

XXIII Congresso Brasileiro de  
**Reprodução Assistida**

31 de julho a 03 de agosto de 2019  
ExpoUnimed - Curitiba - Paraná



## Fragmentação do DNA espermático elevada: O que fazer?

**Edson Borges Jr.**



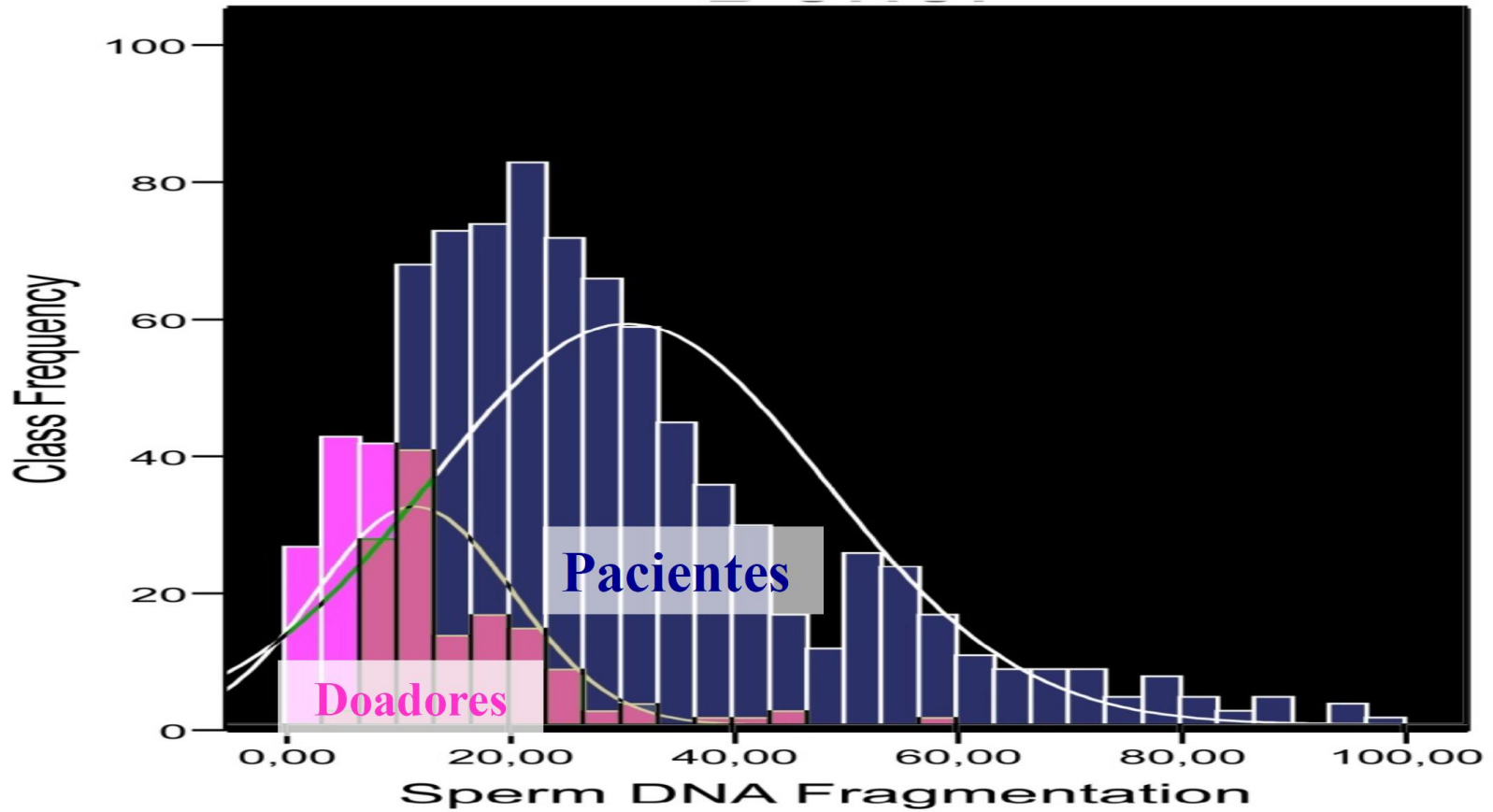
## **Declaração:**

**Declaro o recebimento de honorários para palestras e/ou ensaios clínicos da Merck, Ferring e Abbott (não relacionados ao assunto desta palestra).**

**Nenhum outro conflito de interesse para divulgar.**

**Resolução do Conselho Federal de Medicina  
nº 1.595/2.000**

# Taxa de Fragmentação do DNA espermático



Gosalvez et al. *J Reprod Biotechnol Fertil.* 2015



FERTILITY



[www.sciencedirect.com](http://www.sciencedirect.com)  
[www.rbmonline.com](http://www.rbmonline.com)



