



II Jornadas de Actualización en Salud Integral del Adolescente

El Síndrome de Klinefelter: nuevas perspectivas en la prevención de la fertilidad en la Adolescencia.

Piernicola Garofalo

U.O.C Endocrinología AOOR "Villa Sofia - Cervello"- Palermo

Buenos Aires 26 de Marzo 2014

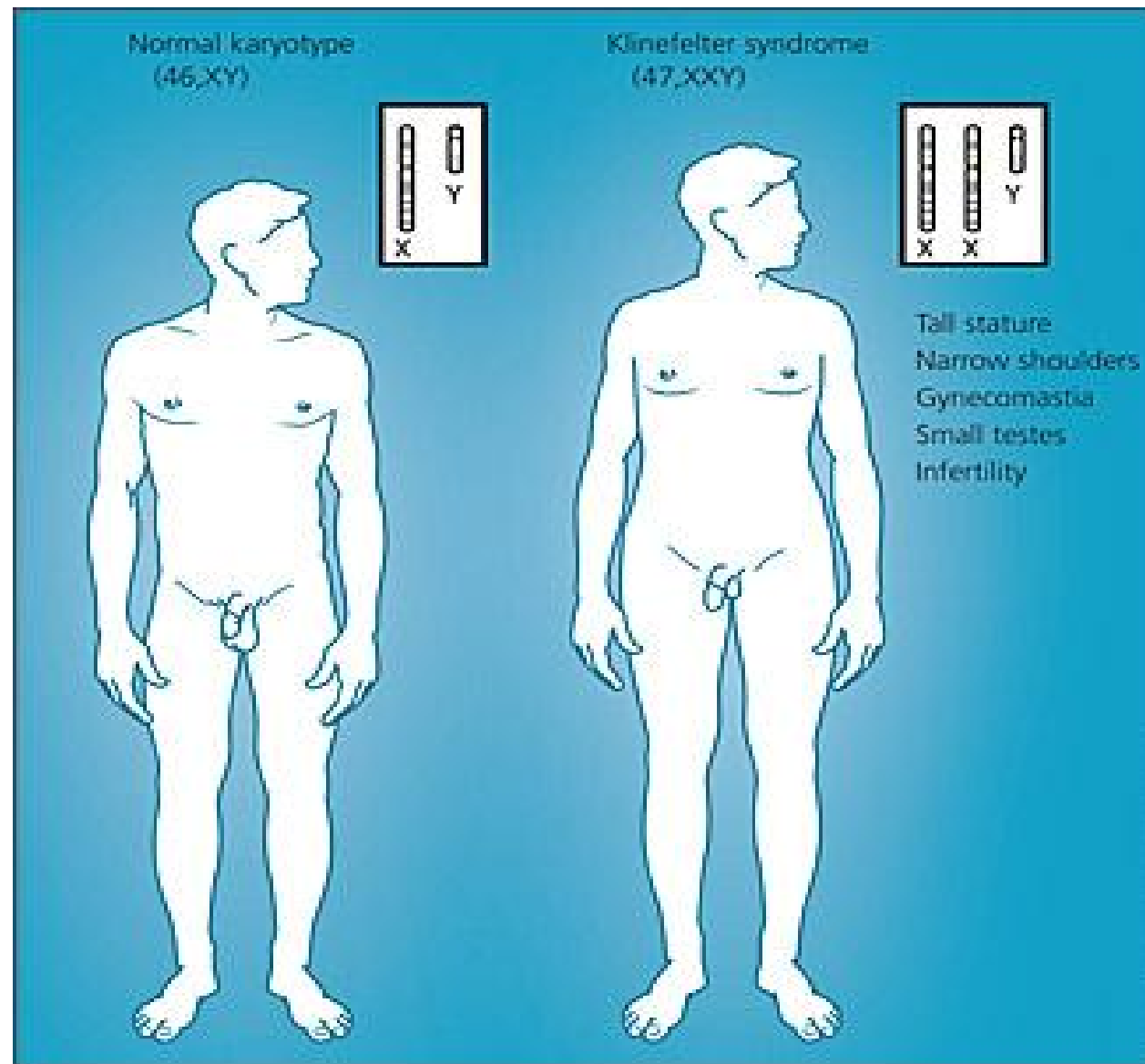
Varadero- Matanzas 16-18 de Octubre 2013



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Update in Endocrinologia Clinica



19-22 Novembre 2009 – Fiera Milano City - Milano



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Klinefelter et al
1942



Update in Endocrinologia Clinica

TABLE 1

Klinefelter Syndrome: Characteristic Clinical Findings

Infertility (azoospermia or oligospermia)

Small, firm testes

Hypergonadotropic hypogonadism

Gynecomastia

Tall, slender body habitus with long legs and shorter torso

Osteoporosis (in young or middle-age men)

Motor delay or dysfunction

Speech and language difficulties

Attention deficits

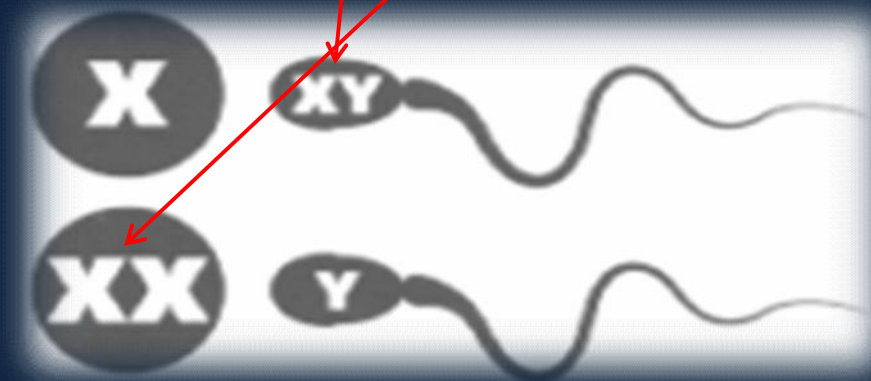
Learning disabilities

Dyslexia or reading dysfunction

Psychosocial or behavioral problems

Klinefelter 47XXY

- Più frequentemente di origine paterna per non disgiunzione durante la prima divisione meiotica della spermatogenesi
- Meno frequentemente di origine materna per non disgiunzione durante la prima o la seconda divisione meiotica della follicologenesi



Klinefelter mosaico

- I casi di mosaicismo sono legati a processi di non disgiunzione mitotica durante i processi di divisione dello ZIGOTE
- 15% degli individui con sindrome di Klinefelter sono mosaici: 47,XXY/46,XY
- La linea spermatogenetica può essere rappresentata diversamente a seconda del grado del mosaicismo

