Fragmentação do DNA do espermatozoide

Edson Borges Jr.

Declaração de Conflito de interesse:

Diretor Científico do FERTGROUP

Resolução do Conselho Federal de Medicina
nº 1.595/2.000

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Esterilidade

- Prevalência ao redor de 14% da população
- 85% dos casais conseguem engravidar em 1 ano, 92% conseguem em 2 anos e 93% em 3 anos.
- 1 em cada 6 casais em idade reprodutiva terá dificuldade para engravidar.

Esterilidade

- A incapacidade de conseguir uma gravidez bem-sucedida com *base no histórico médico, sexual e reprodutivo da paciente, idade, achados físicos, testes de diagnóstico ou qualquer combinação desses fatores*.

- *A necessidade de intervenção médica*, incluindo, mas não se limitando à *utilização de gametas ou embriões de dadores*, a fim de conseguir uma gravidez bem-sucedida, *quer como indivíduo, quer com um parceiro*.

- Em pacientes que têm relações sexuais regulares e desprotegidas e sem qualquer etiologia conhecida para qualquer um dos parceiros, sugestiva de capacidade reprodutiva prejudicada, *a avaliação deve ser iniciada aos 12 meses, quando a parceira tiver menos de 35 anos de idade, e aos 6 meses, quando a parceira tiver 35 anos de idade ou mais*.

Esterilidade

Um Problema Médico (doença) !!!

Um Problema de Saúde Pública !!!

ETIOLOGIA DA INFERTILIDADE MASCULINA

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

Envolver o marido na investigação e tratamento!!

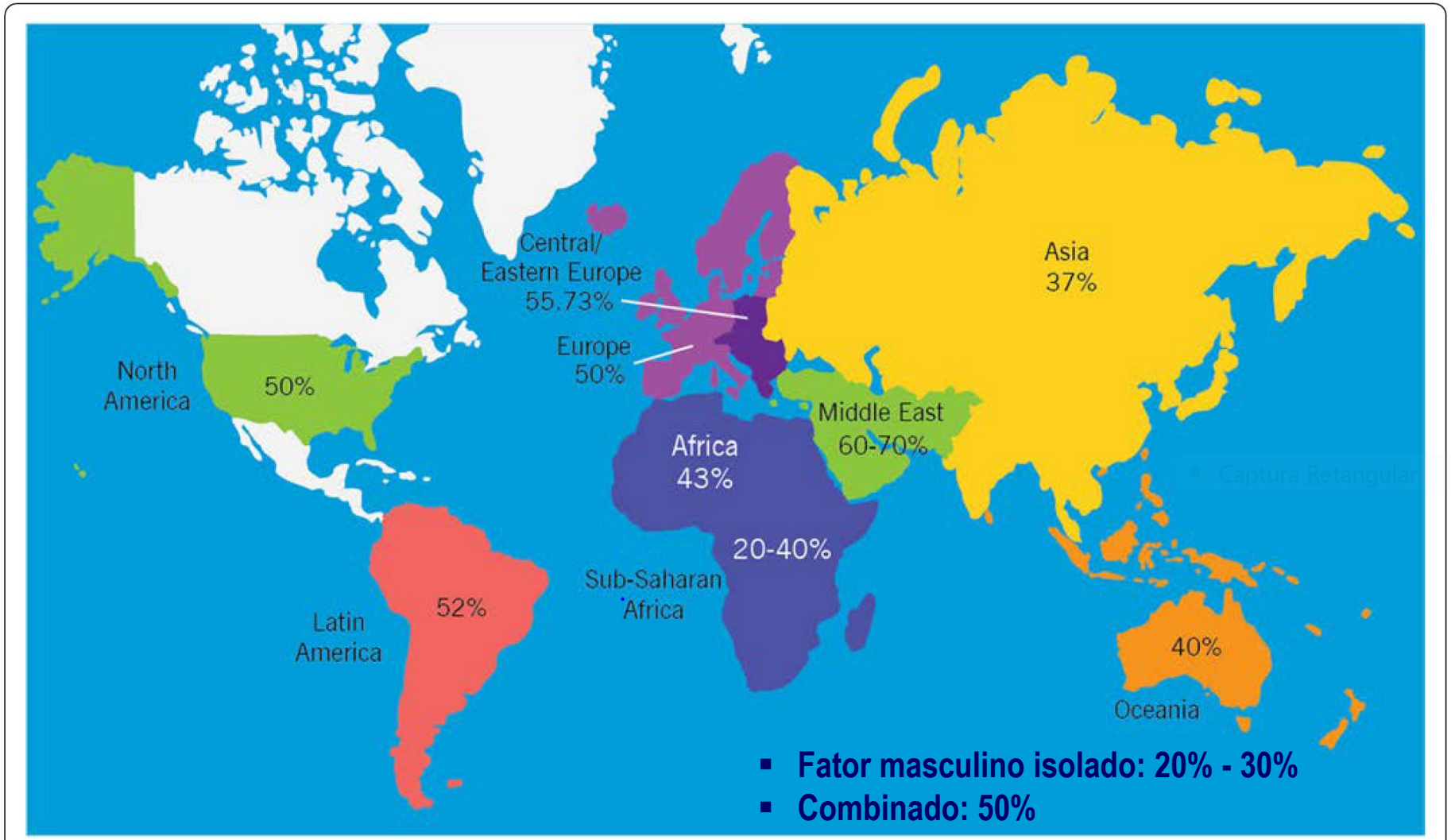


Figure 2 World map containing percentages of infertility cases per region that are due to male factor. This figure demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement.

Agarwal *et al. Reproductive Biology and Endocrinology* (2015) 13:37
DOI 10.1186/s12958-015-0032-1

ANDROLOGIA BASEADA EM EVIDÊNCIAS

- Raros estudos prospectivos, randomizados
  Consequência: resultados inclusivos ou conflitivos

- Etiopatogenia não evidente em 30 - 70% das causas (idiopática)

- Estudos com pouco tempo de acompanhamento, falta de validação por outros grupos, seleção heterogênea de pacientes, grande variação natural da produção espermática

- Nenhum modelo experimental válido para infertilidade masculina

Category	Frequency
Immunological	-
Idiopathic	32.6%
Varicocele	26.6%
Obstruction	15.3%
Normal female factor (unexplained male infertility)	10.7%
Cryptorchidism	
Ejaculatory failure	
Endocrinologic	
Drug/r	
	1.2%
	1.1%
	0.7%
spermia	0.5%
Cancer	0.4%
Systemic disease	0.3%
Infection	0.2%
Torsion	0.1%
Ultrastructural	0.1%
Total	100.0%

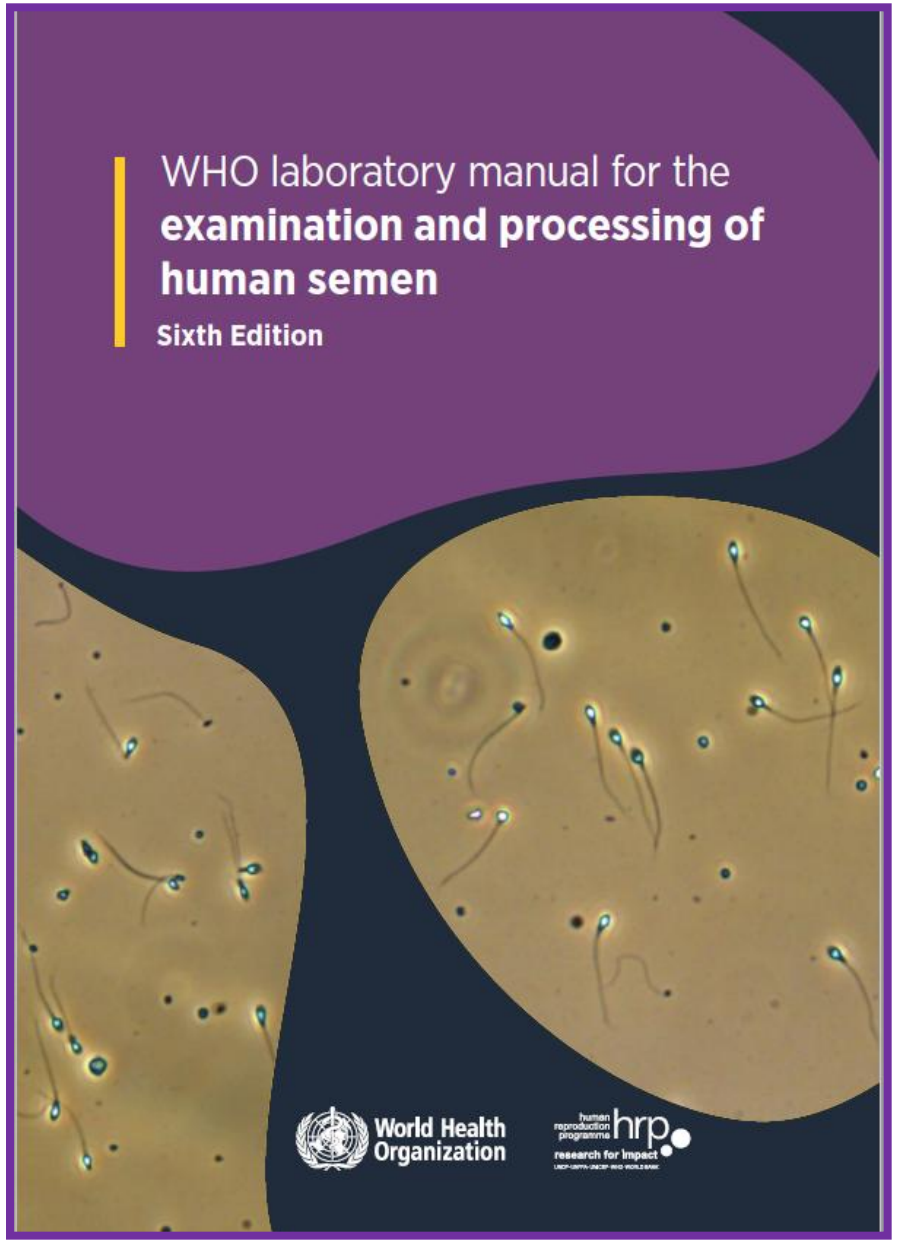
Doença multifactorial com fenótipo heterogêneo

Larry I. Lipshultz. Office evaluation of the subfertile male. In: Larry I. Lipshultz SSH, Craig S. Niederberger, editor. Infertility in the Male. 4th ed: Cambridge university press 2009. p. 153 -76.

ANDROLOGIA BASEADA EM EVIDÊNCIAS

Análise Seminal

VAN LEEUWENHOEK	1677
SIMS	1866
WEISMAN	1940
AMERICAN FERTILITY ASS	1951
FREUND	1966
ELIASSON	1971
O.M.S.	*1980/ 87/ 92/ 99/ 2010/ 2021*



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WHO laboratory manual for the
examination and processing of human semen
Sixth Edition

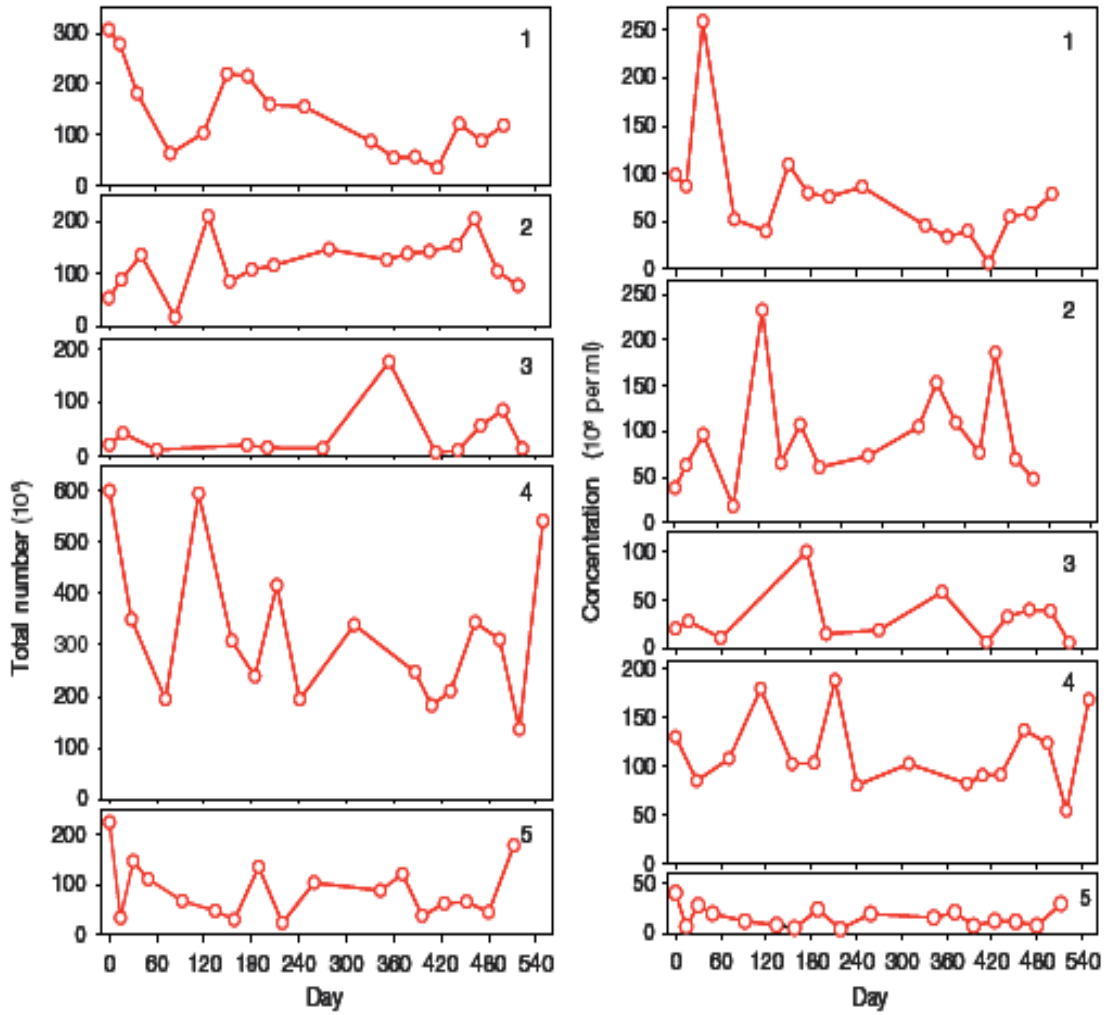
		Centiles									
	N	2.5th	5th	(95% CI)	10th	25th	50th	75th	90th	95th	97.5th
Semen volume (ml)	3586	1.0	1.4	(1.3–1.5)	1.8	2.3	3.0	4.2	5.5	6.2	6.9
Sperm concentration (10^6 per ml)	3587	11	16	(15–18)	22	36	66	110	166	208	254
Total sperm number (10^6 per ejaculate)	3584	29	39	(35–40)	58	108	210	363	561	701	865
Total motility (PR + NP, %)	3488	35	42	(40–43)	47	55	64	73	83	90	92
Progressive motility (PR, %)	3389	24	30	(29–31)	36	45	55	63	71	77	81
Non-progressive motility (NP, %)	3387	1	1	(1–1)	2	4	8	15	26	32	38
Immotile spermatozoa (IM, %)	2800	15	20	(19–20)	23	30	37	45	53	58	65
Vitality (%)	1337	45	54	(50–56)	60	69	78	88	95	97	98
Normal forms (%)	3335	3	4	(3.9–4.0)	5	8	14	23	32	39	45

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/ejaculate)	–	≥ 40	≥ 40	≥ 40	39
Motility (% motile)	≥ 60	≥ 50 (a + b)[2]	≥ 50 (a + b)	≥ 50 (a + b)	40 (a + b + c)
Forward progression (for 1980 only)	≥ 2[3]	≥ 25 (a)	≥ 25 (a)	≥ 25 (a)	32 (a + b)
Morphology (% normal)	80.5[4]	≥ 50	≥ 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

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



Análise Seminal

Investigação:

➢ Análise seminal com morfologia estrita

- 2 amostras (intervalo de 15 dias) ou no intervalo de abstinência ejaculatória
- padronização da coleta
- profissional experiente

✶ ***Fornece dados sobre espermatogênese e permeabilidade do trato reprodutivo***

✶ ***Ondas de espermatogênese ocorrendo simultaneamente, num mesmo túbulo seminífero***

Análise Seminal

Análise Macroscópica

cor, viscosidade, pH, volume, liquefação

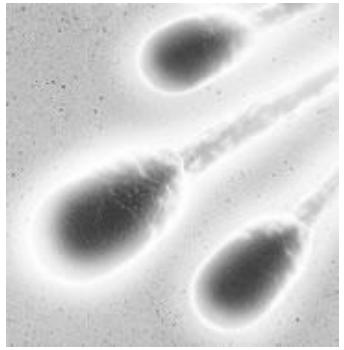
Análise Microscópica

concentração, motilidade, morfologia

Pelo menos duas amostras!

Análise Seminal

Não é um teste de fertilidade!



Avaliação do *status* funcional do testículo no momento da coleta

EDITOR'S CORNER

Evaluation of sperm damage: beyond the World Health Organization criteria

Nabil Aziz, M.R.C.O.G., M.D.,[a] *and Ashok Agarwal, Ph.D., H.C.L.D.*[b]

Fertility and Sterility® Vol. 90, No. 3, September 2008

- ✓ *grande flutuação na concentração, motilidade e morfologia*
- ✓ *variação intra / inter observador*
- ✓ *AS inadequada para o diagnóstico da infertilidade*
- ✓ *AS não investiga as propriedades biológicas e subcelulares do sptz*

☛ ***necessidade de outros testes funcionais mais específicos***

Qualidade seminal e resultados de T.R.A.

