–	Central Precocious Puberty Testotoxicosis Leydig cell tumor	Congenital adrenal hyperplasia Adrenal androgen-secreting tumors Exogenous androgen exposure	–
Prepubertal macro-orchidism	–	–	–	McCune-Albright syndrome Sex-cord stromal tumors
DSD	46,XY Complete gonadal dysgenesis	46,XY Partial gonadal dysgenesis Sex-chromosome gonadal dysgenesis Ovotesticular DSD	Androgen synthesis defects Androgen insensitivity 46,XY Malformative DSD 46,XX male (Testicular DSD)	Androgen synthesis defects Androgen insensitivity

Serum AMH levels are considered low, normal or high as compared to those expected for age in normal boys
AMH-R AMH receptor, DSD disorders of sex development, PMDS persistent Müllerian duct syndrome

Anti-Müllerian hormone as a marker of steroid and gonadotropin action in the testis of children and adolescents with disorders of the gonadal axis

Infertilità maschile: altri ormoni - INSL3



Utile nella ricerca.
In clinica nella valutazione delle patologie gonadiche, marker precoce di danno delle Leydig (prima del testosterone)

British Journal of Pharmacology

REVIEW ARTICLE THEMED ISSUE

Relaxin and insulin-like peptide 3 in the musculoskeletal system: from bench to bedside

Infertilità maschile: ecografia andrologica

human reproduction update

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

Francesco Lotti and Mario Maggi*

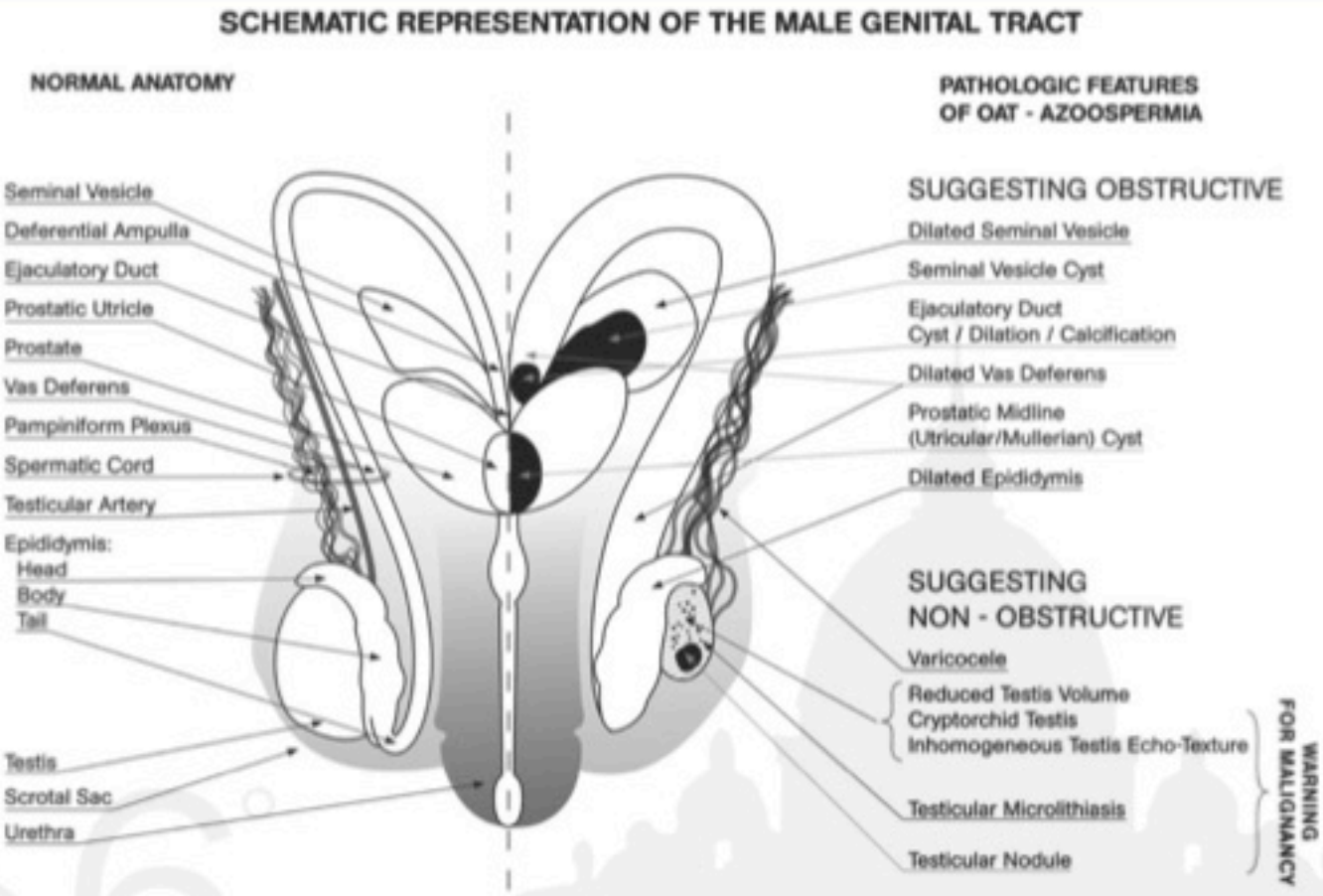
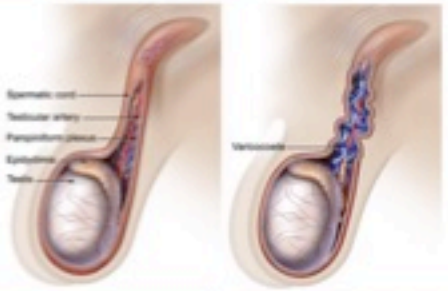
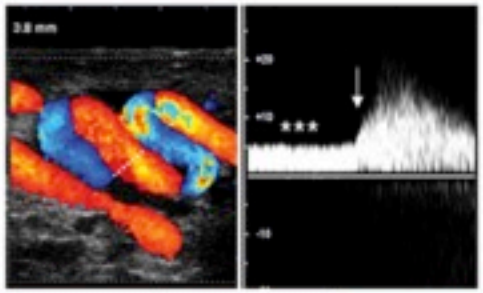