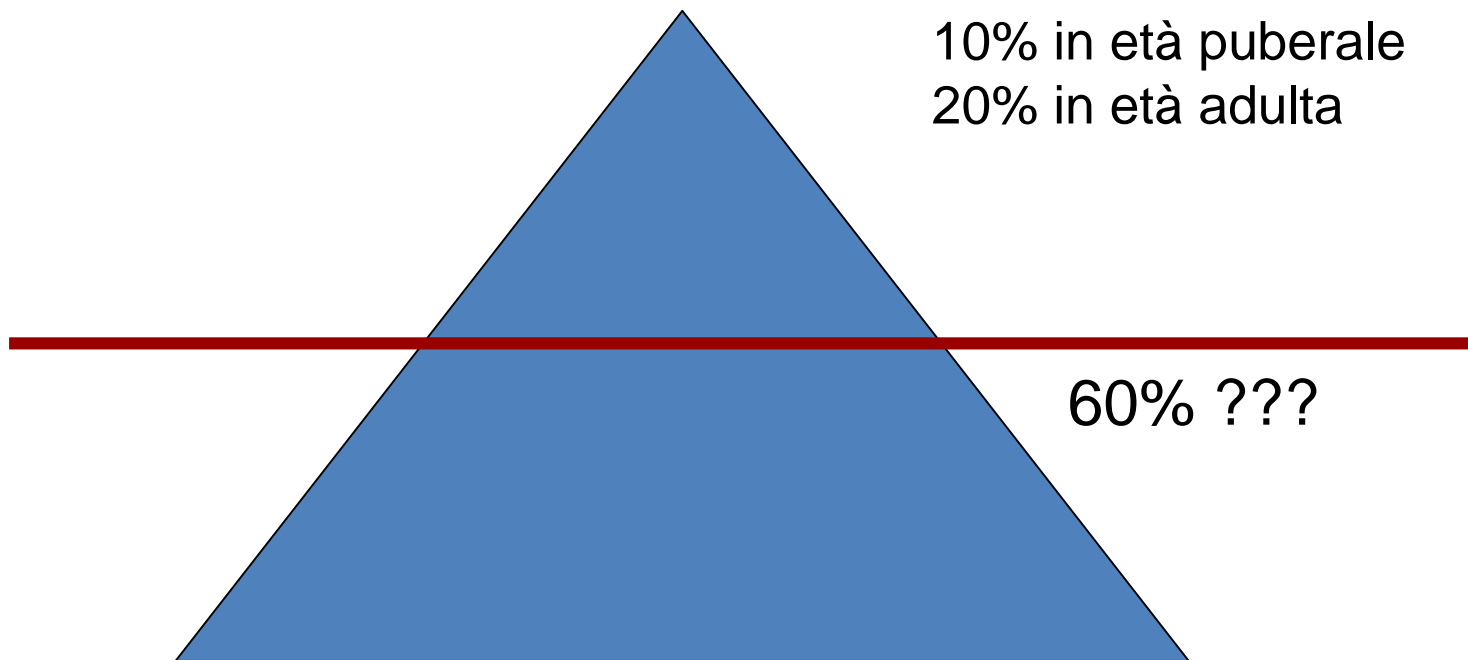


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10% Prenatale
10% in età puberale
20% in età adulta



60% ???



Prevalenza:

Nella popolazione generale (1: 660 nati) = 0.2%
La forma più frequente di ipogonadismo e di aneuploidia
Negli infertili: 2-3%

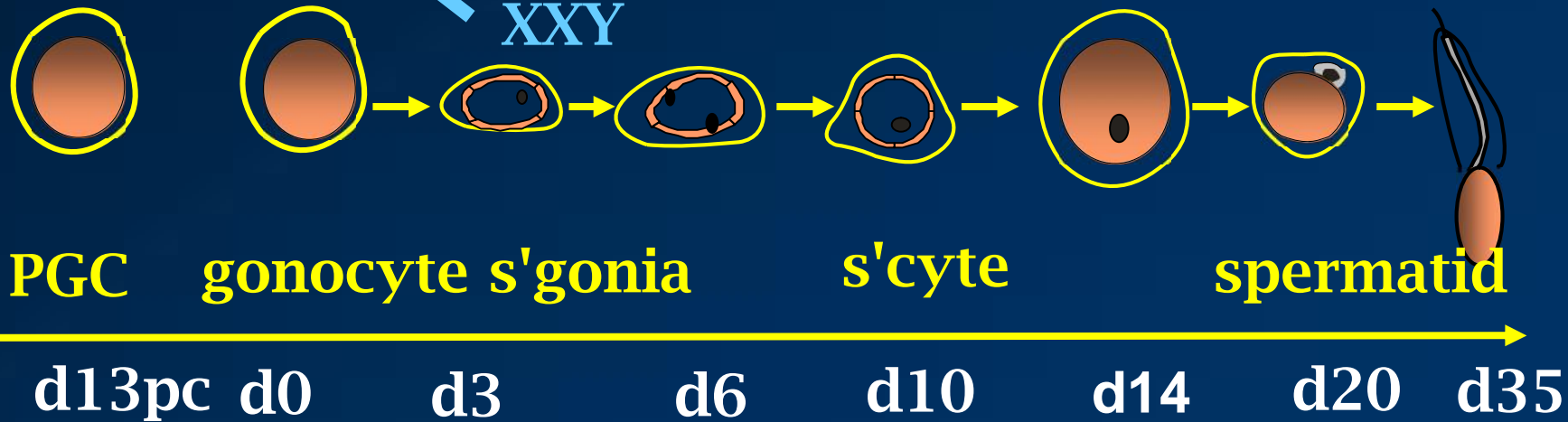
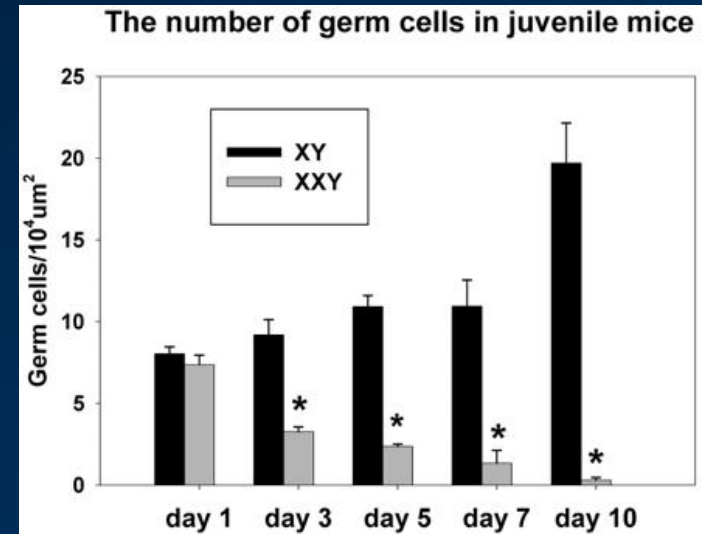
PROGRESSIVE LOSS OF GERM CELLS DURING TESTIS DEVELOPMENT

