

febrasgo
Fundação Brasileira de
Especialidades em Ginecologia e Obstetrícia



Papel do parceiro na Infertilidade

Edson Borges Jr.

CRM: 52.154 - SP



Conflito de Interesse

Ausência de Conflito de Interesse

Resolução do Conselho Federal de Medicina nº
1.595/2.000

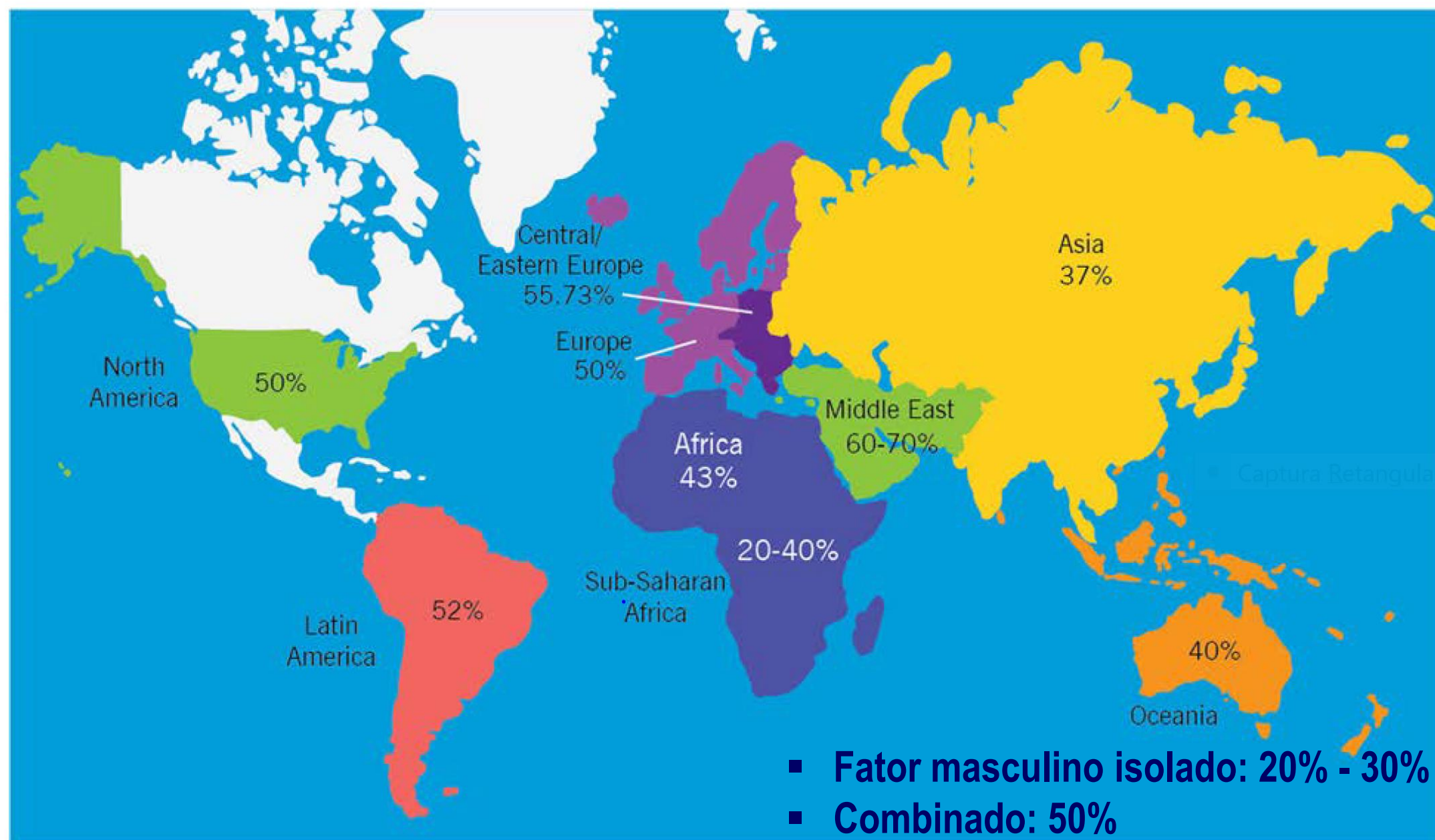


Figure 2 World map containing percentages of infertility cases per region that are due to male factor. This figure demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement.



QUANDO INICIAR A AVALIAÇÃO ?

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

⇒ Antes de 1 ano

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



Etiologia da Infertilidade Masculina

Varicocele	42,2
Idiopática	22,7
Obstrução	14,7
♀ / ♂ Normais	7,9
Criptorquidia	3,4
Imunológica	2,6
Ejaculatório	1,3
Falência Testicular	1,3



Análise Seminal

VAN LEEUWENHOEK

1677

SIMS

1866

WEISMAN

1940

AMERICAN FERTILITY ASS

1951

FREUND

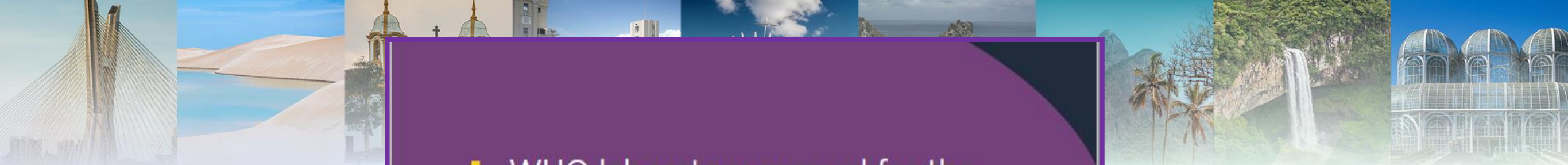
1966

ELIASSON

1971

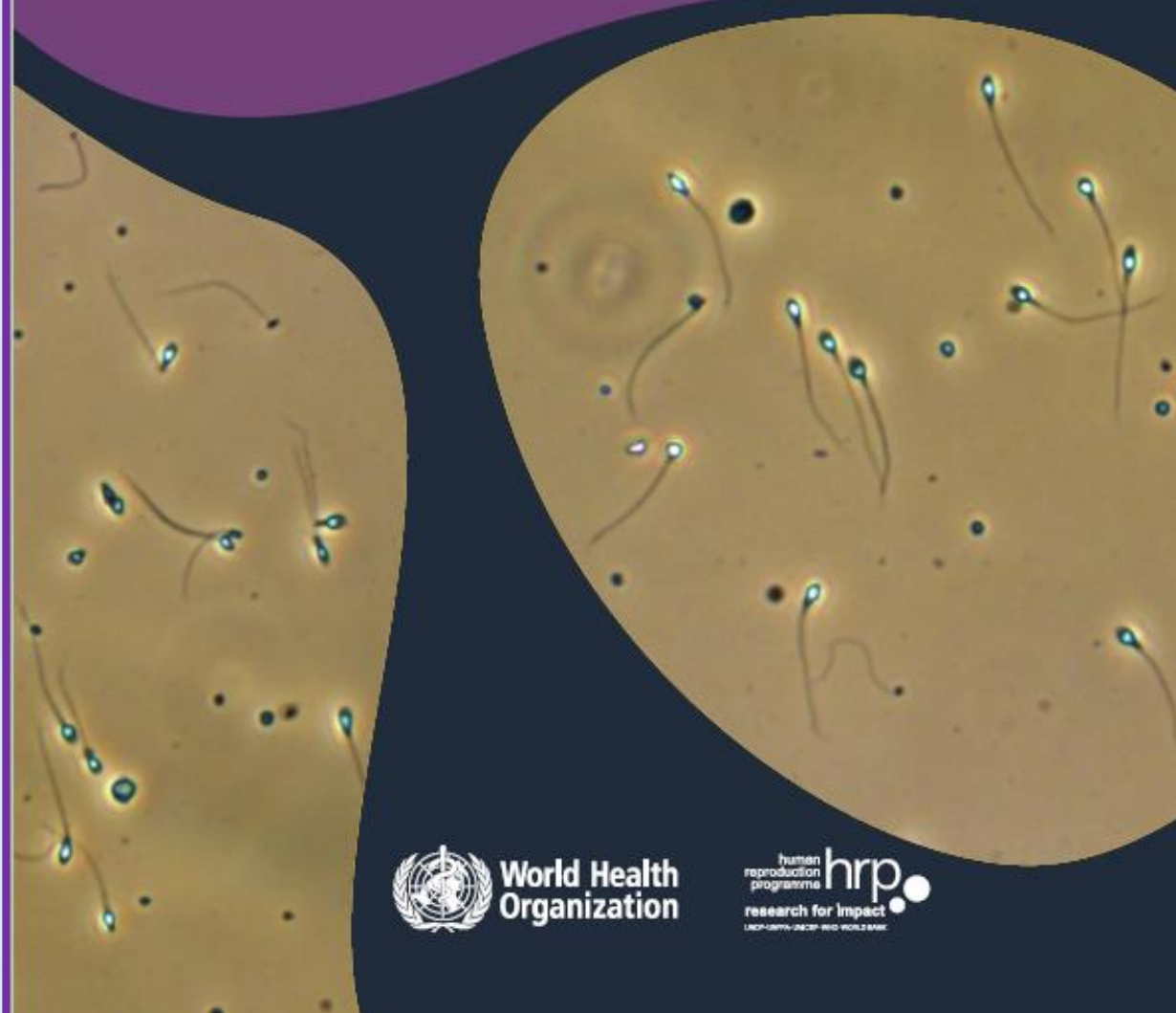
O.M.S.