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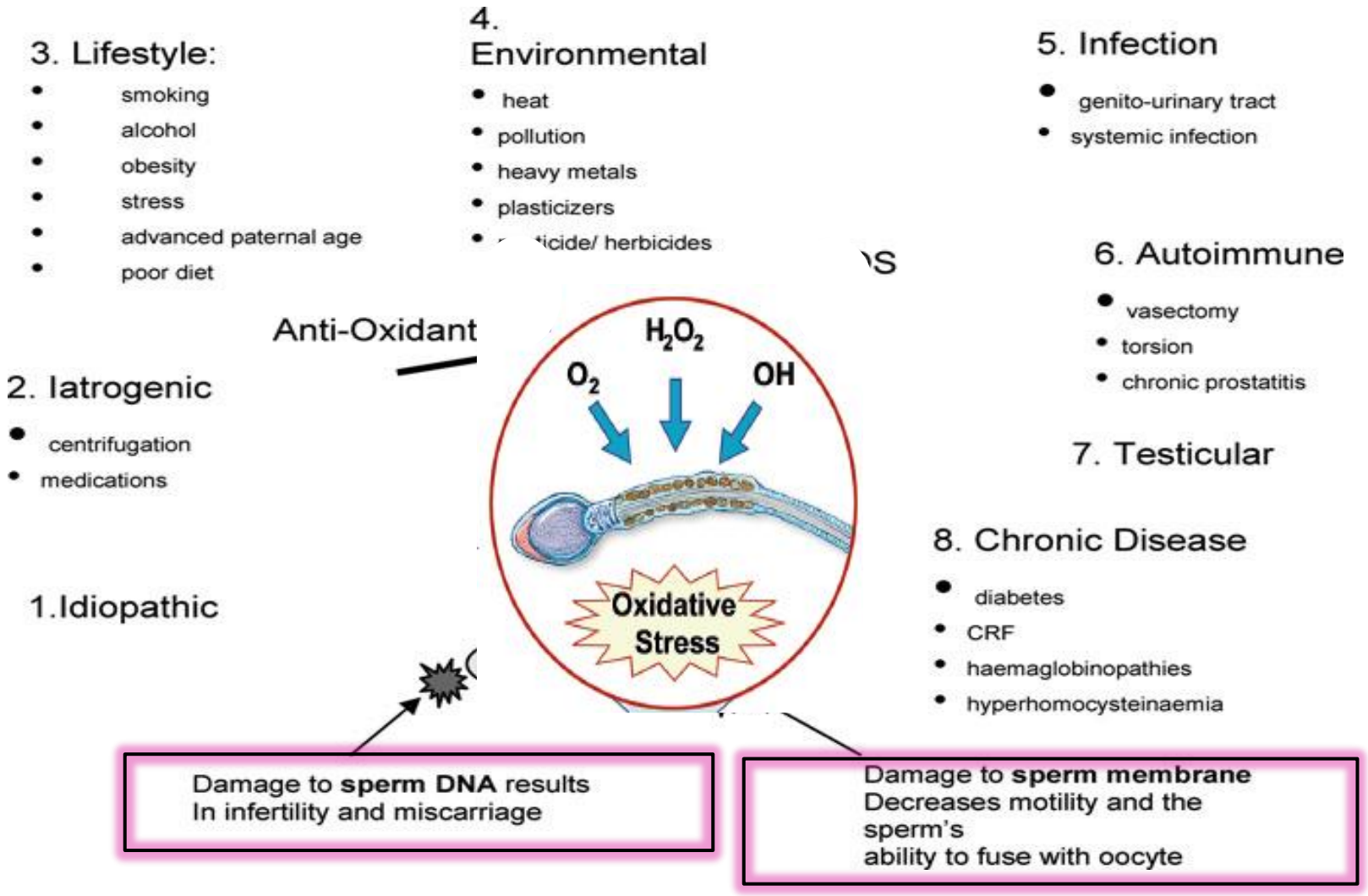


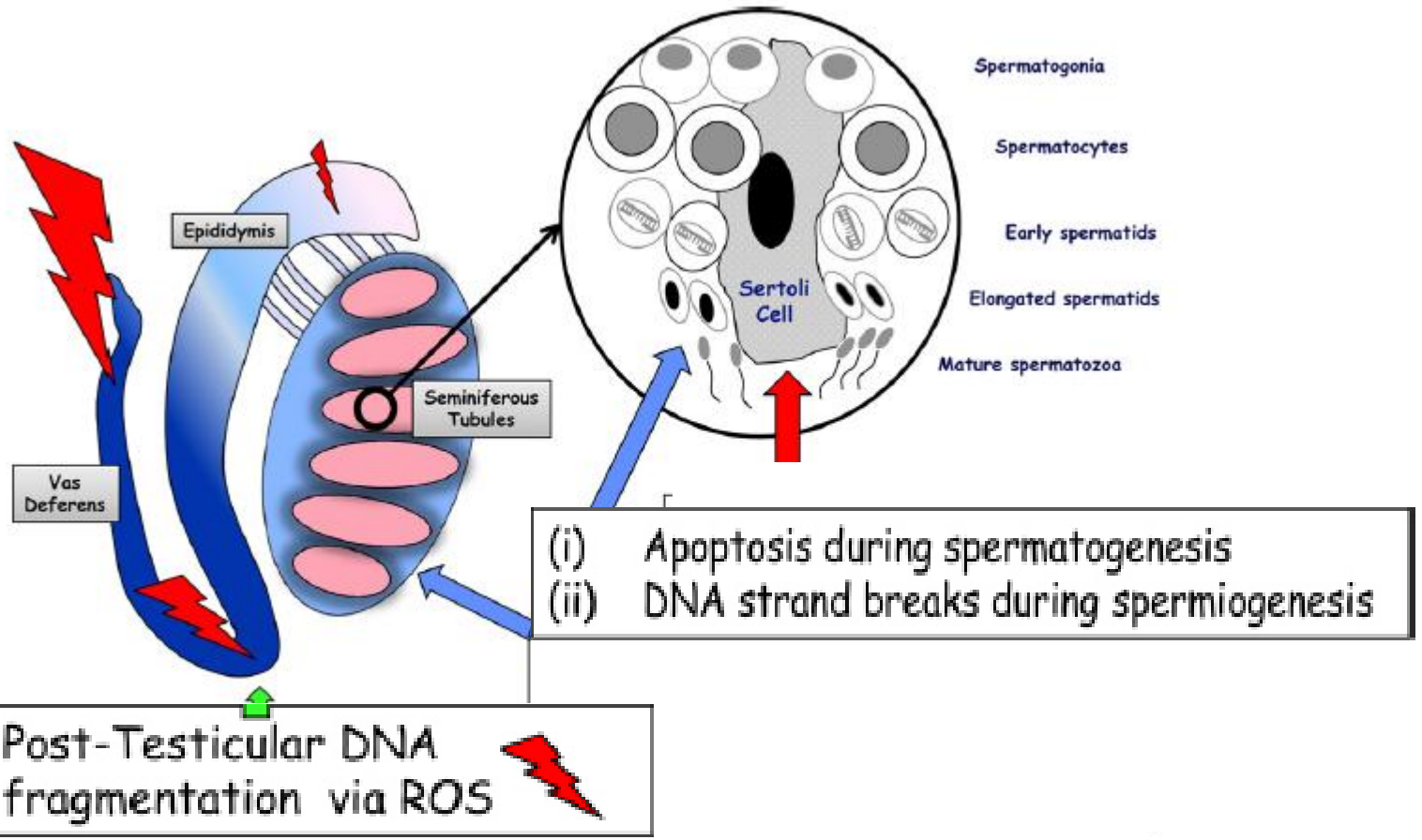
Kelton Tremellen; Human Reproduction Update, Vol.14, No.3 pp. 243–258, 2008

MODERN TRENDS | Fertility and Sterility® Vol. 93, No. 4, March 1, 2010

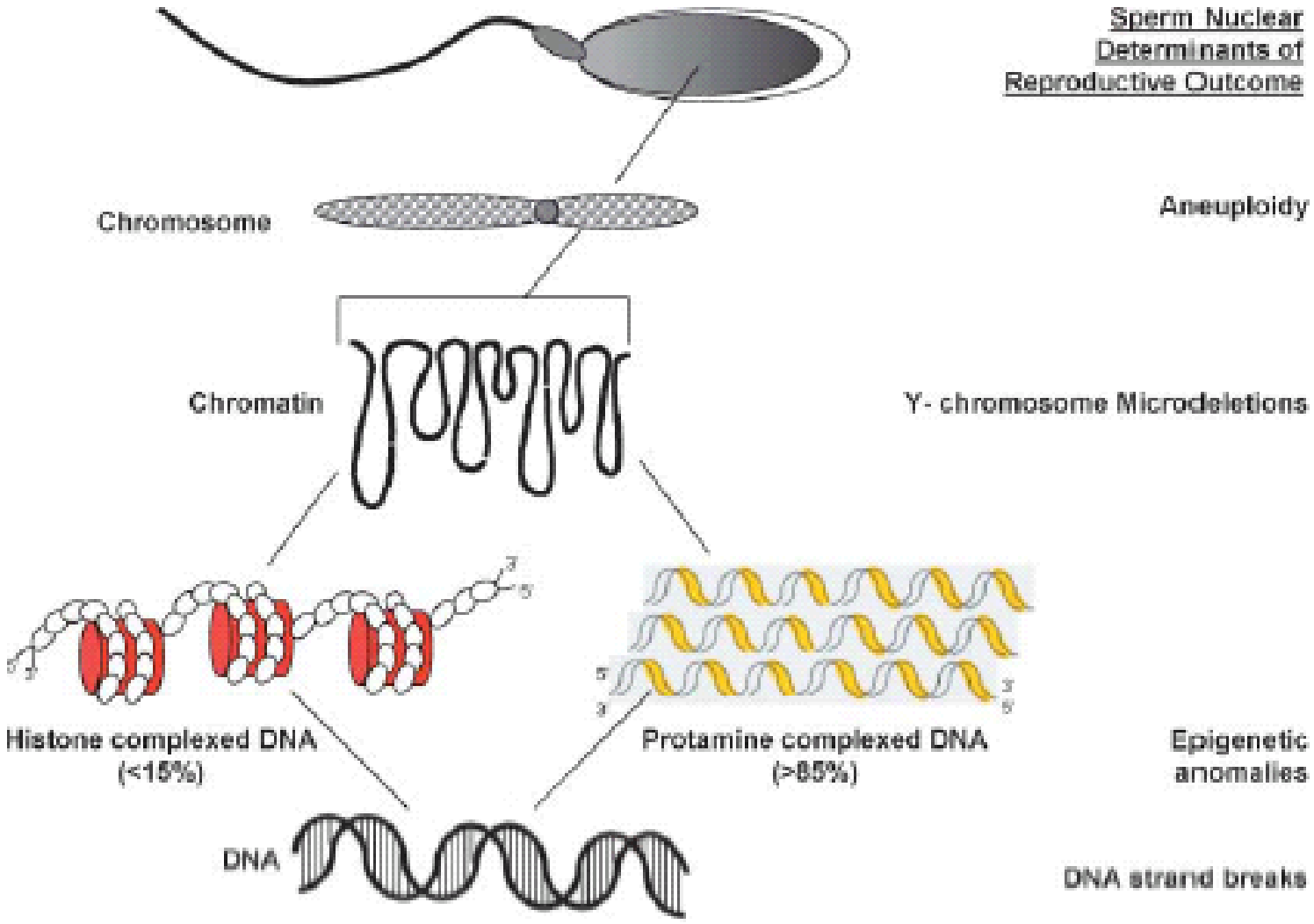
Edward E. Wallach, M.D.
Associate Editor

Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis

Denny Sakkas, Ph.D.,[a,b] *and Juan G. Alvarez, M.D., Ph.D.*[c,d,e]



Sakkas. Sperm DNA fragmentation. Fertil Steril 2010.


Sperm Nuclear Determinants of Reproductive Outcome
Chromosome
Aneuploidy
Chromatin
Y- chromosome Microdeletions
Histone complexed DNA (<15%)
Protamine complexed DNA (>85%)
Epigenetic anomalies
DNA
DNA strand breaks

Review Article
Male reproductive health and infertility
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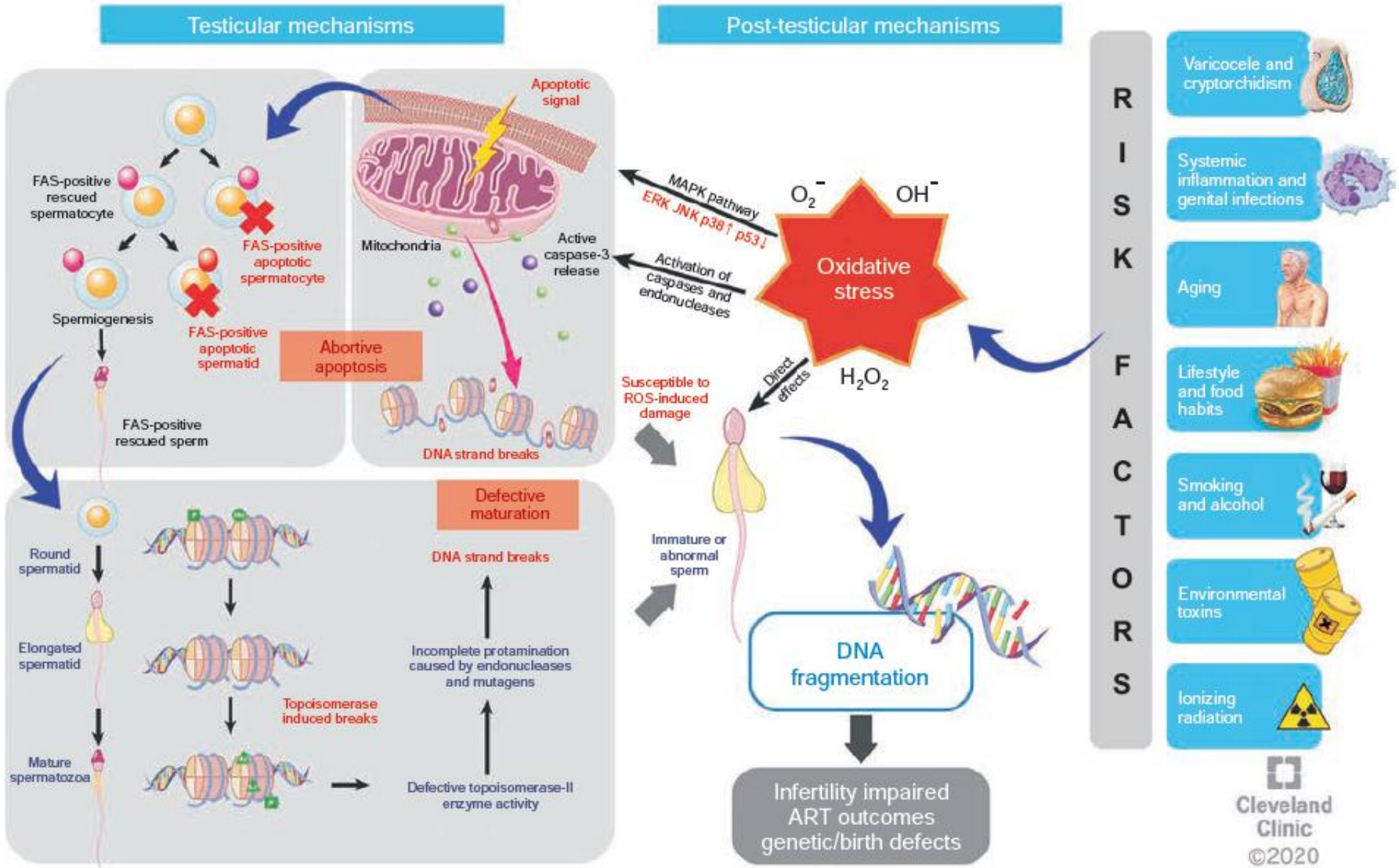
World J Mens Health Published online Aug 6, 2020
https://doi.org/10.5534/wjmh.200128

The World Journal of MEN's HEALTH

Sperm DNA Fragmentation: A New Guideline for Clinicians

Ashok Agarwal[1], Ahmad Majzoub[2,3], Saradha Baskaran[1], Manesh Kumar Panner Selvam[1],



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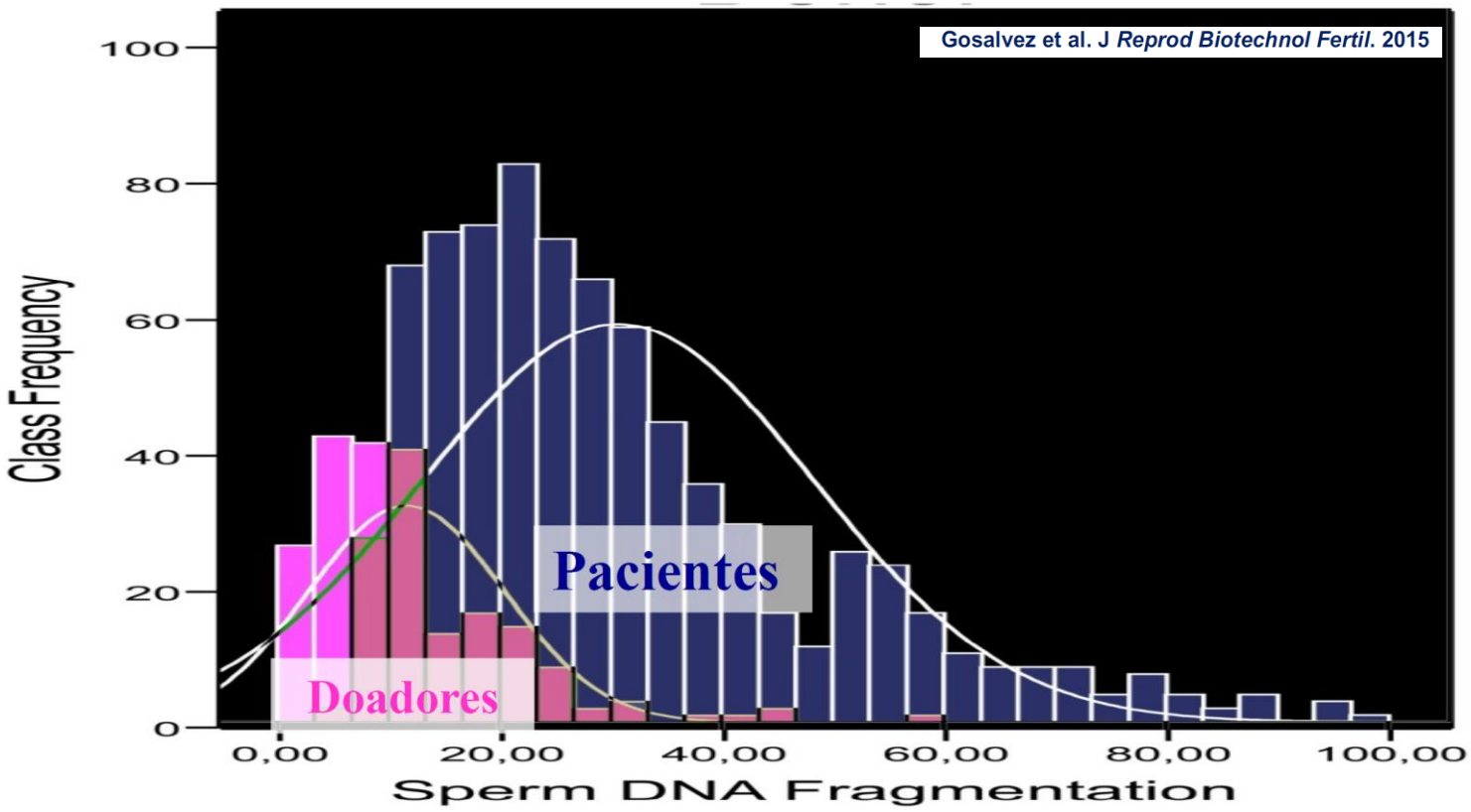
Taxa de Fragmentação do DNA espermático



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www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Sperm Biology

A systematic review and meta-analysis to determine the effect of sperm DNA damage on *in vitro* fertilization and intracytoplasmic sperm injection outcome

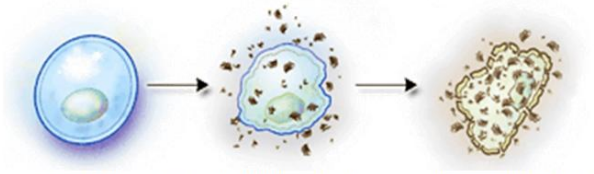
Luke Simon[1,*], Armand Zini[2,*], Alina Dyachenko[2], Antonio Ciampi[2], Douglas T Carrell[1,3,4]

Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis

Dana B. McQueen, M.D., M.A.S., John Zhang, Ph.D., and Jared C. Robins, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois

There is suficiente evidence in the existing literature suggesting that ***sperm DNA damage has a negative effect on clinical pregnancy and miscarriage*** following IVF and/or ICSI treatment



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Mecanismos biológicos da Fragmentação do Espermatozoide