The mouse model of Klinefelter syndrome

number of germ cells

XY

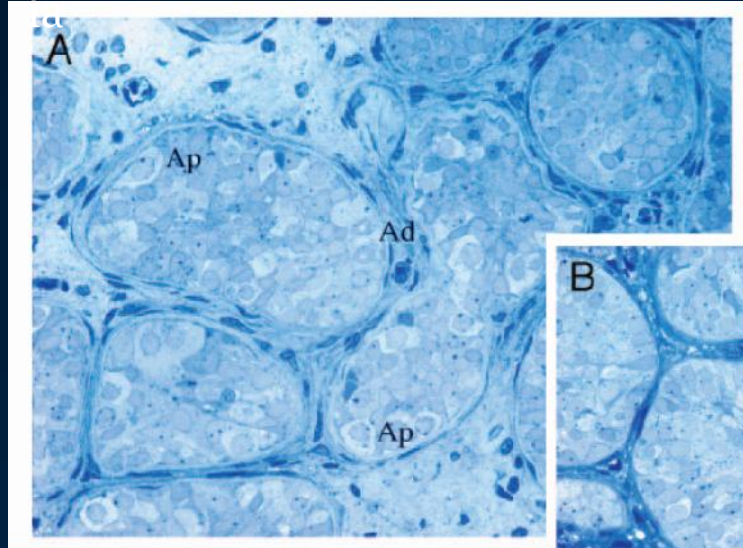
XXY



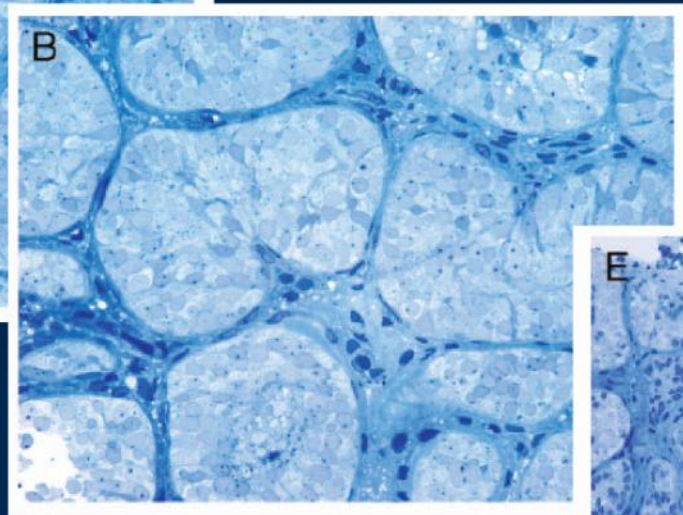
Germ cell loss at puberty in boys with Klinefelter syndrome

Tubules with spermatogon

Tubules without spermatogonia



No spermatogonia

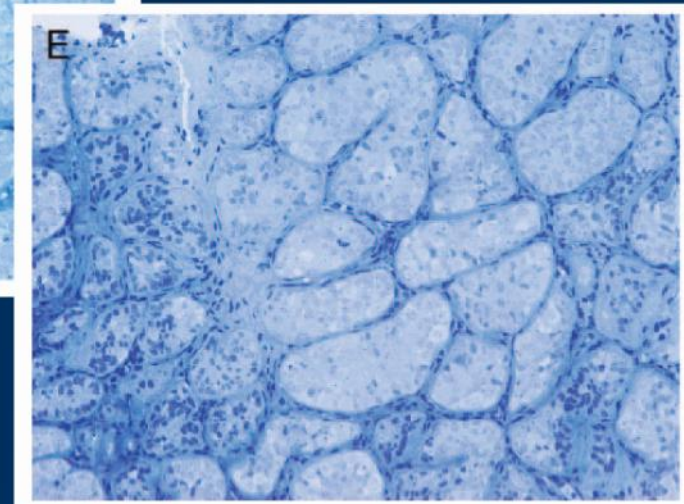


Tubules degeneration

10.7 yrs

Tanner P1/G1

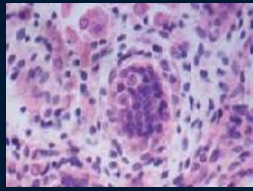
11.7 yrs
Tanner P1/G2



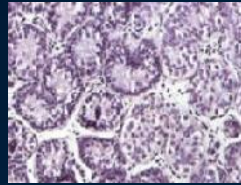
12.5 yrs

Tanner P2/G2

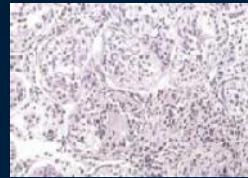
(Wikström et al., JCE&M 89:2263, 2004)



4 yrs



12 yrs



14 yrs



PROGRESSIVE LOSS OF GERM-CELLS WITH ADVANCING AGE

Aksglæde et al 2006

SEVERE IMPAIRMENT OF SPERMATOGENESIS UNTIL THE END OF PUBERTY

Low to normal T

Mild Hypogonad.

Overt Hypogonad.

Puberty

Young Adults

Adults



PROGRESSIVE LOSS OF LEYDIG FUNCTION WITH ADVANCING AGE

Aksglæde et al 2006

SEVERE IMPAIRMENT OF ANDROGEN PRODUCTION FROM PUBERTY TO 40s



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Intervento terapeutico

- Accettazione della diagnosi prenatale (intervento sui genitori)
- Preparazione dei genitori per la comunicazione della diagnosi al ragazzo
- Timing della comunicazione della diagnosi al ragazzo



Importanza del Counseling

L'importanza di queste conoscenze

- ✓ **Counseling riproduttivo**

- ✓ **Tecniche di PMA (Procreazione Medicalmente Assistita)**
 - a) **Recupero di spermatozoi da eiaculato**
 - b) **TESA (testicular sperm aspiration)**
 - c) **TESE (testicular sperm extraction)**
 - d) **Micro-TESE (microdissectionTESE)**
 - e) **ICSI (intracytoplasmatic sperm injection)**

La sindrome di Klinefelter

L'associazione tra KS e infertilità non è un dogma

Sono riportati casi di paternità spontanea, seppure molto rari

Reference	n	Karyotype (peripheral leucocytes)	Testicular biopsy	Pregnancies	Liveborn children	Karyotype of child	Paternity testing
69	1	47,XXY	No	1	1	46,XY	HLA typing
70	1	47,XXY	No	1	1	46,XX	DNA fingerprinting

Table 3: Reported pregnancies after natural intercourse in patients with Klinefelter's syndrome

Liquido seminale e sindrome di Klinefelter

- Azoospermia 90%
 - Criptozoospermia 10%
 - Molto raramente si osservano concentrazioni fino a circa **$5 \times 10^6/\text{ml}$**
-
- Presenza di un mosaicismo intratesticolare
 - Spermatogenesi residua in qualche tubulo seminifero

84 pz. SK 47xxy

Quadro seminale

Concentrazione (milioni/ml)	$0,2 \pm 0,1$
Motilità a+b (%)	$20,0 \pm 7,0$
Morfologia (%)	$19,0 \pm 8,0$

Presenza di spermatozoi
nel liquido seminale

7/84 (8,3%)

Quadro ormonale

FSH medio (U/L)	$30,8 \pm 7,5$
LH medio (U/L)	$17,2 \pm 4,7$
T totale (nmol/L)	$9,5 \pm 1,1$

Età media
(anni)

$30,5 \pm 6,5$

Volume
testicolare
medio (ml)

$1,9 \pm 0,1$

Tecniche di recupero degli spermatozoi

Table 1 - Sperm Retrieval Techniques and their Indications for Assisted Reproduction.