Figure 1 Schematic representation of the normal and pathologic features of the male genital tract (MGT) in relation to male reproductive health. Right side: normal anatomy of the MGT. Left side: pathologic features of the MGT suggesting obstructive or non-obstructive oligo-astheno-teratozoospermia (OAT)/azoospermia. Warnings for malignancy are extensively discussed in the text.

Plesso pampiniforme - varicocele





	Classificazione sec. Sarteschi	Classificazione rivisitata (Dubin-Solbiati)	Corrispondente alla Classificazione sec. Dubin	Classificazione sec. Solbiati	Corrispondente alla Classificazione sec. Dubin
1	**B-mode**: Non si osservano varicosità in B-mode. **ECD:** Si apprezza prolungato reflusso venoso all'emergenza scrotale.	**B-mode**: Ectasie venose di piccolo calibro (>2.5 mm) a livello della regione inguinale. **ECD:** Reflusso inguinale solo durante la manovra di Valsalva, della durata <3 secondi	1	**ECD:** Reflusso inguinale solo durante manovra di Valsalva.	1
2	**B-mode**: Piccole varicosità posteriori, spesso accompagnate da un tronco venoso rettilineo ventrale, che però non scendono al di sotto del livello del polo superiore del testicolo e che incrementano di diametro con la manovra di Valsalva. **ECD:** reflusso venoso nella regione sovratesticolare.	**B-mode:** Ectasie venose di piccolo e medio calibro (>3.0 mm) a livello prevalentemente sopratesticolare. **ECD:** Reflusso sopratesticolare solo durante manovra di Valsalva, della durata >3 secondi.		**ECD:** Reflusso sopratesticolare solo durante manovra di Valsalva.	
3	**B-mode:** In ortostatismo i vasi venosi si dilatano prontamente durante manovra di Valsalva in B-mode, raggiungendo il polo inferiore del testicolo. **ECD:** non evidenzia di reflusso a riposo ma reflussi prolungati durante manovra di Valsalva.	**B-mode:** Ectasie venose di piccolo e medio calibro (>3.0 mm) a livello sopratesticolare e peritesticolare. **ECD:** Reflusso sopra- e peritesticolare a riposo che aumenta durante manovra di Valsalva, della durata >3 secondi	2	**ECD:** Reflusso peritesticolare solo durante manovra di Valsalva.	
4	**B-mode:** I vasi venosi del funicolo appaiono dilatati in a livello funicolare peritesticolare; la manovra di Valsalva determina un ulteriore allargamento dei calibri venosi. Può essere presente ipotrofia del testicolo omolaterale. **ECD:** presenza di reflussi patologici già in condizioni basali, incrementabili durante manovra di Valsalva.	**B-mode:** Ectasie venose peritesticolari con ulteriore dilatazione durante la manovra di Valsalva; eventuale ipotrofia testicolare. **ECD:** Reflusso peritesticolare a riposo che può aumentare o non aumentare durante manovra di Valsalva.	3	**ECD:** Reflusso testicolare a riposo che aumenta durante manovra di Valsalva.	2
5	**B-mode:** I vasi venosi appaiono estremamente dilatati in B-Mode a livello funicolare e peritesticolare, talvolta in maniera abnorme. La manovra di Valsalva determina aumento del calibro venoso. Può essere presente ipotrofia del testicolo omolaterale. **ECD:** reflusso patologico presente a riposo che comunque non incrementa o incrementa pochissimo durante l'esecuzione delle manovre funzionali. Talvolta possono essere presenti varici intratesticolari.	**B-mode:** Ectasie venose peritesticolari che non si dilatano ulteriormente durante la manovra di Valsalva, o varicocele intratesticolare. Eventuale ipotrofia del testicolo omolaterale. **ECD:** Reflusso peritesticolare a riposo che aumenta minimamente durante manovra di Valsalva o ectasie intratesticolari che mostrano segnale colore durante manovra di Valsalva.		**ECD:** Reflusso peritesticolare a riposo che aumenta minimamente durante manovra di Valsalva.	3

Tabella 1. Classificazioni del varicocele. La classificazione rivisitata, integra la classificazione clinica (Dubin) e quella ecografica (Solbiati) del varicocele testicolare. *Modificata da Scrotal Ultrasound. Morphological and functional atlas. A.M. Isidori, A. Lenzi. Forum Service, 2011, ISBN: 9788889620465*

Eur J Med Genet. 2017 Jul 1. pii: S1769-7212(17)30098-8. doi: 10.1016/j.ejmg.2017.06.009. [Epub ahead of print]

Testicular Adrenal Rest Tumor (TART) in congenital adrenal hyperplasia.

Ozisik H[1], Yurekli BS[2], Simsir IY[2], Altun I[2], Soyaltın U[2], Guler E[3], Onay H[4], Sarsik B[5], Saygili F[2].

