



APLICAÇÃO DO CRITÉRIO APHRODITE PARA AVALIAÇÃO DA FERTILIDADE MASCULINA

Edson Borges Jr.

**Fertility Medical Group
FERTGROUP
Instituto Sapieniae**

Declaração

**Sem conflito de interesse para divulgar
relacionado ao assunto desta palestra**

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

Global fertility in 204 countries and territories, 1950–2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021

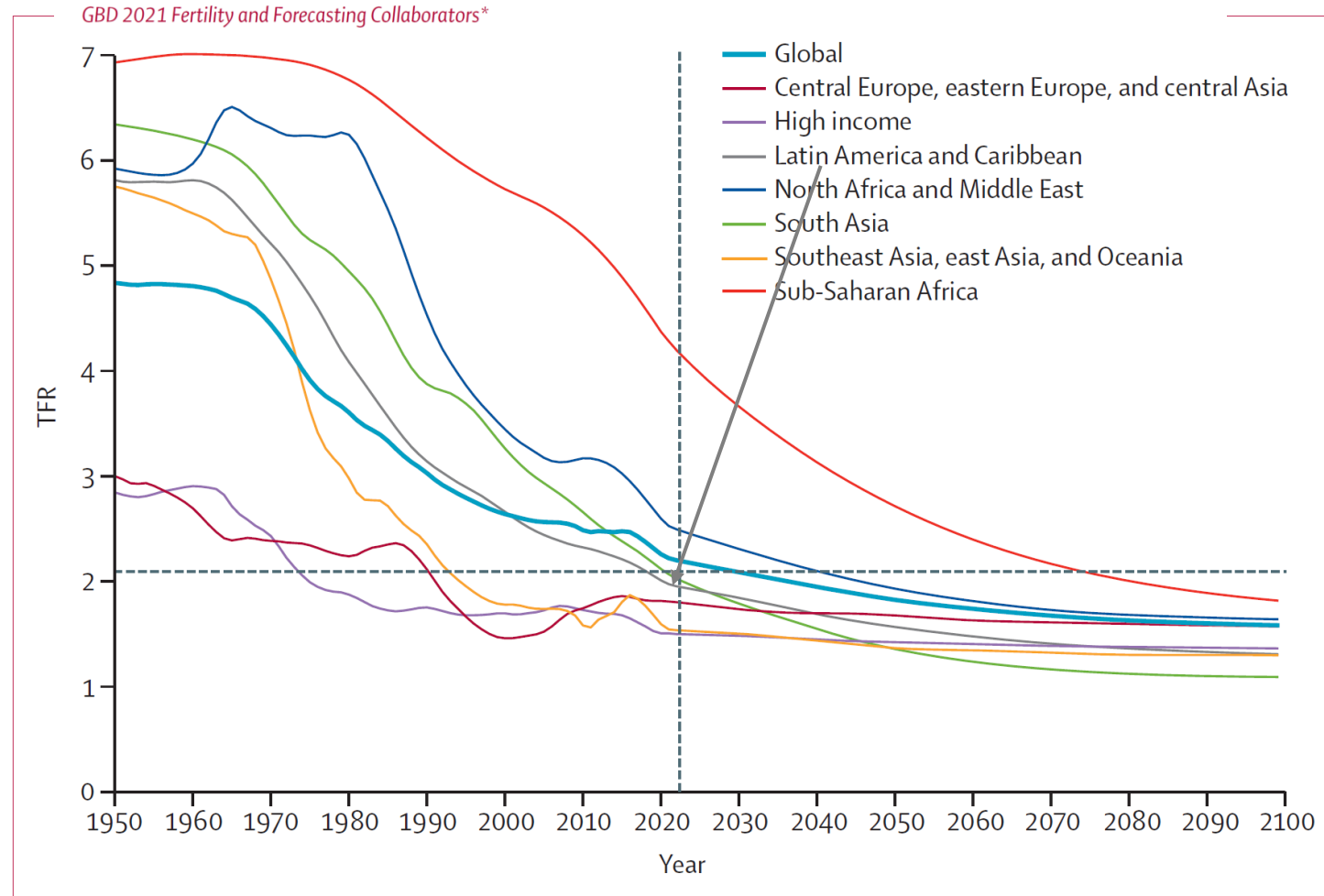


Figure 1: TFR, globally and by GBD super-region, 1950–2100

The dashed horizontal line indicates replacement TFR (2.1), and the dashed vertical line indicates the year 2022 (the first forecast year). GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. TFR=total fertility rate.

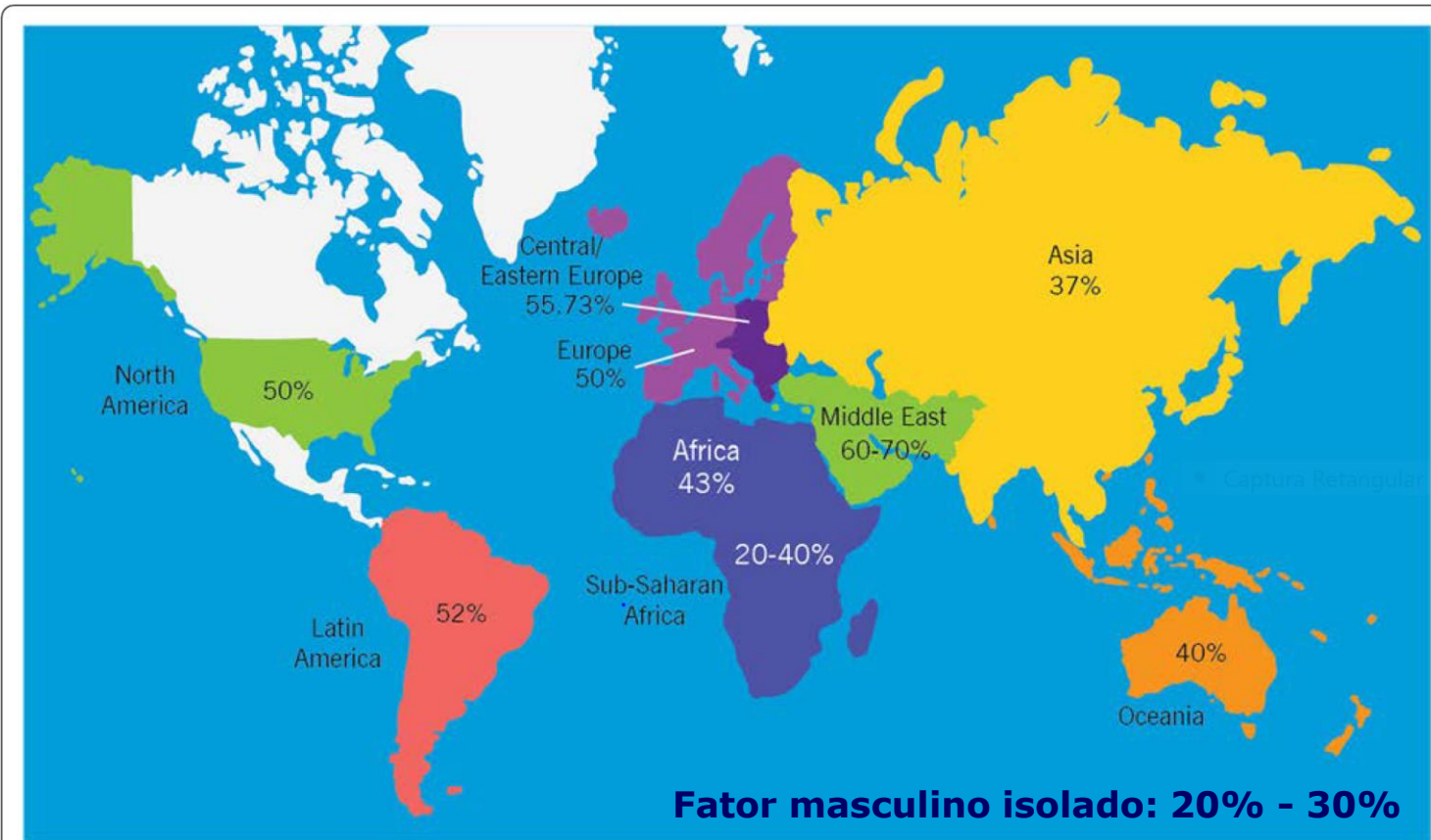


Figure 2 World map containing percentages of infertility cases per region that are due to male factor. This figure demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement.

Physiol Rev 96: 55–97, 2016

Published November 18, 2015; doi:10.1152/physrev.00017.2015

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**

Incidência de Criptorquidia

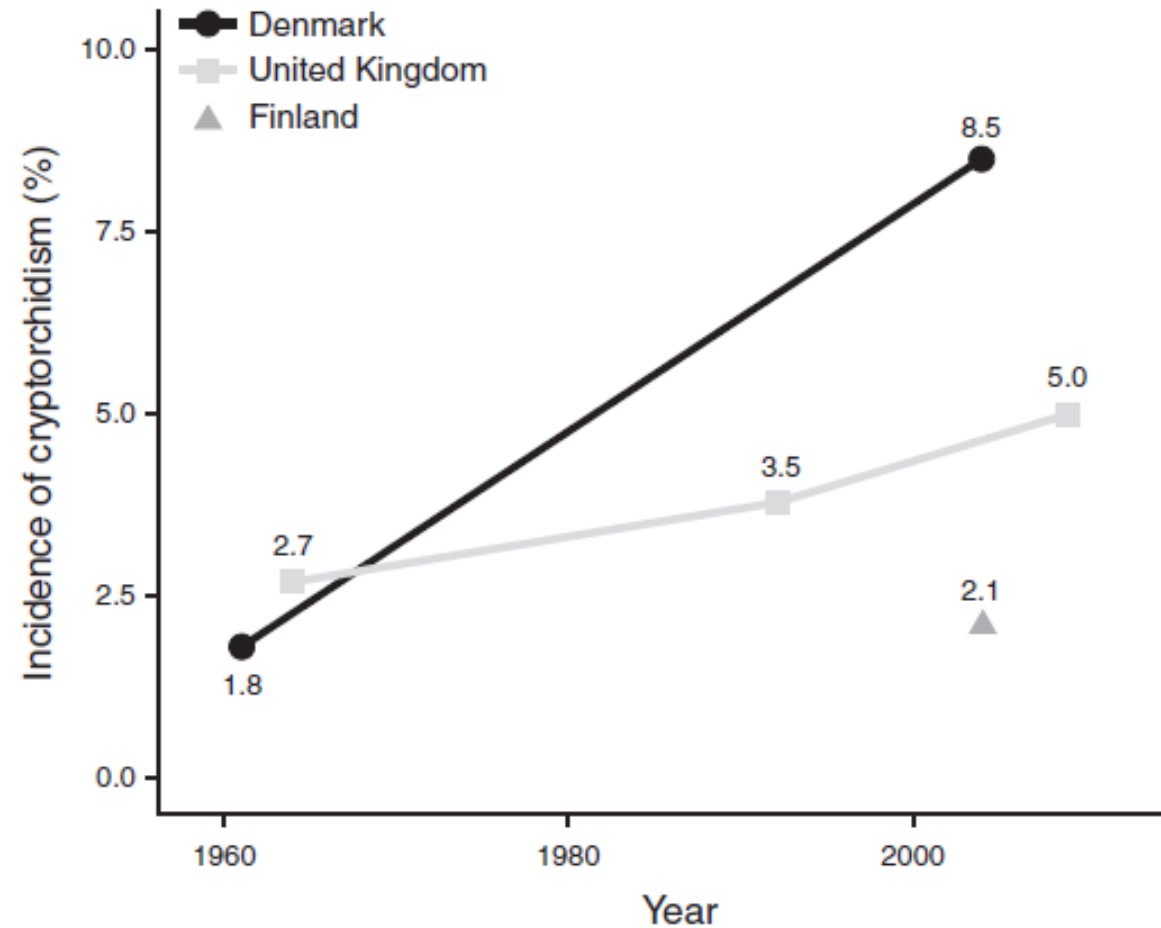


FIGURE 7. Incidence of cryptorchidism at birth on the basis of prospective clinical studies from the 1950s to the 2000s in Denmark, Finland, and United Kingdom. The data points are marked on the year of the publication of the study which represents the preceding incidence rate (3, 47, 61, 184, 377).

