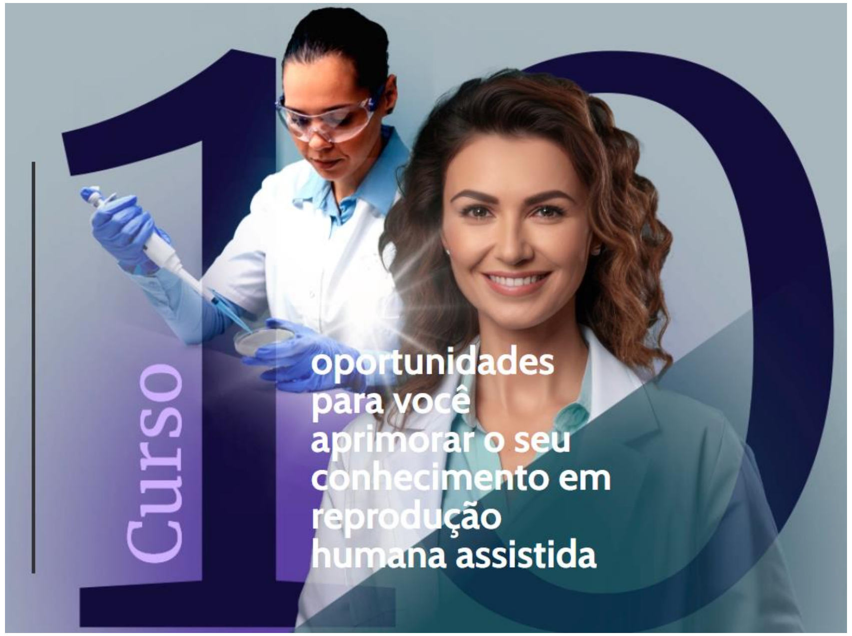




# Suporte Medicamentoso no tratamento do Homem Infértil


**Edson Borges Jr.**

**Fertility Medical Group**
**FERTGROUP**
**Instituto Sapientiae**


FERTGROUP | FERTILITY

# Declaração:

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

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

# AGENDA

- Andrologia baseada em evidências
- Ação do FSH
- Tratamento hormonal
- APHRODITE
- Hábitos e drogas

# Andrologia baseada em evidências

- Raros estudos prospectivos, randomizados
  *Consequência:* resultados inconclusivos 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

# 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!!

| Category | Frequency |
|---|---|
| Immunological | - |
| **Idiopathic** | 32.6% |
| Varicocele | 26.6% |
| Obstruction | 15.3% |
| **Normal female factor (unexplained male infertility)** | 10.7% |
| Cryptorchidism | 2.7% |
| Ejaculatory failure | 2.0% |
| Endocrinologic | 1.5% |
| Drug/radiation | 1.4% |
| Genetic | 1.2% |
| Testicular failure | 1.1% |
| Sexual dysfunction | 0.7% |
| Pyospermia | 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.

# 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.***

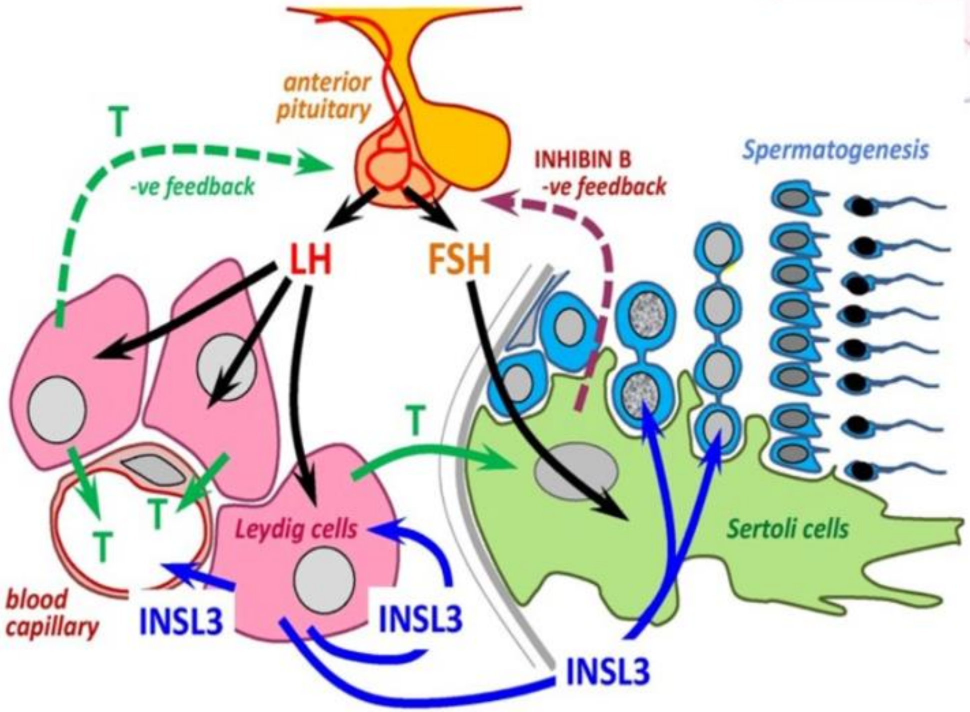
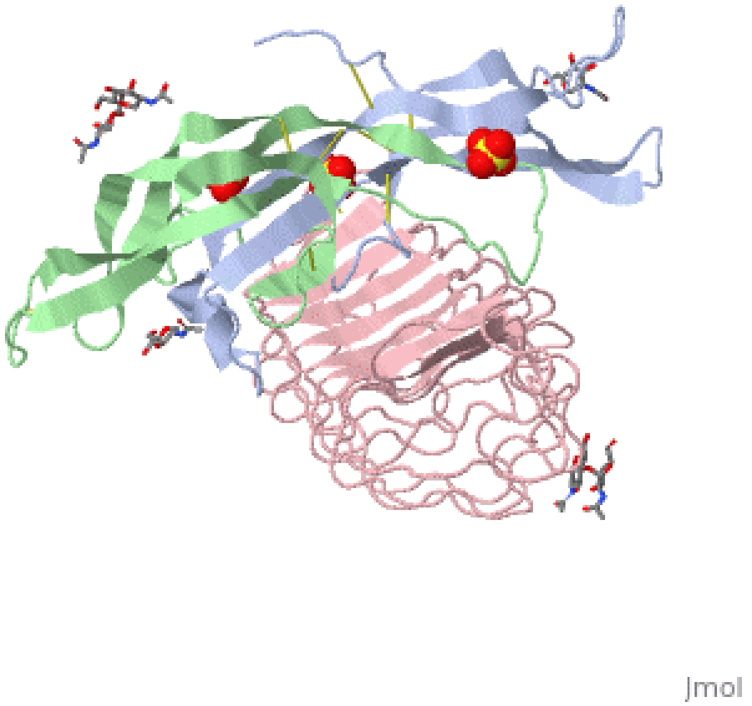



Figure from: Ivell R et al. Front Endocrinol. 2014;5:6.

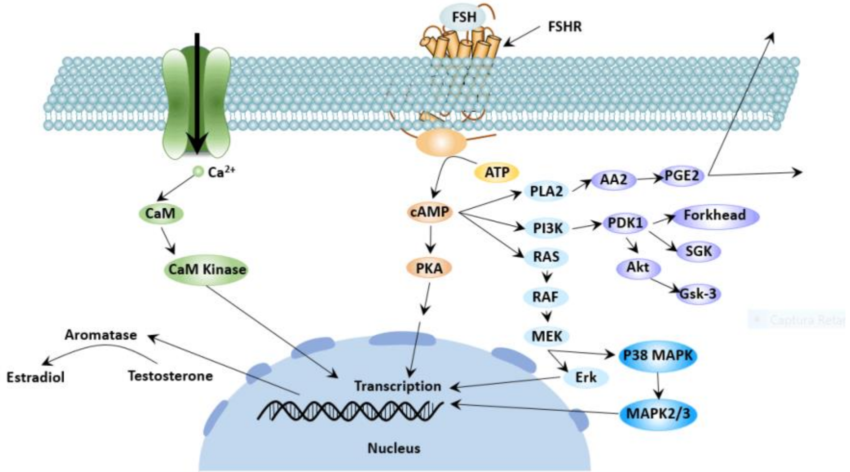
# Ação FSH

FSH é uma glicoproteína formada por duas subunidades: alfa,92 aminoácidos, compartilhada com outros hormônios glicoproteicos, e beta 111 aminoácidos (FSHβ).

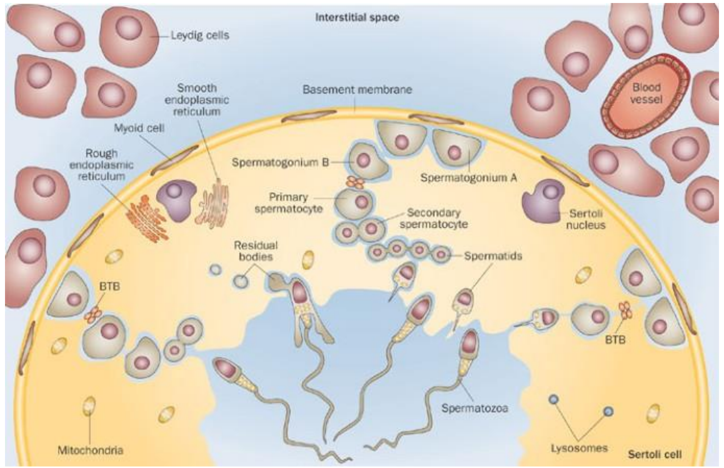


# Ação FSH

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




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

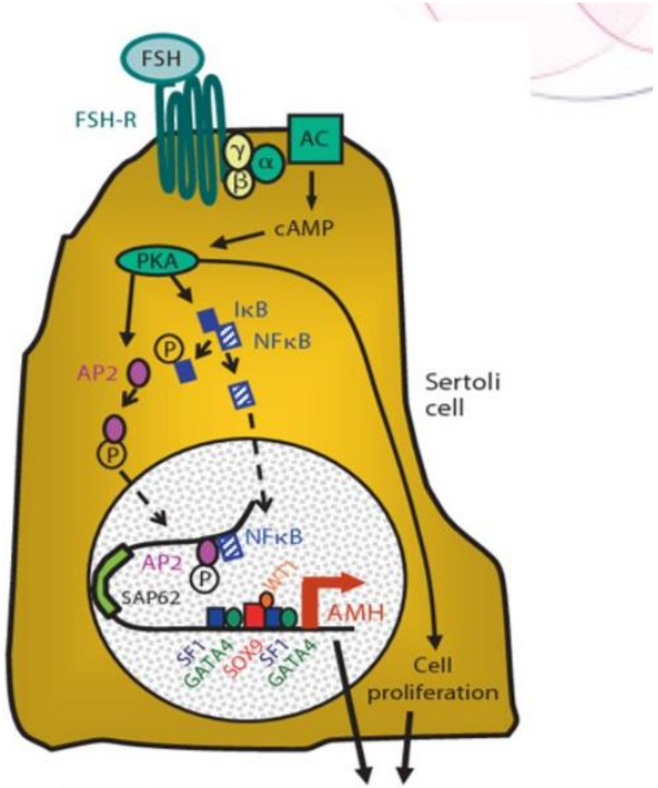


# Ação FSH

- 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.

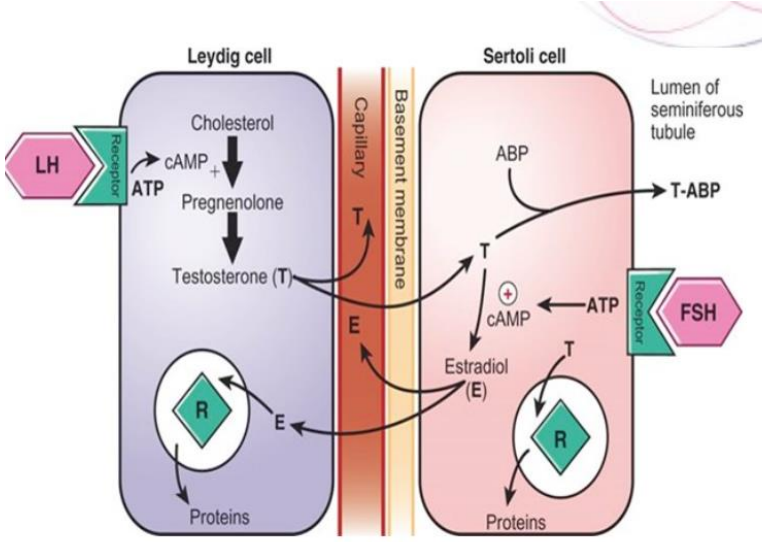




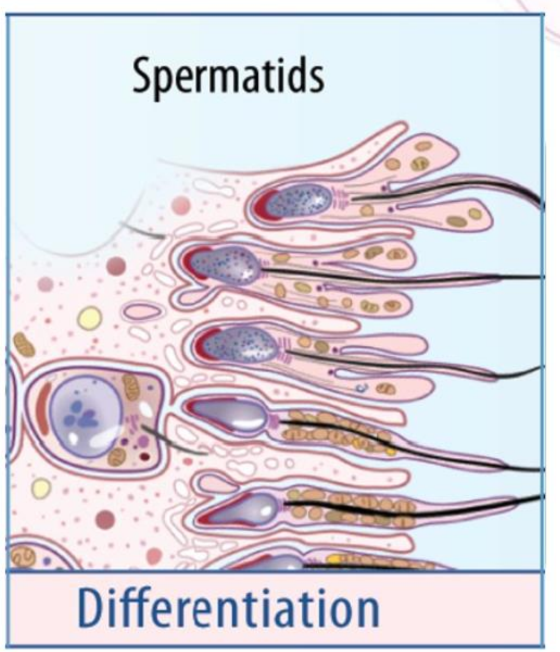
1. Oduwole OO, et al. Front Endocrinol. 2018;9:763.
2. Shiraishi K,Matsuyama H. Endocr J 2017;64:123-31.

