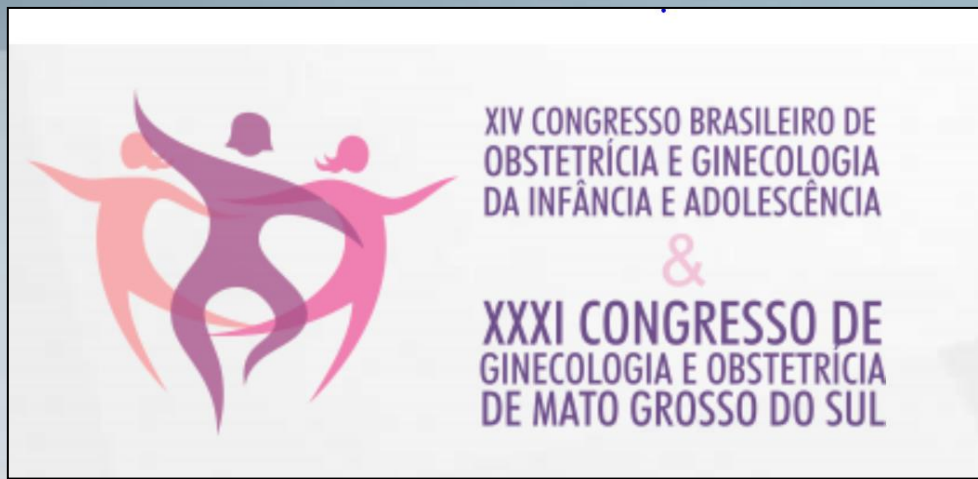




Infertilidade Masculina: Visão para o ginecologista

Edson Borges Jr.

<http://fertility.com.br/producao-cientifica-2016/>

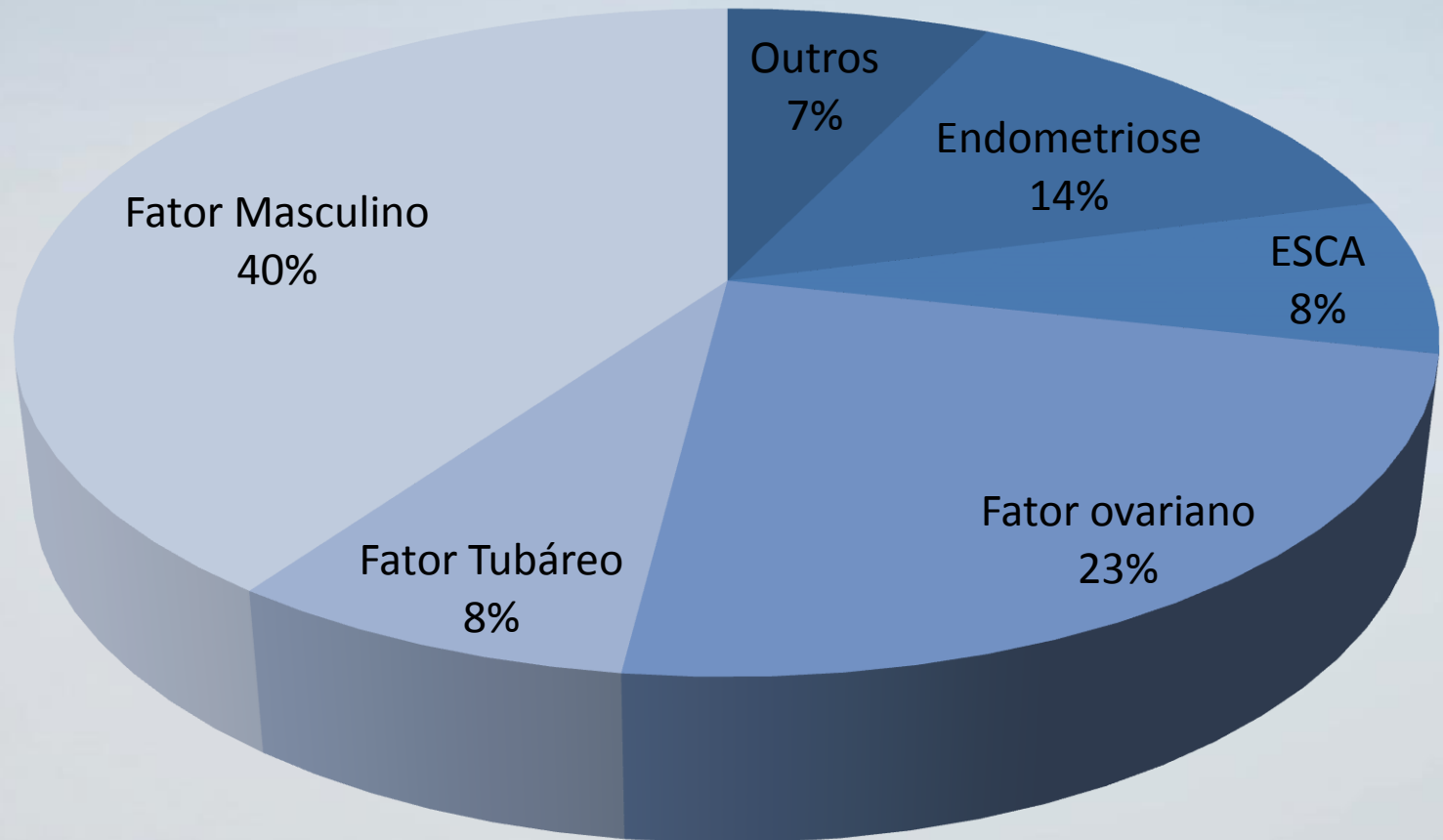
Quando iniciar a avaliação?