1980/ 87/ 92/ 99/ 2010/ 2021



WHO laboratory manual for the examination and processing of human semen

Sixth Edition



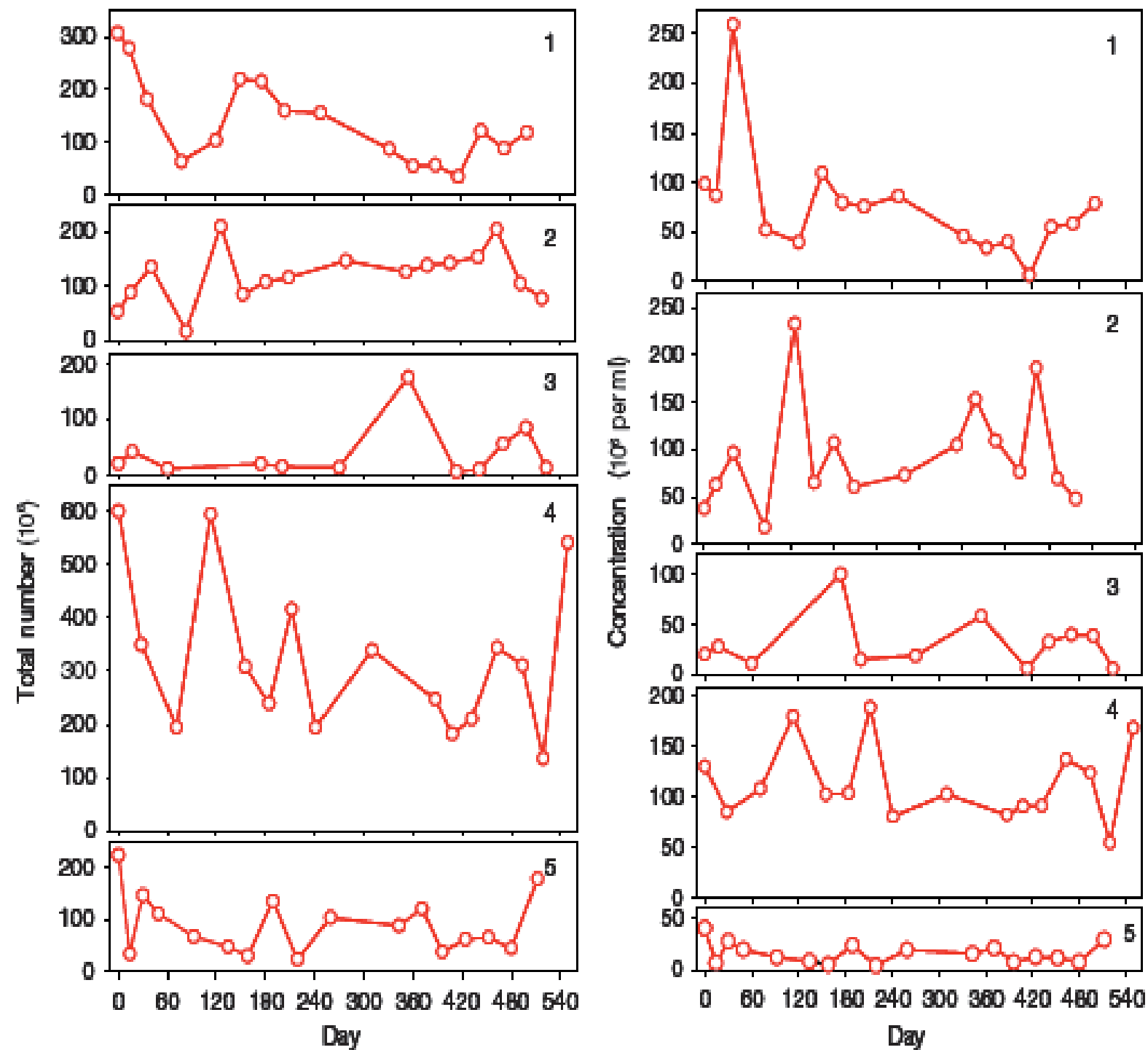
WHO laboratory manual for the examination and processing of human semen

Sixth Edition

		Centiles									
	<i>N</i>	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



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





Análise Seminal

Análise Macroscópica

cor, viscosidade, pH, volume, liquefação

Análise Microscópica

concentração, motilidade, morfologia



Pelo menos duas amostras!

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

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

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

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

TABLE 1

Classification of semen analyses.

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

Morelli. Correspondence. Fertil Steril 2010.



TMSC (total motile sperm count)