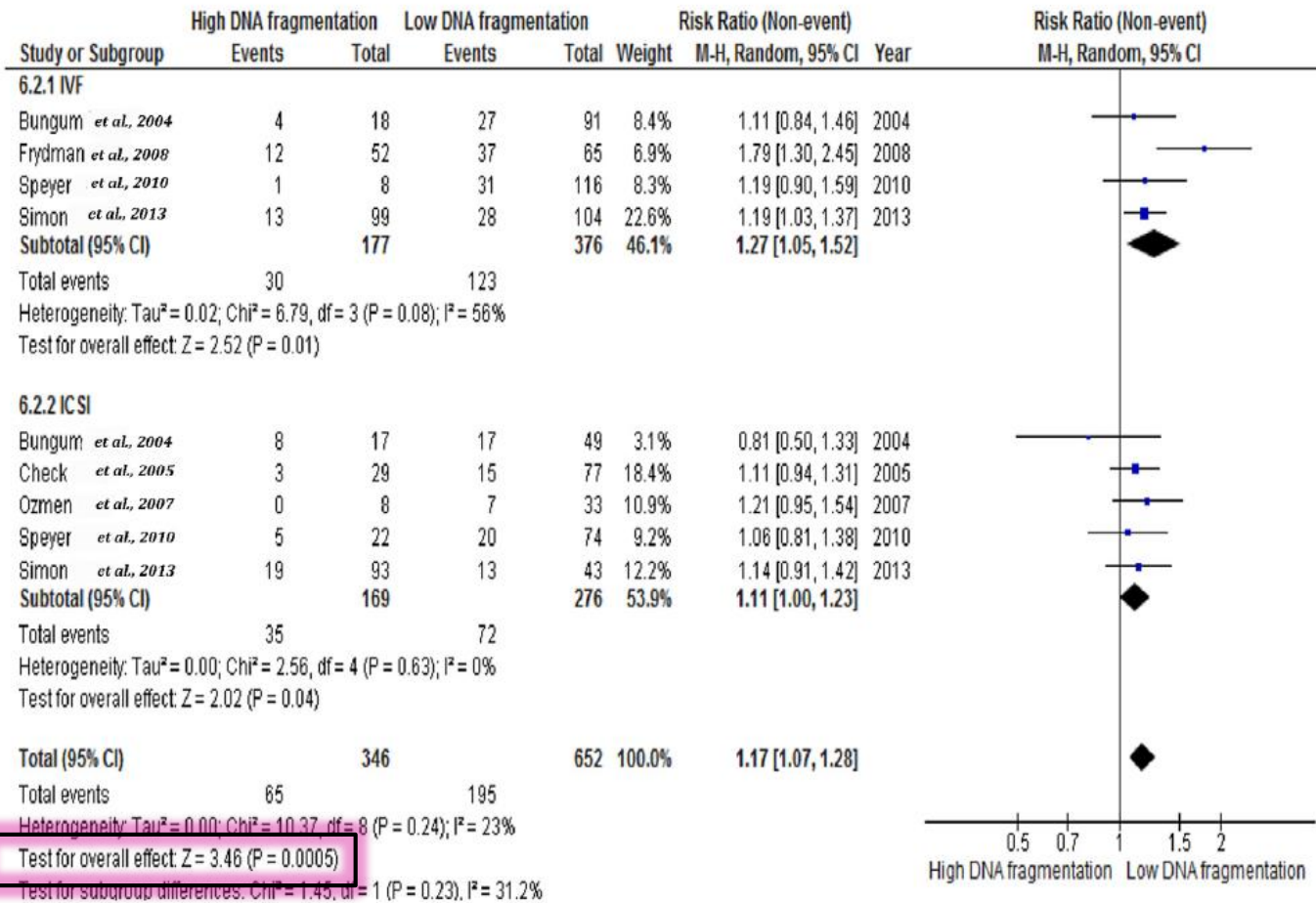
## REVIEW

# 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*



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



Open Access

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<sup>1\*</sup>, Armand Zini<sup>2\*</sup>, Alina Dyachenko<sup>2</sup>, Antonio Ciampi<sup>2</sup>, Douglas T Carrell<sup>1,3,4</sup>

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

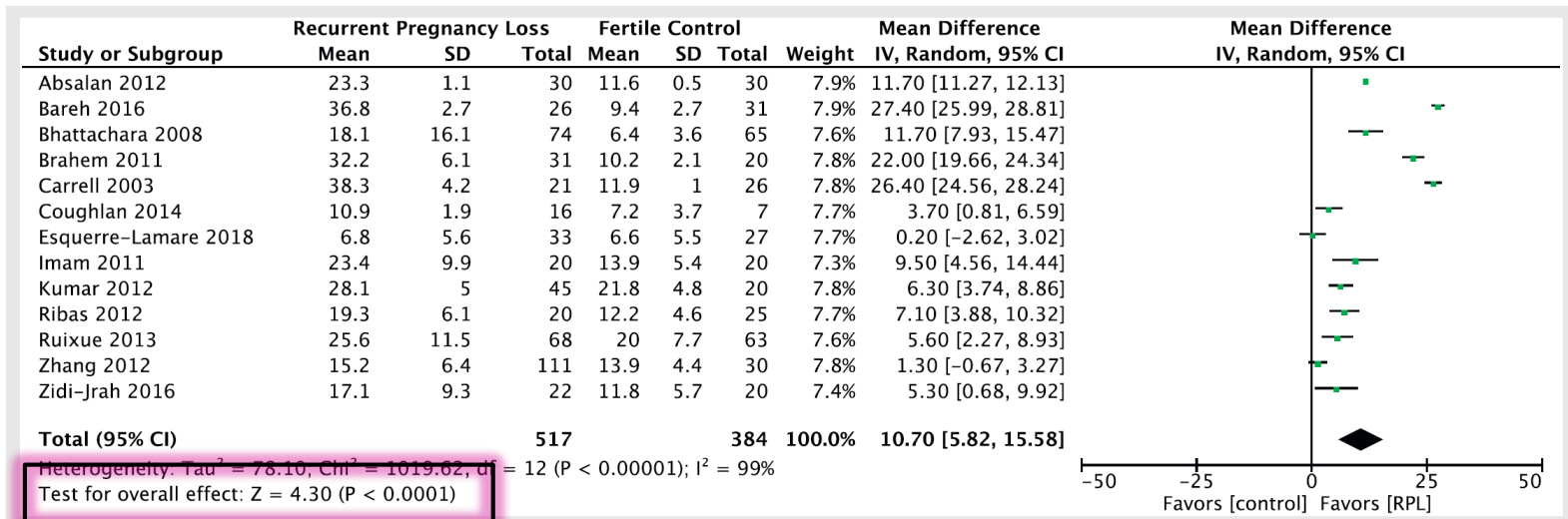
Effect	Number of studies	Fixed effects model		Random effects model	
		OR (95% CI)	P	OR (95% CI)	P
Overall effect	56	1.68 (1.49–1.89)	0.0000*	1.84 (1.5–2.27)	<0.0001*
Sperm DNA damage assays					
SCSA	23	1.18 (0.96–1.44)	0.1115	1.22 (0.93–1.61)	0.1522
TUNEL	18	2.18 (1.75–2.72)	0.0000*	2.22 (1.61–3.05)	<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



Primary outcome in overall analysis.

