MENS
HEALTH
CENTER
VIENNA

Privatklinik
Confraternität

Abklärung und Therapie der männlichen Unfruchtbarkeit

PD Dr. Markus Margreiter

Unfruchtbarkeit - Übersicht

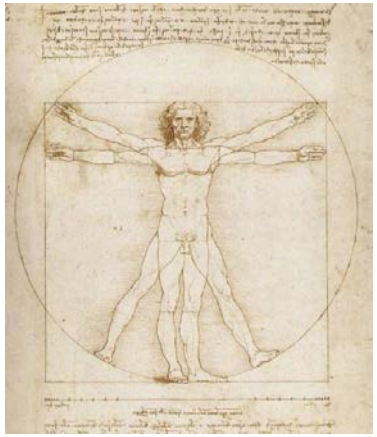
- Betrifft ~ 15% aller Paare
- 30% nur männlicher Faktor
- 30% Kombination männlicher/weiblicher Faktoren
- Azoospermie
  - 1-2% gesamten männlichen Bevölkerung
  - 10% Männern mit unerfülltem Kinderwunsch
- Ausgaben für KiWu bei männlichen Faktor 18 Mrd. $/Jahr

Smit M et al .: Fertil Steril 2009.

Recommendations	Strength rating
Investigate both partners simultaneously, to categorise infertility.	Strong
Include the fertility status of the female partner in the diagnosis and management of male sub-fertility because this might determine the final outcome.	Strong
Examine all men diagnosed with fertility problems, including men with abnormal semen parameters for urogenital abnormalities.	Strong

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
Infertility of known (possible) cause	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm autoantibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter's syndrome (47, XXY)	2.6	13.7

Abklärung des Mannes



3 Klinische Eckpfeiler:

- Krankengeschichte
- Körperliche Untersuchung
- Labortests: Samenanalyse und Hormone

- (Spezialisierte Tests)

Anamnese

- Unfruchtbarkeit
  - Dauer, vorherige Kinder, weiblicher Faktor
- Hormonelle Symptome
  - Gynäkomastie, Galaktorrhoe, Körperbehaarung, Libido, Pubertätsalter
- Angeboren
  - Kryptorchismus, Torsion, Trauma, Familiengeschichte der Unfruchtbarkeit

Sexuelle Anamnese

- Häufigkeit des Verkehrs
- Häufigkeit der Ejakulation
- Schmerzen bei der Ejakulation
- Verwendung von Gleitmitteln
- Timing zum Eisprung

Vorerkrankungen

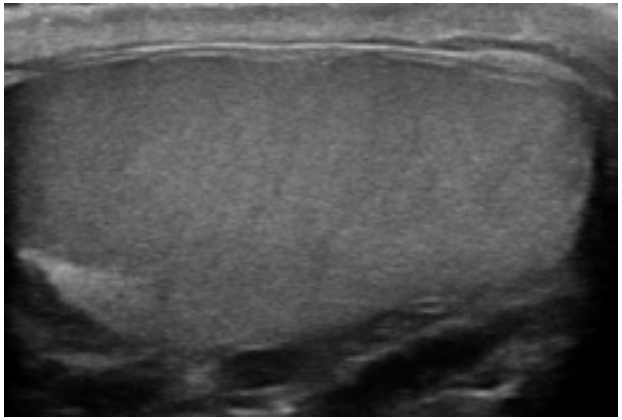
- Infektiös
  - Geschlechtskrankheiten, Mumps
- Operationen
  - Vasektomie, Leistenbruch, Hodenoperationen, RPLND
- Gonadotoxinexposition
  - Chemo, Radiatio, Medikamente
- Andere
  - Anosmie, visuelle Veränderungen, Kopfschmerzen

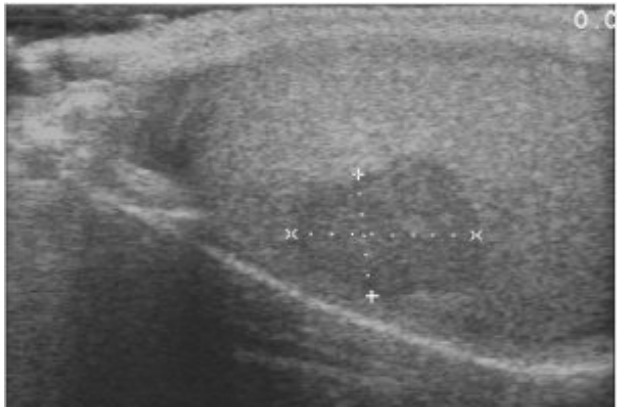
Körperliche Untersuchung

- Allgemeines
  - Sekundäre Geschlechtsmerkmale
- Brust
  - Gynäkomastie
- Uro-Genital
  - Vorhandensein des Vas deferens, Hodengröße, Penisanomalien, Varikozelen, Prostata (Prostatitis)

