27° CBRA
CONGRESSO BRASILEIRO
DE REPRODUÇÃO ASSISTIDA

ASPECTOS EPIGENÉTICOS E A INFERTILIDADE MASCULINA: O QUE JÁ SABEMOS

Edson Borges Jr.

Fertility Medical Group
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Declaração:

Sem conflito de interesse para divulgar relacionado ao assunto desta palestra

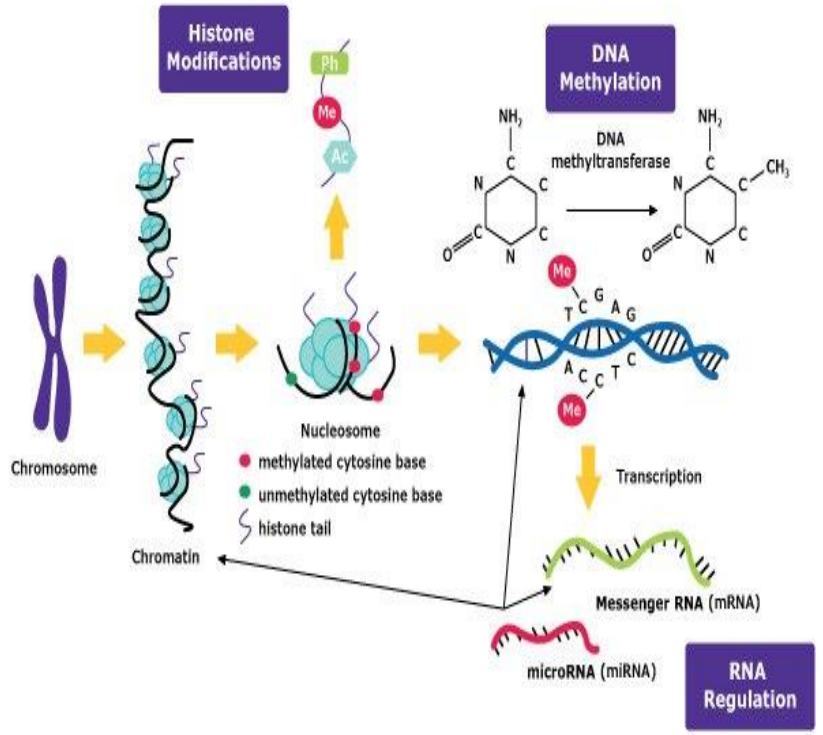
Resolução do Conselho Federal de Medicina nº 1.595/2.000

EPIGENÉTICA

- Aristóteles já acreditava que todas as nossas características têm origem em um processo denominado *"epigênese"*.

- O biólogo Conrad Waddington passou a utilizar a palavra epigenética para se referir à *maneira como os genes interagem com o meio ambiente na construção dos organismos.*

- É a área da biologia que estuda *mudanças no fenótipo que não são causadas por alterações na sequência de DNA e* que se perpetuam nas divisões celulares, meióticas ou mitóticas.



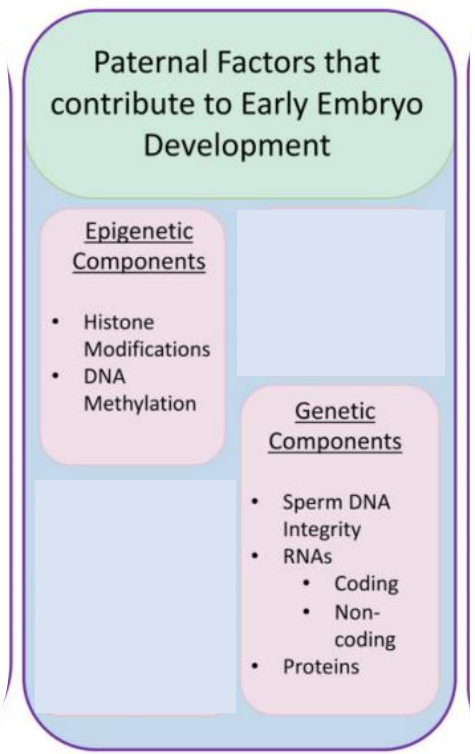
Human Reproduction Update, pp. 1–39, 2023
https://doi.org/10.1093/humupd/dmad006

human reproduction update

Contribution of semen to early embryo development: fertilization and beyond

Montserrat Vallet-Buisan[1], Rajwa Mecca[1], Celine Jones[1], Kevin Coward[1], and Marc Yeste[2,3,4,*]

[1]Nuffield Department of Women's and Reproductive Health, Level 3, Women's Centre, John Radcliffe Hospital, University of Oxford, Oxford, UK [2]Biotechnology of Animal and Human Reproduction (TechnoSperm), Institute of Food and Agricultural Technology, University of Girona, Girona, Spain [3]Unit of Cell Biology, Department of Biology, Faculty of Sciences, University of Girona, Girona, Spain [4]Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain



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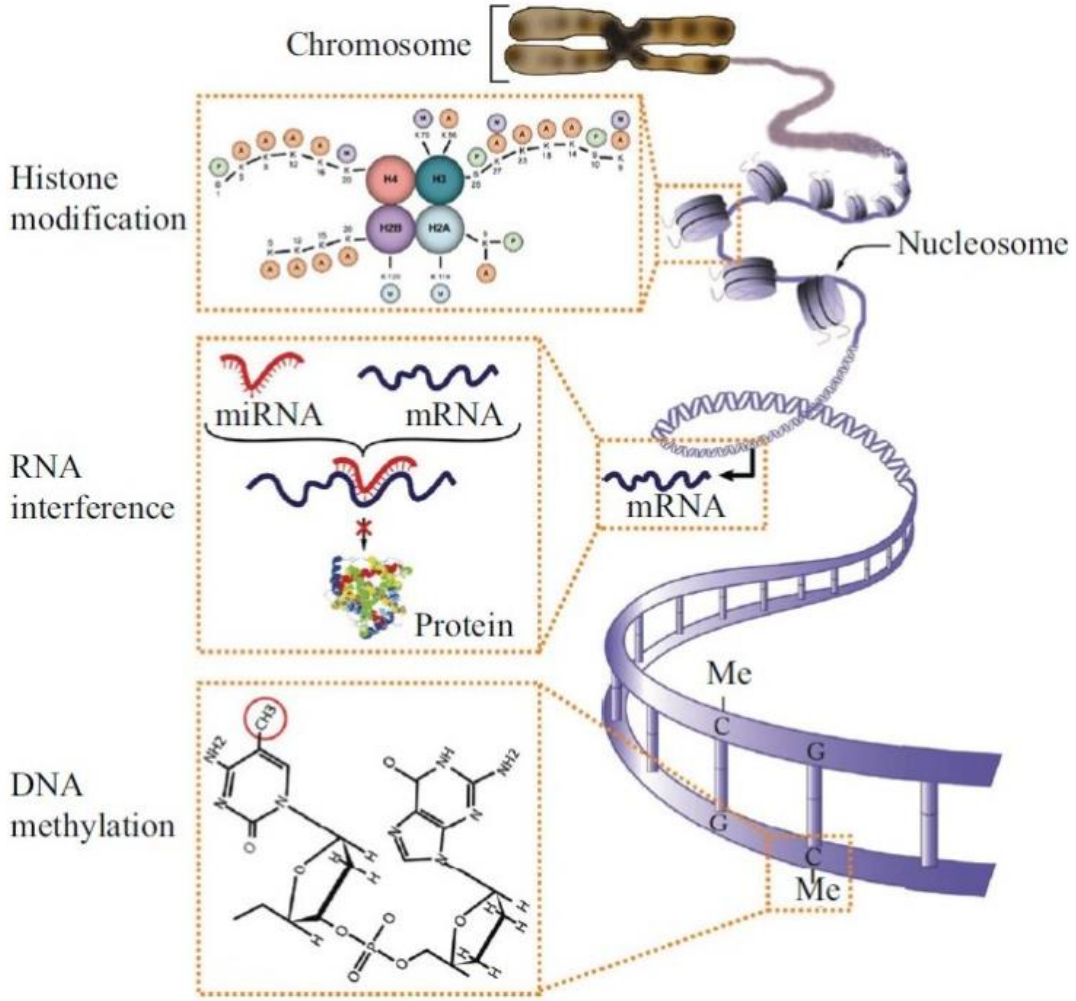
A epigenética refere-se ao processo de regulação gênica sem alterações na sequência do DNA e inclui:

- ❑ DNA methylation
- ❑ Posttranslational histone modifications
- ❑ MicroRNA (miRNA) regulation



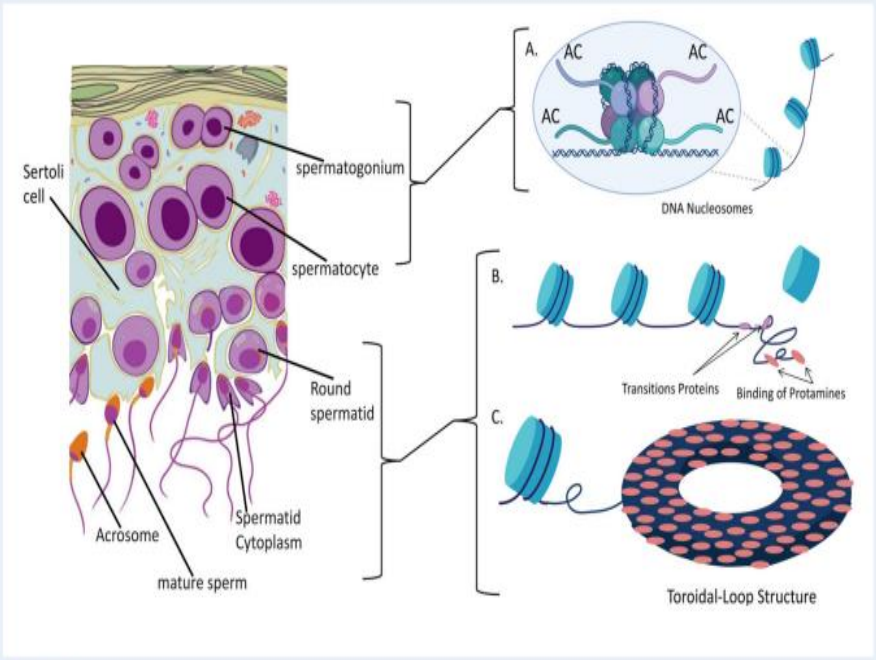


Figure 2. The histone to protamine transition in mammals. During spermatogenesis, histones are replaced by protamines to allow for increased compaction of chromatin within the sperm nucleus. (**A**) During the spermatogonium and primary spermatocyte phases, histones are packed in groups of eight to form a nucleosome. AC represents histone hyperacetylation on the histone tails, which may vary between different histone variants; other epigenetic marks may be applied. (**B**) During the round spermatid phase, remodelling factors, such as transition proteins, help remove chromatin from the nucleosomes and bind it to protamines. (**C**) Protamines form a toroidal loop structure for effective compaction. Figure created with BioRender.com.

A metilação correta do DNA garante a condensação adequada da cromatina na cabeça do espermatozoide, permitindo sua maturação em eventos de fertilização e pós-fertilização

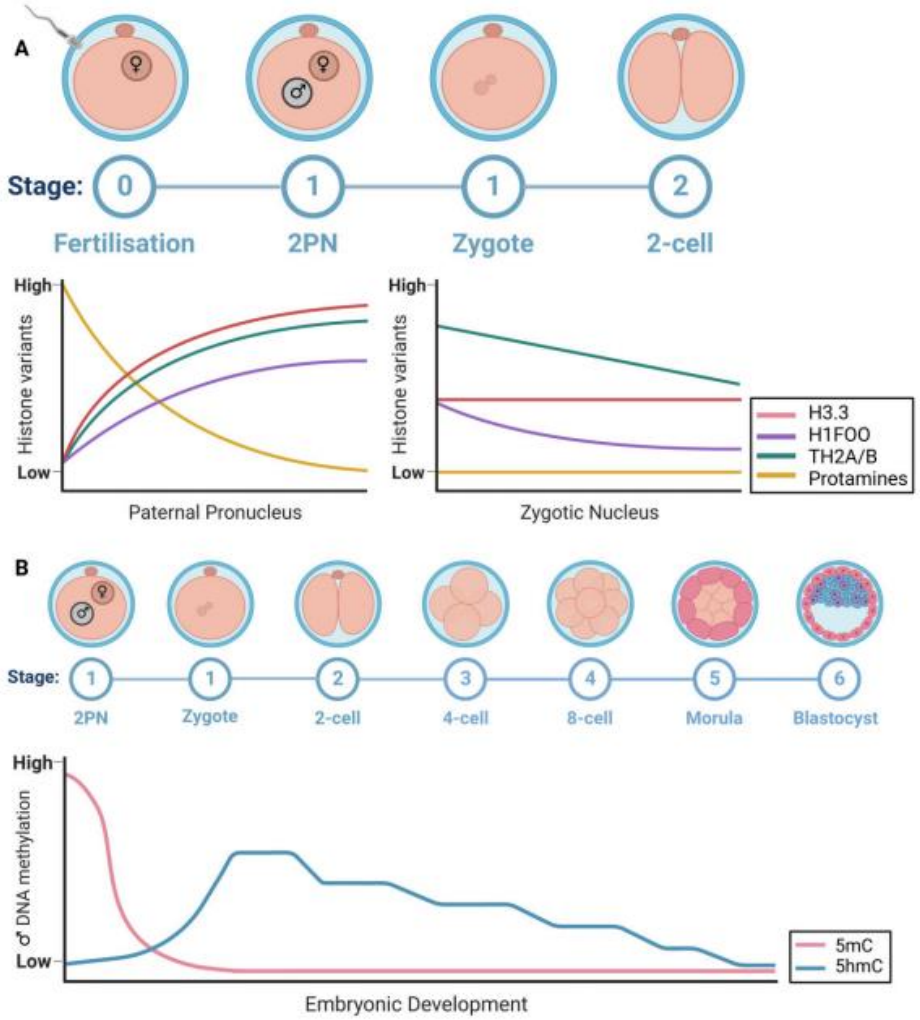


Figure 5. Sperm and zygotic nuclei reprogramming post-fertilization in humans. (**A**) Protamine and histone variant dynamics in early embryo development (adapted from Yang *et al.*, 2015). (**B**) Paternal DNA methylation dynamics in early embryo development. Sperm DNA methylation rapidly decreases; 5mC is converted into 5hmC. **5hmC,** 5-hydroxymethylcystosine; 5mC, 5-methylcystosine; PN, pronucleus; H3.3, histone 3.3; H1FOO, Linker histone H1 FOO; TH2A/B, testis-specific histone H2A/B variants. Created with BioRender.com.