Idade da Puberdade

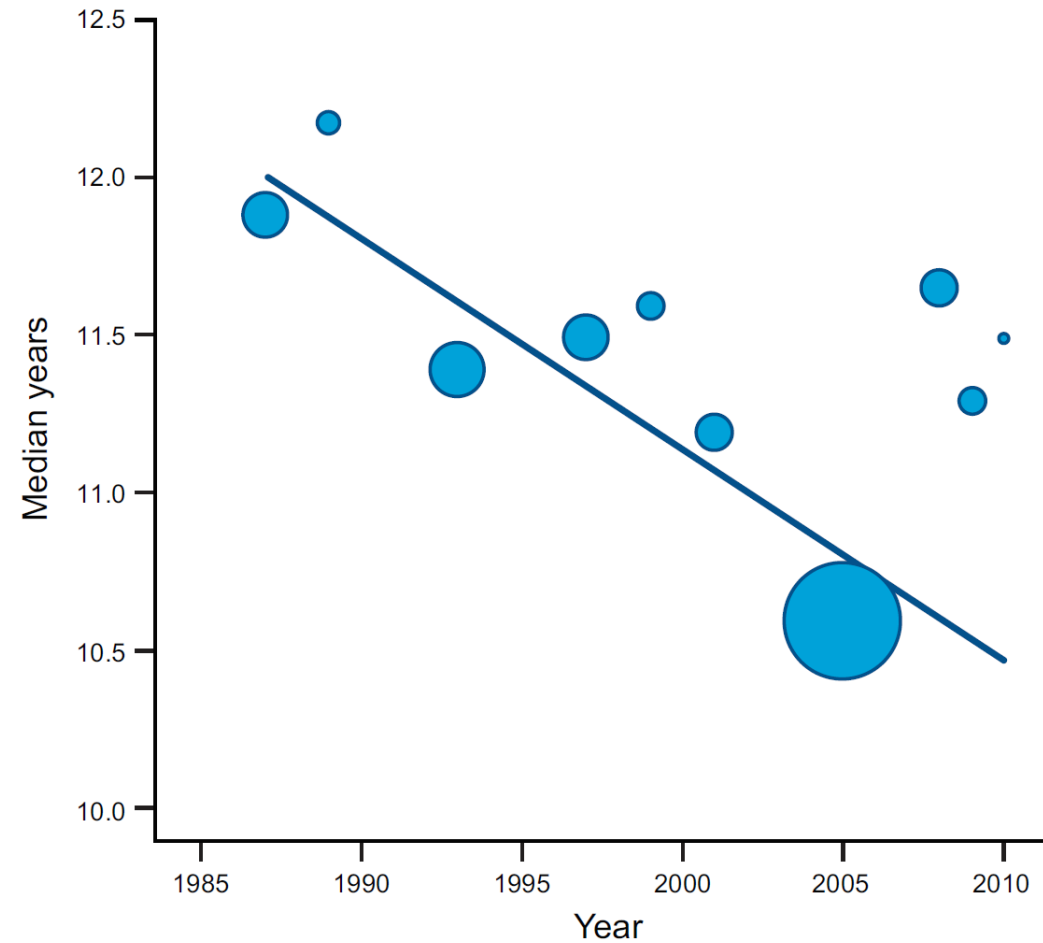


FIGURE 8. Recent changes in male pubertal timing. Testicular volume was >3 ml. [From Mouritsen et al. (293).]

Incidência de Câncer de Testículo

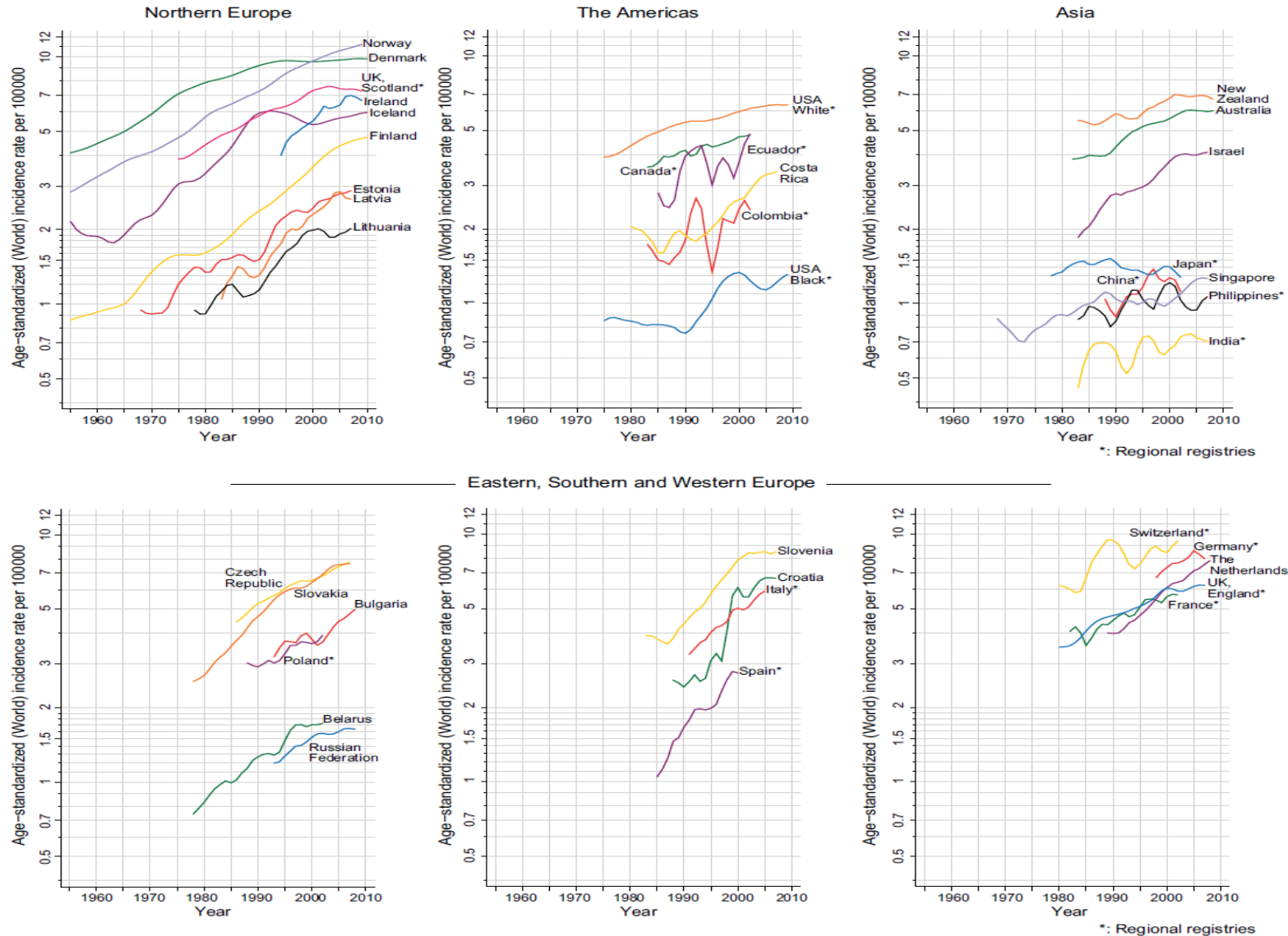


FIGURE 4. Trends in testicular cancer; age-standardized (world) incidence (regional or national), all ages. [Modified from Znaor et al. (481). Courtesy of Dr. Arinana Znaor and statistician Mathieu Laversanne, M.Sc., WHO, International Agency for Research in Cancer (IARC), Lyon, France.]

Decline in sperm count in European men during the past 50 years

P Sengupta^{1,2}, E Borges Jr³, S Dutta⁴ and E Krajewska-Kulak²

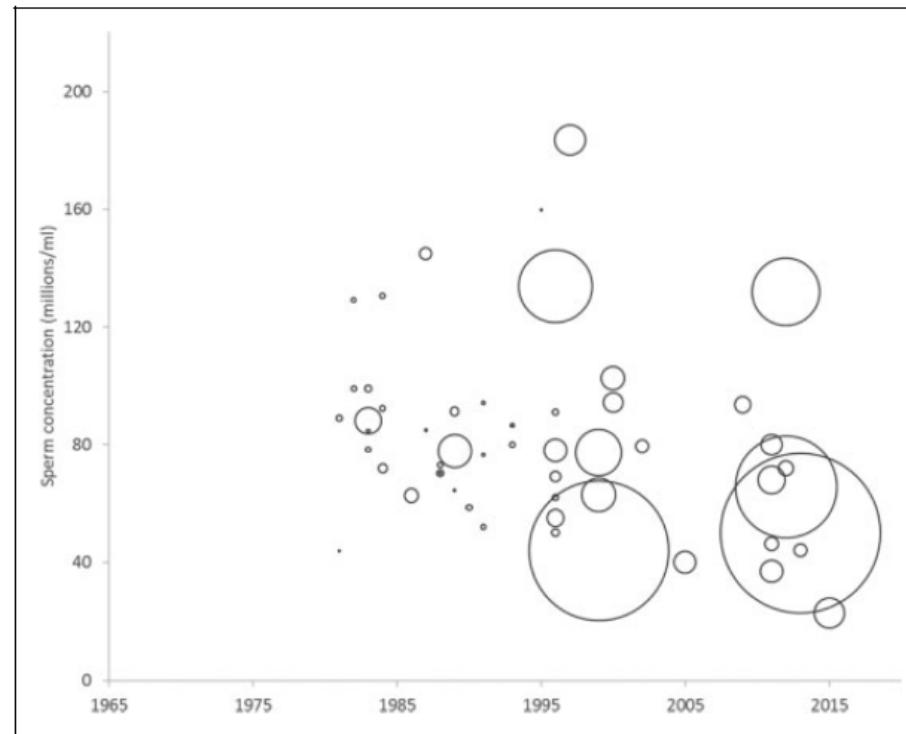
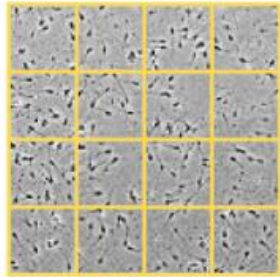


Figure 1. Temporal decline in sperm concentration ($\times 10^6/\text{ml}$) from 1965 to 2015, bubble size corresponds to the number of men in the study.

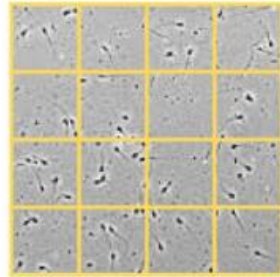
A time dependent decline in sperm concentration was observed from 1965 to 2015 ($r=0.307$, $p=0.02$)
An overall 32.5% decrease in mean sperm concentration

GRAPHICAL ABSTRACT

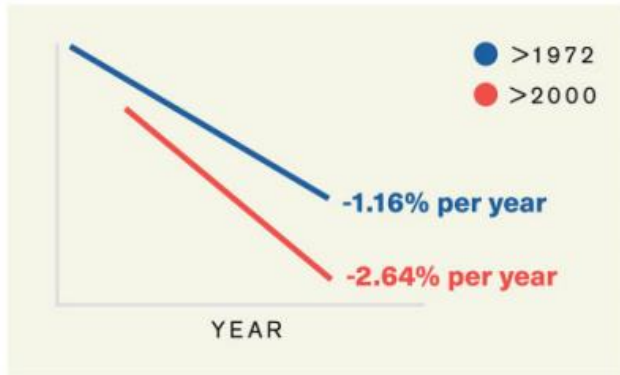
Sperm count is declining at an accelerated pace **globally**



101 mill/ml
(1973)



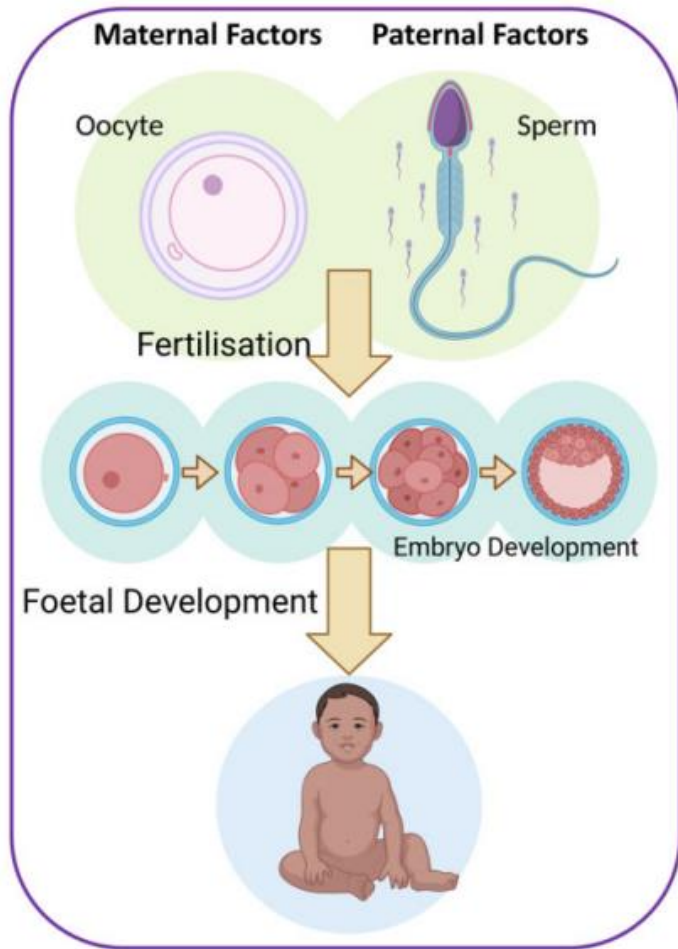
49 mill/ml
(2018)



Sperm count is declining at an accelerated pace globally.