Número total de espermatozoides móveis

= volume x conc/ml x % A+B / 100%

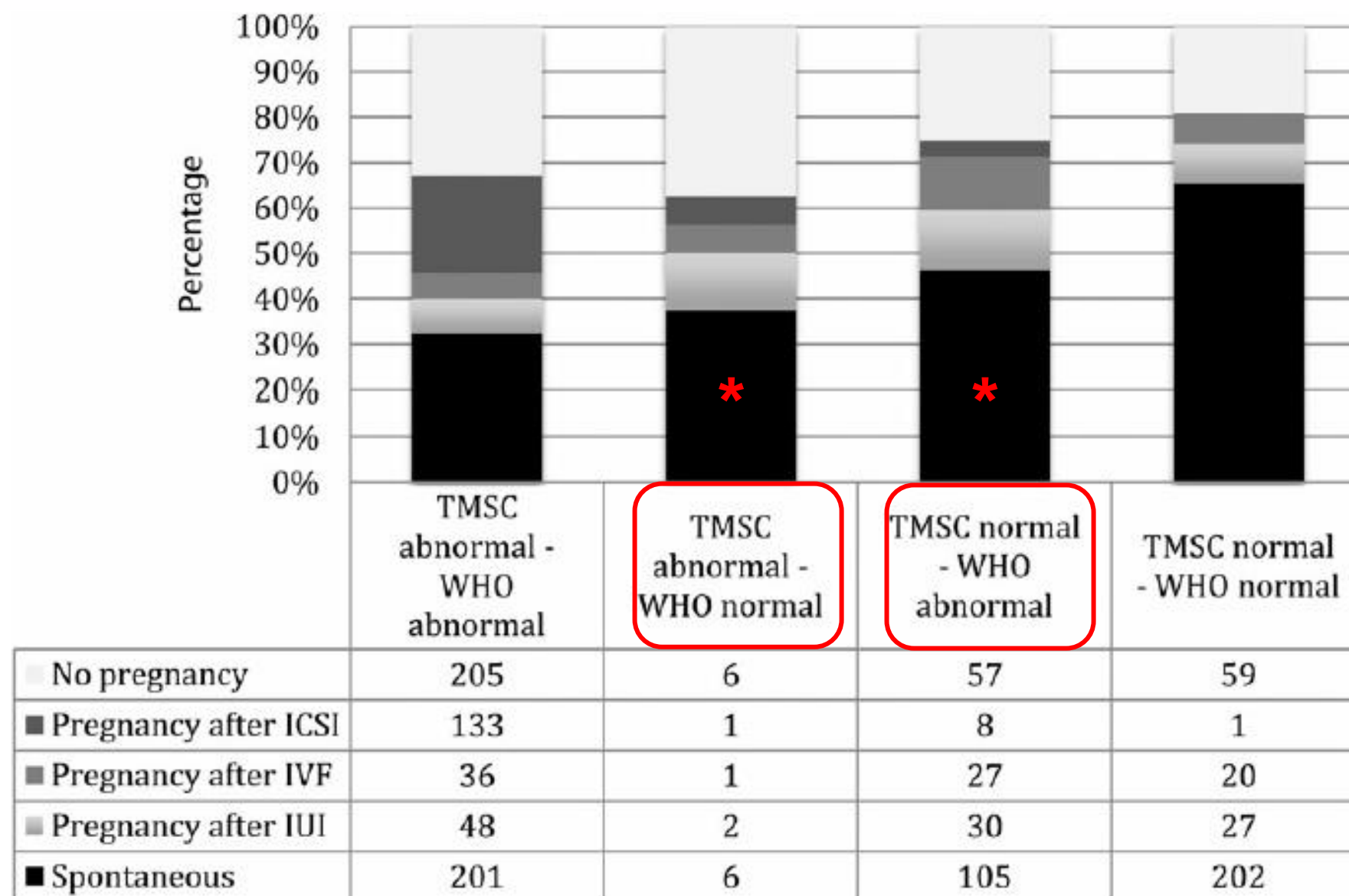
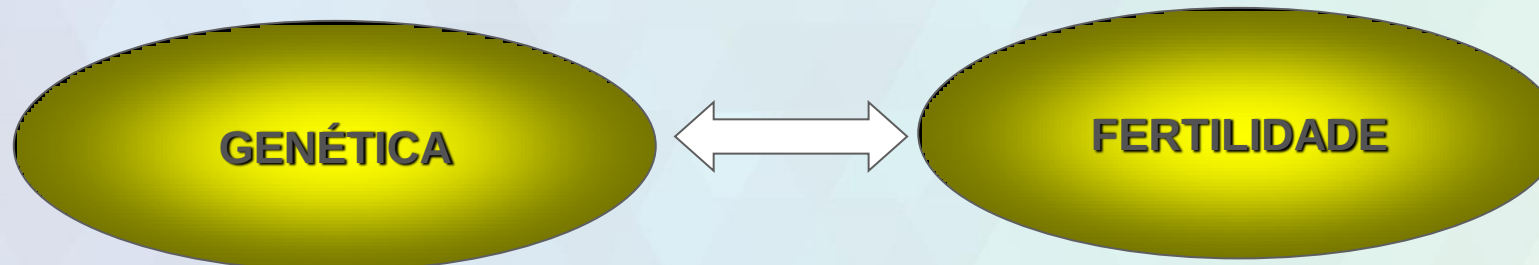
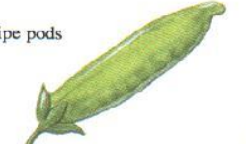


Figure 4 Results showing where the TMSC and WHO classification systems overlap or disagree. The bars on the right and left show the outcome if the two systems are in agreement. The middle bars show the outcome if both systems give contradictory results. TMSC normal – WHO normal = 'real unexplained' infertility.

Genética e Infertilidade Masculina



Gregor Mendel

	Recessive	Dominant	
round, ripe seeds			wrinkled, ripe seeds
yellow peas			green peas
gray seed coat			white seed coat
inflated, ripe pods			constricted, ripe pods
green, unripe pods			yellow, unripe pods
axial flowers			terminal flowers
tall plants			short plants

M. Albury Noyes M. Gerritt

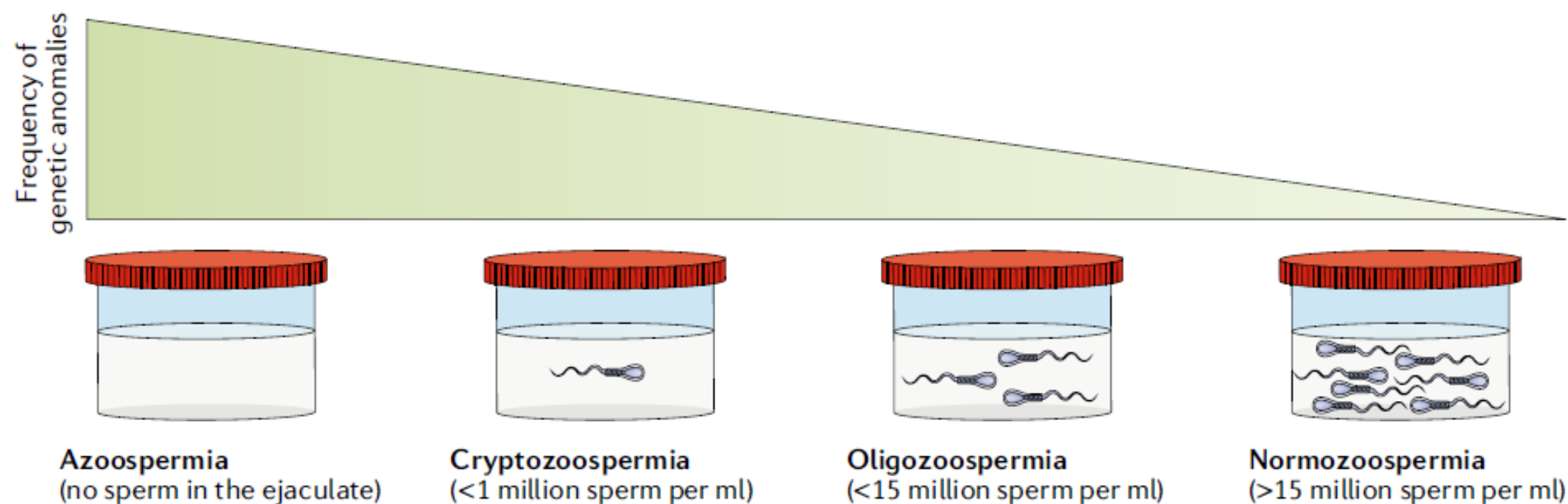


ANORMALIDADES CROMOSSÔMICAS EM HOMENS INFÉRTEIS

REFERÊNCIAS	Nº	CROMOSSÔMOS SEXUAIS	AUTOSSÔMOS	TOTAL
KOULISCHER E SCHOYSMAN (1974)	1000	27 (2.7)	6 (0.6)	33 (3.3)
CHANDLEY (1979)	2372	33 (1.4)	18 (0.7)	51 (2.1)
ZUFFARDI E TIEPOLO (1982)	2542	175 (6.9)	40 (1.6)	215 (8.6)
ABRAMSSON <i>et al</i> (1982)	342	6 (1.8)	4 (1.2)	10 (2.9)
de GARDELLE <i>et al</i> (1983)	318	13 (4.1)	7 (2.2)	20 (6.3)
MATSUDA <i>et al</i> (1989)	295	0 (0)	5 (1.7)	5 (1.7)
YOSHIDA <i>et al</i> (1995)	1007	41 (4.1)	24 (2.4)	65 (6.5)
TOTAL	7876	295 (3.8)	104 (1.3)	399 (5.1)
NASCIDOS	94.465	131 (0.14)	232 (0.25)	366 (0.38)



ALTERAÇÕES CROMOSSÔMICAS MAIORES & DENSIDADE ESPERMÁTICA



Gekas et al. Human Reprod 16:82-90, 2001
Crausz et al. Nat Ver Urol, 15:369-84, 2018



MODERN TRENDS

Edward E. Wallach, M.D.
Associate Editor

Fertility and Sterility® Vol. 93, No. 1, January 2010

The genetic causes of male factor infertility: A review

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

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

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

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



Propedêutica em Infertilidade

Propedêutica Básica Homem

- Espermograma com morfologia estrita
- Número total de espermatozoides móveis (TMSC)
- Cariótipo
- Quando alteração seminal importante
- (conc < 2,0 milhões/ml): avaliação genética (cariótipo, microdeleção Y)
- Quando agenesia de deferentes: pesquisa de CFTR