Hodenultraschall

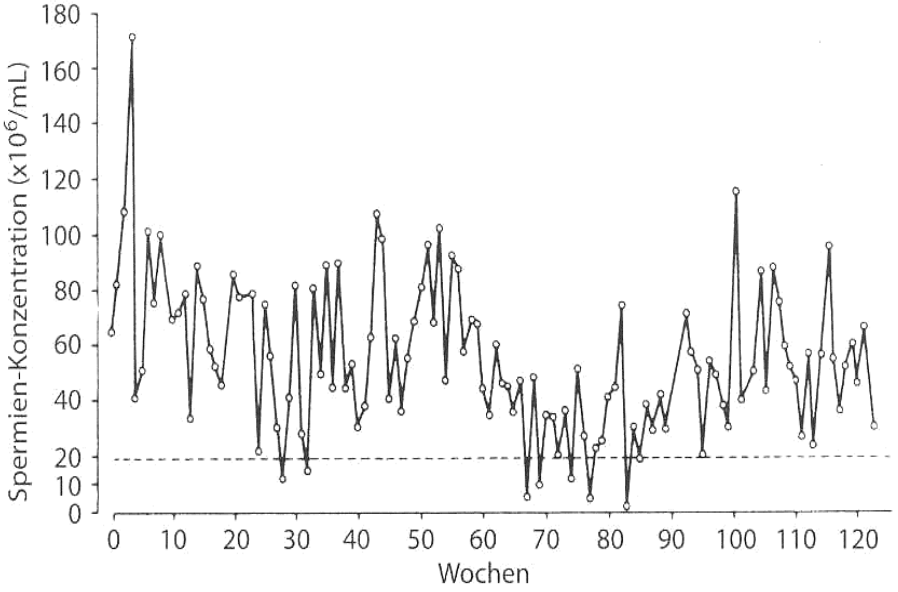
- Ausschluss:
  - Hodentumor
  - Mikrolithiasis
- Bestimmung:
  - Hodenvolumen
- Beschreibung:
  - Veränderungen Nebenhoden





Samenanalyse

- Mind. 3-5 Tage Karenz (kein Samenerguss (GV und/oder Masturbation)
- Wenn pathologisch mind. 2 Analysen (Abstand 4 Wochen)
- Probe nicht älter als 30 Minuten



WHO 2010

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6/ejaculate)	39 (33-46)
Sperm concentration (10^6/mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (106/mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (µmol/ejaculate)	> 2.4
Seminal fructose (µmol/ejaculate)	> 13
Seminal neutral glucosidase (mU/ejaculate)	< 20

WHO Änderungen

WHO	1987 normal	1992 normal	1999 Ref.	2010 threshold range (%) 5	50	95
Ejaculate volume (ml)	2.0	2.0	2.0	1.5	3.7	6.8
Total sperm number	40	40	40	39	255	802
Concentration (M/ml)	20	20	20	15	73	213
Progr. Motility (%)	50	50	50	32	55	72
Vitality (%)	50	75	75	58	79	91
Sperm Morphology (%)	50	30	(15)	4	11	21

Cooper et al. 2009, Hum Reprod Update

The Disappearing Sperms: Analysis of Reports Published Between 1980 and 2015

Spermienkonzentration	1985 - 2015
Verbesserung	3,6 %
Unverändert	15,9 %
Verschlechterung	80,4 %

Sengupta, Am J Health 2017

Endokrine Abklärung

- Indikationen
  - Niedrige Spermienkonzentration (<10 Mio/ml)
  - Beeinträchtigte sexuelle Funktion
  - Anderer HW auf eine Endokrinopathie
- Beginnen mit FSH & Total Testosteron
  - Bei Anomalie: LH, Prolaktin, TSH
  - Spezielle Diagnostik

Normales FSH garantiert keine intakte Spermatogenese, jedoch deutet ein abnormales oder hohes Normal auf eine Abnormalität der Spermatogenese hin

Bekannte genetische Ursachen für männliche Infertilität

Chromosomenanomalie

- Numerische Abnormalitäten:
  - Klinefelter-Syndrom und Varianten (47 XXY; etwa 15% Mosaike (46XY/47XXY))
- Strukturelle Abnormalitäten:
  - X-chromosomal
    - Kallmann-Syndrom
    - Partielles und komplettes Androgen-Insensitivitäts-Syndrom
  - Y-Chromosomal
    - AZF-Deletionen
    - Gr/gr-Deletion

Recommendations	Strength rating
Obtain standard karyotype analysis in all men with damaged spermatogenesis (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Provide genetic counselling in all couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For all men with Klinefelter's syndrome, provide long-term endocrine follow-up and appropriate medical treatment, if necessary.	Strong
Do not test for microdeletions in men with obstructive azoospermia (OA) since spermatogenesis should be normal.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to daughters.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations.	Strong

Where is the threshold for genetic evaluation ?

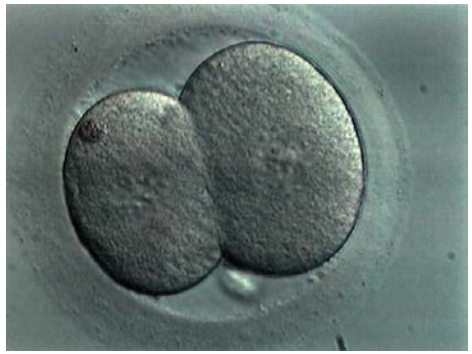
- Normal genetic evaluation < 10 Mio/mL
- AZF deletions: < 5 Mio/mL

Now we do not have enough evidence for a clear cutoff !