- ***ALTERAÇÃO DA PROTAMINA***
- ***APOPTOSE ABORTIVA***
- ***ESTRESSE OXIDATIVO***

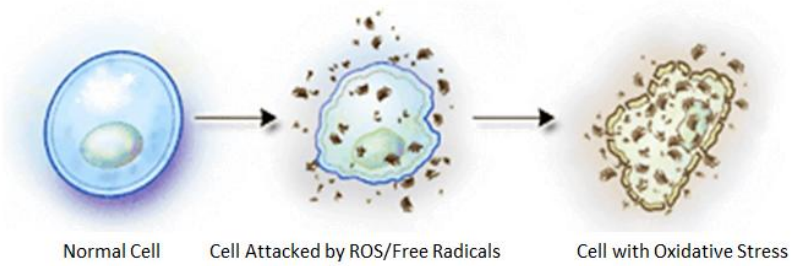
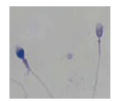
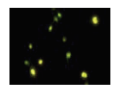
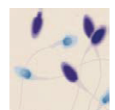
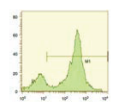
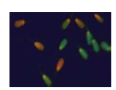
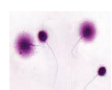
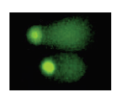


Table 1 Sperm DNA fragmentation (SDF) testing methods

	Test	Principle	Advantage	Disadvantage
 [1]	AO test	Metachromatic shift in fluorescence of AO when bound to single strand (ss)DNA. Uses fluorescent microscopy	Rapid, simple and inexpensive	Inter-laboratory variations and lack of reproducibility
 [2]	AB staining	Increased affinity of AB dye to loose chromatin of sperm nucleus. Uses optical microscopy	Rapid, simple and inexpensive	Inter-laboratory variations and lack of reproducibility
 [3]	CMA3 staining	CMA3 competitively binds to DNA indirectly visualizing protamine deficient DNA. Uses fluorescent microscopy	Yields reliable results as it is strongly correlated with other assays	Inter-observer variability
 [4]	TB staining	Increased affinity of TB to sperm DNA phosphate residues. Uses optical microscopy	Rapid, simple and inexpensive	Inter-observer variability
 [5]	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
 [6]	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
 [7]	SCD or Halo test	Assess dispersion of DNA fragments after denaturation. Uses optical or fluorescent microscopy	Simple test	Inter-observer variability
 [8]	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

[1] Acridine orange (AO) stains normal DNA fluoresces green; whereas denatured DNA fluoresces orange-red. [2] Aniline blue (AB) staining showing sperm with fragmented DNA and normal sperm. [3] Chromomycin A3 (CMA3) staining: protamine deficient spermatozoa appear bright yellow; spermatozoa with normal protamine appear yellowish green. [4] Toulidine blue (TB) staining: normal sperm appear light blue and sperm with DNA fragmentation appear violet. [5] Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay fluorescent activated cell sorting histogram showing percentage of SDF. [6] Sperm chromatin structure assay (SCSA): flow cytometric version of AO staining. [7] Sperm chromatin dispersion (SCD) test: spermatozoa with different patterns of DNA dispersion; large-sized halo; medium-sized halo [2]; very small- sized halo. [8] Comet images showing various levels of DNA damage.

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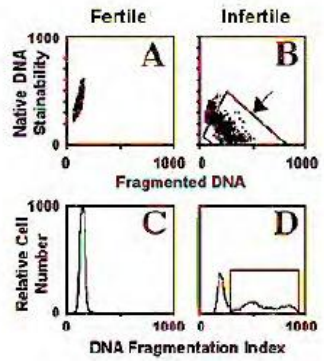
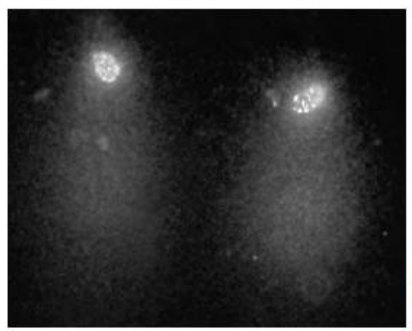
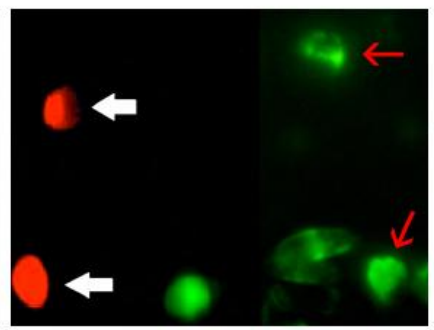
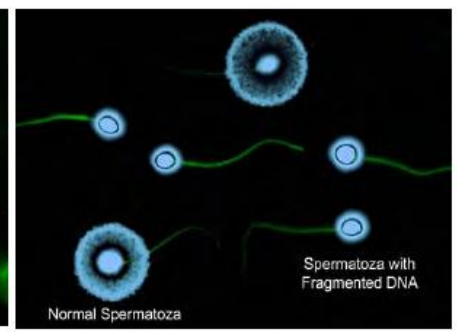
	Labor-intensive	Expensive equipment	Analysis Subjectivity	Validation & Standardization
TUNEL	++++	+++	++	++
SCSA	++	++++	+	++++
Comet	++++	+++	+++	+
SCD	+	+	++	+++

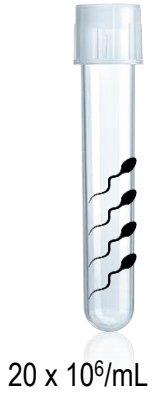




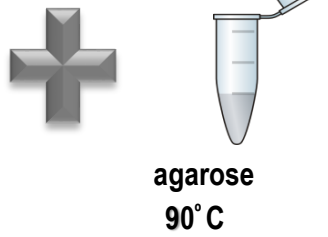




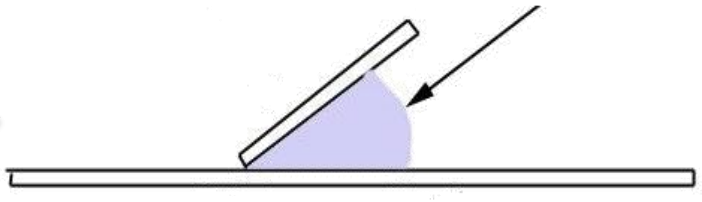
SPERM CHROMATIN DISPERSION TEST



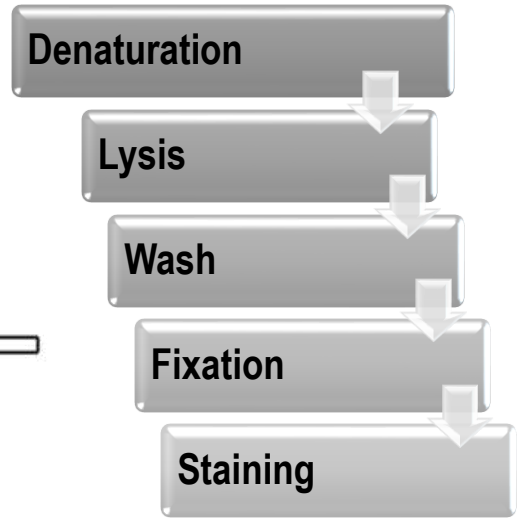
20 x 10^6/mL

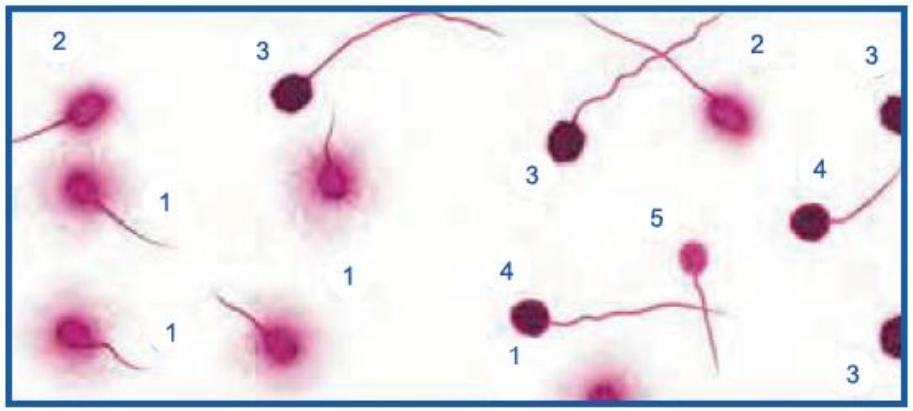


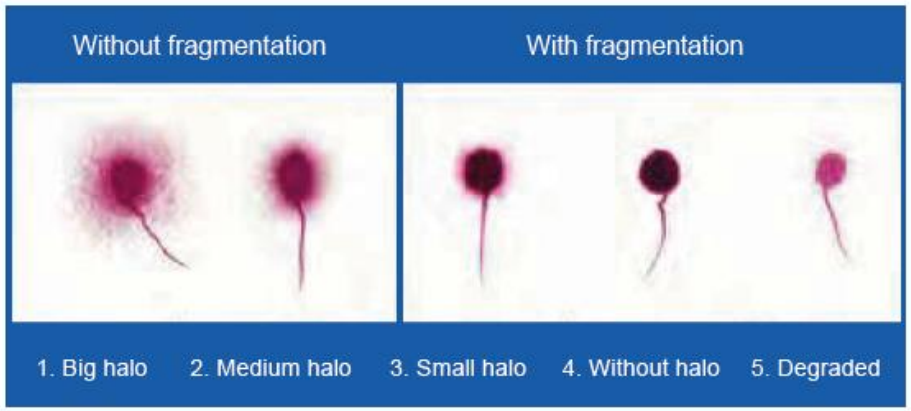
agarose
90°C



Halosperm G2, Halotech







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Review Article

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The World Journal of MEN's HEALTH

Male Oxidative Stress Infertility (MOSI): Proposed Terminology and Clinical Practice Guidelines for Management of Idiopathic Male Infertility

Ashok Agarwal[1,2], Neel Parekh[2], Manesh Kumar Panner Selvam[1,2], Ralf Henkel[1,3], Rupin Shah[4], Sheryl T. Homa[5], Ranjith Ramasamy[6], Edmund Ko[7], Kelton Tremellen[8], Sandro Esteves[9,10], Ahmad Majzoub[1,11], Juan G. Alvarez[12], David K. Gardner[13], Channa N. Jayasena[14,15], Jonathan W. Ramsay[15], Chak-Lam Cho[16], Ramadan Saleh[17], Denny Sakkas[18], James M. Hotaling[19], Scott D. Lundy[2], Sarah Vij[2], Joel Marmar[20], Jaime Gosalvez[21], Edmund Sabanegh[2], Hyun Jun Park[22,23], Armand Zini[24], Parviz Kavoussi[25], Sava Micic[26], Ryan Smith[27], Gian Maria Busetto[28], Mustafa Emre Bakırcıoğlu[29], Gerhard Haidl[30], Giancarlo Balercia[31], Nicolás Garrido Puchalt[32], Moncef Ben-Khalifa[33], Nicholas Tadros[34], Jackson Kirkman-Browne[35,36], Sergey Moskovtsev[37], Xuefeng Huang[38], Edson Borges Jr[39], Daniel Franken[40], Natan Bar-Chama[41], Yoshiharu Morimoto[42], Kazuhisa Tomita[42], Vasan Satya Srini[43], Willem Ombelet[44,45], Elisabetta Baldi[46], Monica Muratori[47], Yasushi Yumura[48], Sandro La Vignera[49], Raghavender Kosgi[50], Marlon P. Martinez[51], Donald P. Evenson[52], Daniel Suslik Zylbersztejn[53], Matheus Roque[54], Marcello Cocuzza[55], Marcelo Vieira[56,57], Assaf Ben-Meir[58], Raoul Orvieto[59,60], Eliahu Levitas[61], Amir Wiser[62,63], Mohamed Arafa[64], Vineet Malhotra[65], Sijo Joseph Parekattil[66,67], Haitham Elbardisi[64], Luiz Carvalho[68,69], Rima Dada[70], Christophe Sifer[71], Pankaj Talwar[72], Ahmet Gudeloglu[73], Ahmed M.A. Mahmoud[74], Khaled Terras[75], Chadi Yazbeck[76], Bojanic Nebojsa[77], Damayanthi Durairajanayagam[78], Ajina Mounir[79], Linda G. Kahn[80], Saradha Baskaran[1], Rishma Dhillon Pai[81], Donatella Paoli[82], Kristian Leisegang[83], Mohamed-Reza Moein[84], Sonia Malik[85], Onder Yaman[86], Luna Samanta[87], Fouad Bayane[88], Sunil K. Jindal[89], Muammer Kendirci[90], Baris Altay[91], Dragoljub Perovic[92], Avi Harlev[93]

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Male Infertility

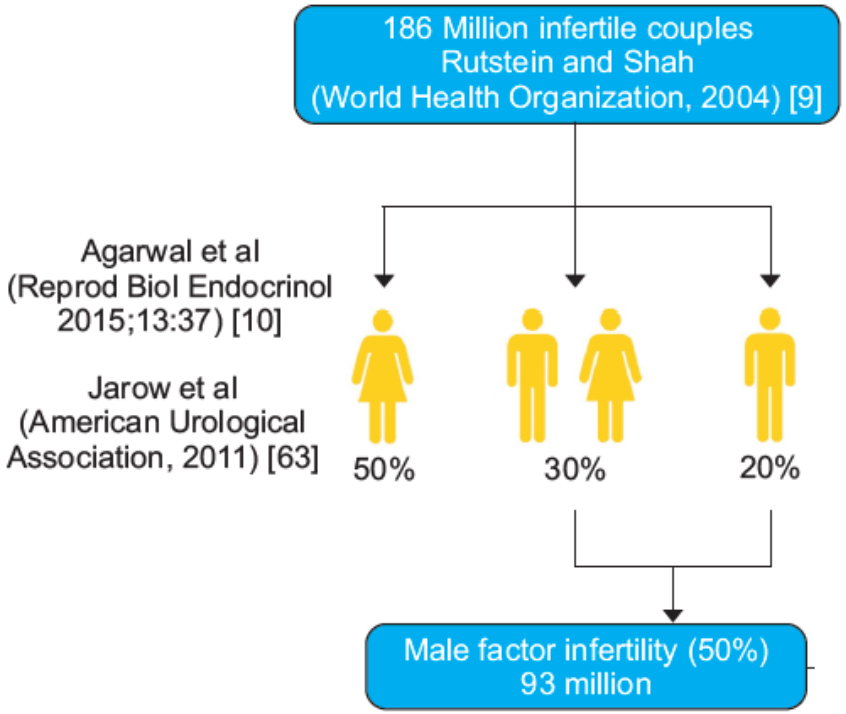
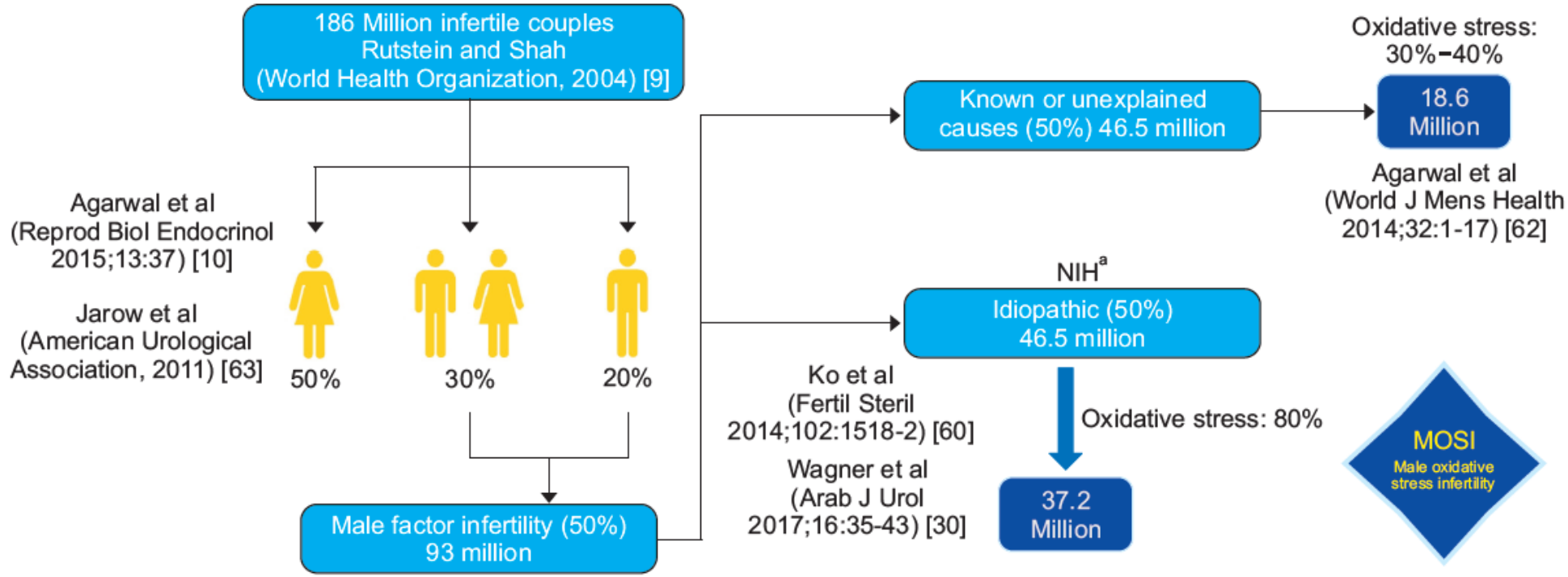


Fig. 3. Worldwide incidence of MOSI in infertile men. [a]National Institutes of Health (NIH) (https://www.nichd.nih.gov/health/topics/menshealth/conditioninfo/infertility) [61], Agarwal et al (2014) [62], Jarow et al (2011) [63].

Male Infertility



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A Global Survey of Reproductive Specialists to Determine the Clinical Utility of Oxidative Stress Testing and Antioxidant Use in Male Infertility

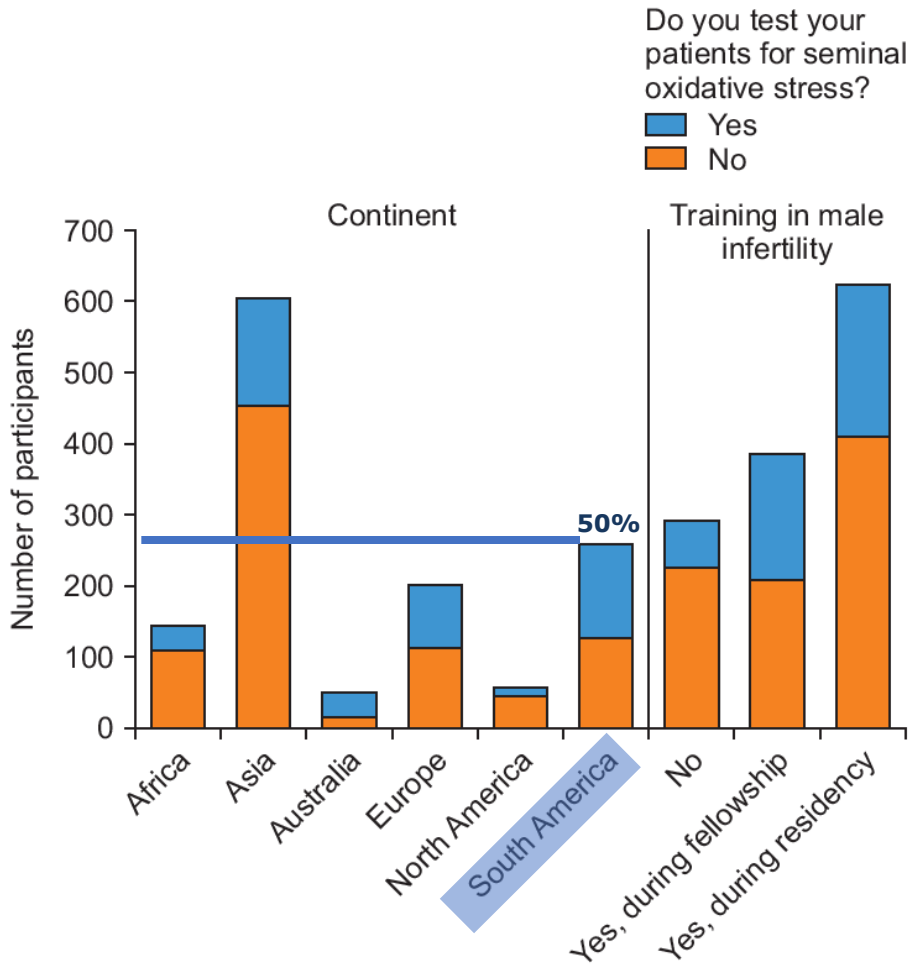

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Fig. 4. Oxidative stress testing based on the geographic origin of the participants and training in male infertility.