⇒ Casais com vida sexual normal, após 1 ano de tentativas, sem anticoncepção e sem gestação

⇒ Antes de 1 ano

- Caso ♂ tenha um fator de risco conhecido para infertilidade (criptorquidia, patologia endócrina, varicocele, etc..)
- Caso ♀ tenha um fator de risco conhecido para infertilidade (idade > 35 anos, SOP, etc..)
- Caso ♂ / ♀ questionem seu potencial fértil

Distribuição dos casos de Infertilidade Fertility 2005 - 2015



ETIOLOGIA DA INFERTILIDADE MASCULINA

VARICOCELE	42,2
IDIOPÁTICA	22,7
OBSTRUÇÃO	14,7
♀ / ♂ normais	7,9
CRIPTORQUIDIA	3,4
IMUNOLÓGICA	2,6
EJACULATÓRIO	1,3
FALÊNCIA TESTICULAR	1,3

ETIOLOGIA DA INFERTILIDADE MASCULINA

- **fator masculino: 40%**
- Infertilidade idiopática: 25-30% dos homens
- Doença multifatorial com fenótipo heterogêneo

① *Envolver o marido na investigação e tratamento!!*

Propedêutica Laboratorial Masculina

- Espermograma com morfologia estrita (OMS 2010)
- Total Motile Sperm Count (TMSC)
- Quando alteração seminal importante
(conc < 2,0 milhões/ml): avaliação genética (cariótipo, microdeleção Y)
- Quando agenesia de deferentes: pesquisa de CFTR

World Health Organization reference values for human semen characteristics^{*,†}

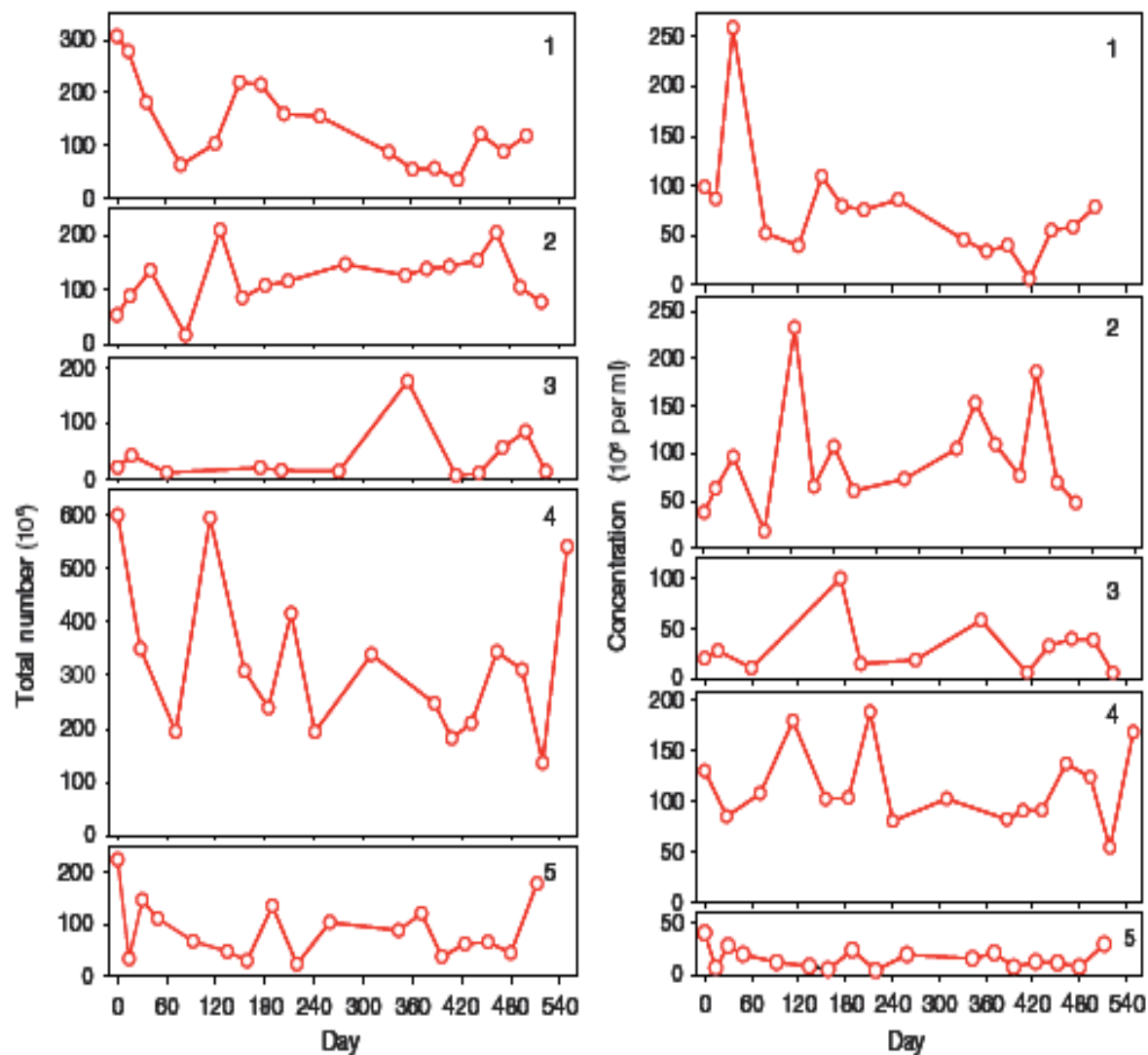
Trevor G. Cooper^{1,10}, Elizabeth Noonan², Sigrid von Eckardstein³, Jacques Auger⁴, H.W. Gordon Baker⁵, Hermann M. Behre⁶, Trine B. Haugen⁷, Thinus Kruger⁸, Christina Wang⁹, Michael T. Mbizvo^{3,†}, and Kirsten M. Vogelsong^{3,†}

- 4.500 amostras seminais
- 14 países
- 4 continentes

FIFTH EDITION

- MAR test / Imonobeads: positivo $\geq 50\%$*

Fig. 2.1 Variation in total number of spermatozoa and sperm concentration over a one-and-a-half-year period



O.M.S. 1980/87/92/99/2010

Table 1. Cut-off values for semen variables as published in consecutive WHO manuals [6–9] and as proposed in the fifth World Health Organization (WHO) manual [1].

Semen variable	1980	1987	1992	1999	2010 ¹
Volume (mL)	–	≥ 2.0	≥ 2.0	≥ 2.0	1.5
Concentration (10^6 mL^{-1})	20–200	≥ 20	≥ 20	≥ 20	15
Total sperm number ($10^6/\text{ejaculate}$)	–	≥ 40	≥ 40	≥ 40	39
Motility (% motile)	≥ 60	$\geq 50 \text{ (a + b)}^2$	$\geq 50 \text{ (a + b)}$	$\geq 50 \text{ (a + b)}$	40 (a + b + c)
Forward progression (for 1980 only)	$\geq 2^3$	$\geq 25 \text{ (a)}$	$\geq 25 \text{ (a)}$	$\geq 25 \text{ (a)}$	32 (a + b)
Morphology (% normal)	80.5 ⁴	≥ 50	$\geq 30^5$	(14) ⁶	4
Viability/vitality (% live)	–	≥ 50	≥ 75	≥ 75	58
White blood cells (10^6 mL^{-1})	< 4.7	< 1.0	< 1.0	< 1.0	< 1.0

Abnormal sperm count and motility on semen analysis are not sufficiently predictive of abnormal Kruger morphology

Fertility and Sterility® Vol. 94, No. 7, December 2010

Sara S. Morelli, M.D.^a
Aimee Seungdamrong, M.D.^{a,b}
David H. McCulloh, Ph.D.^{a,b}
Peter G. McGovern, M.D.^{a,b}

Abnormal morphology by Kruger's strict criteria cannot be predicted reliably by the presence of other abnormal parameters on semen analysis. Assessment of Kruger morphology therefore remains a necessary component of a complete semen analysis in the workup of the infertile couple. (Fertil Steril® 2010;94:2882-4. ©2010 by American Society for Reproductive Medicine.)