Jungwirth, Andro WWS 2019

Therapeutische Optionen bei andrologischer Sub/Infertilität

- Medikamentös
- Operativ
- Reproduktionsmedizinische Maßnahmen



Review Article

Medical treatment of male infertility

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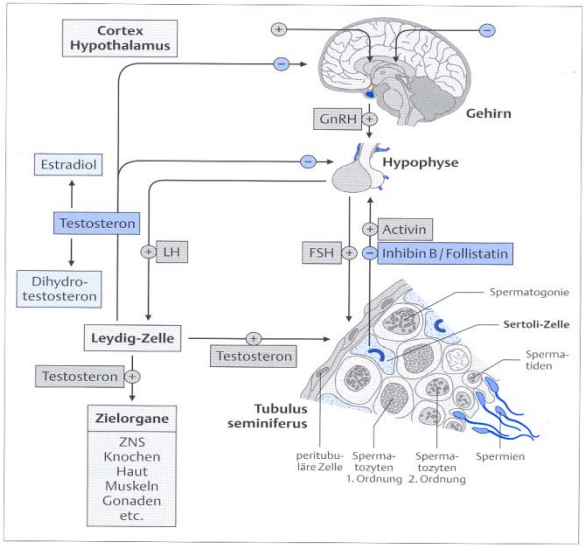

Table 1 Reviewed medical treatment of male infertility

Substance	Administration	Dosage and frequency	Current availability
GnRH	Subcutaneous infusion pump	25-200 ng/kg per pulse every 2 hours	Only in specialty centers or part of clinical trials
Human chorionic-gonadotropin (hCG)	Subcutaneous/ intramuscular	1,500-3,000 IU 2 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Human menopausal gonadotropin (hMG)	Subcutaneous/ intramuscular	75 IU 2-3 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Highly purified or recombinant human follicle-stimulating hormone (rhFSH)	Subcutaneous/ intramuscular	100-150 IU 2-3 times/week	Available, FDA approved for treatment of infertility due to gonadotropin deficiency
Dopamine agonist	Oral	Cabergoline (0.5-1 mg twice weekly), bromocriptine (2.5-5.0 mg twice weekly)	FDA approval for treatment of hyperprolactinaemia
Aromatase inhibitors	Oral	Anastrozole 1 mg/day Letrozole 2.5 mg/day Testolactone	Off label use Off label use Not available in the USA
Selective estrogen receptor modulators (SERMs)	Oral	Clomiphene citrate titrate to 50 mg/day Tamoxifen 20 mg/day, toremifene 60 mg/day, raloxifene 60 mg/day	Off label use Off label use

Operativ

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Surgery for Male Infertility

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- Orchidopexie (vor dem 1. Lebensjahr mit neo-adjuvanter Kryptokur-Therapie)
- TUR von Ejakulationskanälen (TURED)
- Varikozelen-Operation
- Refertilisierungs-OPs (Vaso-Vasostomie)
- Samenzellengewinnung

Varicocele

- 11,7% der erwachsenen Männer
- 25,4% der Männer mit abnormaler Samenanalyse
- Meta-Analyse: Samenverbesserung nach operativer Korrektur einer Varikokelektomie bei azoospermischen Männern vor TESE?
- Eine Varikokelektomie kann eine Schädigung der Spermien-DNA umkehren.
- Metaanalyse: Varikokelektomie kann die Ergebnisse von ART bei oligozoospermischen Männern verbessern

Argawal et al. Urology, 2007. 70: 532
Shiraishi et al. J Urol. 2017 Feb;197(2):485-490
Kroese et al. Cochrane Database Syst Rev, 2012
Kirby et al. Fertil Steril, 2016. 106: 1338

Treatment	Ref.	Recurrence/ Persistence %	Complication rates
Antegrade sclerotherapy	[130]	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema.
Retrograde sclerotherapy	[131]	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation.
Retrograde embolisation	[132, 133]	3.8-10	Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g., reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction.
Open operation			
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele.
Inguinal approach	[134]	13.3	Possibility of missing out a branch of testicular vein.
High ligation	[135]	29	5-10% incidence of hydrocele (< 1%).
Microsurgical inguinal or subinguinal	[136, 137]	0.8-4	Post-operative hydrocele arterial injury, scrotal haematoma.
Laparoscopy	[138, 139]	3-7	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis; bleeding; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum); pneumoscrotum: wound infection.

Recommendations	Strength rating
Treat varicoceles in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicoceles in infertile men who have normal semen analysis and in men with a subclinical varicocele.	Strong
Treat men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility in the couple.	Weak

Perkutane Epidymale Spermatozoen-Aspiration (PESA)