Human Reproduction Update, Vol.29, No.2, pp. 157–176, 2023

Advance Access Publication on November 15, 2022 <https://doi.org/10.1093/humupd/dmac035>



Paternal Factors that contribute to Early Embryo Development

Epigenetic Components

- Histone Modifications
- DNA Methylation

Seminal Plasma Components

- Extracellular Vesicles

Genetic Components

- Sperm DNA Integrity
- RNAs
 - Coding
 - Non-coding
- Proteins

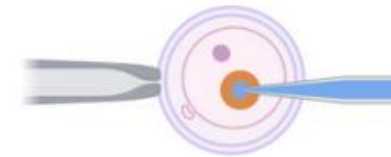
Sperm Centrioles

Fertilisation factors

- PLCZ

Impact of Understanding Paternal Contributions

Improve ART techniques



Help highlight issues leading to miscarriage or congenital disease



Human Reproduction Update, Vol.29, No.4, pp. 395–433, 2023

Paternal Factors that contribute to Early Embryo Development

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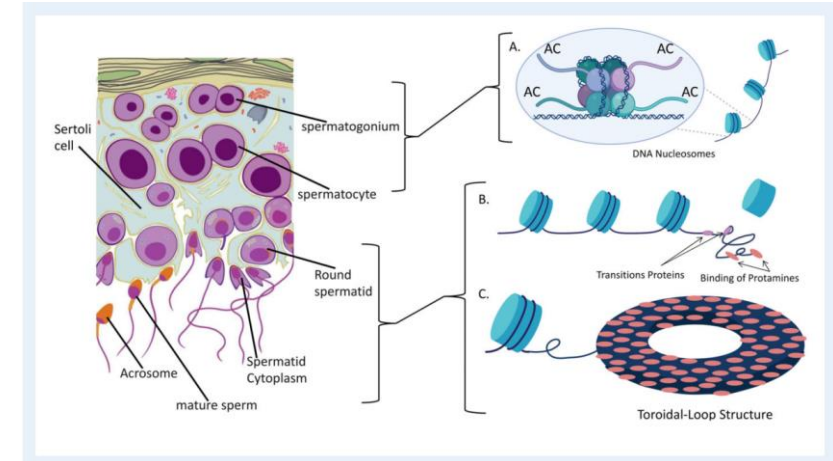
Fertilisation factors

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Human Reproduction Update, Vol.29, No.4, pp. 395–433, 2023

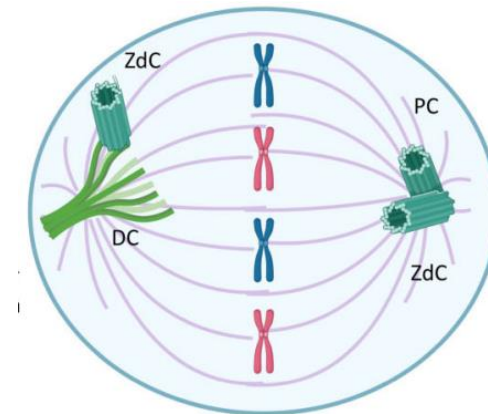
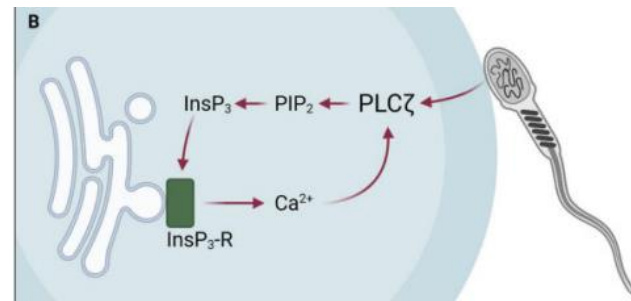
Contribuição do SÊMEN na fertilização e divisão embrionária

- ➔ **Plasma seminal - vesículas extracelulares:** epididimossomos e prostatossomos, com influência na gametogênese, fertilização, embriogênese e receptividade endometrial
- ➔ **Espermatogênese:** material genético e influência epigenética (histonas/protaminas)

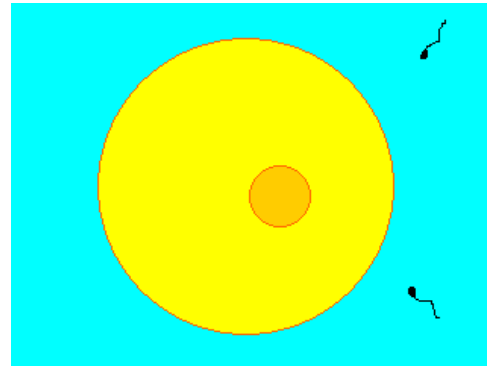


- ➔ **Centríolos:** divisão embrionária

- ➔ **Fertilização:** PLC zeta



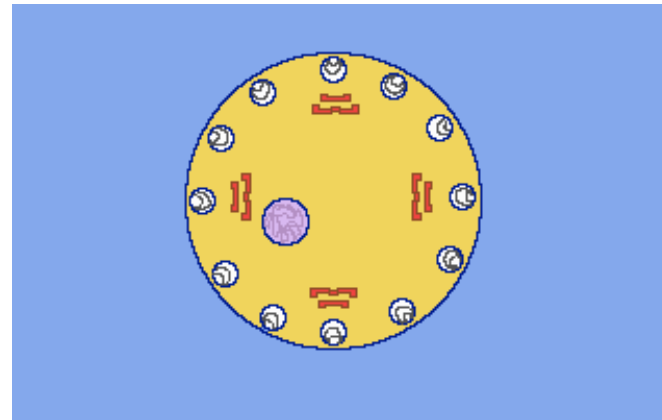
Mecanismos do “efeito paterno” no desenvolvimento embrionário pré-implantacional



EFEITO PATERNO PRECOCE:

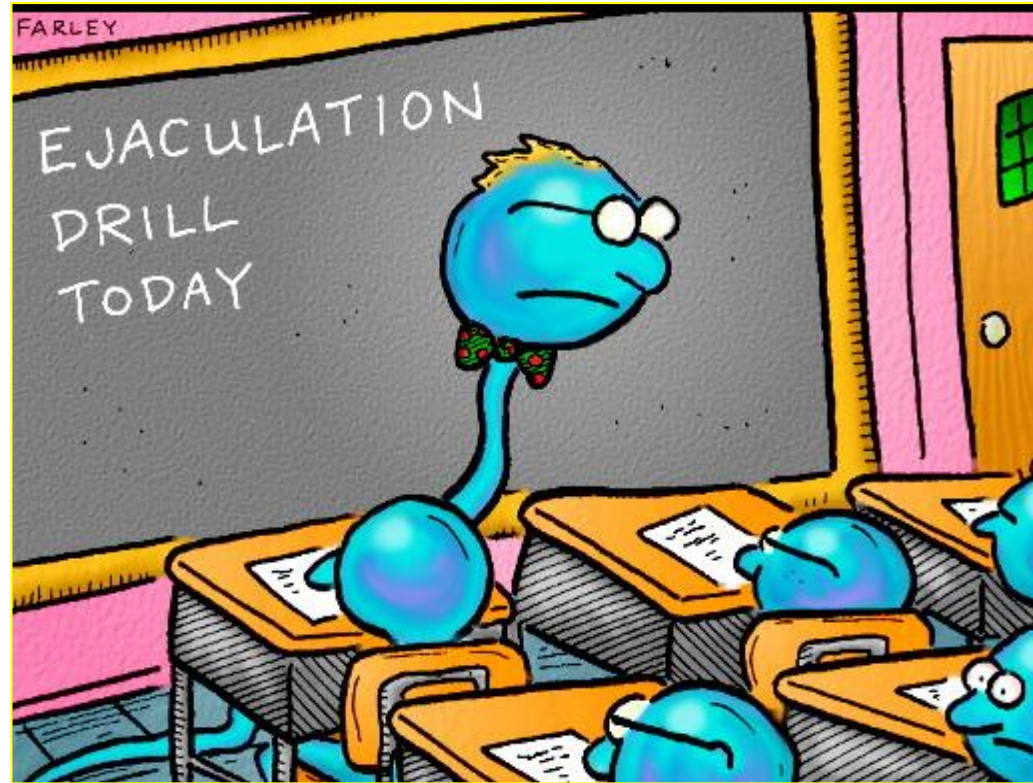
- ➔ anormalidades do centríolo e da ativação ovocitária
- ➔ fecundação e divisão embrionária inicial

Mecanismos do “efeito paterno” no desenvolvimento embrionário pré-implantacional



EFEITO PATERNO TARDIO:

- relacionado com a fragmentação do DNA espermático
- divisão embrionária tardia
- implantação
- desenvolvimento embrionário / fetal



*Qualidade do Espermatozoide
X
Chances de Sucesso*

Qualidade seminal e resultados de T.R.A.



ANDROLOGIA 30, 5

The outcome of intracytoplasmic sperm injection

R. Mercan, S. E. Laney, J. L. Laney
The Howard and Georganos School of Medicine,
Virginia Commonwealth University, Richmond, Virginia

Andrology: The results of the first three basic sperm parameters

Z.P. Nagy, J. Liu, H. Joris, G. Verheyen

Human Reproduction, Volume 10, Issue 1, February 1995, pp. 1-6

<https://doi.org/10.1093/oxfordjournals.oup.com/humrep.a101001>



Journal Article

... is not related to any of the

ACCEPTED: SEPTEMBER 16, 1997

Low sperm count and low sperm motility: is it related to any of the

and S. Oehninger

Obstetrics and Gynecology Eastern

J. ...
... M.D. ...

... University, Cairo, Egypt

Ragaa T. M. ...
Mohamed A. Abou ...
Gamal I. Serour, M.D. *§

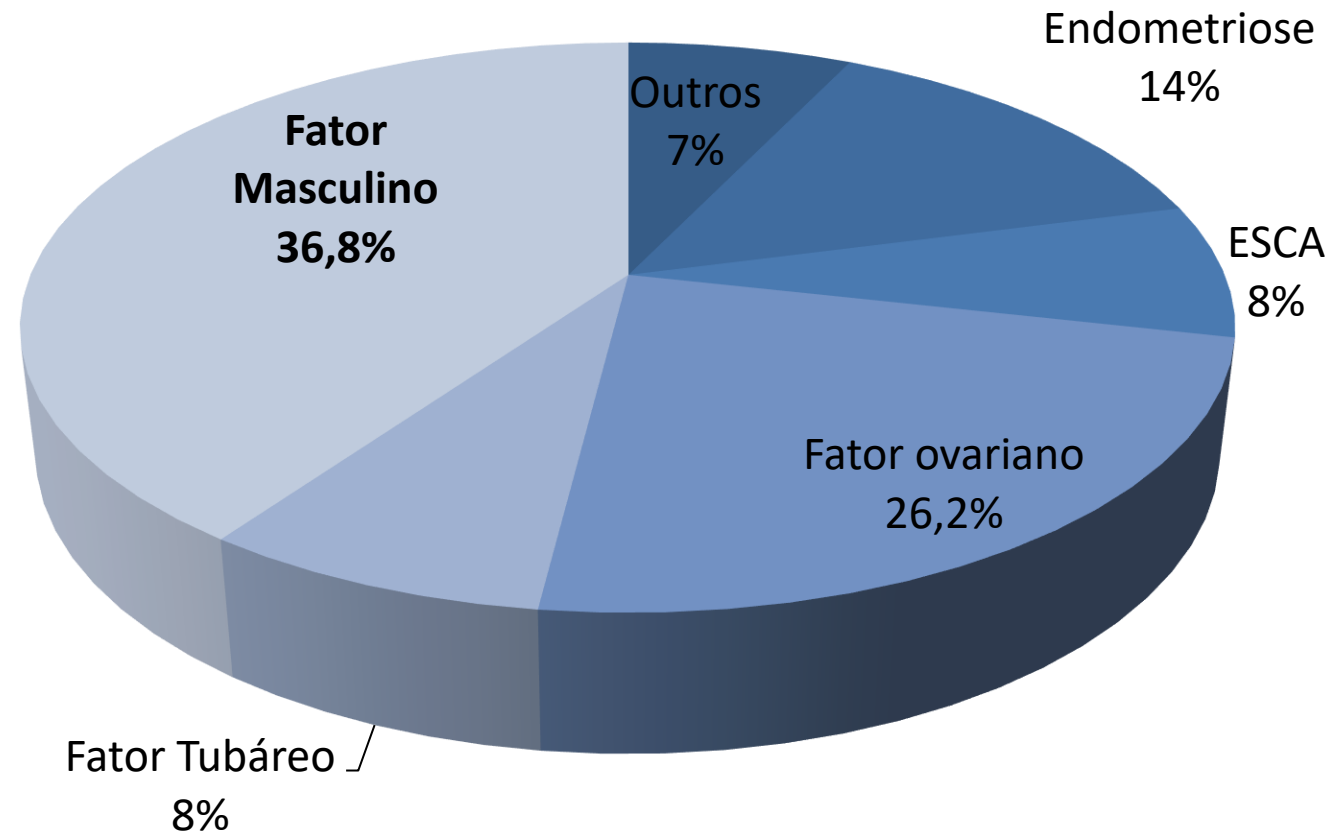
The Egyptian IVF-ET Center, Cairo University

Consequências da Alteração Espermática

- ➔ menores taxas de fertilização
- ➔ desenvolvimento embrionário inadequado
- ➔ maiores taxas de aborto
- ➔ piores condições perinatais
- ➔ maior incidência de doenças epigenéticas
- ➔ maiores taxas de malformações...