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

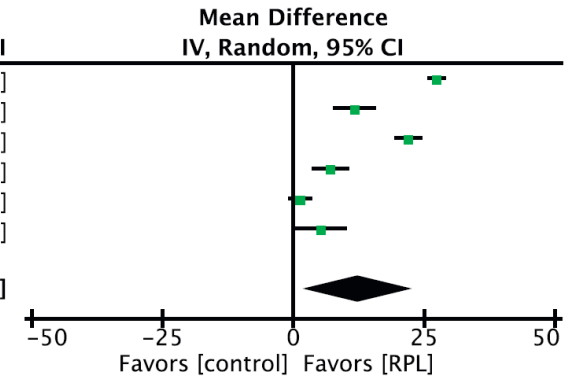
Fertility and Sterility® Vol. 112, No. 1, July 2019

### Recurrent pregnancy loss as 2 or more losses

Study or Subgroup	Recurrent Pregnancy Loss			Fertile Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Bareh 2016	36.8	2.7	26	9.4	2.7	31	16.9%	27.40 [25.99, 28.81]
Bhattachara	18.1	16.1	74	6.4	3.6	65	16.5%	11.70 [7.93, 15.47]
Brahem 2011	32.2	6.1	31	10.2	2.1	20	16.8%	22.00 [19.66, 24.34]
Ribas 2012	19.3	6.1	20	12.2	4.6	25	16.6%	7.10 [3.88, 10.32]
Zhang 2012	15.2	6.4	111	13.9	4.4	30	16.8%	1.30 [-0.67, 3.27]
Zidi-Jrah 2016	17.1	9.3	22	11.8	5.7	20	16.4%	5.30 [0.68, 9.92]
<b>Total (95% CI)</b>			<b>284</b>			<b>191</b>	<b>100.0%</b>	<b>12.51 [2.14, 22.89]</b>

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

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

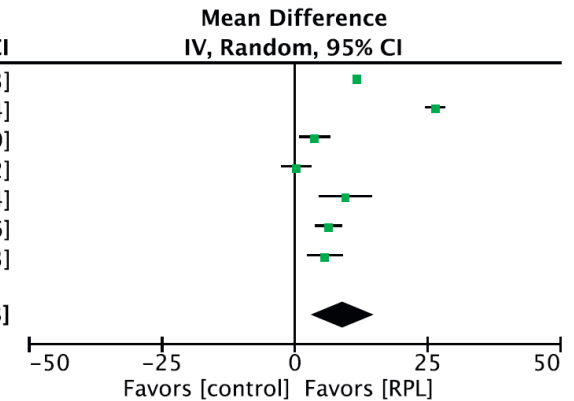


### Recurrent pregnancy loss as 3 or more losses

Study or Subgroup	Recurrent Pregnancy Loss			Fertile Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Absalan 2012	23.3	1.1	30	11.6	0.5	30	14.8%	11.70 [11.27, 12.13]
Carrell 2003	38.3	4.2	21	11.9	1	26	14.6%	26.40 [24.56, 28.24]
Coughlan 2014	10.9	1.9	16	7.2	3.7	7	14.3%	3.70 [0.81, 6.59]
Esquerre-Lamare 2018	6.8	5.6	33	6.6	5.5	27	14.3%	0.20 [-2.62, 3.02]
Imam 2011	23.4	9.9	20	13.9	5.4	20	13.4%	9.50 [4.56, 14.44]
Kumar 2012	28.1	5	45	21.8	4.8	20	14.4%	6.30 [3.74, 8.86]
Ruixue 2013	25.6	11.5	68	20	7.7	63	14.1%	5.60 [2.27, 8.93]
<b>Total (95% CI)</b>			<b>233</b>			<b>193</b>	<b>100.0%</b>	<b>9.12 [3.16, 15.08]</b>

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

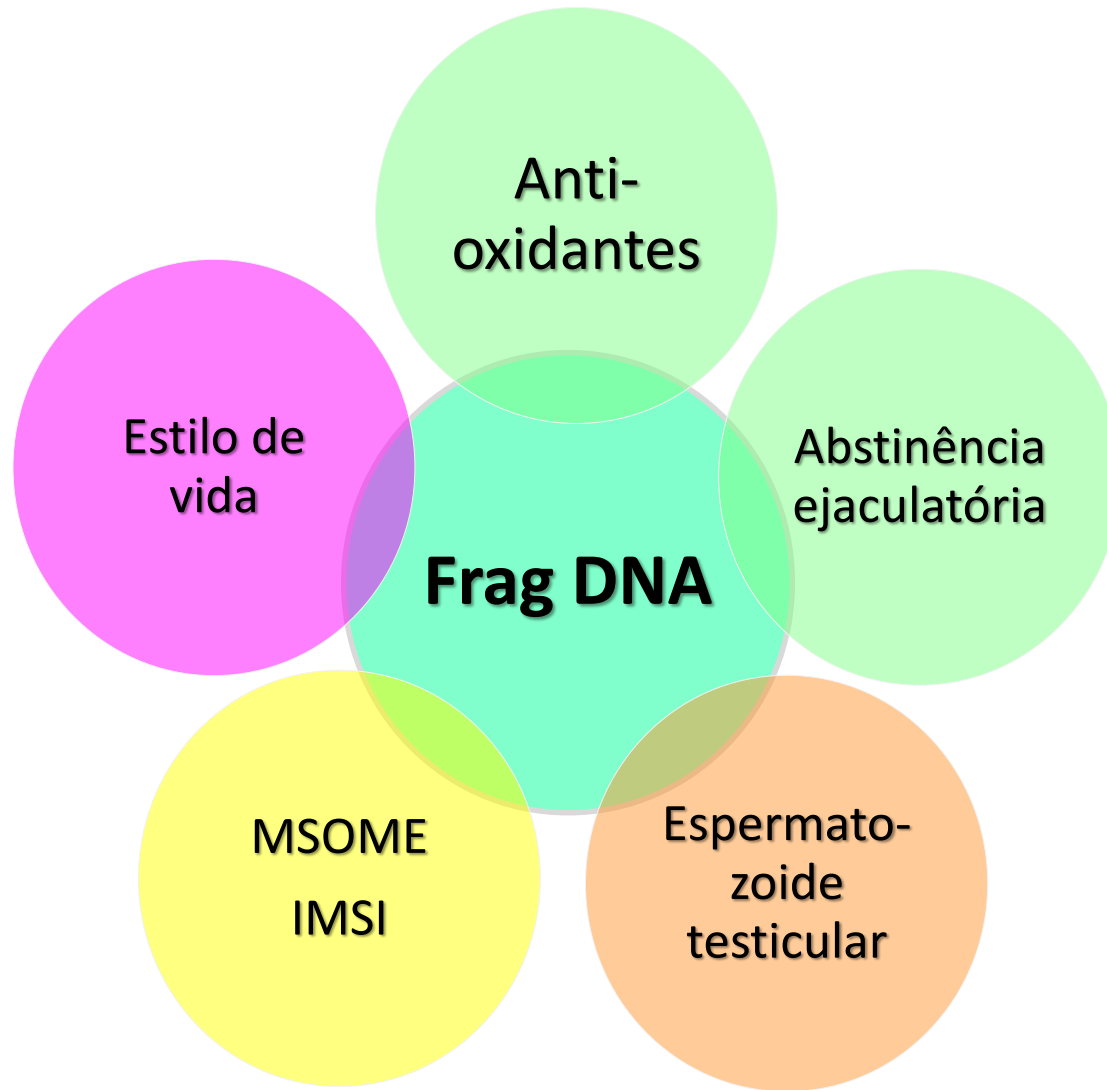
Test for overall effect:  $Z = 3.00$  ( $P = 0.003$ )