Human Reproduction Update, pp. 1–39, 2023
https://doi.org/10.1093/humupd/dmad006

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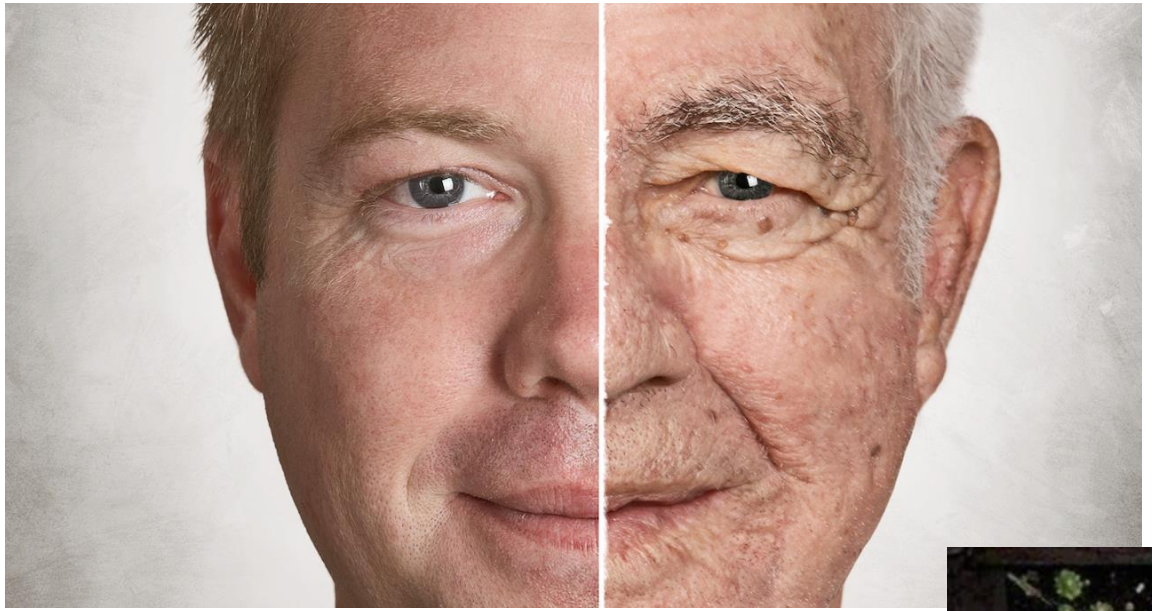

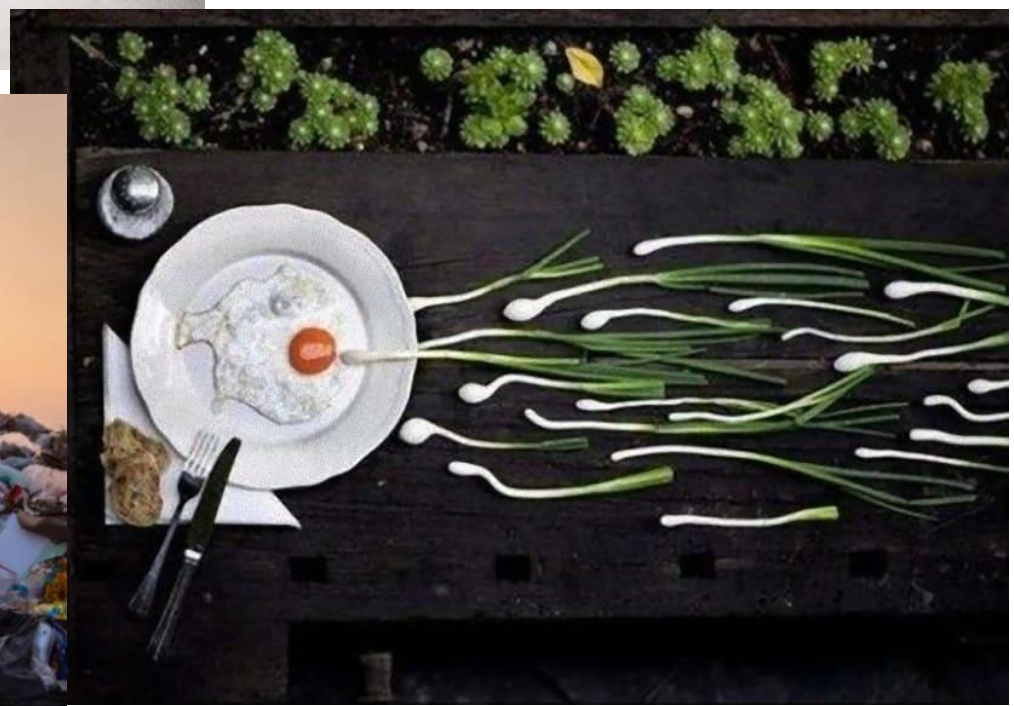

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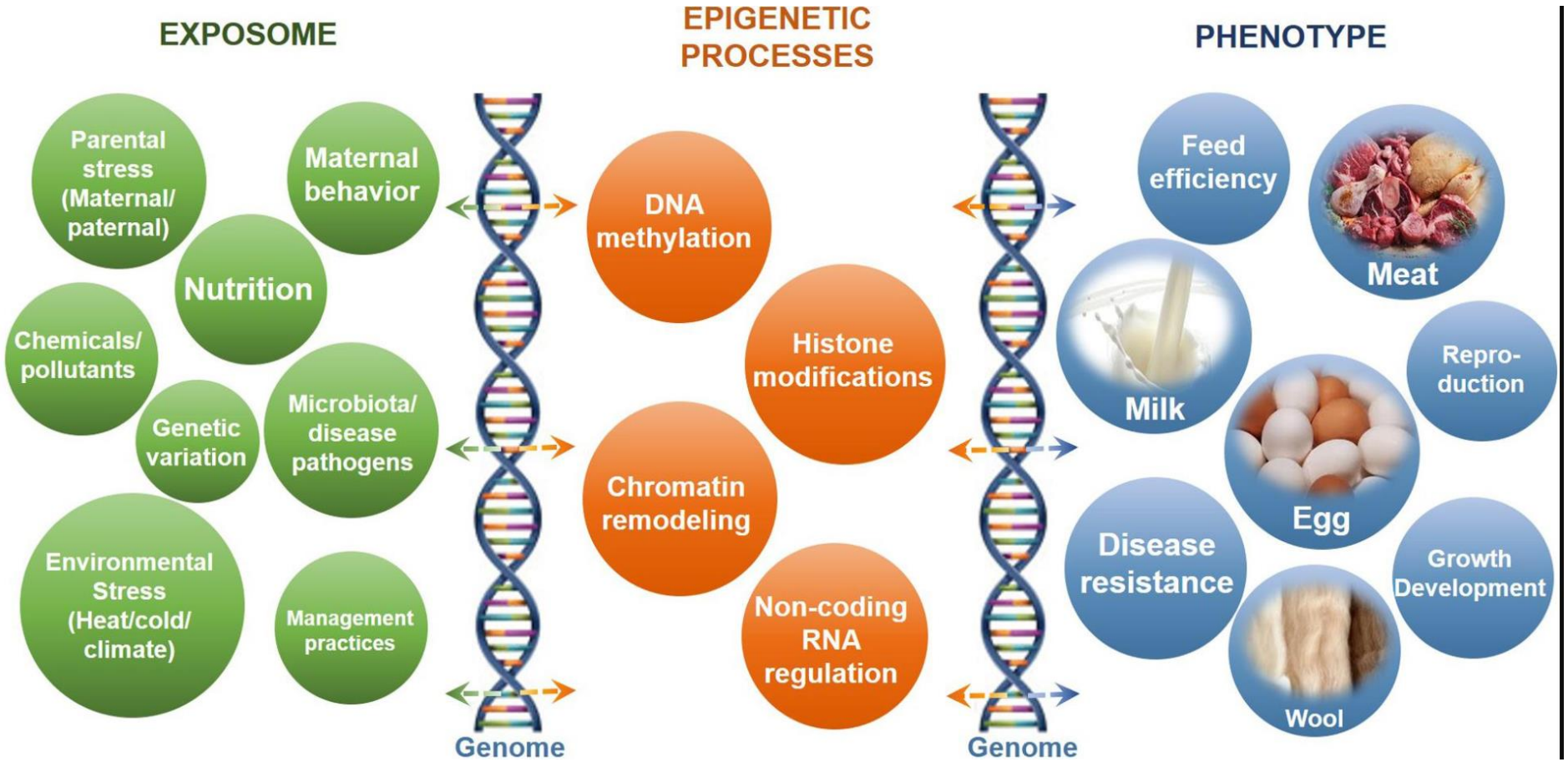
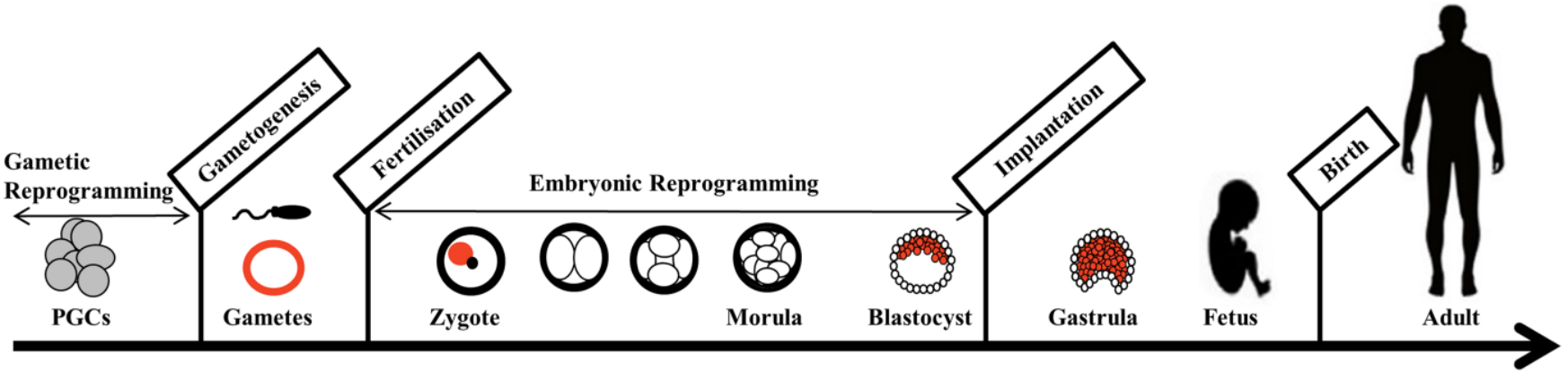

EXPOSOME
EPIGENETIC PROCESSES
PHENOTYPE
Parental stress (Maternal/ paternal)
Maternal behavior
Nutrition
Chemicals/ pollutants
Genetic variation
Microbiota/ disease pathogens
Environmental Stress (Heat/cold/ climate)
Management practices
Genome
DNA methylation
Histone modifications
Chromatin remodeling
Non-coding RNA regulation
Genome
Feed efficiency
Meat
Milk
Repro-duction
Egg
Disease resistance
Growth Development
Wool

Xavier, MJ et al. Human Reproduction Update, Vol.25, No.5, pp. 519–541, 2019



- Durante a vida dos mamíferos, as células são submetidas a duas grandes reprogramações epigenéticas em todo o genoma:
  - ***Reprogramação Gamética***: ocorre em PGCs de embriões durante o desenvolvimento das células germinativas.
  - ***Reprogramação Embrionária:*** começa imediatamente após a fertilização e dura até o estágio de blastocisto do desenvolvimento embrionário

- Em termos evolutivos, essas mudanças criam *a diversidade fenotípica que alimenta a seleção natural*.

- No entanto, em vez de ser adaptativa, *essa variação também pode gerar uma infinidade de estados de doença patológica* que variam de distúrbios genéticos a *condições neurológicas.*

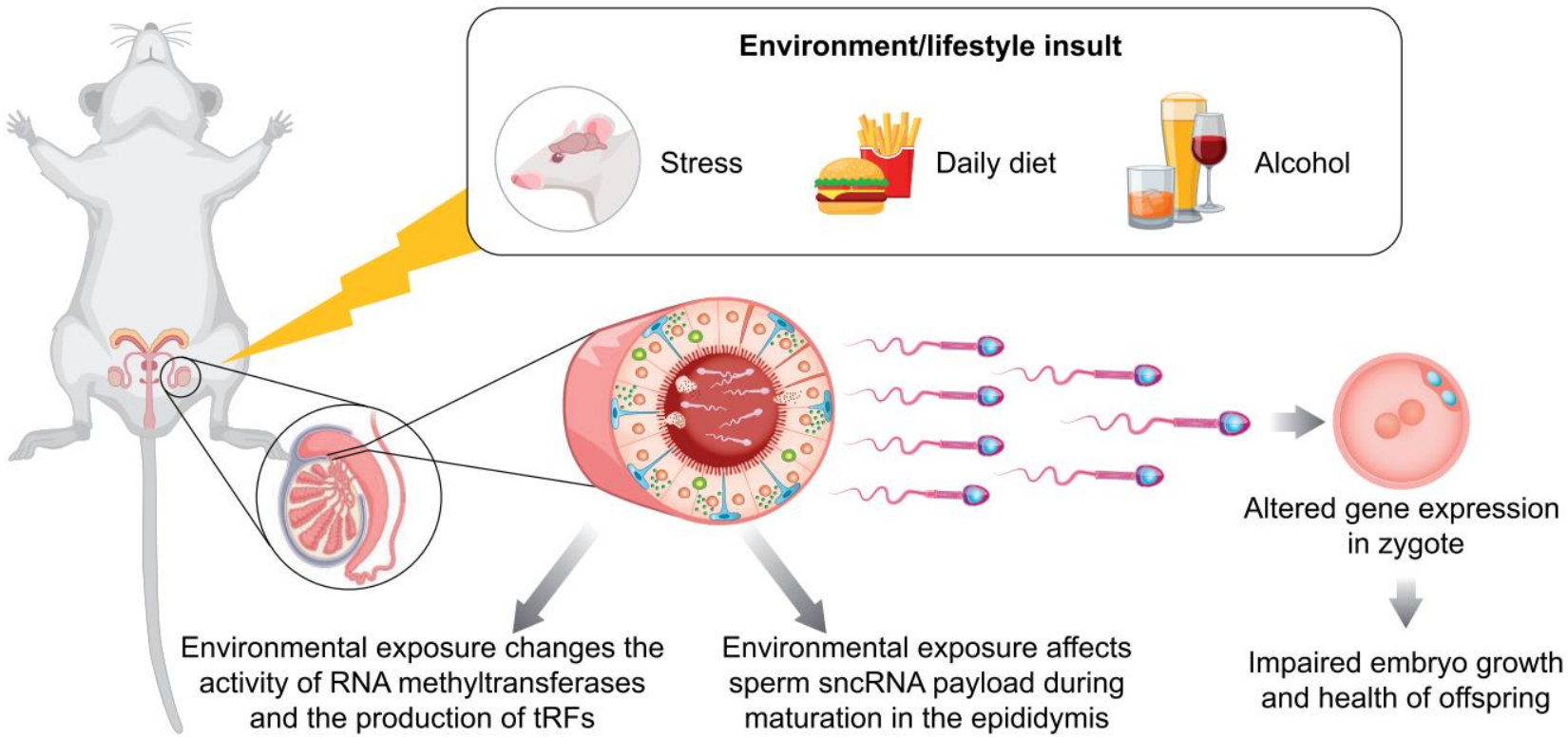
Human Reproduction Update, Vol.28, No.1, pp. 51–66, 2022
Advance Access Publication on October 7, 2021 doi:10.1093/humupd/dmab029

human reproduction update

Contribution of epididymal epithelial cell functions to sperm epigenetic changes and the health of progeny

Hong Chen, Maíra Bianchi Rodrigues Alves, and Clémence Belleannée *

Department of Obstetrics, Gynecology and Reproduction, Université Laval, Quebec, Canada



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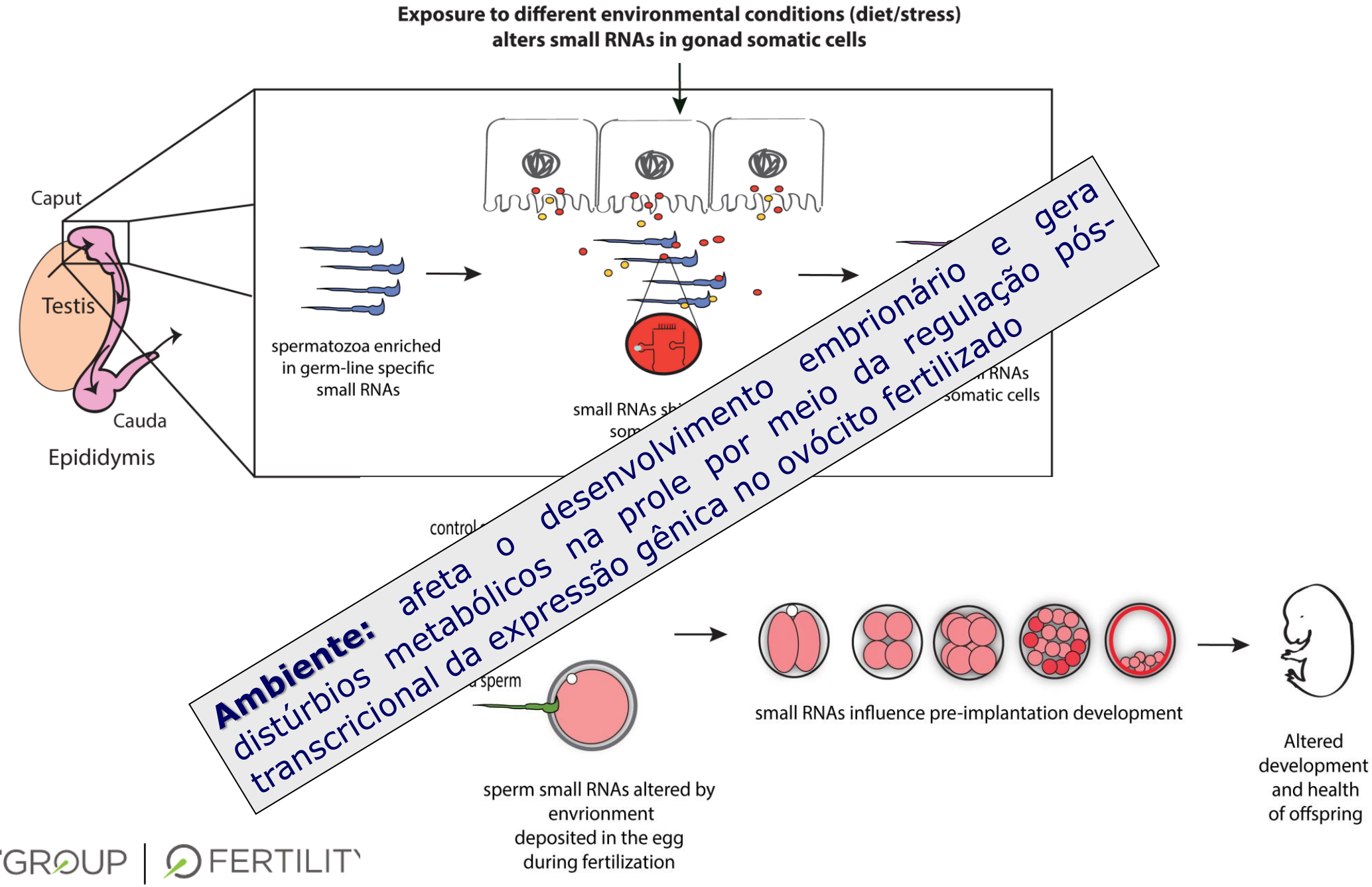