Slama et al, 2005, Nybo Anderson et al, 2004, Bille et al, 2005, Nieschlag et al, 2004, Tesarik et al, 2006, Wyrobek et al, 2006, Borini et al, 2007. Middelburg et al, 2008 ...

FERTILITY MEDICAL GROUP 2005 - 2023



Influência da qualidade do espermatozoide ejaculado nos resultados de ICSI – JBRA, 5: 22-26, 2001

Borges Jr. E., et al

	< 1 x 10⁶/ml motilidade <10%	sem fator masculino	P
Ciclos / pacientes	105 / 82	184 / 141	
Fertilização Normal (2PN)	628 (36,0%)	1256 (67,8%)	0,014
Oócitos não-fertilizados	942 (54,1%)*	362 (19,6%)	0,025
Bons embriões	44,5%	87,1%	0,029
Gestação / ciclo	31,4%	29,9%	0,216
Gestação/ paciente	40,8%	38,9%	0,067
Abortamento	43,5% (10/33)	25,4 % (14/55)	0,012

* Idade materna ≤ 35 anos e Número de ovócitos recuperados ≥ 4

ORIGINAL ARTICLE

Correspondence:

Edson Borges Jr., MD, PhD, Av. Brigadeiro Luis Antonio, 4545, Sao Paulo 01401-002, SP, Brazil.
E-mail: edson@fertility.com.br

*These authors contributed equally to this manuscript.

Keywords:

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

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doi: 10.1111/andr.12199

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

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

- ➔ **Definição: $TMSC = volume \times conc/ml \times \% A+B / 100\%$**
- ➔ **518 ciclos de ICSI**
- ➔ **TMSC normal: > 20 milhões**

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

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

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

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

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

Blastocyst expansion grade on D5	Concentration	0.83	0.66–1.05	0.120
	Motility	1.01	0.79–1.29	0.948
	Progressive motility	1.08	0.85–1.38	0.533
	Morphology	0.99	0.57–1.71	0.962
	TMSC	1.27	1.01–1.60	0.042
	Normal TMSC	1.03	0.98–1.07	0.287
Implantation rate	Concentration	2.387	0.1%	0.492
	Motility	–2.916	0.1%	0.453
	Progressive motility	–1.754	0.0%	0.616
	Morphology	6.084	0.0%	0.502
	TMSC	–0.688	0.0%	0.833
	Normal TMSC	1.705	1.0%	0.222
Pregnancy	Concentration	0.71	0.49–1.05	0.083
	Motility	0.77	0.50–1.19	0.242
	Progressive motility	0.72	0.49–1.05	0.089
	Morphology	2.17	0.78–6.07	0.132
	TMSC	1.40	0.98–2.01	0.066
	Normal TMSC	0.94	0.86–1.03	0.200
Miscarriage	Concentration	0.57	0.30–1.08	0.089
	Motility	1.32	0.61–2.85	0.478
	Progressive motility	1.05	0.54–2.05	0.886
	Morphology	0.84	0.17–4.08	0.826
	TMSC	0.52	0.28–0.90	0.045
	Normal TMSC	1.12	0.91–1.26	0.084

Use of suboptimal sperm increases the risk of aneuploidy of the sex chromosomes in preimplantation blastocyst embryos

Alison Coates, B.Sc.,^{a,b} John S. Hesla, M.D.,^a Amanda Hurliman, M.D.,^a Breanne Coate, B.S.,^a Elizabeth Holmes, M.S.,^a Rebecca Matthews, Ph.D.,^a Emily L. Mounts, M.S.,^a Kara J. Turner, Ph.D.,^b Alan R. Thornhill, Ph.D.,^{b,c} and Darren K. Griffin, D.Sc.^b

- ➔ A infertilidade masculina grave está associada a *um aumento significativo na ocorrência de anormalidades dos cromossomos sexuais em blastocistos*, em comparação com embriões derivados de amostras de sêmen normais.
- ➔ As *taxas de aneuploidia* em embriões derivados de sêmens com *parâmetros normais* não foram significativamente diferentes se *ICSI ou inseminação padrão* foi usada para obter a fertilização.

Effect of the male factor on the clinical outcome of intracytoplasmic sperm injection combined with preimplantation aneuploidy testing: observational longitudinal cohort study of 1,219 consecutive cycles


Rossella Mazzilli, M.D.,^{a,b} Danilo Cimadomo, M.Sc.,^{b,c} Alberto Vaiarelli, M.D.,^{b,d} Antonjo Capalbo, Ph.D.,^{b,e} Lisa Dovere, Ph.D.,^b Erminia Alviggi, M.Sc.,^f Ludovica Dusi, Ph.D.,^g Carlo Foresta, M.D.,^h Francesco Lombardo, M.D.,ⁱ Andrea Lenzi, M.D.,ⁱ Herman Tournaye, M.D.,^j Carlo Alviggi, M.D.,^k Laura Rienzi, M.Sc.,^{b,f,g} and Filippo Maria Ubaldi, M.D.^{b,f,g}

VOL. 108 NO. 6 / DECEMBER 2017

➔ O fator masculino grave prejudica a competência embrionária precoce em termos de *taxa de fertilização e potencial de desenvolvimento*.



Male factor infertility impacts the rate of mosaic blastocysts in cycles of preimplantation genetic testing for aneuploidy

Nicoletta Tarozzi¹ · Marco Nadalini¹ · Cristina Lagalla¹ · Giovanni Coticchio¹  · Carlotta Zacà¹ · Andrea Borini¹

- ➔ Taxa significativamente *maior taxa de blastocistos em mosaico* foi observada no *grupo MF* (3,6% vs. 0,5%, *respectivamente*; $P = 0,03$).
- ➔ Taxa significativamente *maior de blastocistos em mosaico* foi observada no *grupo SMF* (7,7% e 1,8%, *respectivamente*; $P = 0,008$).

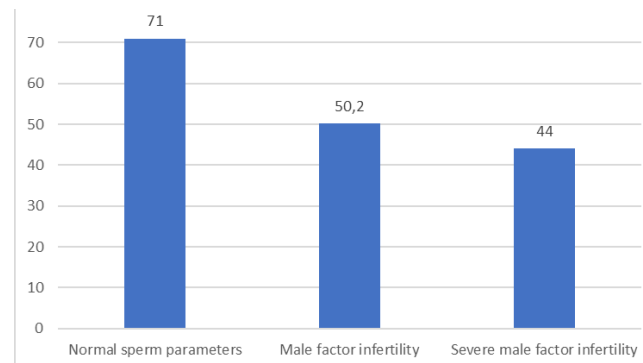
Table 1. Comparison of cycle characteristics and clinical outcomes between ICSI cycles with Normal Sperm Parameters, Male Factor Infertility (< 20M sptz /mL), and Severe Male Factor Infertility (< 1M sptz /mL) .

Variable	Normal sperm parameters	Male factor infertility	Severe male factor infertility	p
Cycles n=3678	2583	795	300	
Female age (years)	33.1 ± 3.8	33.3 ± 2.4	33.8 ± 2.8	0.451
Male age (years)	37.545 ± 0.5	37.870 ± 0.4	37.490 ± 0.2	0.478
Retrieved oocytes (n)	11.2 ± 1.2	17.4 ± 1.0	17.8 ± 4.6	0.384
Fertilization (%)	89.5 ± 8.4	89.8 ± 2.3	88.9 ± 2.8	0.475
High quality embryos rate (%)	31.8 ± 1.0 ^a	27.1 ± 2.4 ^b	24.9 ± 3.0 ^c	<0.001
Blastocyst formation (%)	43.3 ± 4.4	44.3 ± 4.4	38.5 ± 3.8	0.263
Implantation rate	40.4 ± 0.8 ^a	33.6 ± 0.5 ^b	28.5 ± 1.0 ^c	< 0.001
Pregnancy Rate	47.0 ± 5.8 ^a	44.0 ± 2.5 ^{a,b}	35.0 ± 7.3 ^b	0.045
Miscarriage Rate	8.4 ± 6.8 ^a	10.3 ± 5.7	12.4 ± 8.4	0.351

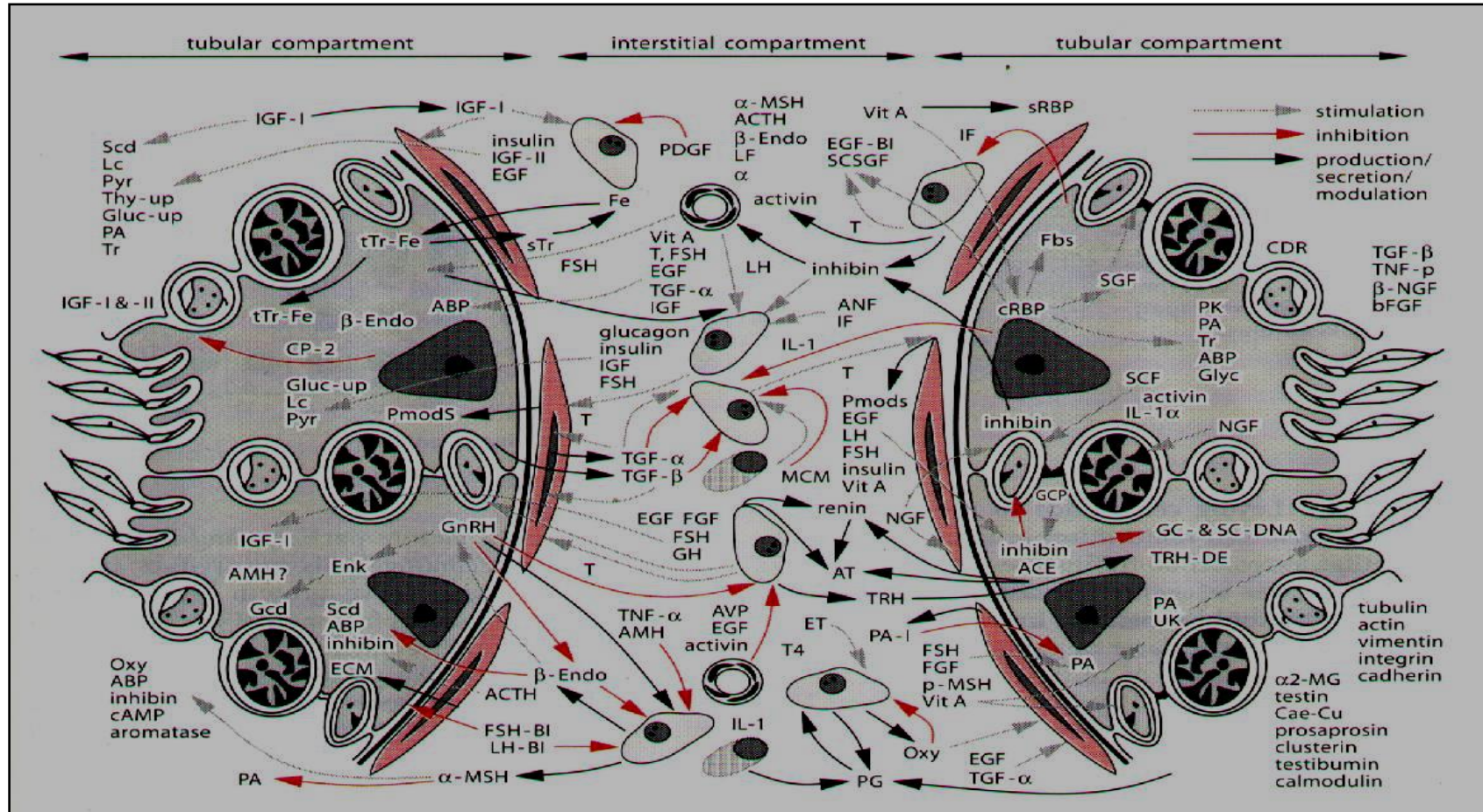
Note: Values are means ± standard errors. a#b#c

Table 2. Incidence of euploidy among ICSI cycles with Normal Sperm Parameters, Male Factor Infertility (< 20M spz /mL), and Severe Male Factor Infertility (< 1M spz /mL) .

