XXXVII Congresso
Brasileiro Urologia

Curitiba | PR

24 a 27 AGOSTO | 2019
Expo Unimed Curitiba

A UROLOGIA COM FOCO NA MEDICINA
PERSONALIZADA E HUMANIZADA

Avaliação genética do homem infértil

Edson Borges Jr.

FERTILITY

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

FERTILITY

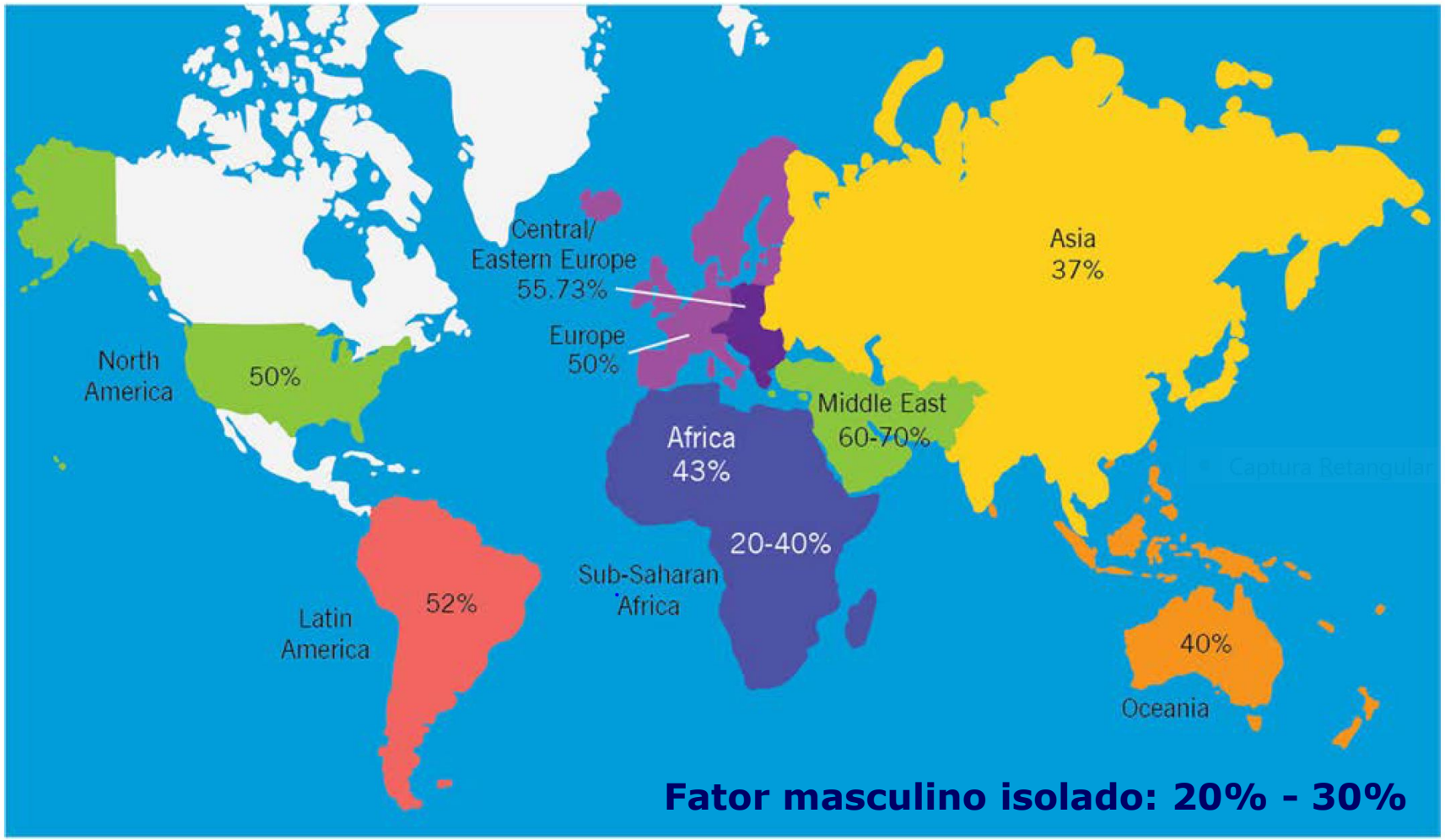
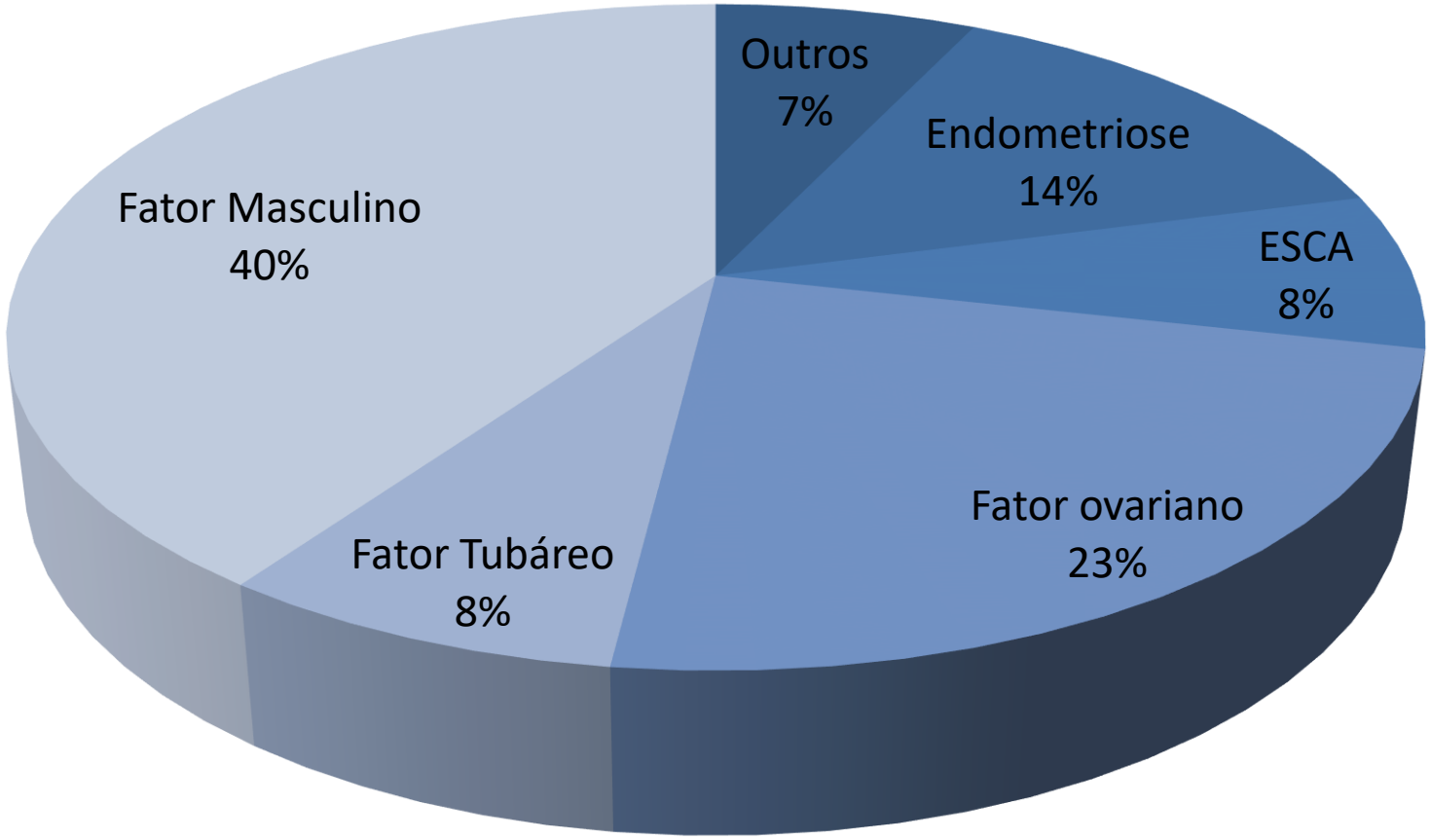


Figure 2 World map containing percentages of infertility cases per region that are due to male factor. This figure demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement.