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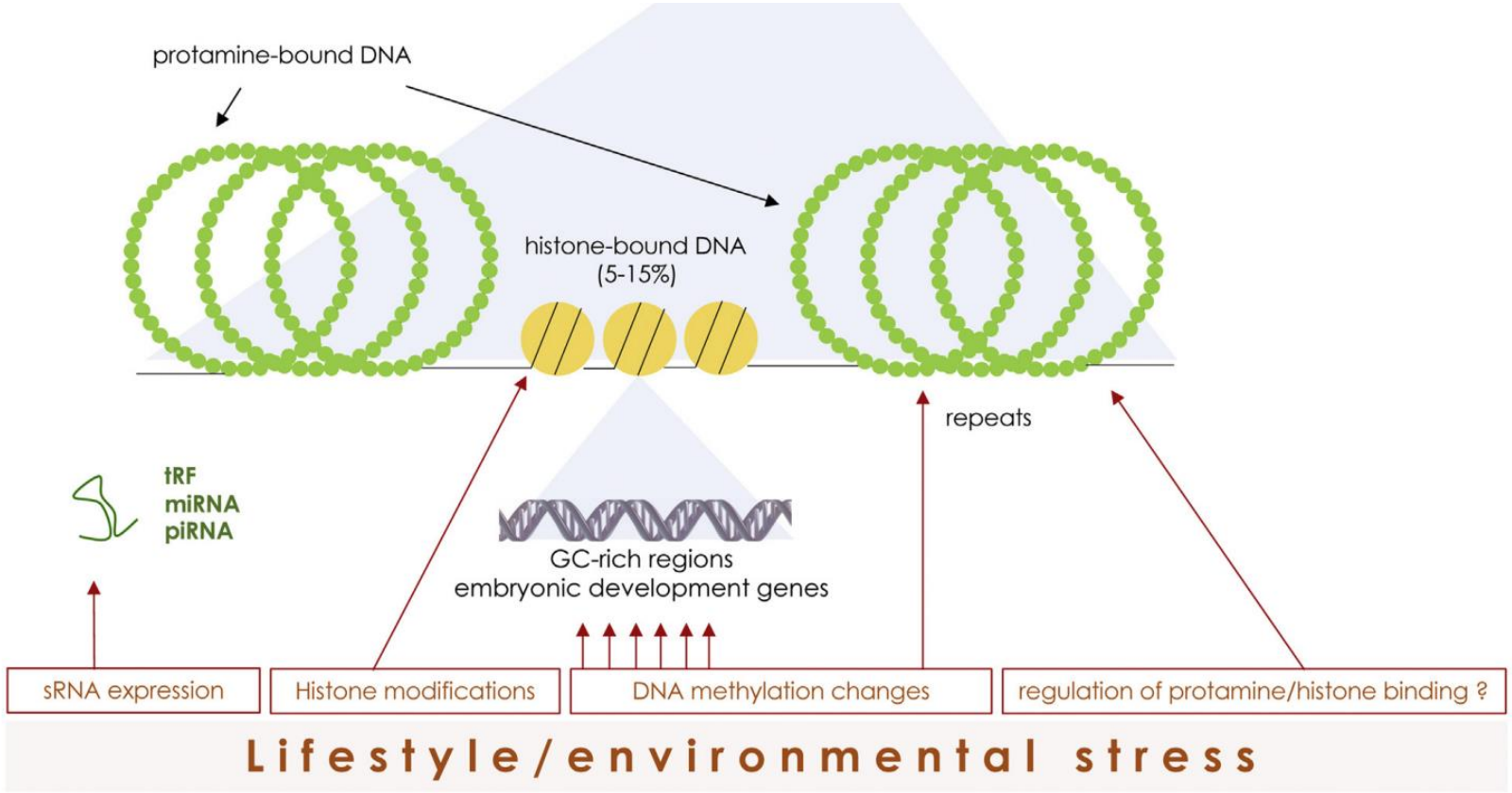
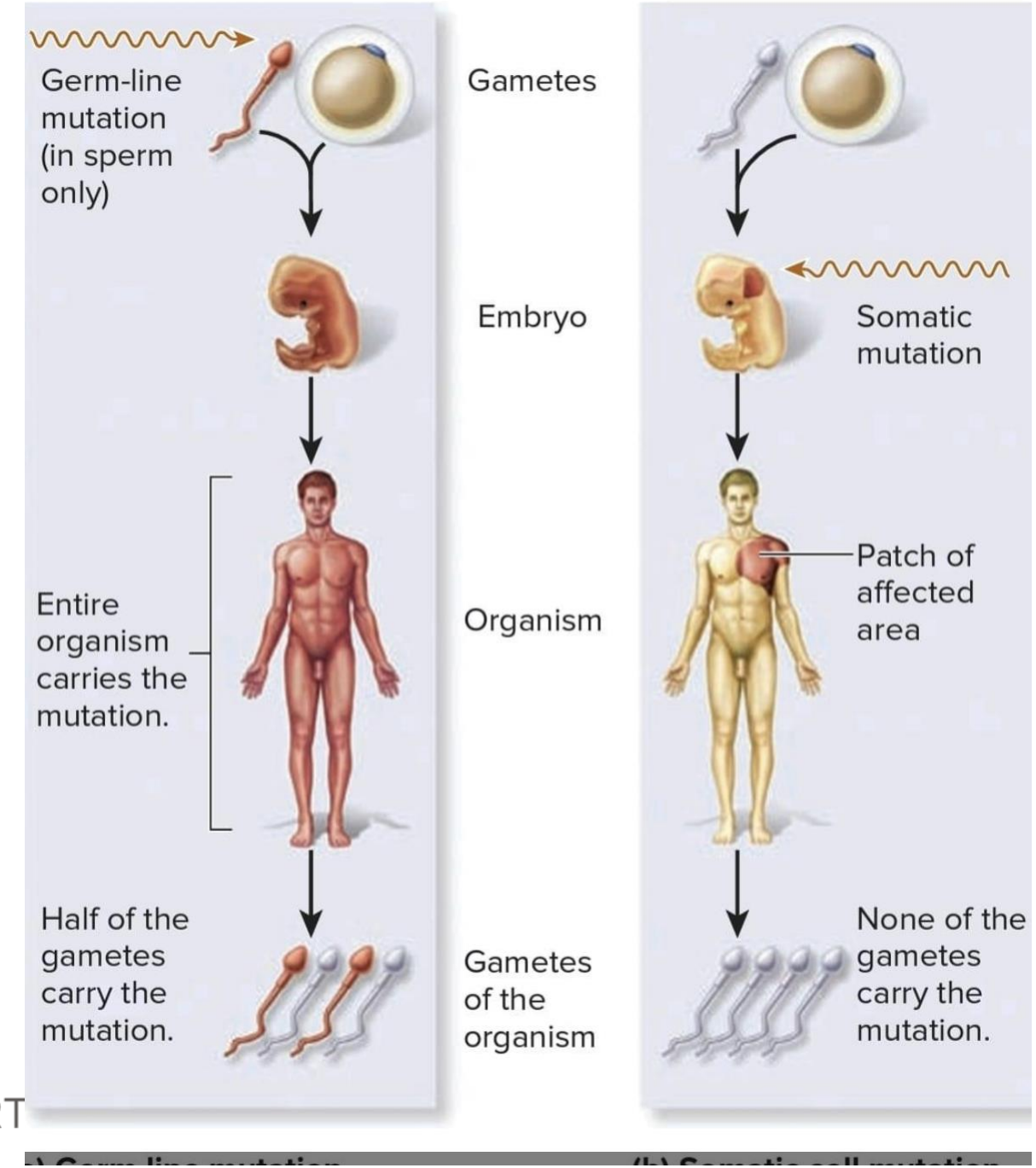
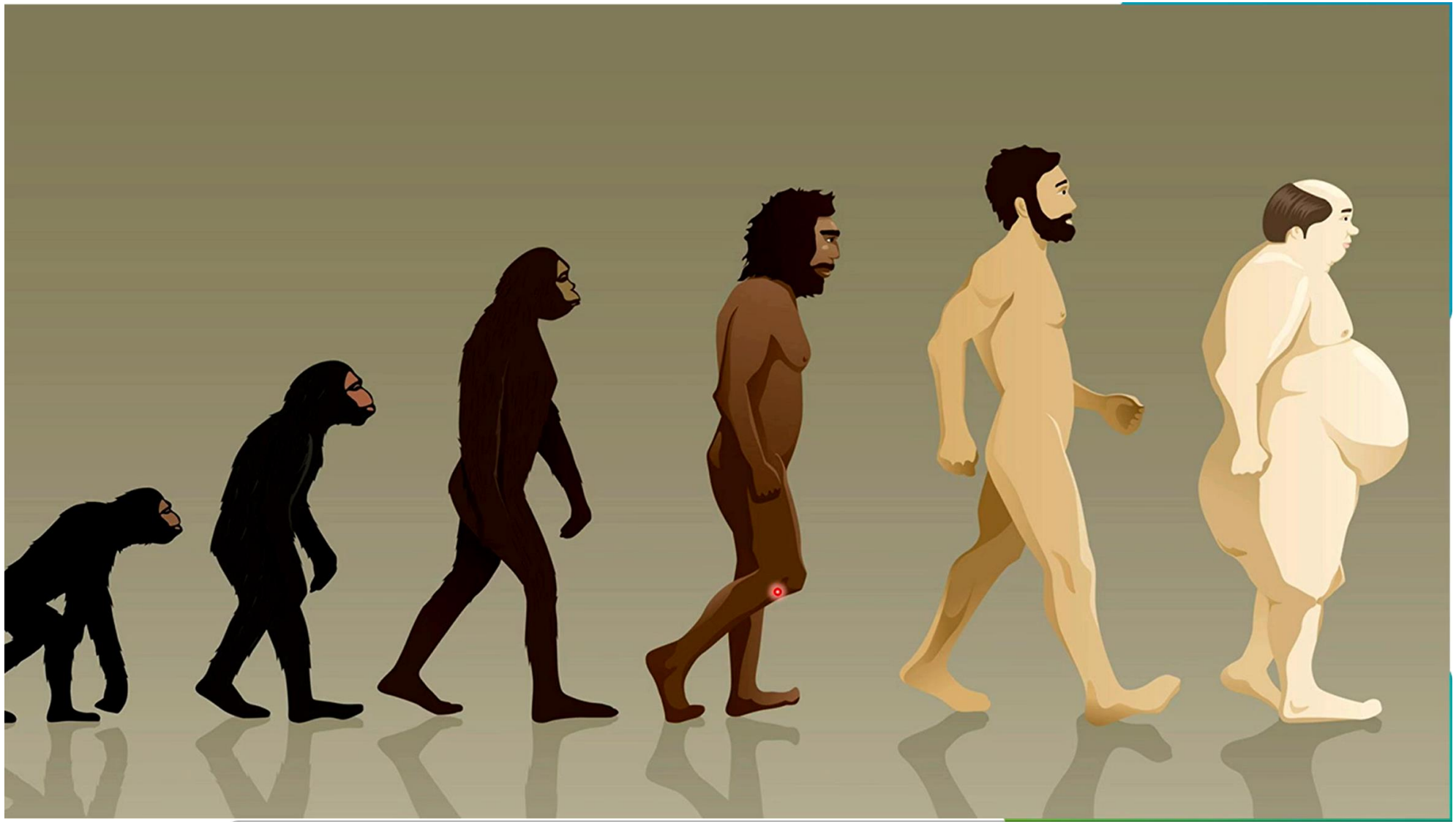
Sharma, U. Frontiers in Cell and Developmental Biology | October 2019 | Volume 7 | Article 215



Existem fortes evidências ***de fatores epigenéticos causados pelo ambiente e transmitidos pelos espermatozoides***, capazes de ***alterar o fenótipo da próxima geração***

MOLECULAR METABOLISM 14 (2018) 1e11
https://doi.org/10.1016/j.molmet.2018.02.006


Germ-line mutation (in sperm only)
Gametes
Embryo
Somatic mutation
Entire organism carries the mutation.
Organism
Patch of affected area
Half of the gametes carry the mutation.
Gametes of the organism
None of the gametes carry the mutation.



European Society of Human Reproduction and Embryology

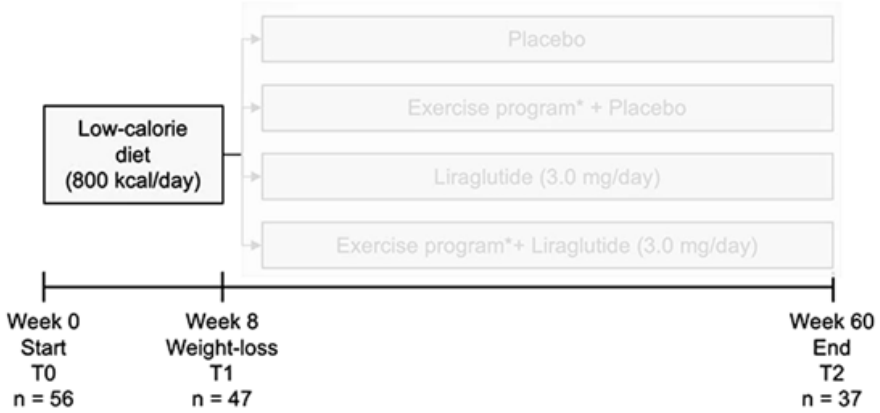
Influence of Diet and Exercise on Sperm and its Epigenome

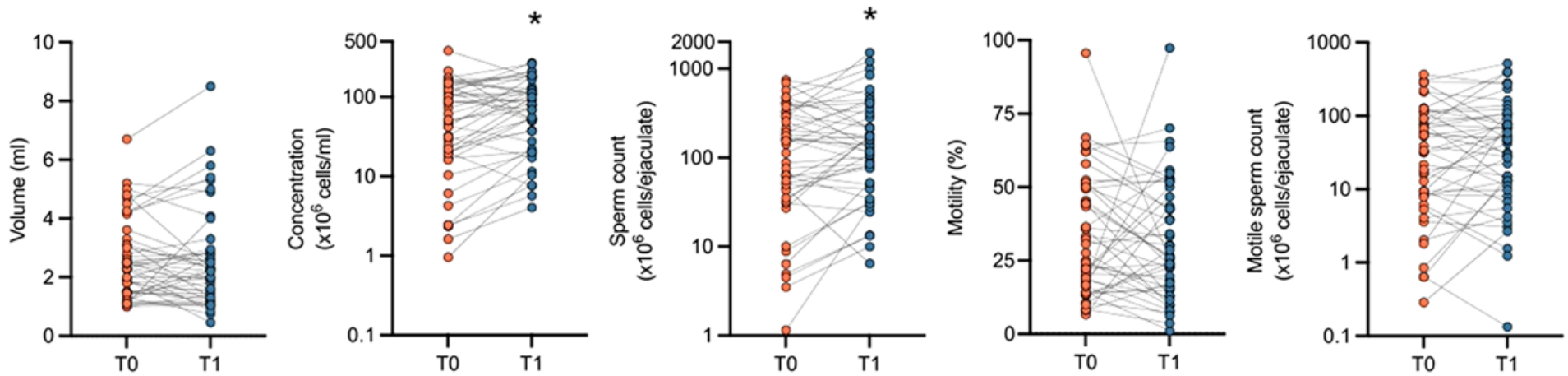
ESHRE Annual Conference 2023, Copenhagen

Prof. Romain Barrès

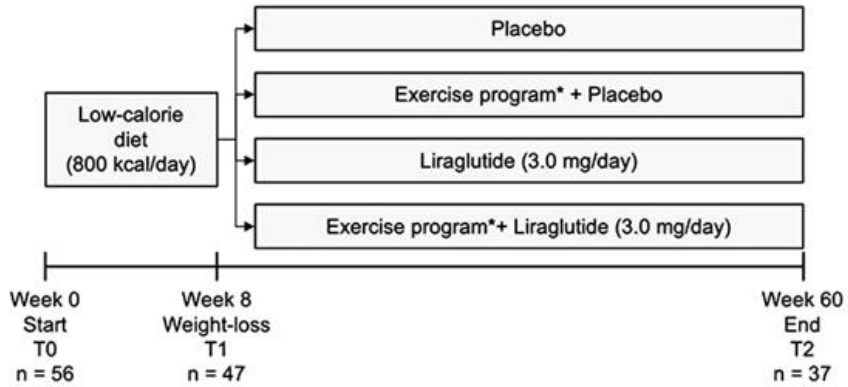
Center for Basic Metabolic Research (CBMR)
University of Copenhagen