Asian Journal of Andrology (2017) 19, 80–90
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www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Sperm Biology

A systematic review and meta-analysis to determine the effect of sperm DNA damage on *in vitro* fertilization and intracytoplasmic sperm injection outcome

Luke Simon[1,*], Armand Zini[2,*], Alina Dyachenko[2], Antonio Ciampi[2], Douglas T Carrell[1,3,4]

Table 3: Meta-analysis summary: Overall and subgroup odds ratios of studies on sperm DNA damage and pregnancy

Effect	*Number of studies*	*Fixed effects model*		*Random effects model*	
		OR (95% CI)	*P*	*OR (95% CI)*	*P*
Overall effect	56	1.68 (1.49–1.89)	0.0000*	1.84 (1.5–2.27)	<0.0001*
Sperm DNA damage assays					
SCSA	23	1.18 (0.96–1.44)	0.1115	1.22 (0.93–1.61)	0.1522
TUNEL	18	2.18 (1.75–2.72)	0.0000*	2.22 (1.61–3.05)	<0.0001*
Comet	7	3.34 (2.32–4.82)	0.0000*	3.56 (1.78–7.09)	0.0003*
SCD	8	1.51 (1.18–1.92)	0.0011*	1.98 (1.19–3.3)	0.0086*
Types of assisted treatment					
IVF	16	1.65 (1.34–2.04)	0.0000*	1.92 (1.33–2.77)	0.0005*
ICSI	24	1.31 (1.08–1.59)	0.0068*	1.49 (1.11–2.01)	0.0075*
Mixed	16	2.37 (1.89–2.97)	0.0000*	2.32 (1.54–3.5)	0.0001*

Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis

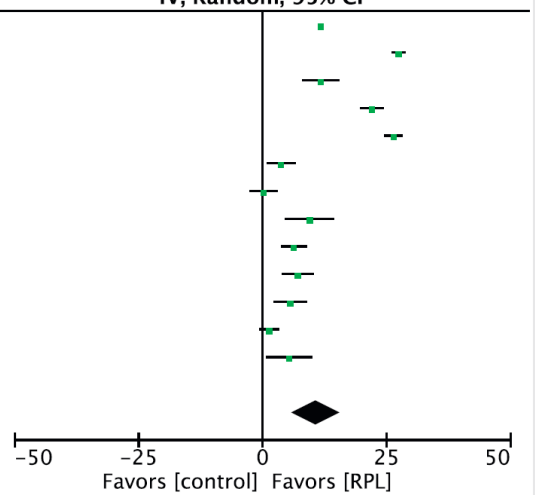
Dana B. McQueen, M.D., M.A.S., John Zhang, Ph.D., and Jared C. Robins, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois

	Recurrent Pregnancy Loss			Fertile Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Absalan 2012	23.3	1.1	30	11.6	0.5	30	7.9%	11.70 [11.27, 12.13]
Bareh 2016	36.8	2.7	26	9.4	2.7	31	7.9%	27.40 [25.99, 28.81]
Bhattachara 2008	18.1	16.1	74	6.4	3.6	65	7.6%	11.70 [7.93, 15.47]
Brahem 2011	32.2	6.1	31	10.2	2.1	20	7.8%	22.00 [19.66, 24.34]
Carrell 2003	38.3	4.2	21	11.9	1	26	7.8%	26.40 [24.56, 28.24]
Coughlan 2014	10.9	1.9	16	7.2	3.7	7	7.7%	3.70 [0.81, 6.59]
Esquerre-Lamare 2018	6.8	5.6	33	6.6	5.5	27	7.7%	0.20 [-2.62, 3.02]
Imam 2011	23.4	9.9	20	13.9	5.4	20	7.3%	9.50 [4.56, 14.44]
Kumar 2012	28.1	5	45	21.8	4.8	20	7.8%	6.30 [3.74, 8.86]
Ribas 2012	19.3	6.1	20	12.2	4.6	25	7.7%	7.10 [3.88, 10.32]
Ruixue 2013	25.6	11.5	68	20	7.7	63	7.6%	5.60 [2.27, 8.93]
Zhang 2012	15.2	6.4	111	13.9	4.4	30	7.8%	1.30 [-0.67, 3.27]
Zidi-Jrah 2016	17.1	9.3	22	11.8	5.7	20	7.4%	5.30 [0.68, 9.92]
Total (95% CI)			**517**			**384**	**100.0%**	**10.70 [5.82, 15.58]**

Heterogeneity: $Tau^2 = 78.10$; $Chi^2 = 1019.62$, df = 12 ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: $Z = 4.30$ ($P < 0.0001$)



Primary outcome in overall analysis.

McQueen. Sperm DNA fragmentation and RPL. Fertil Steril 2019.

Fertility and Sterility® Vol. 112, No. 1, July 2019

Recurrent pregnancy loss as 2 or more losses

Study or Subgroup	Recurrent Pregnancy Loss Mean	SD	Total	Fertile Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bareh 2016	36.8	2.7	26	9.4	2.7	31	16.9%	27.40 [25.99, 28.81]
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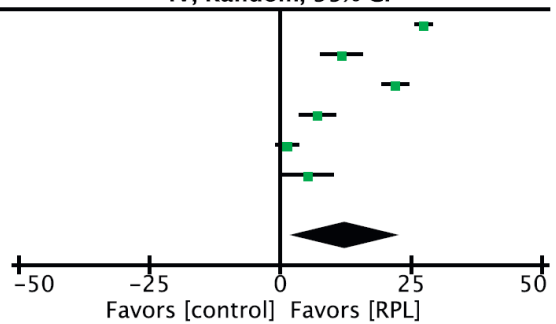
Zidi-Jrah 2016	17.1	9.3	22	11.8	5.7	20	16.4%	5.30 [0.68, 9.92]
Total (95% CI)			**284**			**191**	**100.0%**	**12.51 [2.14, 22.89]**

Heterogeneity: $Tau^2 = 165.76$; $Chi^2 = 538.60$, df = 5 ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: Z = 2.36 (P = 0.02)



Recurrent pregnancy loss as 3 or more losses

Study or Subgroup	Recurrent Pregnancy Loss Mean	SD	Total	Fertile Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
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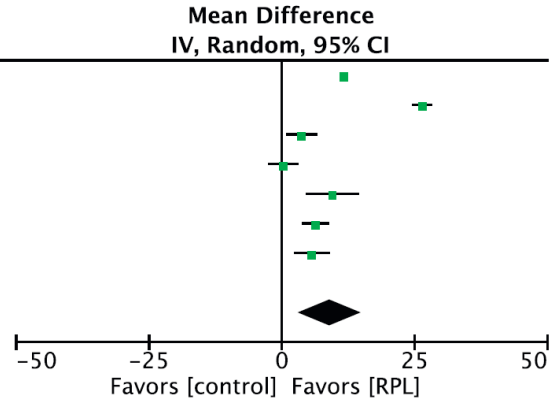
Ruixue 2013	25.6	11.5	68	20	7.7	63	14.1%	5.60 [2.27, 8.93]
Total (95% CI)			**233**			**193**	**100.0%**	**9.12 [3.16, 15.08]**

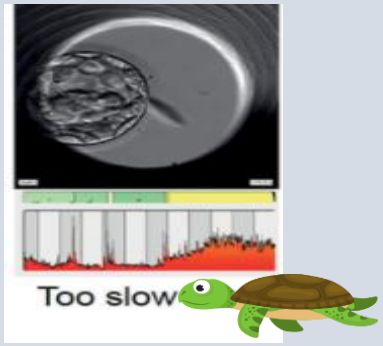
Heterogeneity: $Tau^2 = 62.49$; $Chi^2 = 369.78$, df = 6 ($P < 0.00001$); $I^2 = 98\%$

Test for overall effect: Z = 3.00 (P = 0.003)



Subgroup analysis by definition of recurrent pregnancy loss (RPL).

McQueen. Sperm DNA fragmentation and RPL. Fertil Steril 2019.



A fragmentação do DNA pode interferir na velocidade e no padrão das divisões celulares

Morphokinetic parameter comparison between embryos from couples with high or low sperm DNA fragmentation index

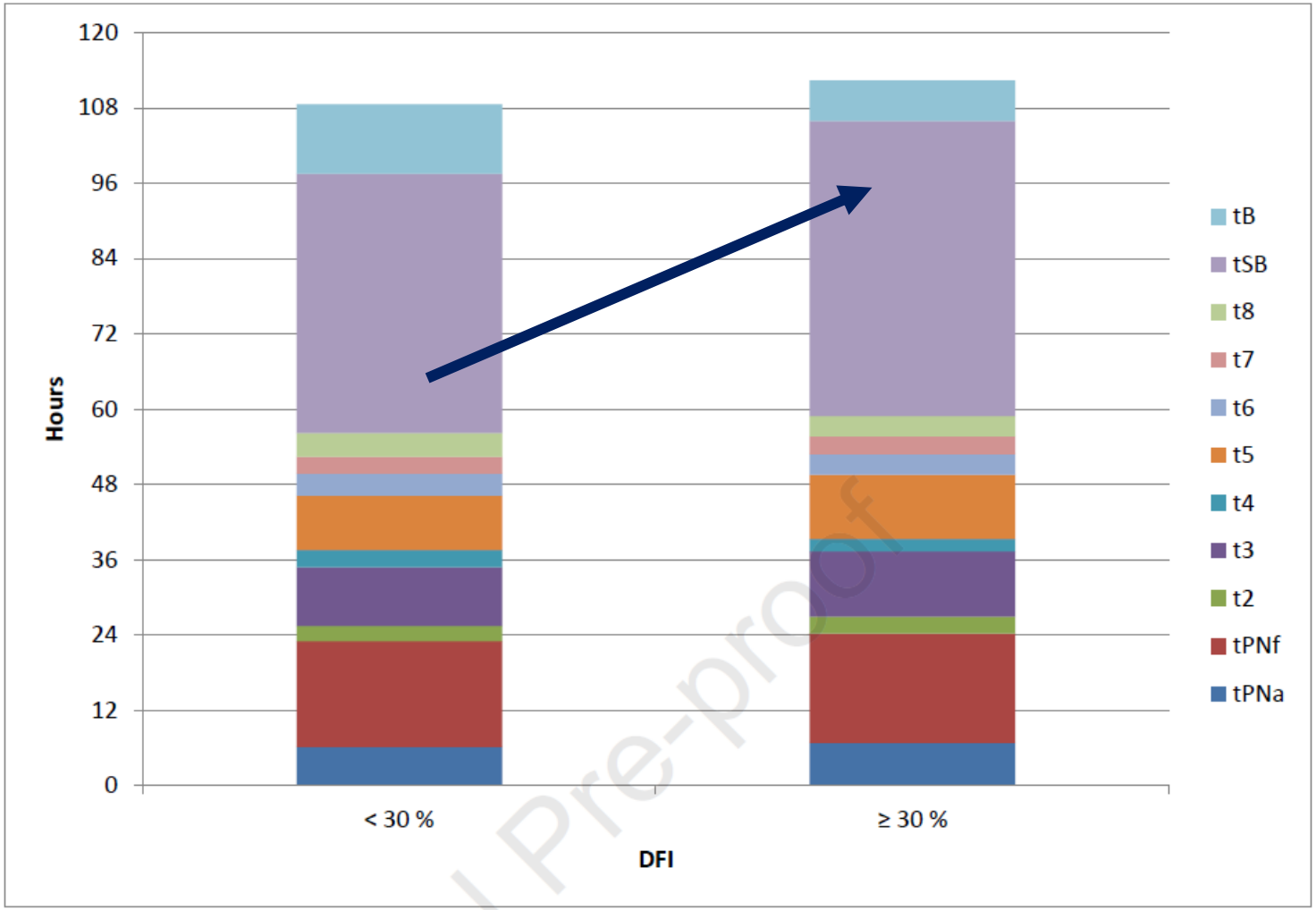
Amanda Souza Setti, M.Sc.,[a,b] Daniela Paes de Almeida Ferreira Braga, Ph.D.,[a,b] Patricia Guilherme, M.Sc.,[a] Rodrigo Provenza, B.Sc.,[a] Assumpto Iaconelli Jr., M.D.,[a,b] and Edson Borges Jr., Ph.D.[a,b]

[a] Fertility Medical Group, Av. Brigadeiro Luis Antonio, São Paulo, Brazil; and [b] Sapientiae Institute – Centro de Estudos e Pesquisa em Reprodução Humana Assistida, Rua Vieira Maciel, São Paulo, Brazil

F&S Science (2021), doi: https://doi.org/10.1016/j.xfss.2021.10.001

- 118 patients, 978 zygotes, ICSI cycles, idiopathic male factor
- Morphokinetic markers: time to pronucleus, appearance and disappearance (tPNa and tPNf), time to two (t2), three (t3), four (t4),five (t5), six (t6), seven (t7), and eight cells (t8), and time of onset (tSB) and blastulation (tB).
- Low (<30%) or high (≥30%) DFI (sperm DNA fragmentation index
- Mixed generalized linear models adjusted for potential confounders, followed by *post hoc* Bonferroni test

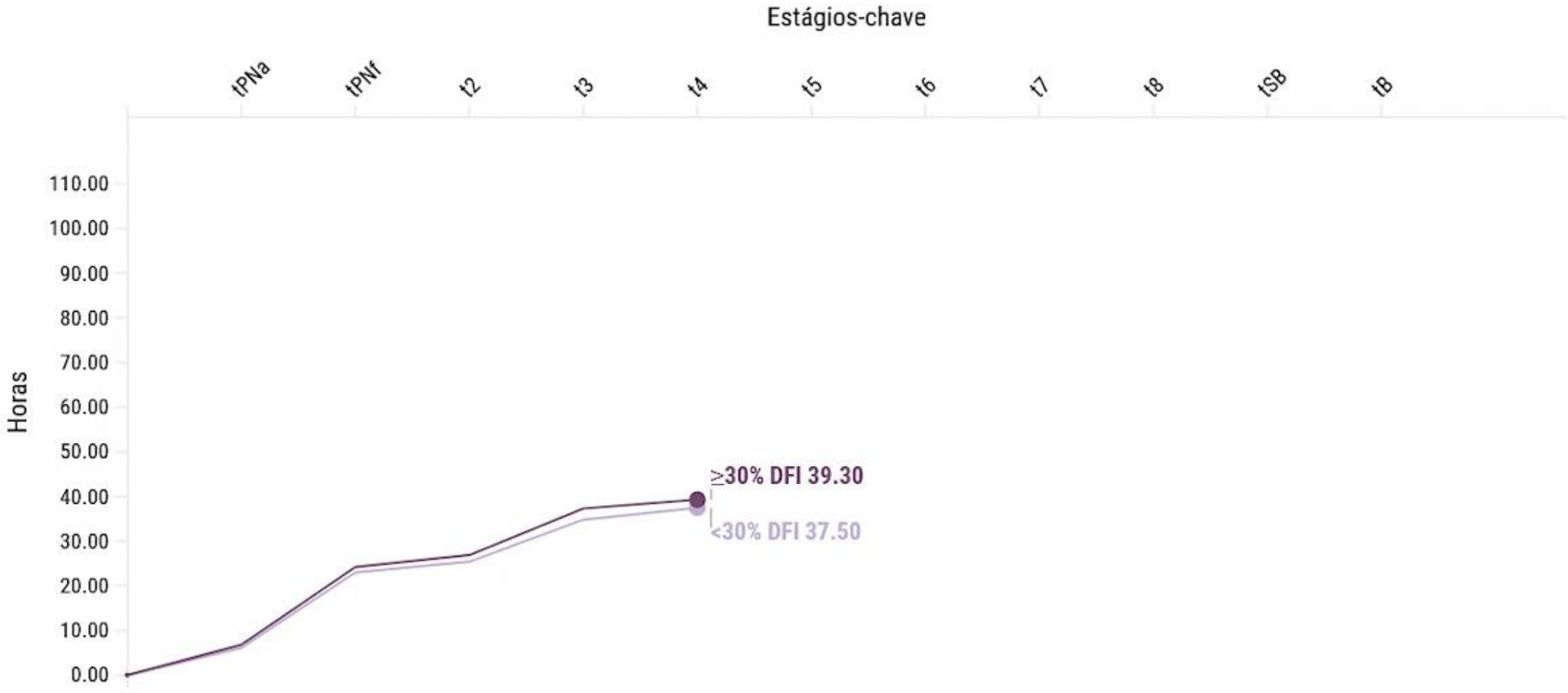
Table 2. Results from multivariate linear regression analysis followed by Bonferroni post hoc for the comparison of embryo morphokinetics between DFI groups (n=978)



Pre-proof

F&S Science (2021), doi: https://doi.org/10.1016/j.xfss.2021.10.001

Morphokinetic markers



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Use of testicular sperm in nonazoospermic males

Akanksha Mehta, M.D.,[a] Sandro C. Esteves, M.D.,[b,c,d] Peter N. Schlegel, M.D.,[e] Craig I. Niederberger, M.D.,[f] Mark Sigman, M.D.,[g] Armand Zini, M.D.,[h] and Robert E. Brannigan, M.D.[i]

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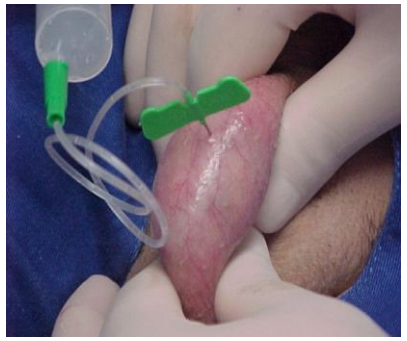

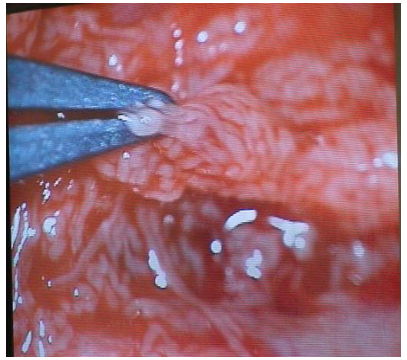

PRO: Emerging body of evidence supports use of testicular sperm for nonazoospermic males in several clinical settings

Pro 1. Akanksha Mehta, M.D., Fertile Battle Team Leader

Pro 2. Peter N. Schlegel, M.D.