DISTRIBUIÇÃO DOS CASOS DE INFERTILIDADE

FERTILITY Medical Group, 2.005 – 2.018



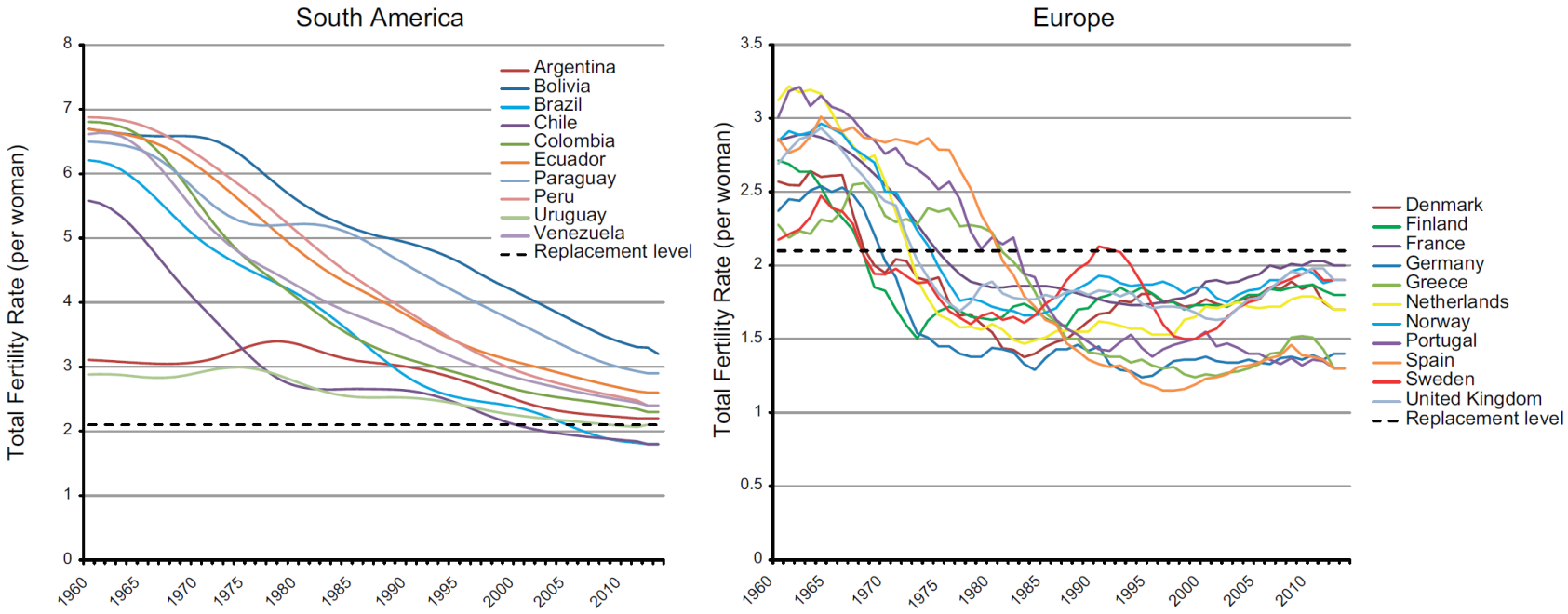
FERTILITY

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

Taxa de Fecundidade



FERTILITY

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Incidência de Criptorquidia

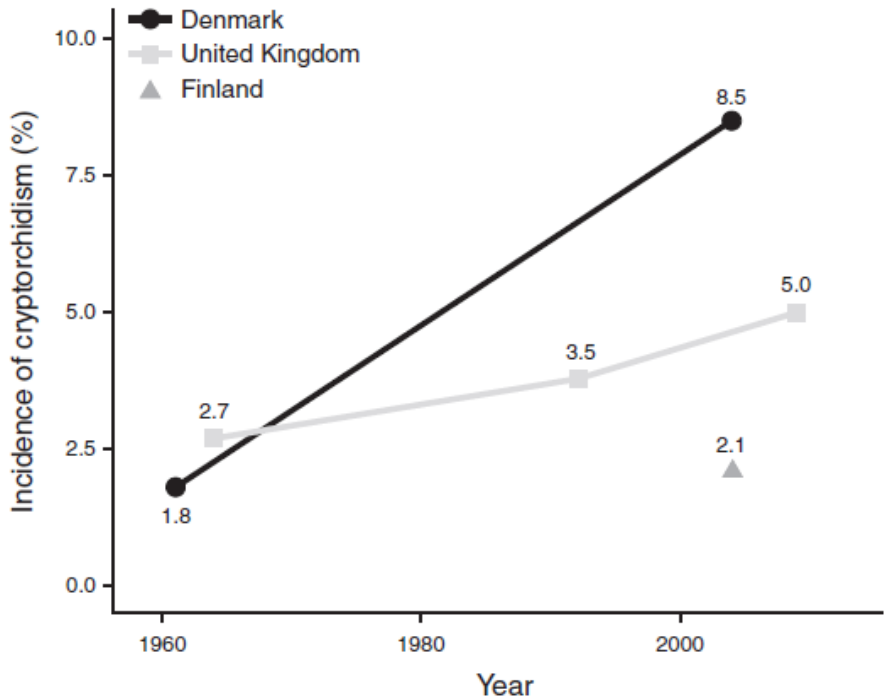

FIGURE 7. Incidence of cryptorchidism at birth on the basis of prospective clinical studies from the 1950s to the 2000s in Denmark, Finland, and United Kingdom. The data points are marked on the year of the publication of the study which represents the preceding incidence rate (3, 47, 61, 184, 377).

FERTILITY

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Incidência de Câncer de Testículo

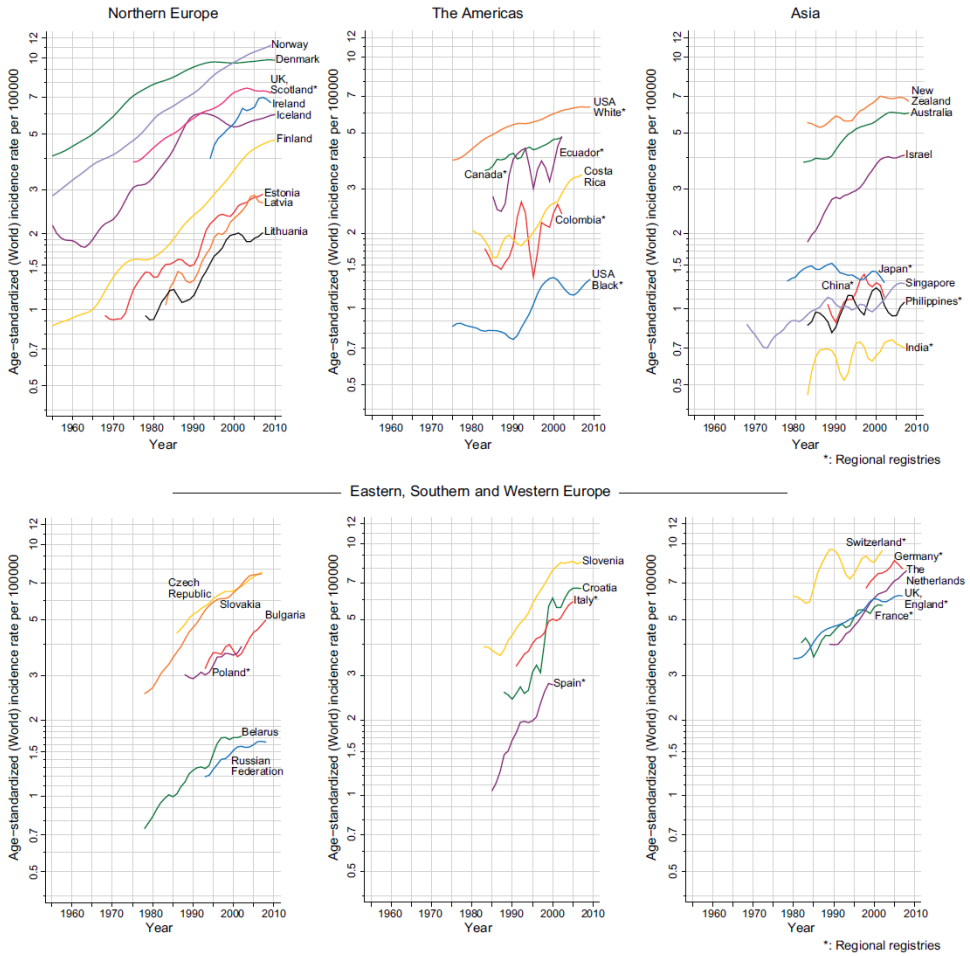

FIGURE 4. Trends in testicular cancer; age-standardized (world) incidence (regional or national), all ages. [Modified from Znaor et al. (481). Courtesy of Dr. Arinana Znaor and statistician Mathieu Laversanne, M.Sc., WHO, International Agency for Research in Cancer (IARC), Lyon, France.]

FERTILITY

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Idade da Puberdade

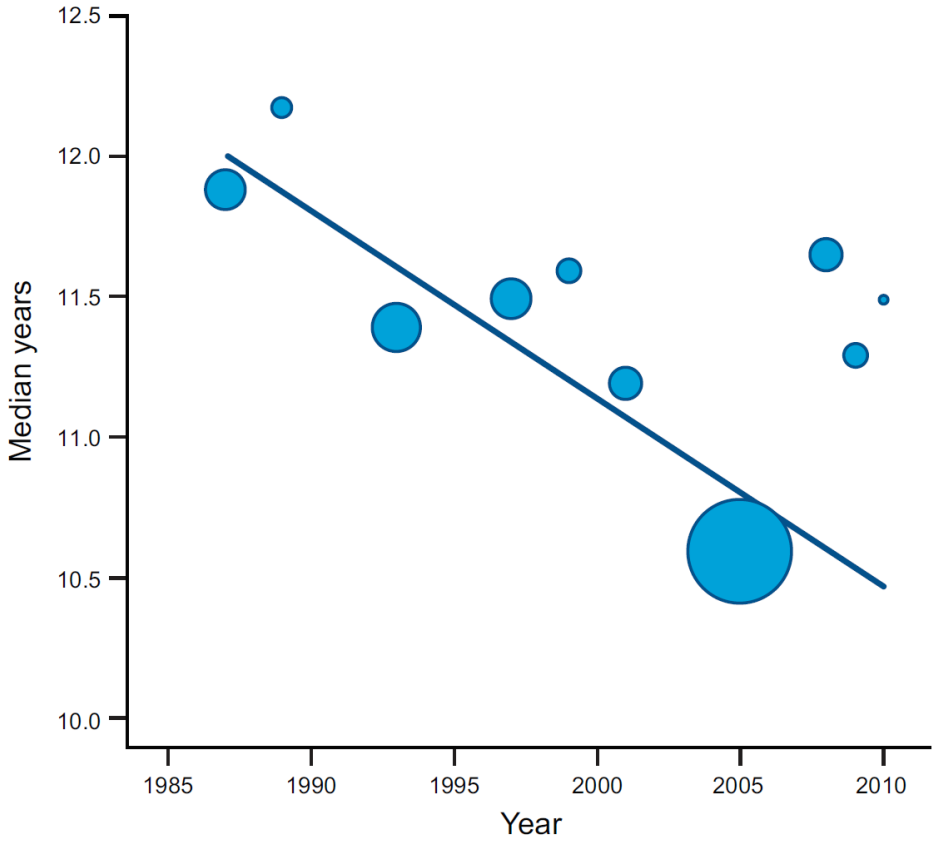


FIGURE 8. Recent changes in male pubertal timing. Testicular volume was >3 ml. [From Mouritsen et al. (293).]