Technique	Acronym	Indications
Percutaneous epididymal sperm aspiration	PESA	OA cases only
Microsurgical epididymal sperm aspiration	MESA	OA cases only
Testicular sperm aspiration	TESA; TEFNA ¹	Failed PESA in OA Epididymal agenesis in CAVD cases Favorable testicular histopathology ² in NOA Previous successful TESA attempt in NOA
Testicular sperm extraction (single or multiple biopsies)	TESE	Failed PESA or TESA in OA NOA cases
Microsurgical testicular sperm extraction	Micro-TESE	NOA cases only

OA: obstructive azoospermia; NOA: nonobstructive azoospermia

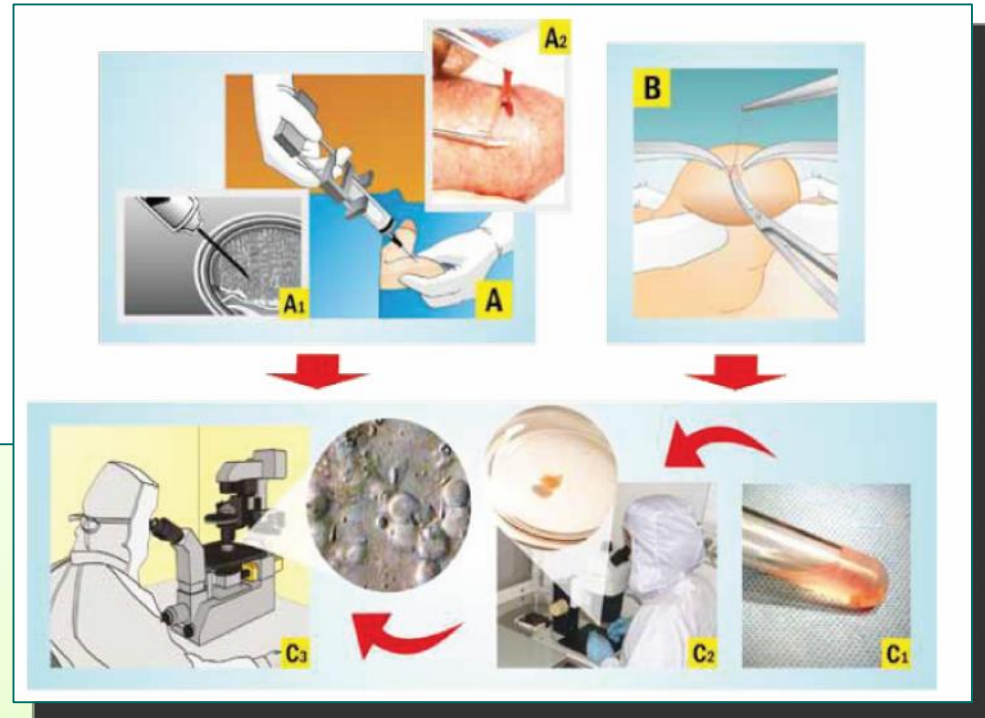
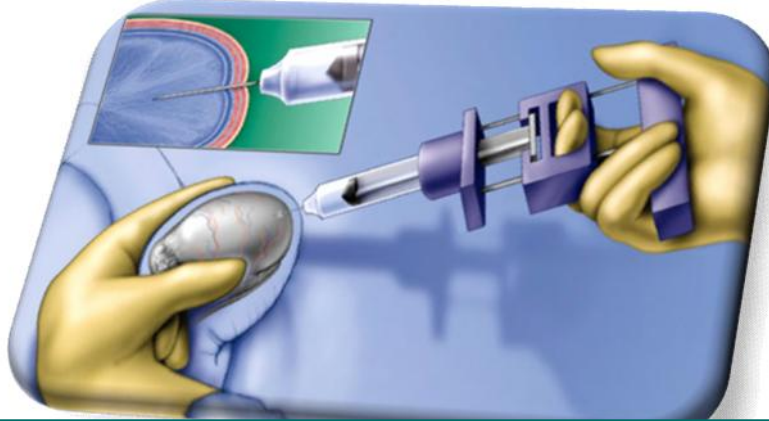
1 - Testicular fine-needle aspiration (TEFNA) is a technical variation of TESA; 2 - Hypospermatogenesis

PESA: *percutaneous epididymal sperm aspiration*





Testicular Sperm Aspiration (TESA)



Ago da 19-21 gauge (Siringa di Menghini)

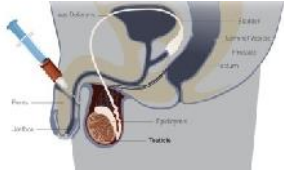
Necessità di prelievi multipli

Indicazioni

- Azoospermia ostruttiva (OA)
- Azoospermia non ostruttiva con istopatologia testicolare favorevole (ipospermatogenesi)

Vantaggi: semplicità di esecuzione, bassi costi, minor invasività, anestesia loco-regionale

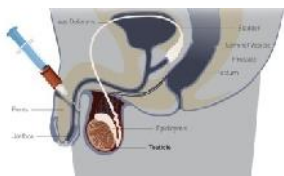
Svantaggi: ridotta sperm retrieval rate (SRR) rispetto a TESE e micro-TESE (specie in caso di NOA)



Testicular Sperm Extraction (TESE)

- Anestesia loco-regionale
- Piccola incisione scrotale
- Apertura tunica vaginale ed esposizione albuginea del testicolo
- Incisione trasversale e prelievo parenchima testicolare (tubuli seminiferi)
- **Indicazioni:** NOA o fallimento PESA, MESA, TESA per OA





Testicular Sperm Extraction (TESE)

Vantaggi

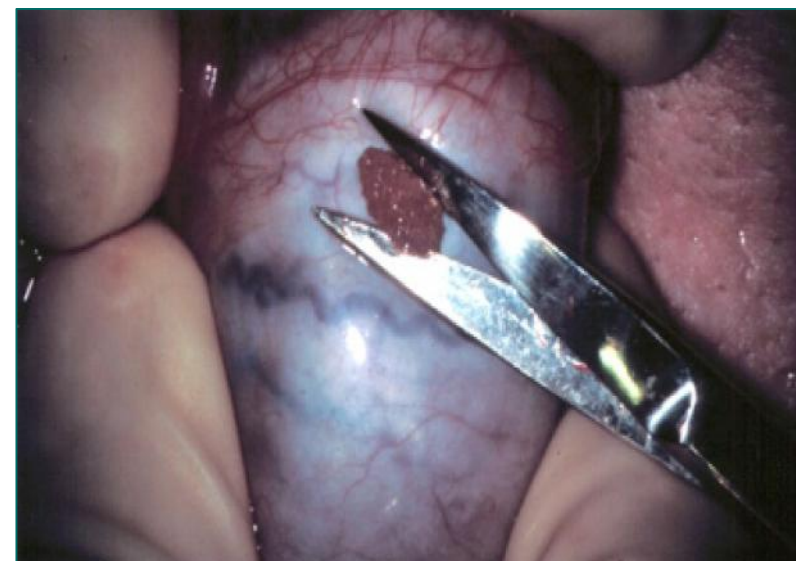
Tassi più elevati di sperm retrieval rate (SRR) rispetto a TESA