Elevated Levels of Ejaculated Sperm DNA Damage: The Case for Use of Testicular Sperm

Pro 3. Sandro C. Esteves, M.D.

Recurrent IVF Failure and Recurrent Pregnancy Loss: The Case for Use of Testicular Sperm

CON: First do no harm—more data is needed before adapting use of testicular sperm in nonazoospermic male

Con 1. Craig I. Niederberger, M.D., Fertile Battle Team Leader

Con 2. Mark Sigman, M.D.

Elevated Levels of Ejaculated Sperm DNA Damage: The Case Against Use of Testicular Sperm

Con 3. Armand Zini, M.D.

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Use of testicular sperm in nonazoospermic males

Fertility and Sterility

Pro 3. Sandro C. Esteves, M.D.

Recurrent IVF Failure and Recurrent Pregnancy Loss: The Case for Use of Testicular Sperm

A justified objection to the use of testicular sperm in non-azoospermic men has been the potential for surgical complica-

Con 3. Armand Zini, M.D.

Recurrent IVF Failure and Recurrent Pregnancy Loss: The Case Against Use of Testicular Sperm

The causes of recurrent IVF failure, recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) remain poorly elucidated, but these conditions

Pro 2. Peter N. Schlegel, M.D.

Elevated Levels of Ejaculated Sperm DNA Damage: The Case for Use of Testicular Sperm

A valid critique of the existing studies evaluating the use of testicular sperm in couples with severe male factor infertility,

Con 2. Mark Sigman, M.D.

Elevated Levels of Ejaculated Sperm DNA Damage: The Case Against Use of Testicular Sperm

In men with sperm in the semen, what justifies performing a surgical procedure to obtain sperm? Those that advocate for this often select cases based on elevated SDF

PRO: Emerging body of evidence supports use of testicular sperm for nonazoospermic males in several clinical settings

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Rationale for Use of Testicular Sperm in

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Rationale Against Use of Testicular Sperm in

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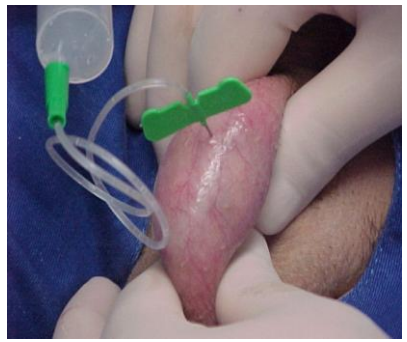

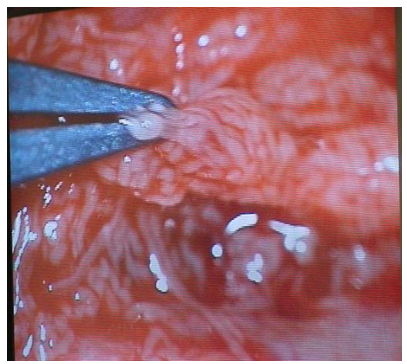

Use of testicular sperm in nonazoospermic males

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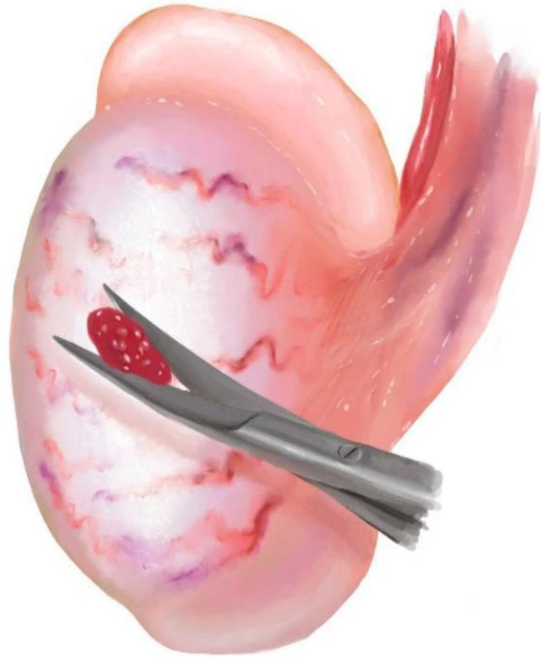

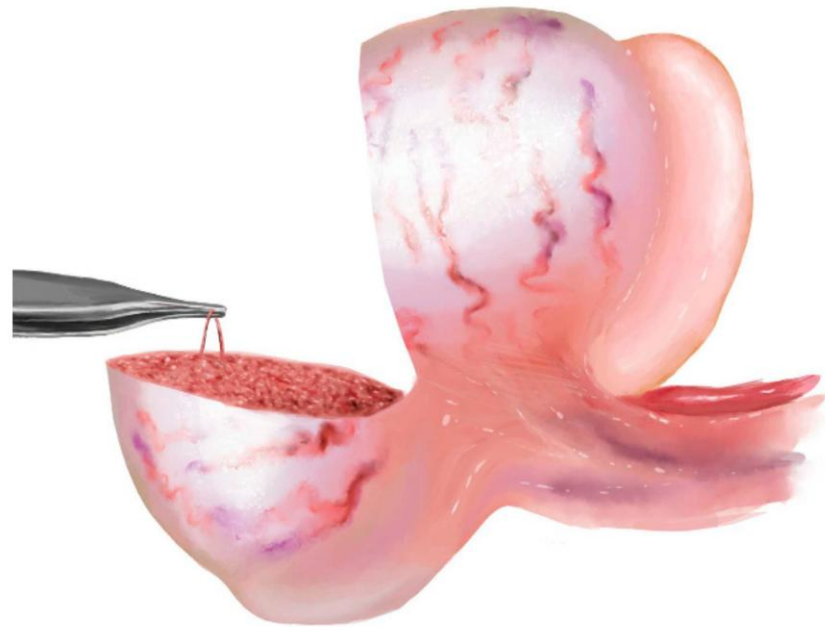

Human Reproduction, Vol.32, No.1 pp. 7–13, 2017
Advanced Access publication on November 5, 2016 doi:10.1093/humrep/dew276

human reproduction OPINION

Use of testicular sperm for ICSI in oligozoospermic couples: how far should we go?

Armand Zini[1,*], Phil V. Bach[2], Ahmad H. Al-Malki[1], and Peter N. Schlegel[2]

- Clinicians should balance these risks prior to the recommendation of TSR-ICSI on the result of a semen analysis or sperm DNA test alone.
- The use of TSR-ICSI in the absence of specific sperm DNA defects is still experimental.

EUROPEAN UROLOGY FOCUS 4 (2018) 299–300

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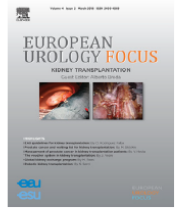

Point of Focus Debate: Con

Should A Couple with Failed In Vitro Fertilization/Intracytoplasmic Sperm Injection and Increased Sperm DNA Fragmentation Use Testicular Sperm for the Next Cycle?

Joshua A. Halpern, Peter N. Schlegel *

Department of Urology, Weill Cornell Medicine, New York, NY, USA

- ***Only in exceptional circumstances*** would testicular sperm retrieval be considered, after counseling the patient regarding risks both known and unknown.

- Immediate sperm retrieval in such a setting without further patient evaluation is ***clinically inappropriate***.

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REVIEW

Testicular versus ejaculated spermatozoa for ICSI in patients without azoospermia: A systematic review

BIOGRAPHY

Hatem Awaga is Assistant Lecturer in Obstetrics and Gynecology at Sohag Faculty of Medicine, Egypt and PhD and fellowship student in the Unit of Human Reproduction, Aristotle University of Thessaloniki, Greece. He received his medical degree in 2007 and his MSc in 2012 from the Sohag Faculty of Medicine.

Hatem A Awaga[1,2], Julia K Bosdou[2], Dimitrios G Goulis[2], Katerina Chatzimeletiou[2], Mohamed Salem[1], Salah Roshdy[1], Grigoris Grimbizis[2], Basil C Tarlatzis[2], Efstratios M Kolibianakis[2,*]

TABLE 3 CLINICAL PREGNANCY AND LIVE BIRTH IN THE TESTICULAR AND EJACULATED SPERMATOZOA GROUPS.

	High DFI only *Pabuccu et al. (2016)*	High DFI and oligozoospermia *Esteves et al. (2015)*	Isolated asthenozoospermia *Al-Malki et al. (2017)*	Asthenozoospermia with or without teratozoospermia *Kahraman et al. (1996)*
Clinical pregnancy	NR	NR	RR: 1.09, 95% CI: 0.56 to 2.14	RR: 2.85, 95% CI: 0.76 to 10.69
Live birth	RR: 2.36, 95% CI: 0.98 to 5.68	RR: 1.75, 95% CI: 1.14 to 2.70	NR	NR

CI = confidence interval; DFI = DNA fragmentation index; NR = not reported; RR = relative risk.

Há *evidências limitadas e de baixa qualidade* que sugerem que uma maior probabilidade de gravidez pode ser esperada usando espermatozoides testiculares e não ejaculados, apenas em homens com alto DFI e oligozoospermia.

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Hatem Awaga is Assistant Lecturer in Obstetrics and Gynecology at Sohag Faculty of Medicine, Egypt and PhD and fellowship student in the Unit of Human Reproduction, Aristotle University of Thessaloniki, Greece. He received his medical degree in 2007 and his MSc in 2012 from the Sohag Faculty of Medicine.

Hatem A Awaga[1,2], Julia K Bosdou[2], Dimitrios G Goulis[2], Katerina Chatzimeletiou[2], Mohamed Salem[1], Salah Roshdy[1], Grigoris Grimbizis[2], Basil C Tarlatzis[2], Efstratios M Kolibianakis[2,*]

O valor da revisão sistemática é que ela mostra claramente que ***não há base para a aplicação clínica de rotina do TESE em homens sem azoospermia*** e, como tal, esta intervenção, que também aumenta o custo geral do tratamento, ***deve ser confinada a um ambiente de pesquisa***.

ORIGINAL ARTICLES: ANDROLOGY

Testicular sperm extraction vs. ejaculated sperm use for nonazoospermic male factor infertility

Fertility and Sterility® Vol. 116, No. 4, October 2021
https://doi.org/10.1016/j.fertnstert.2021.05.087

Lauren M. Kendall Rauchfuss, M.D.,[a] Tana Kim, M.D.,[a] Jessica L. Bleess, PA-C,[a] Matthew J. Ziegelmann, M.D.,[b] and Chandra C. Shenoy, M.D.[a]

[a] Department of Obstetrics and Gynecology and [b] Department of Urology, Mayo Clinic, Rochester, Minnesota

- **Pacientes com infertilidade por fator masculino e oligozoospermia *não melhoraram os resultados de ICSI com o uso de TESE em comparação com espermatozoide ejaculado ejaculado.***

Use of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with cryptozoospermia: a meta-analysis

Nikita Abhyankar, M.B.ChB.,[a] Martin Kathrins, M.D.,[b] and Craig Niederberger, M.D.[a]

[a] Department of Urology, University of Illinois at Chicago, Chicago, Illinois; and [b] Division of Urology, Brigham and Women's Hospital, Boston, Massachusetts

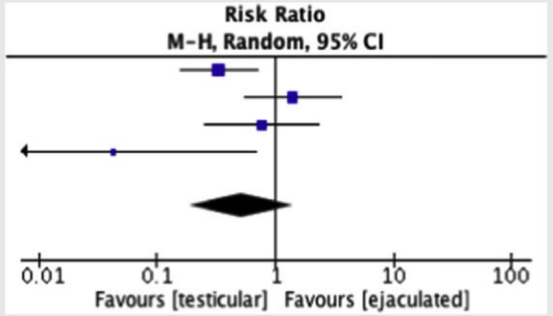
Fertility and Sterility® Vol. 105, No. 6, June 2016 0015-0282/$36.00
http://dx.doi.org/10.1016/j.fertnstert.2016.02.013

- 5 estudos para gestação
- 227 pacientes
- 4.598 ovócitos injetados

Study	Ejaculated Sperm		Testicular sperm		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Ben- Ami 2013	8	68	17	48	33.0%	0.33 [0.16, 071]
Bendikson 2008	9	27	5	21	30.0%	1.40 [0.55, 3.56]
Hauser 2011	4	34	9	59	27.2%	0.77 [0.26, 2.32]
Weissman 2008	0	13	2	2	9.8%	0.04 [0.00, 0.68]
Total (95% CI)		**142**		**130**	**100%**	**0.53 [0.19, 1.42]**
Total events	21		33			

Heterogeneity $Tau^2 = 0.64$, $Chi^2 = 9.21$, df=3, $I^2 = 67\%$

Test for overall effect Z=1.26, (*P*=.21)



Forest plot demonstrating relative risk for pregnancy rates (PRs) with intracytoplasmic sperm injection (ICSI) when using testicular or ejaculated sperm from men with cryptozoospermia.

Abhyankar. ICSI sperm source in cryptozoospermia. Fertil Steril 2016.

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Use of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with cryptozoospermia: a meta-analysis

Nikita Abhyankar, M.B.ChB.,[a] Martin Kathrins, M.D.,[b] and Craig Niederberger, M.D.[a]

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Fertility and Sterility® Vol. 105, No. 6, June 2016 0015-0282/$36.00
http://dx.doi.org/10.1016/j.fertnstert.2016.02.013

- Nossa meta-análise conclui que ***não há diferenças na taxa de fertilização e gestação para homens com criptozoospermia*** ao usar espermatozoide ejaculado versus testicular.

- A literatura existente ***não apoia uma recomendação para homens com criptozoospermia de usar espermatozoide testicular em vez de ejaculado*** para ICSI.

Association of sperm source with miscarriage and take-home baby after ICSI in cryptozoospermia: a meta-analysis of testicular and ejaculated sperm

Volume 6, Issue 6
November 2018
Pages 882-889

[1]F.-Y. Ku, [1,2,3]C.-C. Wu, [4]Y.-W. Hsiao and [5]Y.-N. Kang

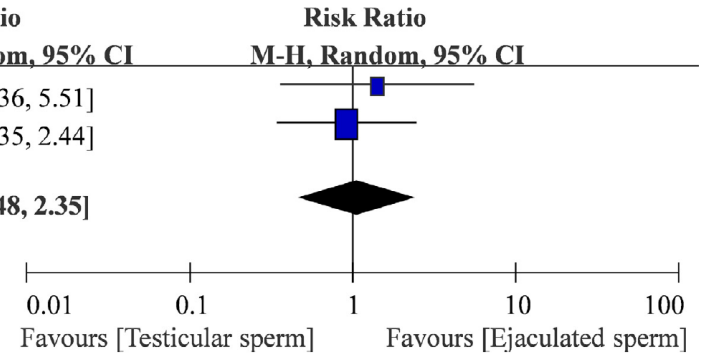
- 2 estudos para abortamento
- 4 estudos para *take home baby*
- 331 pacientes
- 479 ciclos ICSI

Forest plot of meta-analysis of the miscarriage rates.

Study	Testicular sperm Events	Total	Ejaculated sperm Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ben-Ami et al., 2013	6	17	2	8	34.0%	1.41 [0.36, 5.51]
Cui et al., 2016	5	30	10	55	66.0%	0.92 [0.35, 2.44]
Total (95% CI)		**47**		**63**	**100.0%**	**1.06 [0.48, 2.35]**
Total events	11		12			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 1 ($p = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 0.15$ ($p = 0.88$)



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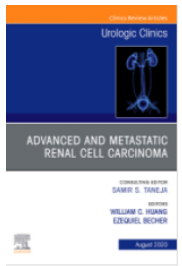
High Sperm DNA Damage
Does Testicular Sperm Make Sense?



Keith Jarvi, MD, FRCSC

Urol Clin N Am 47 (2020) 165–174
https://doi.org/10.1016/j.ucl.2019.12.009

KEYWORDS

• Sperm DNA integrity • In vitro fertilization • Sperm selection • Prospective cohort study
• Live birth rates • Pregnancy rates • Testicular sperm retrieval

KEY POINTS

- High sperm DNA damage increases the risks of pregnancy loss.
- Testicular sperm have less DNA damage than sperm in the ejaculate.
- Using testicular sperm for in vitro fertilization for men with high levels of sperm DNA damage is widely used.
- Presently, there is insufficient evidence to conclude that the use of testicular sperm increases live birth rates compared with ejaculated sperm for men with high levels of sperm DNA damage.
- The use of testicular sperm retrieval for in vitro fertilization to manage men with high sperm DNA damage is not supported by the literature published to date.

DIFFERENCE OF OPINION

Vol. 44 (4): 676-679, July - August, 2018
doi: 10.1590/S1677-5538.IBJU.2018.04.04

Testicular versus ejaculated sperm should be used for intracytoplasmic sperm injection (ICSI) in cases of infertility associated with sperm DNA fragmentation | *Opinion: No*

Mark Sigman [1]

[1] *Department of Urology Brown University and The Miriam Hospitals, RI 02906, EUA*

- A prática testicular recuperação de espermatozoides para casais com SDF elevado e falha FIV/ICSI ***deve ser considerada experimental*** - ensaios controlados randomizados são muito necessários.
- Além disso, ***o potencial risco genético e epigenéticos*** do espermatozoide testicular não deve ser ignorado.

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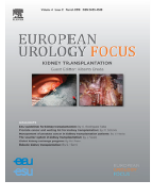
journal homepage: www.europeanurology.com/eufocus



Clinical Consultation Guide – Andrology

European Association of Urology Guidelines Panel on Male Sexual and Reproductive Health: A Clinical Consultation Guide on the Indications for Performing Sperm DNA Fragmentation Testing in Men with Infertility and Testicular Sperm Extraction in Nonazoospermic Men

Tharu Tharakan [a,b], Carlo Bettocchi [c], Joana Carvalho [d], Giovanni Corona [e], Thomas Hugh Jones [f], Ates Kadioglu [g], Juan I. Martínez Salamanca [h], Ege Can Serefoglu [i,j], Paolo Verze [k], Andrea Salonia [l,m,†], Suks Minhas [a,†,],*
on behalf of the EAU Working Panel on Male Sexual Reproductive Health

- O Painel das Diretrizes da EAU sobre Saúde Sexual e Reprodutiva Masculina *não defende o uso clínico de rotina de espermatozoides testiculares em homens não-azoospérmicos com SDF elevado* (TESE-ICSI) fora dos ensaios clínicos.

- Embora os urologistas possam oferecer espermatozoides testiculares em pacientes com alta fragmentação de DNA, *os pacientes devem ser aconselhados quanto aos baixos níveis de evidência para isso* (ou seja, estudos não randomizados).