Abstract

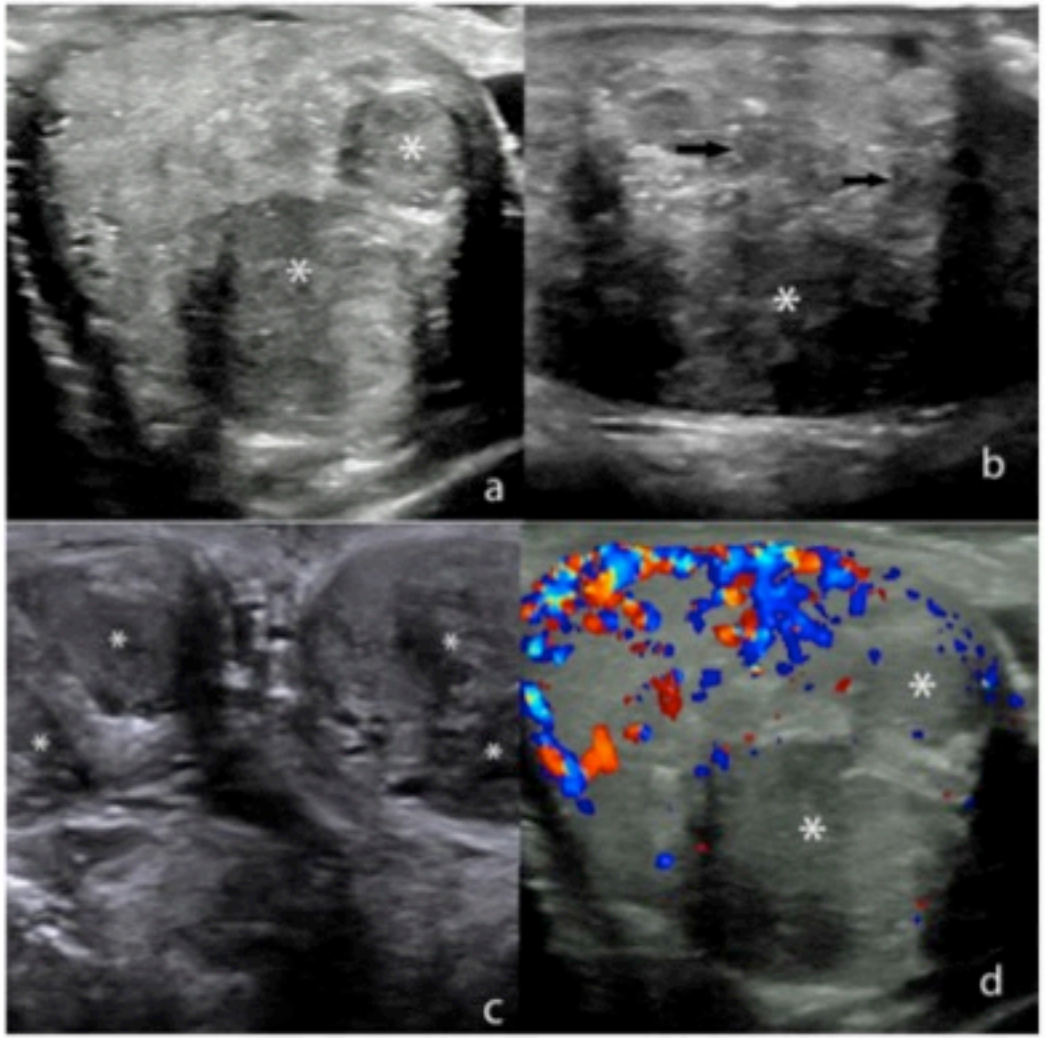
Congenital adrenal hyperplasia is one of the most common autosomal recessive genetic disorders. Testicular adrenal tumors are significant complications of congenital adrenal hyperplasia. We would like to present two patients of testicular adrenal rest tumors. Patient 1 24 year-old male, he was diagnosed with congenital adrenal hyperplasia at the age of 8 due to precocious puberty. He received hydro-cortisone treatment until the age of 18. Testicular mass had been detected and right radical orchiectomy had been applied 6 months ago and reported as testicular adrenal rest tumor. In scrotal ultrasound, a mixed type mass lesion (6 × 4x3 cm) covering a large part of left testis was observed. The imaging findings were consistent with adrenal rest tumor. The patient took adrenocorticotropic hormone supressive therapy with dexamethasone 0.75 mg once a day. Patient 2, 38 year-old male, he had been followed-up as adrenal insufficiency for 35 years. He underwent right orchiectomy operation due to the testicular mass in 2010 and the pathological examination revealed Leydig cell tumor. In scrotal ultrasound, small multifocal lesions were detected on the left testis and resection was done. It was reported as testicular adrenal rest tumor. He is being followed-up with glucocorticoid treatment according to androgen and adrenocorticotropic hormone levels. Early diagnosis of testicular adrenal rest tumor is significant in preventing irreversible testicular damage and infertility. In the differential diagnosis, we should keep in mind that testicular adrenal rest tumor can mimic other testicular tumors such as primary germ cell tumors.