Variable	Normal sperm parameters	Male factor infertility	Severe male factor infertility	p
Cycles n=813	540	198	75	
Biopsied Embryos	1,140	270	120	
Euploidy rate	71.0 ± 17.1 ^a	50.2 ± 35.4 ^{a,b}	44.0 ± 6.4 ^b	0.035



TÚBULO SEMINÍFERO



- 65-70 dias: espermatogônia - espermatozoide
- 3 mitoses + 2 meioses
- $10^{12} - 10^{13}$: produção em vida
- 75% perda por apoptose

Espermatogênese

A espermatogênese ocorre dentro dos túbulos seminíferos testiculares de forma gradual, exigindo estímulos autócrinos, parácrinos e endócrinos que são **controlados pelas ações do FSH e do LH**.

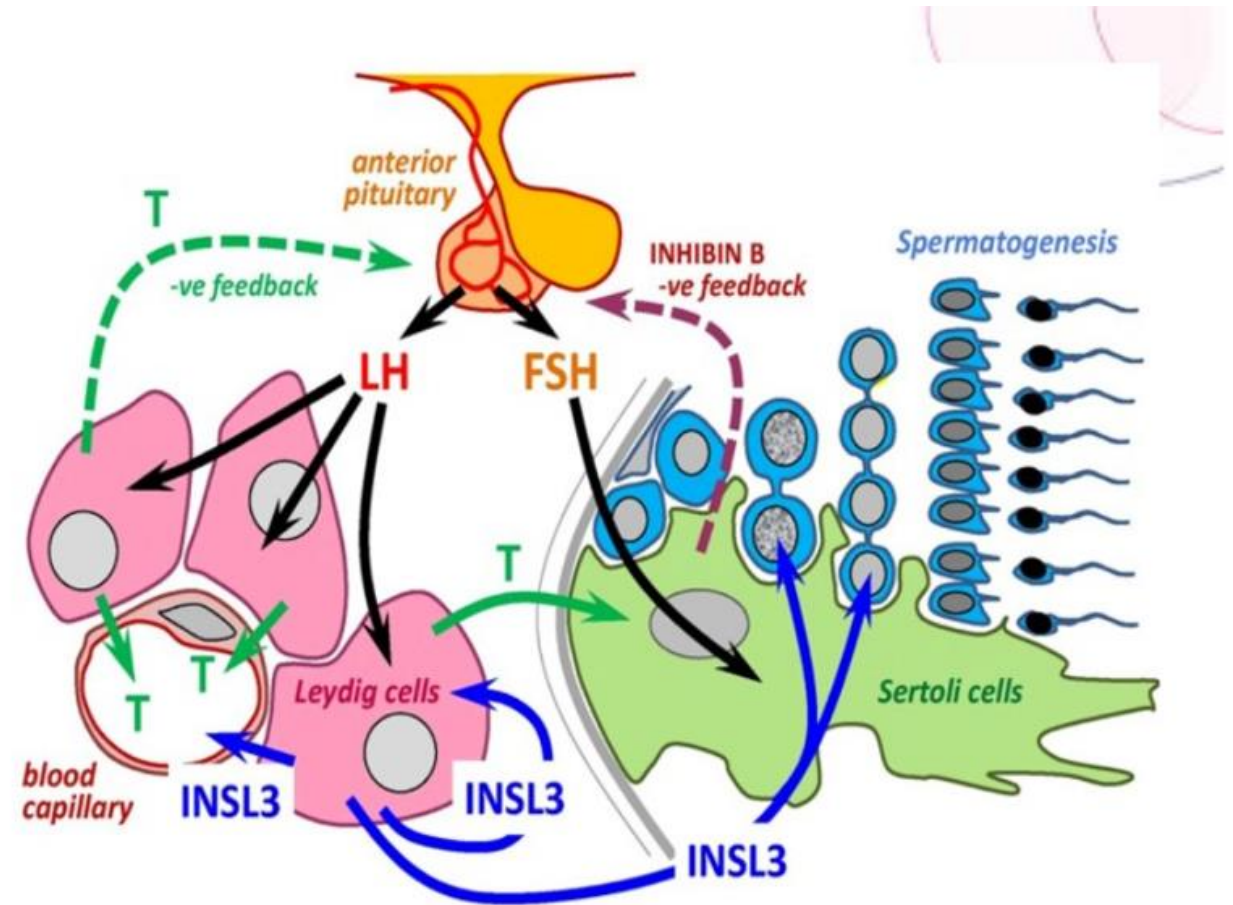
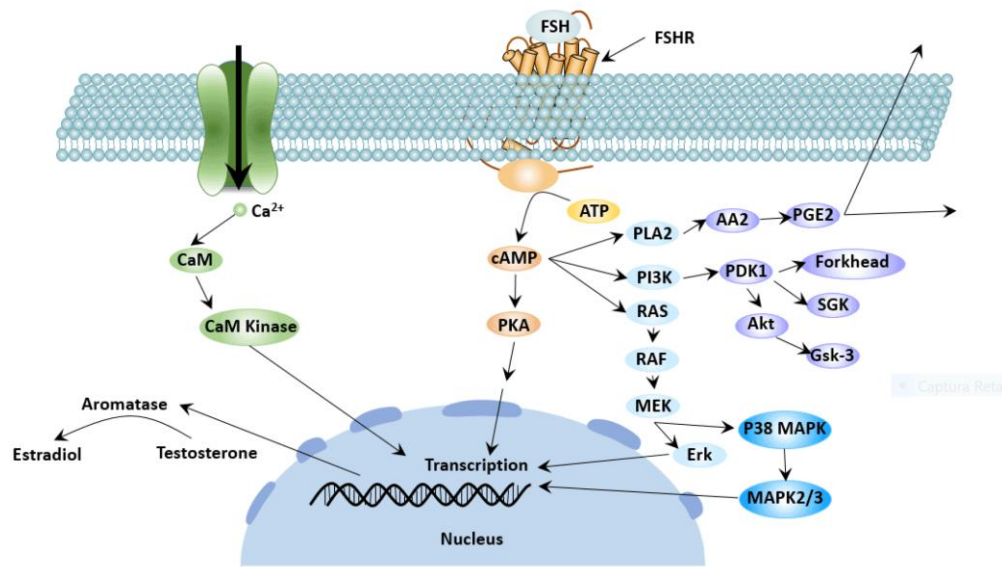


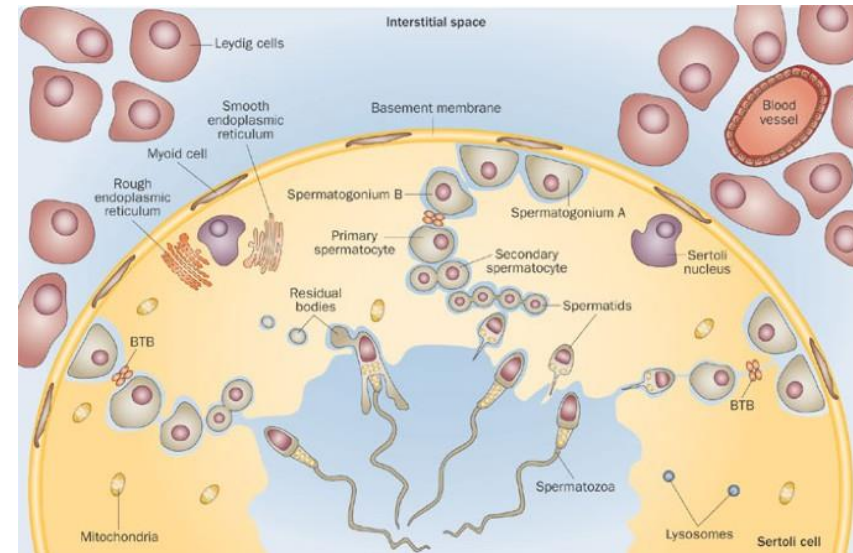
Figure from: Ivell R et al. Front Endocrinol. 2014;5:6.

Ação FSH

- ➔ FSH interage com seu receptor cognato (FSHR), um receptor acoplado à proteína G, **expresso exclusivamente em células de Sertoli**.

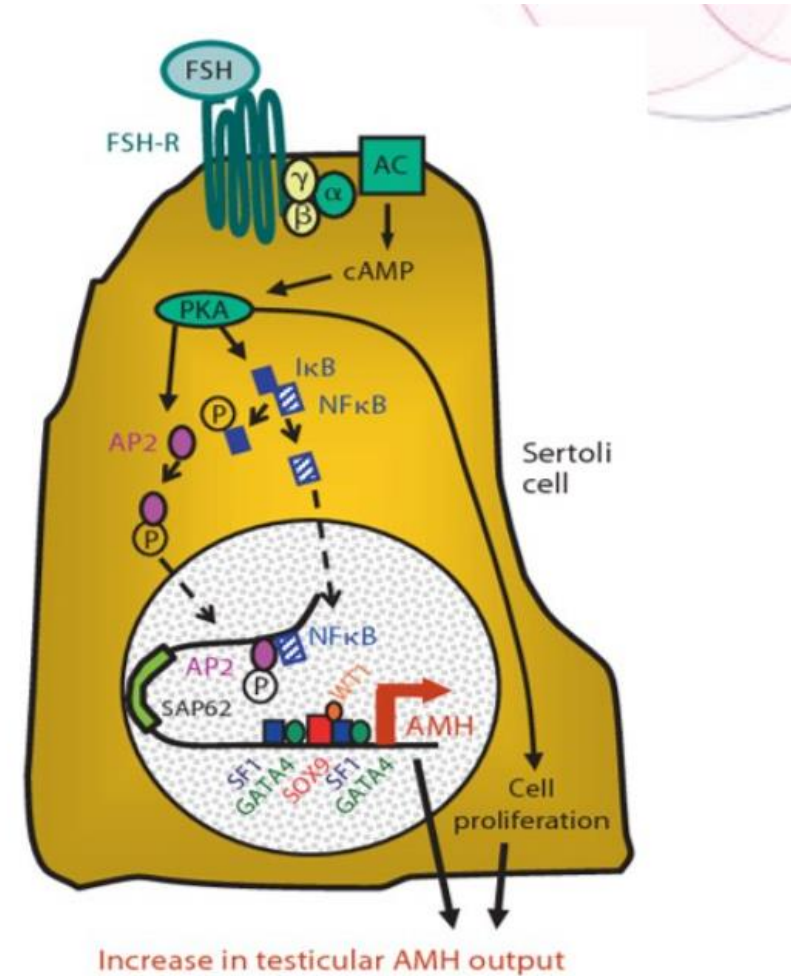


- ➔ As células de Sertoli (contraparte das células da granulosa) **são o nicho da espermatogênese**.



Ação FSH

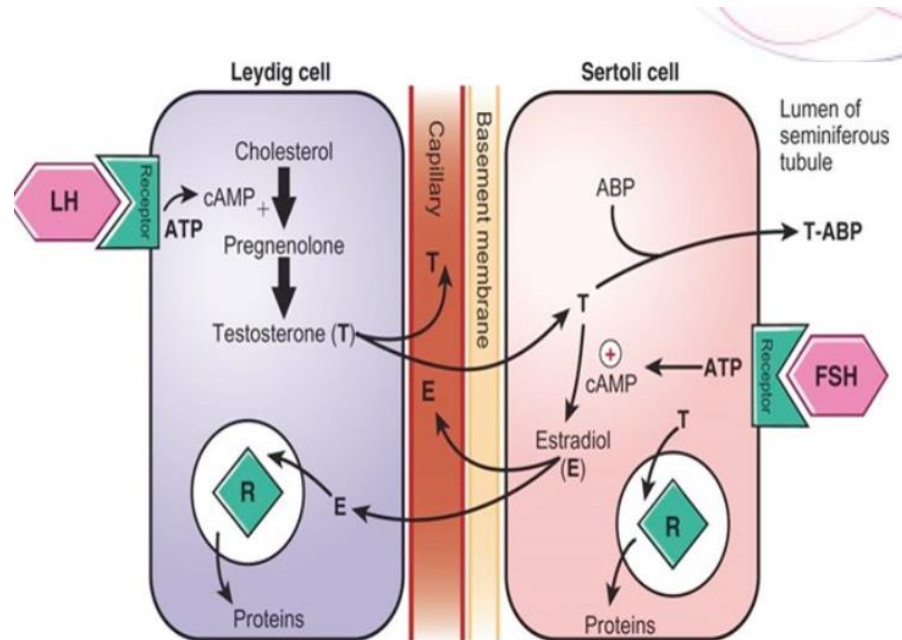
- ➔ FSH fornece indiretamente suporte nutricional e metabólico para a espermatogênese;
- ➔ Aumentando a espermatogênese e em sinergia com a ITT;
- ➔ Não é mandatório para completar a espermatogênese mas, sua deficiência, reduz marcadamente a concentração espermática.