TABLE 1

Classification of semen analyses.

Count ($\geq 2 \times 10^7/\text{mL}$)	Motility ($\geq 50\%$)	Kruger morphology ($> 4\%$)	No.	Percentage of total
Low	Low	Low	158	11
Low	Low	Normal	58	4
Low	Normal	Low	48	3
Low	Normal	Normal	41	3
Normal	Low	Low	69	5
Normal	Low	Normal	92	7
Normal	Normal	Low	187	14
Normal	Normal	Normal	731	53
Total			1,384	

Morelli. Correspondence. Fertil Steril 2010.

ORIGINAL ARTICLE

Correspondence:

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*These authors contributed equally to this manuscript.

Keywords:

intracytoplasmic sperm injection, infertility, sperm count, sperm motility, spermatozoa

Received: 18-Dec-2015

Revised: 8-Mar-2016

Accepted: 21-Mar-2016

doi: 10.1111/andr.12199

Total motile sperm count has a superior predictive value over the WHO 2010 cut-off values for the outcomes of intracytoplasmic sperm injection cycles

^{1,2}*E. Borges Jr, ^{1,2}*A. S. Setti, ^{1,2}D. P. A. F. Braga, ¹R. C. S. Figueira and ^{1,2}A. Iaconelli Jr

- 518 ciclos de ICSI
- OMS / TMSC
- TMSC normal: > 20 milhões

ORIGINAL ARTICLE

Correspondence:
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Antonio, 4545, São Paulo 01401-002, SP, Brazil.
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and ^{1,2}A. Iaconelli Jr

- Grupo I: TMSC < 1 milhão de espermatozóides
- Grupo II: TMSC 1 - 5 milhões de espermatozóides
- Grupo III: TMSC 5 - 10 milhões de espermatozóides
- Grupo IV: TMSC 10 - 20 milhões de espermatozóides
- Grupo V: TMSC > 20 milhões de espermatozóides

ORIGINAL ARTICLE

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and ^{1,2}A. Iaconelli Jr

- OMS: 518 (100%) fator masculino
 - Oligozoospermia: 148
 - Astenozoospermia: 106
 - Teratozoospermia: 361

● TMSC

- normal: 190 (36,7%): ausência de fator masculino
- anormal: 328 (63,3%): fator masculino +

Table 4 Comparison of ICSI outcomes between normal and abnormal TMSC groups

Variables	Normal TMSC group (n = 328)	Abnormal TMSC group (n = 190)	p-value
Paternal age (year-old)	37.4 ± 4.8	38.1 ± 6.1	0.187
Maternal age (year-old)	35.4 ± 3.9	33.5 ± 4.0	<0.001
Number of aspirated follicles	17.8 ± 9.7	20.8 ± 11.2	0.002
Number of obtained oocytes	12.7 ± 7.2	15.1 ± 8.1	0.001
Number of mature oocytes	9.7 ± 5.5	11.2 ± 6.2	0.003
Number of injected oocytes	9.4 ± 4.3	10.2 ± 4.9	0.067
Fertilization rate (%)	84.9 ± 14.4	81.1 ± 15.8	0.016
Number of obtained embryos	8.2 ± 3.8	8.7 ± 4.4	0.204
Number of transferred embryos	2.2 ± 0.6	2.2 ± 0.5	0.469
Implantation rate (%)	25.1 ± 36.0	25.8 ± 35.2	0.832
Pregnancy rate (%)	134/328 (40.9)	94/190 (49.5)	0.060
Miscarriage rate (%)	29/162 (17.9)	23/78 (29.5)	0.041

SD, standard deviation; TMSC: total motile sperm count.

Table 5 Linear and binary regression analysis results for the influences of TMSC and WHO cut-off values on ICSI outcome

Variables	Method	OR or RC	CI or R^2	<i>p</i> -value
Fertilization rate	Concentration	3.994	1.4%	0.015
	Motility	0.097	0.0%	0.957
	Progressive motility	2.299	0.5%	0.163
	Morphology	8.735	0.9%	0.047
	TMSC	3.784	1.5%	0.013
	Normal TMSC	-0.253	0.1%	0.592
Formation of high-quality zygotes on D1	Concentration	1.64	1.09–2.46	0.018
	Motility	1.34	0.85–2.12	0.208
	Progressive motility	1.22	0.80–1.85	0.355
	Morphology	0.89	0.65–1.22	0.461
	TMSC	1.13	1.01–1.28	0.049
	Normal TMSC	0.99	0.97–1.02	0.629
Formation of high-quality embryos on D2	Concentration	0.93	0.76–1.09	0.101
	Motility	0.91	0.79–1.06	0.222
	Progressive motility	1.06	0.92–1.22	0.420
	Morphology	0.84	0.60–1.18	0.314
	TMSC	1.18	1.03–1.35	0.013
	Normal TMSC	0.97	0.94–1.01	0.098
Formation of high-quality embryos on D3	Concentration	0.91	0.79–1.06	0.229
	Motility	0.93	0.79–1.09	0.379
	Progressive motility	1.00	0.85–1.17	0.969
	Morphology	1.18	0.83–1.67	0.354
	TMSC	1.12	1.07–1.29	0.037
	Normal TMSC	0.98	0.95–1.02	0.319
Formation of blastocyst on D5	Concentration	1.11	0.97–1.27	0.116
	Motility	1.03	0.90–1.19	0.660
	Progressive motility	0.91	0.70–1.23	0.303
	Morphology	1.13	0.83–1.55	0.427
	TMSC	1.16	1.04–1.26	0.011
	Normal TMSC	1.00	0.97–1.04	0.802
Blastocyst expansion grade on D5	Concentration	0.83	0.66–1.05	0.120
	Motility	1.01	0.79–1.29	0.948
	Progressive motility	1.08	0.85–1.38	0.533
	Morphology	0.99	0.57–1.71	0.962
	TMSC	1.27	1.01–1.60	0.042
	Normal TMSC	1.03	0.98–1.07	0.287

Propedêutica em infertilidade

*Espermograma com morfologia estrita
(OMS 2010) + TMSC*

②

*Mínimo de duas coletas seminais com intervalo
igual a frequência ejaculatória do homem*

Oligozoospermia / Azoospermia

Vale a pena tratamento?