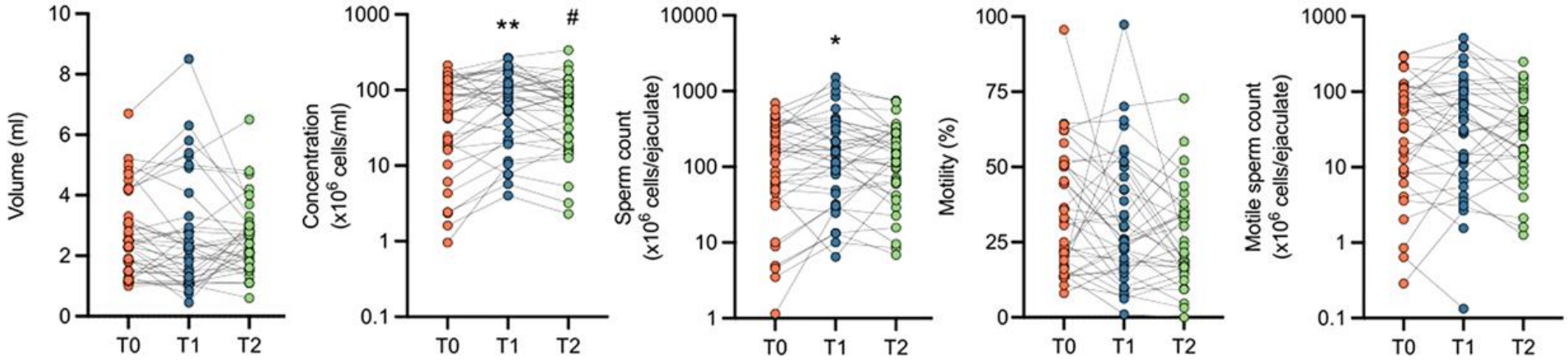
Institut de Pharmacologie Moléculaire et Cellulaire
Université Côte d'Azur





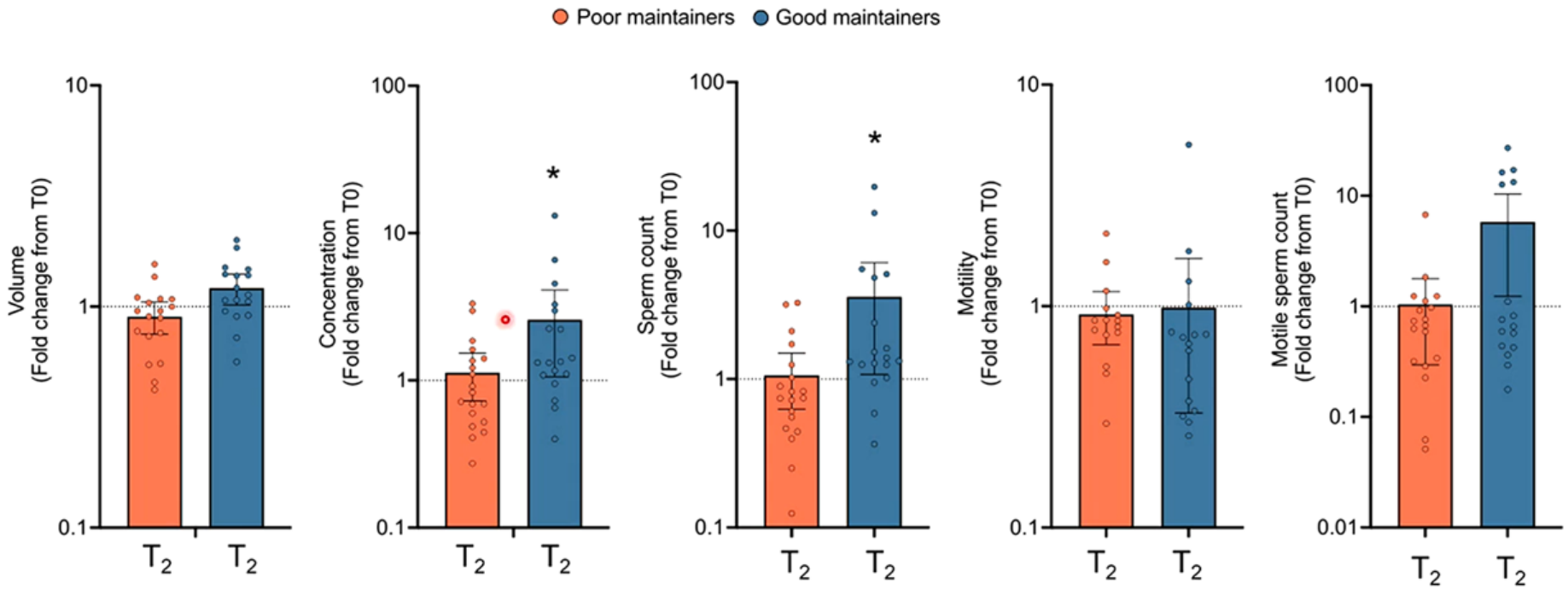
Andersen and Juhl, […] Torekov and Barrès. **Hum Reprod**. 2022





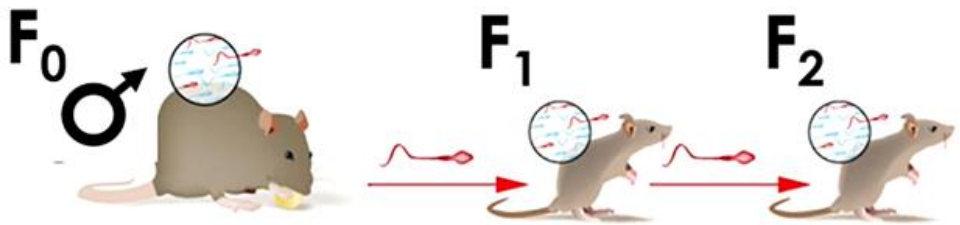
Andersen and Juhl, [...] Torekov and Barrès. **Hum Reprod**. 2022

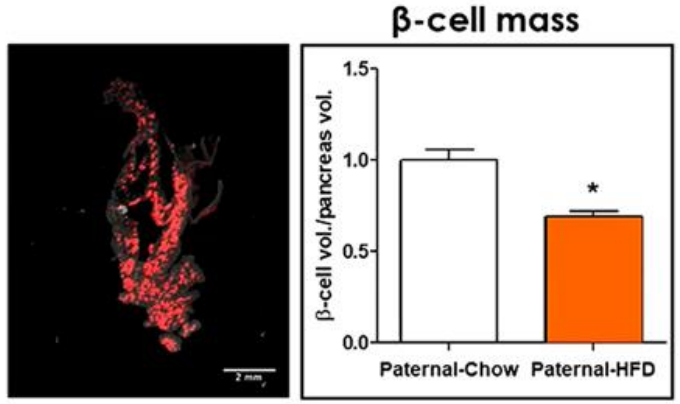
Maintenance of weight loss after 52 weeks is associated with improved sperm concentration and sperm count



Andersen and Juhl, […] Torekov and Barrès. **Hum Reprod**. 2022

Western style diet before conception is associated with epigenetic changes in sperm and an altered metabolic phenotype in the offspring





Ng […], Barrès, […], and Morris, ***Nature***, 2010.
De Castro Barbosa […] and Barrès, ***Molecular Metabolism***, 2015.

nature communications

Article

https://doi.org/10.1038/s41467-023-38314-x

Male reproductive traits are differentially affected by dietary macronutrient balance but unrelated to adiposity

Received: 25 September 2022

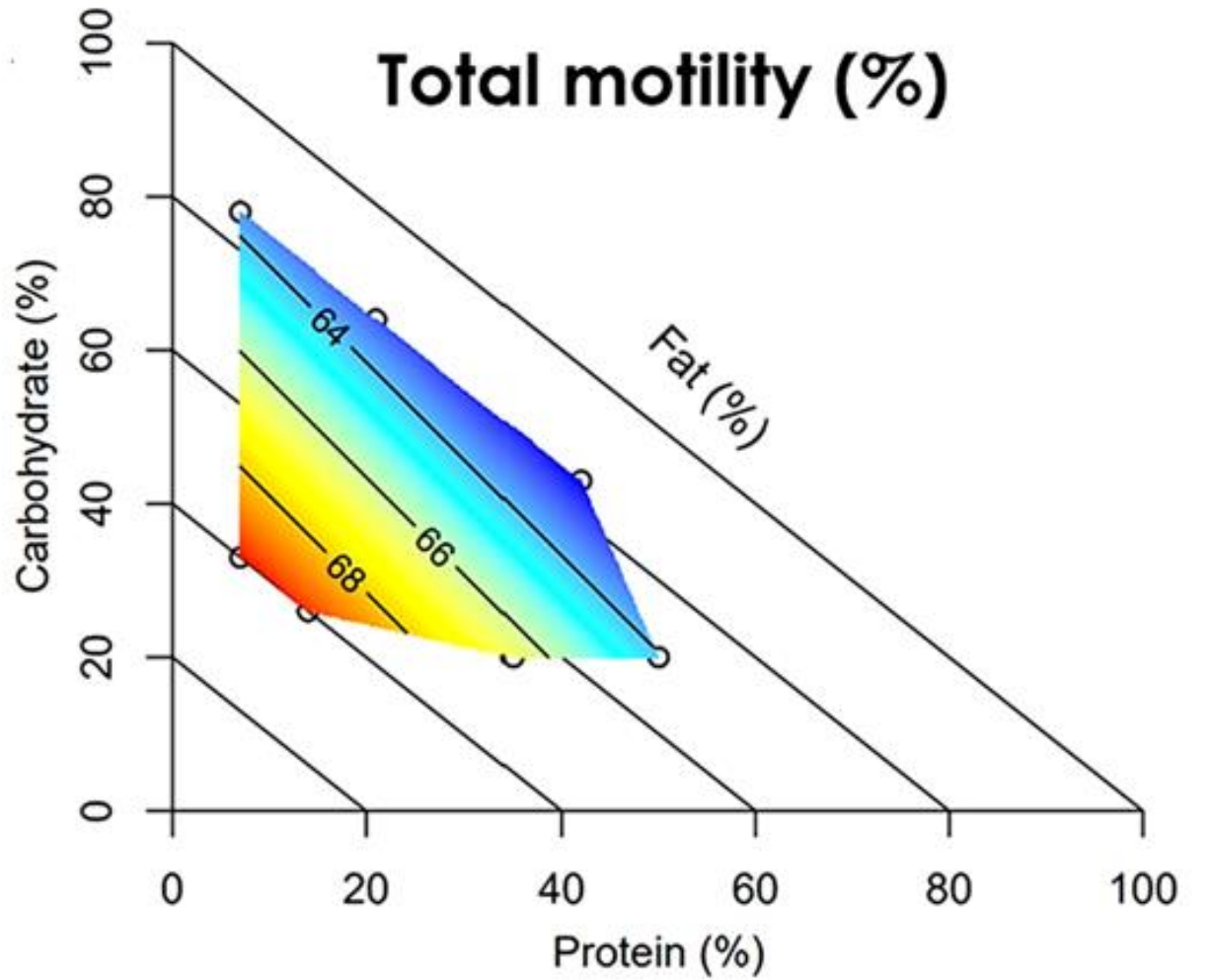
Accepted: 25 April 2023

A. J. Crean[1], S. Afrin[1], H. Niranjan[1], T. J. Pulpitel[1], G. Ahmad[1,2], A. M. Senior[1], T. Freire[1], F. Mackay[1], M. A. Nobrega[3], R. Barrès[4,5], S. J. Simpson[1] & T. Pini[1,6]

Steve Simpson | Angela Crean | Taylor Pini

Crean et al., **Nat Communications**. 2023 May 4;14(1):2566.

Diet and obesity independently impact sperm motility



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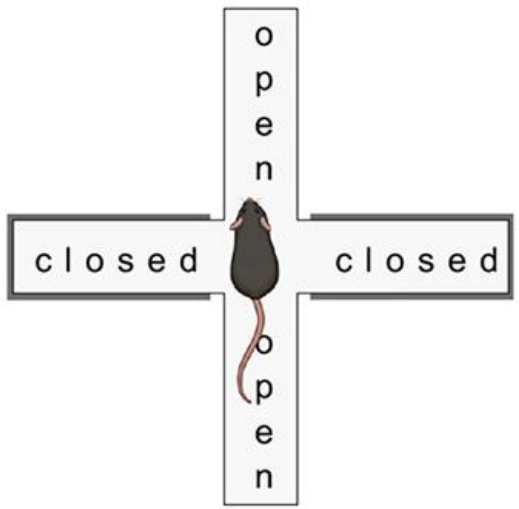
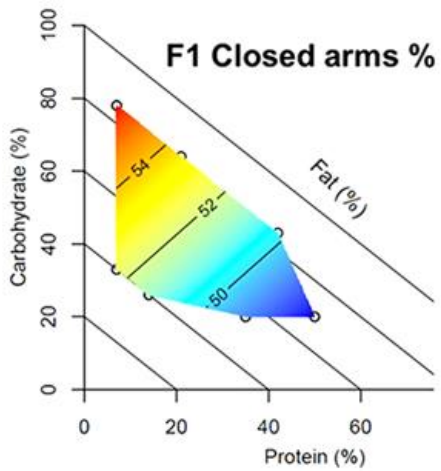
Low protein high carbohydrate paternal diet composition induces an anxiety-like phenotype in male offspring

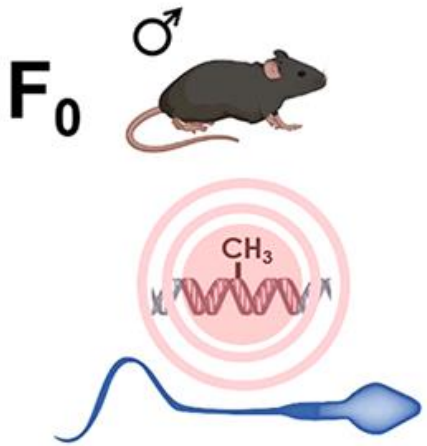
Male offspring

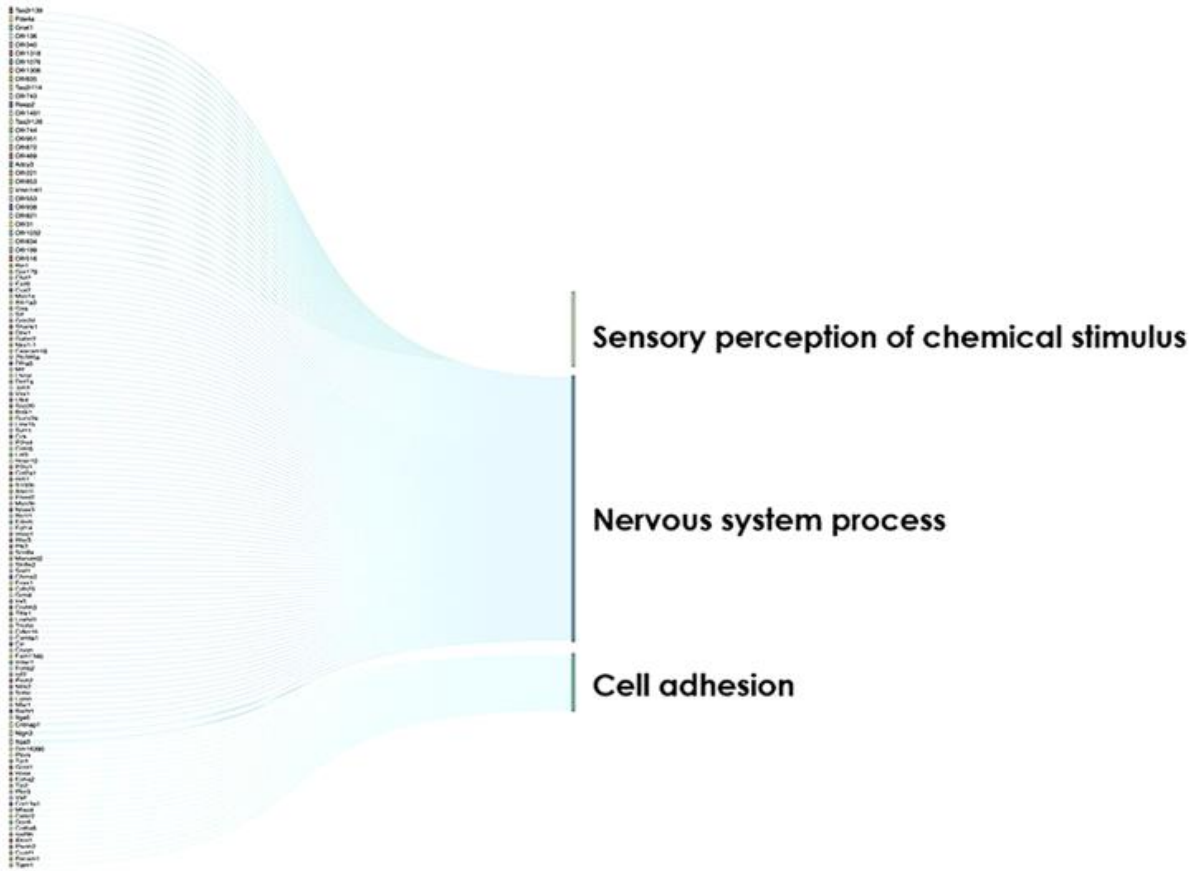




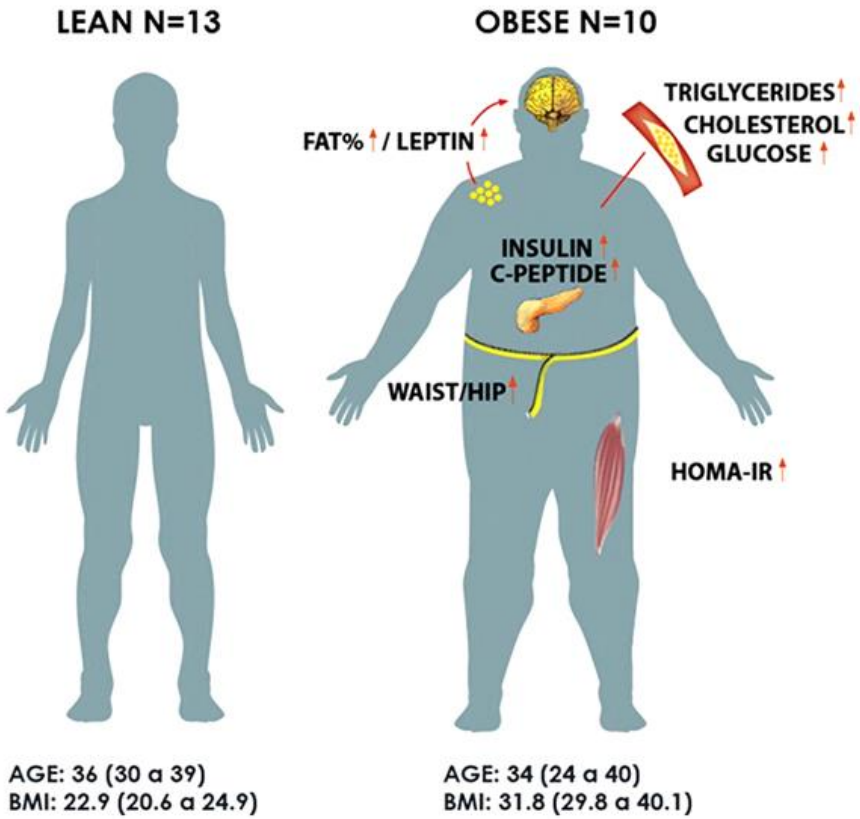
Crean et al., **Unpublished**.