- **26 G Tuberculin syringe**

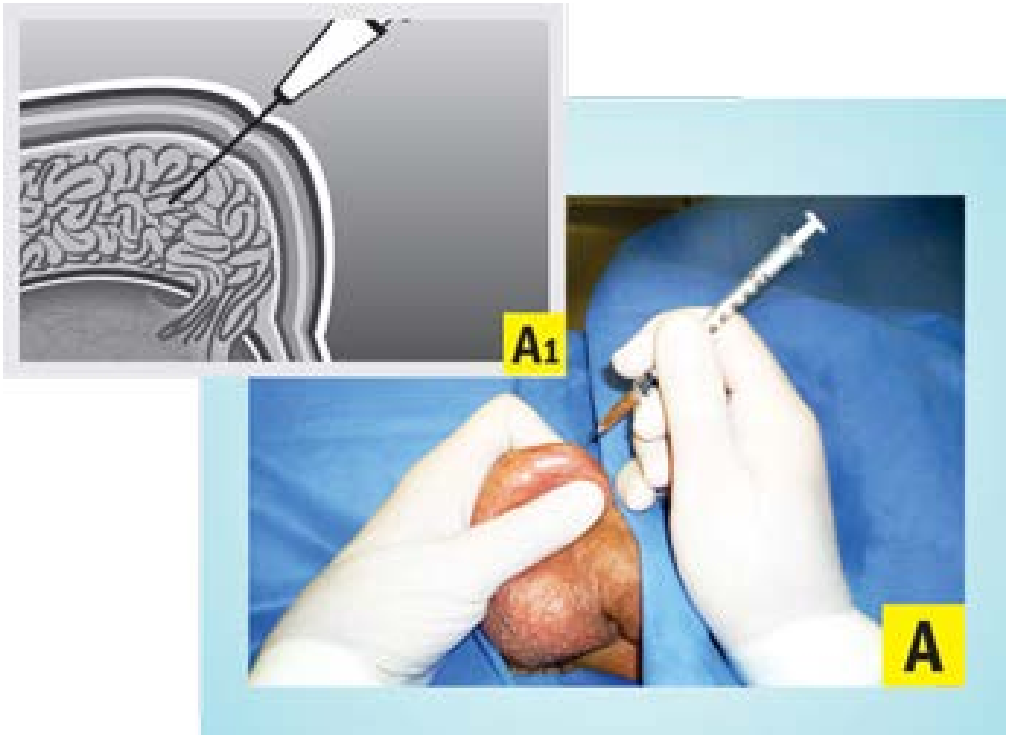


*Image from Esteves SC, et al: Int Brazil J Urol 2011.

Testikuläre Spermatozoen Aspiration (TESA)

- 18-22 G
- Superior testicular pole

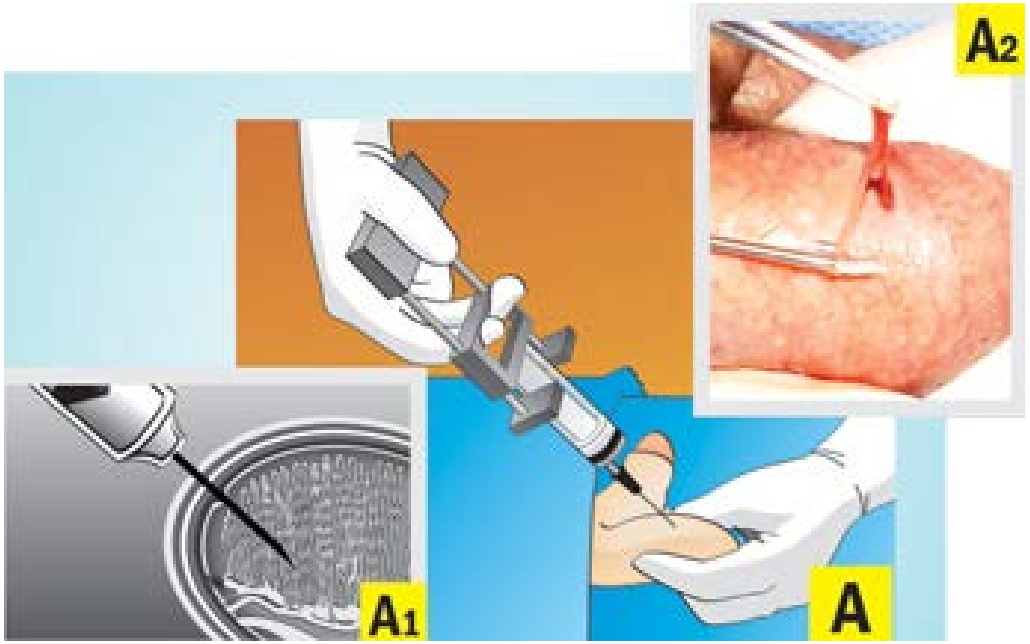
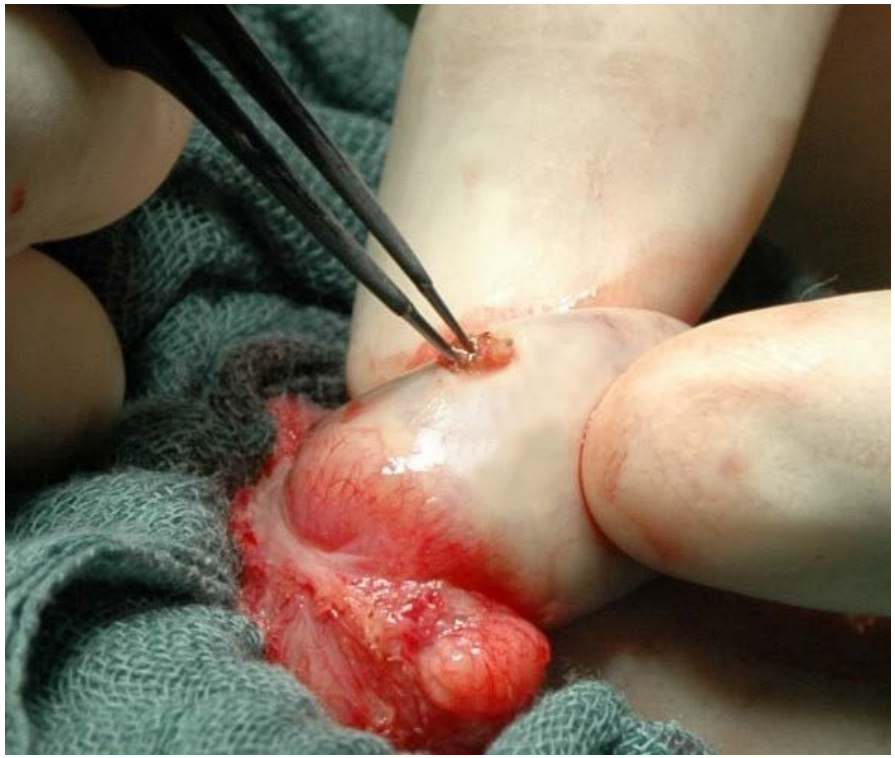
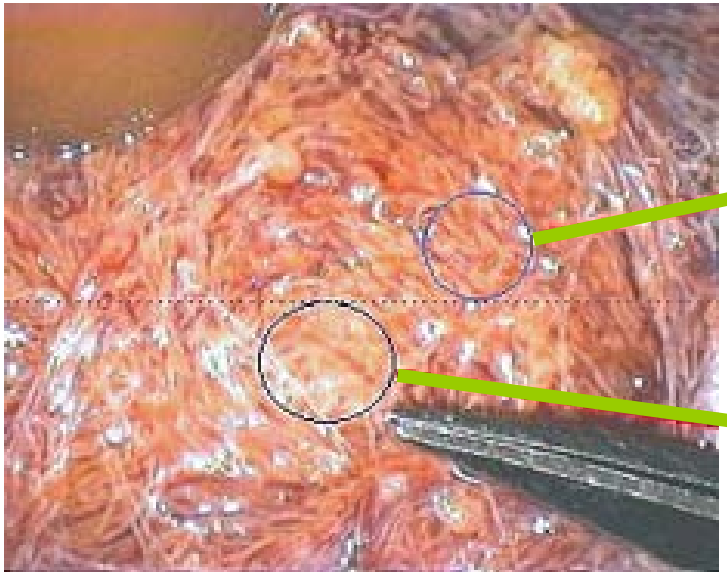