- 1. Tratamento medicamentoso**
- 2. Tratamento cirúrgico**

Drug Therapy for Idiopathic Male Infertility: Rationale Versus Evidence

Rajeev Kumar,* Gagan Gautam and Narmada P. Gupta



THE JOURNAL
of UROLOGY®
Official Journal of the American Urological Association



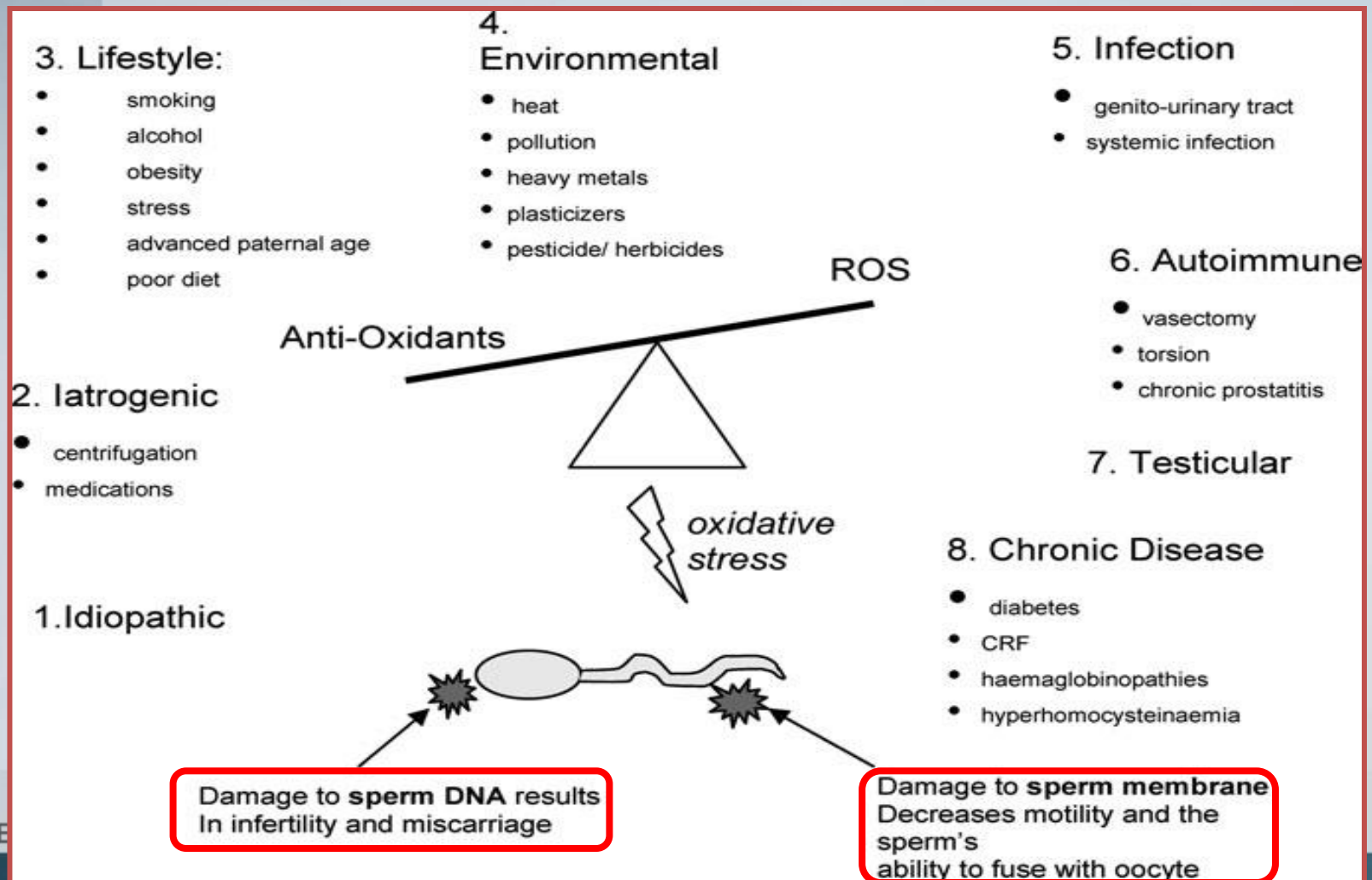
Material e Método: Pesquisa no MEDLINE/PubMed nos últimos 20 anos com foco nas publicações sobre tratamento medicamentoso para infertilidade masculina

Conclusão: Tratamento medicamentoso para infertilidade masculina idiopática é no mínimo empírico. Não existe benefício claro no uso de qualquer medicação nestes pacientes.

Entretanto, andrógenos não devem ser usados devido a seu efeito supressório sobre a espermatogênese.

Oxidative stress and male infertility- a clinical perspective

Kelton Tremellen; *Human Reproduction Update*, Vol.14, No.3 pp. 243–258, 2008



The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy

Parviz Gharagozloo^{1,*} and R. John Aitken²

¹CellOxess LLC, 16 Blue Spruce Drive, Pennington, NJ 08534, USA ²Priority Research Centre in Reproductive Science, Discipline of Biological Sciences, University of Newcastle, Callaghan, NSW 2308, Australia

- ***Impacto dos antioxidantes orais no estresse oxidativo (EO) e DNA espermático***
- 19 / 20 estudos mostraram diminuição do **EO**
- Forte evidência no aumento da motilidade (principalmente nos astenozoospermicos)
- 6 /10 estudos: aumento das taxas de gestação



Antioxidants for male subfertility

Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ

Published Online: March 14, 2012

Oxidative stress may cause sperm cell damage. This damage can be reduced by the body's own natural antioxidant defences. Antioxidants can be part of our diet and taken as a supplement. It is believed that in many cases of unexplained subfertility, and also in instances where there may be a sperm-related problem, taking an oral antioxidant supplement may increase a couple's chance of conceiving when undergoing fertility treatment. This [review](#) identified 34 randomised controlled trials involving 2876 couples. Pooled findings from three small trials suggest an increase in live birth rates for the partners of subfertile men taking an antioxidant supplement as part of an assisted reproductive program. However, further well-designed large randomised [placebo](#)-controlled trials are needed to confirm these findings.