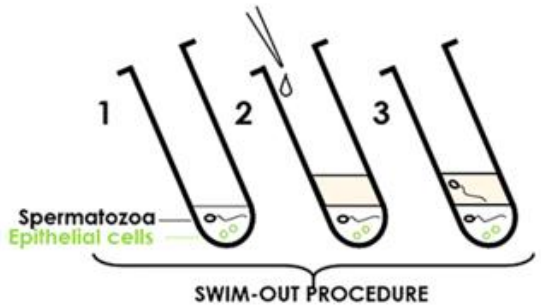
Low protein diet remodels the DNA methylation profile of spermatozoa

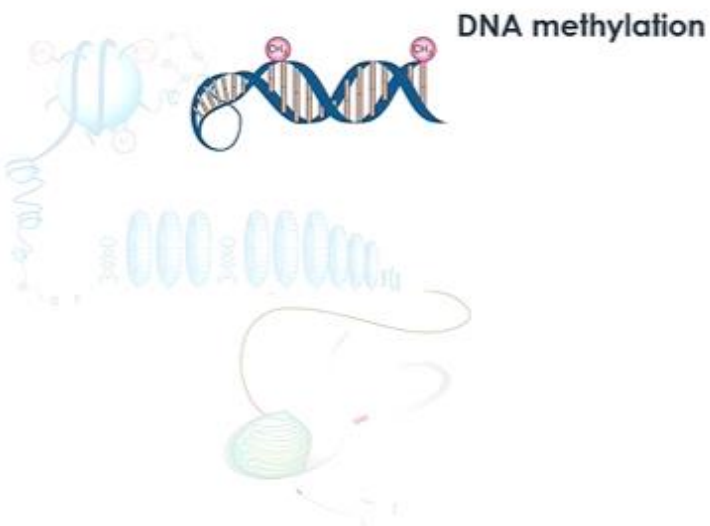




EPIGENETIC PROFILING OF SPERMATOZOA







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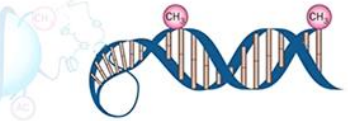
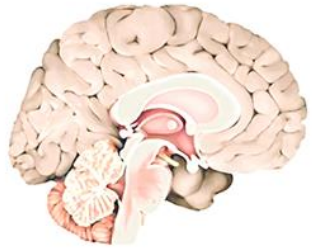
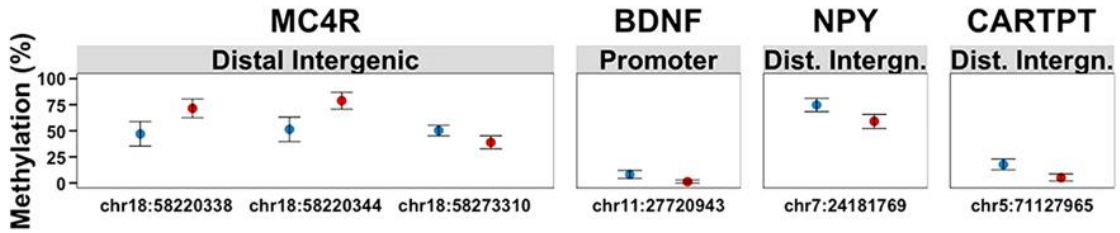
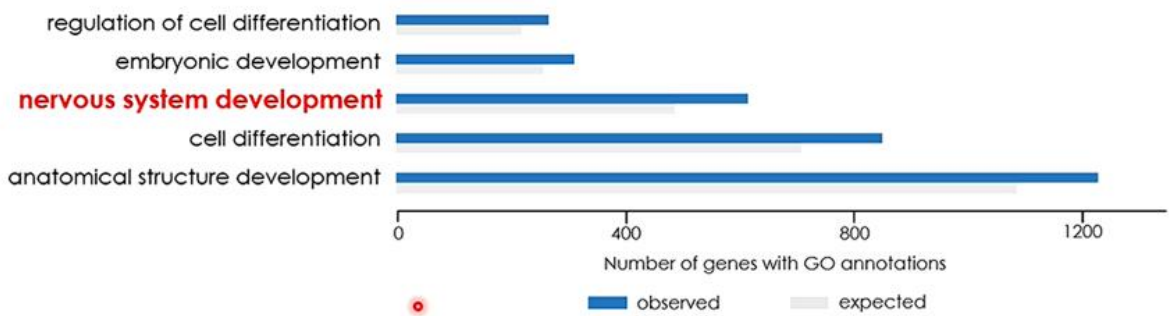
DNA methylation



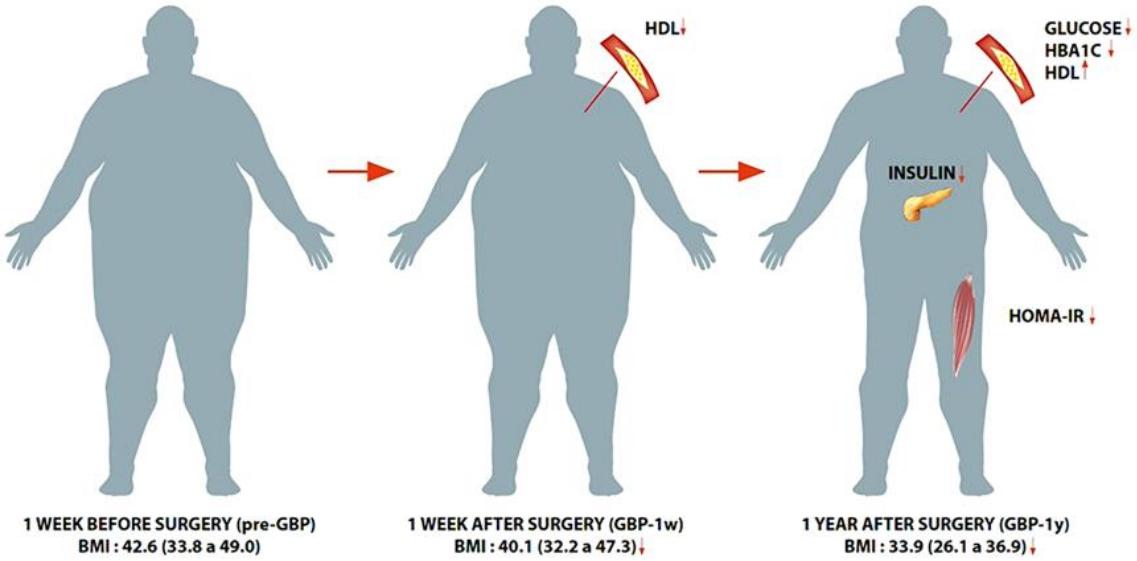




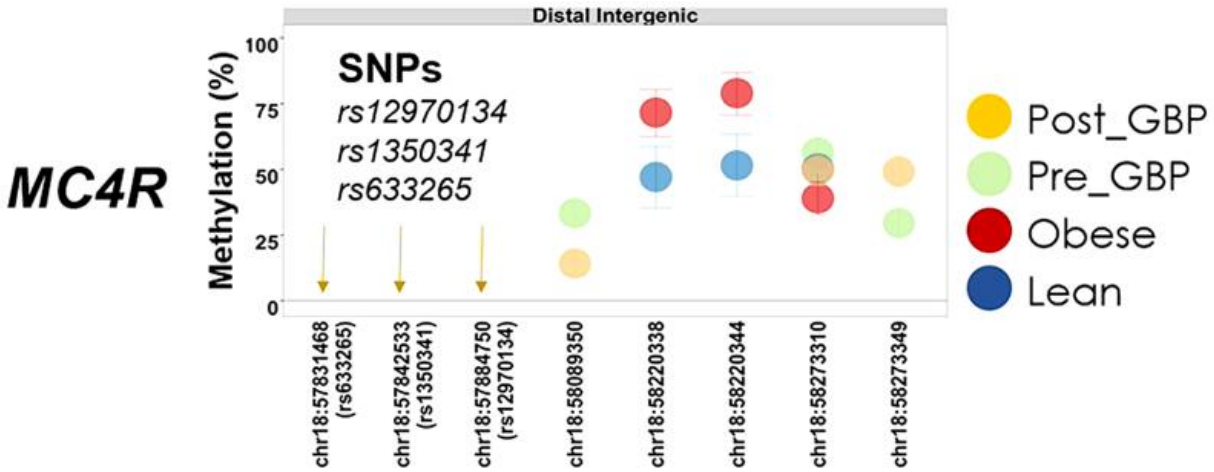
Brain function and the central regulation of appetite



Donkin and Versteyhe, […] and Barrès. ***Cell Metabolism***, 2016.



Sperm DNA metylation response



Metylation response:
environment can change the epigenome sperm in the same individual

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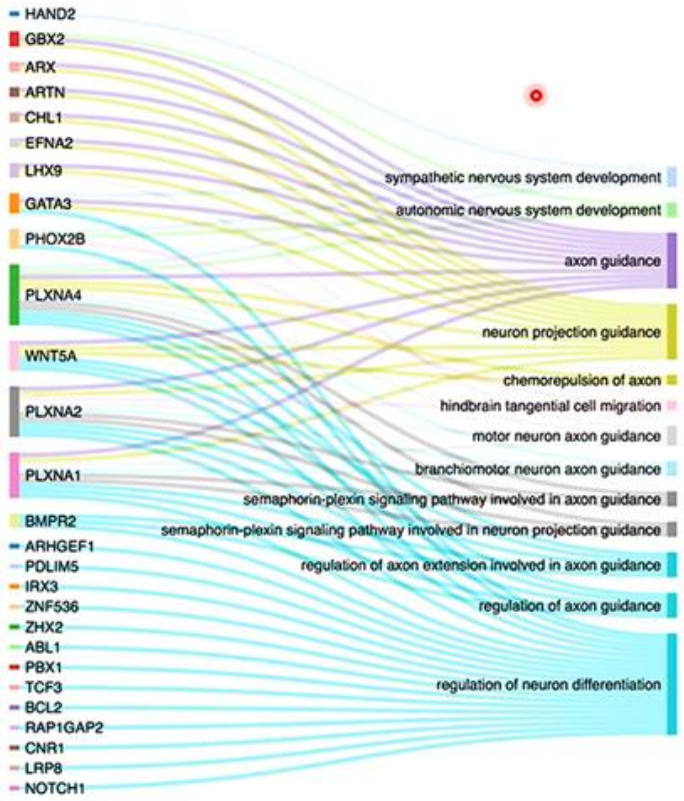
Donkin and Versteyhe, [...] and Barrès. ***Cell Metabolism***, 2016.

DNA methylation variation after exercise training affects brain development genes

Trained



Ingerslev and Donkin, [...] and Barrès. **Clinical Epigenetics**, 2018.

Detrained

- **Environmental factors that lead to epigenetic variation.**
- **Gens related to the brain: hotspots of genetic variation**

Genes related to neurogenesis expressed in the brain and CNS are more susceptible to epigenetic variation

Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort

Jason I Feinberg,[1,2] Kelly M Bakulski,[1,2,3] Andrew E Jaffe,[4,11] Rakel Tryggvadottir,[2] Shannon C Brown,[1,3] Lynn R Goldman,[5,6] Lisa A Croen,[7] Irva Hertz-Picciotto,[8] Craig J Newschaffer,[9,10] M Daniele Fallin[1,11,*] and Andrew P Feinberg[2,12,*]

Int J Epidemiol. 2015

The epigenetic signature of these fathers (DNA metylation) was striking overlap between those with gastric bypass an obese individuals.

Feinberg et al., **Int J Epidemiol**, 2015.

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OBESITY

Paternal obesity—a risk factor for autism?

Susan K. Murphy

The aetiology of autism-spectrum disorders is partly explained by genetic factors, but a substantial component is attributed to environmental exposures. New evidence suggests that paternal obesity increases the risk of having a child with autism, which raises the possibility that obesity-driven, autism-related shifts in epigenetic reprogramming occur during spermatogenesis.

Murphy, S. K. *Nat. Rev. Endocrinol.* **10**, 389–390 (2014); published online 3 June 2014; doi:10.1038/nrendo.2014.81

"**Paternal obesity** was associated with a **73% increased risk** (OR 1.73, 95% CI 1.07–2.82) of having a child diagnosed with autism, compared with the risk of autism in children of **non obese fathers** (BMI ≤25 kg/m2)."

Murphy, **Nat Rev Endocrinol**, 2014

Garrido *et al. Clin Epigenet* (2021) 13:6
https://doi.org/10.1186/s13148-020-00995-2

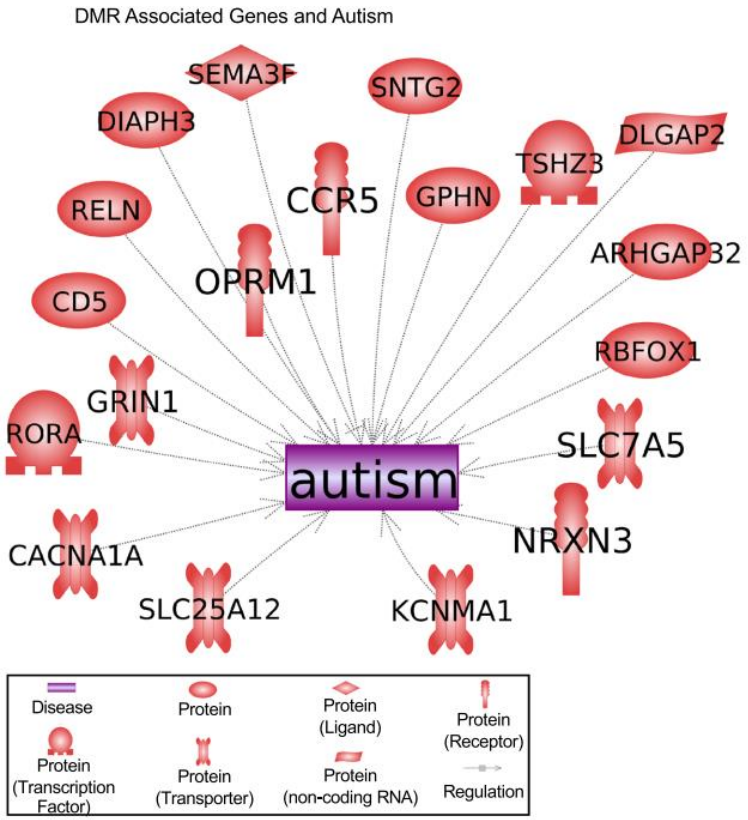
Clinical Epigenetics

RESEARCH Open Access

Sperm DNA methylation epimutation biomarker for paternal offspring autism susceptibility

Nicolás Garrido[1], Fabio Cruz[1], Rocio Rivera Egea[1], Carlos Simon[2,3], Ingrid Sadler-Riggleman[4], Daniel Beck[4], Eric Nilsson[4], Millissia Ben Maamar[4] and Michael K. Skinner[4*]

Exposições paternas dos ancestrais ou no início da vida que alteram a epigenética da linhagem germinativa pode ser um componente molecular da etiologia do TEA.



