Testicular tissue: How should it be retrieved?

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When should I go for sperm recovery surgery?

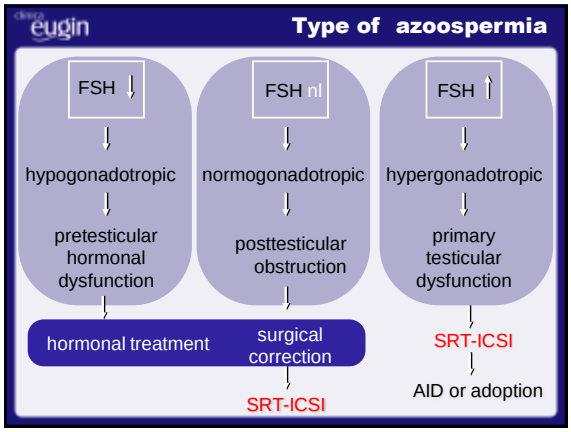
"Absence of any spermatozoon in the ejaculate"

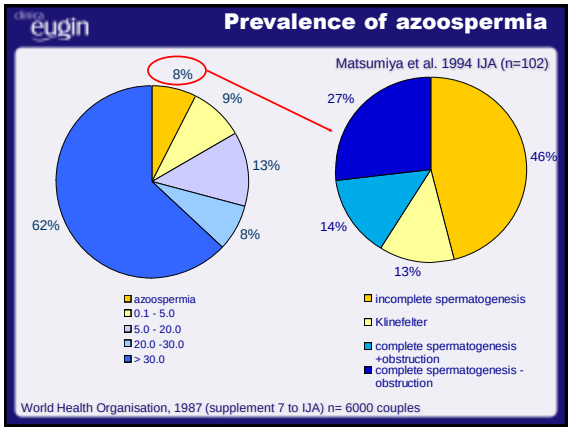
Before going for the final cut…

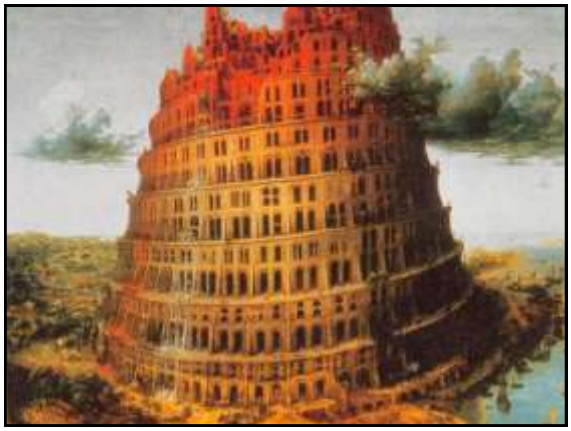
Rule out cryptozoospermia

centrifugation of ejaculate
1000xg for 15 min.

examination of at least 2 ejaculates extended sperm preparation (ESP)


Type of azoospermia
FSH ↓
hypogonadotropic
pretesticular hormonal dysfunction
hormonal treatment
FSH nl
normogonadotropic
posttesticular obstruction
surgical correction
SRT-ICSI
FSH ↑
hypergonadotropic
primary testicular dysfunction
SRT-ICSI
AID or adoption


Prevalence of azoospermia
Matsumiya et al. 1994 IJA (n=102)
8%
9%
13%
62%
8%
27%
46%
14%
13%
azoospermia
0.1 - 5.0
5.0 - 20.0
20.0 -30.0
> 30.0
incomplete spermatogenesis
Klinefelter
complete spermatogenesis +obstruction
complete spermatogenesis - obstruction
World Health Organisation, 1987 (supplement 7 to IJA) n= 6000 couples



Appropriate diagnosis

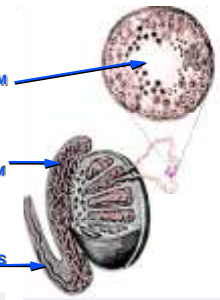
- physical examination
- hormonal profile
- biochemical semen markers
- TR and Sc ultrasound
- genetic analysis
- **Histology**

(McLachlan et al., 2007)

Tournaye - WHO 2001

Sperm recovery for ICSI

- TESTICULAR SPERM FROM SEMINIFEROUS TUBULES
- EPIDIDYMAL SPERM FROM EPIDIDYMIS
- DUCTAL SPERM FROM VAS DEFERENS



Anejaculation does not equal azoospermia

Intratesticular sperm extraction. Basis for successful treatment of infertility in men with ejaculatory azoospermia.

Schulze W, Knuth UA, Jezek D, Benson DM, Fischer R, Naether OG, Baukloh V, Ivell R.

Surgical sperm recovery techniques are widely applied to cope with anejaculation In ART centres

there are many less invasive alternatives!