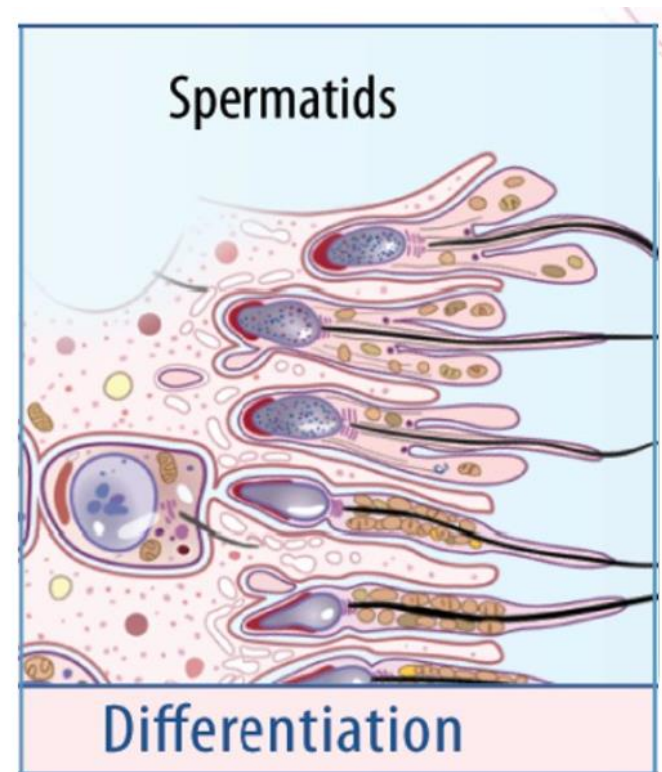
1. Oduwale OO, et al. Front Endocrinol. 2018;9:763.
2. Shiraishi K, Matsuyama H. Endocr J 2017;64:123-31.

Ação LH

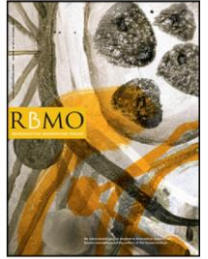
➔ A principal função do LH é **estimular a produção de testosterona (TT) pelas células de Leydig.**



➔ Está relacionada à progressão pós-meiótica dos espermátides redondas para espermatozoides maduros (**espermio gênese**).



APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function



RBMO VOLUME 48 ISSUE 4 2024

Sandro C. Esteves^{a,b,c,†,*}, Peter Humaidan^{d,†}, Filippo M. Ubaldi^e, Carlo Alviggi^f,
Leen Antonio^g, Christopher L.R. Barratt^h, Hermann M. Behreⁱ, Niels Jørgensen^j,
Allan A. Pacey^k, Manuela Simoni^{l,m,n,†}, Daniele Santi^{l,m,n,†}

APHRODITE (Addressing male Patients with Hypogonadism and/or infertility Owing to altered, Idiopathic Testicular function)

KEY MESSAGE

The proposed APHRODITE criteria offer a standardized approach to classify patients with male infertility, to improve communication and clinical management among andrologists, urologists and ART experts.

01 Hipogonadismo / Hipogonadotrófico

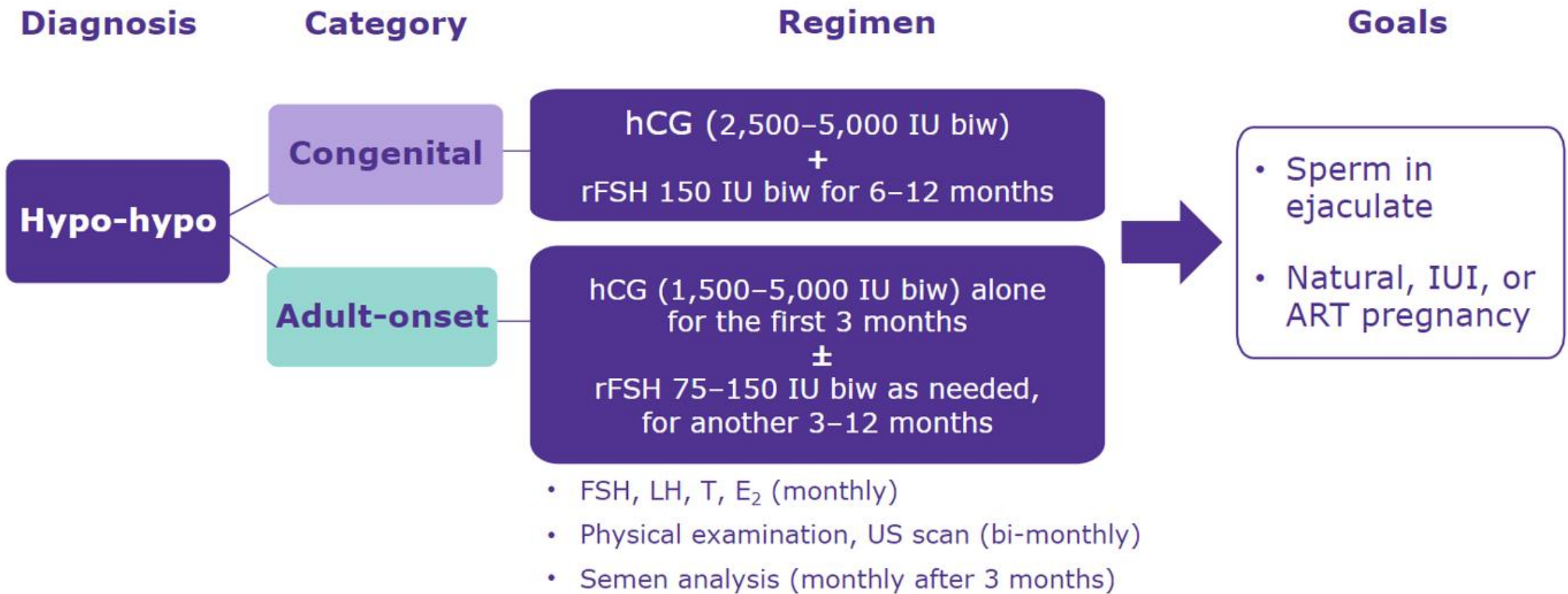
Deficiência da ação ou secreção de gonadotrofinas

Definição: falência gonadal associada a gametogênese diminuída e deficiência de produção de hormônios androgênicos.

	Níveis
FSH/LH	↓
TESTOSTERONA	↓
Espermograma	Azoo /oligo grave

Tratamento:

- congênito: FSH + hCG
- adquirido: hCG (FSH se necessário)



02 Hipogonadismo funcional

Definição: Parâmetros seminais alterados (oligozoospermia idiopática ou azoospermia não obstrutiva) com FSH e testosterona normais.

	Níveis
FSH/LH	nl
TESTOSTERONA	nl
Espermograma	Azoo /oligo grave

Tratamento:

- FSH

03 Hipogonadismo bioquímico

Definição: Parâmetros seminais alterados com FSH normal e testosterona total diminuída (oligozoospermia idiopática ou azoospermia não obstrutiva).

	Níveis
FSH/LH	nl
TESTOSTERONA	↓
Espermograma	Azoo /oligo grave

Tratamento:

- FSH + hCG

04 Hipogonadismo hipergonadotópico

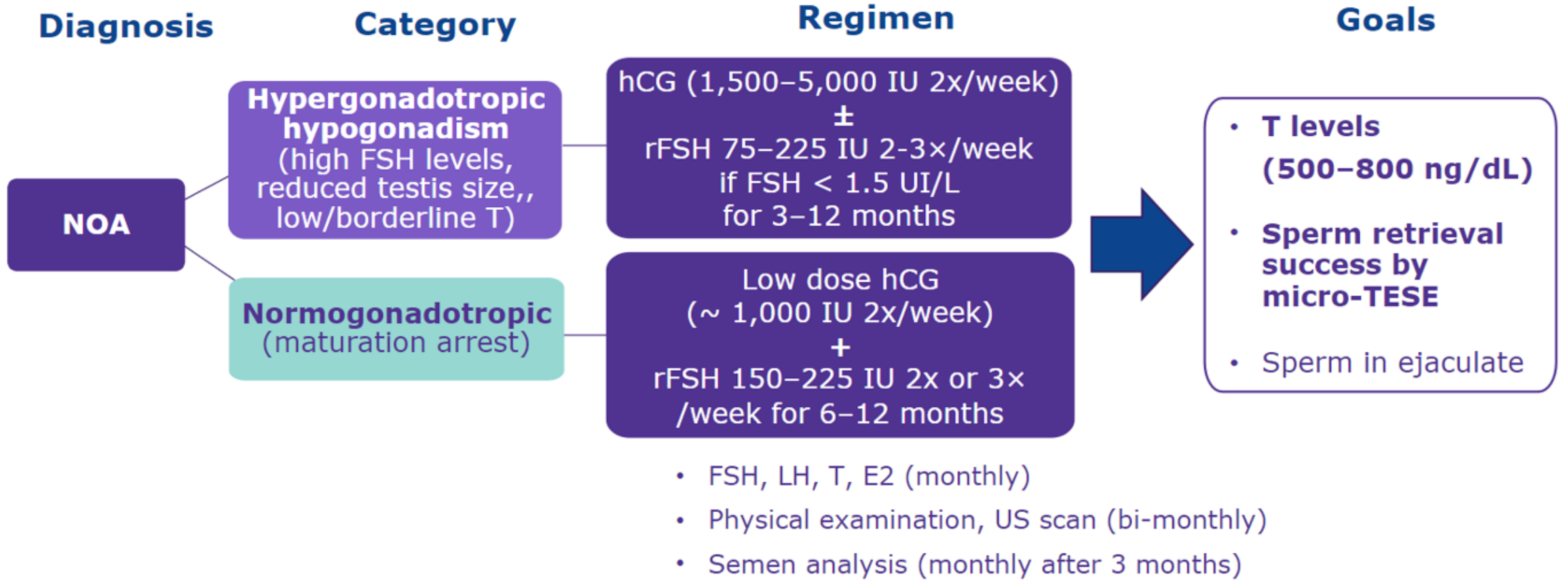
Definição: Parâmetros seminais alterados com FSH aumentado e testosterona total normal ou diminuída (azoospermia não obstrutiva).

Níveis	
FSH/LH	↑
TESTOSTERONA	↓
Espermograma	Azoo /oligo grave

Tratamento:

- hCG (+ FSH, se necessário)*

* se FSH < 1,5 mUI/mL durante o uso de hCG



05 Infertilidade inexplicada

Espermatogênese com capacidade diminuída

Definição: Parâmetros seminais e hormonais normais

	Níveis
FSH/LH	nl
TESTOSTERONA	nl
Espermograma	nl

Tratamento:

- FSH



Gonadotropin therapy in males with idiopathic infertility

Aim

- To increase sperm quantity and sperm quality, thus improving natural or ART pregnancy rates¹⁻³

• Treatment⁴



rFSH, uFSH, hMG

- 75–300 IU on alternate days
- 150 IU 2-3×/week
- **Duration:** 3–6 months
- **Follow-up:** semen analysis, DNA fragmentation index (DFI) %

1. Omar MI, et al. Eur Urol. 2019;75:615-25

2. Santi D, et al. Reprod Biomed Online. 2018;37:315-26.

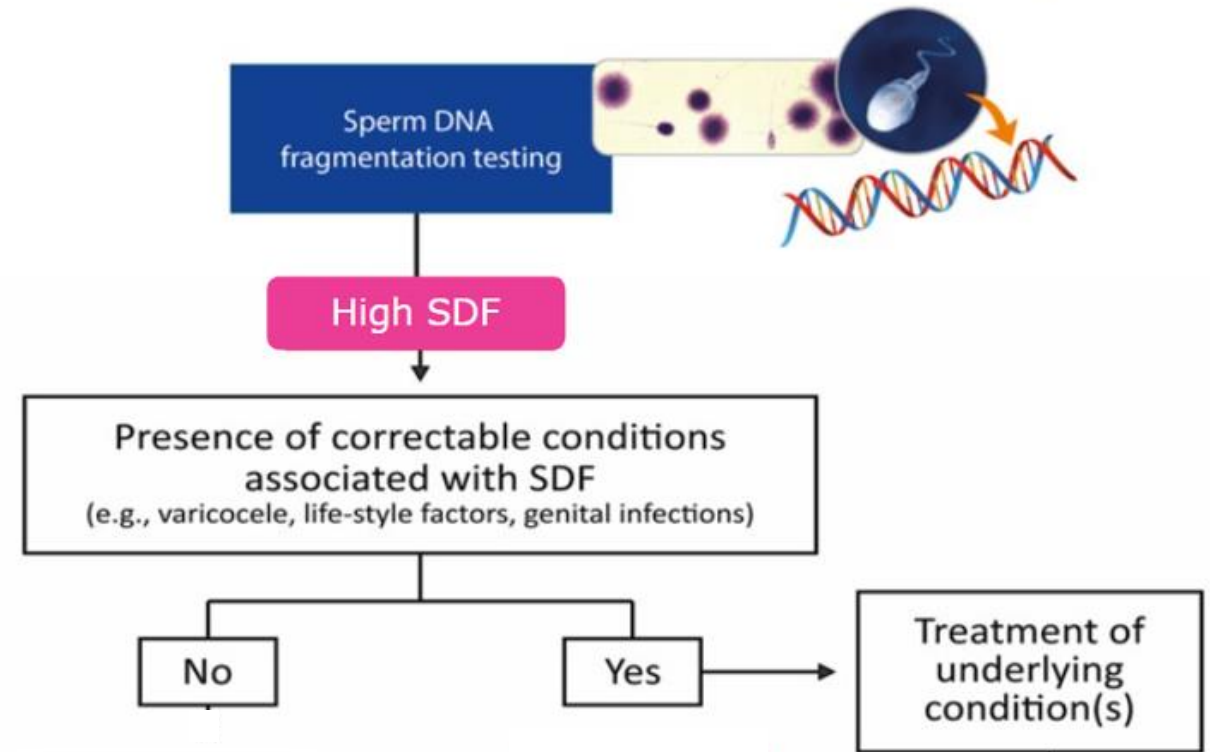
3. Esteves SC. Andrology. 2020;8:52-80.