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***



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

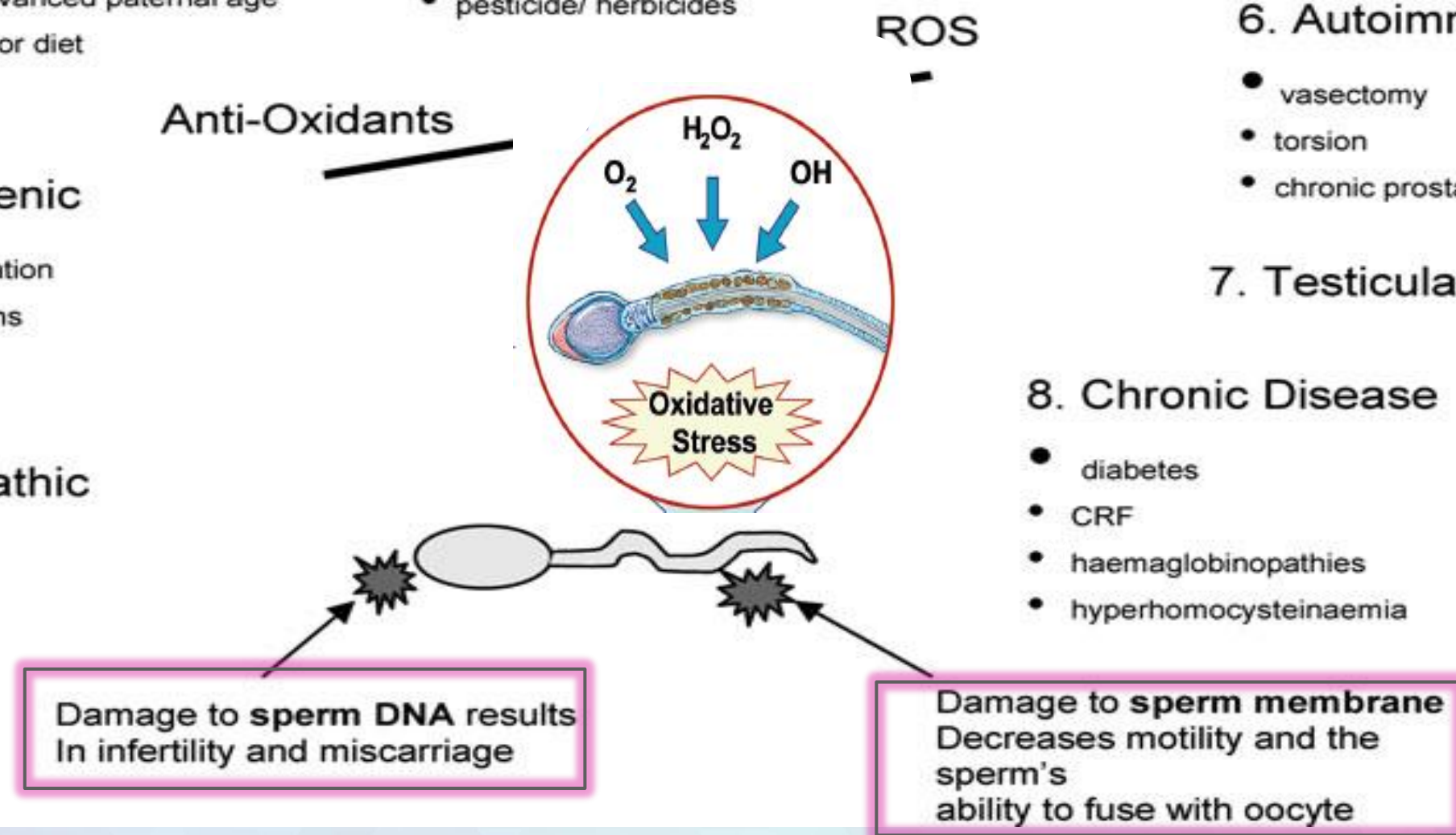
8. Chronic Disease

- diabetes
- CRF
- haemoglobinopathies
- hyperhomocysteinaemia

2. Iatrogenic

- centrifugation
- medications

1. Idiopathic



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



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

Ashok Agarwal^{1,2}, Neel Parekh², Manesh Kumar Panner Selvam^{1,2}, Ralf Henkel^{1,3}, Rupin Shah⁴, Sheryl T. Homa⁵, Ranjith Ramasamy⁶, Edmund Ko⁷, Kelton Tremellen⁸, Sandro Esteves^{9,10}, Ahmad Majzoub^{1,11}, Juan G. Alvarez¹², David K. Gardner¹³, Channa N. Jayasena^{14,15}, Jonathan W. Ramsay¹⁵, Chak-Lam Cho¹⁶, Ramadan Saleh¹⁷, Denny Sakkas¹⁸, James M. Hotaling¹⁹, Scott D. Lundy², Sarah Vij², Joel Marmar²⁰, Jaime Gosalvez²¹, Edmund Sabanegh², Hyun Jun Park^{22,23}, Armand Zini²⁴, Parviz Kavoussi²⁵, Sava Micic²⁶, Ryan Smith²⁷, Gian Maria Busetto²⁸, Mustafa Emre Bakircioglu²⁹, Gerhard Haidl³⁰, Giancarlo Balercia³¹, Nicolás Garrido Puchalt³², Moncef Ben-Khalifa³³, Nicholas Tadros³⁴, Jackson Kirkman-Browne^{35,36}, Sergey Moskovtsev³⁷, Xuefeng Huang³⁸, Edson Borges Jr³⁹, Daniel Franken⁴⁰, Natan Bar-Chama⁴¹, Yoshiharu Morimoto⁴², Kazuhisa Tomita⁴², Vasan Satya Srin⁴³, Willem Ombelet^{44,45}, Elisabetta Baldi⁴⁶, Monica Muratori⁴⁷, Yasushi Yumura⁴⁸, Sandro La Vignera⁴⁹, Raghavender Kosgi⁵⁰, Marlon P. Martinez⁵¹, Donald P. Evenson⁵², Daniel Suslik Zylbersztejn⁵³, Matheus Roque⁵⁴, Marcello Cocuzza⁵⁵, Marcelo Vieira^{56,57}, Assaf Ben-Meir⁵⁸, Raoul Orvieto^{59,60}, Eliahu Levitas⁶¹, Amir Wiser^{62,63}, Mohamed Arafa⁶⁴, Vineet Malhotra⁶⁵, Sijo Joseph Parekattil^{66,67}, Haitham Elbardisi⁶⁴, Luiz Carvalho^{68,69}, Rima Dada⁷⁰, Christophe Sifer⁷¹, Pankaj Talwar⁷², Ahmet Gudeloglu⁷³, Ahmed M.A. Mahmoud⁷⁴, Khaled Terras⁷⁵, Chadi Yazbeck⁷⁶, Bojanic Nebojsa⁷⁷, Damayanthi Durairajanayagam⁷⁸, Ajina Mounir⁷⁹, Linda G. Kahn⁸⁰, Saradha Baskaran¹, Rishma Dhillon Pai⁸¹, Donatella Paoli⁸², Kristian Leisegang⁸³, Mohamed-Reza Moein⁸⁴, Sonia Malik⁸⁵, Onder Yaman⁸⁶, Luna Samanta⁸⁷, Fouad Bayane⁸⁸, Sunil K. Jindal⁸⁹, Muammer Kendirci⁹⁰, Baris Altay⁹¹, Dragoljub Perovic⁹², Avi Harlev⁹³