Anejaculation: no need for surgery

- psychotherapy:
  need for cryopreservation?
- medical treatment: Viagra™
  Tur-Caspa et al.,1999
- Penile Vibrostimulation
- Electroejaculation

Obstructive azoospermia

surgical correction
or
ART?

Obstructive azoospermia

Scrotal exploration:

- diagnostic value
- Opportunity for reconstructive surgery (vaso-vasostomy or epididymo-vasostomy)

If reconstruction not feasible: Microsurgical epididymal sperm aspiration (MESA) + freezing

Heindenreich et al., 2000

PESA

Percutaneous epididymal sperm aspiration

- Less invasive than MESA
- Local anesthesia
  (Rosenlund et al., 1998)

- May cause more epididymal damage and fibrosis
- Not relevant if reconstruction is not possible

- Less espermatozoa than MESA 20% unsuccessfull *(Lin et al., 2000)*

In OA: Epididymis is the preferred site

Testicular sperm in OA: FNA or TESE

FNA: High sperm retrieval rate in men with normal spermatogenesis
Tournaye et al., 1998

TESE: Sometimes preferred whenever cryopreservation is an option and motile epididymal sperm has not been obtained

Epididymal vs testicular sperm: outcome?

Use of surgical sperm retrieval in azoospermic men: a meta-analysis

James D. M. Nicopoullos, M.B.B.S.,[a] Carole Gilling-Smith, Ph.D.,[a] Paula A. Almeida, Ph.D.,[a] Julian Norman-Taylor, M.R.C.O.G.,[a] Ian Grace, B.Sc.,[b] and Jonathan W. A. Ramsay, M.S.[a,c]

Fertil Steril, 2004

In obstructive azoospermia: no significant difference in any outcome measure between the use of epididymal or testicular sperm

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Which is the best sperm retrieval technique for non-obstructive azoospermia? A systematic review

P. Donoso[1,3], H. Tournaye[2] and P. Devroey[2]

Ideal surgical technique

- Minimal trauma to the testis
- Sufficient amount of motile sperm to inject in all oocytes
- Sufficient amount to cryopreserve the remainder

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FNA in NOA

- May limit haematoma, inflammation and desvascularisation *(Schlegel et al., 1997)*
- Advantages: simplicity, low cost, minimally invasive and less post-op pain *(Tournaye et al., 1999)*

TESE versus FNA for ICSI in NOA

Study	Unit of study (ov)	SRR (%) FNA/TESE
Friedler *et al.* (1997)	37 patients FNA prior to TESE	11/43
Ezeh *et al.* (1998)	35 patients FNA prior to TESE	14/77
Rosenlund *et al.* (1998)	22 patients FNA 19 ve 21gauge (G) prior to TESE	21 G 16.7/50 19G 60/70
Tournaye *et al.* (1999)	14 patients FNA 14 patients TESE	7.1/64.3
Nassar *et al.* (2001)	49 cycles FNA 26 cycles TESE	24.5/19.2
Khadra *et al.* (2003)	84 patients undergoing FNA. TESE was only performed if FNA failed	53.6/71.8
Hauser *et al.* (2006)	87 patients FNA prior to TESE	24.1/62.1
El-Haggaret al. (2008)	100 patients (one testis FNA, the other microTESE)	10/54
Overall		24% vs 57%

To date, NO randomized trial compared SRR of FNA with TESE in NOA

Novero, V. et al. 1996. Seminoma discovered in two males undergoing successful testicular sperm extraction for intracytoplasmic sperm injection. Fertil. Steril., 65, 1015-1054

Multiple testicular sampling in non-obstructive azoospermia—is it necessary?

R.Hauser[1,2], A.Botchan[1], A.Amit[2], D.Ben Yosef[2], H.Gamzu[2], G.Paz[2], J.B.Lessing[2], L.Yogev[2] and H.Yavetz[2]

[1]The Institute for the Study of Fertility, and [2]Ben Hacine IVF Unit, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel

[3]To whom correspondence should be addressed at: The Institute for the Study of Fertility, Lis Maternity Hospital, 6 Weizman Street, Tel Aviv 64239, Israel

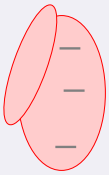
advised to use donor spermatozoa. As a result, testicular sperm retrieval procedures in non-obstructive azoospermic men are becoming increasingly popular.