# Ação LH

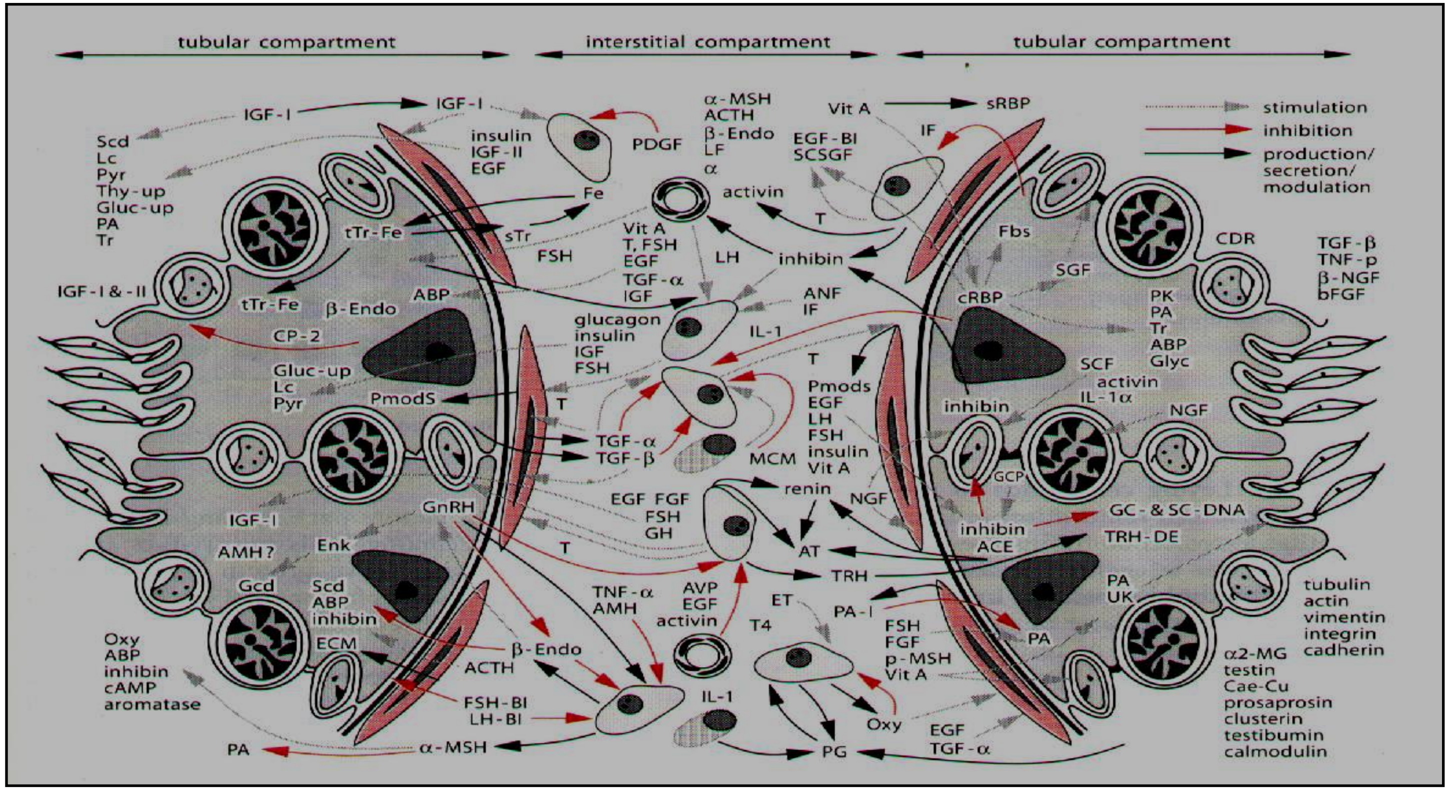
- A principal função do LH é ***estimular a produção de testosterona (TT) pelas células de Leydig.***




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



# TÚBULO SEMINÍFERO




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

# Medical Therapy

- Gonadotropins (FSH, LH, hCG)
- Androgens (testosterone and similar)
- Selective estrogen receptor modulator - *SERMs* (clomifene, taxoxifen, raloxifene, toremifene)
- Aromatase inhibitors (testolactona, letrozol, anastrazol)
- Oral Antioxidants (vitamins, zinc, carnitin, etc.)

# Medical Therapy

- Gonadotropins (FSH, LH, hCG)
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Oral Antioxidants (vitamins, zinc, carnitin, etc.)

# Tratamento clínico

Volume 176(4), October 2006, p 1307–1312

**Drug Therapy for Idiopathic Male Infertility: Rationale Versus Evidence**

Rajeev Kumar,* Gagan Gautam and Narmada P. Gupta

THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association
ELSEVIER

***Material e método:***

Pesquisa no MEDLINE / PubMed nos últimos 20 anos com foco em publicações sobre tratamento medicamentoso para infertilidade masculina

***Conclusão:***

- O tratamento medicamentoso para a infertilidade masculina idiopática *é pelo menos empírico*.
- *Não há benefício claro* no uso de qualquer medicamento nesses pacientes.

# Tratamento clínico

ANDROLOGY

ISSN: 2047-2919 ANDROLOGY

REVIEW ARTICLE

Correspondence:
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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

[1]G. M. Colpi, [2]S. Francavilla, [3]G. Haidl, [4]K. Link, [5]H. M. Behre, [6]D. G. Goulis, [7]C. 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 | ØOOO | 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 |

# Tratamento clínico

Cochrane Library

Cochrane Database of Systematic Reviews

*Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD005071.
DOI: 10.1002/14651858.CD005071.pub4.

**Gonadotrophins for idiopathic male factor subfertility (Review)**

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

- Six RCTs with 456 participants
- **Live birth rate per couple randomly assigned (27% vs 0%;** Peto odds ratio (OR) 9.31, 95% confidence interval (CI) 1.17 to 73.75, one study, **(30 participants, very low-quality evidence)** and the **spontaneous pregnancy rate per couple randomly assigned (16% vs 7%;** Peto OR 4.94, 95% CI 2.13 to 11.44,

# Tratamento clínico

Cochrane Library

Cochrane Database of Systematic Reviews

*Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD005071.
DOI: 10.1002/14651858.CD005071.pub4.

## Gonadotrophins for idiopathic male factor subfertility (Review)

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

**Authors' conclusions**

Encouraging preliminary data suggest a beneficial effect on live birth and pregnancy of gonadotrophin treatment for men with idiopathic male factor subfertility, but because the numbers of trials and participants are small, evidence is insufficient to allow final conclusions.

*Expert Opin. Biol. Ther.* (2009) 9(5):659-666 Drug Evaluation

Expert Opinion

# Recombinant FSH in the treatment of oligozoospermia

Carlo Foresta†, Riccardo Selice, Alberto Ferlin & Andrea Garolla

- Positive results in men without change of tubular maturation (hypospermatogenesis or late maturation arrest)
- Worst prognosis regarding > FSH
- Polymorphism of the FSH receptor gene?

# Medical Therapy

Gonadotropins (FSH, LH, hCG)

Androgens (testosterone and similar)

- Selective estrogen receptor modulator - *SERMs* (clomifene, taxoxifen, raloxifene, toremifene)

Aromatase inhibitors (testolactona, letrozol, anastrazol)

Oral Antioxidants (vitamins, zinc, carnitin, etc.)


# Effects of the selective estrogen receptor modulators for the treatment of male infertility: a systematic review and meta-analysis

Rossella Cannarella, Rosita A. Condorelli, Laura M. Mongioì, Federica Barbagallo, Aldo E. Calogero & Sandro La Vignera

https://doi.org/10.1080/14656566.2019.1615057

Table 3. Main therapeutic schemes reported in the literature.

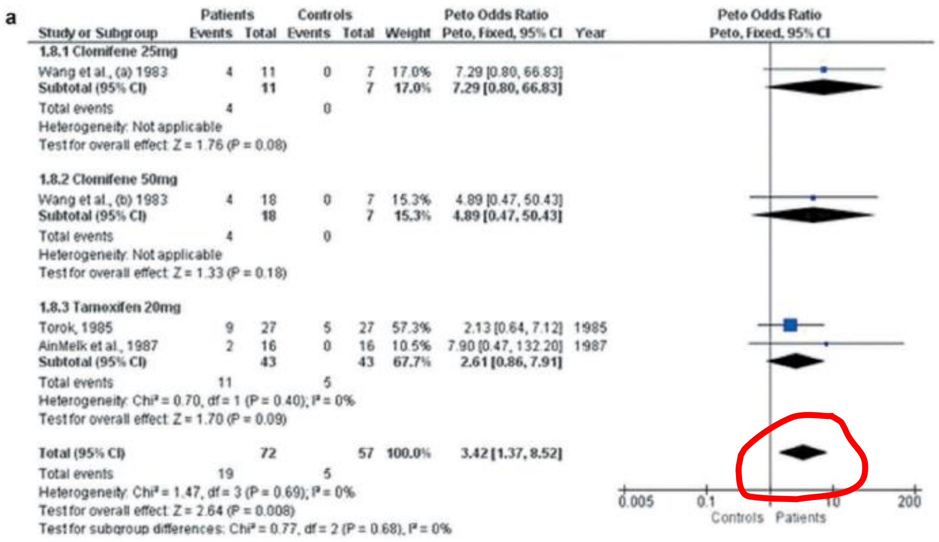
| Drug | Therapeutic scheme |
| --- | --- |
| Clomiphene citrate | 25 mg on alternate days for 3–6 months |
| | 25 mg daily for 3–6 months |
| | 50 mg daily for 3–6 months |
| Tamoxifen | 10 mg twice a day for 3–6 months |
| | 20 mg daily for 3–6 months |
| | 30 mg daily for 3–4 months |
| Toremifene | 60 mg daily for 3 months |
| Raloxifene | 60 mg daily for 3 months |


# Effects of the selective estrogen receptor modulators for the treatment of male infertility: a systematic review and meta-analysis

Rossella Cannarella, Rosita A. Condorelli, Laura M. Mongioì, Federica Barbagallo, Aldo E. Calogero & Sandro La Vignera

https://doi.org/10.1080/14656566.2019.1615057

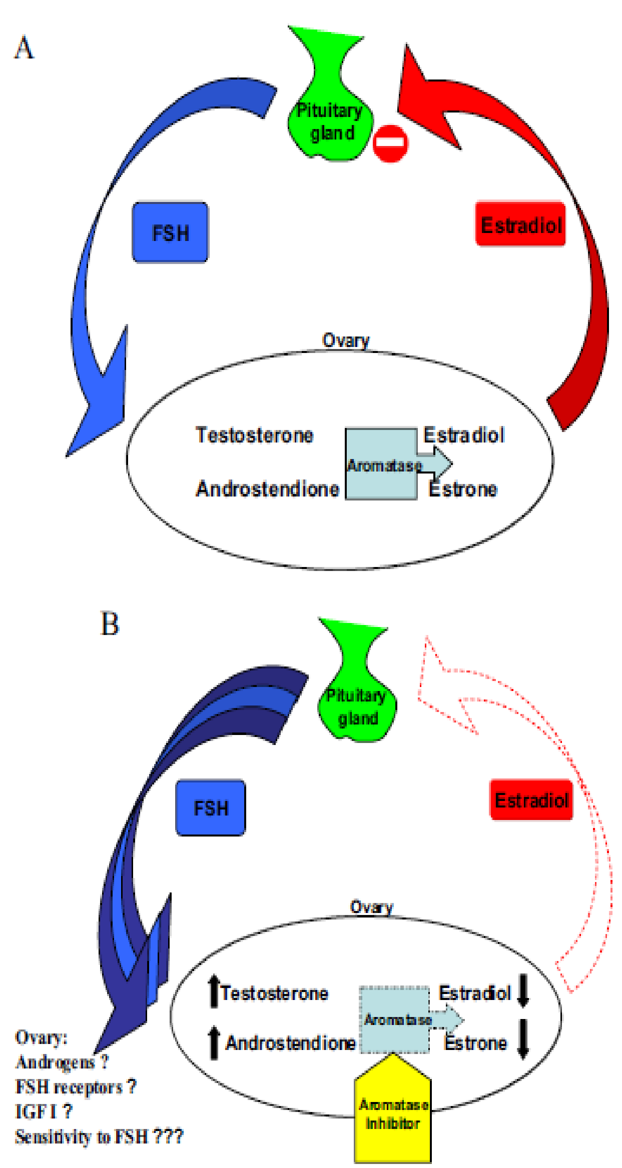
- ❖ 16 controlled and not-controlled trials were lastly included.
- ❖ Increased significantly sperm concentration, total sperm count, and serum LH, FSH, TT levels compared with baseline values.




SERMs may be effective in the treatment of infertile patients with idiopathic infertility.
However, *the paucity of data does not allow to draw a definitive conclusion*.

# Medical Therapy

- Gonadotropins (FSH, LH, hCG)
- Androgens (testosterone and similar)
- Selective estrogen receptor modulator - *SERMs* (clomifene, taxoxifen, raloxifene, toremifene)
- ➔ Aromatase inhibitors (testolactona, letrozol, anastrazol)
- Oral Antioxidants (vitamins, zinc, carnitin, etc.)