Azoospermia in paziente con deficit della 21-idrossilasi

Genitourinary Radiology

Testicular Adrenal Rest Tumors in a Patient with Congenital Adrenal Hyperplasia

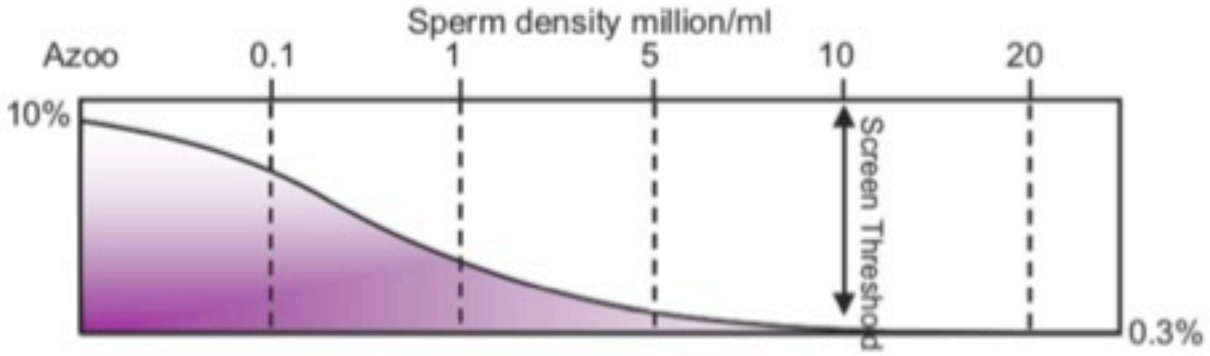
Jeffrey Dee Olpin *, Benjamin Witt



Idiopathic (primary) spermatogenic failure

Karyotype

Prevalence

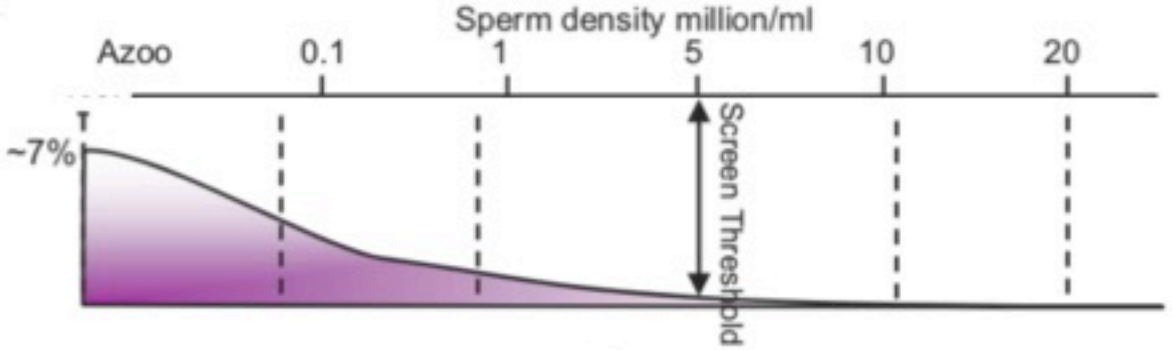


Predominant chromosomal defects	Numerical Structural	Translocation Inversion
Range of potential outcomes	Man	Normal male → clinical phenotype e.g. Klinefelters Spermatogenic defects with normal or aneuploid sperm
	Offspring	Inherited or *de novo* aneuploidy Failed conceptus → live birth: healthy or with disability

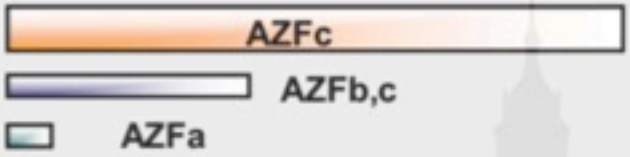
Idiopathic (primary) spermatogenic failure

Yq microdeletion

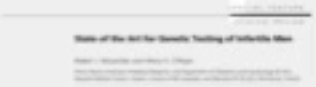
Prevalence



Description



Consequence of detection		
	Man	Identifies definitive cause of disability prognosis for sperm recovery; risk of sperm aneuploidy
	Offspring	Vertical transmission & infertility



Infertilità maschile: diagnostica genetica - CFTR

Obstructive azoospermia

CFTR mutation

	Cystic Fibrosis	BCAV / idiopathic epididymal
Genotype	homozygous	heterozygote / compound heterozygote
Mutation	Severe coding	Milder coding / 5T allele
Consequence	Clinical CF	Renal anomalies / sinopulmonary disease