With accumulated data and increased experience, it has been shown that testicular spermatozoa can be found in only part of the testes of non-obstructive azoospermic men. At present, there are no means of predicting the presence of such spermatozoa-positive (Hauser *et al.*, 1994; Tournaye *et al.*, 1995). The only diagnostic method available is the performance of surgical

Focal versus diffuse distribution

55 testes (29 NOA men): each testis 3 TESE biopsies

overall recovery rate: 28/55 (51%) and 18/29 (62%)

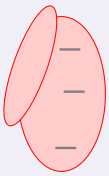


+ in 3 locations	15	53.6%
+ in 2 locations	5	17.9%
+ in 1 location	8	28.9%

46% of the cases only sperm after multiple biopsies

Hauser et al. 1998

Location of the biopsy

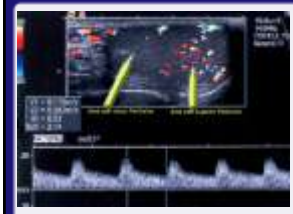


Contradictory results:

•Hauser et al., 1998 (n=55 testicles): no advantage of particular site (upper pole, midline or proximal pole)

•Witt et al., 1997: (small series, n=20 testicles) midline portion highest SRR

Doppler ultrasound prior to TESE

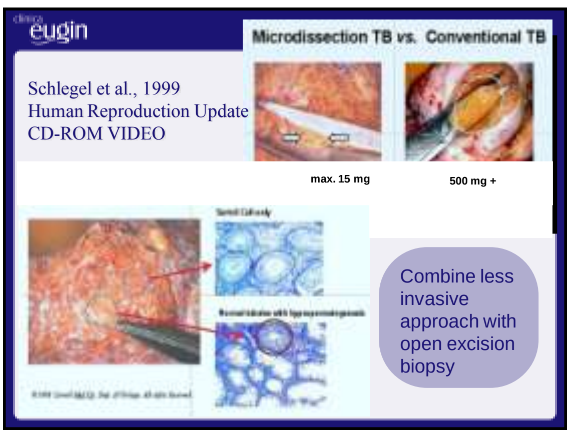


•Aim: trace regions with better vascularisation *(Herwig et al., 2004 and 2007)*

•SRR in areas with good vs poor vascularity: 38% vs 14% *(Tunc et al., 2005)*

This technique could reduce the number of biopsies and minimize testicular damage.

More studies are required!



Micro-TESE versus random-TESE

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Colpi et al. (2009)	Randomized controlled	138 testicles	52/42		

Overall 47% vs 35%

- Unclear if recovery rate improve if no enlarged tubules are present like in maturation arrest *(Okada et al., 2002)*
- What about cryopreservation ?

The Cochrane Collaboration
Cochrane Reviews

Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia

Last up to date december 2007

- It is not certain whether any SRR technique for ICSI is better than another for leading to more pregnancies
- There are too few trials to show which SRT might be better
- Complications are haematoma and fibrosis identified by ultrasound

Complications

Blood supply from internal spermatic artery, cremasteric and vassal arteries that penetrate the tunica albuginea and septa *(Ron-El et al., 1998)*

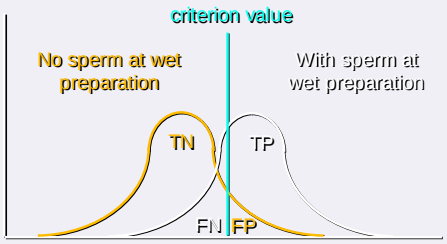
Testicular damage due to surgical anoxa:

interference of vascular supply to seminiferous tubules
or
Increased intra testicular pressure secondary to bleeding (Silber, 2000)

Complications

- **Haematoma**: in up to 80% of patients based on US *(Schlegel and Su, 1997)*
- **Fibrosis**
- **Testicular atrophy**: NOA men at high risk of developing androgen deficiency after TESE *(Tash and Schlegel, 2001; Schill et al., 2003)*

Can we predict the outcome of a TESE in NOA?



Can we predict the outcome of TESE in NOA?

Parameter or exam	Sensitivity %	Specificity %	Overall predictive value %	Reference
Semen analysis	38.2	77.9		Tournaye et al, 1997
Testicular volume	7.6-50	6.7-71		Salihu et al, 2003
FSH	9-71	40-90		Salihu et al, 2003
Inhibin B	44.6	63.4		Vernaeve et al, 2002
FSH, total T, inhibin B	71	71.4		Tsujimura et al, 2004
Testicular volume + hormones			80.8	Samli et al, 2004
Doppler ultrasound imaging	47.3	89		Har-Toov et al, 2004
Histopathology	58.8	88.5		Tournaye et al, 1997

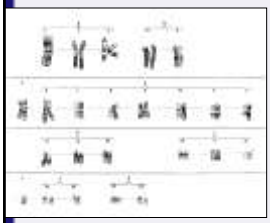
•Non invasive tests may exclude a significant number of men from ART

•The absence of sperm in one single testicular biopsy does not preclude the presence of some spermatozoa in the rest of the testes *(Gottschalk-Sabag et al., 1995).*

human reproduction REVIEW Andrology 2010

Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009?