*Image from Esteves SC, et al: Int Brazil J Urol 2011.

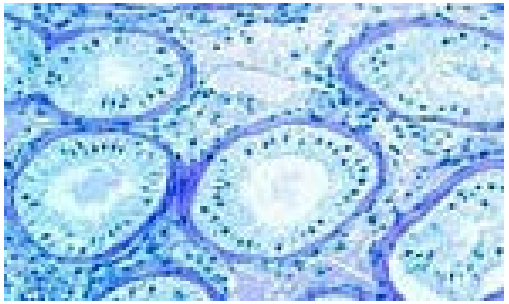
Testikuläre Spermatozoen-Extraktionen (TESE)



Micro-TESE



Sertoli – Cell - Only



Hypospermatogenesis

Outcomes

Procedure	Anesthetic	Sperm Retrieval Rate	Yield
MESA	General	95-100%	Cryo in 98-100% 15-95 x 10^6 15-42% motility
PESA	Local	80-100%	Cryo 43-96% 10^3-10^6
Testicular Fine Needle Aspiration	Local	52-100%	Cryo 38% 10^5-10^6
Testicular Large Needle Aspiration	Local	98-100%	Cryo 100% 10^5-10^6
Testicular Core Needle Biopsy	Local	82-100%	Cryo Sufficient 10^5-10^6
TESE	General, Regional, Local	100%	Cryo Sufficient 10^5-10^6
Microdissection TESE	General	100%	Cryo Sufficient 10^5-10^6

Diagnostik und Therapie sollte

in Stufen erfolgen unter Berücksichtigung von

- Lebensalter
- Zeitraum des unerfüllt gebliebenen Kinderwunsches
- In Abhängigkeit von der Zeit des Kinderwunsches
- Vorbefunden

Die reproduktionsmedizinische Diagnostik und Therapie erfordert bei auffälligen Befunden

die Auswahl von Maßnahmen,

- die mit möglichst geringer Invasivität
- möglichst geringen Kosten und
- möglichst hoher Sicherheit

dem Paar zu einem gemeinsamen Kind verhelfen können

Fertilität als Marker für Männergesundheit

American Journal of Epidemiology
Vol. 170, No. 5
DOI: 10.1093/aje/kwp168
Advance Access publication July 27, 2009

Original Contribution

Good Semen Quality and Life Expectancy: A Cohort Study of 43,277 Men

Tina Kold Jensen, Rune Jacobsen, Kaare Christensen, Niels Christian Nielsen, and Erik Bostofte

Initially submitted March 11, 2009; accepted for publication May 26, 2009.