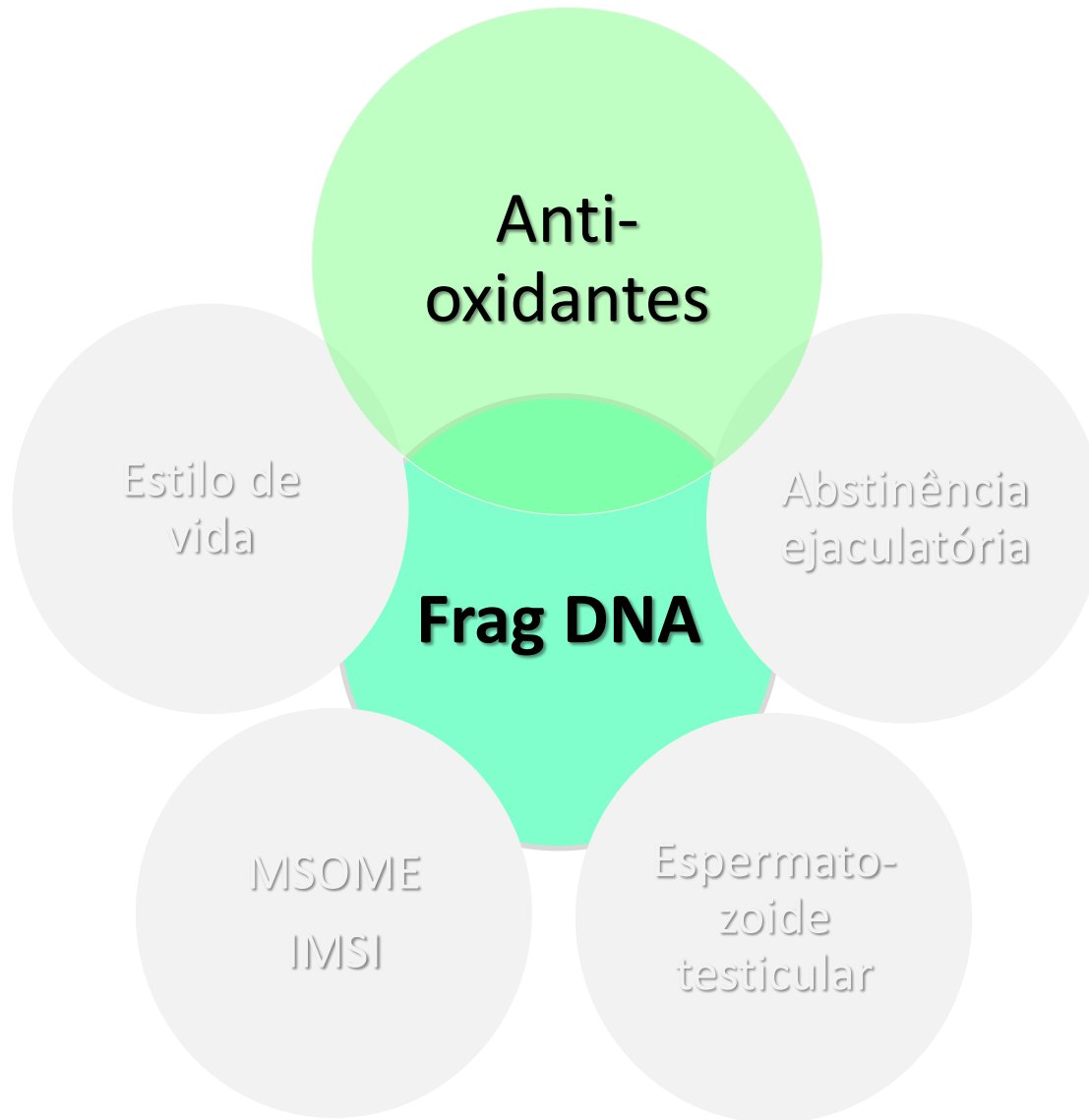


Subgroup analysis by definition of recurrent pregnancy loss (RPL).

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









## 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)



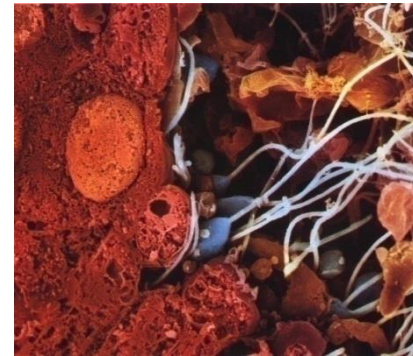
## Antioxidants for male subfertility (Review)