Female partner screen
Residual CF risk / PGD

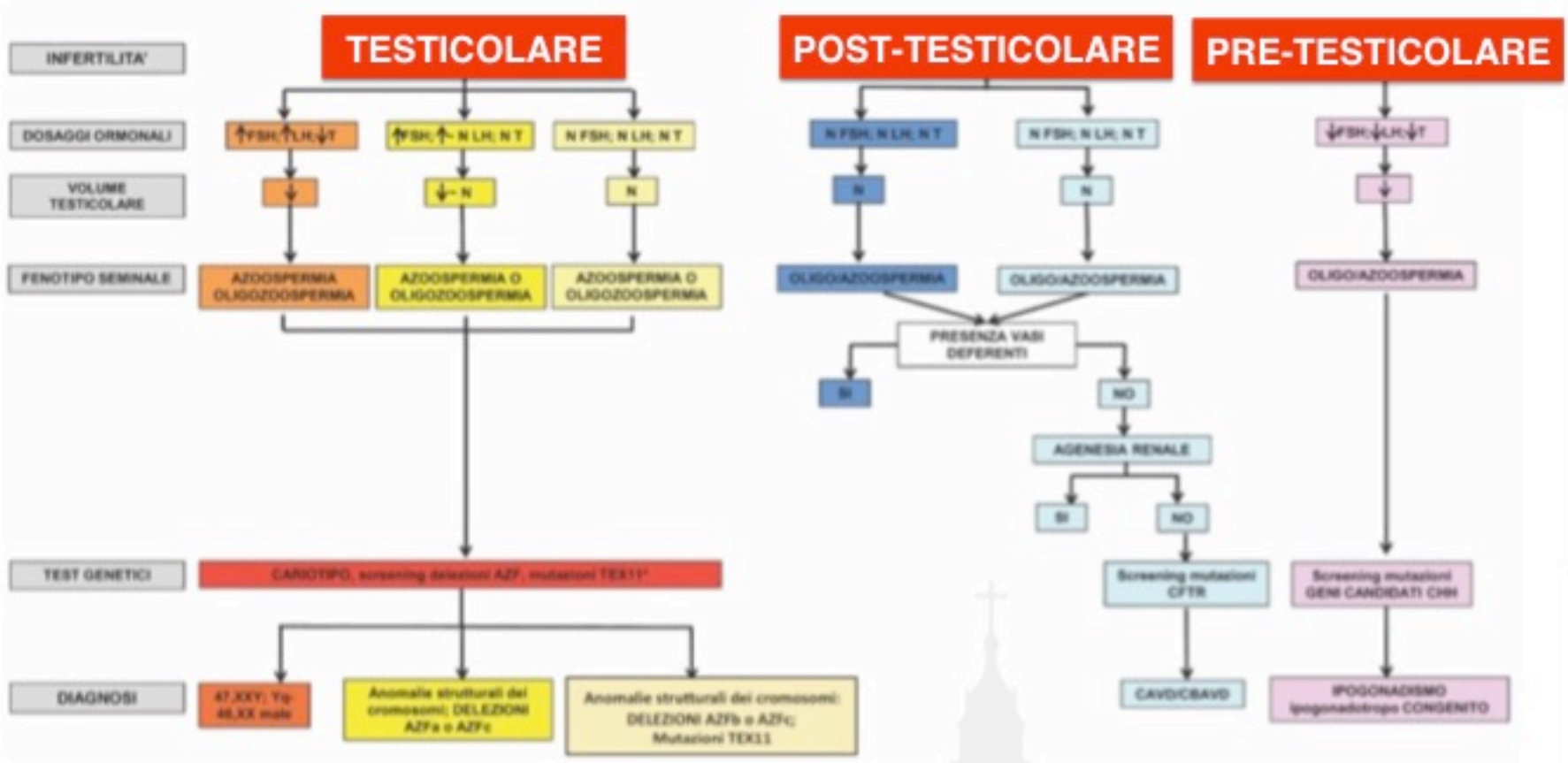
Infertilità maschile: diagnostica genetica - indicazioni