Infertilität und PCa

Risk of prostate cancer for men fathering through assisted reproduction: nationwide population based register study

Yahia Al-Jebari,[1] Angel Elenkov,[1,2,3] Elin Wirestrand,[1] Indra Schütz,[1] Aleksander Giwercman,[1,3] Yvonne Lundberg Giwercman[1]

Conclusions

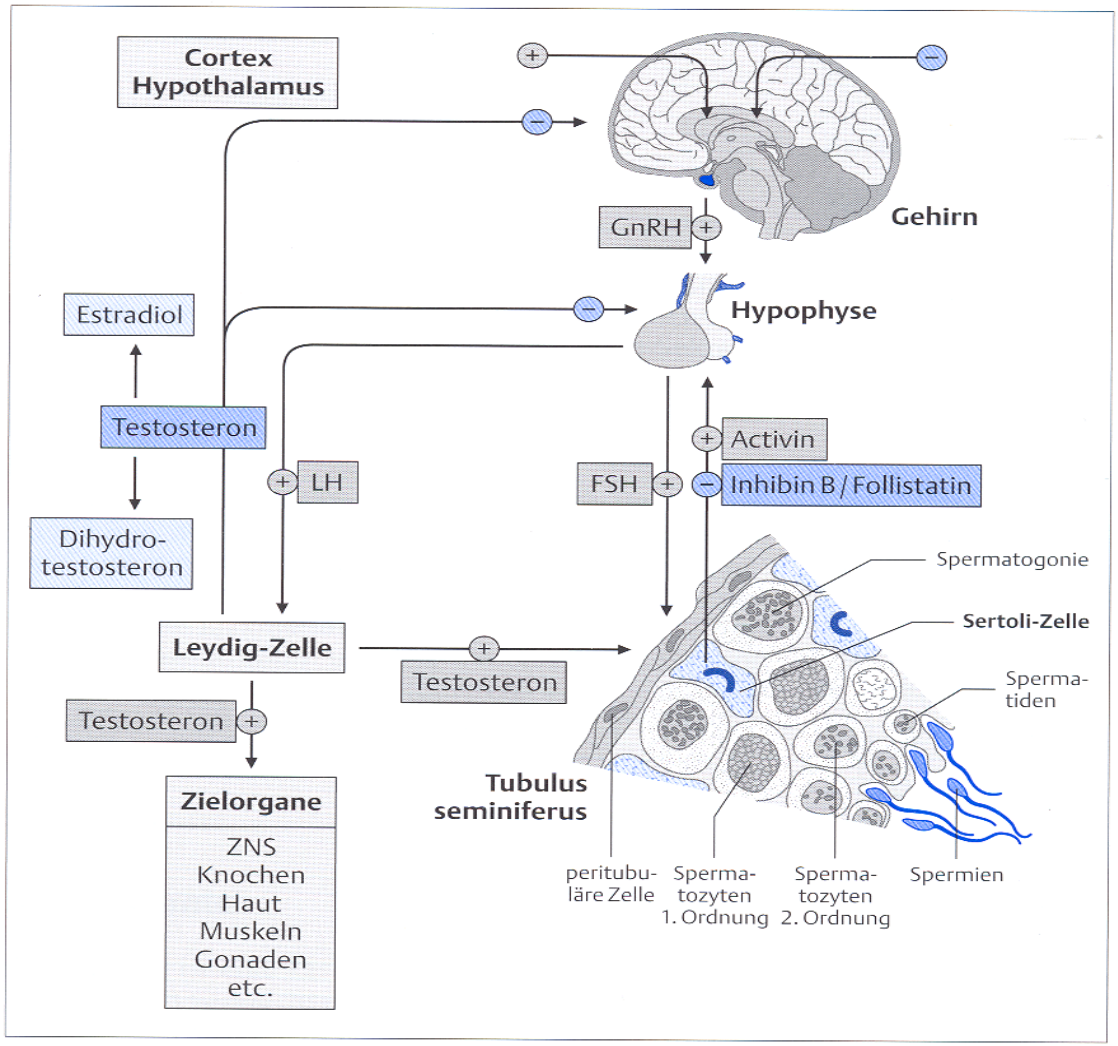
- Men who achieved fatherhood through assisted reproduction techniques, particularly through ICSI, are at increased risk for early onset prostate cancer and thus constitute a risk group in which testing and careful long term follow-up for prostate cancer may be beneficial.

Vielen Dank für Ihre Aufmerksamkeit!