# Changes in hormonal profile and seminal parameters with use of aromatase inhibitors in management of infertile men with low testosterone to estradiol ratios

Odysseas Gregoriou, M.D., Panagiotis Bakas, M.D., Charalampos Grigoriadis, M.D., Maria Creatsa, M.D., Dimitrios Hassiakos, M.D., and Georgios Creatsas, M.D.

2nd Department of Obstetrics and Gynecology, Aretaieion Hospital, University of Athens, Athens, Greece

VOL. 98 NO. 1 / JULY 2012

Inhibits the conversion of androgens to estrogens

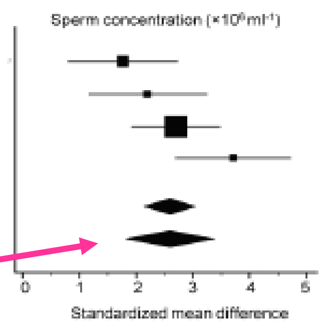
***TT – E2 / Androstenedione – estrone***

***T(ng/dL) / E2 (pg/mL) < 10***

***“better spermatogenesis”***

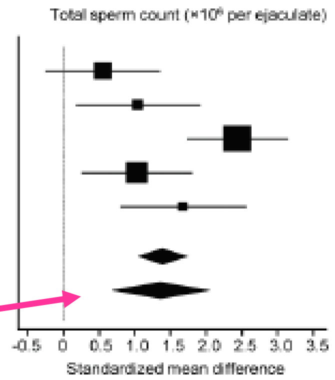
**a** Sperm concentration

| Author, year - drug | Patients (*n*) | s.m.d. | s.e. | 95% CI | *P* value |
|---|---|---|---|---|---|
| Pavlovich *et al.*[21] 2001 - Testolactone | 12 | 1.775 | 0.470 | 0.800–2.750 | |
| Raman *et al.*[22] 2002 - Testolactone | 12 | 2.209 | 0.507 | 1.158–3.261 | |
| Raman *et al.*[22] 2002 - Anastrazole | 25 | 2.705 | 0.388 | 1.925–3.486 | |
| Shoshany *et al.*[25] 2017 - Anastrazole | 21 | 3.714 | 0.506 | 2.691–4.736 | |
| Total (fixed effects) | 70 | 2.589 | 0.230 | 2.135–3.043 | < 0.001 |
| Total (random effects) | 70 | 2.595 | 0.393 | 1.817–3.372 | < 0.001 |
| Test for heterogeneity | Q | df | Significance level | $I^2$ | 95% CI |
| | 8.595 | 3 | *P*=0.03 | 65.1% | 0–88.15 |



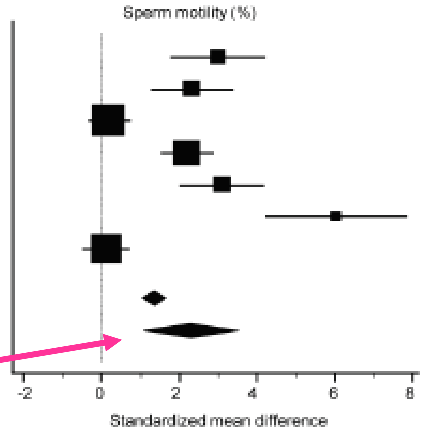

**b** Total spem count

| Author, year - drug | Patients (*n*) | s.m.d. | s.e. | 95% CI | *P* value |
|---|---|---|---|---|---|
| Clark *et al.*[19] 1989 - Testolactone after Placebo | 13 | 0.561 | 0.388 | -0.239–1.361 | |
| Clark *et al.*[19] 1989 - Testolactone first | 12 | 1.054 | 0.422 | 0.178–1.930 | |
| Saylam *et al.*[23] 2011 - Letrozole | 27 | 2.442 | 0.357 | 1.727–3.158 | |
| Gregoriou *et al.*[24] 2012 - Letrozole | 15 | 1.035 | 0.380 | 0.258–1.813 | |
| Gregoriou *et al.*[24] 2012 - Anastrazole | 14 | 1.685 | 0.431 | 0.800–2.570 | |
| Total (fixed effects) | 81 | 1.390 | 0.176 | 1.044–1.737 | < 0.001 |
| Total (random effects) | 81 | 1.363 | 0.344 | 0.683–2.042 | < 0.001 |
| Test for heterogeneity | Q | df | Significance level | $I^2$ | 95% CI |
| | 15.25 | 4 | *P*=0.004 | 73.78% | 34.76–89.46 |




**c** Sperm motility

| Author, year - drug | Patients (*n*) | s.m.d. | s.e. | 95% CI | *P* value |
|---|---|---|---|---|---|
| Pavlovich *et al.*[21] 2001 - Testolactone | 12 | 3.004 | 0.586 | 1.788–4.219 | |
| Raman *et al.*[22] 2002 - Testolactone | 12 | 2.332 | 0.518 | 1.257–3.406 | |
| Raman *et al.*[22] 2002 - Anastrazole | 25 | 0.199 | 0.279 | -0.362–0.760 | |
| Saylam *et al.*[23] 2011 - Letrozole | 27 | 2.199 | 0.342 | 1.514–2.885 | |
| Gregoriou *et al.*[24] 2012 - Letrozole | 15 | 3.101 | 0.535 | 2.005–4.198 | |
| Gregoriou *et al.*[24] 2012 - Anastrazole | 14 | 6.029 | 0.885 | 4.209–7.848 | |
| Shoshany *et al.*[25] 2017 - Anastrazole | 21 | 0.120 | 0.303 | -0.492–0.733 | |
| Total (fixed effects) | 126 | 1.342 | 0.151 | 1.044–1.640 | < 0.001 |
| Total (random effects) | 126 | 2.291 | 0.619 | 1.073–3.510 | < 0.001 |
| Test for heterogeneity | Q | df | Significance level | $I^2$ | 95% CI |
| | 89.84 | 6 | *P*< 0.001 | 93.3% | 88.7–96 |





Asian Journal of Andrology (2020) 22, 360-367
www.asiaandro.com; www.ajandrology.com

FERTGROUP

Del Giudice *et al.* Asian J Andrology, 22:360-367, Jul-Aug 2020

| Study, year, country | Study design | Treatment enclosed | Sample size (n) | Age (year), median (range); mean±s.d. | Infertility etiology, n (%) | Follow-up (month) | LE |
|---|---|---|---|---|---|---|---|
| Clark and Sherins[19] 1989, USA | Prospective, randomized, double-blind, placebo-controlled crossover (single center) | Testolactone 2 g daily Placebo | Total: 25 | NR | Idiopathic | Baseline, 8, 16 | 1b |
| Pavlovich *et al.*[21] 2001, USA | Prospective, nonrandomized, case–control (single center) | Testolactone 100–200 mg daily | Total: 104<br>Testolactone (*n*=74)<br>Control (*n*=40) | 37 (31–43)<br>40 (37–40) | Idiopathic: 12 (26.6), Klinefelter's syndrome: 6 (13.3), Chromosome Y microdeletion: 5 (11.1), cryptorchidism: 5 (11.5), varicocele: 14 (21.1) | Baseline, 3 | 2a |
| Raman and Schlegel[22] 2002, USA | Prospective, nonrandomized, case–control (single center) | Testolactone 100–200 mg daily<br>Anastrozole 1 mg daily | Total: 140<br>Testolactone (*n*=74)<br>Anastrozole (*n*=101) | NR | Testolactone (*n*=74): Klinefelter's syndrome: 17 (22.9), varicocele repair: 18 (24.3), varicocele present: 12 (16.2), overweight (BMI >35 kg $m^{-2}$): NR;<br>Anastrozole (*n*=101): Klinefelter's syndrome: NR, varicocele repair: 30 (29.7), varicocele present: 33 (32.6), overweight (BMI >35 kg $m^{-2}$): 16 (15.8) | Baseline, 3 | 2a |
| Saylam *et al.*[23] 2011, Turkey | Prospective, nonrandomized (single center) | Letrozole 2.5 mg daily | Total: 27 | 34.92±6.66 | Idiopathic hypoandrogenic | Baseline, 6 | 2a |
| Gregoriou *et al.* 2012, Greece[24] | Prospective, nonrandomized study (single center) | Letrozole 2.5 mg daily<br>Anastrozole 1 mg daily | Total: 29<br>Letrozole (*n*=15)<br>Anastrozole (*n*=14) | NR | Idiopathic hypoandrogenic | Baseline, 6 | 2a |
| Cavallini *et al.*[20] 2013, Italy | Prospective, randomized, double-blind, placebo-controlled (multicentric) | Letrozole 2.5 mg daily<br>Placebo | Total: 45<br>Letrozole (*n*=22)<br>Placebo (*n*=23) | 44 (37–52)<br>45 (38–53) | Idiopathic hypoandrogenic: 28 (62.2)<br>Cryptorchidism: 17 (37.7) | Baseline, 3, 6 | 1b |
| Helo *et al.*[26] 2015, USA | Prospective, randomized, double-blind (single center) | Clomiphene citrate 25 mg daily<br>Anastrozole 1 mg daily | Total: 26<br>Clomiphene citrate (*n*=13)<br>Anastrozole (*n*=13) | 35±6.5<br>33±3.9 | Idiopathic hypoandrogenic | Baseline, 3 | 1b |
| Shoshany *et al.*[25] 2017, USA | Retrospective survey[25] (single center) | Anastrozole 1 mg daily | Total: 86 | 37 (32–41) | Idiopathic hypoandrogenic: 71 (82.5), cryptorchidism: 11 (12.7), varicocele repair: 4 (4.6) | Baseline, 4 | 3 |

BMI: body mass index; LE: level of evidence; NR: not reported; s.d.: standard deviation

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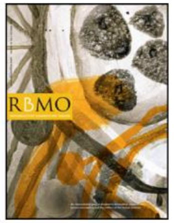
# APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function



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. Behre[i], 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.

FERTGROUP | FERTILITY

## Grupo APHRODITE

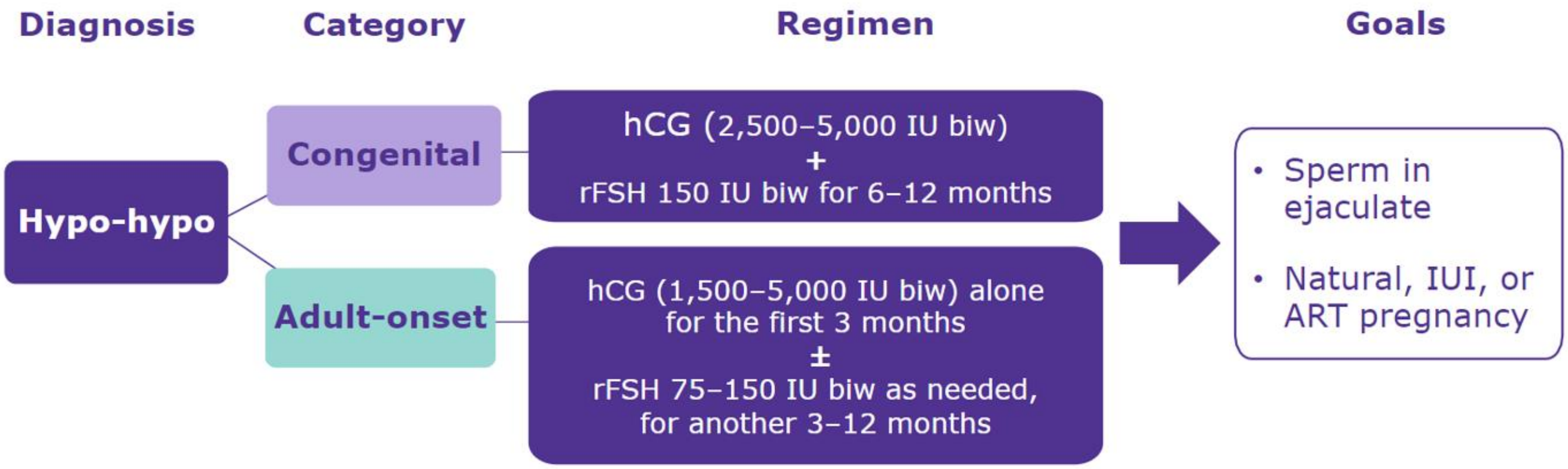
## 01 Hipogonadismo / Hipogonadotrófico

*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)




- FSH, LH, T, $E_2$ (monthly)
- Physical examination, US scan (bi-monthly)
- Semen analysis (monthly after 3 months)

# 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

## Grupo APHRODITE

### 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

## Grupo APHRODITE

### 04 Hipogonadismo hipergonadotópico

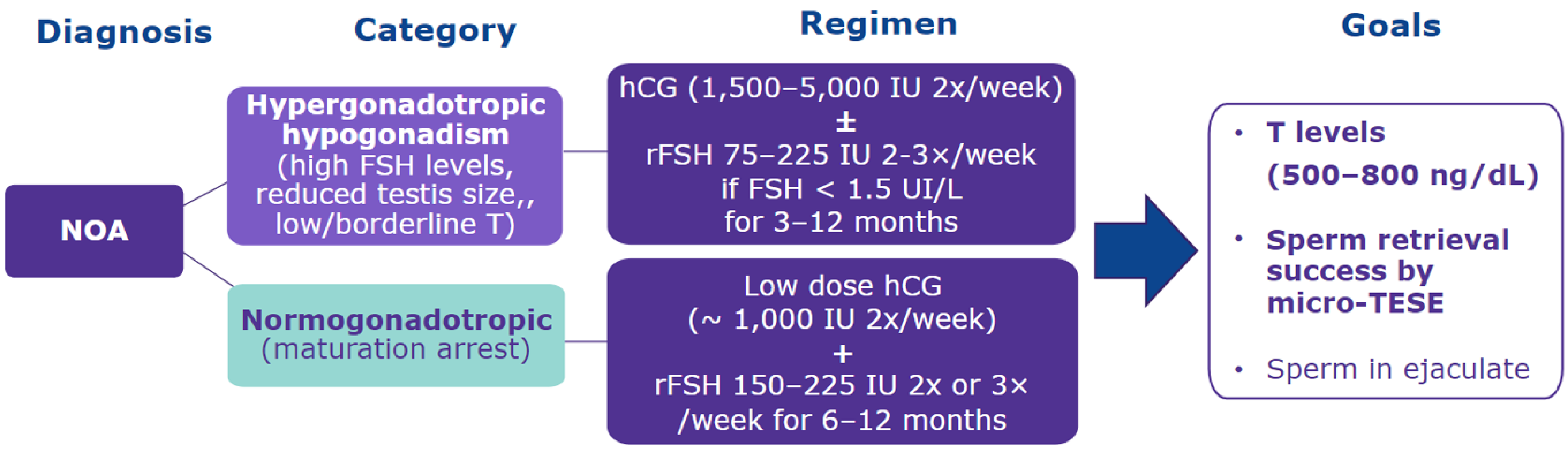
**Definição:** Parâmetros seminais alterados com FSH aumentado e testosterona total normal ou diminuída (azoospermia não obstrutiva).