FERTILITY

Article

Human and Experimental Toxicology
1–9

DOI: 10.1177/0960327117703690
journals.sagepub.com/home/het

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

P Sengupta[1,2], E Borges Jr[3], S Dutta[4] and E Krajewska-Kulak[2]

Purpose: To investigate whether the sperm concentration of European men is deteriorating over the past 50 years of time.
Materials and Methods: We analysed the data published in English language articles in the past 50 years in altering sperm concentration in European men.

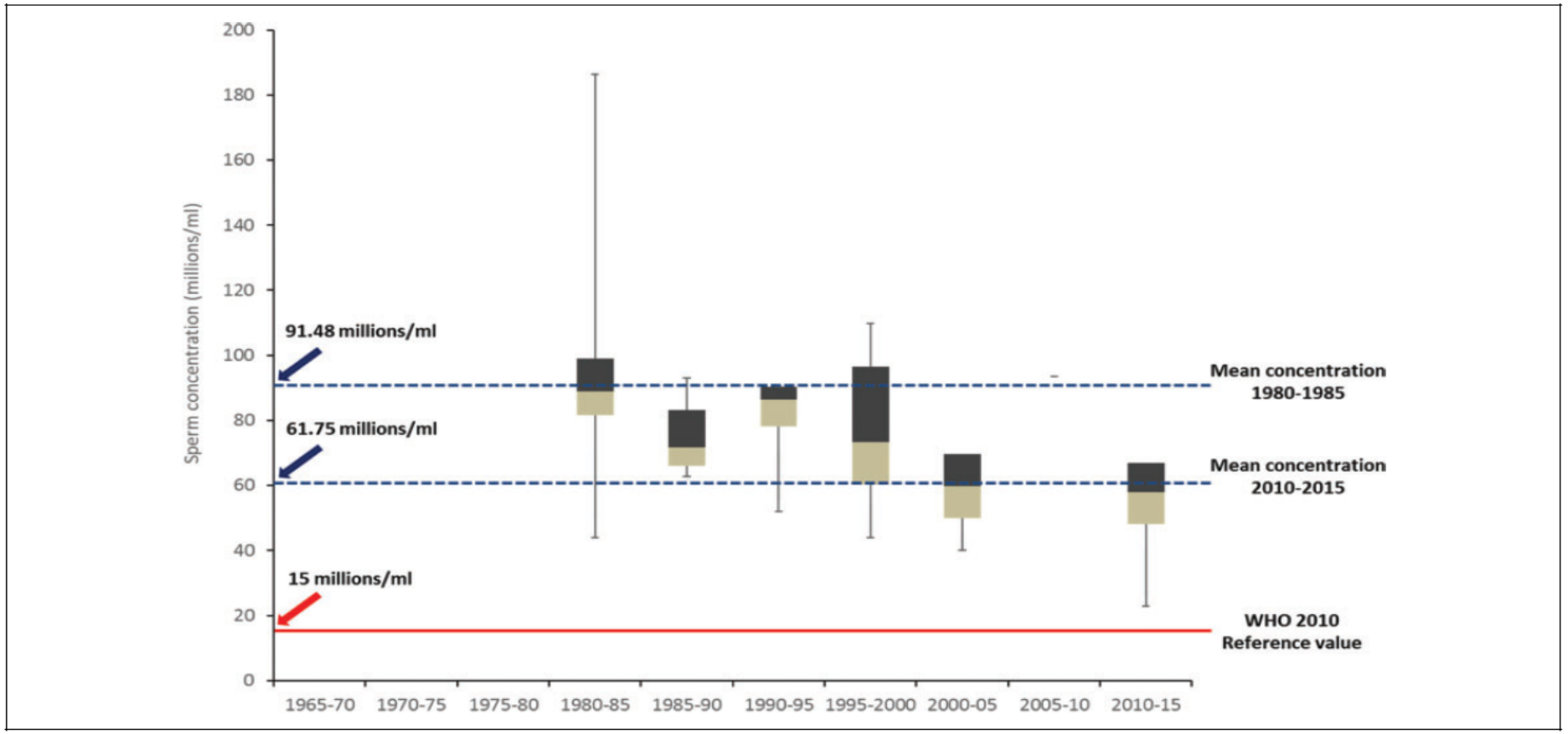


Figure 2. Box and whisker plot of sperm concentration data of European men of the past 50 years.

Declínio tempo-dependente na concentração espermática observada de 1965 to 2015 (r= -0.307, p<0.02; diminuição de 32.5%)

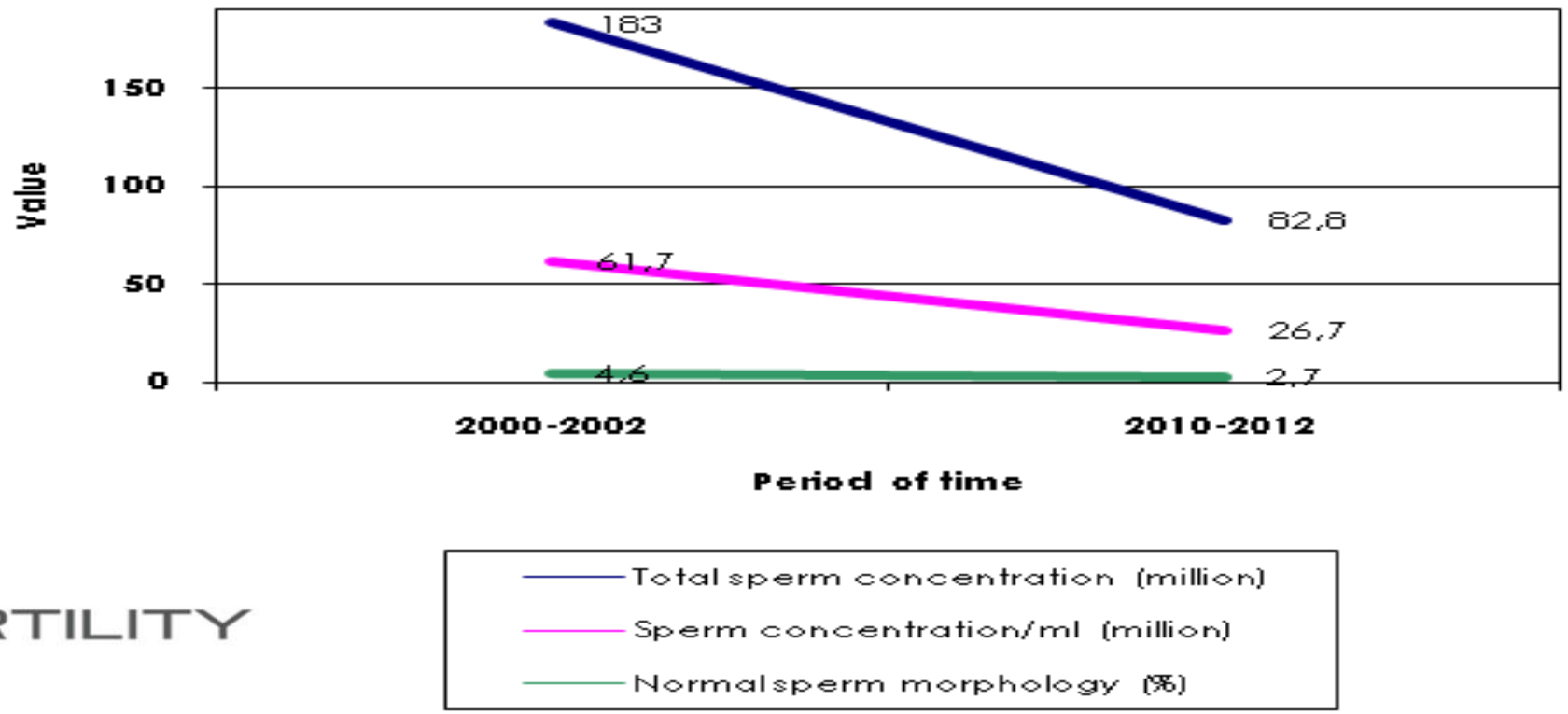
FERTILITY

ORIGINAL ARTICLE

Vol. 41 (4): 757-763, July - August, 2015
doi: 10.1590/S1677-5538.IBJU.2014.0186

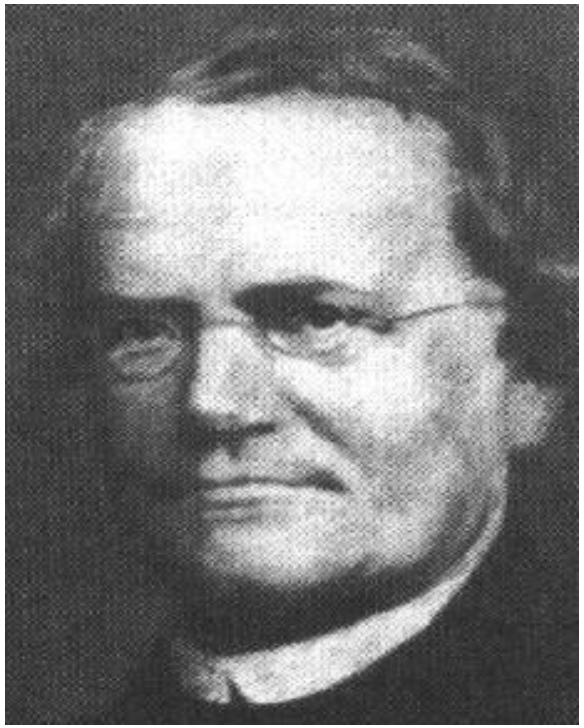
Decline in semen quality among infertile men in Brazil during the past 10 years