4. Personal recommendation

Idiopathic infertility

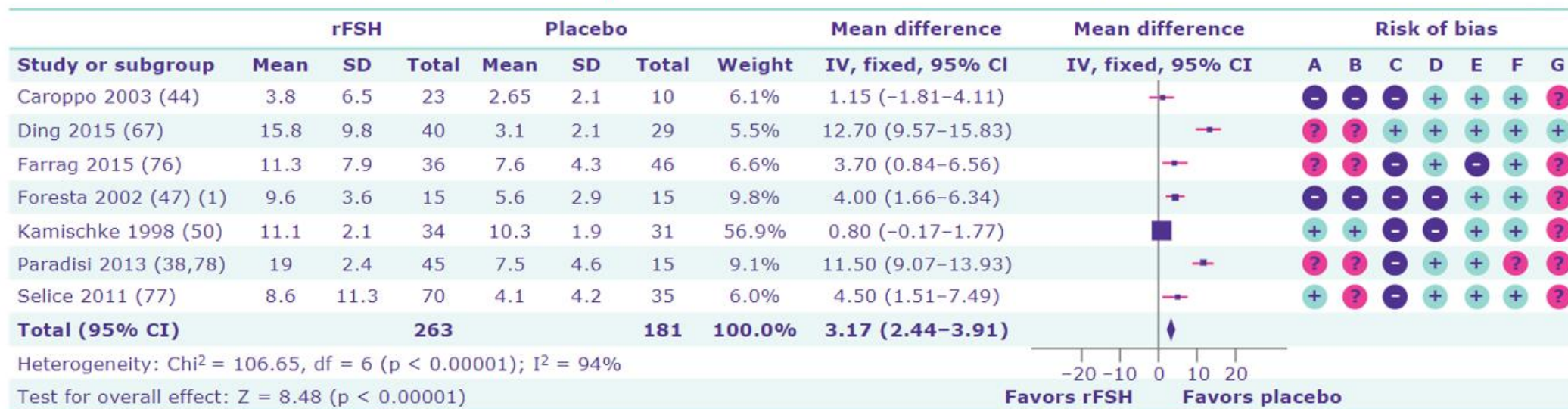
Follicle stimulating hormone therapy

rFSH 150 IU
2x/week for
minimum
3 months



Gonadotropin therapy in males with idiopathic infertility

Effect of rFSH vs. placebo on sperm concentration (RCTs)



Risk of bias legend
 (A) Random sequence generation (selection bias)
 (B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance...
 (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

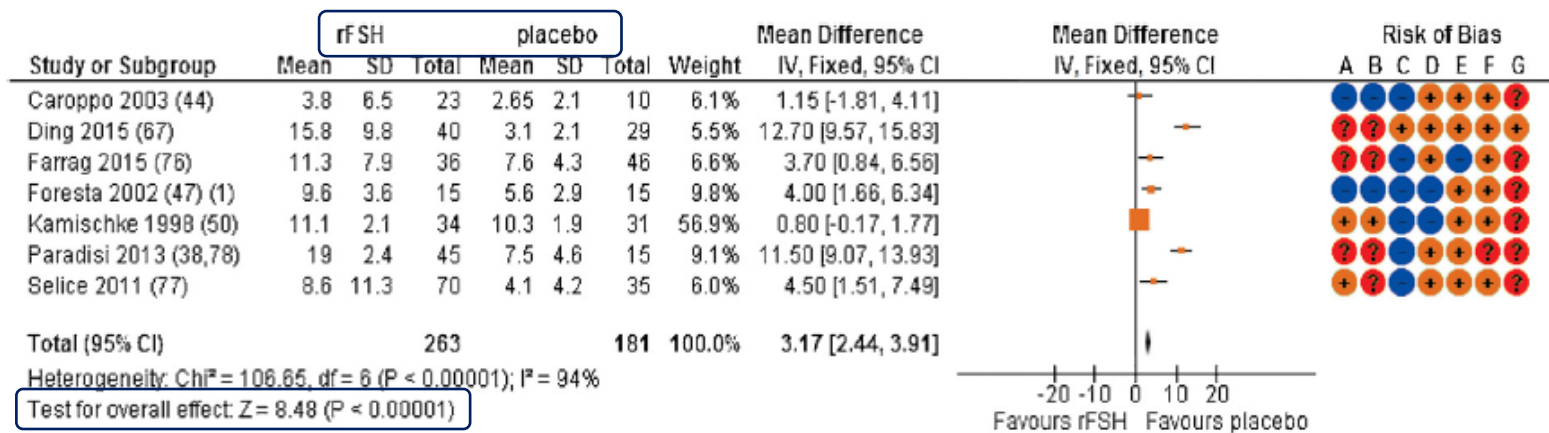
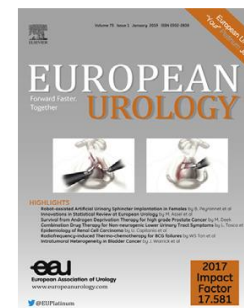
CI, confidence interval; IV, inverse variance;
 OR, odds ratio; SD, standard deviation.

Omar MI, et al. Eur Urol. 2019;75:615-25.

Benefits of Empiric Nutritional and Medical Therapy for Semen Parameters and Pregnancy and Live Birth Rates in Couples with Idiopathic Infertility: A Systematic Review and Meta-analysis

Muhammad Imran Omar^{a,*}, Raj Prasenjit Pal^b, Brian D. Kelly^c, Harman Maxim Bruins^d, Yuhong Yuan^e, Thorsten Diemer^f, Csilla Krausz^g, Herman Tournaye^h, Zsolt Kopaⁱ, Andreas Jungwirth^j, Suks Minhas^k

EUROPEAN UROLOGY 75 (2019) 615–625



Footnotes

(1) 3 arm trial - results of 100 IU contributing to the meta-analysis; 50 IU (n=15); 5.8 (2.8)

Pregnancy rates were higher for patients receiving recombinant FSH (OR 3.30, 95% CI 1.39–7.82; 343 participants; five studies; I2 = 0%; p = 0.007)

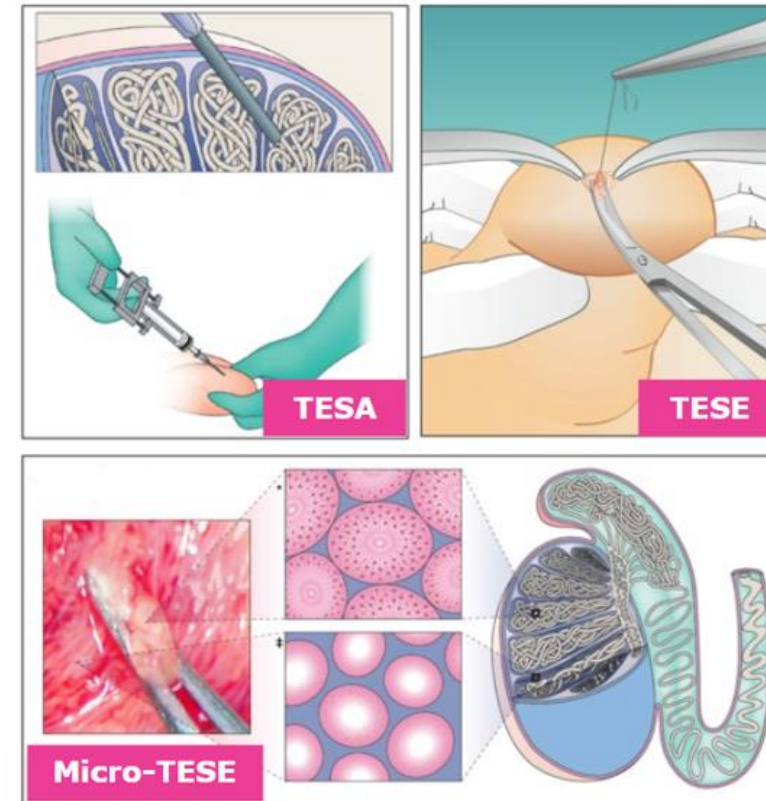
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance...)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Sperm retrieval success rates are suboptimal (~ 30–50%) in males with NOA

Gonadotropin therapy has been used to optimize or induce spermatogenesis and thus increase sperm retrieval success or sperm in ejaculate.

- ➔ Ramasamy et al. 2009
- ➔ Shiraishi et al. 2012
- ➔ Hussein et al. 2013
- ➔ Esteves 2015
- ➔ Laursen et al. 2019



NOA, nonobstructive azoospermia;
TESA, testicular sperm aspiration;
TESE, testicular sperm extraction;
Micro-TESE, microsurgical testicular sperm extraction.

Figures from: Esteves SC et al. F1000Research 2019;8(Faculty Rev):2054.
Ramasamy R, et al. J Urol. 2009;182:1108-13
Shiraishi K et al. Human Reproduction 2012;27:331-9.
Hussein A, et al. BJU Int. 2013;111(3 Pt B):E110-E114. Esteves SC. Asian J Androl. 2015;17:459-70.
Laursen RJ, et al. Int Urol Nephrol. 2019;51:453-56

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/...	
	1.2%
	1.1%
	0.7%
Aspermia	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

Consequência do tratamento
convencional da infertilidade masculina:
gestação e nascimento

**Interpretação extremamente
difícil**

Fatores fora do âmbito andrológico influenciam no
resultado terapêutico!!



Gonadotrophins for idiopathic male factor subfertility (Review)

Attia AM, Abou-Setta AM, Al-Inany HG

Conclusões dos autores

Dados preliminares encorajadores sugerem um efeito benéfico sobre nascidos vivos e gravidez do tratamento com gonadotrofina para homens com subfertilidade idiopática de fator masculino, *mas como o número de ensaios e participantes são pequenos, as evidências são insuficientes para permitir conclusões finais.*

REVIEW ARTICLE

Correspondence:
 Aleksander Giwercman, Department of Translational Medicine and Reproductive Medicine Centre, Lunds University and Skane University Hospital, CRC 91-10-058, Jan Waldenströms Gata 35, 21248 Malmö, Sweden.
 E-mail: aleksander.giwercman@med.lu.se

*The first version was prepared by a G.M. Colpi; S. Francavilla; G. Haidl; K. Link. Subsequently, important input was given by H.M. Behre; D.G. Goulis; C. Krausz. A. Giwercman coordinated the work of the group.