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

**Tratamento:**

- hCG (+ FSH, se necessário)*

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




- FSH, LH, T, E2 (monthly)
- Physical examination, US scan (bi-monthly)
- Semen analysis (monthly after 3 months)

## Grupo APHRODITE

## 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 rates[1-3]

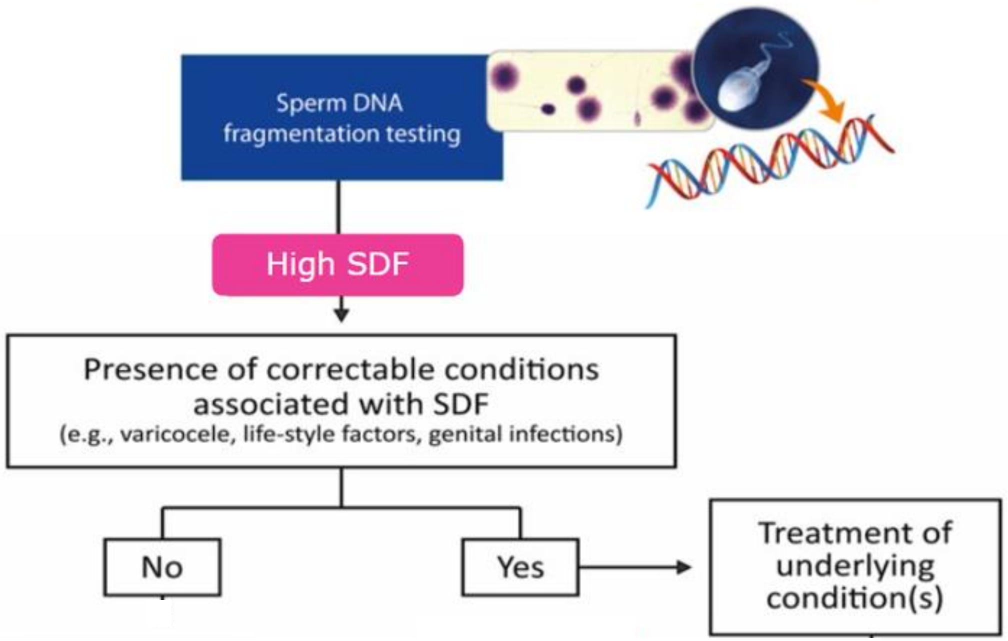
- **Treatment**[4]
  - ➔ rFSH, uFSH, hMG
    - 75–300 IU on alternate days
    - 150 IU 2-3×/week
- **Duration**: 3–6 months
- **Follow-up**: semen analysis, DNA fragmentation index (DFI) %


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 administration after gonadotropin-releasing-hormone agonist: a therapeutic option in severe testiculopathies

Carlo Foresta, M.D.,[a] Riccardo Selice, M.D.,[a] Afra Moretti, B.S.,[a] Mauro Antonio Pati, B.S.,[a] Marina Carraro, B.S.,[a] Bruno Engl, M.D.,[b] and Andrea Garolla, M.D.[a]

- ✓ GnRH depot 3,75 mg: 4 meses
- ✓ FSHr 150 UI 2/2 dias
  hCG 2.000 2X/semana } 3 meses

TABLE 3

Sperm parameters observed in treated (basal, after GnRH agonist, and after GnRH agonist + recombinant FSH + hCG) and in nontreated groups (basal, after 30 days, and after 4 months).

| | Spermatozoa (millions/mL) | Total spermatozoa (millions) | Normal morphology (%) | Motility A + B (%) | Total aneuploidies |
|---|---|---|---|---|---|
| Group A, treated (n = 57) | | | | | |
| Basal | 1.8 ± 0.7 | 4.9 ± 1.6 | 8.6 ± 4.2 | 20.7 ± 8.4 | 4.7 ± 2.1 |
| 30 days after GnRH-a | 3.2 ± 1.6 | 7.8 ± 2.4 | 10.8 ± 5.2 | 18.3 ± 8.6 | 3.8 ± 1.7 |
| 3 months more of GnRH-a + rFSH + hCG | 6.6 ± 2.3[a] | 12.3 ± 3.5[a] | 19.7 ± 5.7[a] | 28.9 ± 11.7 | 1.8 ± 0.6[a] |
| Group B, nontreated (n = 30) | | | | | 5.4 ± 2.3 |
| Basal | 1.7 ± 0.9 | 4.2 ± 1.0 | 9.5 ± 3.6 | 18.1 ± 9.9 | 4.8 ± 2.5 |
| After 30 days | 2.0 ± 0.9 | 4.7 ± 1.9 | 10.7 ± 3.3 | 16.1 ± 7.1 | 4.6 ± 2.0 |
| After 4 months | 2.3 ± 1.1 | 5.9 ± 1.5 | 10.3 ± 3.1 | 20.2 ± 9.1 | 1.4 ± 0.5 |

JBRA Assisted Reproduction 2024;**00**(0):000-000
doi: 10.5935/1518-0557.20240039

Case report

# Two livebirths achieved in cases of hypergonadotropic hypogonadism nonobstructive azoospermia, treated with GnRH agonist and gonadotrophins: a case series and review of the literature

Mauro Bibancos de Rose[1,2], Arhon Bizelli Sicard[2], Natalia Alvarenga Aguiar[2], Beatriz de Oliveira Onório[2], Antonio Alberto Rodrigues Almendra[2], Wagner Eduardo Matheus[3], Andrea Garolla[4], Carlo Foresta[4], Daniela Paes de Almeida Ferreira Braga[1], Amanda Souza Setti[1], Edson Borges Jr.[5]

- Pituitary desensibilization using a ***GnRH agonist (leuprorelin acetate 3.75 mg***, Lupron Depot®; AbbVie Inc., North Chicago, Illinois, USA) ***for 4 months.***
- Testicular stimulation using ***menotropin 1,200 IU (Menopur®, Ferring*** Pharmaceuticals, Saint-Prex, Switzerland), ***every other day***, and
- ***hCG 5,000 IU (Choriomon®***, Meizler, UCB, Biopharma, Belgium), ***every two weeks***, ***both for three months***.
- Testicular stimulation started one month after the beginning of GnRH agonist treatment.

# Medical Therapy

- Gonadotropins (FSH, LH, hCG)
- Androgens (testosterone and similar)
- Selective estrogen receptor modulator - *SERMs* (clomifene, taxoxifen, raloxifene, toremifene)
- Aromatase inhibitors (testolactona, letrozol, anastrazol)
- Oral Antioxidants (vitamins, zinc, carnitin, etc.)

3. Lifestyle:

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

4. Environmental

- heat
- pollution
- heavy metals
- plasticizers
- ‹icide/ herbicides

5. Infection

- genito-urinary tract
- systemic infection

6. Autoimmune

- vasectomy
- torsion
- chronic prostatitis

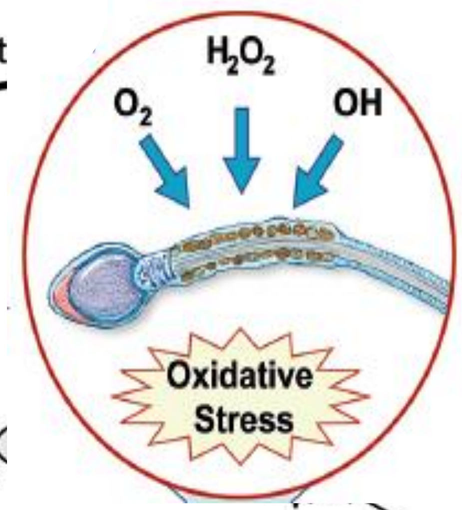
7. Testicular

2. Iatrogenic

- centrifugation
- medications

Anti-Oxidant

'S




8. Chronic Disease

- diabetes
- CRF
- haemaglobinopathies
- hyperhomocysteinaemia

1.Idiopathic

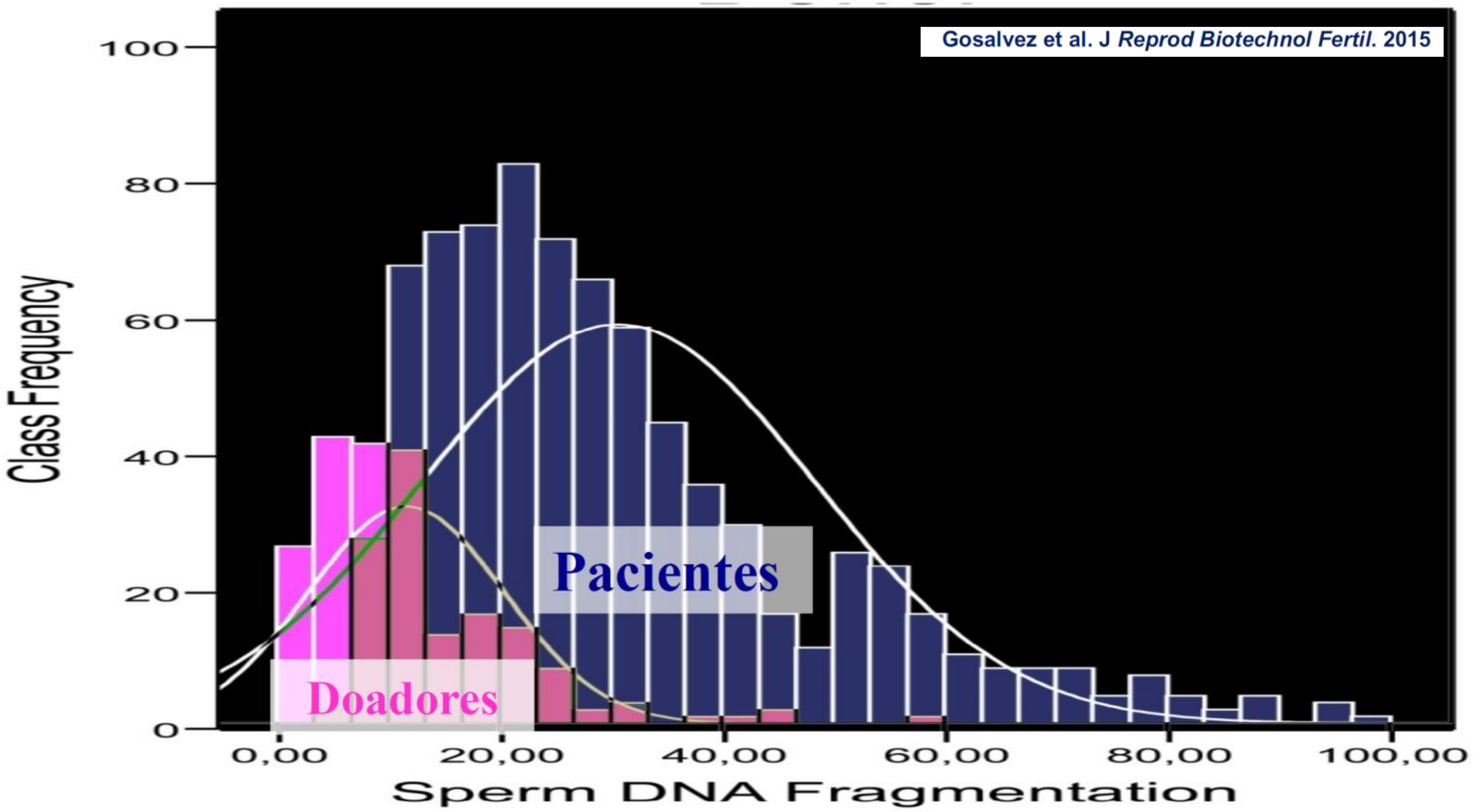
Damage to **sperm DNA** results
In infertility and miscarriage