- 34 estudos randomizados - 2.876 casais
- Aumento da taxa gestação (OR=4,18)
- Aumento na taxa de nascidos vivos (OR=4,85)

The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis

Lynne Robinson^{1,*}, Ioannis D. Gallos^{1,2}, Sarah J. Conner^{1,2},
Madhurima Rajkhowa¹, David Miller³, Sheena Lewis⁴,
Jackson Kirkman-Brown^{1,2}, and Arri Coomarasamy^{1,2}

- **16 estudos – 2969 casais**
- Aumento significativo de *abortamento* em homens com aumento da *fragDNA espermática*: RR = 2,16 (1,54 – 3,03)
- TUNEL: RR = 3,94 (2,45 – 6,32)

Tratamento Medicamentoso

*Tratamento hormonal: sem eficácia
(algumas vezes prejudicial)*

- ③ *Uso de antioxidantes: efeito parcial em alguns casos*

FragDNA espermático: > abortamento

Tratamiento Cirúrgico

● Cirugía de Varicocele



Cirurgia de Varicocele

➤ INCIDÊNCIA DE VARICOCELE EM HOMENS INFÉRTEIS

5.228 homens / 1.803 com varicocele (35%)

➤ MELHORA SEMINAL E % DE GESTAÇÕES APÓS VARICOCELECTOMIA

- ✓ 3.507 pacientes operados
- ✓ Melhora seminal: 51 - 92%
- ✓ Gestação: 25 - 55% (média = 30%)

MALE FACTOR

Fertil Steril 88:639-48, 2007

Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis

Joel L. Marmar, M.D.,^a Ashok Agarwal, Ph.D.,^b Sushil Prabakaran, M.D.,^b Rishi Agarwal,^b Robert A. Short, Ph.D.,^c Susan Benoff, Ph.D.,^d and Anthony J. Thomas, Jr., M.D.^b

Aumento 2,8x chances de gestação espontânea

Cirurgia de Varicocele

- Principal causa conhecida de lesão testicular
- Melhora seminal após 2-3 ciclos da espermatogênese (6-9 meses)
- Melhores resultados em alterações seminais moderadas

④ *Casal tem de ter TEMPO!!*

AZOOSPERMIA

- 1% dos homens
- 10 -15% dos homens inférteis

AZOOSPERMIA

- **Obstrutiva:** espermatogênese normal
- **Não-Obstrutiva:** alteração da espermatogênese

The importance of semen analysis in the context of azoospermia

Nabil Aziz

Liverpool Women's Hospital & The University of Liverpool, Liverpool, United Kingdom

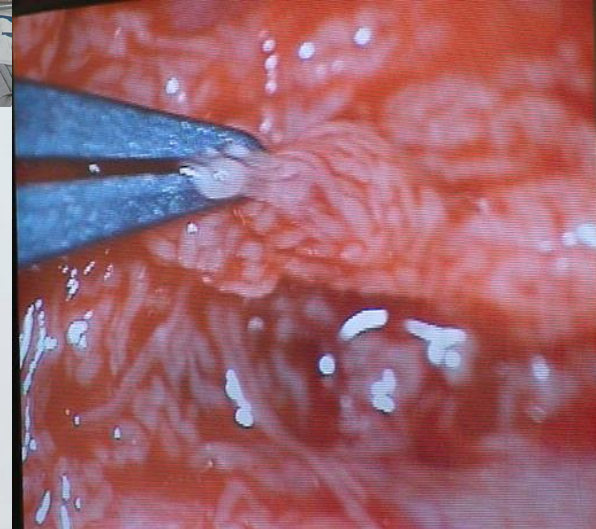
Reference	Recommended centrifugation
Mortimer (1994) (23)	1000 x g for 15 minutes
the Nordic Association for Andrology (24)	At least 1000 x g for 15 minutes
WHO manual (1999) (25)	600 x g for 15 minutes to concentrate samples with low sperm counts (less than 2 sperm per 400x field) Less than 3000 x g for 15 minutes for all samples in which spermatozoa are not detected
Corea et al. (2005) (20)	A minimum of 1000 x g for 15 minutes was adequate for the detection of azoospermia
WHO manual (2010) (2)	3000 x g for 15 minutes for all samples in which no spermatozoa are detected