European Academy of Andrology guideline Management of oligo-astheno-teratozoospermia

¹G. M. Colpi, ²S. Francavilla, ³G. Haidl, ⁴K. Link, ⁵H. M. Behre, ⁶D. G. Goulis, ⁷C. Krausz and ^{4,*}A. Giwercman

Table 1 Recommendations and levels of evidence for medical and surgical treatment of oligo-astheno-teratozoospermia

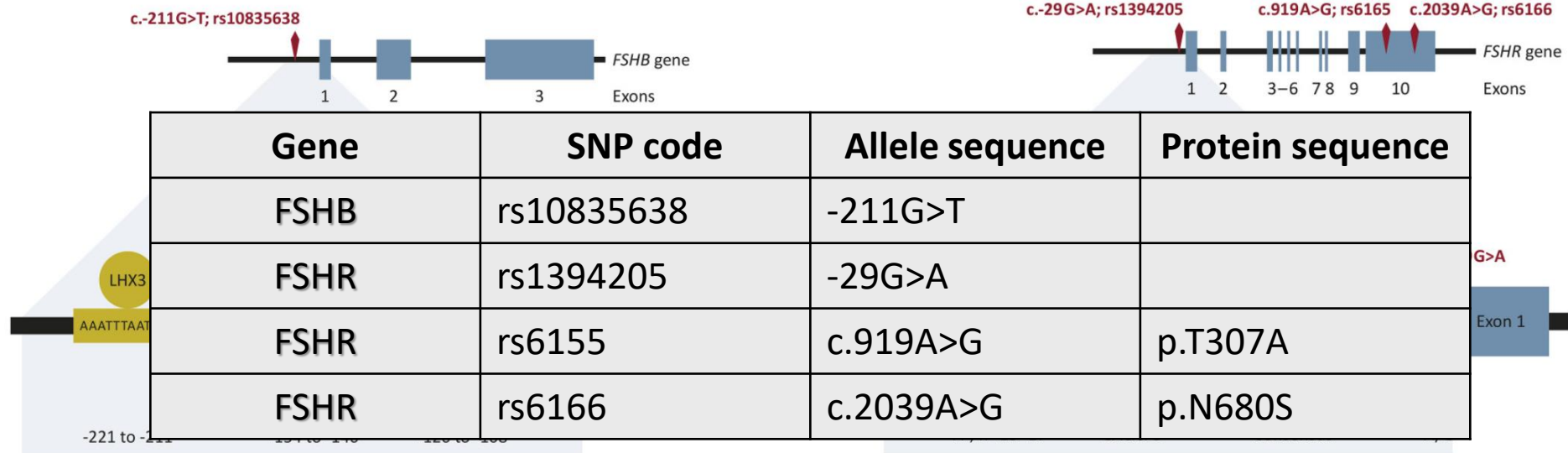
Intervention	Recommendation*	Level of evidence	Comments
FSH	2	∅∅∅∅	Treatment with FSH can be suggested with low evidence in selected men from infertile couples (normogonadotropic men with idiopathic oligozoospermia or OAT) in an attempt to improve quantitative and

Ação FSH

O *FSH β* humano é codificado pelo gene *FSHB* localizado no cromossomo 11p21. Através interação com seu receptor - *FSHR*, localizado no cromossomo 2p21, atua em seu único alvo, as células de Sertoli

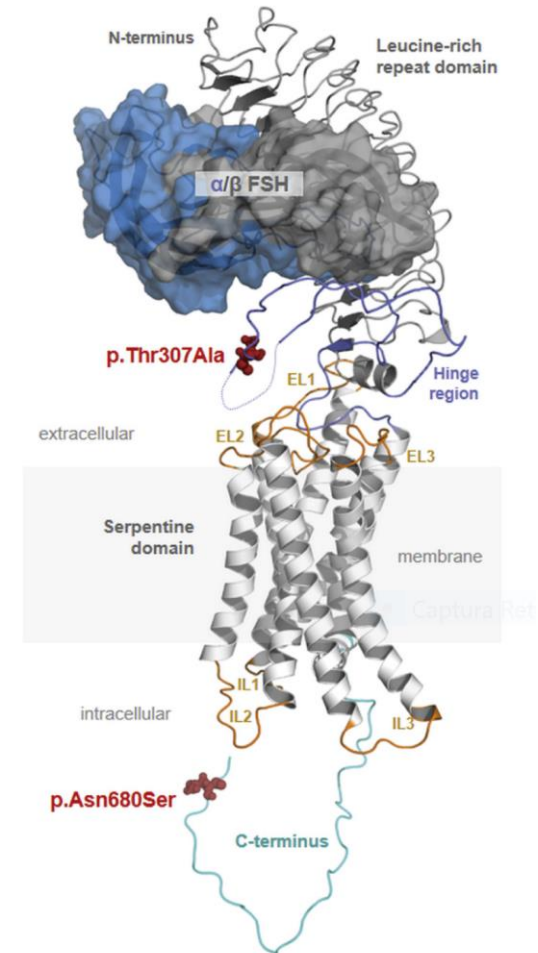
FSHB gene

FSHR gene



Polimorfismo FSH

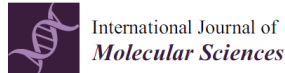
Polimorfismos na subunidade beta do hormônio estimulador do folículo (*FSHB*) (*rs10835638, c.-211G> T*) e receptor do hormônio folículo estimulante (*FSHR*) (*rs1394205, c.-29G> A; rs6165, c.919A> G; rs6166, c.2039 A> G*) podem alterar a espermatogênese e afetar a capacidade reprodutiva masculina.



Prospects for FSH Treatment of Male Infertility

Manuela Simoni ✉, Giulia Brigante, Vincenzo Rochira, Daniele Santi, Livio Casarini

The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 7, July 2020, Pages 2105–2118, <https://doi.org/10.1210/clinem/dgaa243>



Review

FSH for the Treatment of Male Infertility

Livio Casarini ^{1,2,*}, Pascale Crépieux ³, Eric Reiter ³, Clara Lazzaretti ^{1,4}, Elia Paradiso ^{1,4}, Vincenzo Rochira ^{1,5}, Giulia Brigante ^{1,5}, Daniele Santi ^{1,5} and Manuela Simoni ^{1,2,3,5}

Int. J. Mol. Sci. **2020**, *21*, 2270 doi:10.3390/ijms21072270



Review

Follicle-stimulating Hormone (FSH) Action on Spermatogenesis: A Focus on Physiological and Therapeutic Roles

Daniele Santi ^{1,2}, Pascale Crépieux ³, Eric Reiter ³, Giorgia Spaggiari ³, Giulia Brigante ^{1,2}, Livio Casarini ¹, Vincenzo Rochira ^{1,2} and Manuela Simoni ^{1,2,3,*}

J. Clin. Med. **2020**, *9*, 1014; doi:10.3390/jcm9041014

Polimorfismos de nucleotídeo único (SNPs) nos genes da subunidade beta do hormônio estimulante do folículo (FSHB) e do receptor do hormônio estimulador do folículo (FSHR)

- ➔ Afetando o volume testicular e a produção de espermatozoides
- ➔ FSHR p.N680S (c.2039A> G) e as variantes FSHB –211G> T podem ser marcadores genéticos para prever a resposta de FSH

FSHB -211 G>T Polymorphism as Predictor for TESE Success in Patients With Unexplained Azoospermia

Alexander Siegfried Busch,^{1,2*} Frank Tüttelmann,^{3*} Jann-Frederik Cremers,⁴ Maria Schubert,⁴ Verena Nordhoff,¹ Andreas N. Schüring,⁵ Michael Zitzmann,⁴ Jörg Gromoll,^{1*} and Sabine Kliesch^{4*}

(J Clin Endocrinol Metab 104: 2315–2324, 2019)

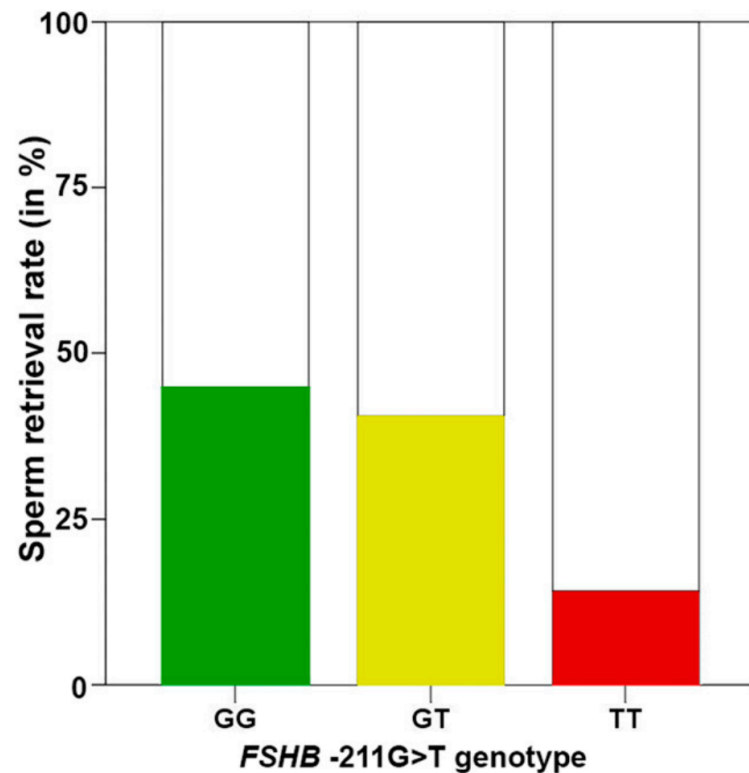
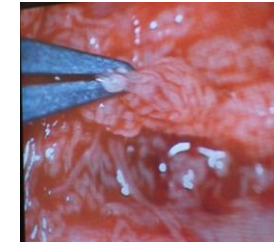


Figure 1. SRR stratified by *FSHB* -211G>T in patients with unexplained azoospermia (n = 659). Colored bars indicate positive sperm retrieval by TESE; white bars indicate a negative outcome.

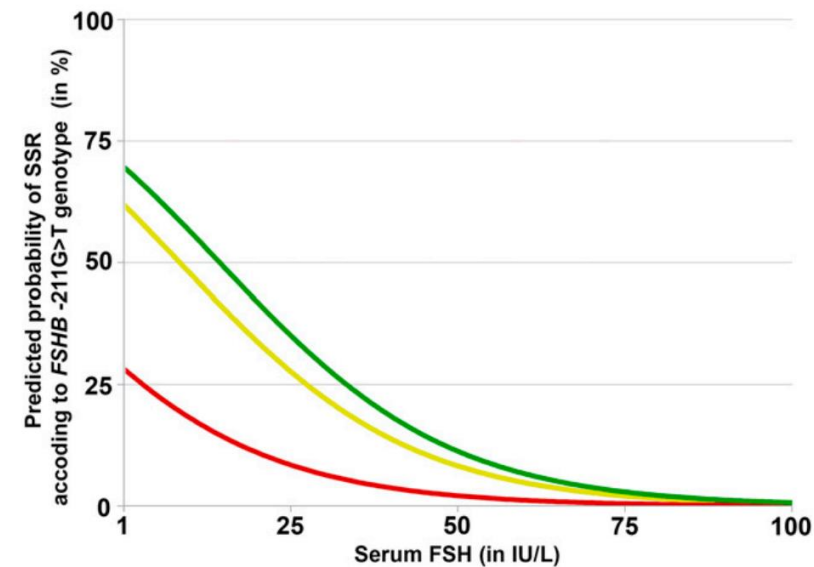


Figure 2. Predicted probabilities of positive sperm retrieval according to serum FSH level stratified by *FSHB* -211G>T in patients with unexplained azoospermia (n = 654): wild-type homozygotes (GG; green), heterozygotes (GT; yellow), minor allele homozygotes (TT; red). The predicted probability for positive sperm retrieval at the same serum FSH level is lower in T-allele carriers.

Considerações -1



- ➔ **hCG (+FSH) induz a produção espermática no hipogonadismo (hipogonadotrópicos e bioquímico);**
- ➔ **FSH pode aumentar a quantidade e qualidade dos espermatozoides em casos de hipogonadismos funcionais e na infertilidade idiopática;**
- ➔ **hCG (+FSH) pode aumentar as chances de recuperação de espermatozoides (microTESE) nos casos de azoo não-obstrutiva;**

Considerações - 2



- ➔ Polimorfismos na subunidade beta do hormônio estimulador do folículo (FSHB) e do receptor do hormônio folículo estimulante (FSHR) podem alterar a espermatogênese e afetar a ação do tratamento com o FSH;
- ➔ Faltam estudos de RCT comparando tratamento com gonadotropinas e placebo na taxas de nascidos vivos (tanto em TRA como na concepção natural);
- ➔ Apesar de faltarem estudos comparando drogas/regimes terapêuticos, as evidências sugerem que o uso de altas doses de FSH (300 UI) e tratamentos mais longos (6 meses) trazem melhores resultados.



Direção

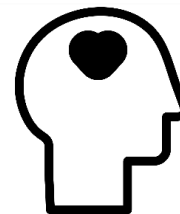
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Instituto Sapientiae

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Christina Morishima
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Raphaela Medeiros



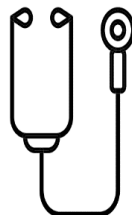
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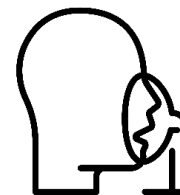
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e Equipe



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E-mail: edson@fertility.com.br