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



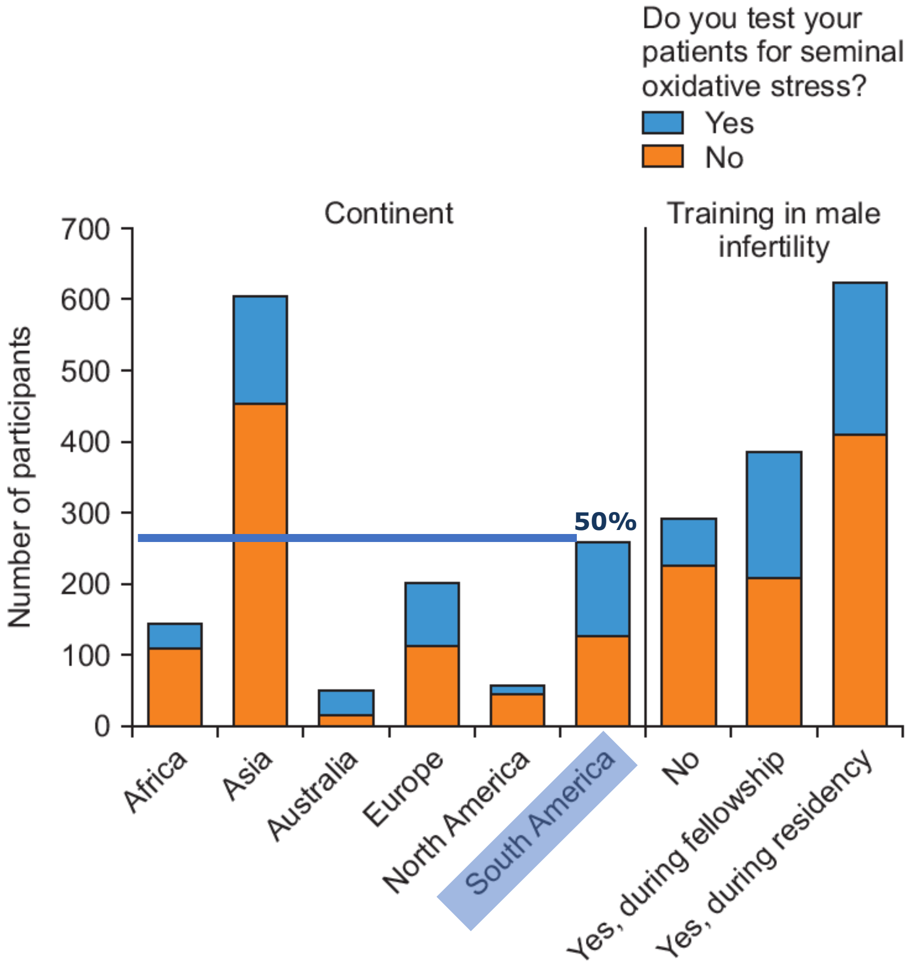
*Kelton Tremellen; Human Reproduction Update, Vol.14, No.3 pp. 243–258, 2008*

# Taxa de Fragmentação do DNA espermático




FERTGROUP | FERTILITY

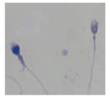
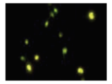
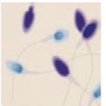
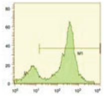
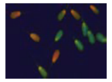
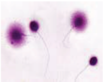
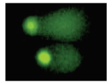
# A Global Survey of Reproductive Specialists to Determine the Clinical Utility of Oxidative Stress Testing and Antioxidant Use in Male Infertility




FERTGROUP | FERTILI

Fig. 4. Oxidative stress testing based on the geographic origin of the participants and training in male infertility.

**Table 1** Sperm DNA fragmentation (SDF) testing methods

| | Test | Principle | Advantage | Disadvantage |
|---|---|---|---|---|
|  [1] | AO test | Metachromatic shift in fluorescence of AO when bound to single strand (ss)DNA. Uses fluorescent microscopy | Rapid, simple and inexpensive | Inter-laboratory variations and lack of reproducibility |
|  [2] | AB staining | Increased affinity of AB dye to loose chromatin of sperm nucleus. Uses optical microscopy | Rapid, simple and inexpensive | Inter-laboratory variations and lack of reproducibility |
|  [3] | CMA3 staining | CMA3 competitively binds to DNA indirectly visualizing protamine deficient DNA. Uses fluorescent microscopy | Yields reliable results as it is strongly correlated with other assays | Inter-observer variability |
|  [4] | TB staining | Increased affinity of TB to sperm DNA phosphate residues. Uses optical microscopy | Rapid, simple and inexpensive | Inter-observer variability |
|  [5] | TUNEL | Quantifies the enzymatic incorporation of dUTP into DNA breaks. Can be done using both optical microscopy and fluorescent microscopy. Uses optical microscopy, fluorescent microscopy and flow cytometry | Sensitive, reliable with minimal inter-observer variability. Can be performed on few sperm | Requires standardization between laboratories |
|  [6] | SCSA | Measures the susceptibility of sperm DNA to denaturation. The cytometric version of AO test. Uses flow cytometry | Reliable estimate of the percentage of DNA-damaged sperm | Requires the presence of expensive instrumentation (flow cytometer) and highly skilled technicians |
|  [7] | SCD or Halo test | Assess dispersion of DNA fragments after denaturation. Uses optical or fluorescent microscopy | Simple test | Inter-observer variability |
|  [8] | SCGE or comet assay | Electrophoretic assessment of DNA fragments of lysed DNA. Uses fluorescent microscopy | Can be done in very low sperm count. It is sensitive and reproducible | Requires an experienced observer. Inter-observer variability |

[1] Acridine orange (AO) stains normal DNA fluoresces green; whereas denatured DNA fluoresces orange-red. [2] Aniline blue (AB) staining showing sperm with fragmented DNA and normal sperm. [3] Chromomycin A3 (CMA3) staining: protamine deficient spermatozoa appear bright yellow; spermatozoa with normal protamine appear yellowish green. [4] Toulidine blue (TB) staining: normal sperm appear light blue and sperm with DNA fragmentation appear violet. [5] Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay fluorescent activated cell sorting histogram showing percentage of SDF. [6] Sperm chromatin structure assay (SCSA): flow cytometric version of AO staining. [7] Sperm chromatin dispersion (SCD) test: spermatozoa with different patterns of DNA dispersion; large-sized halo; medium-sized halo [2]; very small- sized halo. [8] Comet images showing various levels of DNA damage.

Review Article

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The World Journal of MEN's HEALTH

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

Ashok Agarwal[1,2], Neel Parekh[2], Manesh Kumar Panner Selvam[1,2], Ralf Henkel[1,3], Rupin Shah[4], Sheryl T. Homa[5], Ranjith Ramasamy[6], Edmund Ko[7], Kelton Tremellen[8], Sandro Esteves[9,10], Ahmad Majzoub[1,11], Juan G. Alvarez[12], David K. Gardner[13], Channa N. Jayasena[14,15], Jonathan W. Ramsay[15], Chak-Lam Cho[16], Ramadan Saleh[17], Denny Sakkas[18], James M. Hotaling[19], Scott D. Lundy[2], Sarah Vij[2], Joel Marmar[20], Jaime Gosalvez[21], Edmund Sabanegh[2], Hyun Jun Park[22,23], Armand Zini[24], Parviz Kavoussi[25], Sava Micic[26], Ryan Smith[27], Gian Maria Busetto[28], Mustafa Emre Bakırcıoğlu[29], Gerhard Haidl[30], Giancarlo Balercia[31], Nicolás Garrido Puchalt[32], Moncef Ben-Khalifa[33], Nicholas Tadros[34], Jackson Kirkman-Browne[35,36], Sergey Moskovtsev[37], Xuefeng Huang[38], Edson Borges Jr[39], Daniel Franken[40], Natan Bar-Chama[41], Yoshiharu Morimoto[42], Kazuhisa Tomita[42], Vasan Satya Srini[43], Willem Ombelet[44,45], Elisabetta Baldi[46], Monica Muratori[47], Yasushi Yumura[48], Sandro La Vignera[49], Raghavender Kosgi[50], Marlon P. Martinez[51], Donald P. Evenson[52], Daniel Suslik Zylbersztejn[53], Matheus Roque[54], Marcello Cocuzza[55], Marcelo Vieira[56,57], Assaf Ben-Meir[58], Raoul Orvieto[59,60], Eliahu Levitas[61], Amir Wiser[62,63], Mohamed Arafa[64], Vineet Malhotra[65], Sijo Joseph Parekattil[66,67], Haitham Elbardisi[64], Luiz Carvalho[68,69], Rima Dada[70], Christophe Sifer[71], Pankaj Talwar[72], Ahmet Gudeloglu[73], Ahmed M.A. Mahmoud[74], Khaled Terras[75], Chadi Yazbeck[76], Bojanic Nebojsa[77], Damayanthi Durairajanayagam[78], Ajina Mounir[79], Linda G. Kahn[80], Saradha Baskaran[1], Rishma Dhillon Pai[81], Donatella Paoli[82], Kristian Leisegang[83], Mohamed-Reza Moein[84], Sonia Malik[85], Onder Yaman[86], Luna Samanta[87], Fouad Bayane[88], Sunil K. Jindal[89], Muammer Kendirci[90], Baris Altay[91], Dragoljub Perovic[92], Avi Harlev[93]

FERTGROUP | FERTILITY

Table 4. Effect of antioxidants on male infertility: Double blind placebo controlled studies[a]

| Study reference | Infertility type | Cases | Antioxidants | Duration | Outcome |
|---|---|---|---|---|---|
| Micic et al (2019) [119] | Idiopathic oligo-asthenozoo-spermia | Placebo group (n=50)<br>Treatment group (n=125) | Proxeed plus=2 times/d<br>• LC=1,000 g, LAC=0.5 g, fumarate=0.725 g, fructose=1 g, citric acid=50 mg, zinc=10 mg, coenzyme Q10=20 mg, selenium=50 μg, Vit C=90 mg, folic acid=200 μg, Vit B12=1.5 μg | 3 months | Increase in semen volume, progressive motility and vitality<br>Decrease in sperm DNA fragmentation index |
| Busetto et al (2018) [113] | Idiopathic OAT, with and without varicocele | Varicocele (n=45)<br>Without varicocele (n=49) | LC=1,000 mg, LAC=500 mg, fumarate=725 mg, fructose=1,000 mg, Coenzyme Q10=20 mg, Vit C=90 mg, Zinc=10 mg, folic acid=200 μg, Vit B12=1.5 μg | 6 months | Increase in sperm concentration, total sperm count, motility, and progressive motility |
| Safarinejad et al (2012) [116] | Idiopathic infertility | Placebo group (n=114)<br>Treatment group (n=114) | Coenzyme Q10=200 mg/d | 26 weeks | Increase in sperm concentration, motility and normal sperm morphology |
| Safarinejad (2009) [114] | Idiopathic OAT | Placebo group (n=106)<br>Treatment group (n=106) | Coenzyme Q10=300 mg/d | 26 weeks | Increase in sperm concentration and motility |
| Balercia et al (2009) [120] | Idiopathic asthenozoo-spermia | Placebo group (n=30)<br>Treatment group (n=30) | Coenzyme Q10=200 mg/d | 3 months | Increase in sperm concentration and motility |
| Tremellen et al (2008) [28] | Male factor infertility | Placebo group (n=20)<br>Infertile men (n=40) | Menevit=1 capsule/d<br>• Lycopene=6 mg, Vit E=400 IU, Vit C=100 mg, Zinc=25 mg, selenium=26 μg, folate=0.5 mg, garlic-1,000 mg, palm oil (vehicle) | 3 months | Improved pregnancy rates in couples undergoing IVF-ICSI treatment for severe male factor infertility |
| Balercia et al (2005) [115] | Idiopathic asthenozoo-spermia | Placebo group (n=15)<br>Treatment group (n=45):<br>LC group: n=15;<br>LAC group: n=15;<br>LC+LAC group: n=15 | LC=3 g/d<br>LAC=3 g/d<br>LC+LAC=2 g+1 g/d | 6 months | Increase in sperm motility and normal sperm morphology |

OAT: oligoasthenoteratozoospermia, LC: L-carnitine, LAC: L-acetylcarnitine, Vit: vitamin, IVF-ICSI: *in vitro* fertilization/intracytoplasmic sperm injection.

[a]Only double blind placebo control studies on idiopathic male infertility patients were included. Except for three studies (94, 96, and 142), others used a combination of antioxidant supplements for a period of 3 to 6 months.

FERTGROUP | F

Human Reproduction, Vol.26, No.7 pp. 1628–1640, 2011
Advanced Access publication on May 5, 2011 doi:10.1093/humrep/der132

human reproduction

REVIEW *Andrology*

## The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy

Parviz Gharagozloo[1,*] and R. John Aitken[2]

[1]CellOxess LLC, 16 Blue Spruce Drive, Pennington, NJ 08534, USA [2]Priority Research Centre in Reproductive Science, Discipline of Biological Sciences, University of Newcastle, Callaghan, NSW 2308, Australia

### *Impact of Oral antioxidants in Oxidative Stress (OS) and Sperm DNAfrag*

- 19 / 20 studies show decrease on ***OS***
- Strong evidence: *increase sperm motility* (mainly in asthenozoospermics)
- 6 /10 studies: *increase pregnancy rates*

**COCHRANE SUMMARIES**
Independent high-quality evidence for health care decision making

# Antioxidants for male subfertility

*Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ*

**Published Online:** March 14, 2012

Oxidative stress may cause sperm cell damage. This damage can be reduced by the body's own natural antioxidant defences. Antioxidants can be part of our diet and taken as a supplement. It is believed that in many cases of unexplained subfertility, and also in instances where there may be a sperm-related problem, taking an oral antioxidant supplement may increase a couple's chance of conceiving when undergoing fertility treatment. This review identified 34 randomised controlled trials involving 2876 couples. Pooled findings from three small trials suggest an increase in live birth rates for the partners of subfertile men taking an antioxidant supplement as part of an assisted reproductive program. However, further well-designed large randomised placebo-controlled trials are needed to confirm these findings.