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

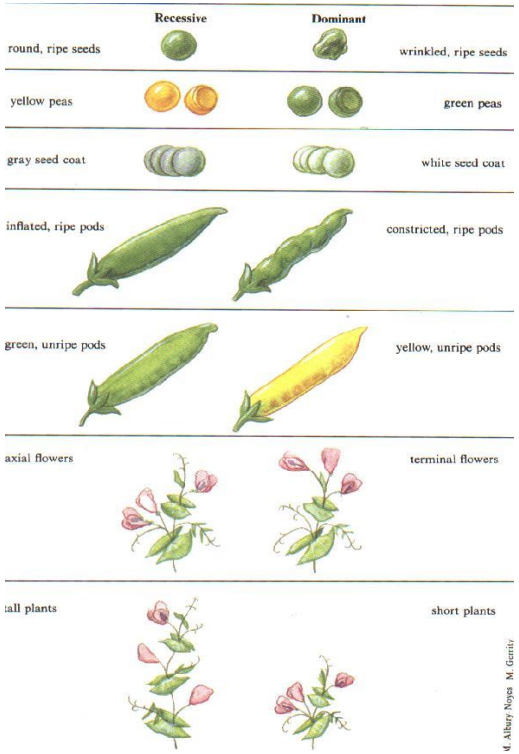


Genética e Infertilidade Masculina

GENÉTICA ⟺ FERTILIDADE



Gregor Mendel



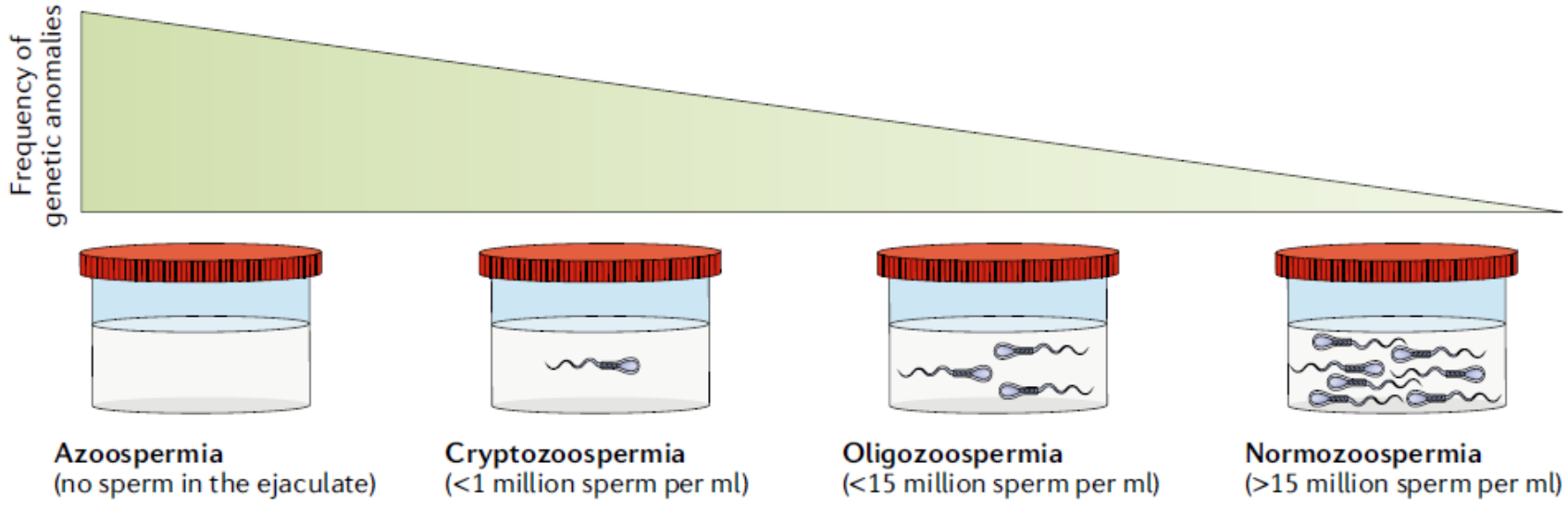
FERTILITY

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 *et al* (1982)	342	6 (1.8)	4 (1.2)	10 (2.9)
de GARDELLE *et al* (1983)	318	13 (4.1)	7 (2.2)	20 (6.3)
MATSUDA *et al* (1989)	295	0 (0)	5 (1.7)	5 (1.7)
YOSHIDA et al (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)

FERTILITY

Alterações cromossômicas maiores & densidade espermática



FERTILITY

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

Investigação Genética em Infertilidade Masculina

- alterações cromossômicas
  (Klinefelter / translocações)
- deleções gênicas (cromossomo Y)
- mutações genéticas (CFTR)
- outras doenças genéticas

(polimorfismos, mutações, gens de expressão testicular)

- doenças do *imprinting*
- *ICSI – crianças diferentes??*

FERTILITY

Síndrome de Klinefelter

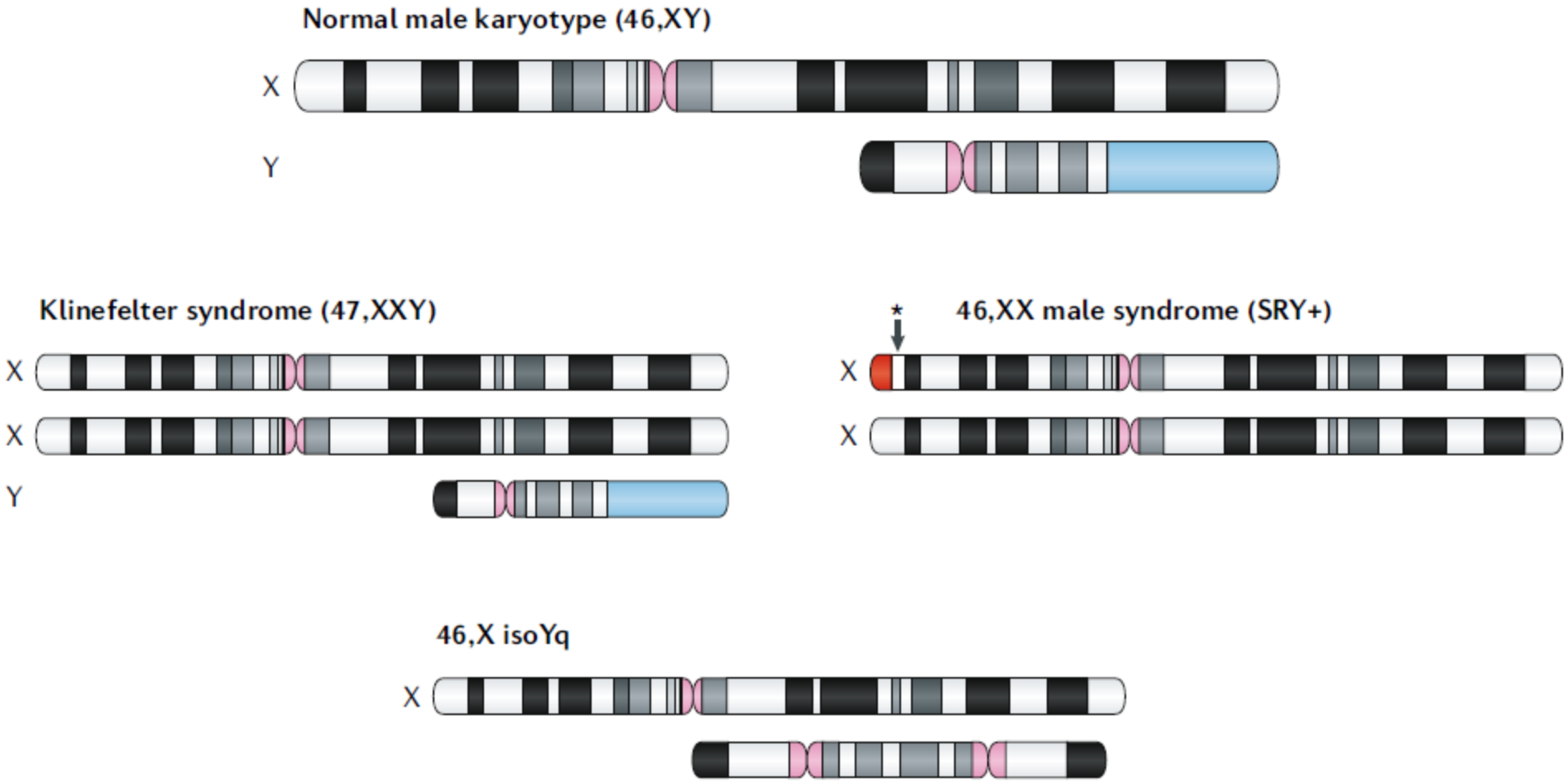
- 1 / 500 homens
- 1- 2 % homens inférteis
- 2 - 5% oligo graves
- 5 - 10 % azoospérmicos
- 47, XXY = 90 % 46, XY / 47, XXY = 10 % (+ 30 cariótipos)