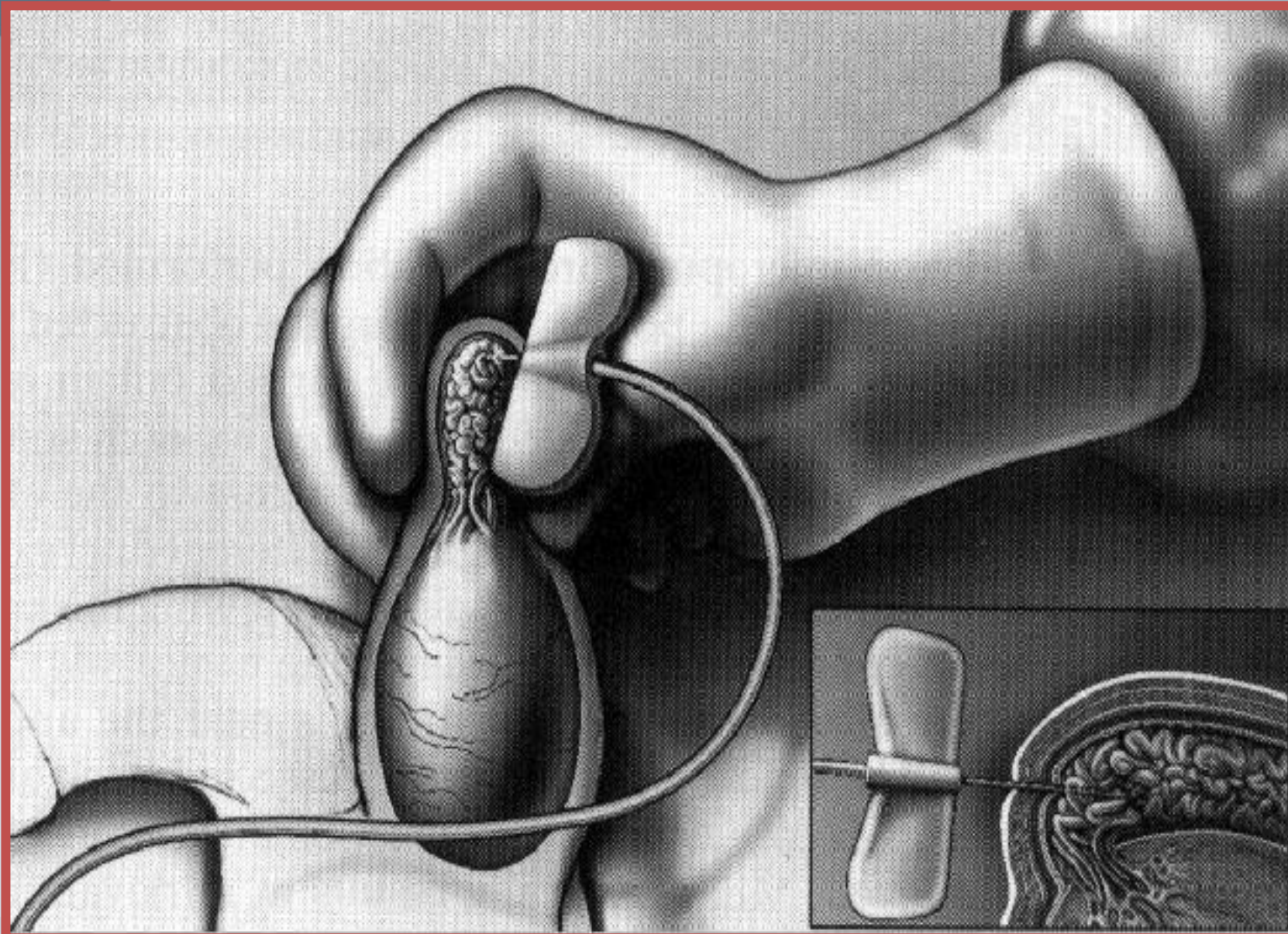
18,6% Azoo Ob
22,8% Azoo
NOB



Sptz
móveis/imóveis

PESA / TESA / microTESE



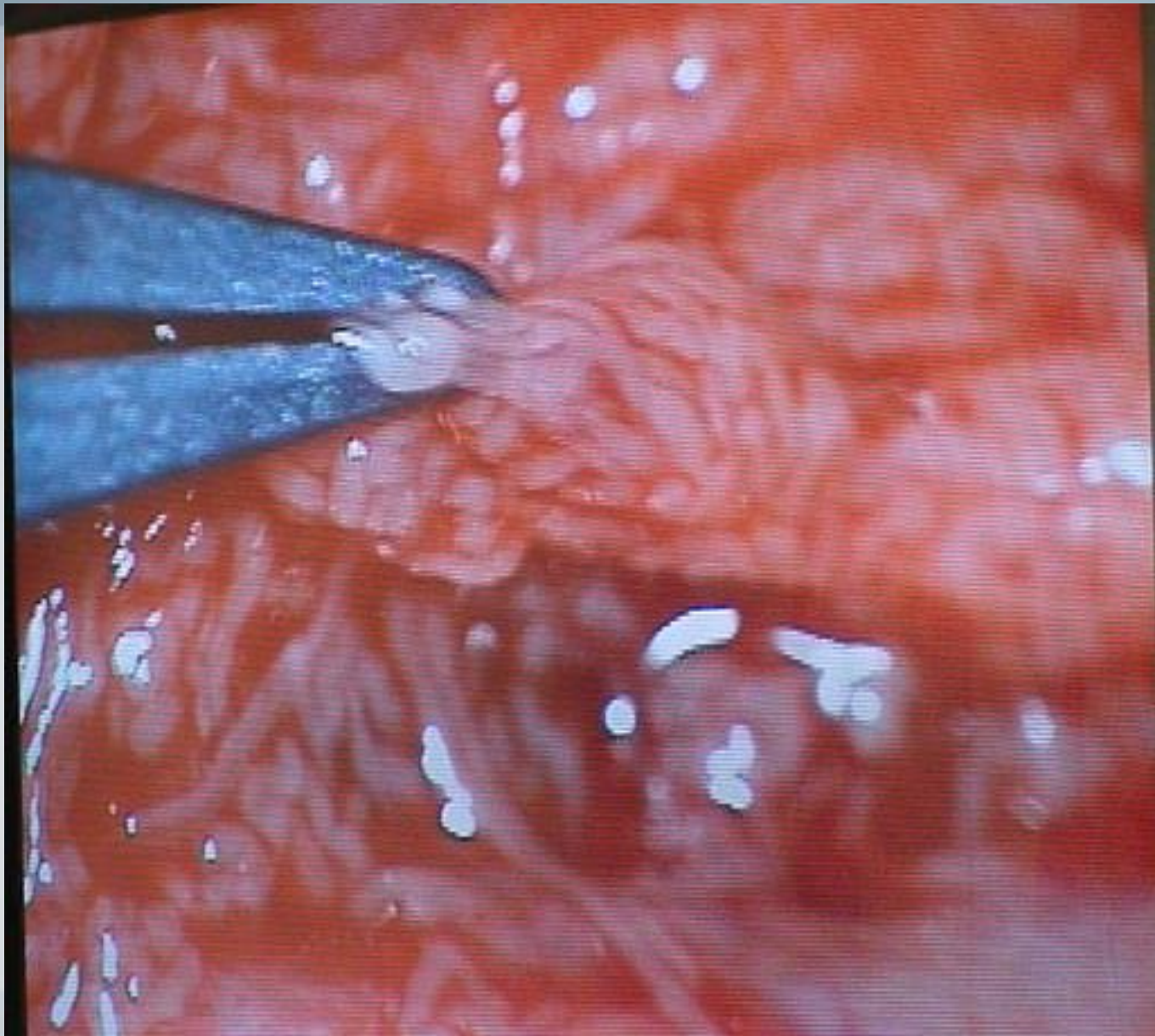






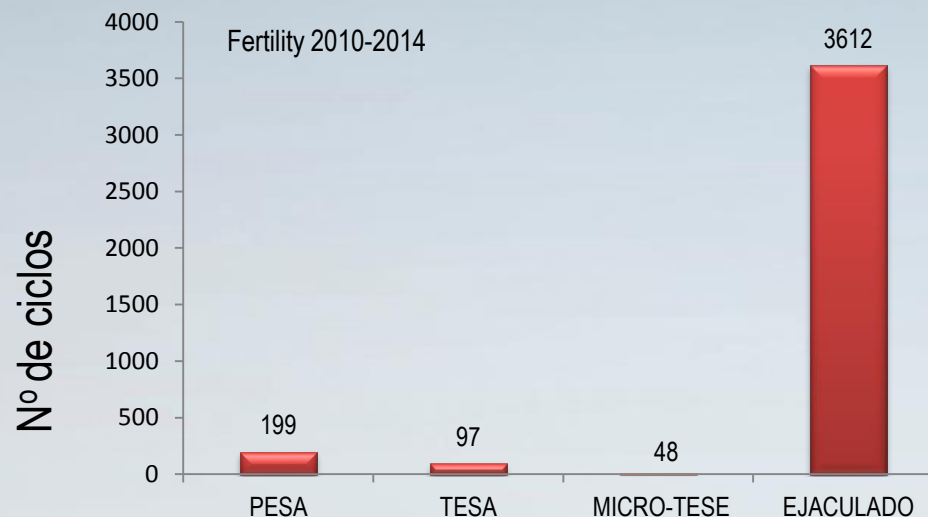






Características gerais dos ciclos de ICSI – *Fertility* (2010-2014)

“Origem do espermatozoide”



Características	PESA	TESA	MICRO-TESE	EJACULADO
Nº de ciclos	199	97	48	3612
Idade média $\pm$ DP	34.9 $\pm$ 4.6	34.8 $\pm$ 5.4	32.2 $\pm$ 2.7	35.8 $\pm$ 4.7
Nº de folículos aspirados $\pm$ DP	20.4 $\pm$ 15.4	18.1 $\pm$ 11.3	15.9 $\pm$ 14.4	15.8 $\pm$ 12.4
Nº de oócitos recuperados $\pm$ DP	14.2 $\pm$ 10.8	13.3 $\pm$ 9.3	11.0 $\pm$ 11.4	11.0 $\pm$ 9.0
Nº de oócitos micromanipulados $\pm$ DP	9.8 $\pm$ 6.4	8.9 $\pm$ 5.1	8.0 $\pm$ 6.9	7.8 $\pm$ 5.8

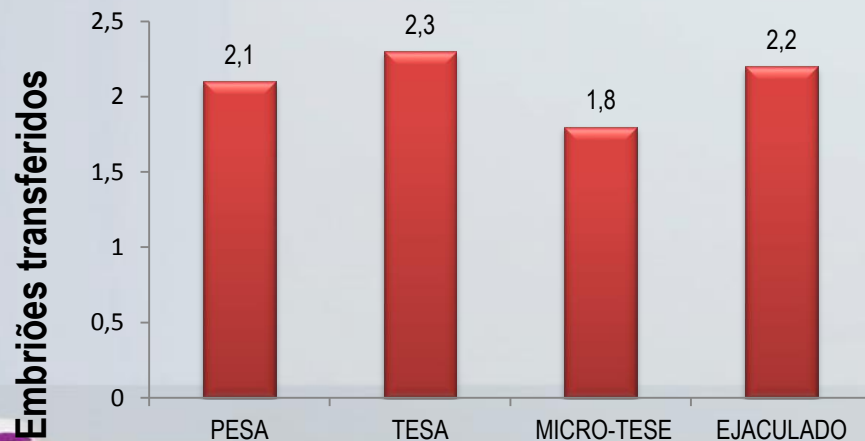
Resultados clínicos e laboratoriais – *Fertility* (2010-2014)

“Origem do espermatozoide”



COMPARAÇÃO	VALOR DE P
PESA VS TESA	< 0.001
PESA VS MICRO-TESE	> 0.05