- 34 randomizing studies – 2.876 couples
- Pregnacy rate (OR=4,18)
- Take home baby rate (OR=4,85)

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD007411.

## Antioxidants for male subfertility (Review)

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

61 studies with a total population of 6,264 subfertile men, aged between 18 and 65 combined 18 different oral antioxidants.

- **Live birth:** ***OR 1.79***, 95% CI 1.20 to 2.67, P = 0.005, **7 RCTs, 750 men**.
- **Clinical pregnancy rate:** ***OR 2.97***, 95% CI 1.91 to 4.63, P < 0.0001, **11 RCTs, 786 men**.

# Sperm DNA fragmentation index as a promising predictive tool for male infertility diagnosis and treatment management – meta-analyses

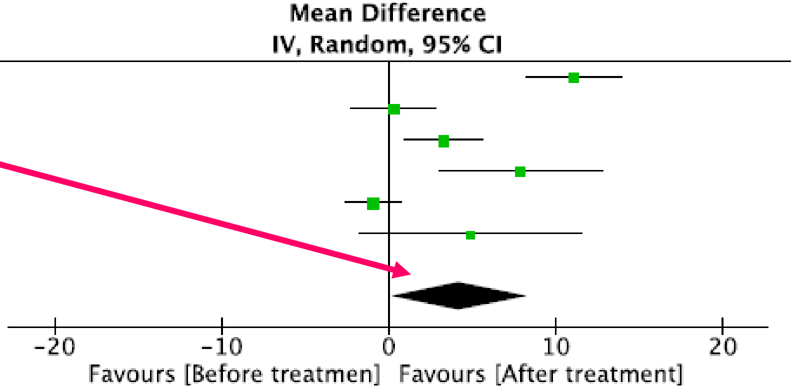
Daniele Santi[1,2,*], Giorgia Spaggiari[1,2], Manuela Simoni[1,2]

RBMO VOLUME 37 ISSUE 3 2018


- 383 men with idiopathic infertility or with abnormal semen analyses were treated with FSH for a maximum of 3 months
- rFSH used in three studies and uFSH in other three (uFSH)

| Study or Subgroup | Before FSH therapy Mean | SD | Total | After FSH therapy Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Colacurci 2012 | 23.7 | 9.4 | 65 | 12.6 | 7 | 65 | 17.6% | 11.10 [8.25, 13.95] |
| Garolla 2014 | 24.4 | 9.5 | 92 | 24.1 | 8.2 | 92 | 17.9% | 0.30 [-2.26, 2.86] |
| Garolla 2017 | 26.7 | 7.9 | 84 | 23.4 | 7.4 | 84 | 18.1% | 3.30 [0.99, 5.61] |
| Palomba 2011 | 24.6 | 12.7 | 36 | 16.7 | 7.8 | 36 | 15.0% | 7.90 [3.03, 12.77] |
| Ruvolo 2013 | 10.5 | 4.2 | 53 | 11.4 | 4.5 | 53 | 18.7% | -0.90 [-2.56, 0.76] |
| Simoni 2016 | 57.8 | 17.3 | 55 | 52.9 | 18.2 | 55 | 12.6% | 4.90 [-1.74, 11.54] |
| **Total (95% CI)** | | | **385** | | | **385** | **100.0%** | **4.24 [0.24, 8.25]** |

Heterogeneity: $Tau^2 = 21.64$; $Chi^2 = 59.65$, df = 5 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: Z = 2.08 (P = 0.04)



Asian Journal of Andrology (2017) 19, 80–90
www.asiaandro.com; www.ajandrology.com


Open Access

ORIGINAL ARTICLE

Sperm Biology

# A systematic review and meta-analysis to determine the effect of sperm DNA damage on *in vitro* fertilization and intracytoplasmic sperm injection outcome

Luke Simon[1,*], Armand Zini[2,*], Alina Dyachenko[2], Antonio Ciampi[2], Douglas T Carrell[1,3,4]

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

| *Effect* | *Number of studies* | *Fixed effects model* | | *Random effects model* | |
|---|---|---|---|---|---|
| | | *OR (95% CI)* | *P* | *OR (95% CI)* | *P* |
| Overall effect | 56 | 1.68 (1.49–1.89) | 0.0000* | 1.84 (1.5–2.27) | <0.0001* |
| Sperm DNA damage assays | | | | | |
| SCSA | 23 | 1.18 (0.96–1.44) | 0.1115 | 1.22 (0.93–1.61) | 0.1522 |
| TUNEL | 18 | 2.18 (1.75–2.72) | 0.0000* | 2.22 (1.61–3.05) | <0.0001* |
| Comet | 7 | 3.34 (2.32–4.82) | 0.0000* | 3.56 (1.78–7.09) | 0.0003* |
| SCD | 8 | 1.51 (1.18–1.92) | 0.0011* | 1.98 (1.19–3.3) | 0.0086* |
| Types of assisted treatment | | | | | |
| IVF | 16 | 1.65 (1.34–2.04) | 0.0000* | 1.92 (1.33–2.77) | 0.0005* |
| ICSI | 24 | 1.31 (1.08–1.59) | 0.0068* | 1.49 (1.11–2.01) | 0.0075* |
| Mixed | 16 | 2.37 (1.89–2.97) | 0.0000* | 2.32 (1.54–3.5) | 0.0001* |

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

FERTGROUP | FERTILITY

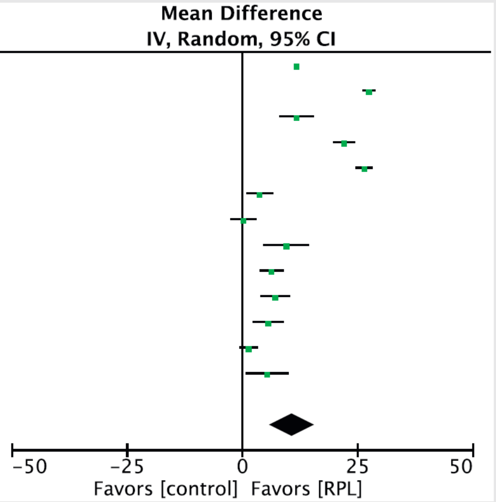
# Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis

Dana B. McQueen, M.D., M.A.S., John Zhang, Ph.D., and Jared C. Robins, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois

| Study or Subgroup | Recurrent Pregnancy Loss Mean | SD | Total | Fertile Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Absalan 2012 | 23.3 | 1.1 | 30 | 11.6 | 0.5 | 30 | 7.9% | 11.70 [11.27, 12.13] |
| Bareh 2016 | 36.8 | 2.7 | 26 | 9.4 | 2.7 | 31 | 7.9% | 27.40 [25.99, 28.81] |
| Bhattachara 2008 | 18.1 | 16.1 | 74 | 6.4 | 3.6 | 65 | 7.6% | 11.70 [7.93, 15.47] |
| Brahem 2011 | 32.2 | 6.1 | 31 | 10.2 | 2.1 | 20 | 7.8% | 22.00 [19.66, 24.34] |
| Carrell 2003 | 38.3 | 4.2 | 21 | 11.9 | 1 | 26 | 7.8% | 26.40 [24.56, 28.24] |
| Coughlan 2014 | 10.9 | 1.9 | 16 | 7.2 | 3.7 | 7 | 7.7% | 3.70 [0.81, 6.59] |
| Esquerre–Lamare 2018 | 6.8 | 5.6 | 33 | 6.6 | 5.5 | 27 | 7.7% | 0.20 [−2.62, 3.02] |
| Imam 2011 | 23.4 | 9.9 | 20 | 13.9 | 5.4 | 20 | 7.3% | 9.50 [4.56, 14.44] |
| Kumar 2012 | 28.1 | 5 | 45 | 21.8 | 4.8 | 20 | 7.8% | 6.30 [3.74, 8.86] |
| Ribas 2012 | 19.3 | 6.1 | 20 | 12.2 | 4.6 | 25 | 7.7% | 7.10 [3.88, 10.32] |
| Ruixue 2013 | 25.6 | 11.5 | 68 | 20 | 7.7 | 63 | 7.6% | 5.60 [2.27, 8.93] |
| Zhang 2012 | 15.2 | 6.4 | 111 | 13.9 | 4.4 | 30 | 7.8% | 1.30 [−0.67, 3.27] |
| Zidi–Jrah 2016 | 17.1 | 9.3 | 22 | 11.8 | 5.7 | 20 | 7.4% | 5.30 [0.68, 9.92] |
| **Total (95% CI)** | | | **517** | | | **384** | **100.0%** | **10.70 [5.82, 15.58]** |

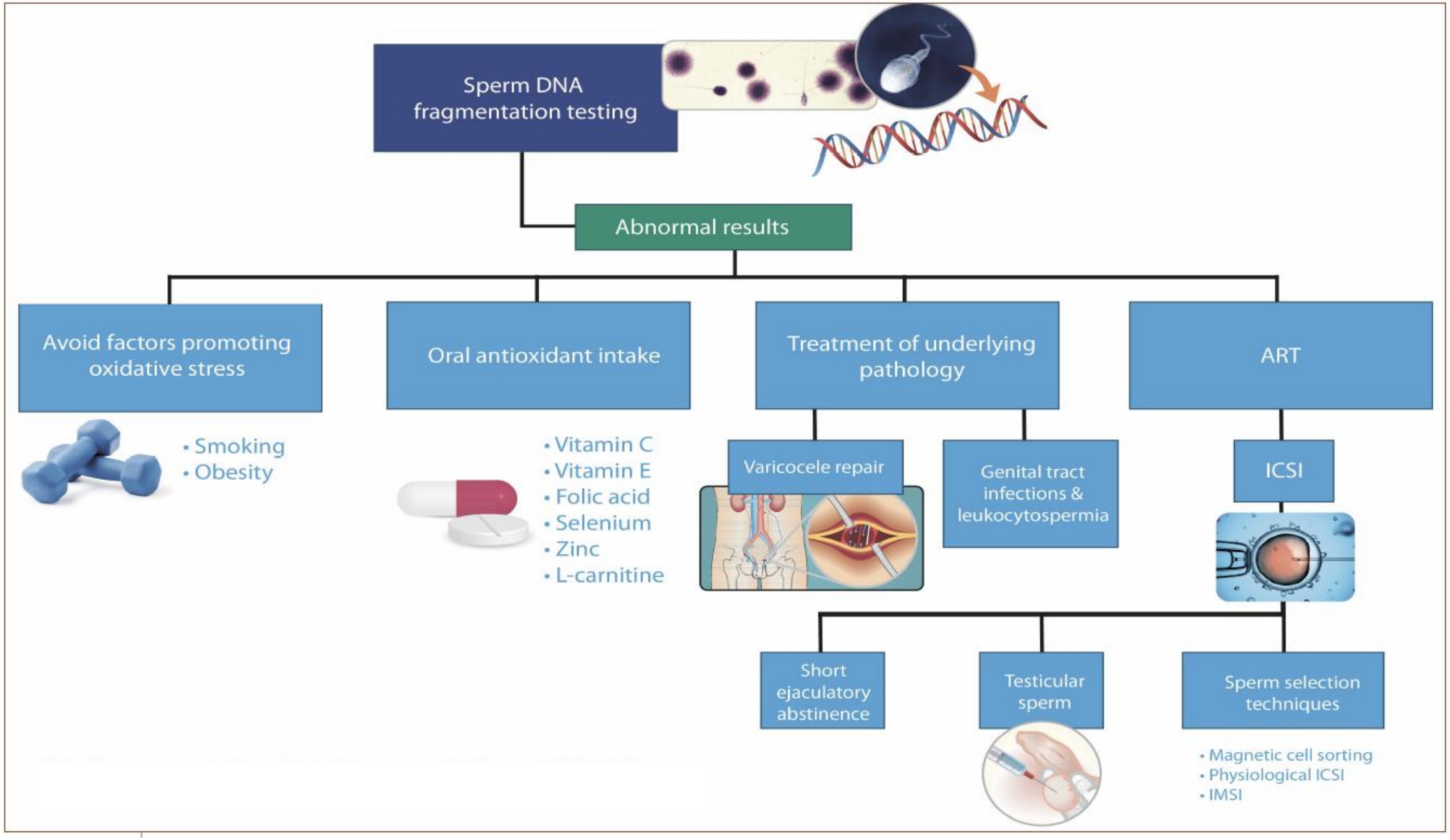
Heterogeneity: $Tau^2 = 78.10$; $Chi^2 = 1019.62$, df = 12 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.30$ ($P < 0.0001$)




Primary outcome in overall analysis.