Male Infertility

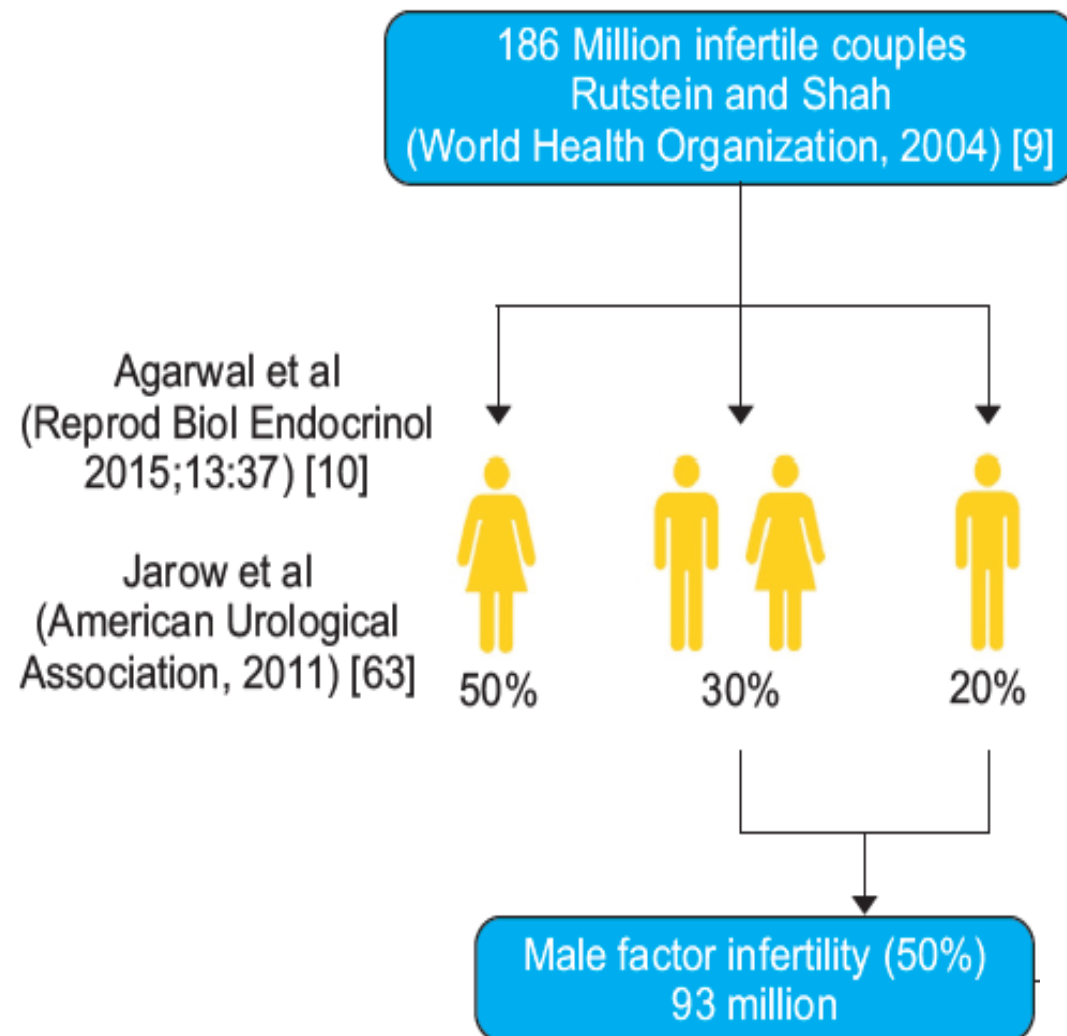


Fig. 3. Worldwide incidence of MOSI in infertile men. ^aNational Institutes of Health (NIH) (<https://www.nichd.nih.gov/health/topics/menshealth/conditioninfo/infertility>) [61], Agarwal et al (2014) [62], Jarow et al (2011) [63].

Male Infertility

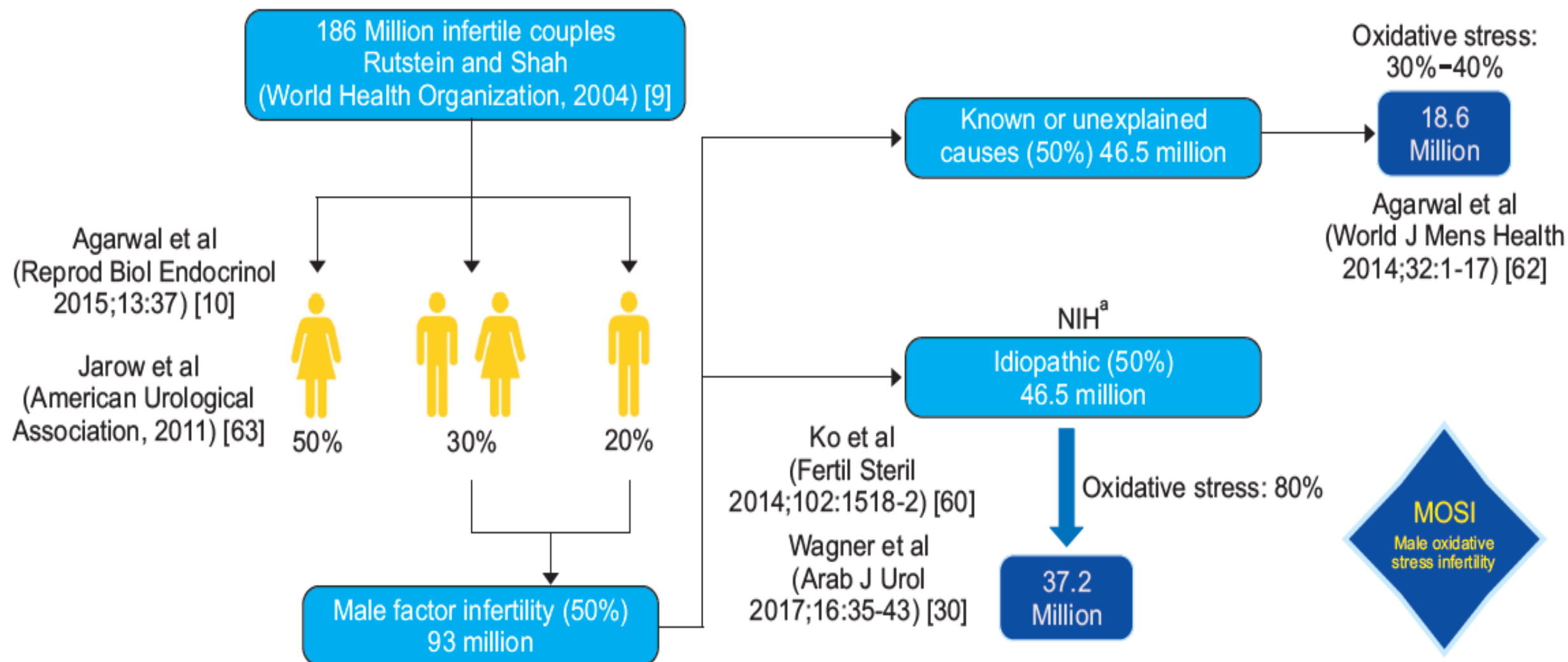
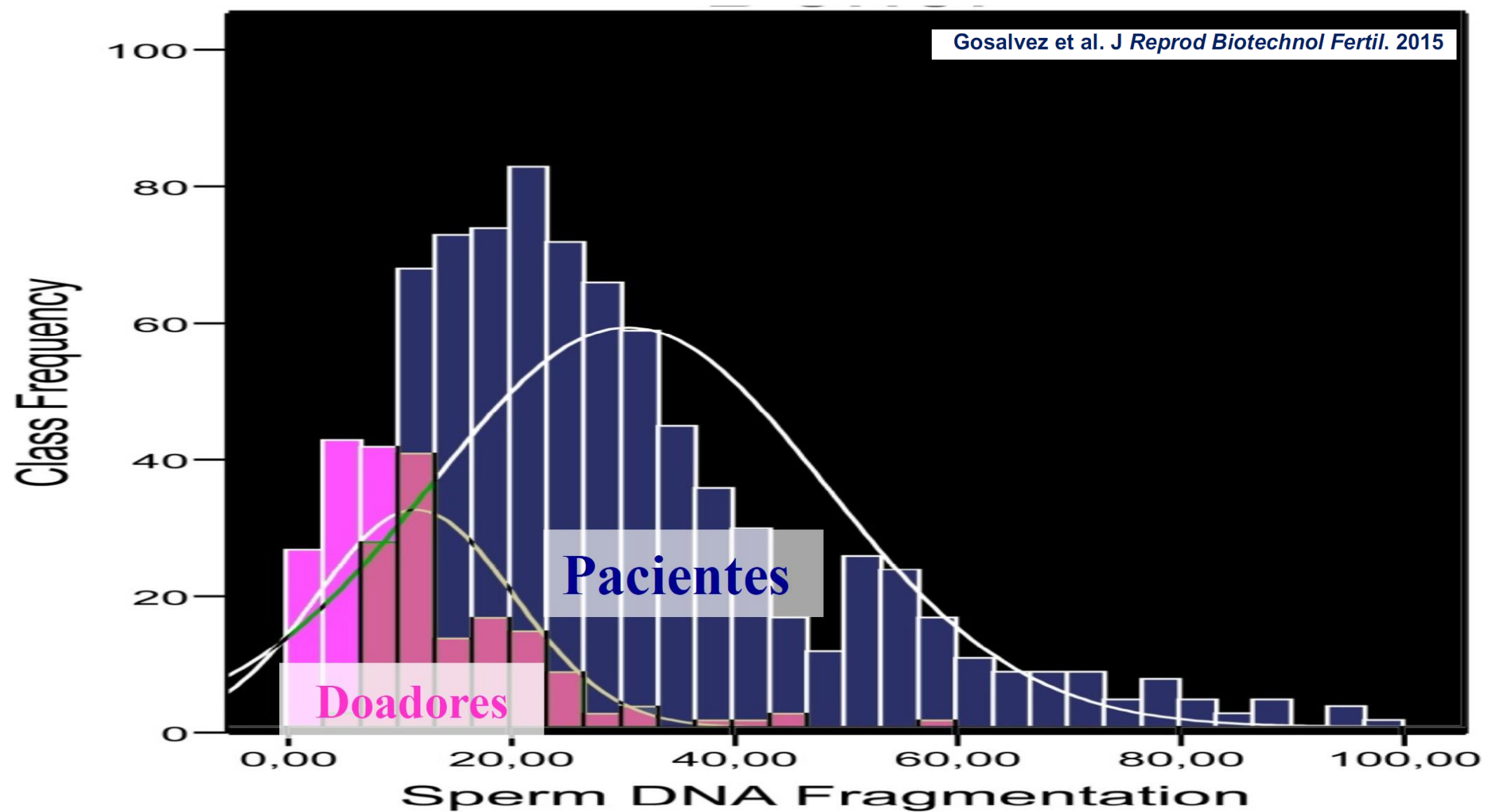