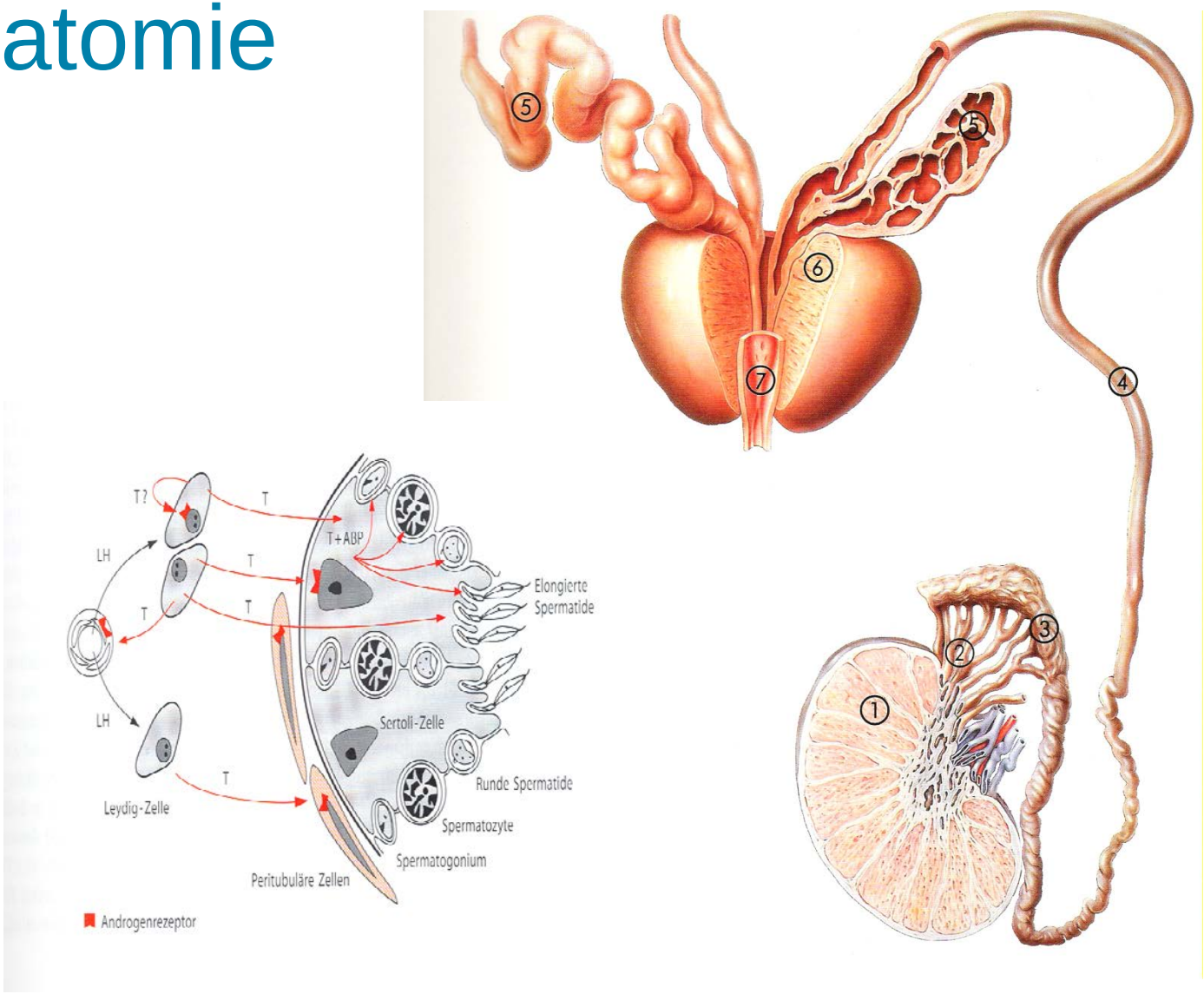
Wichtige Rahmenaspekte der menschlichen Fortpflanzung:

- bei fertilen Paaren (<35 Jahren) und optimalem Timing des GV (12-36 h vor Ovulation) kommt es
  - pro Zyklus in maximal 20% und
  - pro Jahr in etwa 80 %
  - zu einer klinisch nachweisbaren Schwangerschaft
- diese Raten reduzieren sich bei gesunden (!) Frauen
  - zwischen 35- 40 Jahren um etwa 30-40 %
  - und ab > 40 Jahren um mehr als 75%

Hormoneller Regelkreis



Anatomie


5
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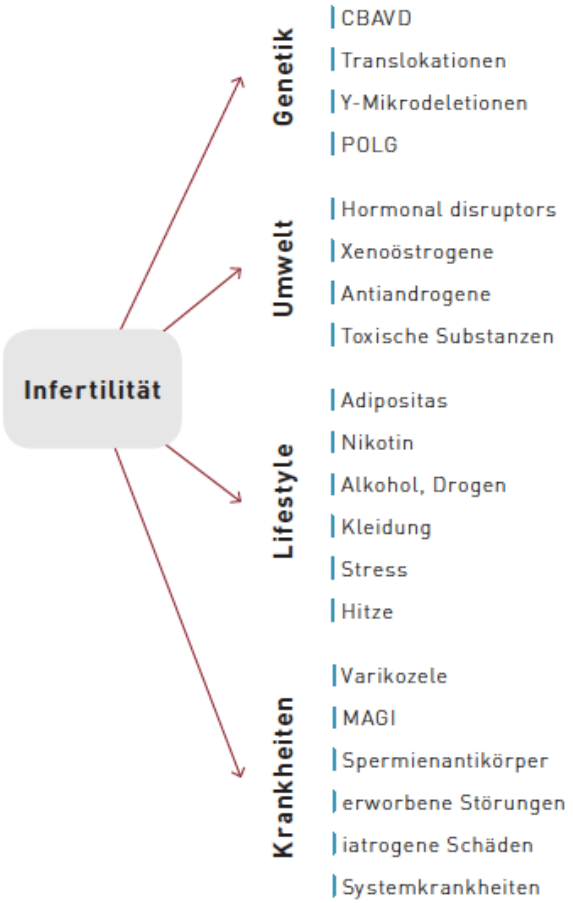
Elongierte Spermatide
Sertoli-Zelle
Runde Spermatide
Spermatozyte
Spermatogonium
Leydig-Zelle
Peritubuläre Zellen
Androgenrezeptor