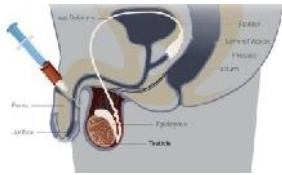
Possibilità di esame istopatologico (diagnosi di testiculopatia)

Svantaggi

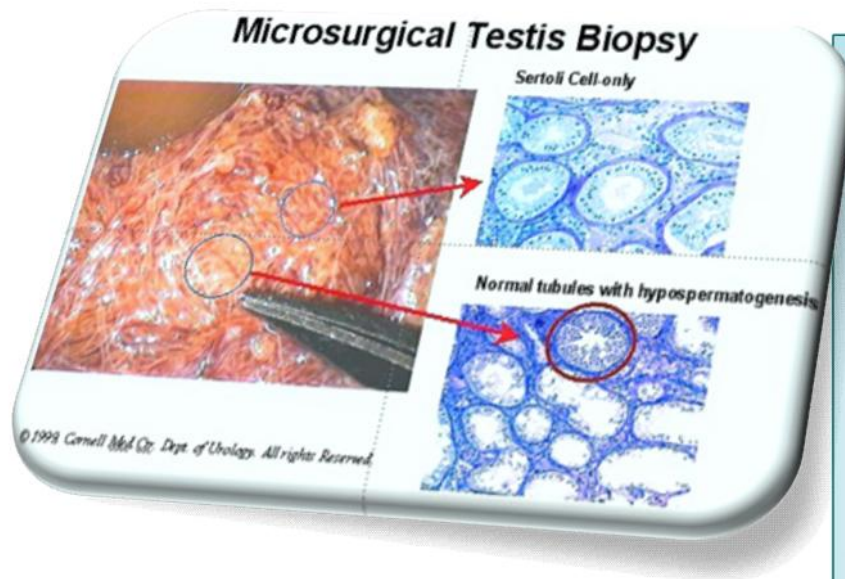
Maggior invasività e danno parenchima testicolare (perdita parenchima, danno vascolare, depauperamento cellule di Leydig e deficit androgenico))

Spesso necessità di prelievi multipli o bilaterali in caso di NOA (specialmente in presenza di arresto maturativo o sindrome a sole cellule di Sertoli)

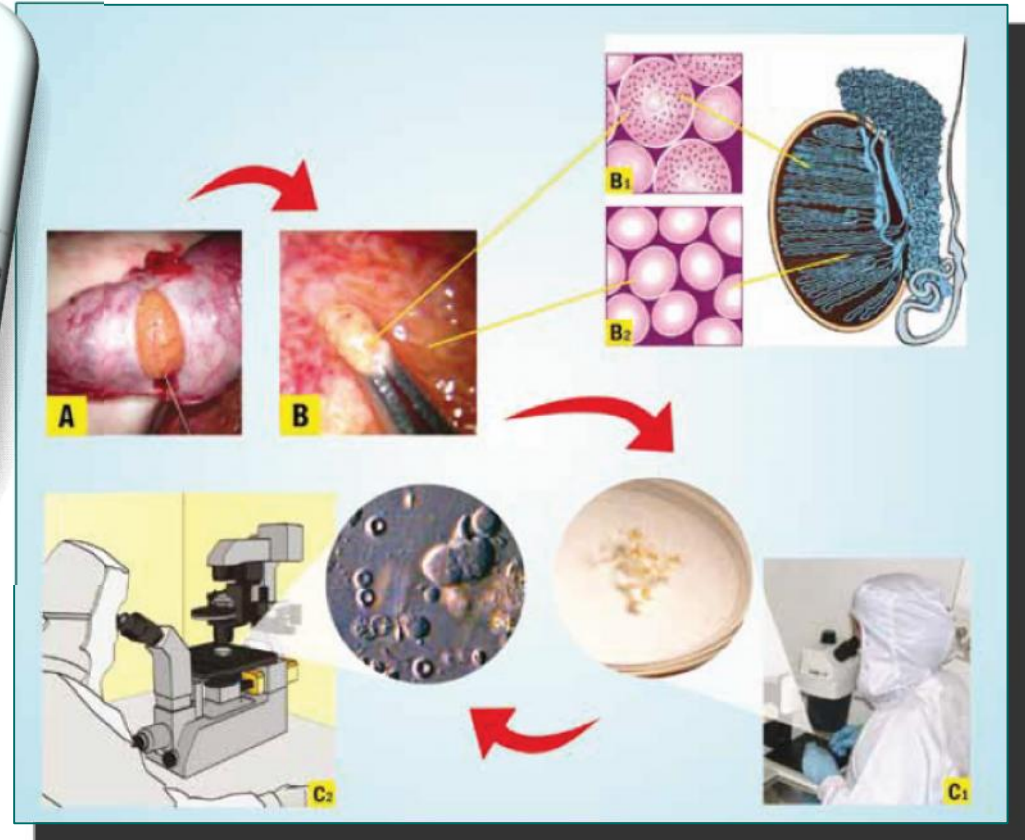


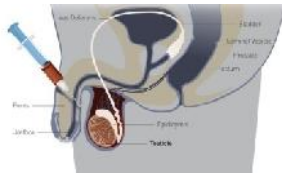


Microdissection-TESE (micro-TESE)



Questa tecnica permette di identificare al microscopio operatore i tubuli seminiferi più grandi e quindi quelli con maggiore probabilità di spermatogenesi residua.



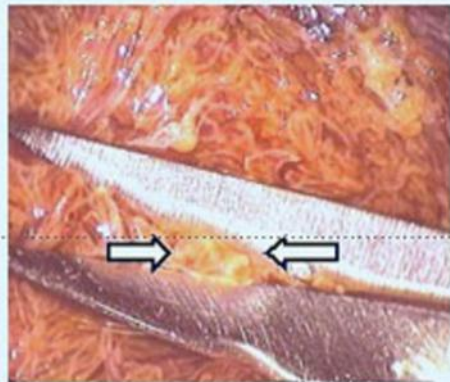


TESE vs *micro-TESE*

Clinical Comparison of Conventional Testicular Sperm Extraction and Microdissection Techniques for Non-Obstructive Azoospermia

Ibrahim Fathi Ghalayini^{a, d}, Mohammed A. Al-Ghazo^a, Osama Bani Hani^a,
Rami Al-Azab^a, Ibrahim Bani-Hani^a, Faheem Zayed^b, Yazan Haddad^c

Microdissection TB vs. Conventional TB



5 -15 mg



>500 mg

5 -15 mg

>200 mg

Micro-TESE

Vantaggi

➤ Maggior probabilità di recupero di spermatozoi rispetto alla TESE (NOA)

➤ Magnificazione dell'immagine e ridotto danno testicolare

Svantaggi

➤ Tempi operatori prolungati

➤ Costi più elevati

➤ Learning curve più lunga

PROGNOSTIC FACTORS FOR TESE/ICSI: parenchyma (MTESE)