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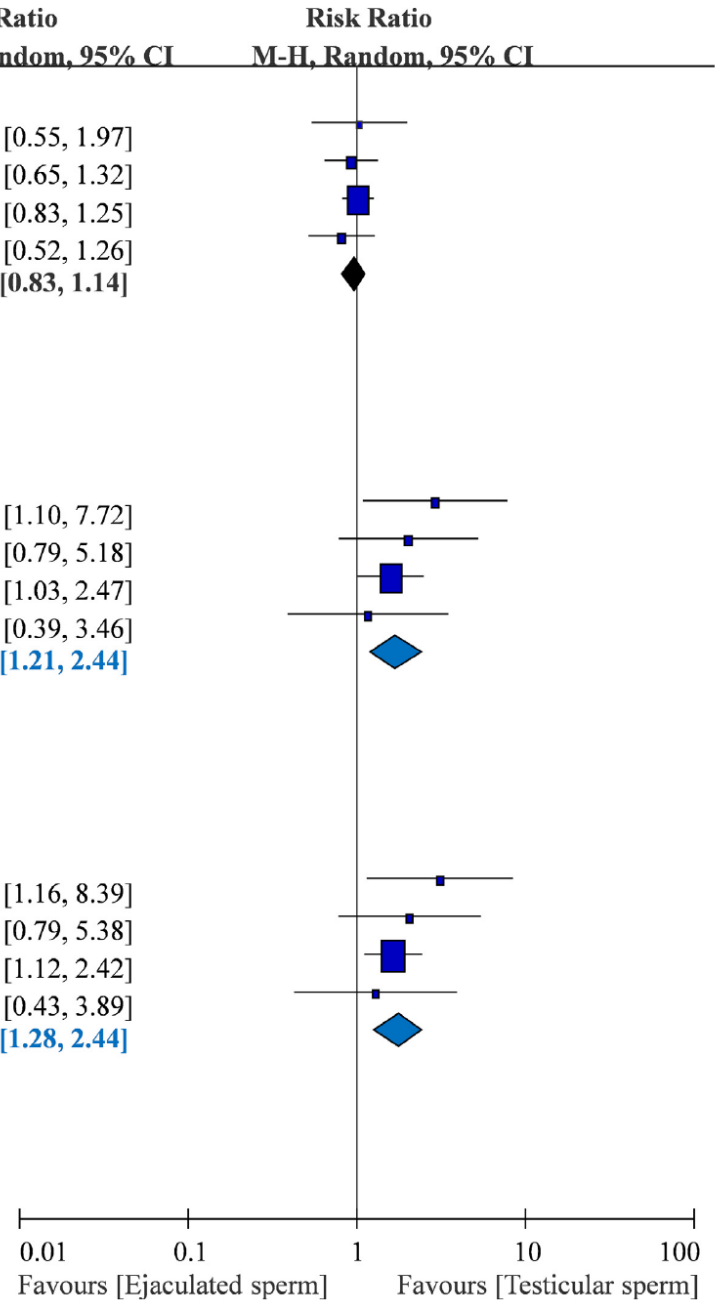
Recommendação: ALTA

Subgroup & Study	Testicular sperm Events	Total	Ejaculated sperm Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Take home baby (By pregnancy)						
Ben-Ami et al., 2013	11	17	5	8	6.1%	1.04 [0.55, 1.97]
Bendikson et al., 2008	8	9	5	5	19.9%	0.93 [0.65, 1.32]
Cui et al., 2016	25	30	45	55	61.0%	1.02 [0.83, 1.25]
Hauser et al., 2011	9	12	4	4	12.9%	0.81 [0.52, 1.26]
Subtotal (95% CI)		**68**		**72**	**100.0%**	**0.97 [0.83, 1.14]**
Total events	53		59			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 3 (p = 0.81); I^2 = 0%						
Test for overall effect: Z = 0.35 (p = 0.72)						
1.2.2 Take home baby (By embryo transfer)						
Ben-Ami et al., 2013	11	40	5	53	12.8%	2.92 [1.10, 7.72]
Bendikson et al., 2008	8	19	5	24	13.7%	2.02 [0.79, 5.18]
Cui et al., 2016	25	113	45	324	63.1%	1.59 [1.03, 2.47]
Hauser et al., 2011	9	54	4	28	10.3%	1.17 [0.39, 3.46]
Subtotal (95% CI)		**226**		**429**	**100.0%**	**1.72 [1.21, 2.44]**
Total events	53		59			
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 3 (p = 0.60); I^2 = 0%						
Test for overall effect: Z = 3.05 (p = 0.002)						
1.2.3 Take home baby (By ICSI cycle)						
Ben-Ami et al., 2013	11	48	5	68	10.5%	3.12 [1.16, 8.39]
Bendikson et al., 2008	8	21	5	27	11.1%	2.06 [0.79, 5.38]
Cui et al., 2016	25	56	45	166	69.9%	1.65 [1.12, 2.42]
Hauser et al., 2011	9	59	4	34	8.5%	1.30 [0.43, 3.89]
Subtotal (95% CI)		**184**		**295**	**100.0%**	**1.77 [1.28, 2.44]**
Total events	53		59			
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 3 (p = 0.61); I^2 = 0%						
Test for overall effect: Z = 3.48 (p = 0.0005)						



Test for subgroup differences: Chi² = 16.36, df = 2 (p = 0.0003), I^2 = 87.8%

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ORIGINAL ARTICLE: ANDROLOGY

Reproductive outcomes of testicular versus ejaculated sperm for intracytoplasmic sperm injection among men with high levels of DNA fragmentation in semen: systematic review and meta-analysis

Sandro C. Esteves, M.D., Ph.D.,[a] Matheus Roque, M.D.,[b] Cara K. Bradley, Ph.D.,[c] and Nicolás Garrido, Ph.D.[d]
[a] ANDROFERT, Center for Male Reproduction, São Paulo, Brazil; [b] ORIGEN, Center for Reproductive Medicine, Rio de Janeiro, Brazil; [c] Genea, Sydney, New South Wales, Australia; and [d] IVI Foundation, Valencia, Spain

Fertility and Sterility® Vol. 108, No. 3, September 2017

Potential confounders

- Cinco estudos envolvendo 143 pacientes apresentaram taxas de SDF pareadas para espermatozoides testiculares e ejaculados, revelando SDF mais baixo em espermatozoides testiculares (DM 24,58%).

Os limites do SDF foram 7% (um estudo), 15% (um estudo) e 30% (três estudos).

- Quatro estudos envolvendo 507 ciclos e 3.840 ovócitos relataram resultados clínicos de Testi-ICSI e Ejac-ICSI.

O SDF alto foi definido de acordo com os limiares utilizados em cada estudo: 15% (um estudo), 29% (um estudo) e 30% (dois estudos).

Review Article
Male reproductive health and infertility

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World J Mens Health Published online Jun 25, 2020
https://doi.org/10.5534/wjmh.200084

The World Journal of MEN's HEALTH

The Use of Testicular Sperm for Intracytoplasmic Sperm Injection in Patients with High Sperm DNA Damage: A Systematic Review

Rafael F. Ambar[1,2,3], Ashok Agarwal[1], Ahmad Majzoub[1,4,5], Sarah Vij[6], Nicholas N. Tadros[7], Chak-Lam Cho[8,9], Neel Parekh[6], Edson Borges Jr.[10], Sidney Glina[11]

[1]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA, [2]Department of Urology, Centro Universitario em Saude do ABC/Andrology Group at Ideia Fertil Institute of Human Reproduction, Santo André, [3]Hope Clinic–Human Reproduction, São Paulo, Brazil, [4]Department of Urology, Hamad Medical Corporation, [5]Weill Cornell Medicine-Qatar, Doha, Qatar, [6]Department of Urology, Cleveland Clinic, Cleveland, OH, [7]Division of Urology, Southern Illinois University, Springfield, IL, USA, [8]Department of Surgery, Union Hospital, [9]S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, [10]Fertility Medical Group, Sapientiae Institute, São Paulo, [11]Department of Urology, Centro Universitario em Saude do ABC, Santo André, Brazil

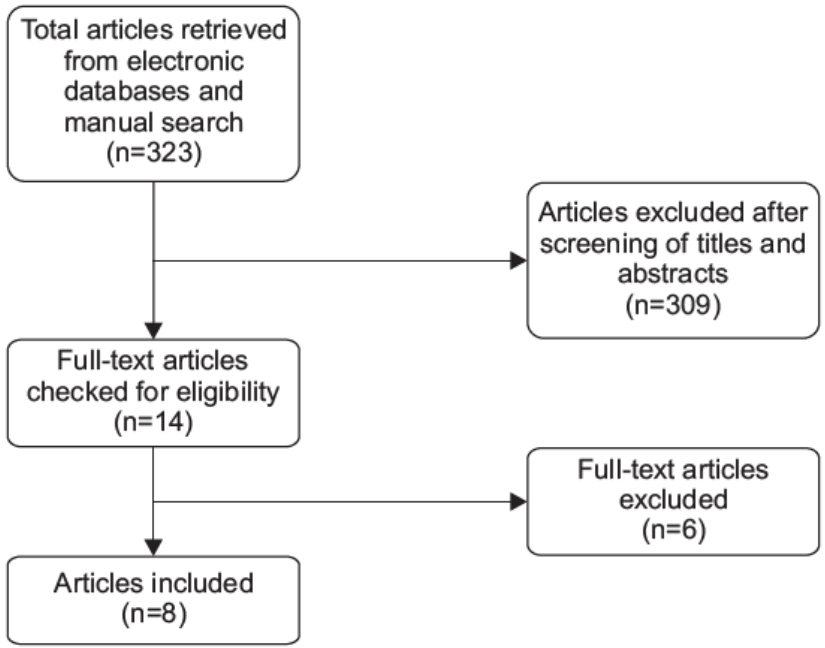

Fig. 1. Flow diagram of literature review and study selection.

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Table 1. Evidence on the use of testicular *vs.* ejaculated sperm

Study reference	Study population	Study design	Subject (n)	SDF assay	Fertilization rate	Pregnancy rate	Miscarriage rate	Live birth rate	Quality of evidence[a]
Arafa et al [8] (2018)	- SDF>30% after treatment - Previous ICSI failure	Case-crossover study	T-ICSI: 36 Ej-ICSI: 36	Halo Sperm	T-ICSI: 47.8% Ej-ICSI: 46.4% (NS)	T-ICSI: 38.89% Ej-ICSI: 13.5% (p <0.0001)	T-ICSI (n): 0 Ej-ICSI (n): 2 (p<0.0001)	T-ICSI (n): 17 Ej-ICSI (n): 3 (p<0.0001)	++, low
Herrero et al [7] (2019)	- 2 previous ICSI failures - Fresh sperm	Prospective study	- T-ICSI and TUNEL: 50 - Ej-ICS and TUNEL: 46 - T-ICSI and SCSA: 52 - Ej-ICSI and SCSA: 44	SCSA/TUNEL	T-ICSI: 62.7% Ej-ICSI: 63.6% (NS)	T-ICSI: 27.9% Ej-ICSI: 10% (p<0.025)	T-ICSI: 25% Ej-ICSI: 41.7% (p<0.05)	Cumulative live birth rate: T-ICSI: 23.4% Ej-ICSI:11.4% (p<0.05)	+, low
Zhang et al [9] (2019)	- DFI>30% - Oligozoospermia or normozoospermia	Prospective study	T-ICSI: 61 Ej-ICSI: 41	SCSA	T-ICSI: 70.4% Ej-ICSI: 75% (NS)	T-ICSI: 36% Ej-ICSI: 14.6% (p=0.017)	T-ICSI: 0% Ej-ICSI: 3.3% (p=0.159)	T-ICSI: 41% Ej-ICSI: 9.8% (p=0.001)	++, low
Alharbi et al [10] (2019)	- At least 1 failed ICSI cycle - SDF 15%–30% and SDF >30% - Only fresh embryo transfer	Retrospective	- T-ICSI: 37 - Ej-ICSI: 56 (second ICSI, SDF unknown) - Ej-ICSI-high SDF (15%–30% or >30% - at least 1 failed ICSI): 31	SCSA	NR	T-ICSI: 48.6% Ej-ICSI: 48.2% Ej-ICSI-high SDF: 38.7% (NS for both)	T-ICSI: 11.1% Ej-ICSI: 11.1% Ej-ICSI-high SDF: 38.7% (NS for both)	T-ICSI: 36.4% Ej-ICSI: 33.3% Ej-ICSI-high SDF: 30% (NS for both)	+, very low

SDF: sperm DNA fragmentation, ICSI: intracytoplasmic sperm injection, DFI: DNA fragmentation index, T-ICSI: ICSI using testicular sperm, Ej-ICSI: ICSI using ejaculated sperm, TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling, SCSA: sperm chromatin structure assay, SCIT: sperm chromatin integrity test, NS: not significant, NR: not reported.

[a]Extract from Guyatt et al's guideline [12].

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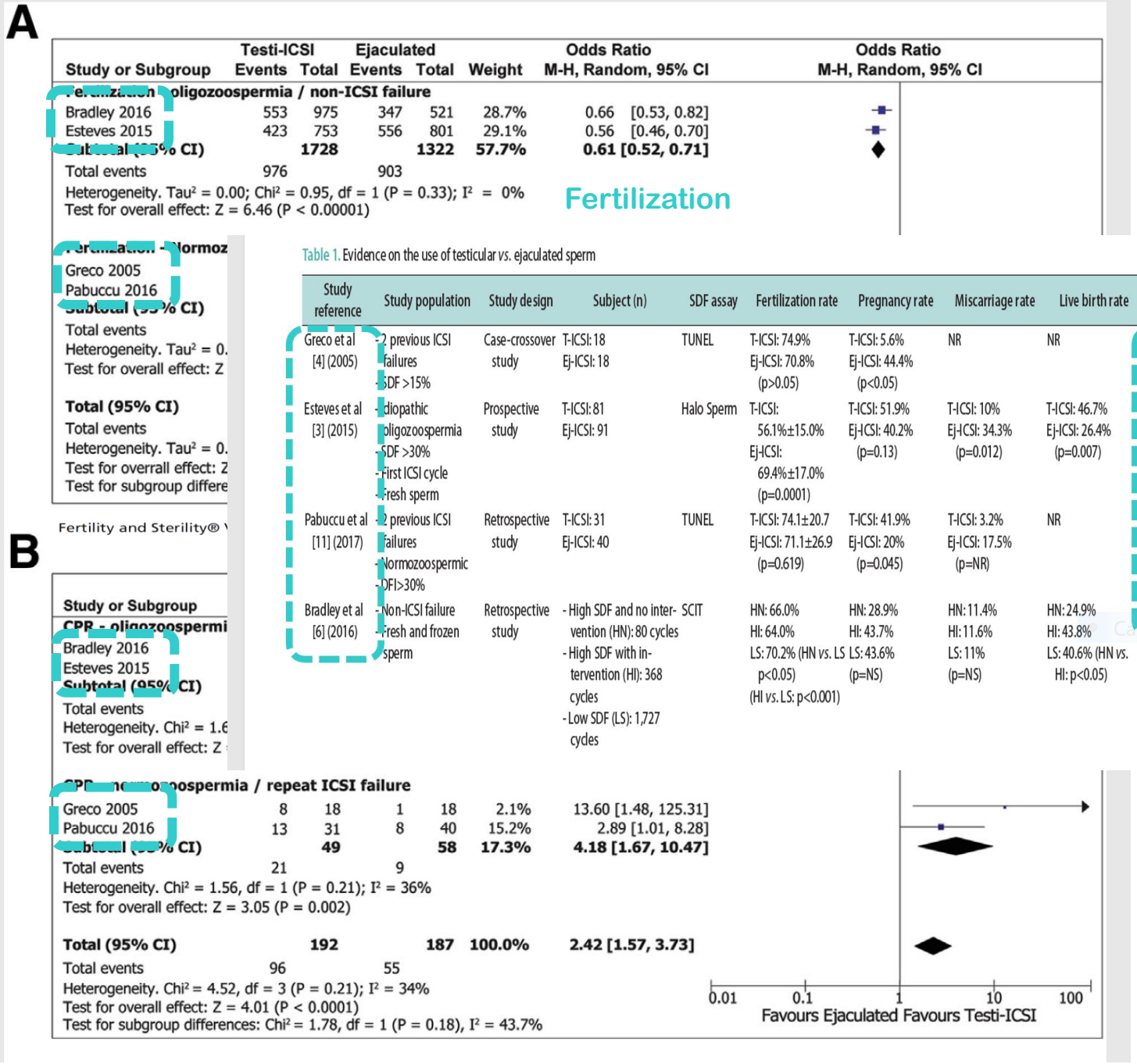
Table 1. Evidence on the use of testicular *vs.* ejaculated sperm

Study reference	Study population	Study design	Subject (n)	SDF assay	Fertilization rate	Pregnancy rate	Miscarriage rate	Live birth rate	Quality of evidence[a]
Greco et al [4] (2005)	- ≥2 previous ICSI failures - SDF >15%	Case-crossover study	T-ICSI: 18 Ej-ICSI: 18	TUNEL	T-ICSI: 74.9% Ej-ICSI: 70.8% (p>0.05)	T-ICSI: 5.6% Ej-ICSI: 44.4% (p<0.05)	NR	NR	+, very low
Esteves et al [3] (2015)	- Idiopathic oligozoospermia - SDF >30% - First ICSI cycle - Fresh sperm	Prospective study	T-ICSI: 81 Ej-ICSI: 91	Halo Sperm	T-ICSI: 56.1%±15.0% Ej-ICSI: 69.4%±17.0% (p=0.0001)	T-ICSI: 51.9% Ej-ICSI: 40.2% (p=0.13)	T-ICSI: 10% Ej-ICSI: 34.3% (p=0.012)	T-ICSI: 46.7% Ej-ICSI: 26.4% (p=0.007)	+++, moderate
Pabuccu et al [11] (2017)	- ≥2 previous ICSI failures - Normozoospermic - DFI>30%	Retrospective study	T-ICSI: 31 Ej-ICSI: 40	TUNEL	T-ICSI: 74.1±20.7 Ej-ICSI: 71.1±26.9 (p=0.619)	T-ICSI: 41.9% Ej-ICSI: 20% (p=0.045)	T-ICSI: 3.2% Ej-ICSI: 17.5% (p=NR)	NR	+, very low
Bradley et al [6] (2016)	- Non-ICSI failure - Fresh and frozen sperm	Retrospective study	- High SDF and no intervention (HN): 80 cycles - High SDF with intervention (HI): 368 cycles - Low SDF (LS): 1,727 cycles	SCIT	HN: 66.0% HI: 64.0% LS: 70.2% (HN *vs.* LS p<0.05) (HI *vs.* LS: p<0.001)	HN: 28.9% HI: 43.7% LS: 43.6% (p=NS)	HN: 11.4% HI: 11.6% LS: 11% (p=NS)	HN: 24.9% HI: 43.8% LS: 40.6% (HN *vs.* HI: p<0.05)	+, very low



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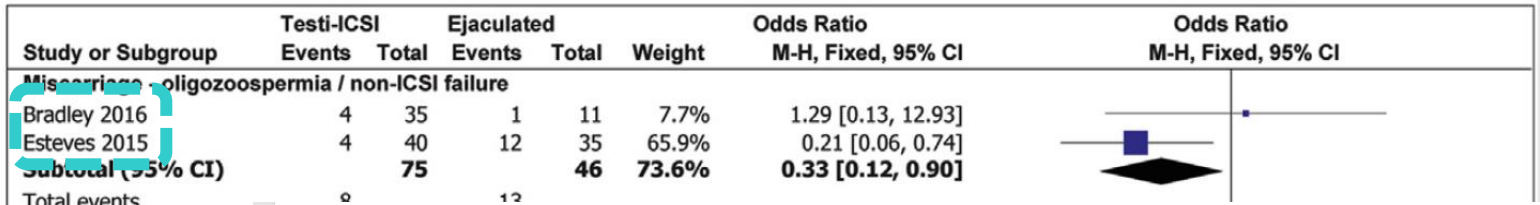