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Taxa de Fragmentação do DNA espermático





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^{1,*}, Armand Zini^{2,*}, Alina Dyachenko², Antonio Ciampi², Douglas T Carrell^{1,3,4}

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

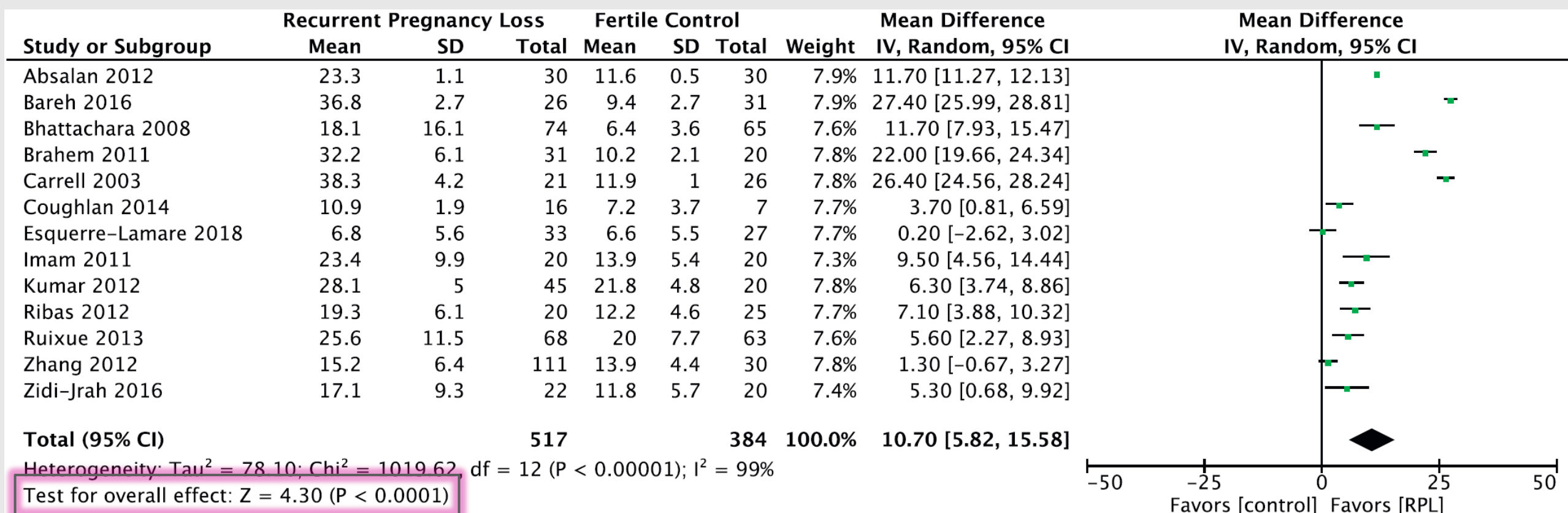
Effect	Number of studies	Fixed effects model		Random effects model	
		OR (95% CI)	P	OR (95% CI)	P
Overall effect	56	1.68 (1.49–1.89)	0.0000*	1.84 (1.5–2.27)	<0.0001*
Sperm DNA damage assays					
SCSA	23	1.18 (0.96–1.44)	0.1115	1.22 (0.93–1.61)	0.1522
TUNEL	18	2.18 (1.75–2.72)	0.0000*	2.22 (1.61–3.05)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

Asian Journal of Andrology (2017) 19, 80–90

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

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

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

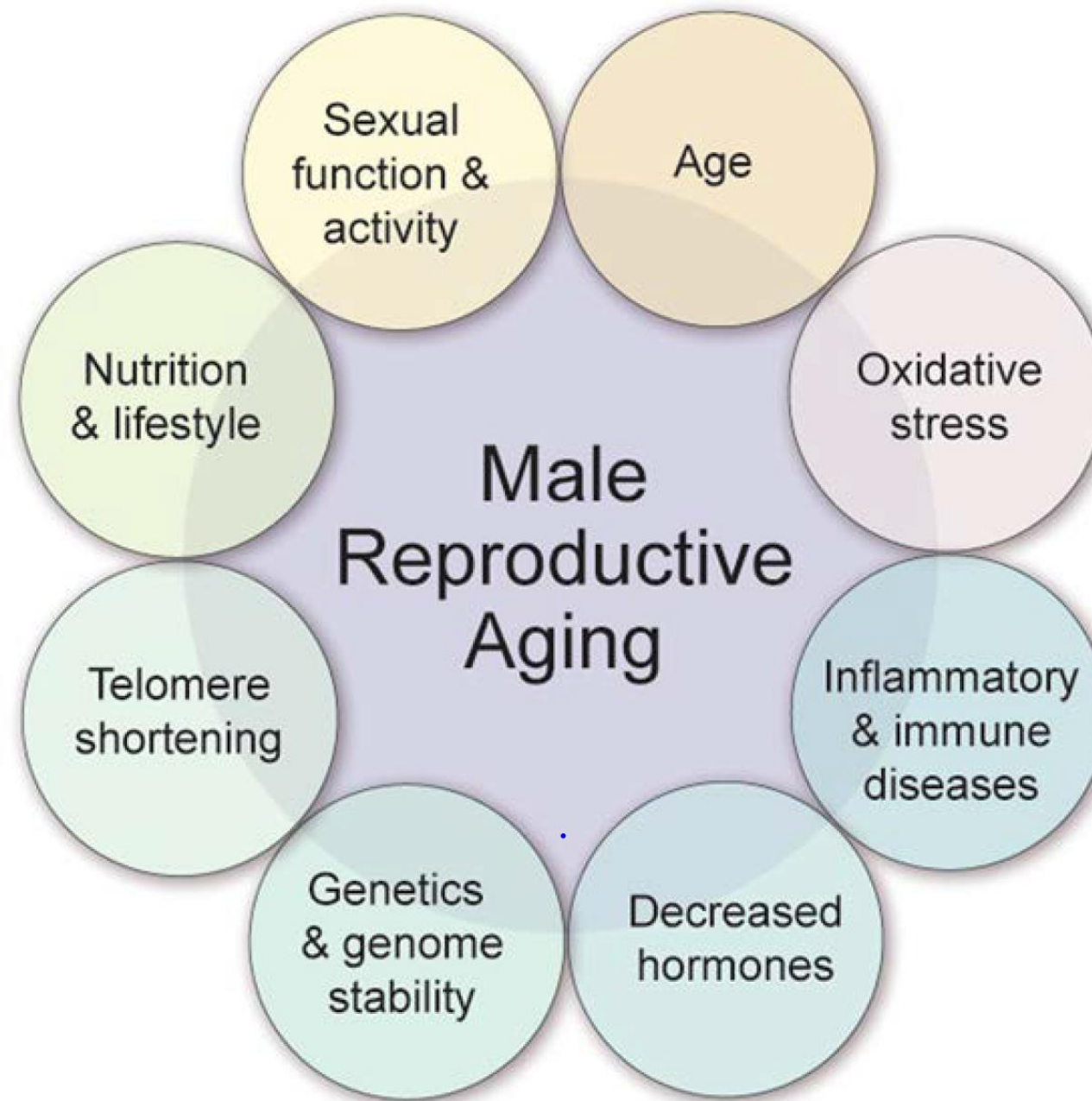
^a Adjusted for maternal age, maternal BMI, total FSH dose, number of retrieved oocytes, and paternal age.