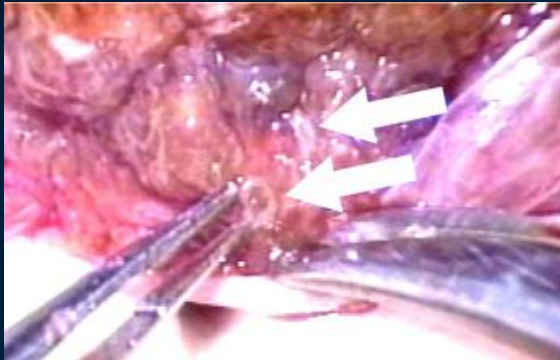


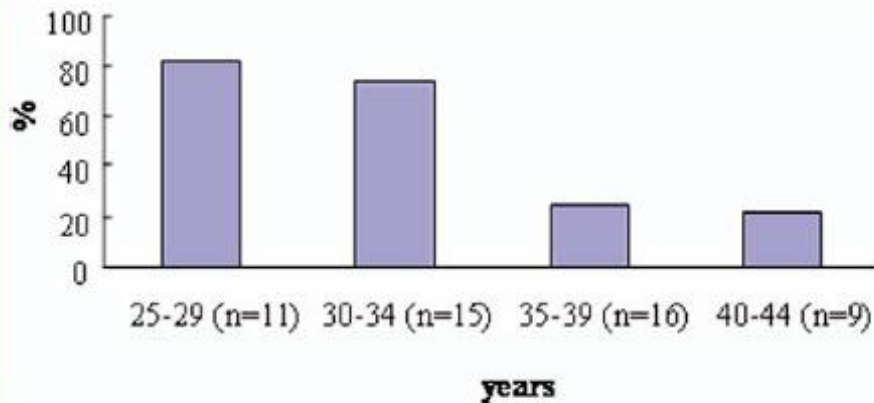
Table 2. Relation between morphologic appearance of testicular parenchyma and spermatozoa retrieval

Seminiferous Tubules Without Sclerotic Changes	Testicular Spermatozoa Retrieval (n)	
	Success	Failure
Present	16	1
Absent	0	29

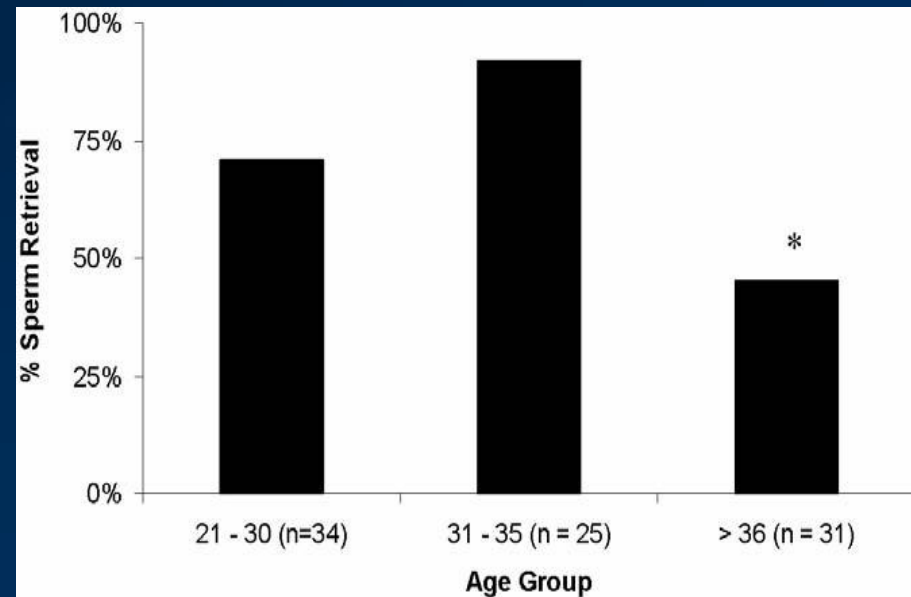
(Koga et al., Urology, 2007)

PROGNOSTIC FACTORS FOR TESE/ICSI: AGE

Age-specific success rate of testicular sperm extraction in nonmosaic Klinefelter's syndrome patients. *Vertical axis*, percentage of successful testicular sperm extraction (TESE); *horizontal axis*, 5-year age brackets.



Okada. Age limits success of TESE in KFS. Fertil Steril 2005.



Okada et al. Fertil Steril 2005

Ramasamy et al. J Urol 2009

PERCENTAGE OF PREGNANCIES AFTER TESE IN AZOOSPERMIC SUBJECTS WITH NON MOSAIC KS

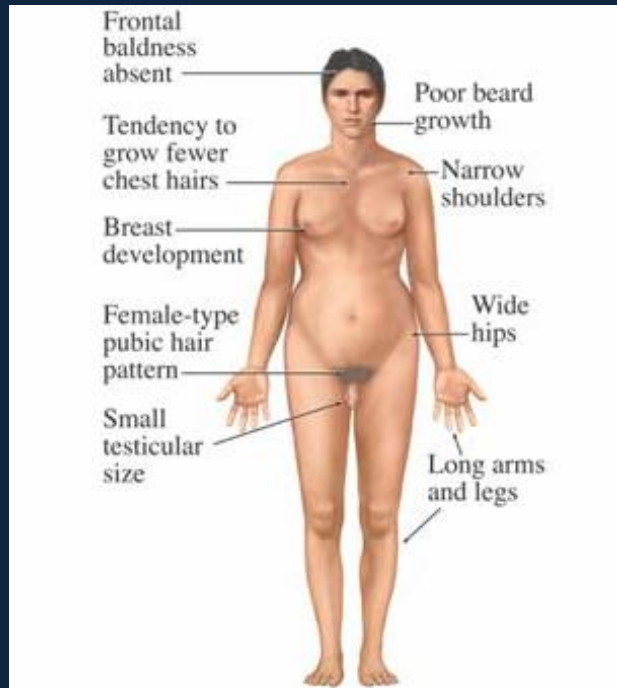


Weighted Mean on patients' number

Arithmetic Mean

*80 % of studies
Interval 5.5-42.8%*

84 SK non mosaico



Età (anni)	31.3±9.1
FSH (UI/L)	32.7±13.3
LH (UI/L)	19.9±6.9
Testosterone totale (nmol/L)	10.6±4.6
SHBG (nmol/L)	27.5±12.5
Testosterone libero (nmol/L) (calcolato)	0.22±0.1
Estradiolo (pmol/L)	104.6±37.1
Inibina B (pg/ml)	26.9±46.1
Volume testicolare medio (ml)	3.9±0.9
Altezza (cm)	180.9±8.8
Peso (Kg)	86.5±19.4
BMI (Kg/m ²)	26.1±5.4
Apertura delle braccia (cm)	181.4±16.3
Circonferenza vita (cm)	98.0±16.2
Lunghezza del pene (cm)	8.4±1.9
Circonferenza del pene (cm)	9.5±1.2

84 SK non mosaico

7 (8.3%)
 Severa oligozoospermia
 (criptozoospermia)