Ursachen
Männliche Unfruchtbarkeit



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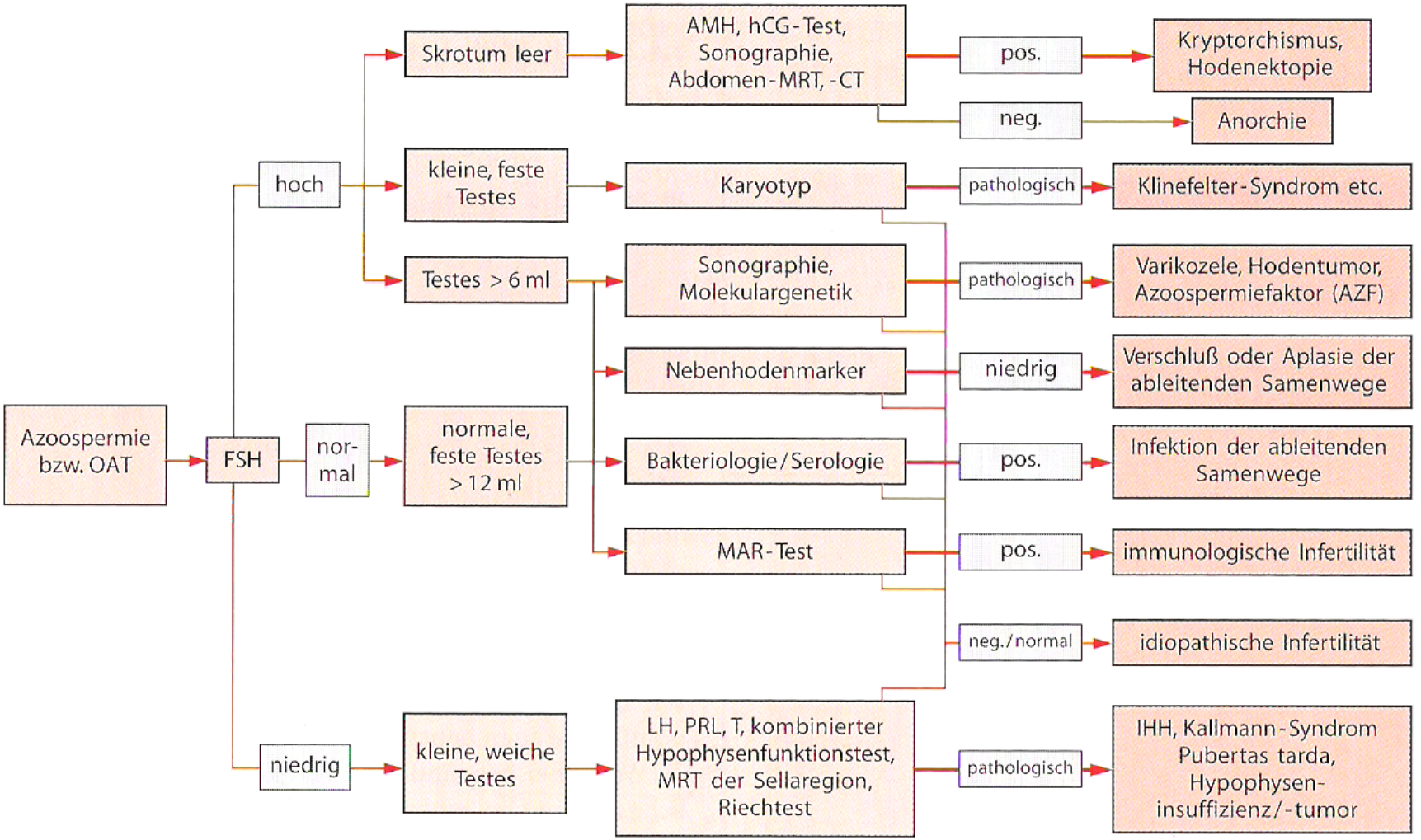
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter's syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotrophic hypogonadism	0.4	0.4
Residual after pituitary surgery	<0.1	0.3
Others	0.8	0.8
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6


Azoospermie bzw. OAT
FSH
hoch
normal
niedrig
Skrotum leer
kleine, feste Testes
Testes > 6 ml
normale, feste Testes > 12 ml
kleine, weiche Testes
AMH, hCG-Test, Sonographie, Abdomen-MRT, -CT
Karyotyp
Sonographie, Molekulargenetik
Nebenhodenmarker
Bakteriologie/Serologie
MAR-Test
LH, PRL, T, kombinierter Hypophysenfunktionstest, MRT der Sellaregion, Riechtest
pos.
neg.
pathologisch
pathologisch
niedrig
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neg./normal
pathologisch
Kryptorchismus, Hodenektopie
Anorchie
Klinefelter-Syndrom etc.
Varikozele, Hodentumor, Azoospermiefaktor (AZF)
Verschluß oder Aplasie der ableitenden Samenwege
Infektion der ableitenden Samenwege
immunologische Infertilität
idiopathische Infertilität
IHH, Kallmann-Syndrom Pubertas tarda, Hypophysen-insuffizienz/-tumor