PESA VS EJACULADO	> 0.05
TESA VS MICRO-TESE	> 0.05
TESA VS EJACULADO	< 0.001
MICRO-TESE VS EJACULADO	> 0.05

ANOVA



COMPARAÇÃO	VALOR DE P
PESA VS TESA	> 0.05
PESA VS MICRO-TESE	> 0.05
PESA VS EJACULADO	> 0.05
TESA VS MICRO-TESE	> 0.05
TESA VS EJACULADO	> 0.05
MICRO-TESE VS EJACULADO	> 0.05

ANOVA

Resultados clínicos e laboratoriais – *Fertility* (2010-2014)

“Origem do espermatozoide”



COMPARAÇÃO	VALOR DE P
PESA VS TESA	> 0.05
PESA VS MICRO-TESE	> 0.05
PESA VS EJACULADO	> 0.05
TESA VS MICRO-TESE	> 0.05
TESA VS EJACUALDO	> 0.05
MICRO-TESE VS EJACULADO	> 0.05

QUI-QUADADRO

COMPARAÇÃO	VALOR DE P
PESA VS TESA	> 0.05
PESA VS MICRO-TESE	> 0.05
PESA VS EJACULADO	> 0.05
TESA VS MICRO-TESE	> 0.05
TESA VS EJACUALDO	> 0.05
MICRO-TESE VS EJACULADO	> 0.05

ANOVA



FERTILITY

Falha na recuperação do espermatozoide *Fertility* (2010-2014)

Técnica	Nº Ciclos	Ciclos com ausência de espermatozóide	% de falha
PESA	199	27*	13.5
TESA	97	21	22.6
microTESE	48	21	43.8