↓

FNAC

Ipospermatogenesi grave

77 (91.7%)
 Azoospermia

↓

FNAC

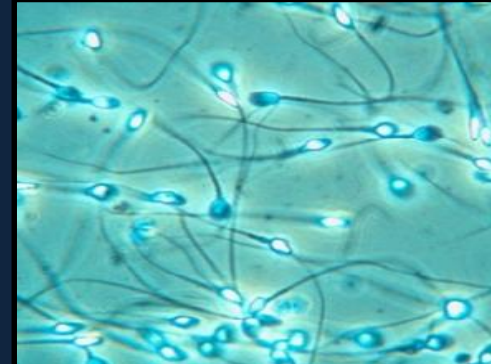
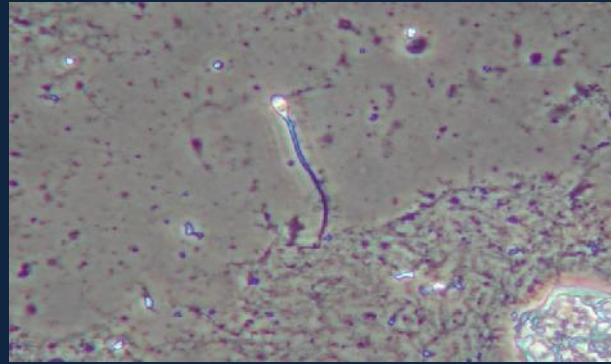
49	24	4
SSCS	Ipo grave	Arr. M.

↓

24 TESE



Recupero di spermatozoi alla TESE in soggetti con SK



9/24 (37,5%)

Parametri clinici dei pazienti con e senza spermatozoi nel LS e alla TESE

	Recupero Sp.zoi	Non recupero Sp.zoi
Età media (anni)	30,0±7,2	29,5±7,8
Volume testicolare medio (ml)	2,0±0,5	1,7±0,8

	Recupero Sp.zoi	Non recupero Sp.zoi
FSH (U/L)	33,1±13,4	38,6±14,9
LH (U/L)	18,4±5,7	21,6±7,0
T totale (nmol/L)	11,6±3,0	10,3±3,9
SHBG (nmol/L)	24,3±10,2	27,6±13,0
T libero calc. (nmol/L)	0,26±0,08	0,21±0,08
Estradiolo (nmol/L)	107,6±32,9	105,3±30,5
Inibina B (ml)	28,9±28,9	37,4±59,7

*P tutte >0.05

Aneuploidie dei cromosomi sessuali nei soggetti con SK con spermatozoi nel LS

High Incidence of Sperm Sex Chromosomes Aneuploidies in Two Patients with Klinefelter's Syndrome

C. FORESTA, C. GALEAZZI, A. BETTELLA, M. STELLA, AND C. SCANDELLARI

Third Chair of Medical Pathology, University of Padova, Padova; and Laboratory of Cytogenetic, San Bortolo Hospital (M.S.), Vicenza, Italy

Analysis of Meiosis in Intratesticular Germ Cells from Subjects Affected by Classic Klinefelter's Syndrome

CARLO FORESTA, CARLO GALEAZZI, ANDREA BETTELLA, PAOLA MARIN, MARCO ROSSATO, ANDREA GAROLLA, AND ALBERTO FERLIN

University of Padua, Department of Medical and Surgical Sciences, Clinica Medica 3, 35128 Padua, Italy

Chromosome abnormalities in sperm of individuals with constitutional sex chromosomal abnormalities

A. Ferlin, A. Garolla, C. Foresta

University of Padova, Department of Histology, Microbiology, and Medical Biotechnologies, Centre for Male Gamete Cryopreservation, Padova (Italy)

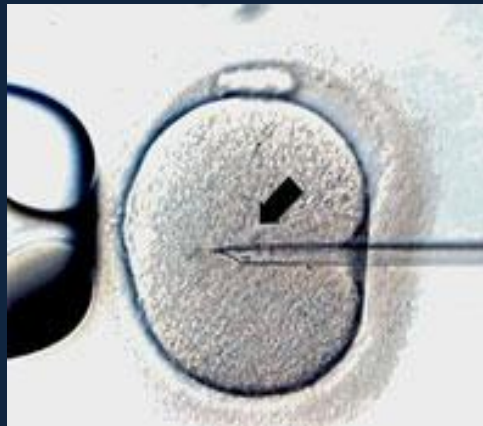
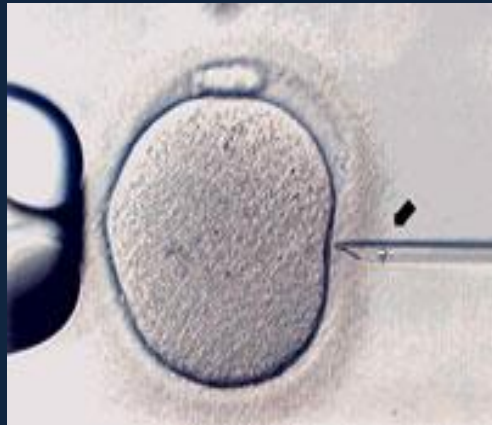
Aneuploidie dei cromosomi sessuali nei soggetti con SK con spermatozoi nel LS

	Spermatozoi euploidi (%)		Spermatozoi disomici (%)			Altro (%)	Aneuploidie Totali (%)
	X	Y	XX	YY	XY		
Soggetti Klinefelter (n. 7)	51.6±1.7*	26.9±1.5*	6.2±0.9*	0.4±0.6	13.3±2.5*	1.8±1.9*	21.5±2.3*
Soggetti normozoospermici (n. 103)	49.4±1.6	49.0±1.7	0.1±0.5	0.1±0.9	0.2±0.5	0.1±0.4	1.6±0.5
Soggetti con severa oligozoospermia non genetica (n. 387)	48.3±1.5	48.0±1.6	0.6±0.8	0.6±0.8	1.4±1.8	0.1±0.3	3.7±0.4

*P <0.01 vs. altri gruppi

Risultati della ICSI in soggetti con sindrome di Klinefelter

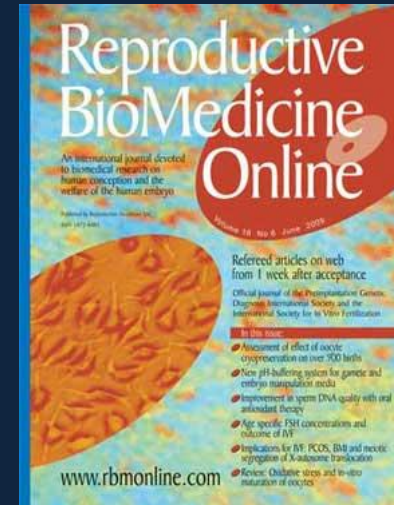
RISCHI GENETICI?



TESE-ICSI in SK non mosaico

Table 1. The baseline characteristics of the Klinefelter syndrome and control (non-obstructive azoospermia with normal karyotype) groups.