Test genetici	Indicazioni per l'analisi
Cariotipo	Azoo o <10 milioni spermatozoi/ml da testicolopatia primaria; aborti ricorrenti; familiarità per aborti, malformazioni, malattie cromosomiche
Screening microdelezioni del cromosoma Y (AZFa, AZFb, AZFc)	Azoo- o <5 milioni spermatozoi/ml da testicolopatia primaria
Screening delezione gr/gr	Oligozoospermia (< 39 milioni spermatozoi totali)
Geni candidati CHH (pannello più ampio possibile di geni)	Sindrome di Kallmann o CHH normosmico
CFTR	Assenza congenita di vasi deferenti (uni/bilaterale)
Recettore Androgenico (AR)	Azoo- o <5 milioni spermatozoi/ml con segni di insensibilità agli androgeni
*TEX11**	Azoospermia idiopatica (da arresto spermatocitico
AURKC	Macrocefalia spermatica
DPYL2	Globozoospermia

CHH: ipogonadismo ipogonadotropo congenito; *potenzialmente inseribile nella diagnostica genetica.

INSL-3, CGR8 - criptorchidismo
Promotore e recettore FSH

Infertilità maschile: diagnostica genetica - flow chart



Infertilità maschile: diagnostica citologica

Figure 1. Testicular examination of a man with small testes due to Klinefelter syndrome. The testis should be gently but firmly circumscribed with the fingers of 1 hand and pulled up to the scrotal skin to reduce overestimation of size due to inclusion of subtunical fluid in volumetry. The epididymis that lies posterior and extends to the superior aspect of the testis should not be included in the volumetry. Prader orchidometry with standard sizes of ovoid (2 cc ovoid shown) correlates well with ultrasound.

Utile nella ricerca.
In clinica nella diagnosi differenziale tra azoospermia ostruttiva e secretiva

Utile nella terapia per il recupero di spermatozoi (ed eventuale congelamento per IVF)


Approach to Male Infertility and Induction of Spermatogenesis

Caso 1- IPOGONADISMO PRIMARIO

ANAMNESI	ESAME OBIETTIVO	LIQUIDO SEMINALE	ORMONI	ECOGRAFIA
Chemioterapia	Ipotrofia testicolare, ginecomastia, ipoandrogenizzazione	Azospermia, ipoposia, pH normale o ridotto	Testosterone totale basso, LH ed FSH alti	ipotrofia testicolare, disomogeneità

Crioconservazione preventiva se possibile

TESE ed ICSI

Caso 2 - IPOGONADISMO SECONDARIO

ANAMNESI	ESAME OBIETTIVO	LIQUIDO SEMINALE	ORMONI	ECOGRAFIA
Anosmia	Normotrofia testicolare	Oligo o azospermia	Testosterone totale basso, LH ed FSH bassi	Normotrofia testicolare

Genetica: sdr. di Kallmann (ad insorgenza tardiva)

Terapia con gonadotropine

CASO 3 - OSTRUTTIVO

ANAMNESI	ESAME OBIETTIVO	LIQUIDO SEMINALE	ORMONI	ECOGRAFIA
Frequenti sinusiti	Normotrofia Testicolare; epididimi aumentati di dimensioni	Azoospermia; pH normale, assente carnitina; normale fruttosio e ac. citrico	Normali	Dilatazione epididimo e dotto eiaculatore

FNA Testis: normale spermatogenesi

Genetica: mutazione CFTR mild

MESE ed ICSI

CASO 4 - INFEZIONI

ANAMNESI	ESAME OBIETTIVO	LIQUIDO SEMINALE	ORMONI	ECOGRAFIA
Negativa	Epididimi dolenti	Leuco-citospermia, agglutinazioni, aumentata viscosità	Normali	Disomogeneità e aumento delle dimensioni dell'epididimo