- não disjunção meiótica do cromossomo X
  (40 % paterna / 60 % materna)
- *fenotipo:* alta estatura, obesidade, diminuição da inteligência, acondroplasia, ginecomastia, testículos diminuídos / normais

> *probabilidade de gerar prole c/ alterações genéticas*

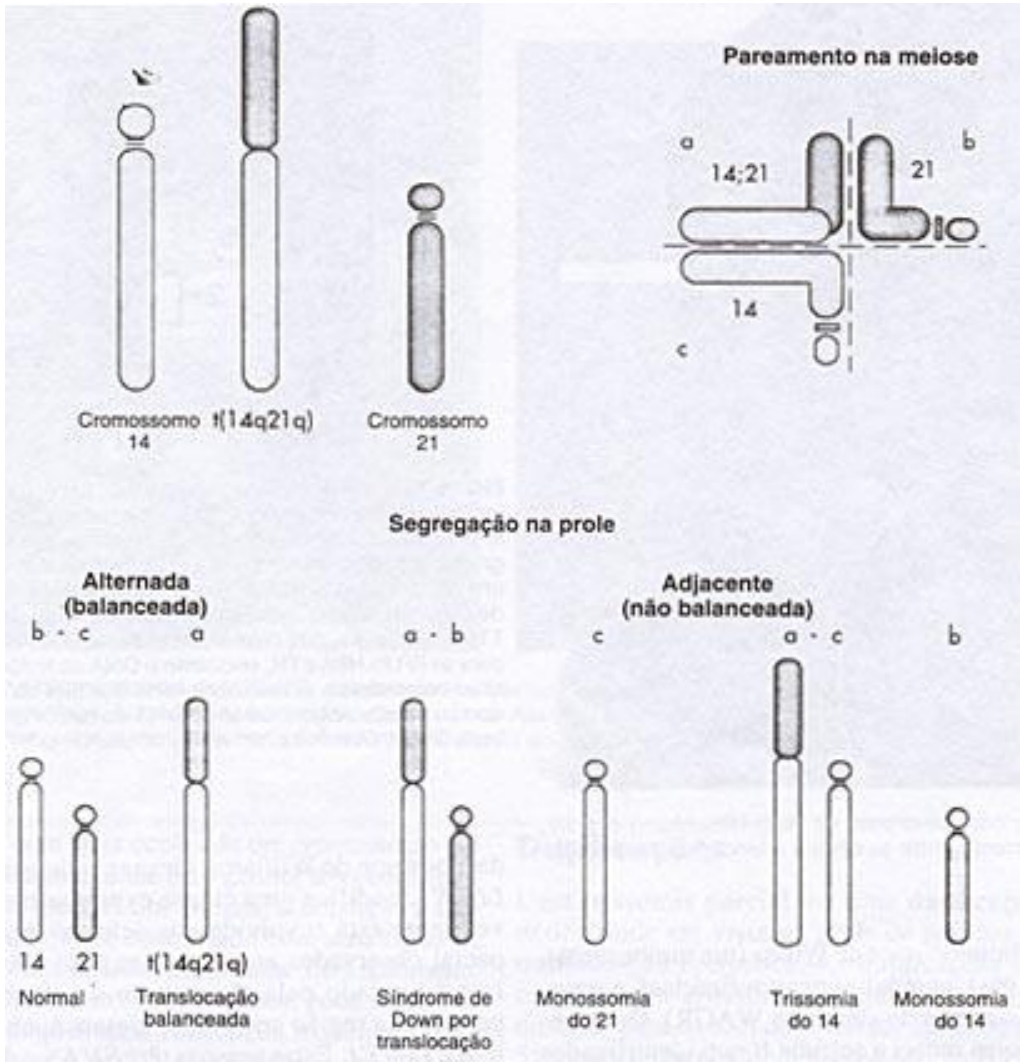
FERTILITY

Outras alterações no cariótipo



FERTILITY

Translocação Robertsoniana



- Os braços curtos de dois cromossomos não-homólogos são perdidos e os fundem no centrômero, formando um só cromossomo.
- Confinado aos cromossomos 13, 14, 15, 21 e 22
- Espermatozóides alterados: abortamento / síndrome Down

➔ 0,8% homens inférteis

FERTILITY

MicroDeleção do Cromossomo Y

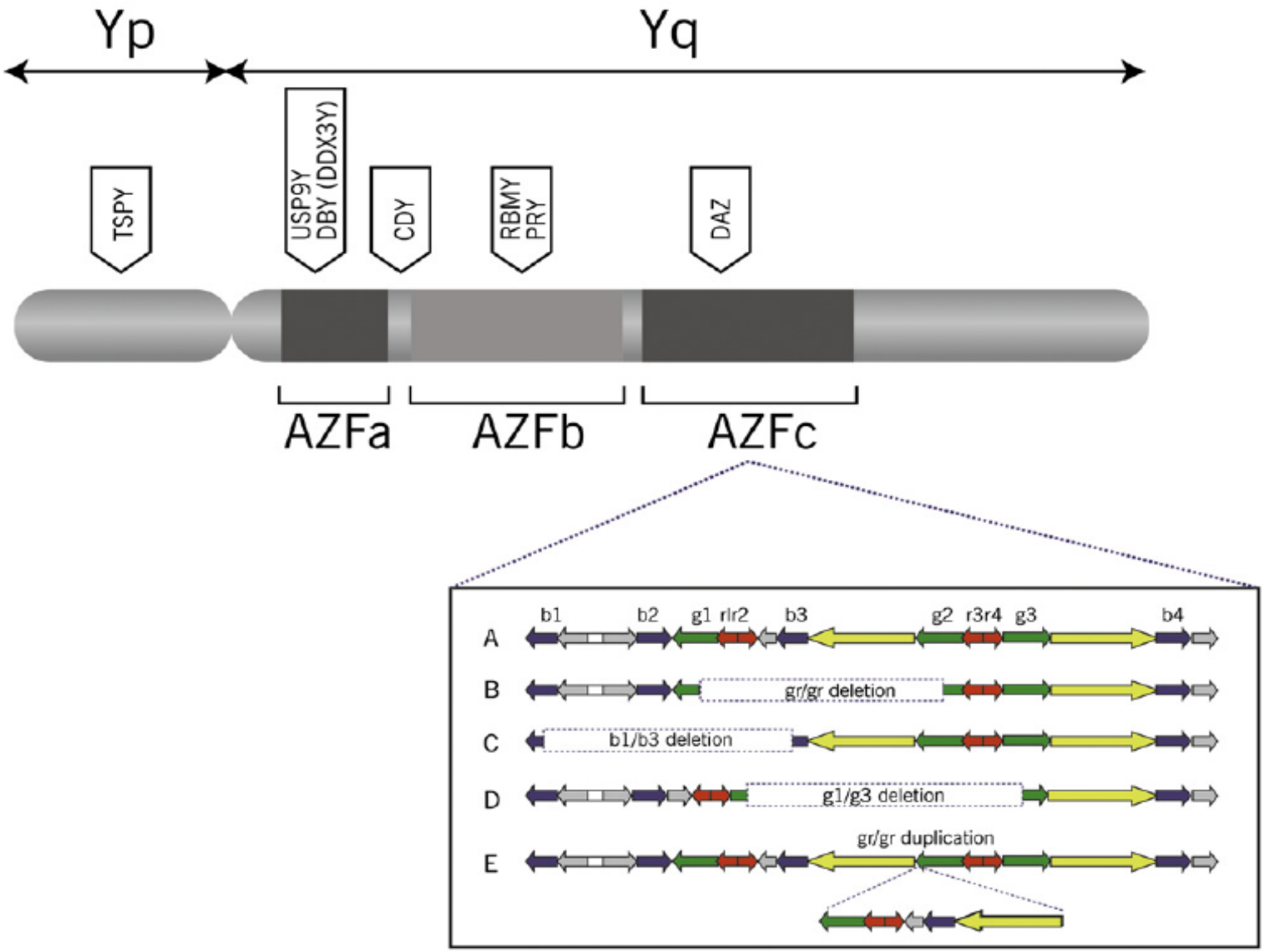
- 1:10.000 nascidos
- 3 - 13 % homens inférteis
- 5 - 20 % oligo grave / azoospérmicos
- braço longo do cromossomo Y

- **AZF a** = *SCOS syndrome* (tipo I)
- **AZF b** = *maturation arrest*
- **AZF c (daz)** = SCOS c / focos espermatogênese (tipo II)
- **DAZ h** = deleção no cromossomo 3

FERTILIDADE FUTURA DO FILHO ?

RTILITY

Image of Y chromosome displaying AZF regions and associated genes. Enlarged portion of AZFc region highlights discussed microdeletions. (A) Normal AZFc region; (B) gr/gr deletion; (C) b1/b3 deletion; (D) g1/g3 deletion; (E) gr/gr duplication.



O'Flynn O'Brien. Genetic causes of MF infertility. Fertil Steril 2010.