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

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




Esteves et al. J Assist Reprod Genet, 2016

# Antioxidants to reduce sperm DNA fragmentation: an unexpected adverse effect

Dr Yves Ménézo

RBM Online - Vol 14. No 4. 2007 418-421 Reproductive BioMedicine Online; www.rbmonline.com/Article/2669 on web 28 February 2007

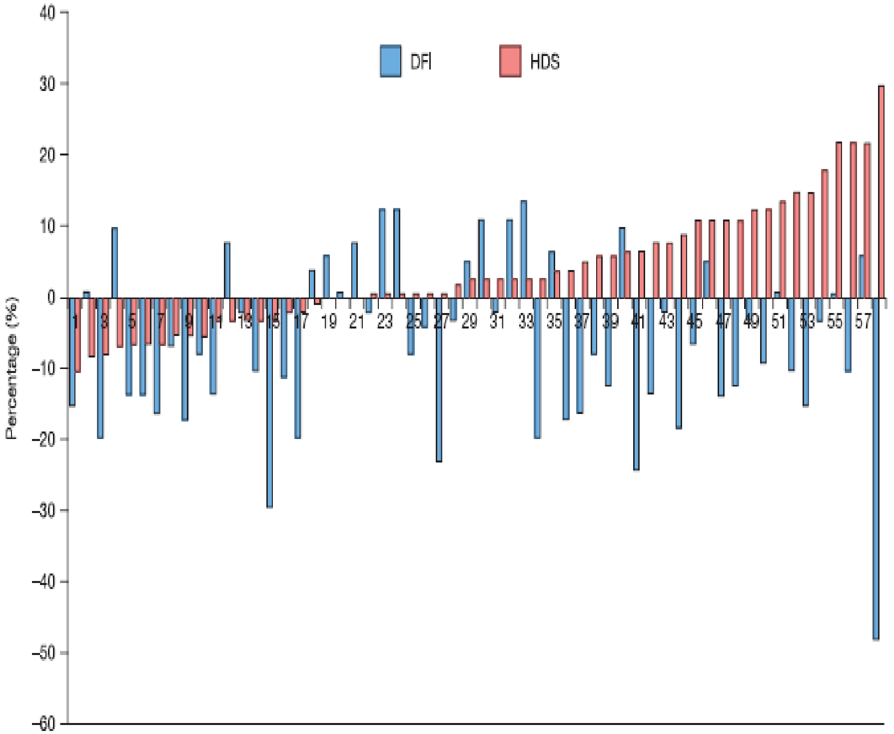



**Figure 2.** Individual variations in DNA fragmentation index and sperm decondensation in spermatozoa after 90 days treatment with antioxidant. DFI = DNA fragmentation index, HDS = high DNA stainability. Patients are ranked according to degree of HDS. – Decrease

**Table 1.** Difference in DNA fragmentation index (DFI) and degree of high DNA stainability (HDS) in 58 patients following treatment with antioxidants.

| | *Before treatment* | *After treatment* | *P-value* |
|---|---|---|---|
| DFI (%) | 32.4 | 26.2 | 0.0004 |
| HDS (%) | 17.5 | 21.5 | 0.0009 |

FERTGROU

Received: 11 July 2018 | Revised: 22 August 2018 | Accepted: 4 September 2018
DOI: 10.1111/and.13162

ORIGINAL ARTICLE

WILEY andrologia

# The excessive use of antioxidant therapy: A possible cause of male infertility?

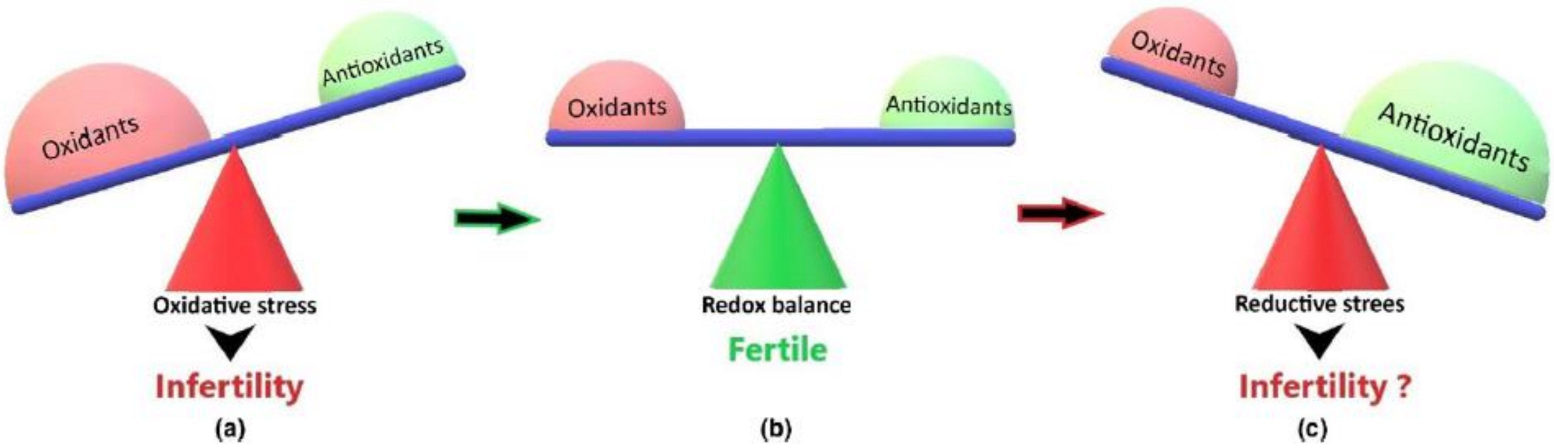
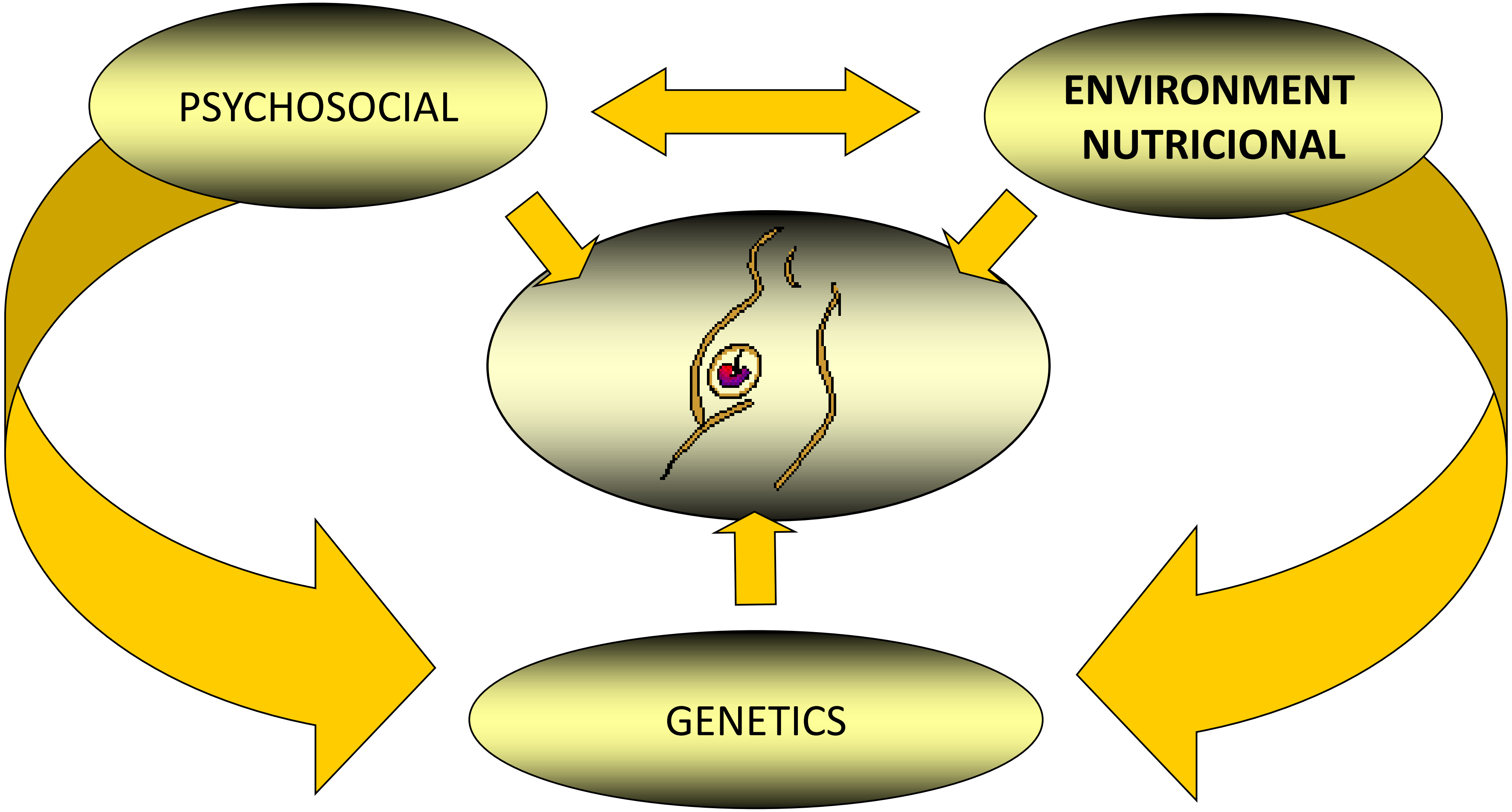



**FIGURE 1** Redox balance; effects of oxidants and antioxidants. While among others, oxidative stress (a) is a cause of ageing, neurodegenerative diseases and infertility, reductive stress (c) can be a cause of cancer, cardiomyopathy, blood-brain-barrier dysfunction and infertility. Optimal physiological functions are carried out at balanced redox levels (b)

Administration of exogenous antioxidants may instead either lead to oxidative stress induced by the *"antioxidant paradox"*

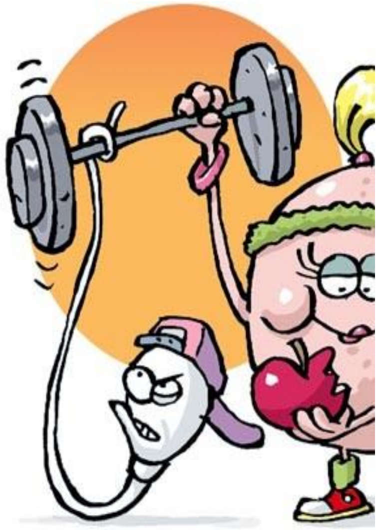
FERTGROUP | FERTILITY

# Determinants of Reproductive Function




FERTGROUP | FERTILITY

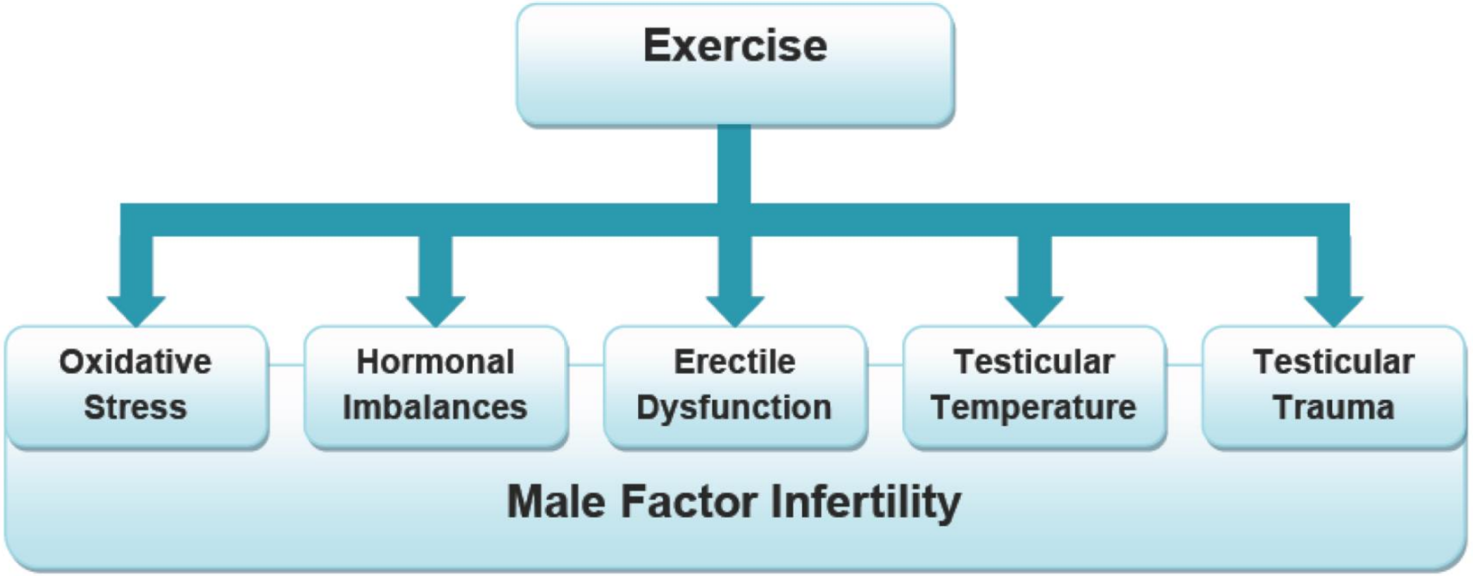
# Exercícios



# Social Habits and Environment

**Excessive exercising:**
Differences in the seminal profiles in different modalities. More marked as intensity and volume of exercise increase, especially for *morphology and volume (severe energy restriction – decrease TT)*

**Sedentary:**
Worse anabolic microenvironment and worse maintenance of homeostasis for suitable spermatogenesis – *Aggravate values for several sperm and hormonal parameters*