G. Fullerton[1], M. Hamilton, and A. Maheshwari



•Medline and EMBASE search (1980 – 2009)

•Only non-mosaic Klinefelter patients included

•13 articles involving 373 men

Non-mosaic Klinefelter patients

- Overall success rate for sperm retrieval was 44% (range 16-60%)
- TESE: 42% (95/228) versus micro-TESE: 55% (61/110) (p=0.010)

- No known predictors for successful sperm retrieval but age of the man at biopsy looks promising *(Okada et al, 2005; Kyono et al, 2007)*

- Birth of 101 children (12 twin and 3 triplet)

Genetic risk to the offspring has NOT been found to be greater than that of patients with NOA with normal karyotype

NOA patients with a history of orchidopexy

n=79	Successful TESE	Failed TESE
n of cases (%)	41 (51.9%)	38 (48.1%)
age at TESE	32.0 (95%CI 29.7-34.4)	35.1 (95%CI 32.3-37.8)
age at orchidopexy	10.6 (95%CI 7.3-13.8)	15.5 (95%CI 11.3-19.8)
testicular volume (ml)	10 (95%CI 8.3-11.9)	8.5 (95%CI 5.9-11.1)
testosterone (ng/ml)	4.4 (95%CI 3.7-5.1)	3.4 (95%CI 2.2-4.5)
FSH (IU/L)	24.1 (95%CI 17.9-30.3)	28.8 (95%CI 19.4-38.2)

Vernaeve et al. (2004)

Testicular sperm extraction (TESE) and ICSI in patients with permanent azoospermia after chemotherapy*

M.Meseguer[1,2,3], N.Garrido[1,2], J.Remohí[1,2,3], A.Pellicer[1,2,3,4], C.Simón[1,2,3], J. M.Martínez-Jabaloyas[5] and M.Gil-Salom[1,2,4]

Hum Reprod, 2003

Patient	Cancer type	Treatment	Age at TESE	Time since CT (years)	Serum FSH (mIU/ml)	Max testicular volume (ml)	Histology	TESE
1	NSGCT	PVBx4, RPLND	44	15	44.8	16	MA	+
2	Osteosarcoma	HDMTX/VCR/ADR	37	24	13.3	15	SCO	-
3	Leukaemia	CP/TX/VCR/ADR	32	9	35	15	SCO	-
4	NSGCT	BEPx4	31	8	27	20	Hyposp	+
5	NSGCT	BEPx4	30	4	57	19	SCO	+
6	Hodgkin's	MOPPx6, RT	35	15	11.6	16	SCO	+
7	NSGCT	PVBx4	39	10	8	16	SCO	-
8	Hodgkin's	MOPPx6, RT	29	11	24	12	SCO	-
9	NHL	CHOP, RT	34	6	8.8	17	SCO	-
10	NSGCT	PVBx3, RPLND	39	17	36.4	16	SCO	-
11	NSGCT	BEPx4, RPLND	28	7	13.1	10	Hyposp	+
12	Hodgkin's	MOPPx6, RT	35	8	23.8	14	SCO	-

Sperm + 41,6% (5/12)

- Potential genetic risk!
- Freezing semen before starting gonadotoxic treatment is the strategy of choice!

How successful is repeat testicular sperm extraction in patients with azoospermia?

Valérie Vernaeve[1,2], G.Verheyen[2], A.Goossens[2], A.Van Steirteghem[2], P.Devroey[2] and H.Tournaye[2]

Table II. Consecutive sperm retrieval in patients with nonobstructive azoospermia

Rank	*n*	Successful sperm recovery (*n*)	Successful sperm recovery (%)
Total	784	384	49
1	628	261	41.6
2	103	77	74.7
3	34	28	82.3
4	11	11	100
5	6	5	83.3
6	2	2	100

Hum Reprod, 2006

Best moment for second biopsy?

Remains controversial:

- No difference:

≥ 3 months vs < 3 months (75% vs 95%) Amer et al., 1999

≥ 6 months vs < 6 months (82% vs 76.5%) Vernaeve et al., 2006

- Best to wait:

≥ 6 months vs < 6 months (25% vs 80%) Schlegel and Su, 1997

Conclusions

•**Proper differentiation between OA and NOA**, preferably based on histopathology, is necessary

•**Obstructive azoospermia: The epididymis is the preferred site**

- Sperm will always be recovered
- Reanastomosis if possible - MESA, PESA, FNA, TESE

•**Non-obstructive azoospermia: The testicle is the preferred site**

- Sperm retrieved in ~ 50% of the patients
- Multiple biopsies versus micro-dissection testicular biopsy
- No good predictive parameters for outcome of TESE