Microdeleções no cromossomo Y

AZFa – 5%

AZFb – 15%

AZFc – 60%

RTILITY

Microdeleções no cromossomo Y

- 5%
- Ausência completa de células germinativas
- Síndrome de células de Sertoli

Microdeleções no cromossomo Y

- 15%
- Parada de maturação

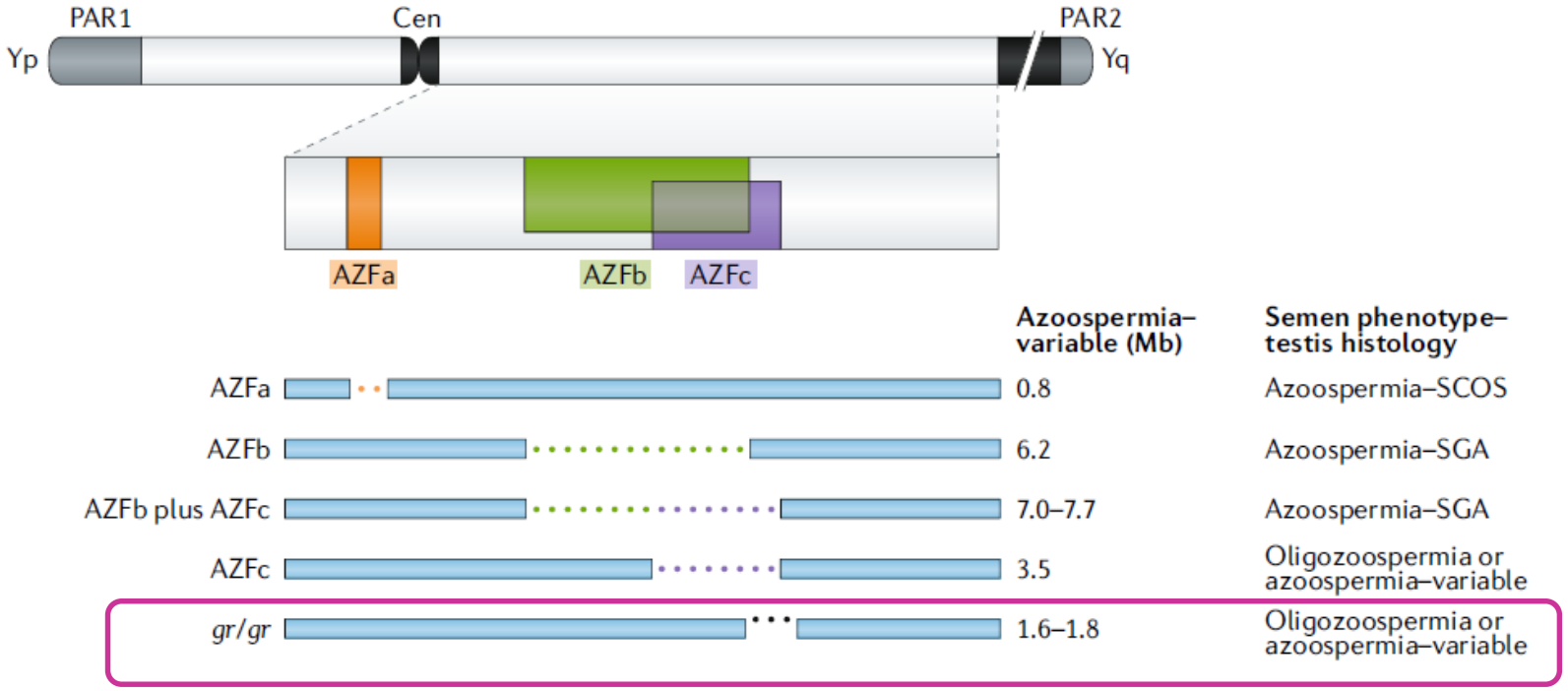
RTILITY

Microdeleções no cromossomo Y

- 60%
- Amplo espectro
  - oligozoospermia grave
  - azoospermia

Deleção parcial Y (*gr/gr* deleção)

a



b

Deletion	Frequency (%)		
	Azoospermic patients	Oligozoospermic patients	Controls
AZF deletions	5–10	2–5	0
gr/gr deletions*	3.5	0.9	0.9

FERTILITY

MicroDeleção parcial do Cromossomo Y

- Uma relação entre deleções terminais AZFb+c e distúrbios anormais do crescimento e distúrbios neuropsiquiátricos foi descrito.

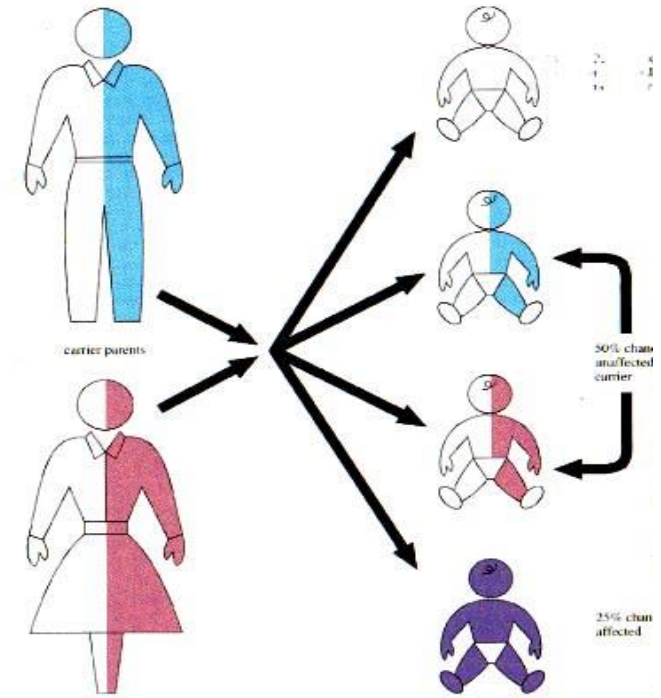
- A exclusão de dois genes que são expressos no sistema nervoso central, NLGN4Y e KDM5D, pode ser responsável pela fenótipo neuropsiquiátrico.

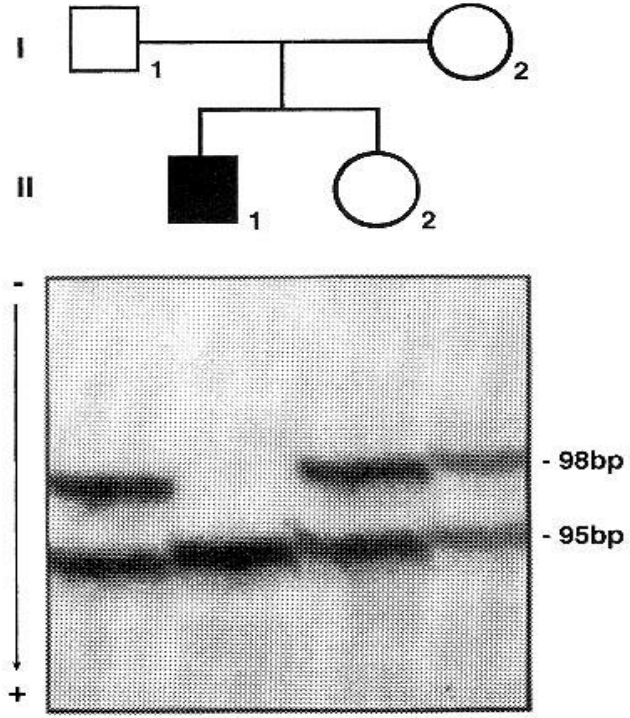
ERTILITY

Castro, A. et al. Pseudoautosomal abnormalities in terminal AZFb+c deletions are associated with isochromosomes Yp and may lead to abnormal growth and neuropsychiatric function. *Hum. Reprod.* **32**, 465–475 (2017).

Fibrose Cística

Herança autossômica recessiva





FERTILITY

Agenesia Congênita Bilateral dos Ductos Deferentes

- 1 / 1.000 homens
- 1- 2 % homens inférteis
- 10 % azoospermias obstrutivas
- autossômica recessiva (CFTR gen) ➡ braço longo do cromossomo 7

- 🗁 forma mínima da fibrose cística (60-70%)
- 🗁 agenesia bilateral / unilateral dos deferentes
- 🗁 obstrução epididimária idiopática (47 %)

FERTILITY

+ 2.000 MUTAÇÕES

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)
AZFa deletion	Azoospermia, Sertoli cell–only syndrome	0.5–1.0 (2)
AZFb deletion	Azoospermia, spermatogenic arrest	0.5–1.0 (2)
AZFc deletion	Severe oligozoospermia to nonobstructive azoospermia	6–12
Partial AZF-c deletions	From azoospermia to normozoospermia	3–5 (2)

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

FERTILITY

Mutação no gen receptor de andrógeno (Síndrome de Morris)

- ligado ao cromossomo X, recessiva (Xq11-12)
- ~2% homens inférteis
- consequência: síndrome da insensibilidade androgênica
- alteração na espermatogênese

- *incidência ~ azoospermia, oligo moderada ou grave*
- *criptorquidia / hipospádia / ginecomastia (eventual)*
- *Síndrome de Kennedy (doença neurodegenerativa)*

FERTILITY

Outras alterações genéticas

Spermatogenic qualitative defects	Globozoospermia	*DPY19L2*	First step: detection of homozygous or heterozygous deletion of the gene based on quantitative PCR[78] Second step: direct sequencing of the entire gene
	Sperm macrocephaly	*AURKC*	First step: mutation panel including the most frequent *AURKC* mutations (exons 3 and 6) Second step: direct sequencing of the entire gene (Sanger)
	MMAF	*DNAH1*	Direct sequencing of the entire gene (Sanger or NGS)
	PCD	26 candidate genes[c] + *DNAH1*	Screening of a panel of candidate genes (NGS-based)