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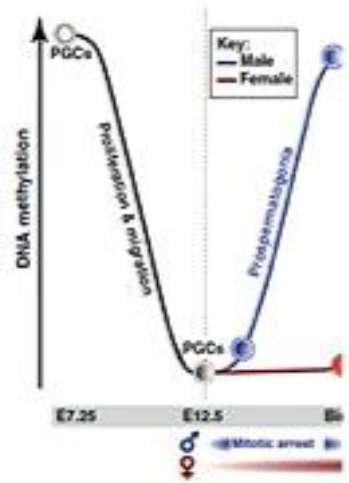
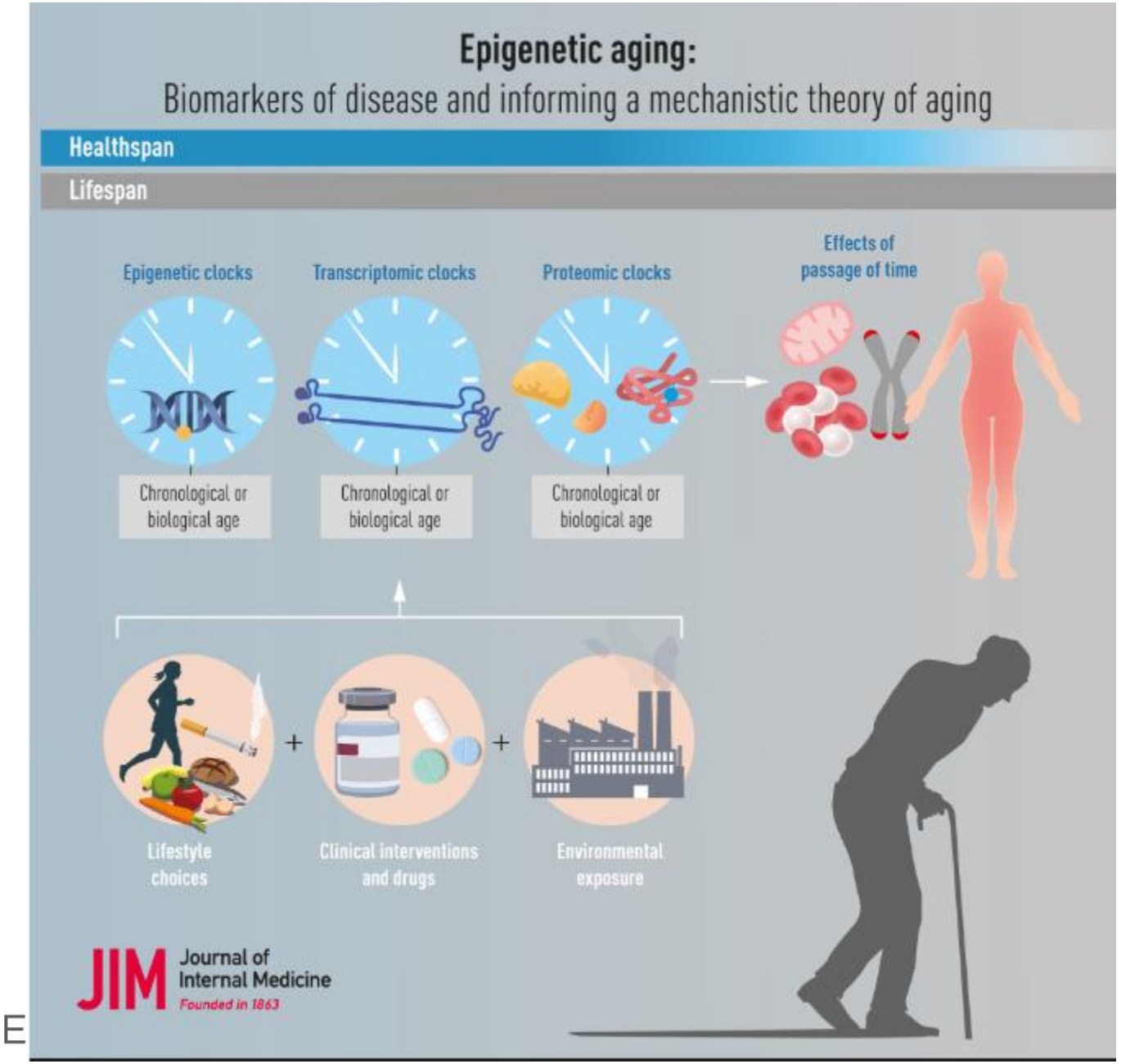
A Unique Gene Regulatory Network Resets the Human Germline Epigenome for Development

Walfred W.C. Tang,[1,2,3,5] Sabine Dietmann,[3,5] Naoko Irie,[1,2,3] Harry G. Leitch,[3] Vasileios I. Floros,[4] Charles R. Bradshaw,[1] Jamie A. Hackett,[1,2,3] Patrick F. Chinnery,[4] and M. Azim Surani[1,2,3,*]



Region escaping reprogramming were related to "[…] genes expressed in brain and participated in neural development. Comparison of the escapee geneswith the NHGRI GWAS catalog revealed characteristic trait and disease associations, such as "obesity-related traits," "schizophrenia," […]"

Tang et al., **Cell**, 2015.


Epigenetic aging:
Biomarkers of disease and informing a mechanistic theory of aging
Healthspan
Lifespan
Epigenetic clocks
Transcriptomic clocks
Proteomic clocks
Effects of passage of time
Chronological or biological age
Chronological or biological age
Chronological or biological age
Lifestyle choices
Clinical interventions and drugs
Environmental exposure
JIM
Journal of Internal Medicine
Founded in 1863

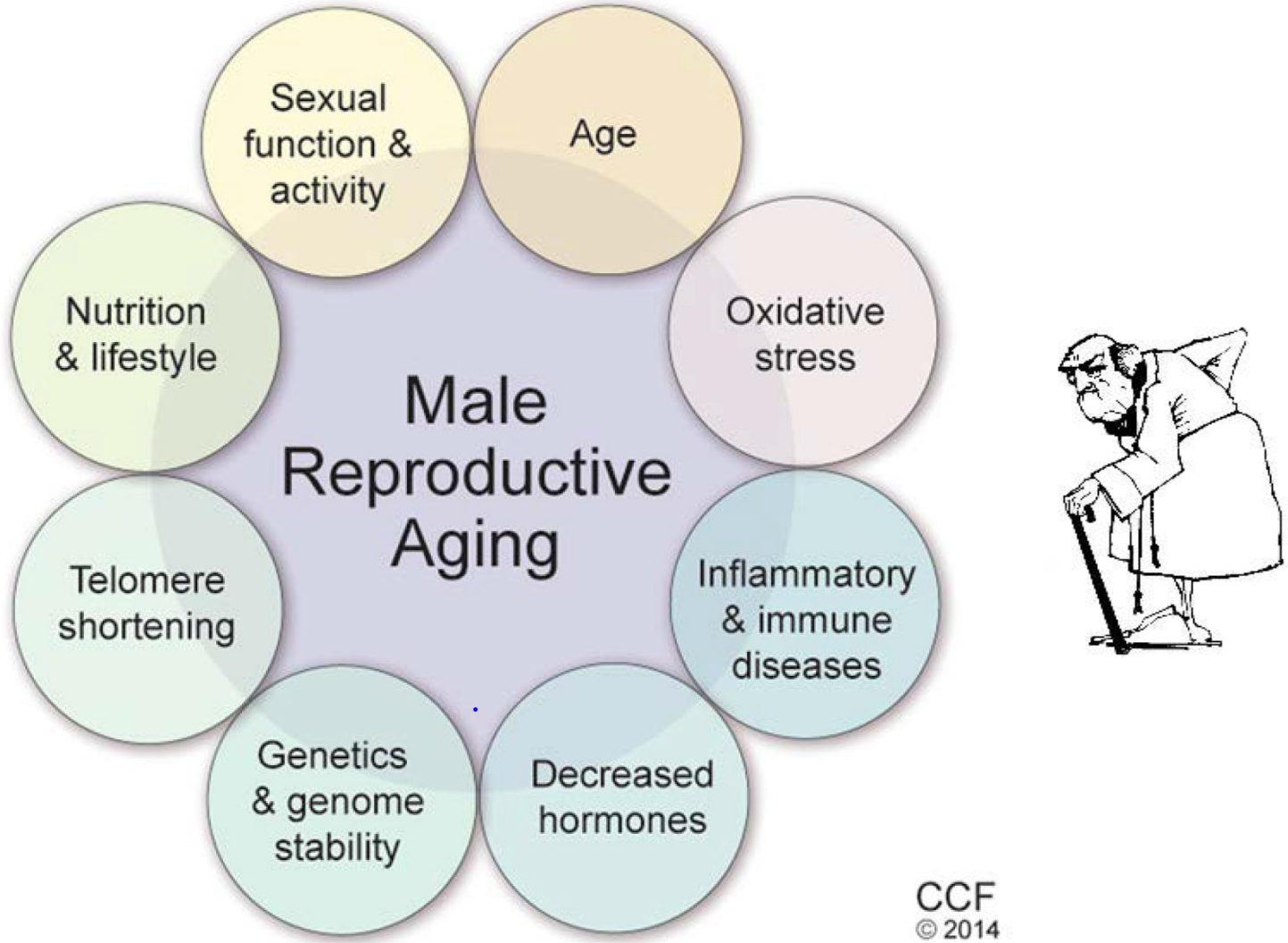
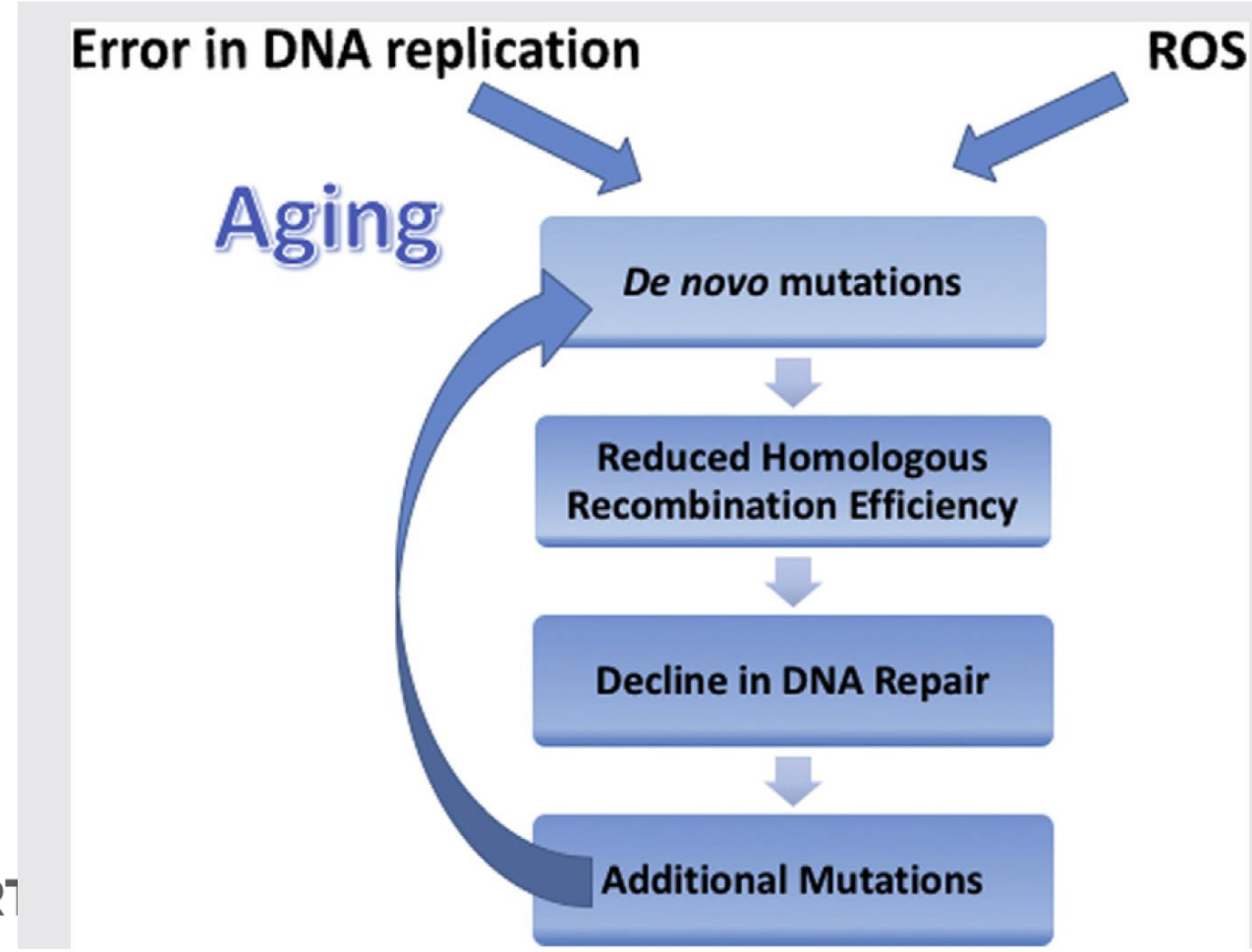
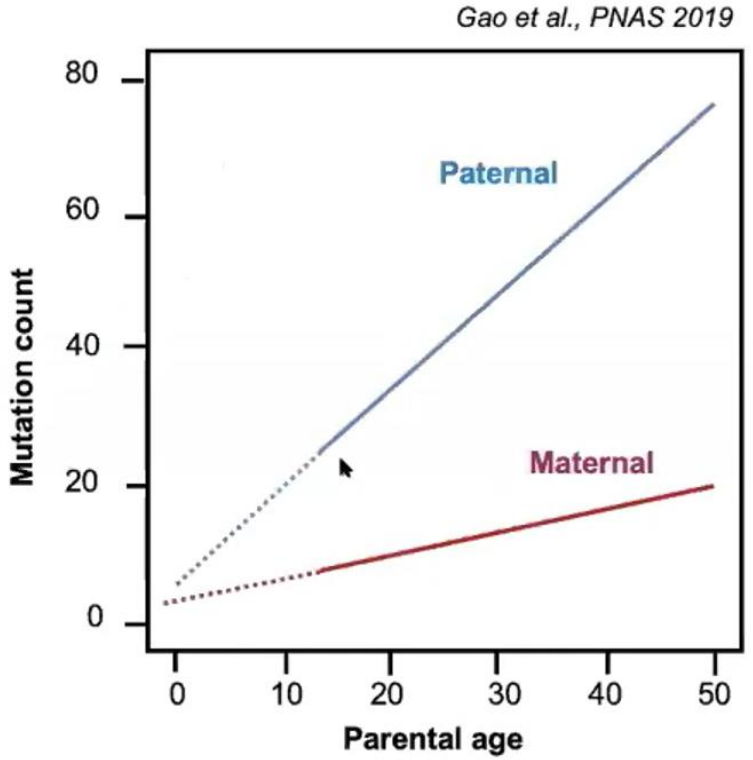


Figure 1 Main factors involved in impaired male infertility due to reproductive aging.