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

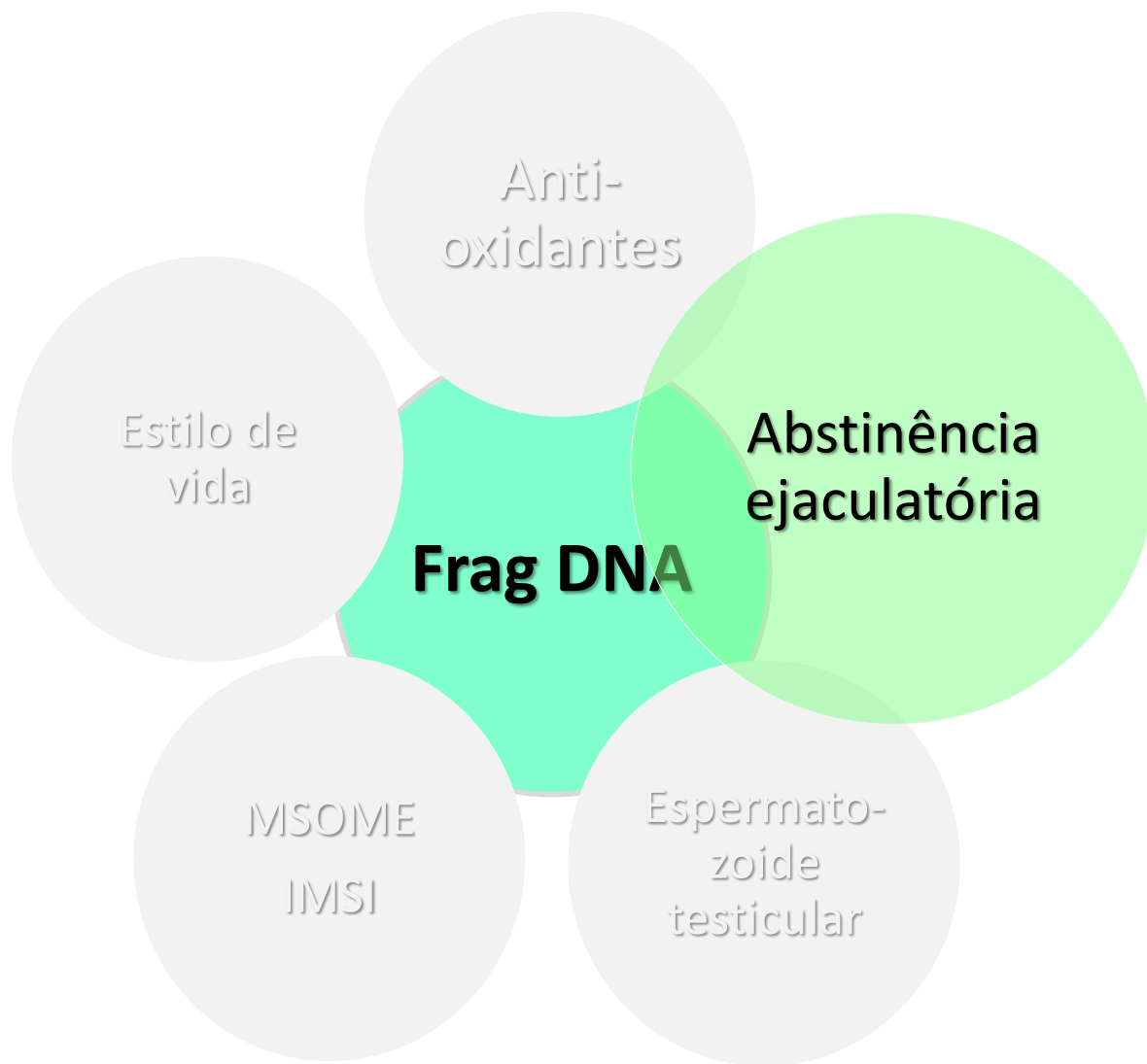
- 61 estudos com uma população total de 6.264 homens subférteis, com idades entre 18 e 65 anos, combinaram 18 diferentes antioxidantes orais.
- **Nascidos vivos: *OR 1.79***, 95% CI 1.20 to 2.67, P = 0.005, 7 RCTs, 750 homens
- **Gestação clínica: *OR 2.97***, 95% CI 1.91 to 4.63, P < 0.0001, 11 RCTs, 786 homens

# 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: 3g/dia



65 dias – tempo da espermatogênese



## ORIGINAL ARTICLE

**Correspondence:**

Edson Borges Jr., Fertility Medical Group, Av.  
Brigadeiro Luis Antonio, 4545, Sao Paulo, Brazil.  
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

<sup>1,2</sup>E. Borges Jr., <sup>1,2</sup>D. P. A. F. Braga , <sup>2</sup>B. F. Zanetti , <sup>1,2</sup>A. Iaconelli Jr. and <sup>1,2</sup>A. S. Setti

<sup>1</sup>Fertility Medical Group, Sao Paulo, Brazil, and <sup>2</sup>Sapientiae Institute, Sao Paulo, Brazil



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

<b>SEMEN PARAMETER</b>	<b>R</b>	<b>SLOPE</b>	<b>R<sup>2</sup> (%)</b>	<b>P-VALUE</b>
Semen volume (mL)	0.1405	1.62102	5.28	<0.001
Sperm count (x10 <sup>6</sup> /mL)	3.1261	52.2206	2.59	<0.001
Total sperm count (x10 <sup>6</sup> )	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 <sup>6</sup> )	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