Aetiological categories are listed according to their frequency (from the most frequent to the least frequent). AZF, azoospermia factor; CBAVD, congenital bilateral absence of the vas deferens; EAA, European Academy of Andrology; EMQN, European Molecular Genetics Quality Network; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MMAF, multiple morphological abnormalities of the sperm flagella; NGS, next-generation sequencing; PAIS, partial androgen insensitivity; PCD, primary ciliary dyskinesia. [a]Two different

Human Reproduction, Vol.27, No.1 pp. 36–43, 2012
Advanced Access publication on November 10, 2011 doi:10.1093/humrep/der374

human reproduction ORIGINAL ARTICLE *Andrology*

The prevalence of chromosomal abnormalities in subgroups of infertile men†

E.C. Dul[1,*], H. Groen[2], C.M.A. van Ravenswaaij-Arts[3], T. Dijkhuizen[3], J. van Echten-Arends[1], and J.A. Land[1]

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

FERTILITY

Riscos epigenéticos

FERTILITY

espermatogênese
espermiogênese

maturação

capacitação
hiperativação

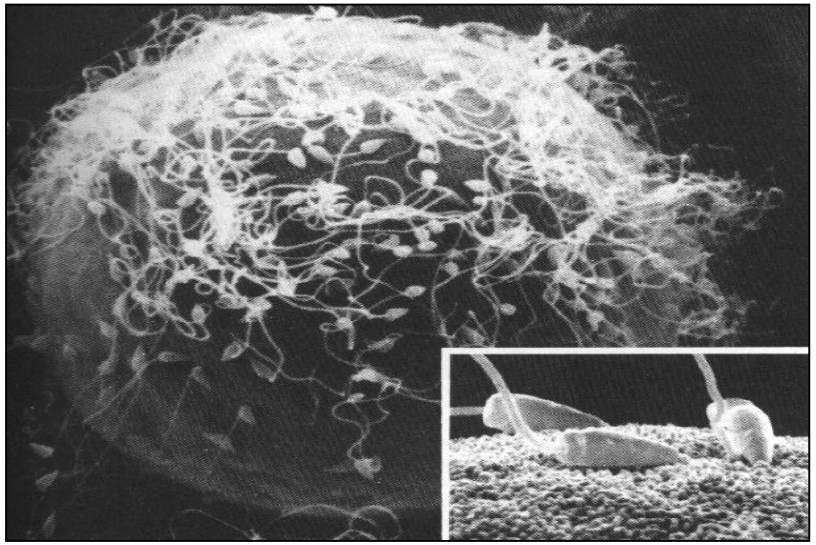
interação zona
pelúcida

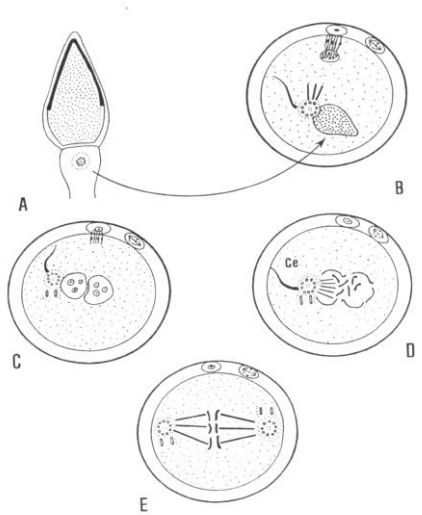
reação acrossômica

penetração zona
pelúcda

fusão
espermatozóide
óvulo

descondensação
pronúcleo





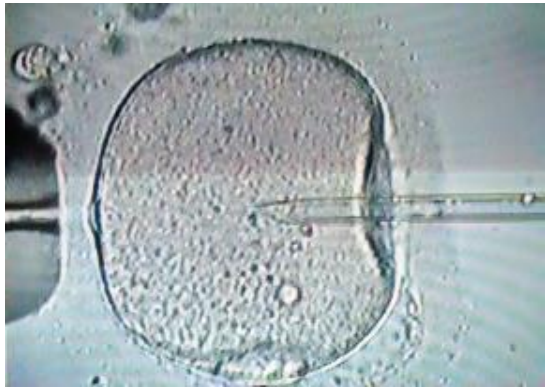
FERTILITY

espermatogênese
espermiogênese

maturação

capacitação
hiperativação

interação zona
pelúcida

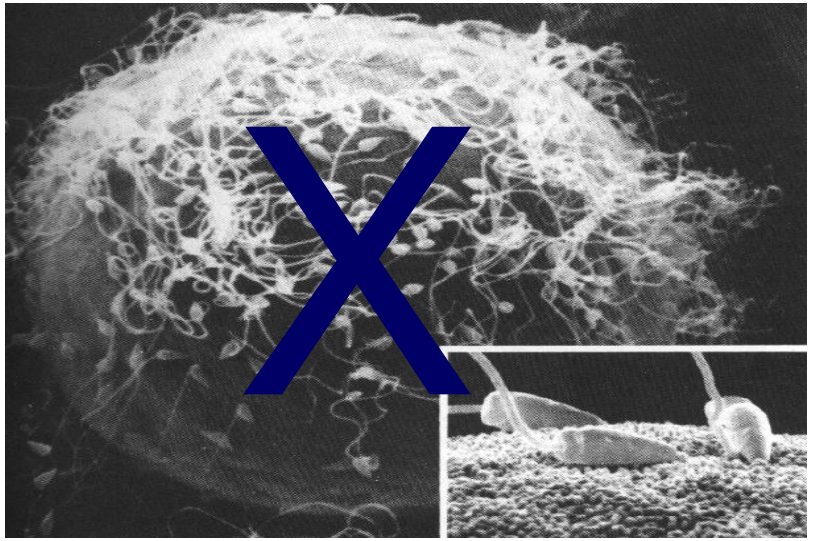


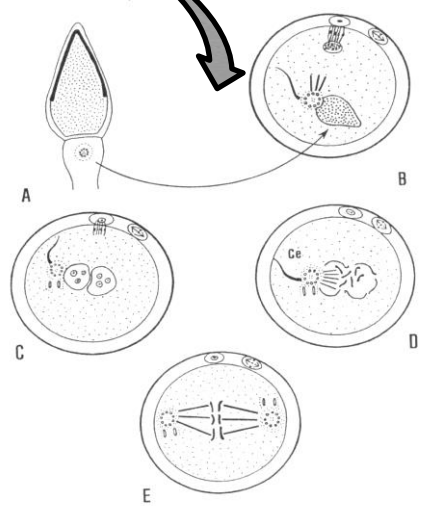
reação acrossômica

descondensação
pronúcleo

fusão
espermatozóide
óvulo

penetração zona
pelúcda





FERTILITY

Human Reproduction Update, Vol.20, No.6 pp. 840–852, 2014
Advanced Access publication on June 24, 2014 doi:10.1093/humupd/dmu033

human reproduction update

A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously

Gabija Lazaraviciute[1], Miriam Kauser[1], Sohinee Bhattacharya[1], Paul Haggarty[2], and Siladitya Bhattacharya[1,*]

[1]Division of Applied Health Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK [2]Division of Lifelong Health, Rowett Institute of Nutrition and Health, University of Aberdeen, Greenburn Road, Bucksburn, Aberdeen AB21 9SB, UK

Fig… …isorder between IVF/ICSI versus spontaneously conceived children.

Aumento das doenças de imprinting nas crianças nascidas por FIV/ICSI

- …nn syndrome (BWS), Angelman syndrome (AS),
- …Willi syndrome (PWS), and Silver-Russell syndrome (SRS).

FERTILITY

Hattori *et al. Clinical Epigenetics* (2019) 11:21
https://doi.org/10.1186/s13148-019-0623-3

Clinical Epigenetics

RESEARCH Open Access

Association of four imprinting disorders and ART

Hiromitsu Hattori[1,2†], Hitoshi Hiura[1†], Akane Kitamura[1], Naoko Miyauchi[1], Norio Kobayashi[1], Souta T…
Hiroaki Okae[1], Koichi Kyono[2], Masayo Kagami[3], Tsutomu Ogata[4] and Takahiro Arima[1*]

- frequências aumentadas de 4,4… …3 associadas à ART, respectivamente;

Beckwith-Wiedemann… …el-Russell syndrome (SRS).

- tra… …orrer logo após a fertilização em um momento e… …nerável e pode ser afetado pelas técnicas de m… …ara FIV ou ICSI e pelo meio de cultura do óvulo fertilizado.