^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.

**O jornal é de 1904,
veja a idade da vítima!**





ngular

Figure 1 Main factors involved in impaired male infertility due to reproductive aging.

Paternal age and reproduction

Gideon A. Sartorius^{1,2} and Eberhard Nieschlag^{1,3}

¹Centre of Reproductive Medicine and Andrology of the University, Domagkstrasse 11, D-48149 Muenster, Germany ²Present address: University Women's Hospital Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland

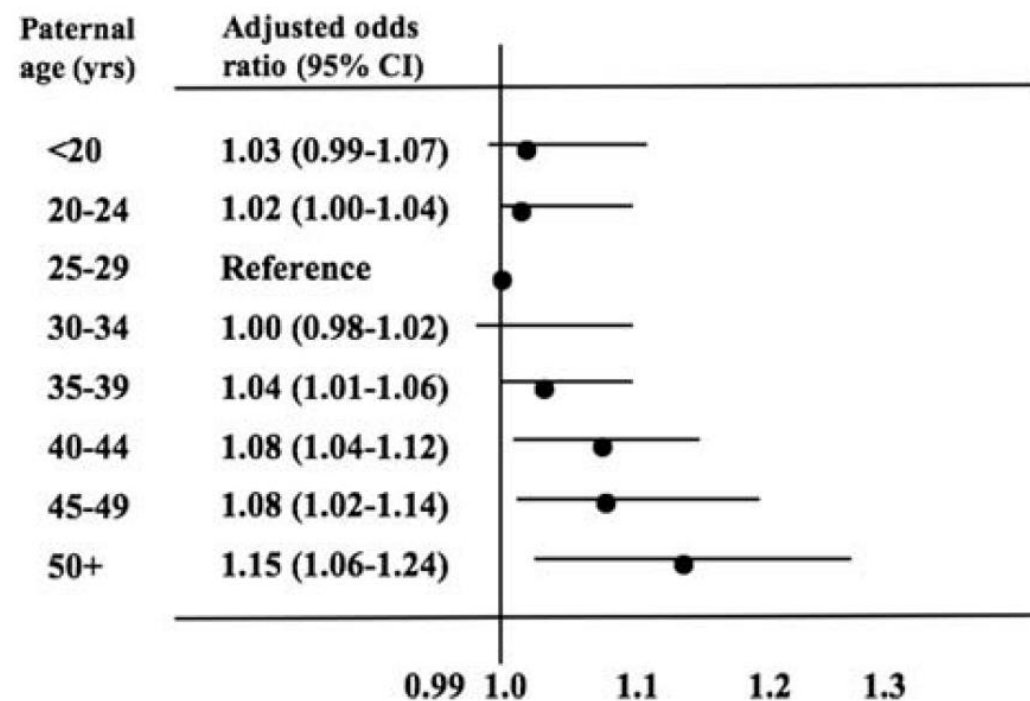


Figure 4 Relative risk of birth defects depending on paternal age.

Retrospective analysis of 5 213 248 subjects in the USA. Increased risk for heart defects, circulatory/respiratory defects, diaphragmatic hernia, tracheo-oesophageal fistulas, musculo-skeletal anomalies (data extracted from Yang *et al.*, 2007).

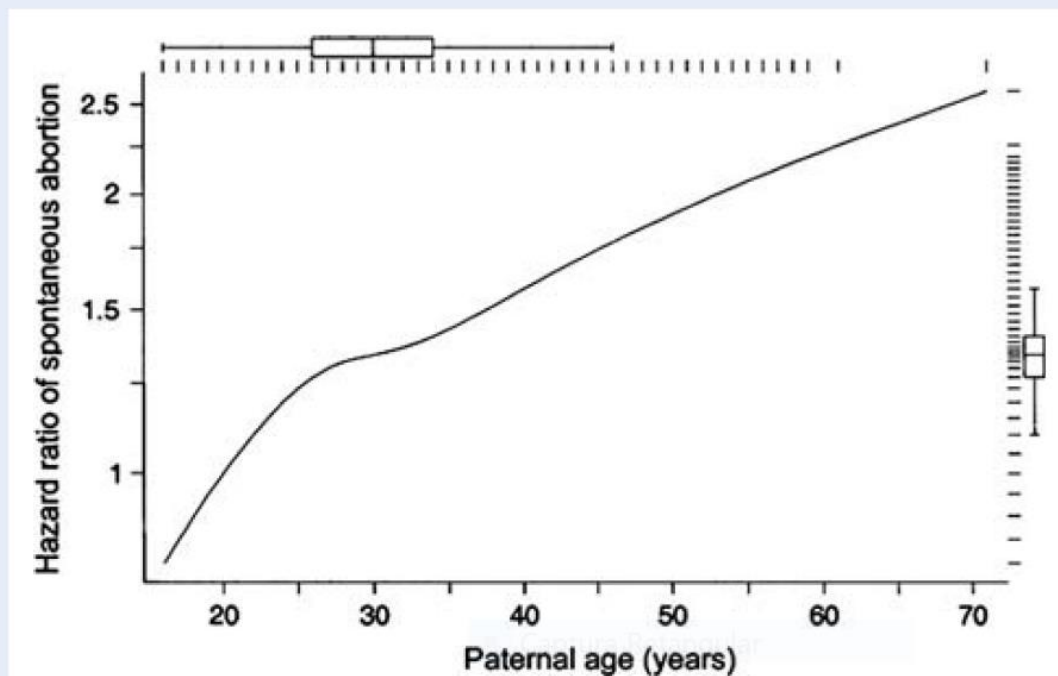


Figure 3 Hazard ratios of spontaneous miscarriages between 6 and 20 weeks according to paternal age adjusted for different confounders including maternal age (using prospective data from 5121 Californian women, men aged 20 years as referent).

Boxplots along the top and right side indicate data distribution according to each axis (with permission from Slama *et al.*, 2005).

Table XI Summary results of the meta-analyses of the association between paternal factors and perinatal and paediatric outcomes.