Linear model analysis of the association between sperm parameters and  
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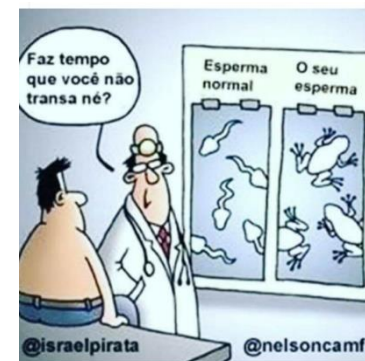
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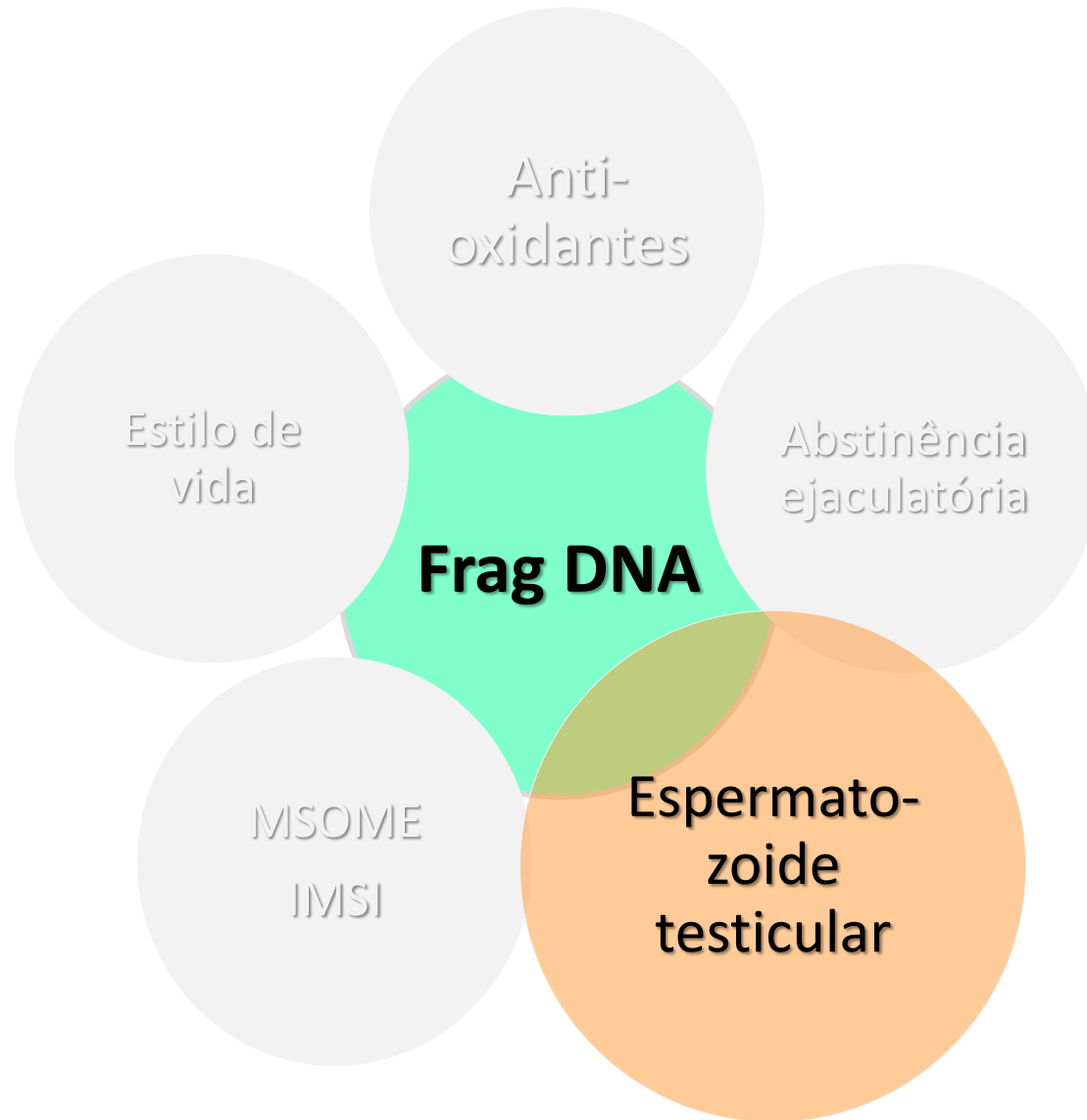
<sup>1,2</sup>E. Borges Jr., <sup>1,2</sup>D. P. A. F. Braga , <sup>2</sup>B. F. Zanetti , <sup>1,2</sup>A. Iaconelli Jr.  
and <sup>1,2</sup>A. S. Setti

<sup>1</sup>Fertility Medical Group, Sao Paulo, Brazil, and <sup>2</sup>Sapientiae Institute, Sao Paulo, Brazil



## Abstinência ejaculatória $\leq 4$ dias:

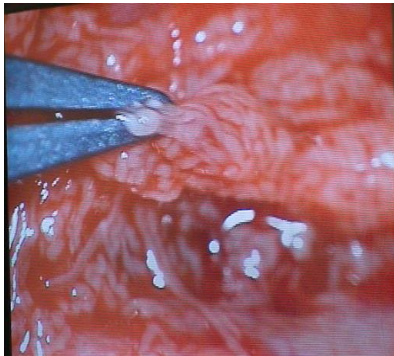
- Frag DNA espermático significativamente menor, maiores taxas de fertilização, embriões de alta qualidade no dia 3, desenvolvimento a blastocisto, implantação e gestação quando comparados ao grupo de abstinência ejaculatória  $> 4$  dias.
- Taxas de implantação significativamente maiores e taxas de gestação tendendo a serem maiores com *um dia de abstinência ejaculatória*, comparado a 2 – 4 de abstinência ejaculatória.