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Esteves et al [3] (2015)	- Idiopathic oligozoospermia - SDF >30% - First ICSI cycle - Fresh sperm	Prospective study	T-ICSI: 81 Ej-ICSI: 91	Halo Sperm	T-ICSI: 56.1%±15.0% Ej-ICSI: 69.4%±17.0% (p=0.0001)	T-ICSI: 51.9% Ej-ICSI: 40.2% (p=0.13)	T-ICSI: 10% Ej-ICSI: 34.3% (p=0.012)	T-ICSI: 46.7% Ej-ICSI: 26.4% (p=0.007)	+++, moderate
Pabuccu et al [11] (2017)	- 2 previous ICSI failures - Normozoospermic - DFI>30%	Retrospective study	T-ICSI: 31 Ej-ICSI: 40	TUNEL	T-ICSI: 74.1±20.7 Ej-ICSI: 71.1±26.9 (p=0.619)	T-ICSI: 41.9% Ej-ICSI: 20% (p=0.045)	T-ICSI: 3.2% Ej-ICSI: 17.5% (p=NR)	NR	+, very low
Bradley et al [6] (2016)	- Non-ICSI failure - Fresh and frozen sperm	Retrospective study	- High SDF and no intervention (HN): 80 cycles - High SDF with intervention (HI): 368 cycles - Low SDF (LS): 1,727 cycles	SCIT	HN: 66.0% HI: 64.0% LS: 70.2% (HN *vs.* LS p<0.05) (HI *vs.* LS: p<0.001)	HN: 28.9% HI: 43.7% LS: 43.6% (p=NS)	HN: 11.4% HI: 11.6% LS: 11% (p=NS)	HN: 24.9% HI: 43.8% LS: 40.6% (HN *vs.* HI: p<0.05)	+, very low

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The World Journal of MEN's HEALTH

Rafael F. Amb

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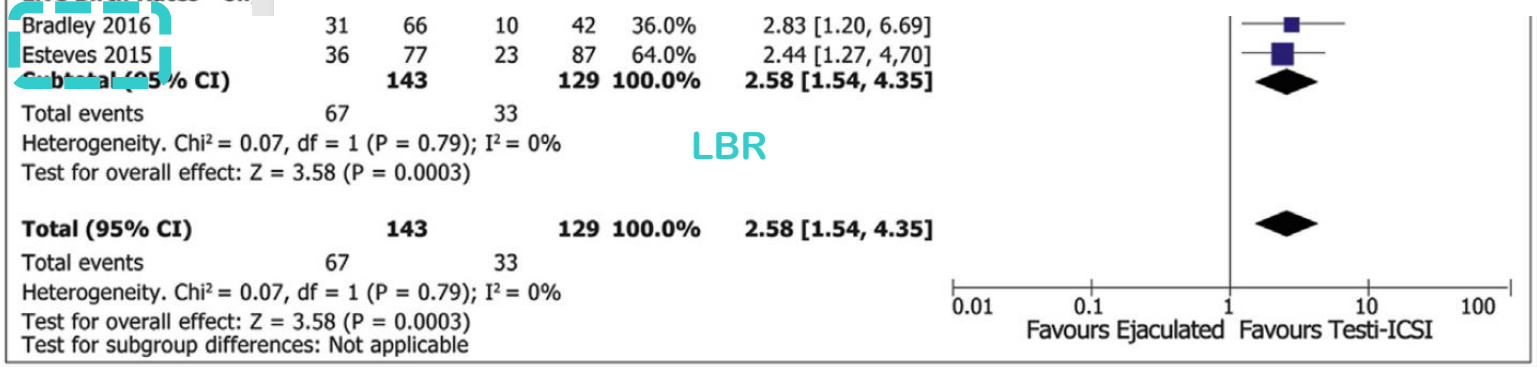

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Review Article
Male reproductive health and infertility
pISSN: 2287-4208 / eISSN: 2287-4690
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https://doi.org/10.5534/wjmh.200084

The World Journal of MEN's HEALTH

The Use of Testicular Sperm for Intracytoplasmic Sperm Injection in Patients with High Sperm DNA Damage: A Systematic Review

Rafael F. Ambar[1,2,3], Ashok Agarwal[1], Ahmad Majzoub[1,4,5], Sarah Vij[6], Nicholas N. Tadros[7], Chak-Lam Cho[8,9], Neel Parekh[6], Edson Borges Jr.[10], Sidney Glina[11]

[1]American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA, [2]Department of Urology, Centro Universitario em Saude do ABC/Andrology Group at Ideia Fertil Institute of Human Reproduction, Santo André, [3]Hope Clinic–Human Reproduction, São Paulo, Brazil, [4]Department of Urology, Hamad Medical Corporation, [5]Weill Cornell Medicine-Qatar, Doha, Qatar, [6]Department of Urology, Cleveland Clinic, Cleveland, OH, [7]Division of Urology, Southern Illinois University, Springfield, IL, USA, [8]Department of Surgery, Union Hospital, [9]S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, [10]Fertility Medical Group, Sapientiae Institute, São Paulo, [11]Department of Urology, Centro Universitario em Saude do ABC, Santo André, Brazil

- É importante enfatizar que a maioria dos artigos publicados sobre o uso de espermatozoides testiculares em pacientes com SDF elevada consiste em pequenas coortes ou séries de casos, comparando diferentes populações de pacientes.

- Além disso, vários desses estudos carecem de grupos de controle adequados, uma avaliação adequada de possíveis fatores femininos e, mais importante, alguns não relatam taxas de nascidos vivos.

- Esses estudos também não levam em consideração os custos e riscos mais elevados envolvidos na coleta e no uso de espermatozoides testiculares.

frontiers in Cell and Developmental Biology

REVIEW
published: 09 October 2019
doi: 10.3389/fcell.2019.00215

Paternal Contributions to Offspring Health: Role of Sperm Small RNAs in Intergenerational Transmission of Epigenetic Information

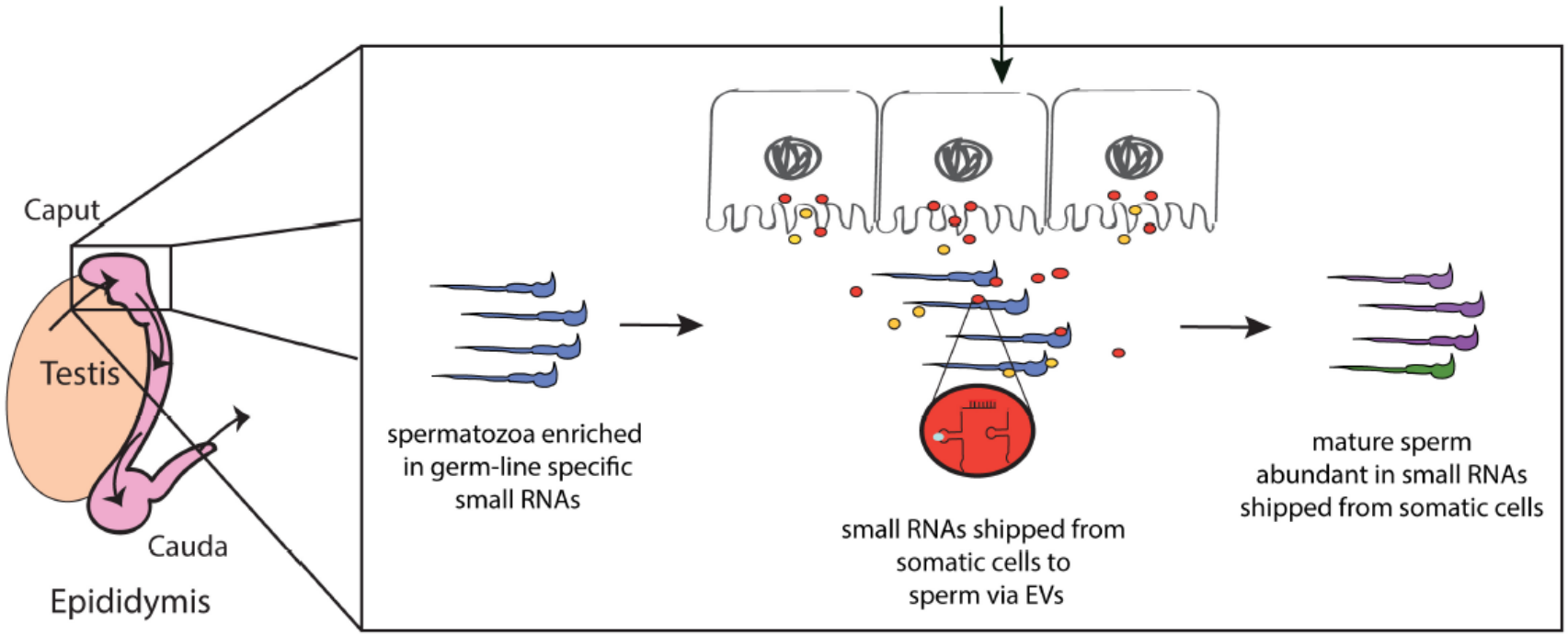
*Upasna Sharma**

Department of Molecular, Cell and Developmental Biology, University of California, Santa Cruz, Santa Cruz, CA, United States

October 2019 | Volume 7 | Article 215

Volume 7, Issue 5
Special thematic issue on the Epididymis
September 2019
Pages 741-747

O epidídimo pode servir como um órgão sensor do ambiente e transmitir essas informações (na forma de pequenos RNAs) para o espermatozóide em maturação e, portanto, para a descendência



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Espermatozoide testicular x ejaculado

- Menor eficiência na fertilização, desenvolvimento embrionário, implantação e gestação a termo (Rubio et al., 2001; Chatziparasidou *et al.*, 2015; Ramasamy *et al.,* 2015).
- Maiores taxas de aneuploidia (Bernardini et al., 2000; Rodrigo *et al.*, 2004; Gianaroli et al.,2005; Moskovtsev *et al.,* 2012; Vozdova *et al.*, 2012).
- Perda gestacional ou falha recorrente de sucesso em FIV/ICSI: etiologia bastante controversa, 50% das vezes sem diagnóstico, com possibilidade de sucesso na continuidade do tratamento (N Engl J Med 2012;366:2483–91).

Complicações operatórias

- **Aspiração por agulha fina**: com hemorragia testicular (Friedler et al., 1997), alterações inflamatórias transitórias ou hematomas com duração de até 6 meses de pós-operatório em até 80% pacientes, ou desvascularização do testículo (Schlegel e Su,1997).

- **TESE convencional:** hipogonadismo requerendo TRH em 2,5% dos pacientes, atrofia testicular em 25% dos pacientes e alterações testiculares crônicas em 23% dos pacientes (Okada et al., 2002).

- **microTESE:** alterações inflamatórias e endocrinológicas, com duração de até 12 meses, a fibrose e atrofia testicular (Deruyver et al., 2014).

Considerações

- Metanálises: vários testes de *fragDNA* (funções diferentes), sem grupo controle.
- Outras técnicas para a seleção de espermatozoides sem *fragDNA* no ICSI.
- *fragDNA* espermático: única função espermática a ser considerada?? (função epigenética e hormonal dos epidídimos).

Volume 7, Issue 5
Special thematic issue on the Epididymis
September 2019
Pages 741-747

- Recuperação de espermatozoides testiculares: procedimento cirúrgico não isento de complicações!!
- *primum non nocere !!*

Reproductive BioMedicine Online (2015) 30, 120–127

www.sciencedirect.com
www.rbmonline.com

ELSEVIER

REVIEW

The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis

A Osman *, H Alsomait, S Seshadri, T El-Toukhy, Y Khalaf

Assisted Conception Unit, Guys Hospital, Great Maze Pond, SE1 9RT, UK

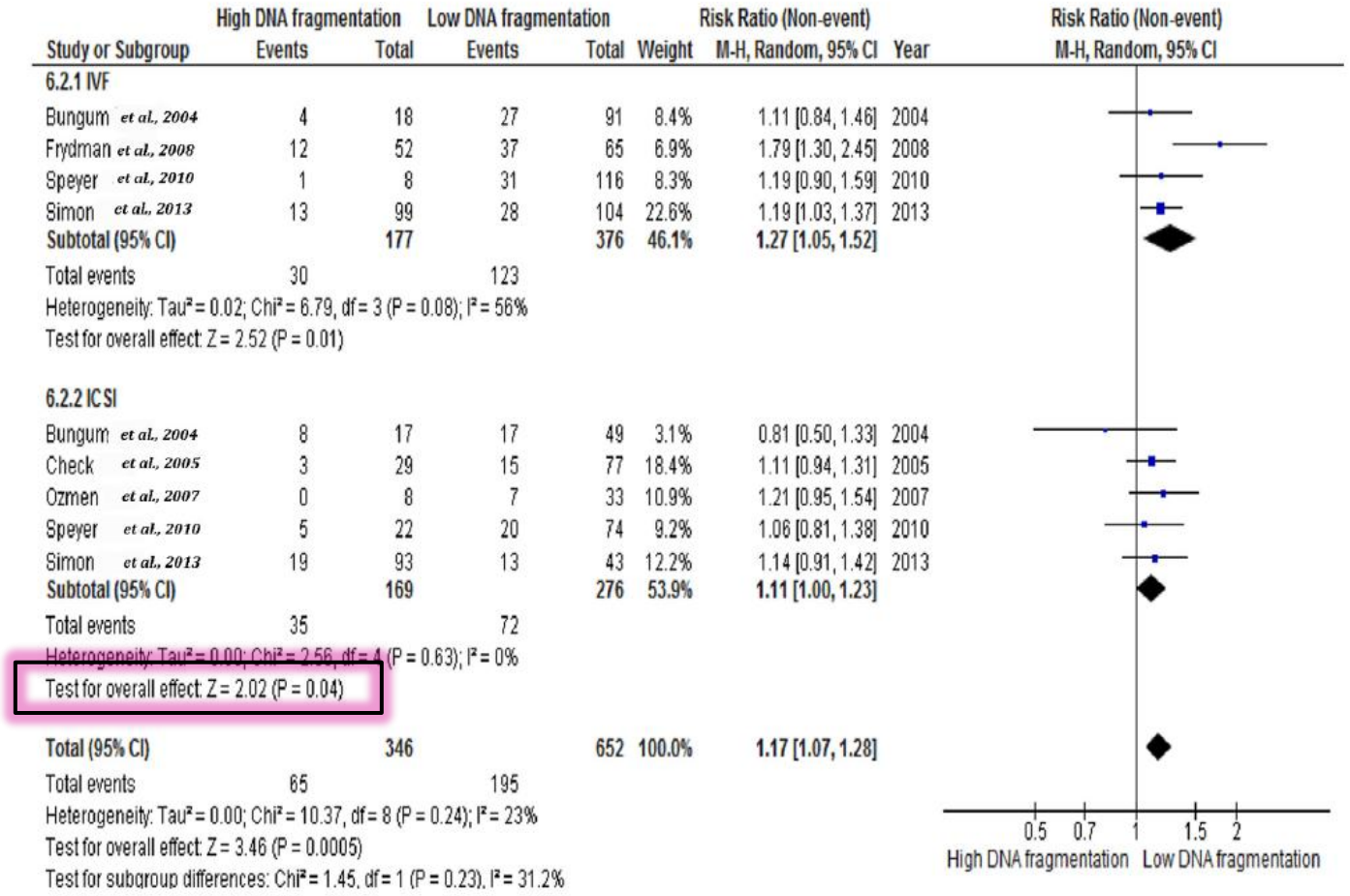

Figure 2 Live birth rate in high and low sperm DNA fragmentation groups. ICSI = intracytoplasmic sperm injection.

Sperm DNA fragmentation is correlated with poor embryo development, lower implantation rate, and higher miscarriage rate in reproductive cycles of non–male factor infertility

Edson Borges Jr., M.D., Ph.D.,[a,b] Bianca Ferrarini Zanetti, Ph.D.,[a,b] Amanda Souza Setti, M.Sc.,[a,b] Daniela Paes de Almeida Ferreira Braga, Ph.D.,[a,b] Rodrigo Rosa Provenza, B.Sc.,[a] and Assumpto Iaconelli Jr., M.D.[a,b]

[a] Fertility Medical Group and [b] Instituto Sapientiae, Centro de Estudos e Pesquisa em Reprodução Humana Assistida, São Paulo, Brazil

https://doi.org/10.1016/j.fertnstert.2019.04.029

- 475 ciclos de ICSI / ausência de fator masculino
- fragDNA espermático ≥ 30% x < 30%
- Estudo coorte prospectivo

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Effect of SDF on laboratory and clinical outcomes.

Variable	< 30% SDF (n = 433)	≥30% SDF (n = 42)	*P* value
Laboratory outcomes[a]			
Fertilization rate	90.10 ± 3.50	85.67 ± 1.03	.226
Normal cleavage speed rate	72.16 ± 1.30	61.56 ± 4.40	.010
High-quality embryos at day 3 rate	36.47 ± 1.51	23.89 ± 5.51	.021
Blastocyst rate	56.25 ± 2.01	39.01 ± 1.40	.016
Blastocyst quality rate	30.54 ± 2.27	11.32 ± 7.72	< .001
Clinical outcomes[b]			
Implantation rate	46.09 ± 0.55	33.21 ± 1.96	< .001
Chemical pregnancy rate	34.99	33.11	.940
Clinical pregnancy rate	32.42	30.33	.774
Miscarriage rate	17.8	39.9	.018

[a] Adjusted for maternal age, maternal BMI, total FSH dose, number of retrieved oocytes, and paternal age.
[b] Adjusted for maternal age, maternal BMI, total FSH dose, number of retrieved oocytes, paternal age, number of transferred embryos, endometrial thickness.

Borges. Sperm DNA fragmentation and ICSI outcomes. Fertil Steril 2019.

Oocyte ability to repair sperm DNA fragmentation: the impact of maternal age on intracytoplasmic sperm injection outcomes

Amanda Souza Setti, M.Sc.,[a,b] Daniela Paes de Almeida Ferreira Braga, Ph.D.,[a,b] Rodrigo Rosa Provenza, B.Sc.,[a] Assumpto Iaconelli Jr., M.D.,[a,b] and Edson Borges Jr., Ph.D.[a,b]

[a] Fertility Medical Group, São Paulo; and [b] Sapientiae Institute–Centro de Estudos e Pesquisa em Reprodução Humana Assistida, São Paulo, Brazil

Fertility and Sterility® Vol. 116, No. 1, July 2021

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Oocyte ability to repair sperm DNA fragmentation:
The effect of maternal age on ICSI outcomes

GZLM results for the association between SDF and ICSI outcomes according to maternal age ranges (n=540)

	≤36 years old (n=285)			37-40 years old (n=147)			>40 years old (n=108)		
	≤30% SDF (n=171)	>30% SDF (n=114)	p	≤30% SDF (n=99)	>30% SDF (n=48)	p	≤30% SDF (n=64)	>30% SDF (n=44)	p
Fertilization (%)	89.1	89.5	0.645	79.4	83.4	0.356	78.3	76.5	0.745
High-quality D3-embryos (%)	42.6	42.5	0.977	38.1	36.0	0.676	54.4	33.1	**0.005**
Blastocyst development (%)	85.3	84.2	0.645	42.6	51.6	0.224	49.6	30.2	**0.035**
Embryos transferred (n)	1.2 ± 0.2	2.0 ± 0.3	0.843	1.1 ± 0.1	1.1 ± 0.2	0.473	1.1 ± 0.1	1.2 ± 0.1	0.789

Values are mean ± standard error, unless otherwise noted. GZLM – generalized linear model, ICSI – intracytoplasmic sperm injection, SDF – sperm DNA fragmentation, COS – controlled ovarian stimulation, FSH – follicle-stimulating hormone, IU – international unit.