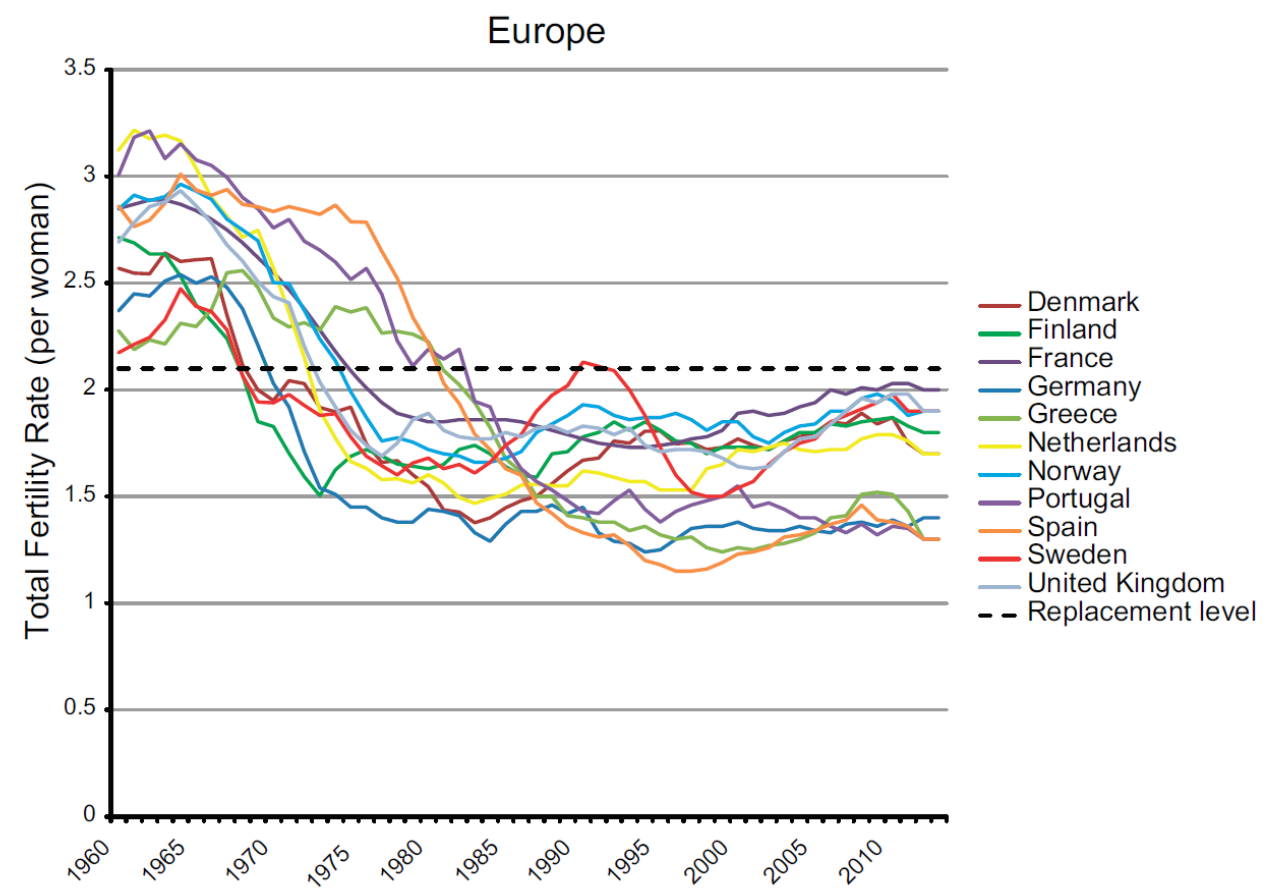
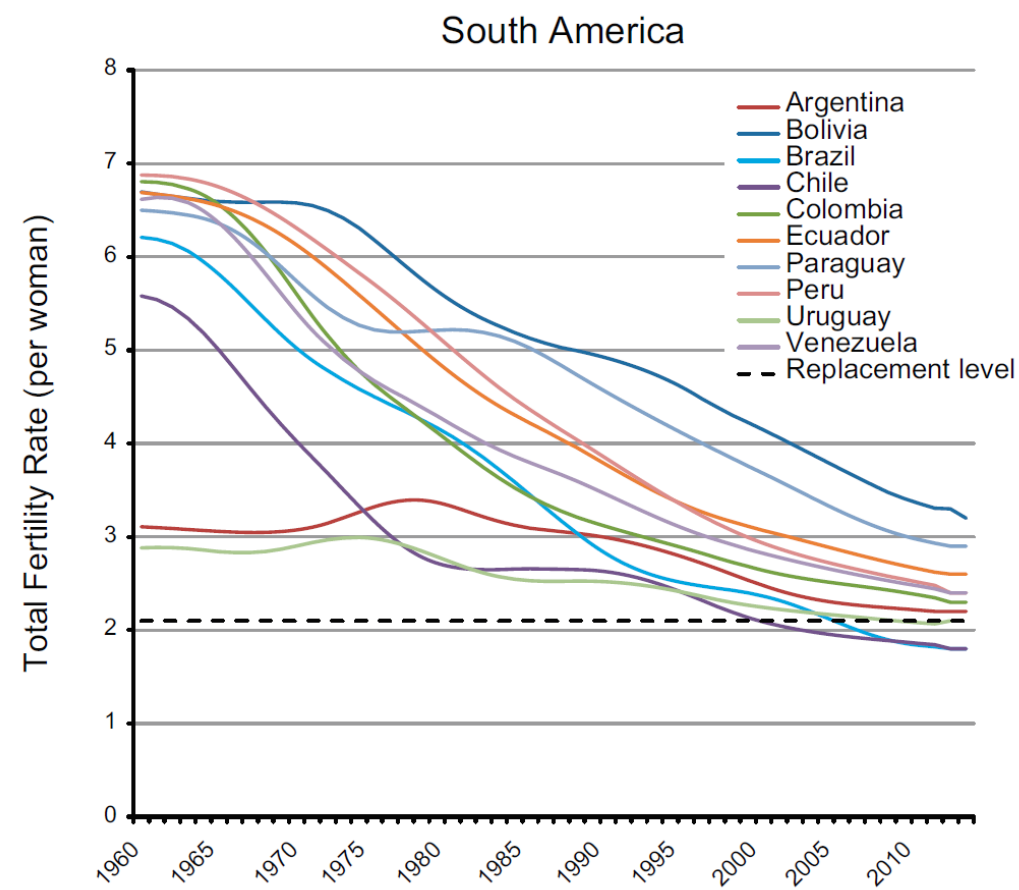
Exposure	Outcome	Pooled estimate (with 95% CI)	Certainty of evidence GRADE
Paternal age	PTB	1.02 (1.00–1.05)	⊕⊕○○
	Low BW	1.00 (0.97–1.03)	⊕⊕○○
	Stillbirth	1.19 (1.10–1.30)	⊕⊕○○
	Children with any birth defects	1.05 (1.02–1.07)	⊕⊕⊕○
	CHDs	1.03 (0.99–1.06)	⊕⊕⊕○
	Orofacial clefts	0.99 (0.95–1.04)	⊕⊕○○
		1.14 (1.02–1.29)*	
	Gastroschisis	0.88 (0.78–1.00)	⊕⊕⊕○
	Spina bifida	0.97 (0.90–1.04)	⊕⊕⊕○
	Trisomy 21	1.13 (1.05–1.23)	⊕⊕⊕○
Paternal BMI	Acute lymphoblastic leukaemia	1.08 (0.96–1.21)	⊕⊕⊕○
	Autism and ASDs	1.25 (1.20–1.30)	⊕⊕⊕○
Paternal smoking	Schizophrenia	1.31 (1.23–1.38)	⊕⊕⊕○
	No meta-analysis		
	PTB	1.16 (1.00–1.35)	⊕⊕○○
	Low BW	1.10 (1.00–1.21)	⊕⊕○○
	SGA	1.22 (1.03–1.44)	⊕⊕○○
	CHDs	1.75 (1.25–2.44)	⊕⊕○○
	Orofacial clefts	1.51 (1.16–1.97)	⊕⊕○○
	Brain tumours	1.12 (1.03–1.22)	⊕⊕○○

*Exposure: Paternal age >45 years.

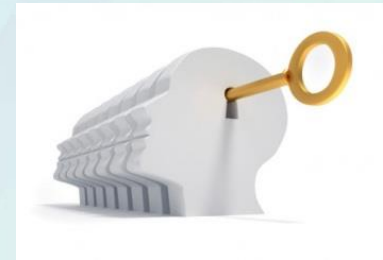
MALE REPRODUCTIVE DISORDERS AND FERTILITY TRENDS: INFLUENCES OF ENVIRONMENT AND GENETIC SUSCEPTIBILITY

Niels E. Skakkebaek, Ewa Rajpert-De Meyts, Germaine M. Buck Louis, Jorma Toppari, Anna-Maria Andersson, Michael L. Eisenberg, Tina Kold Jensen, Niels Jørgensen, Shanna H. Swan, Katherine J. Sapra, Søren Ziebe, Lærke Priskorn, and Anders Juul

Taxa de Fecundidade



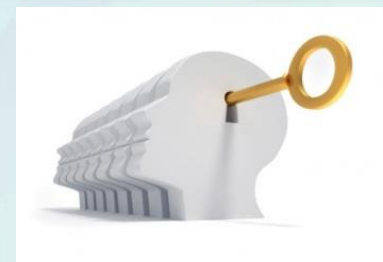
Take home message



- Análise seminal da OMS: não é um teste de fertilidade
- Número total de espermatozoides móveis (TMSC): melhor forma de avaliar a capacidade funcional dos espermatozoides
- fragDNA espermático: importante na avaliação da capacidade fértil do homem



Take home message



- Infertilidade por estresse oxidativo masculino (MOSI): novo diagnóstico de infertilidade masculina
- Quanto maior a alteração seminal: maior a possibilidade de alteração genética
- Idade masculina: relação direta com malformações na prole e maiores chances de perda da gravidez

FERTILIZAÇÃO IN VITRO | CONGELAMENTO DE EMBRIÕES, ÓVULOS, SÊMEN E TECIDOS | REVERSÃO DE VASECTOMIA | COITO PROGRAMADO | INSEMINAÇÃO ARTIFICIAL



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