❖ TRA pode induzir variação epigenética que pode ser transmitida à próxima geração

FERTILITY

ANDROLOGY

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REVIEW ARTICLE

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children, follow-up, ICSI, intracytoplasmic sperm injection, offspring

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Long-term follow-up of ICSI-conceived offspring compared with spontaneously conceived offspring: a systematic review of health outcomes beyond the neonatal period

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- Espermatogênese prejudicada em homens adultos jovens concebidos por ICSI, como indicado pela redução da qualidade do sêmen, e possivelmente maiores níveis de FSH e menores níveis de inibina B, em comparação com seus pares de CN

FERTILITY

INVITED SESSION

SESSION 01: KEYNOTE SESSION

Monday 2 July 2018 Forum (Auditorium) 08:30–09:30

O-001 Human Reproduction Keynote Lecture - Semen quality of young adult ICSI offspring: The first results

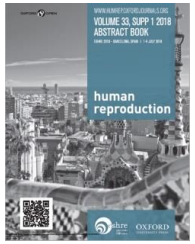
F. Belva[1], M. Bonduelle[1], M. Roelants[2], D. Michielsen[3], A. Van Steirteghem[4], G. Verheyen[4], H. Tournaye[4]

- UZ Brussel, entre 03/2013 – 04/2016, 54 jovens
- Saúde reprodutiva e metabólica de jovens 18-22 anos, nascidos de ICSI com espermatozóide ejaculado x concepção natural (CN)

FERTILITY

O-001 Human Reproduction Keynote Lecture - Semen quality of young adult ICSI offspring: The first results

F. Belva[1], M. Bonduelle[1], M. Roelants[2], D. Michielsen[3], A. Van Steirteghem[4], G. Verheyen[4], H. Tournaye[4]



ICSI:

- menor concentração espermática/mL, total, TMSC (17,7 mil/ml, 31,9 mil e 12,7 mil) que os nascidos por **CN** (37 mil/ml; 86.8 mil; 38.6 mil)
- **CN:** dobro na concentração espermática/mL (**ratio 1.9**, 95% CI 1.1-3.2)
- **ICSI:** duas vezes menor concentração espermática total (**ratio 2.3**, 95% CI 1.3-4.1) e TMSC (**ratio 2.1**, 95% CI 1.2-3.6)

ICSI:

- 3X menor chance de ter concentração espermática/mL (15 mil/mL) abaixo OMS (**AOR 2.7**; 95% CI 1.1–6.7)
- 4X menor chance de ter concentração espermática total (39 mil) (**AOR 4.3**; 95% CI 1.7-11.3)

FERTILITY

Human Reproduction, Vol.34, No.5 pp. 932–941, 2019
Advanced Access publication on March 13, 2019 doi:10.1093/humrep/dez022

human reproduction REVIEW *Reproductive genetics*

A systematic review and standardized clinical validity assessment of male infertility genes

Manon S. Oud[1], Ludmila Volozonoka[2,3], Roos M. Smits[4], Lisenka E.L.M. Vissers[1], Liliana Ramos[4], and Joris A. Veltman[1,2,*]

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❖ 78 genes ligados a 92 fenótipos de infertilidade masculina

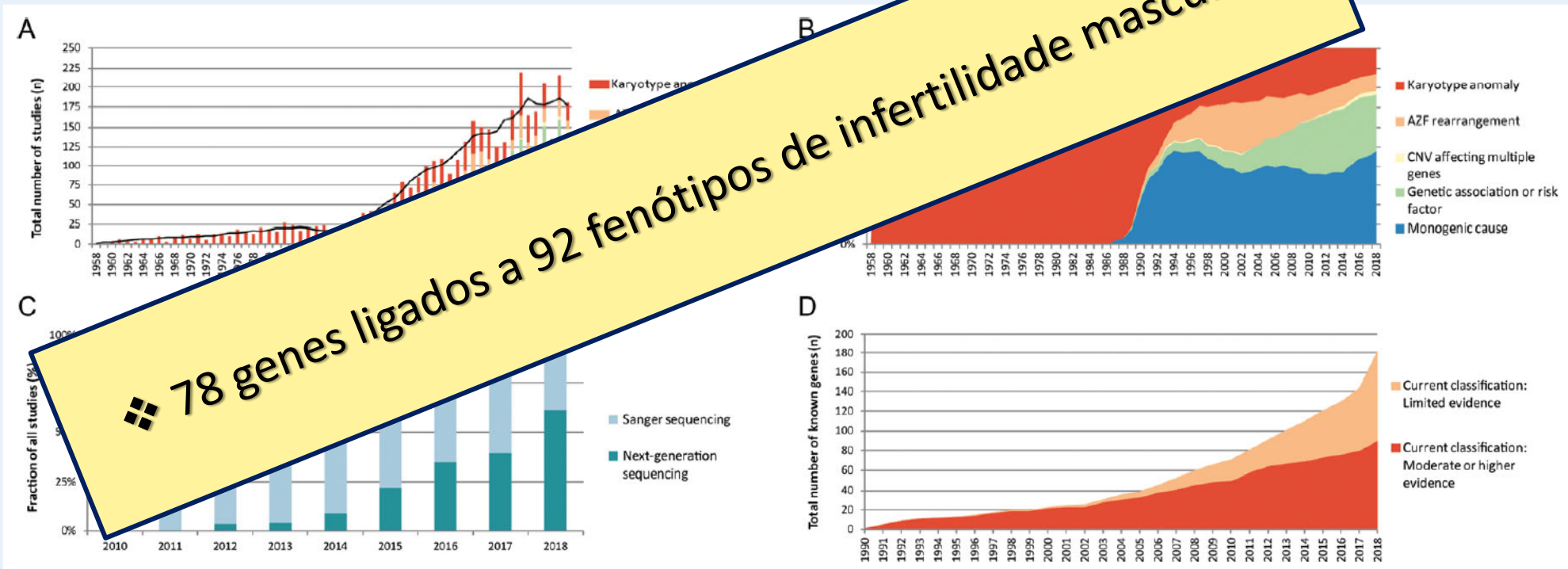
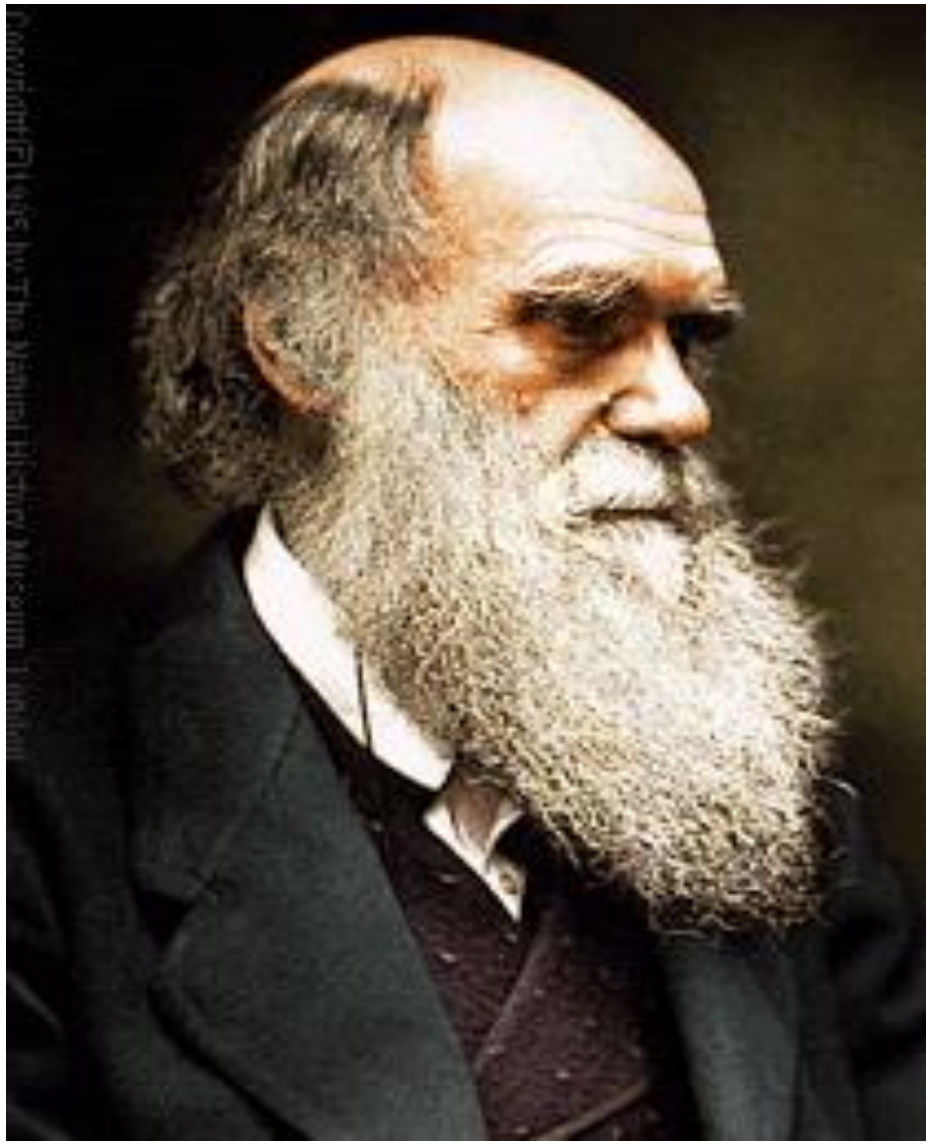


Figure 2 Genetic studies in male infertility between 1958 and 2018. (**A**) Graphical overview of genetic studies in male infertility. (**B**) Graphical representation of type of genetic research in male infertility. (**C**) The use of Sanger sequencing and next-generation sequencing for the discovery of genes in male infertility. (**D**) Increase of genes linked to human male infertility. AZF, azoospermia factor; CNV, copy number variants.

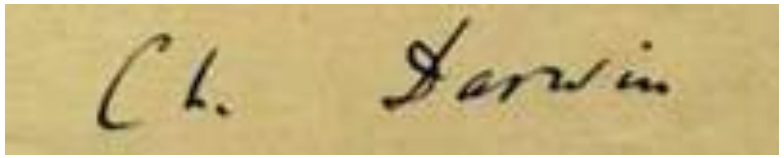
Investigação Genética em Infertilidade Masculina

- Cariótipo com banda G no sangue
- Microdeleção Y (AZF)
- Pesquisa Fibrose Cística (CFTR)
- aSNP (exoma), aCGH / NGS
- Painel genético

FERTILITY



“A seleção natural é o principal agente responsável pelas modificações das populações em resposta às alterações ambientais”.



“Risco potencialmente aumentado para a transmissão de doenças genéticas que estariam bloqueadas pela infertilidade ”

FERTILITY