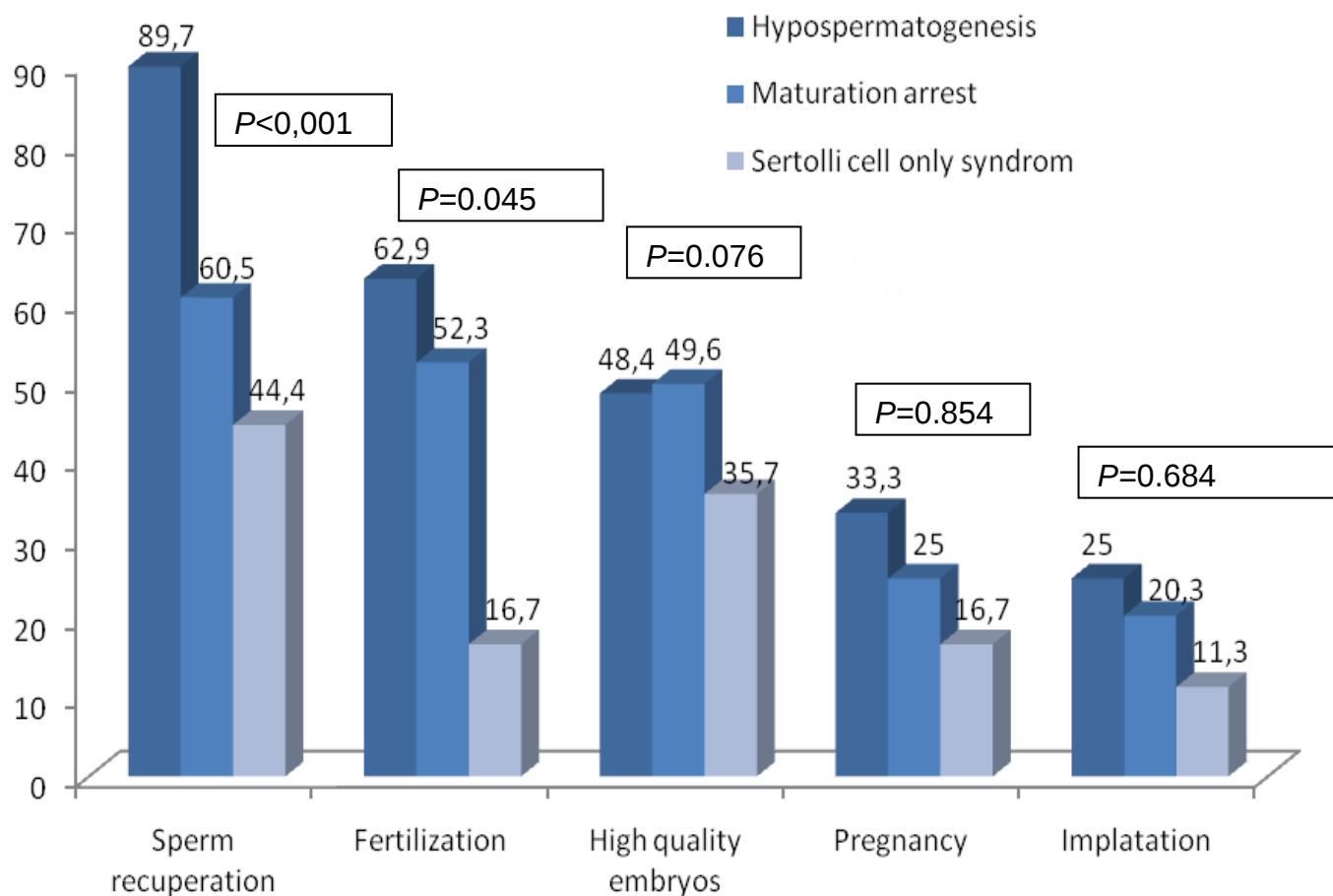
* 100%
após TESA



The prognostic value of the testicular histopathological pattern for sperm retrieval and intracytoplasmic sperm injection outcomes in non-obstructive azoospermic patients

O valor prognóstico do padrão histopatológico testicular na recuperação de espermatozoides e nos resultados da injeção intracitoplasmática de espermatozoides em pacientes com azoospermia não-obstrutiva

Edson Borges Jr.^{a,b}, Daniela Paes de Almeida Braga^{a,b}, Rita de Cássia Savio Figueira^a, Amanda Souza Setti^b, Assumpto Iaconelli Jr.^{a,b}, Fabio Firmbach Pasqualotto^c



5

Azoospermia

Obstrutiva

Recuperação
espermática na
maioria dos casos

PESA

Não
obstrutiva

Recuperação
espermática em
50% dos casos

TESA
microTESE

The prevalence of chromosomal abnormalities in subgroups of infertile men[†]

E.C. Dul^{1,*}, H. Groen², C.M.A. van Ravenswaaij-Arts³, T. Dijkhuizen³, J. van Echten-Arends¹, and J.A. Land¹

- ✓ 1.223 homens candidatos ICSI: 79 azoospérmicos (6,5%)
- ✓ 3,1% com anormalidades cromossômicas
- ✓ 15,2% dos azoo (OR=7,70 - $p<0,001$)
- ✓ FSH alto e anormalidade cromossômica (OR=2,96 - $p=0,013$)
- ✓ Azoospérmicos com história andrológica positiva < incidência de anormalidade cromossômica (OR=0,28 - $p=0,047$)

The genetic causes of male factor infertility: A review

Katherine L. O'Flynn O'Brien, B.A.,^a Alex C. Varghese, Ph.D.,^b and Ashok Agarwal, Ph.D.^a

Prevalence and phenotypes of common chromosomal abnormalities associated with male infertility.

Genetic abnormality	Phenotype	Prevalence, %
Chromosomal abnormalities	Azoospermia to normozoospermia	5 (total infertile population); 15 (azoospermic)
Klinefelter syndrome	Azoospermia to severe oligozoospermia	5 (severe oligozoospermia); 10 (azoospermic)
Robertsonian translocation	Azoospermia to normozoospermia	0.8 (total infertile population); 1.6 (oligozoospermic); 0.09 (azoospermic)
Y chromosome microdeletions	Azoospermia to oligozoospermia	10–15 (azoospermic); 5–10 (oligozoospermic)
AZF _a deletion	Azoospermia, Sertoli cell-only syndrome	0.5–1.0 (2)
AZF _b deletion	Azoospermia, spermatogenic arrest	0.5–1.0 (2)
AZF _c deletion	Severe oligozoospermia to nonobstructive azoospermia	6–12
Partial AZF-c deletions	From azoospermia to normozoospermia	3–5 (2)

- *Klinefelter:* 7 - 13% azoospermicos
- *MicroDeleção Y:* 2 - 20% oligo grave / azoospermicos
- *CBAVD:* 1 - 2% homens inférteis
10% azoospermias obstrutivas

Alteração Seminal Grave (oligo/azoospermia)

⑥ *SEMPRE PENSAR EM DOENÇA
GENÉTICA ASSOCIADA*

"Take home message"

- Envolvimento do homem
- A.S. (OMS 2010) com morfologia estrita + TMSC
- fragDNA espermático: > abortamento
- Tratamento medicamentoso: AO
- Varicocelectomia: casal com "tempo"
- Azoospermia obstrutiva: recuperação maioria dos casos
- Azoospermia não-obstrutiva: ~ 50%
- Alteração seminal grave: doença genética

Obrigado !

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