Parameter	Klinefelter syndrome	Controls
No. of patients	33	113
No. of TESE attempts	39	130
Male age years (mean ± SD)	32.0 ± 6.4 ^a	34.3 ± 5.8 ^b
Female age years (mean ± SD)	28.5 ± 6.1	29.9 ± 5.4
Successful retrieval of spermatozoa/total TESE attempts (%)	22/39 (56)	57/130 (44)
Successful retrieval of spermatozoa/first TESE attempt (%)	17/33 (52)	45/113 (40)
Successful retrieval of spermatozoa/2nd or further TESE attempt (%)	5/6 (83)	12/17 (71)



TESE-ICSI nei pazienti KS è comparabile ai pazienti con azoospermia non-obstruttiva e cariotipo normale

Table 2. The embryological data and pregnancy outcome of the Klinefelter syndrome and control (non-obstructive azoospermia with normal karyotype) groups.

Parameter	Klinefelter syndrome	Controls
No. of cumulus–oocyte complexes (mean ± SD)	13.1 ± 7.7	11.2 ± 6.4
Fertilization rate (%)	48	54
No. of embryos transferred (mean ± SD)	2.4 ± 1.2	2.7 ± 1.0
Biochemical pregnancy/embryo transfer (%)	11/18 (61)	19/46 (41)
Clinical pregnancy/embryo transfer (%)	7/18 (39)	15/46 (33)
Implantation rate (%)	23	26
Live birth rate/embryo transfer (%)	28	26

There were no statistically significant differences between the two groups.

RISCHIO ANEUPLOIDIE NELLA PROGENIE

I figli nati da pazienti Klinefelter mediante la PMA non presentano una più elevata incidenza di anomalie numeriche dei cromosomi sessuali, anche se esiste una maggiore incidenza nella produzione di gameti con aneuploidie.

Gandini L et al, 2010

Dai dati ottenuti dalle diagnosi pre-impianto, risulta che gli embrioni di coppie con maschio Klinefelter presentano il 54% di embrioni con cariotipo normale rispetto al 77,2% dei controlli.

Staessen et al, Hum Reprod Update, 2003

TESE-ICSI in SK non mosaico

BAMBINI NATI

TABLE 1

Pregnancies induced by ICSI with sperm from nonmosaic Klinefelter patients.

First author, year (reference)	Sperm origin	Pregnancy outcome	Comment
Staessen, 1996 (31)	TESE	Biochemical pregnancy	
Boune, 1997 (32)	Ejaculation	Twin birth	Frozen sperm
Hinney, 1997 (33)	Ejaculation	1st trimester abortion	
Tournaye, 1997 (34)	TESE	2× singleton birth	
Palermo, 1998 (35)	TESE	Singleton and twin birth	
Reubinoff, 1998 (23)	TESE-FNA	Singleton birth	
Nodar, 1999 (36)	TESE	Twin birth	
Ron-El, 1999 (37)	TESE	Singleton birth	
Kitamura, 2000 (38)	TESE	Singleton birth	
Levron, 2000 (14)	TESE	2× singleton, one twin, and one triplet birth	
Ron-El, 2000 (39)	TESE	Twin birth	Reduced triplet due to 47,XXY
Ron-El, 2000 (40)	TESE	Twin birth	Frozen sperm
Greco, 2001 (41)	TESE	Twin birth	
Kyono, 2001 (42)	TESE	Clinical pregnancy—2nd trimester	
Poulakis, 2001 (43)	TESE	2× singleton births	
Crüger, 2001 (44)	Ejaculation	Singleton birth	
Friedler, 2001 (45)	TESE	Singleton birth	2× twin and one singleton birth*
Rosenlund, 2002 (46)	TESE	Singleton birth	Frozen sperm and blastocyst
Bergere, 2002 (13)	TESE	Singleton birth	
Yamamoto, 2002 (10)	TESE	4× singleton and twin birth	
Tachdjian, 2003 (12)	Ejaculation	Twin birth	

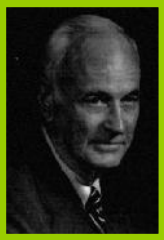
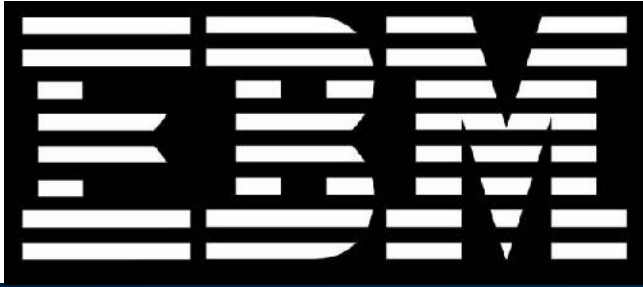
* The other reported pregnancies (two twin and one singleton) have already been documented in earlier publications (33, 35, 36).

Denschlag. ART in Klinefelter syndrome patients. Fertil Steril 2004.

- **39** bambini nati sani dopo ICSI da KS non mosaico
- **34** nati da ICSI+TESE
- **5** nati da gravidanze con spermatozoi eiaculati freschi o crioconservati
- **1** gravidanza trigemina con un feto 47XXY

Conclusioni

- La SK non è sinonimo di infertilità
- Fondamentale eseguire una diagnosi precoce
- Utile la crioconservazione nei soggetti con spermatozoi nel liquido seminale o alla TESE
- Consulenza genetica pre-tecnica PMA
- Possibilità concreta di gravidanza



1942 Infertility

Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone. Klinefelter H. The Journ of Clin Endocr 1942.

Paternity in Klinefelter's syndrome--a case report. Laron Z. Arch Androl. 1982.

1982 Spontaneous pregnancy

Fertility in a 47,XXY patient: assessment of biological paternity by deoxyribonucleic acid fingerprinting. Terzoli G. Fertil Steril. 1992.

1996 Sperm recovery

Testicular sperm recovery in nine 47,XXY Klinefelter patients. Tournaye H. Hum Reprod. 1996.

Delivery of normal twins following the intracytoplasmic injection of spermatozoa from a patient with 47,XXY Klinefelter's syndrome. Bourne H. Hum Reprod. 1997.

1997 Pregnancy

with assisted techniques

Pregnancy after intracytoplasmic sperm injection with sperm from a man with a 47,XXY Klinefelter's karyotype. Hinney B. Fertil Steril. 1997.

Mi nombre es Vincent Graffeo, voy a compartir mi experiencia como paciente "invisible" para que sea un tesoro para todos. Me enteré de que él sufre de una rara enfermedad a los 39 años, ahora soy 43. No Cromopatia ser afectados por cualquier avería se confundirá, incluso desde que descubrí siendo un tema de Klinefelter me di cuenta de algunas dificultades que me encontré en la vida, sino que también tiene problemas de salud y las dificultades académicas. Actualmente tengo el cargo de presidente de la Asociación Nacional Askis organización sin fines de lucro con Honor. para todos los sujetos con síndrome de Klinefelter de Siano visible en todo el mundo.

notra la Asociación colabora con el SIMA para la protección de los niños que vienen después de nosotros d.

"GRACIAS"



Nuestra asociación nació el 20/03/2012 se amplía a todo el país cualquier persona puede tener la condición y tutt rappresentarci en el Mundo



Todos
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bajo el mismo
cielo



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