Oocyte ability to repair sperm DNA fragmentation:
The effect of maternal age on ICSI outcomes

Association between SDF and clinical ICSI outcomes for female age ≤36 years old

Female age	Response variable	SDF index		
≤36 years old (n=285)		≤30% SDF	>30% SDF	p
	Pregnancy (%)	40.0	39.1	0.840
	Implantation (%)	42.3	41.5	0.880
	Miscarriage (%)	9.3	11.1	0.665

Oocyte ability to repair sperm DNA fragmentation:
The effect of maternal age on ICSI outcomes

Association between SDF and clinical ICSI outcomes for female age between 37- 40 years old

Female age	Response variable	SDF index		
		≤30% SDF	>30% SDF	p
37-40 years old (n=147)	Pregnancy (%)	27.7	28.6	0.781
	Implantation (%)	28.9	30.6	0.750
	Miscarriage (%)	31.5	22.2	0.875

Oocyte ability to repair sperm DNA fragmentation:
The effect of maternal age on ICSI outcomes

Association between SDF and clinical ICSI outcomes for female age > 40 years old

Female age	Response variable	SDF index		
		≤30% SDF	>30% SDF	p
>40 years old (n=108)	Pregnancy (%)	20.0	7.7	**0.040**
	Implantation (%)	19.7	11.9	**0.043**
	Miscarriage (%)	12.5	100	**<0.001**

Oocyte ability to repair sperm DNA fragmentation: the impact of maternal age on intracytoplasmic sperm injection outcomes

Amanda Souza Setti, M.Sc.,[a,b] Daniela Paes de Almeida Ferreira Braga, Ph.D.,[a,b] Rodrigo Rosa Provenza, B.Sc.,[a] Assumpto Iaconelli Jr., M.D.,[a,b] and Edson Borges Jr., Ph.D.[a,b]

[a] Fertility Medical Group, São Paulo; and [b] Sapientiae Institute–Centro de Estudos e Pesquisa em Reprodução Humana Assistida, São Paulo, Brazil

Ovócitos mais velhos, quando injetados com espermatozoides derivados de amostras ***com alto índice de SDF***, desenvolvem-se em embriões de má qualidade que levam, consequentemente, a ***menores taxas de implantação e gravidez e a maiores taxas de aborto espontâneo***, em ciclos de injeção intracitoplasmática de espermatozoides de mulheres com idade materna avançada.

Received: 22 March 2022 | Revised: 21 March 2023 | Accepted: 27 March 2023

DOI: 10.1111/andr.13435

ANDROLOGY WILEY

ORIGINAL ARTICLE

The effect of sperm DNA fragmentation on ICSI outcomes depending on oocyte quality

Daniela Paes Almeida Ferreira Braga[1] | Amanda Setti[1] | Christina Morishima[2] | Rodrigo R. Provenza[1] | Assumpto Iaconelli Jr.[1] | Edson Borges Jr.[1]

- Coorte 2.942 ovócitos fertilizados de 525 ciclos de ICSI.
- Baixa fragmentação <30%de fragmentação do DNA do espermatozoide, n = 1468
- Alta fragmentação ≥30% de fragmentação, n = 486.
- Ovócitos maduros foram examinados para dismorfismos intracitoplasmática e extracitoplasmática

- ***Significant increases in the rates of fertilization, high-quality embryo, implantation, and pregnancy were noted for cycles with <30% sperm DNA fragmentation*** than cycles with ≥30% sperm DNA fragmentation (regardless of the presence of oocyte dimorphisms).

- ***The presence of dimorphisms significantly impacted laboratory and clinical outcomes***.

- ***The lowest fertilization and high-quality embryo rates*** were observed when a high sperm DNA fragmentation index was associated with the presence of dark cytoplasm, vacuoles, resistant membrane, and non-resistant membrane.

- ***The lowest implantation and pregnancy rates*** were observed when a high sperm DNA fragmentation index was associated with the presence of vacuoles, defective perivitelline space, and fragmented polar body.

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Andrology. 2023;11:1682–1693

- ***The effect of sperm DNA fragmentation on miscarriage rates*** was significantly influenced by the presence of centrally located cytoplasmic granulation, a defective perivitelline space and non-resistant membrane.

Conclusion: A high sperm DNA fragmentation index increases the likelihood of miscarriage in intracytoplasmic sperm injection cycles, an effect that may potentially be magnified by the presence of oocyte dysmorphisms.

Andrology. 2023;11:1682–1693

COCHRANE SUMMARIES
Independent high-quality evidence for health care decision making

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)

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Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD007411.

Antioxidants for male subfertility (Review)

Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG

- 61 estudos com uma população total de 6.264 homens subférteis, com idades entre 18 e 65 anos, combinaram 18 diferentes antioxidantes orais.

- **Nascidos vivos:** ***OR 1.79***, 95% CI 1.20 to 2.67, P = 0.005, 7 RCTs, 750 homens

- **Gestação clínica:** ***OR 2.97***, 95% CI 1.91 to 4.63, P < 0.0001, 11 RCTs, 786 homens

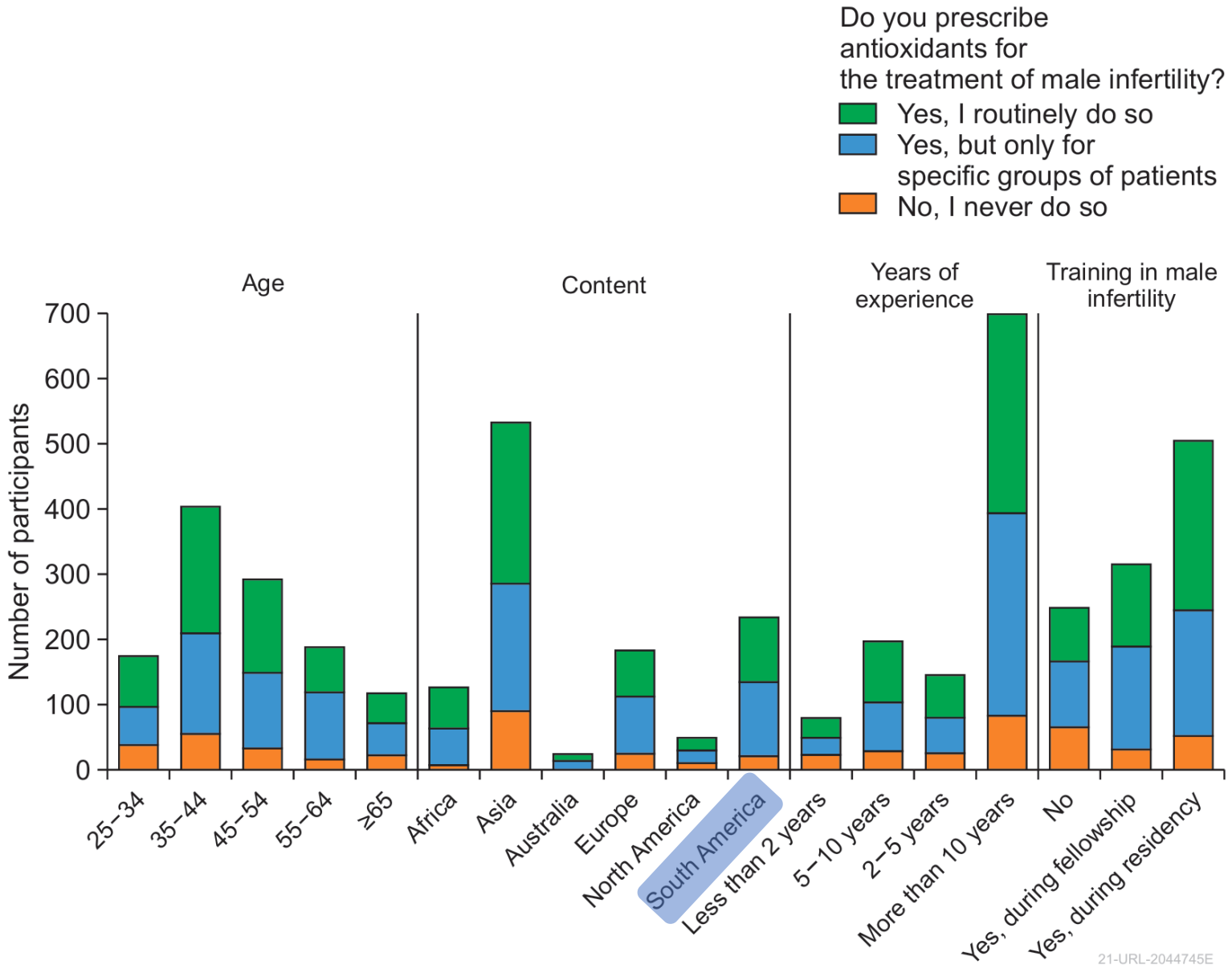
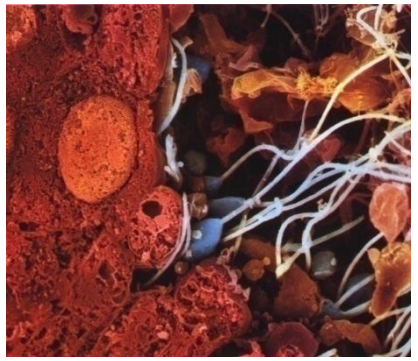


Fig. 5. Antioxidant prescription based on the age, geographic origin, experience of the participants and their training in male infertility.

Antioxidantes orais – como prescrever

- Vitamina C: 500 mg/dia
- Vitamina E: 400 mg/dia
- Ácido fólico (folato): 2-5 mg/dia
- Zinco: 25 mg/dia
- Selênio: 26 mg/dia
- L-carnitina: 300 mg/dia



65 dias – tempo da espermatogênese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O seu esperma
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ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

ORIGINAL ARTICLE

Correspondence:
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E-mail: science@sapientiae.org.br

Keywords:
Ejaculatory abstinence, ICSI, semen quality, sperm DNA fragmentation

Received: 13-Jul-2018
Revised: 4-Oct-2018
Accepted: 7-Nov-2018

doi: 10.1111/andr.12572

Revisiting the impact of ejaculatory abstinence on semen quality and intracytoplasmic sperm injection outcomes

[1,2]E. Borges Jr., [1,2]D. P. A. F. Braga, [2]B. F. Zanetti, [1,2]A. Iaconelli Jr. and [1,2]A. S. Setti

[1]Fertility Medical Group, Sao Paulo, Brazil, and [2]Sapientiae Institute, Sao Paulo, Brazil

Linear model analysis of the association between sperm parameters and EA length (n = 818)

SEMEN PARAMETER	R	SLOPE	R^2 (%)	P-VALUE
Semen volume (mL)	0.1405	1.62102	5.28	<0.001
Sperm count ($x10^6$/mL)	3.1261	52.2206	2.59	<0.001
Total sperm count ($x10^6$)	18.941	170.650	8.37	<0.001
Total sperm motility (%)	-0.3355	19.0885	0.23	0.212
Progressive sperm motility (%)	-0.1895	19.1802	0.07	0.483
TMSC ($x10^6$)	9.6396	102.629	6.14	<0.001
Morphology (%)	0.0227	1.29926	0.23	0.215
SDF (%)	0.5355	9.34201	2.57	<0.001

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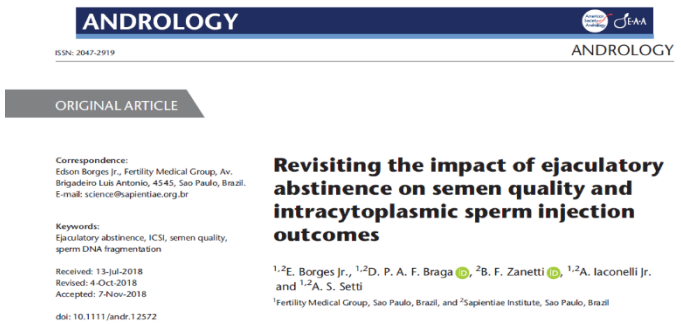

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[1]Fertility Medical Group, Sao Paulo, Brazil, and [2]Sapientiae Institute, Sao Paulo, Brazil

Abstinência ejaculatória ≤ 4 dias:

- Frag DNA espermático significativamente menor, maiores taxas de fertilização, embriões de alta qualidade no dia 3, desenvolvimento a blastocisto, implantação e gestação quandocomparados ao grupo de abstinência ejaculatória > 4 dias.

- Taxas de implantação significativamente maiores e taxas de gestação tendendo a serem maiores com ***um dia de abstinência ejaculatória***, comparado a 2 – 4 de abstinência ejaculatória.

Received: 7 March 2018 | Revised: 4 June 2018 | Accepted: 12 June 2018

DOI: 10.1111/and.13090

Check for updates

ORIGINAL ARTICLE

WILEY ANDROLOGIA

Paternal lifestyle factors in relation to semen quality and in vitro reproductive outcomes

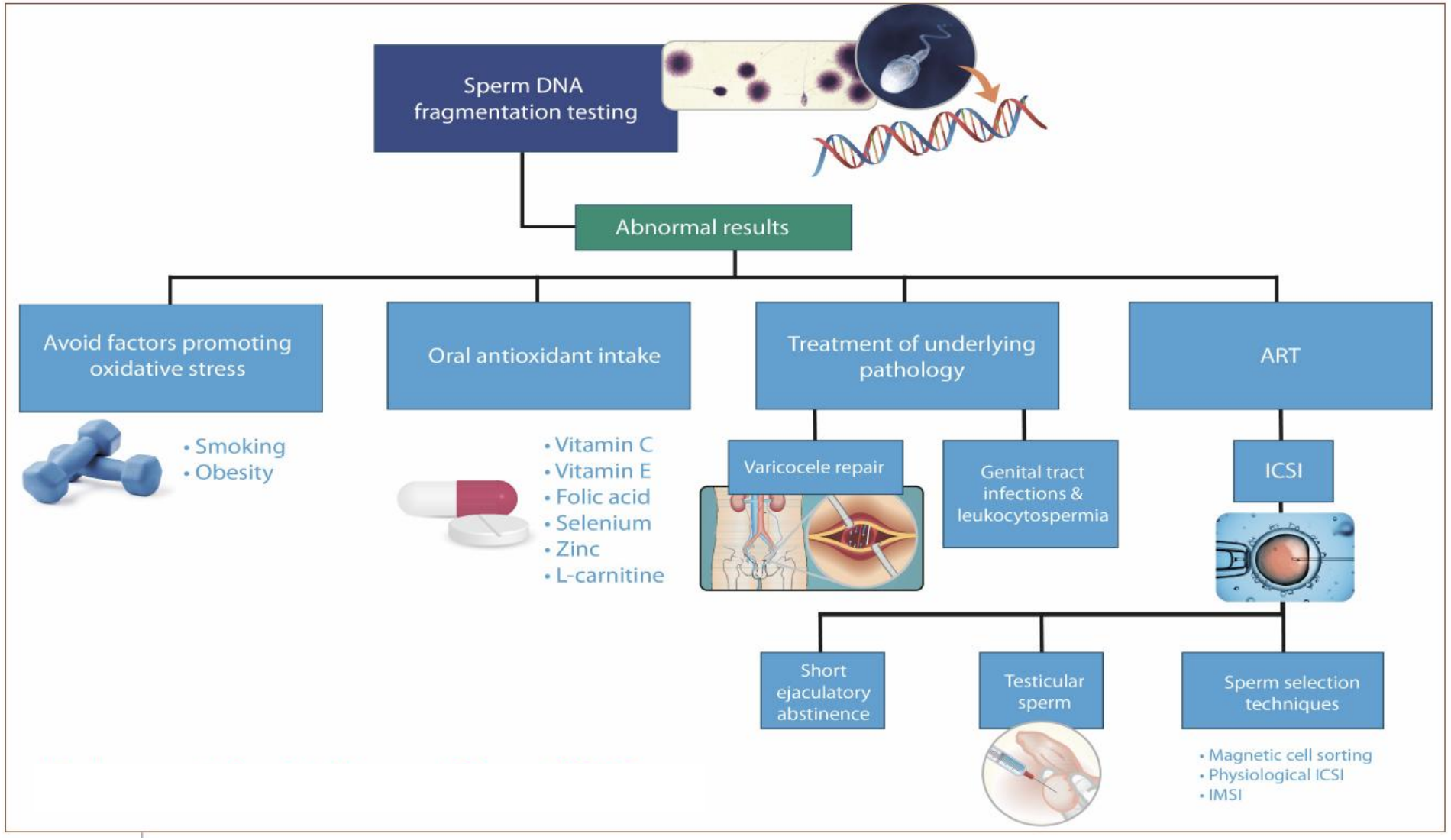
Edson Borges Jr[1,2] | Daniela Paes de Almeida Ferreira Braga[1,2] | Rodrigo R. Provenza[1] | Rita de Cassia Savio Figueira[1] | Assumpto Iaconelli Jr[1,2] | Amanda Souza Setti[1,2]

- ❖ Fator masculino isolado
- ❖ 1º. ciclo de tratamento
- ❖ Idade mulher < 36 anos
- ❖ 233 ciclos ICSI

1. Quantos cigarros/dia?
2. Consumo semanal de álcool?
3. Frequência de exercícios ?
4. Medicações nos últimos 3 meses? Qual?
5. Exposição a agentes tóxicos, pesticidas, radiação etc..

Linear regression analyses' results for the influence of paternal lifestyle factors on semen quality (n=965)

	Cigarette smoking		Alcohol consumption	
	B	p	B	p
Semen volume	-0.417	0.047	-0.1363	0.592
Sperm count/mL	-7.363	0.014	-12.527	0.040
Total sperm count	-4.43	0.023	-34.91	0.156
Total sperm motility	2.316	0.347	0.342	0.895
Progressive sperm motility	-0.369	0.887	2.547	0.240
TMSC	- 1.38	0.045	-16.33	0.278
Sperm morphology	-0.0563	0.779	0.3751	0.180
SDF	0.014	0.033	5.833	0.002



Esteves et al. J Assist Reprod Genet, 2016

Original Article
Male reproductive health and infertility

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Apr 20, 2023
https://doi.org/10.5534/wjmh.230008

The World Journal of MEN's HEALTH

Controversy and Consensus on the Management of Elevated Sperm DNA Fragmentation in Male Infertility: A Global Survey, Current Guidelines, and Expert Recommendations

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Fig. 25. Treatment strategies for infertile men with elevated SDF. ICSI: intracytoplasmic sperm injection, SDF: sperm DNA fragmentation.

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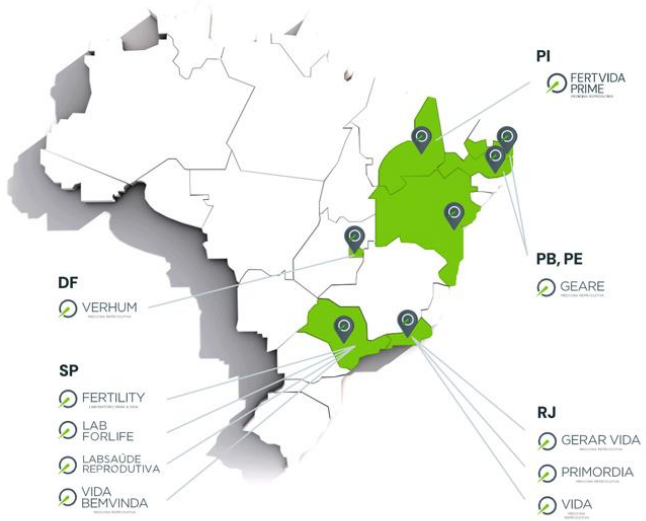

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Obrigado!

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