# Use of testicular sperm in nonazoospermic males

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

VOL. 109 NO. 6 / JUNE 2018



**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.**

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

## 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.

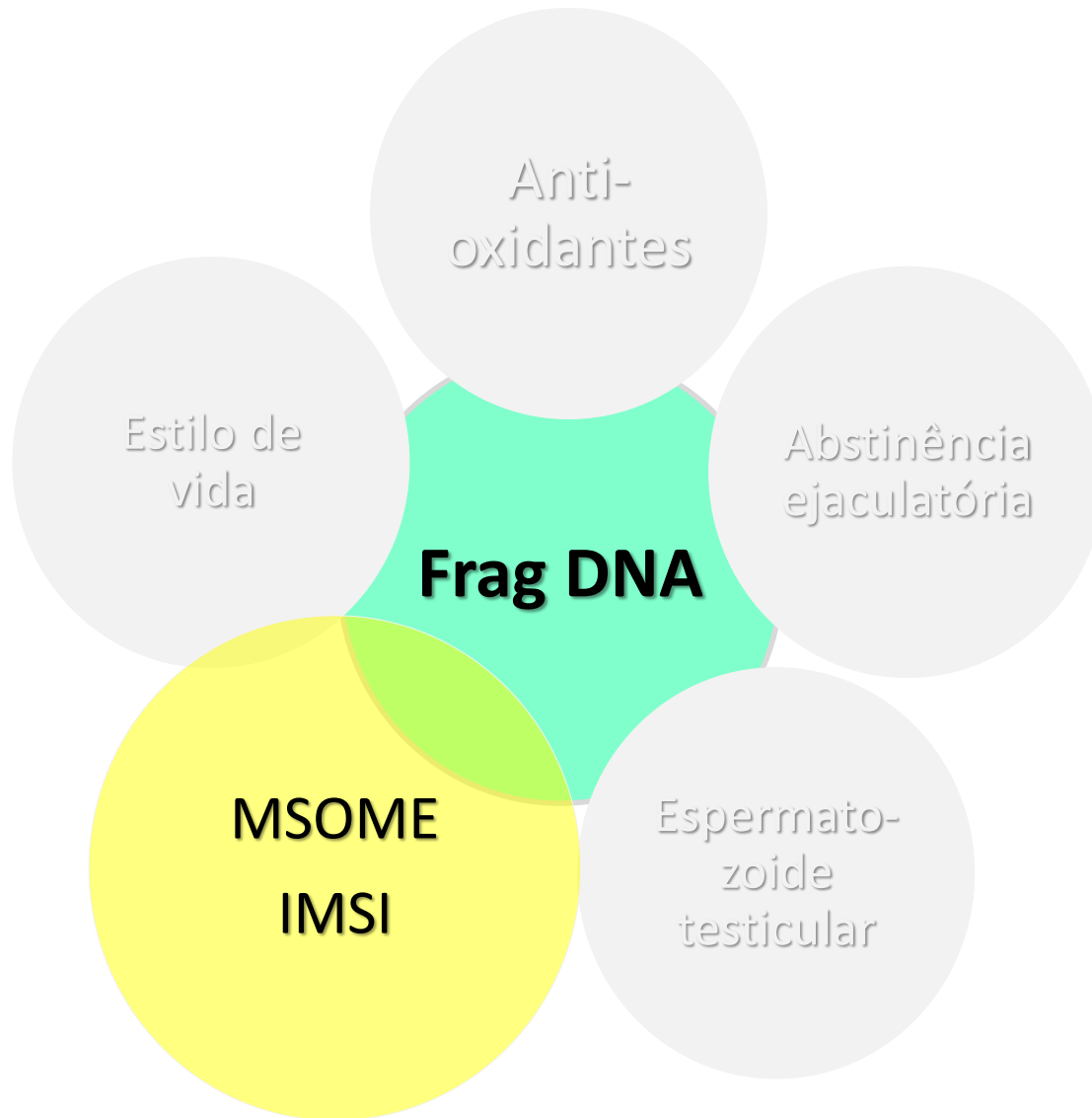
Hatem A Awaga<sup>1,2</sup>, Julia K Bosdou<sup>2</sup>, Dimitrios G Goulis<sup>2</sup>, Katerina Chatzimeletiou<sup>2</sup>, Mohamed Salem<sup>1</sup>, Salah Roshdy<sup>1</sup>, Grigoris Grimbizis<sup>2</sup>, Basil C Tarlatzis<sup>2</sup>, Efstratios M Kolibianakis<sup>2,\*</sup>

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

	High DFI only <i>Pabuccu et al. (2016)</i>	High DFI and oligozoospermia <i>Esteves et al. (2015)</i>	Isolated asthenozoospermia <i>Al-Malki et al. (2017)</i>	Asthenozoospermia with or without teratozoospermia <i>Kahraman et al. (1996)</i>
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.**



**MSOME** Motile Sperm Organellar Morphology Examination

**IMSI** Intracytoplasmic Morphologically Select Sperm Injection



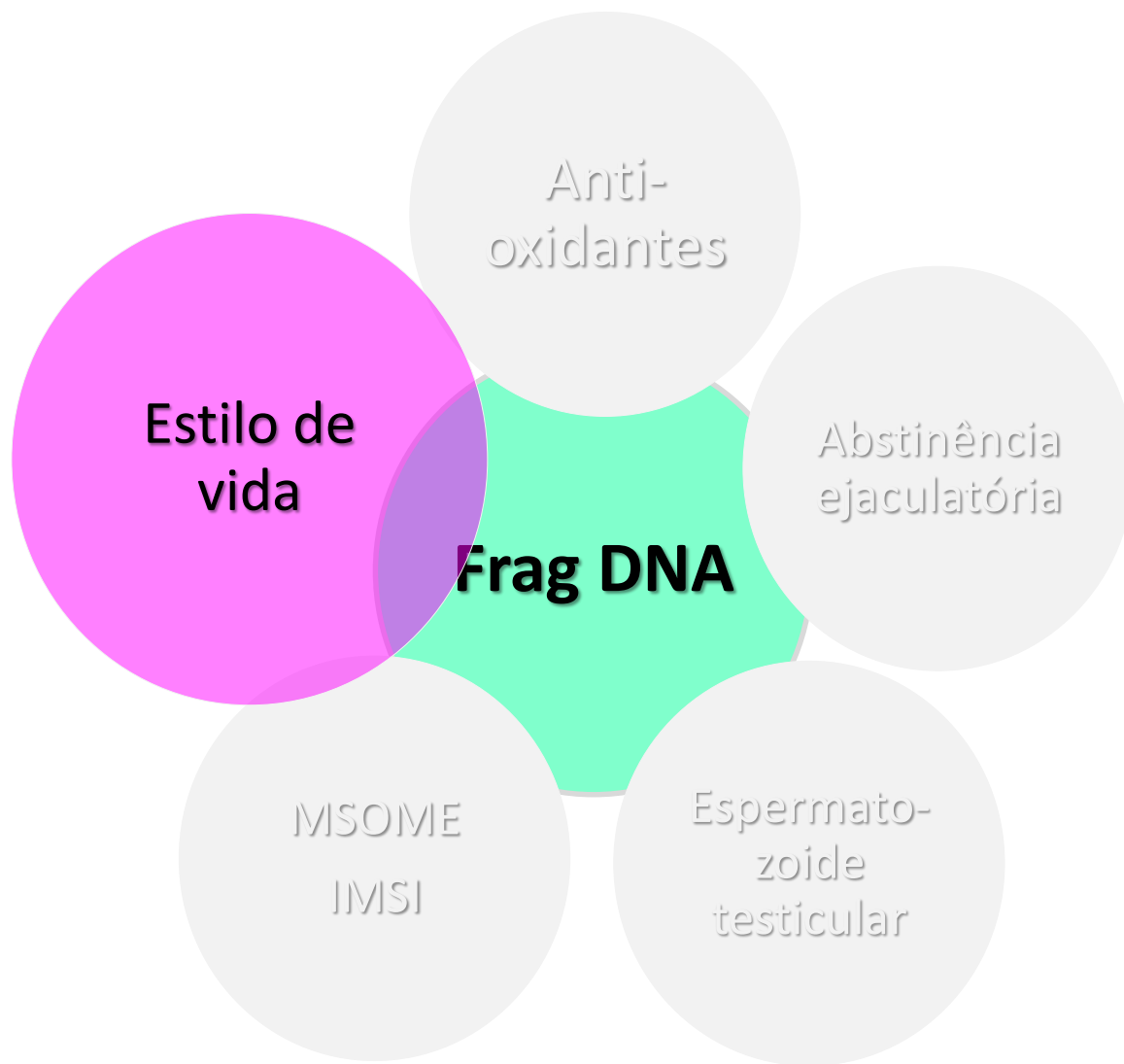
# Sperm Organelle Morphologic Abnormalities: Contributing Factors and Effects on Intracytoplasmic Sperm Injection Cycles Outcomes