Microbiologia: alla spermiocoltura positività per E. coli

Terapia antibiotica mirata ed antiossidanti

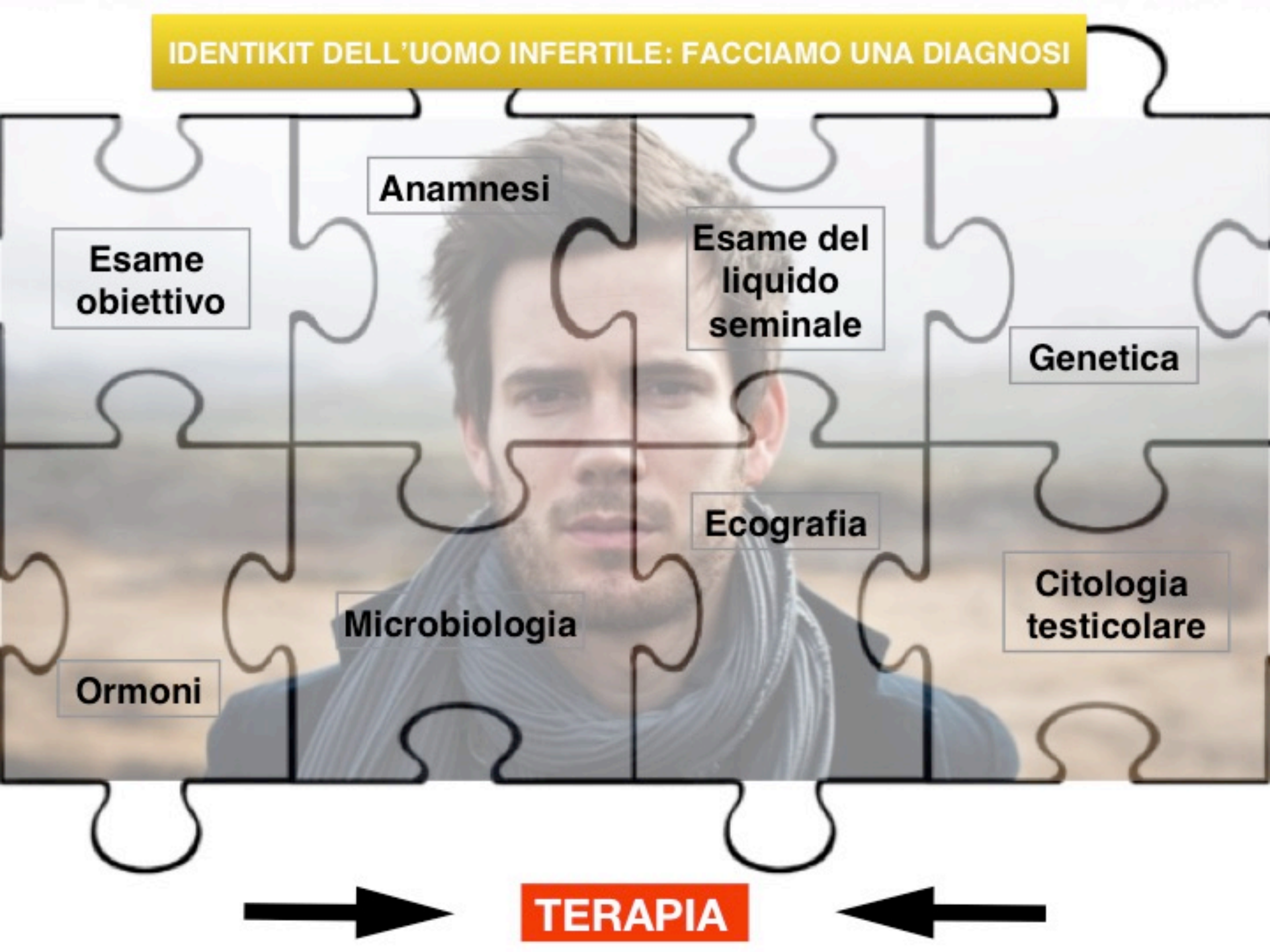
CASO 5 - DISTURBI SESSUALI

ANAMNESI	ESAME OBIETTIVO	LIQUIDO SEMINALE	ORMONI	ECOGRAFIA
Non rapporti per problemi psicologici	Normale	Normale	Normale	Normale

Valutazione psicologica - comportamentale


Esame del
liquido
seminale

IDENTIKIT DELL'UOMO INFERTILE: FACCIAMO UNA DIAGNOSI



TERAPIA