Replications erros and de novo mutations





Influence of paternal age on assisted reproductive technology cycles and perinatal outcomes

Audrey M. Marsidi, M.D.,[a] Lauren M. Kipling, M.P.H.,[b] Jennifer F. Kawwass, M.D.,[a] and Akanksha Mehta, M.D.[c]

[a] Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory Reproductive Center, Atlanta, Georgia; [b] Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia; and [c] Department of Urology, Emory University School of Medicine, Atlanta, Georgia

Fertil Steril 2021;116:380-7

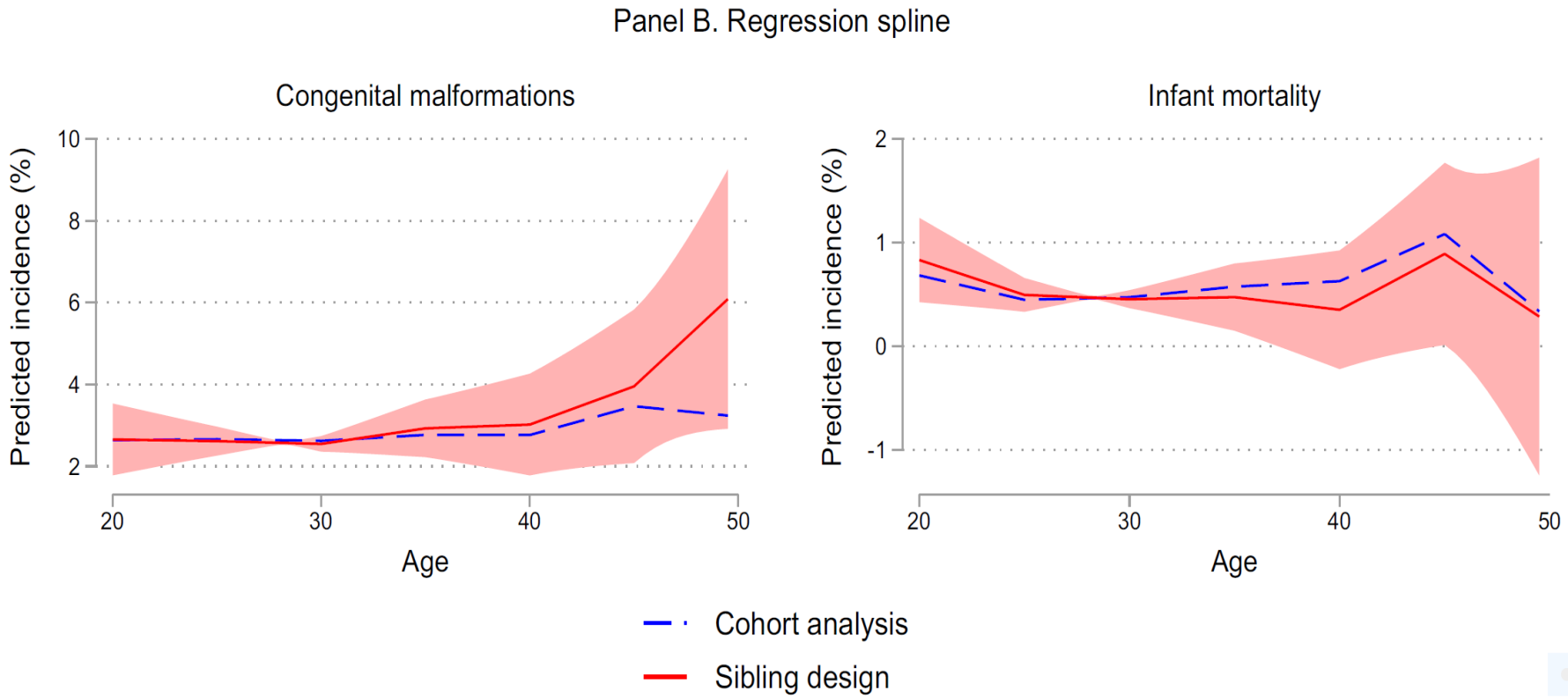
- 77,209 fresh nondonor cycles
- Compared with paternal age ≤ 45 years, paternal age ≥ 46 years was associated with:
  - **a lower likelihood of pregnancy per cycle** (adjusted risk ratio [aRR] 0.81; 95% confidence interval [CI] 0.76–0.87) and per transfer (aRR 0.85; 95% CI 0.81–0.90);
  - **a lower likelihood of live birth per cycle** (aRR 0.76; 95% CI 0.72–0.84) **and per transfer** (aRR 0.82; 95% CI 0.77–0.88),
    (after controlling for maternal age and other confounders).

European Journal of Epidemiology (2021) 36:849–860
https://doi.org/10.1007/s10654-021-00734-8

REPRODUCTIVE EPIDEMIOLOGY

Parental age and birth defects: a sibling study

Hans K. Hvide[1,2,3] · Julian Johnsen[4] · Kjell G. Salvanes[2,5,6,7,8]



Human Reproduction Update, Vol.26, No.5, pp. 650–669, 2020
Advance Access Publication on May 2, 2020 doi:10.1093/humupd/dmaa010

human reproduction update

Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis

Nadia A. du Fossé[1,*], Marie-Louise P. van der Hoorn[1], Jan M.M. van Lith[1], Saskia le Cessie[2,3], and Eileen E.L.O. Lashley[1]

Pooled risk estimates for miscarriage for age categories 30–34, 35–39, 40–44 and ≥45 years of age were:

- **1.04** (95% CI 0.90,1.21),
- **1.15** (0.92, 1.43),
- **1.23** (1.06, 1.43),
- **1.43** (1.13, 1.81) respectively (reference category 25–29 years)

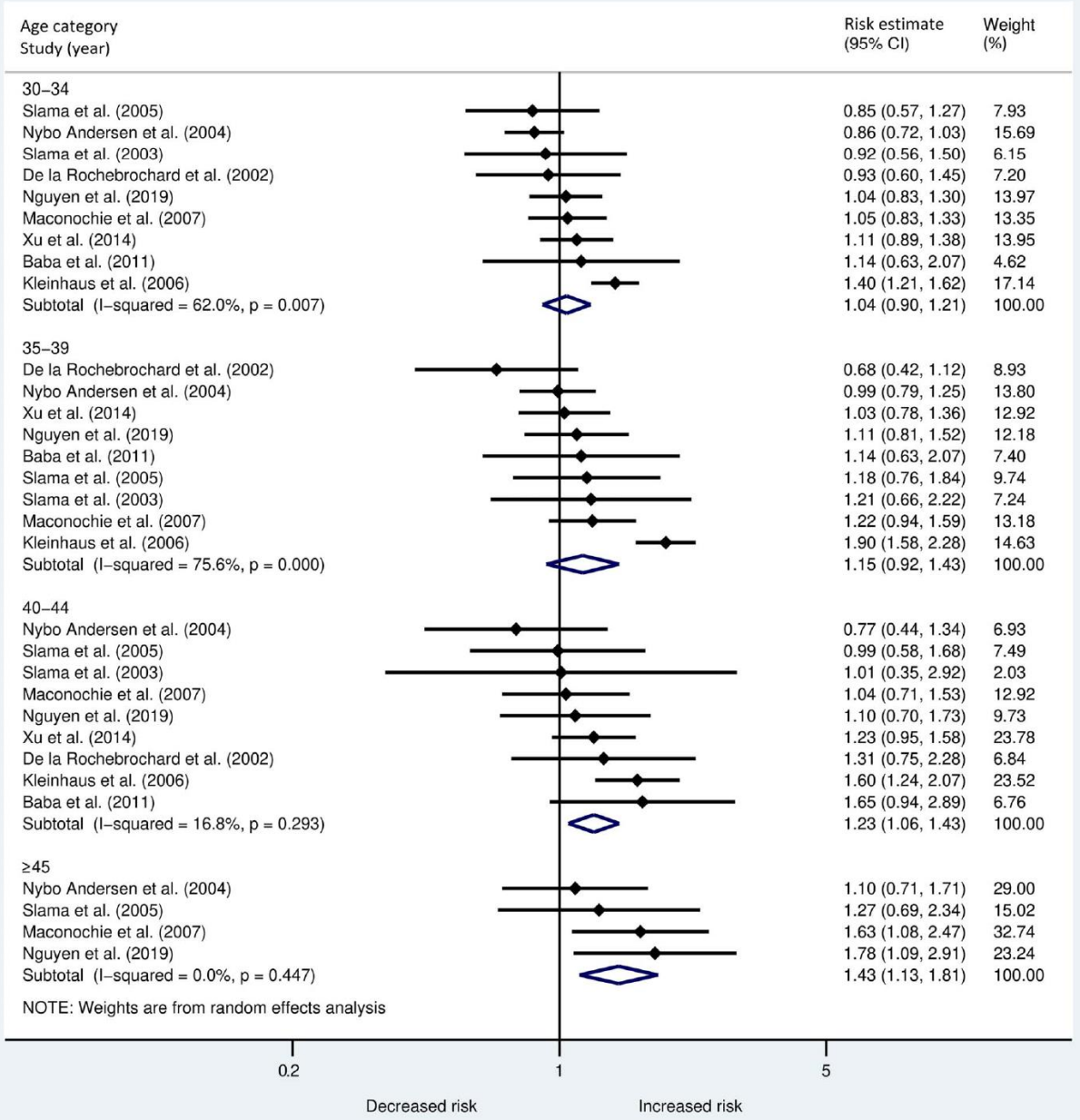


Figure 2 Forest plot describing the association between paternal age in different age categories and the risk of miscarriage <20 weeks.

FERTGROUP | FERTILITY

Received: 6 September 2019 | Revised: 19 November 2019 | Accepted: 19 November 2019

DOI: 10.1111/andr.12737

ORIGINAL ARTICLE

ANDROLOGY WILEY

Increasing paternal age and ejaculatory abstinence length negatively influence the intracytoplasmic sperm injection outcomes from egg-sharing donation cycles

Amanda S. Setti[1,2] | Daniela Paes Almeida Ferreira Braga[1,2] | Assumpto Iaconelli Junior[1,2] | Edson Borges Junior[1,2]

Paternal variable	Fertilization (%)	D3 high-quality embryos (%)	D3 normal embryo development (%)	Blastocyst development (%)	High-quality blastocysts (%)	Implantation (%)	Pregnancy chance	Miscarriage chance	Live birth chance
Age									
B	−0.276	−0.040	−2.750	−0.070	−44.058	−0.060	Exp(B) 0.664	Exp(B) 1.019	Exp(B) 0.812
SE	0.085	0.017	0.8625	0.035	20.248	0.007	0.187	0.052	0.100
CI	−0.44 to −0.11	−0.07 to −0.01	−4.44 to −1.06	−0.14 to −0.002	−84.07 to −4.05	−0.08 to −0.05	0.457 to 0.967	0.918 to 1.131	0.665 to 0.991
P	.001	.021	.001	.043	.031	<.001	.033	.718	.041
EA									
B	−0.083	−0.003	−0.300	−0.589	13.8125	−0.012	Exp(B) 0.051	Exp(B) 0.861	Exp(B) 0.169
SE	0.847	0.015	0.014	0.243	88.143	0.003	1.803	0.190	1.195
CI	−0.44 to −0.11	−0.01 to −0.001	−0.06 to −0.02	−1.07 to −0.11	−160.34 to 187.97	−0.20 to −0.35	0.001 to 1.870	0.589 to 1.258	0.015 to 1.851
P	.765	.028	.036	.016	.876	<.001	.103	.435	.142

Received: 31 March 2021 | Revised: 29 July 2021 | Accepted: 30 July 2021

DOI: 10.1111/and.14211

ORIGINAL ARTICLE

First International Journal of Andrology ANDROLOGIA WILEY

Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

Amanda Souza Setti[1,2] | Daniela Paes de Almeida Ferreira Braga[1,2] | Livia Vingris[3] | Assumpto Iaconelli Jr.[2,4] | Edson Borges Jr.[2,4]

RESULTS

First International Journal of Andrology
ANDROLOGIA
Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

Variable	Mean ± SD
Semen analysis	
Male age (years)	41.3 ± 6.8
Ejaculatory abstinence length (days)	3.2 ± 2.5

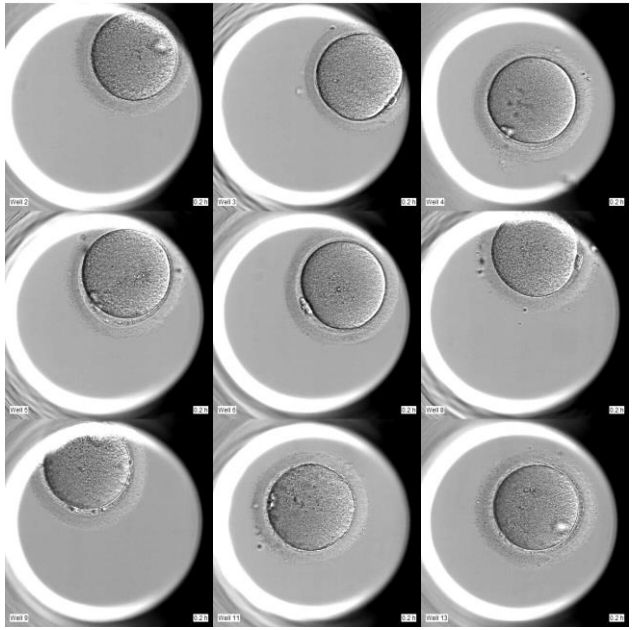
RESULTS

Paternal age	t2	B: 0.043, CI: 0.006 – 0.081, p: 0.043
	t3	B: 0.056, CI: 0.001 – 0.110, p: 0.044
	t4	B: 0.066, CI: 0.014 – 0.118, p: 0.012
	t6	B: 0.080, CI: -0.002 – 0.163, p: 0.046
	tB	B: 0.195, CI: 0.003 – 0.387, p: 0.046
	MN	Exp(B): 1.027, CI: 1.043 – 1.203, p: 0.004
	ACP	Exp(B): 1.116, CI: 1.034 – 1.205, p: 0.005
	IR	B: -1.933, CI: -2.426 – -1.441, p<0.001
	CP	Exp(B): 0.899, CI: 0.860 – 0.940, p<0.001

First International Journal of Andrology
ANDROLOGIA

Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

FERTILITY MEDICAL GROUP



FERTGROUP | FERTILITY

Received: 14 February 2022 | Revised: 20 April 2022 | Accepted: 9 May 2022

DOI: 10.1111/and.14485

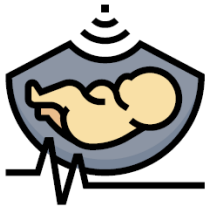
ORIGINAL ARTICLE

First International Journal of Andrology
ANDROLOGIA
WILEY

Paternal ageing impacts blastulation and the outcomes of pregnancy at different levels of maternal age: A clustering analysis of 21,960 oocytes and 3837 ICSI cycles

Amanda Souza Setti[1,2] | Daniela Paes de Almeida Ferreira Braga[1,2] | Patricia Guilherme[1] | Livia Vingris[1] | Assumpto Iaconelli Jr[1,2] | Edson Borges Jr[1,2]

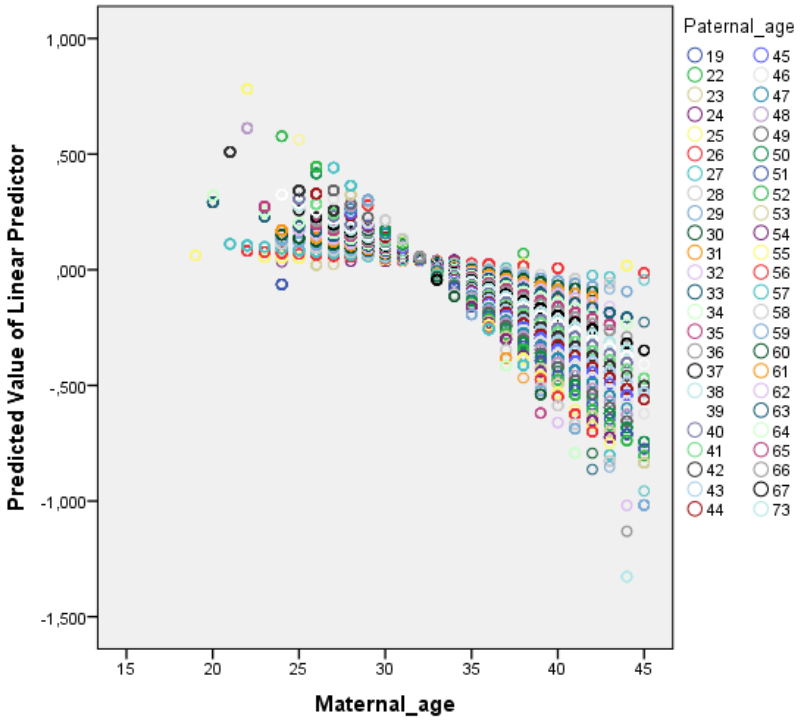
Variable	Value (n=3837)
Female age (y-old)	35.3 ± 4.5
Female BMI	24.2 ± 3.9
Male age (y-old)	38.0 ± 6.4



Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

Predective value of the interation term

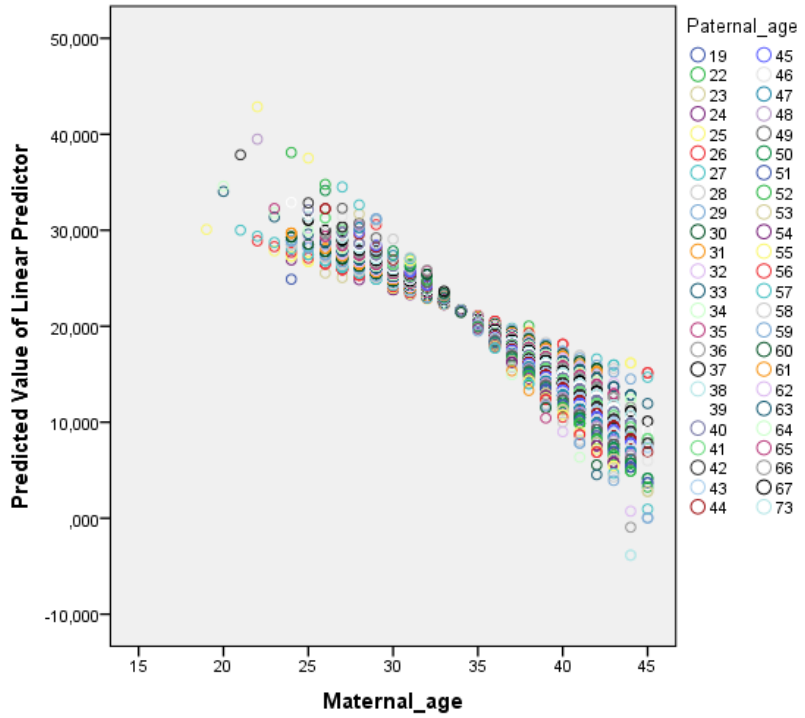
Dependent variable	B	OR	CI	p-value
Blastocyst development	- 0.005	0.995	0.994 – 0.996	< 0.001



Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

Predective value of the interation term

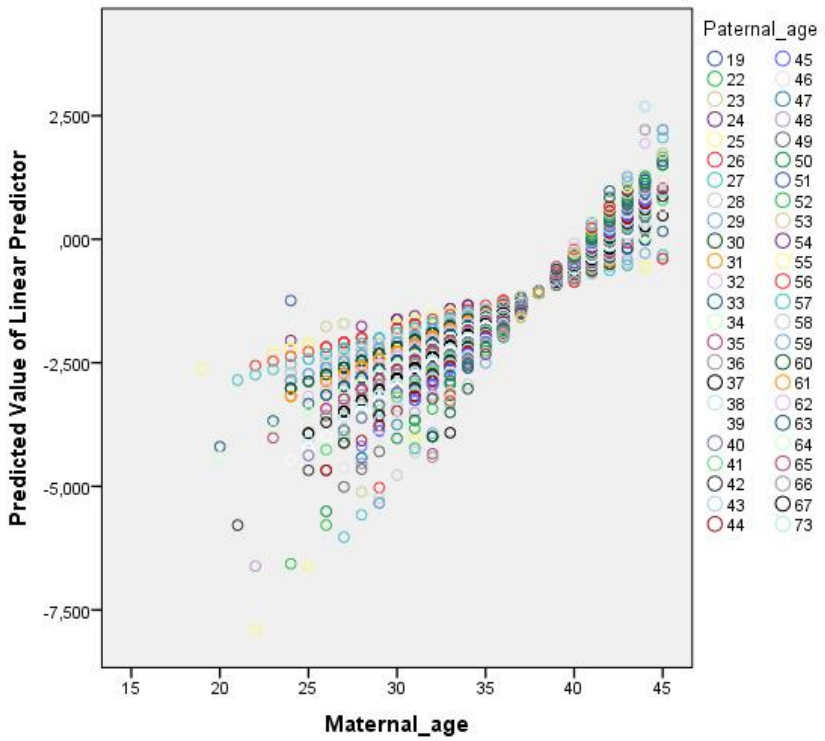
Dependent variable	B	OR	CI	p-value
Implantation rate	- 0.041	0.960	0.947 – 0.973	< 0.001



Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

Predective value of the interation term

Dependent variable	B	OR	CI	p-value
Miscarriage rate	0.011	1.012	1.005 – 1.018	0.001

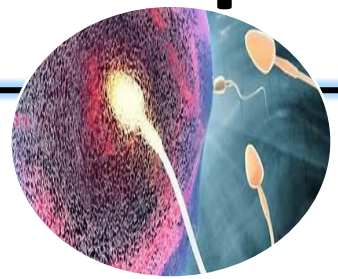


Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

For every ***1-year increase in paternal age***, the odds ratio of live-birth reduces by:

- **1%** in females aged 37 years,
- **1.6%** in those aged 38 years,
- **2.4%** in 39-year-old females,
- **5%** in 42-year-old females and so on.

Misleading concept



Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

Human Reproduction Update, Vol.24, No.3 pp. 320–389, 2018
Advanced Access publication on February 15, 2018 doi:10.1093/humupd/dmy005

human reproduction update

The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis

Nan B. Oldereid[1,*], Ulla-Britt Wennerholm[2], Anja Pinborg[3], Anne Loft[4], Hannele Laivuori[5,6,7,8], Max Petzold[9], Liv Bente Romundstad[10,11], Viveca Söderström-Anttila[12], and Christina Bergh[13]

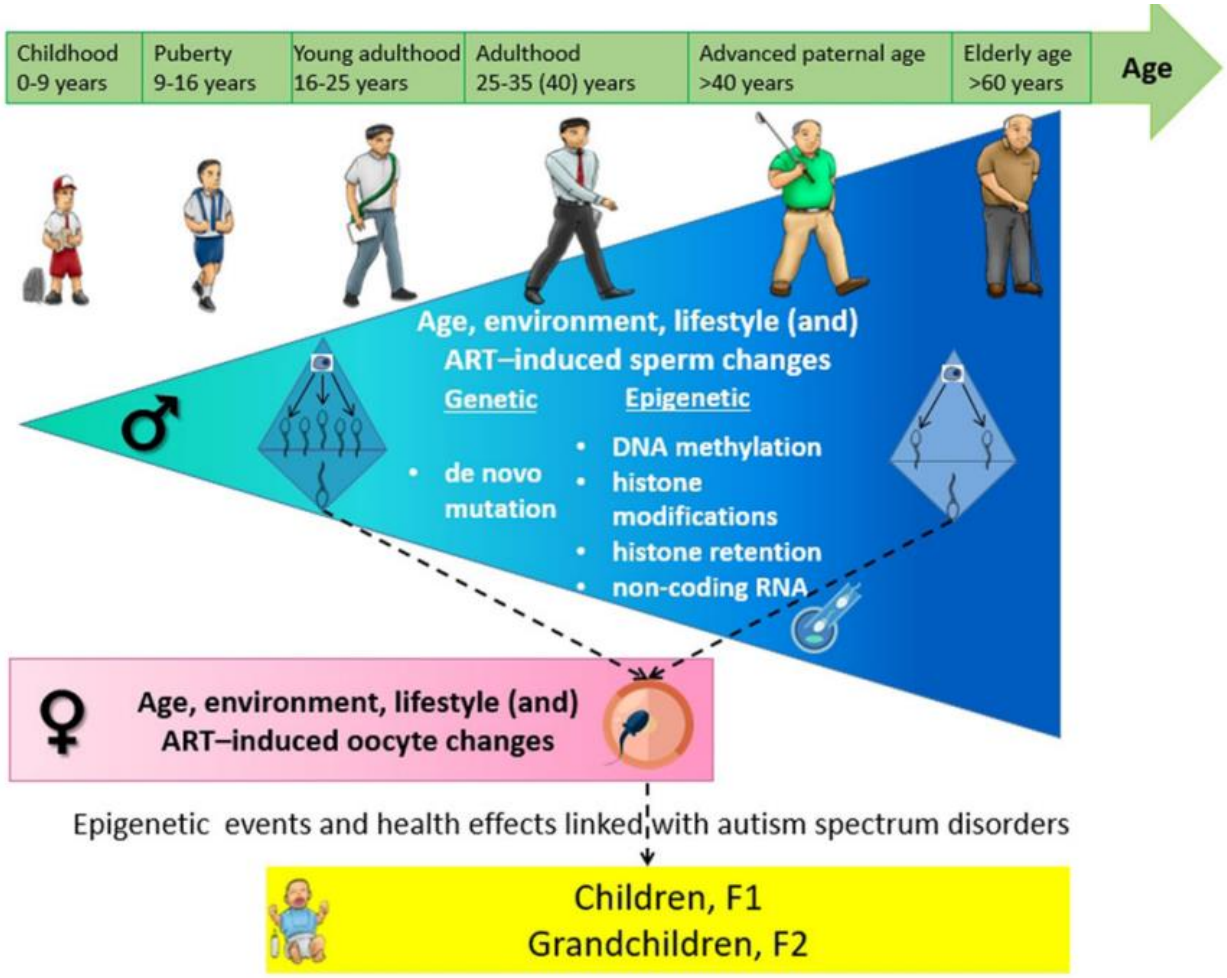
[1]Livio IVF-klinikken Oslo, Sørkedalsveien 10A, 0369 Oslo, Norway [2]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Sahlgrenska University Hospital East, SE-416 85 Gothenburg, Sweden [3]Department of Obstetrics and Gynecology, Hvidovre Hospital, Institute of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark [4]Fertility Clinic, Section 4071, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK- 2100 Copenhagen, Denmark [5]Department of Obstetrics and Gynecology, Tampere University Hospital, Teiskontie 35, FI-33521 Tampere, Finland [6]Faculty of Medicine and Life Sciences, University of Tampere, Arvo Ylpön katu 34, FI-33520 Tampere, Finland [7]Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 8, FI-00290 Helsinki, Finland [8]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Tukholmankatu 8, FI-00290 Helsinki, Finland [9]Swedish National Data Service and Health Metrics Unit, University of Gothenburg, 405 30 Gothenburg, Sweden [10]Spiren Fertility Clinic, Norwegian University of Science and Technology, Trondheim NO-7010, Norway [11]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway [12]Mehiläinen Felicitas, Mannerheimtie 20A, 00100 Helsinki, Finland [13]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden

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)	⊕⊕⊕◯
★	Acute lymphoblastic leukaemia	1.08 (0.96–1.21)	⊕⊕⊕◯
★	Autism and ASDs	1.25 (1.20–1.30)	⊕⊕⊕◯
★	Schizophrenia	1.31 (1.23–1.38)	⊕⊕⊕◯
Paternal BMI	No meta-analysis		
Paternal smoking	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.

FERTGROUP | FERTILITY



- *Age is a powerful factor* in humans and rodent models associated *with increased de novo mutations and a modified sperm epigenome.*

- *Age affects all known epigenetic mechanisms*, including DNA methylation, histone modifications and profiles of small non-coding (snc)RNA.

Riscos epigenéticos da RA

Inheritance of epigenetic dysregulation from male factor infertility has a direct impact on reproductive potential

Michelle M. Denomme, Ph.D.,[a] Blair R. McCallie, B.Sc.,[a] Jason C. Parks, B.Sc.,[a] Keith Booher, Ph.D.,[b] William B. Schoolcraft, M.D.,[c] and Mandy G. Katz-Jaffe, Ph.D.[a,c]

[a] Fertility Labs of Colorado, Lone Tree, Colorado; [b] Zymo Research Corp., Irvine, California; and [c] Colorado Center for Reproductive Medicine, Lone Tree, Colorado

- ***Alterações de metilação e transcrição*** em blastocistos de homens com OAT (MF) demonstram uma ***consequência epigenética na embriogênese***, alterando significativamente os principais genes do desenvolvimento e afetando a competência embrionária.

Human Reproduction, Vol.36, No.1, pp. 48–60, 2021
Advance Access Publication on December 15, 2020 doi:10.1093/humrep/deaa278

human reproduction ORIGINAL ARTICLE *Early Pregnancy*

DNA methylation defects in spermatozoa of male partners from couples experiencing recurrent pregnancy loss

Kushaan Khambata[1,*], Sanketa Raut[1], Sharvari Deshpande[1], Sweta Mohan[1], Shobha Sonawane[1], Reshma Gaonkar[1], Zakiya Ansari[1], Mamata Datar[1], Vandana Bansal[2], Anushree Patil[3], Himangi Warke[4], and Nafisa H. Balasinor[1,*]

- Defeitos na *metilação do DNA e padrões de imprinting* aberrantes nos espermatozoides de homens cujas parceiras sofreram RPL idiopático.

ANDROLOGY

ISSN: 2047-2919 *Andrology*, 2018, 6, 635–653 ANDROLOGY

REVIEW ARTICLE

Correspondence:
Sarah R. Catford, Hudson Institute of Medical Research, 27-31 Wright St, Clayton, VIC 3168, Australia.
E-mail: sarah.catford@monashhealth.org

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

Received: 4-Jun-2017
Revised: 13-Jun-2018
Accepted: 19-Jun-2018

doi: 10.1111/andr.12526

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

[1,2,3]S. R. Catford, [1,2]R. I. McLachlan, [4]M. K. O'Bryan and [3,5]J. L. Halliday

[1]Hudson Institute of Medical Research, Clayton, VIC, Australia, [2]Department of Obstetrics and Gynecology, Monash University, Clayton, VIC, Australia, [3]Public Health Genetics, Murdoch Childrens Research Institute, Parkville, VIC, Australia, [4]The School of Biological Sciences, Monash University, Clayton, VIC, Australia, [5]Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia

- 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

Human Reproduction, Vol.31, No.12 pp. 2811–2820, 2016
Advanced Access publication on October 5, 2016 doi:10.1093/humrep/dew245

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

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], and H. Tournaye[4]

Table III Differences in sperm parameters between the ICSI and the control group: unadjusted and adjusted results from multiple linear regression analysis.

	Unadjusted			Adjusted for covariates		
	Ratio	95% CI	*P*-value	Ratio	95% CI	*P*-value
Concentration	1.9	1.2–3.1	0.008	1.9	1.1–3.2	0.017
Total count	2.4	1.4–4.2	0.001	2.3	1.3–4.1	0.005
Total motile count	2.3	1.4–3.9	0.001	2.1	1.2–3.6	0.007
Morphology	1.1	0.8–1.4	0.43	1.1	0.8–1.4	0.52

Human Reproduction, Vol.32, No.2 pp. 439–446, 2017
Advanced Access publication on December 22, 2016 doi:10.1093/humrep/dew324

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Reproductive hormones of ICSI-conceived young adult men: the first results

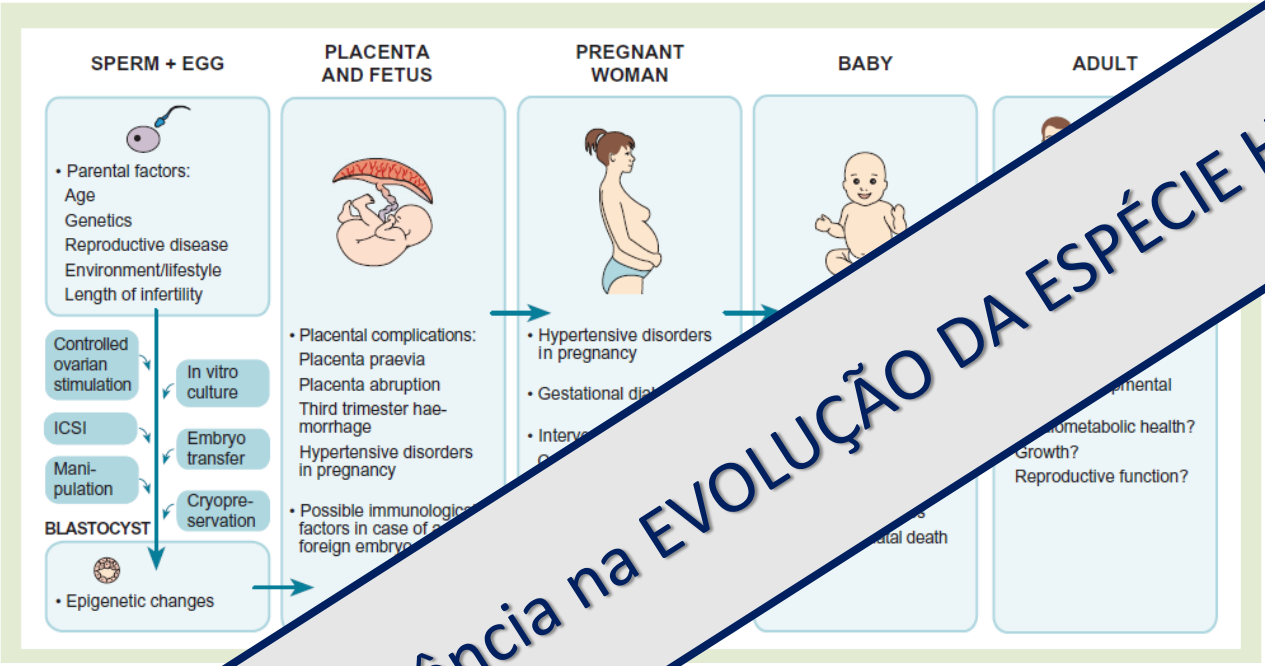
Florence Belva[1,*], Mathieu Roelants[2], Jean De Schepper[3], André Van Steirteghem[4], Herman Tournaye[4], and Maryse Bonduelle[1]

Table III Correlations between reproductive hormone levels and semen parameters and testis volume.

	FSH		Testosterone		LH		Inhibin B	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Sperm concentration	−0.3	0.001	0.1	0.30	−0.2	0.01	0.2	0.02
Total sperm count	−0.3	0.001	0.1	0.62	−0.2	0.02	0.2	0.01
Total motile count	−0.4	0.01	0.1	0.31	−0.2	0.06	0.2	0.01
Sperm morphology	−0.2	0.03	0.1	0.23	−0.1	0.1	−0.1	0.84
Testis volume	−0.2	0.05	0.2	0.04	−0.1	0.6	0.4	<0.01

Homens concebidos por ICSI mais propensos a ter níveis baixos de inibina B e FSH alto (percentil 90)

FIV / ICSI



Human Reproducti

Influência na EVOLUÇÃO DA ESPÉCIE HUMANA ???

- A téc[illegible] pode interromper f[illegible] néticos normais [illegible] para o [illegible] e saúde a longo

[illegible]enta a aptidão reprodutiva de casais subférteis, removendo tecnologicamente vários tipos de barreiras seletivas e alterando outras barreiras;

- De acordo com o princípio básico da evolução, as gerações subsequentes serão, assim, geneticamente e epigeneticamente adaptadas a um ambiente em qual reprodução depende cada vez mais da intervenção tecnológica.

FERTGROUP | FERTILITY

Obrigado!

Dr. Edson Borges Jr.
www.fertility.com.br
E-mail: edson@fertility.com.br

FERTGROUP | FERTILITY