Daniela Paes de Almeida Ferreira Braga, Amanda S. Setti, Rita C. S. Figueira, Marcillo Nichi, Ciro D. Martinhago, Assumpto Iaconelli, Jr., and Edson Borges, Jr.

**Table 1.** Multivariate regression analysis of factors contributing to motile sperm organelle morphology defects incidence with variables including sperm DNA fragmentation percentage, patient’s age, and sperm aneuploidy frequency

Predictor Variables	Response Variable			
	MSOME	Slope	R <sup>2</sup>	P
Percentage of sperm DNA fragmentation	Normal cells	-0.016	0.030	.145
	Abnormal shape	0.010	0.009	.411
	Abnormal size	0.004	0.189	<.001
	Large vacuoles	0.004	0.067	.029
	Small vacuoles	0.006	0.063	.034
Patient’s age	Normal cells	-0.012	0.002	.715
	Abnormal shape	-0.001	0.030	.148
	Abnormal size	0.053	0.156	.135
	Large vacuoles	0.065	0.118	<.001
	Small vacuoles	0.198	0.104	<.001
Sperm aneuploidy	Normal cells	0.00291	0.009	.805
	Abnormal shape	0.00115	0.001	.960
	Abnormal size	0.08637	0.006	.528
	Large vacuoles	0.00291	0.009	.805
	Small vacuoles	0.00115	0.001	.960








**ORIGINAL ARTICLE**

WILEY **ANDROLOGIA**  
First International Journal of Andrology

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

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

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



### 3. Lifestyle:

- smoking
- alcohol
- obesity
- stress
- advanced paternal age
- poor diet

### 4. Environmental

- heat
- pollution
- heavy metals
- plasticizers
- pesticide/ herbicides

### 5. Infection

- genito-urinary tract
- systemic infection

### 6. Autoimmune

- vasectomy
- torsion
- chronic prostatitis

### 7. Testicular

### 8. Chronic Disease

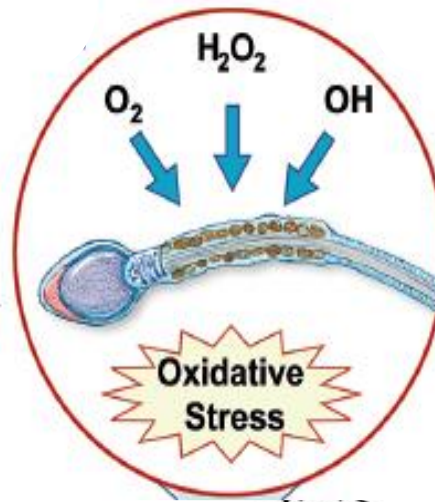
- diabetes
- CRF
- haemaglobinopathies
- hyperhomocysteinaemia

### 2. Iatrogenic

- centrifugation
- medications

### 1. Idiopathic

Anti-Oxidant



Damage to **sperm DNA** results  
In infertility and miscarriage

Damage to **sperm membrane**  
Decreases motility and the  
sperm's  
ability to fuse with oocyte

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



FERTILITY

# 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.,<sup>a,b</sup> Bianca Ferrarini Zanetti, Ph.D.,<sup>a,b</sup> Amanda Souza Setti, M.Sc.,<sup>a,b</sup> Daniela Paes de Almeida Ferreira Braga, Ph.D.,<sup>a,b</sup> Rodrigo Rosa Provenza, B.Sc.,<sup>a</sup> and Assumpto Iaconelli Jr., M.D.<sup>a,b</sup>

<sup>a</sup> Fertility Medical Group and <sup>b</sup> Instituto Sapientiae, Centro de Estudos e Pesquisa em Reprodução Humana Assistida, São Paulo, Brazil

- ➔ 475 ciclos de ICSI / ausência de fator masculino
- ➔ fragDNA espermático  $\geq 30\%$  x  $< 30\%$
- ➔ Estudo coorte prospectivo



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

**Descriptive analysis of seminal parameters according to SDF groups.**

<b>Parameter</b>	<b>&lt; 30% SDF (n = 433)</b>	<b>≥30% SDF (n = 42)</b>	<b>P value</b>
Paternal age, y	38.68 ± 5.65	41.19 ± 6.35	.009
Ejaculatory abstinence, d	3.92 ± 2.42	5.51 ± 5.46	.002
Seminal volume, mL	2.94 ± 0.50	3.79 ± 1.09	.001
Seminal concentration, ×10 <sup>6</sup> /mL	77.70 ± 29.83	81.09 ± 33.23	.677
Total sperm count, ×10 <sup>6</sup>	214.58 ± 72.95	303.71 ± 78.80	.003
Total sperm motility, %	63.45 ± 12.75	55.52 ± 17.55	<.001
Progressive sperm motility, %	54.90 ± 14.27	46.50 ± 16.77	<.001
Total motile sperm count	121.11 ± 98.24	146.89 ± 139.09	.120
SDF, %	17.48 ± 8.70	37.67 ± 6.39	<.001