*The Open Reproductive Science Journal*, 2011, *3*, 105-113


# Substâncias ocupacionais e recreativas

FERTGROUP | FERTILITY

# Cigarro

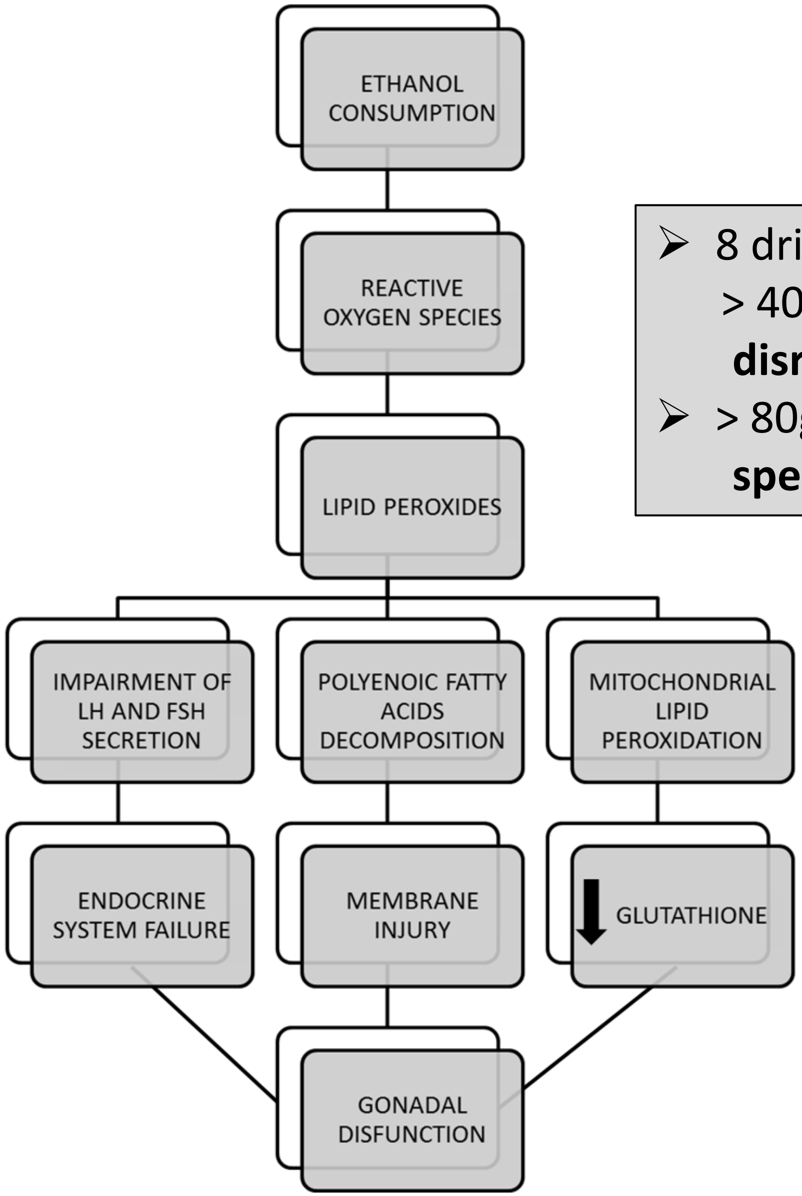
# Social Habits and Environment

- Cigarette smoke contains over 4,000 chemicals.
- 35% of reproductive-aged males smoke


## Cigarette Smoking:

- declines in semen parameters: sperm concentration, viability, forward motility and morphology
- decline in sperm penetration ability and fertilization
- increase in seminal leukocytes and reactive oxygen species (ROS) levels
- sperm DNA integrity: the health of future offspring (transgenerational damage)


# Álcool




- 8 drinks/week or
  > 40g;day:
  **disrupt spermatogenesis**
- > 80g/day:
  **spermatogenesis arrest /SCOS**

FERTGROUP | FERTILI . .

# Social Habits and Environment

## Caffeine:

- declines in semen parameters: sperm concentration, viability, forward motility and morphology
- decline in sperm penetration ability and fertilization
- increase in seminal leukocytes and reactive oxygen species (ROS) levels
- No conclusive evidence of intake < 800 mg/day


# Fatores Ocupacionais / Hábitos / Alimentação

# Social Habits and Environment

## Endocrine disruptor compounds

Synthetic and naturally occurring chemicals that are characterized by their ability to mimic the effects of endogenous hormones

| Chemical | Possible reproductive effects |
|---|---|
| **BPA** | Inhibits binding to androgen receptor, decreased semen quality, erectile dysfunction, chromosomal abnormalities in oocyte, recurrent miscarriage, |
| **Disinfection by-products** | |
| **Organochemicals and Pesticides**<br>e.g. DDT, DDE, Methoxyclor | Change in hormone levels, irregular menstruation, decreased fertility, decreased semen quality, chromosomal abnormalities in sperm, altered histology of testes, decreased libido, fetal loss, miscarriage |
| **Dioxins** | Changes in hormone levels, altered puberty, altered start of menarche, endometriosis, decreased fertility, fetal loss |
| **Phthalates** | Decreased semen quality, oligozoospermia, earlier menarche, altered menstrual cycle, infertility |
| **Solvents** | Change in hormone levels, decreased semen quality, irregular menstruation, decreased fertility, miscarriage, fetal loss |

*The Open Reproductive Science Journal*, 2011, *5*, 125-137 125

Open Access

# Cell Phones and their Impact on Male Fertility: Fact or Fiction

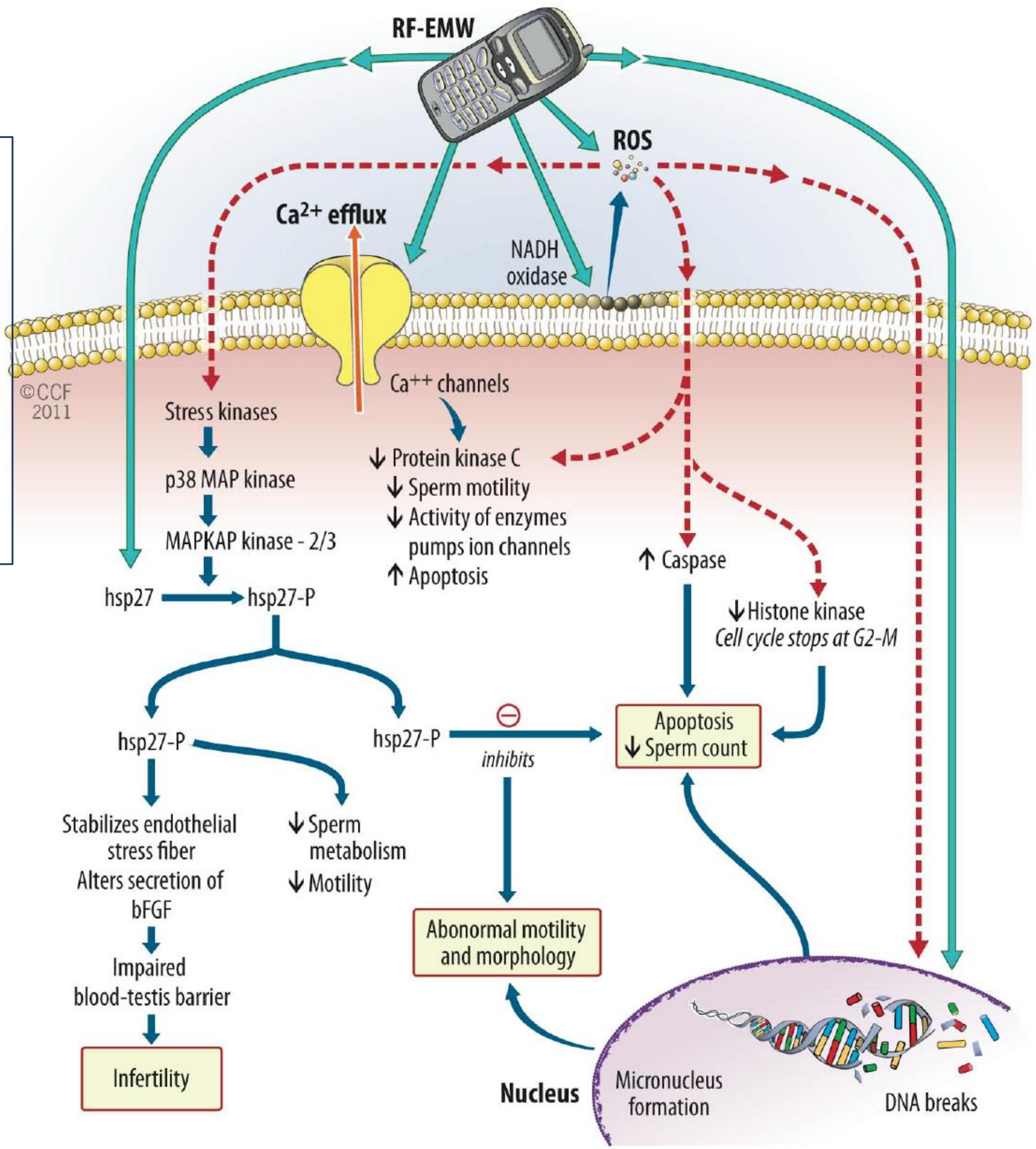
Alaa J. Hamada, Aspinder Singh and Ashok Agarwal*

*Center for Reproductive Medicine, Cleveland Clinic, Cleveland, Ohio, USA*

- Our bodies act as *parasitic antennas* that receive these waves and convert them into electric and magnetic fields. While thermal effects at the present level of cell phone radiation are negligible, most of the biological interactions are attributed to **non-thermal effects**.

- The generated electrical currents may alter the hormonal milieu and testicular microenvironment, necessary for sperm production. Additionally, sperm are electrically active cells and their exposure to cell phone electromagnetic waves and currents may affect their motility, morphology and even their count.

Leaky plasma membranes, calcium depletion and oxidative stress are the postulated cellular mechanisms mediating the harmful effects of cell phones radiation on sperm and male fertility potentials




**Can the conditions of "Modern life" interfere with male fertility?**

**Food / Weight / Habits**

Received: 7 March 2018 | Revised: 4 June 2018 | Accepted: 12 June 2018
DOI: 10.1111/and.13090

Check for updates

WILEY ANDROLOGIA
First International Journal of Andrology

ORIGINAL ARTICLE

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

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

- ❖ 965 patients evaluated
- ❖ 233 ICSI cycles
- ❖ 1st. treatment cycle
- ❖ Age woman <36 years
- ❖ Male factor isolated

1. How many cigarettes / day?
2. Weekly alcohol consumption?
3. Frequency of exercises?
4. Medications in the last 3 months? Which one?
5. Exposure to toxic agents, pesticides, radiation, etc.

FERTGROUP | FERTILITY

**TABLE 2** Linear regression analyses' results for the influence of paternal lifestyle factors on semen quality ($n$ = 965)

| Lifestyle factors | Cigarette smoking | | Alcohol consumption | | Occupation exposure | | Physical activity | | Medication use | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *B* | *p* | *B* | *p* | *B* | *p* | *B* | *p* | *B* | *p* |
| Semen quality | | | | | | | | | | |
| Semen volume | −0.417 | 0.047 | −0.1363 | 0.592 | −0.2611 | 0.702 | 0.1146 | 0.436 | 0.0219 | 0.880 |
| Sperm count/ml | −7.363 | 0.014 | −12.527 | 0.040 | −31.10 | 0.169 | −3.329 | 0.494 | 0.984 | 0.838 |
| Total sperm count | −4.43 | 0.023 | −34.91 | 0.156 | −80.79 | 0.299 | 5.85 | 0.728 | −2.75 | 0.868 |
| Total sperm motility | 2.316 | 0.347 | 0.342 | 0.895 | −7.362 | 0.285 | −0.728 | 0.617 | −0.595 | 0.684 |
| Progressive sperm motility | −0.369 | 0.887 | 2.547 | 0.240 | −7.660 | 0.297 | −0.983 | 0.528 | −0.225 | 0.885 |
| TMSC | −1.38 | 0.045 | −16.33 | 0.278 | −43.23 | 0.330 | 0.094 | 0.992 | −1.319 | 0.889 |
| Sperm morphology | −0.0563 | 0.779 | 0.3751 | 0.180 | 0.2071 | 0.713 | −0.1977 | 0.098 | −0.0633 | 0.598 |
| SDF | 0.014 | 0.033 | 5.833 | 0.002 | −2.334 | 0.586 | −1.1684 | 0.221 | 0.6005 | 0.521 |

*Note*. B: unstandardised regression coefficient; SDF: sperm DNA fragmentation; TMSC: total motile sperm count.

*Andrologia*. 2018;e13090.
https://doi.org/10.1111/and.13090

**TABLE 3** Linear regression analyses' results for the association between paternal lifestyle factors and ICSI outcomes ($n$ = 233)

| Lifestyle factors | Cigarette smoking | | Alcohol consumption | | Occupation exposure | | Physical activity | | Medication use | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *B* | *p* | *B* | *p* | *B* | *p* | *B* | *p* | *B* | *p* |
| ICSI outcomes | | | | | | | | | | |
| Fertilisation rate | −1.349 | 0.039 | −3.617 | 0.041 | 3.71 | 0.759 | 1.600 | 0.473 | −2.236 | 0.406 |
| High-quality embryos rate on day 3 | 4.383 | 0.450 | 9.559 | 0.166 | −11.24 | 0.619 | 1.359 | 0.704 | 6.925 | 0.182 |
| Blastocyst formation rate on day 5 | −14.244 | 0.025 | −34.801 | 0.042 | 0.13 | 0.996 | −6.411 | 0.111 | −3.691 | 0.548 |
| Implantation rate | 5.384 | 0.451 | −0.770 | 0.190 | −23.94 | 0.475 | −2.913 | 0.469 | 9.502 | 0.142 |

*Note*. B: unstandardised regression coefficient; ICSI: intracytoplasmic sperm injection

*Andrologia*. 2018;e13090.
https://doi.org/10.1111/and.13090

# Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes

Fertility and Sterility® Vol. 97, No. 1, January 2012

Daniela Paes de Almeida Ferreira Braga, D.V.M., M.Sc.,[a,b] Gabriela Halpern, M.Sc.,[a] Rita de Cássia S. Figueira, M.Sc.,[a]
Amanda S. Setti, B.Sc.,[b] Assumpto Iaconelli Jr., M.D.,[a] and Edson Borges Jr., M.D., Ph.D.[a,b]

## ***Xenobióticos***

- *Concentração*: negativamente influenciada pelo IMC e álcool; positivamente influenciada pelo consumo de cereal e no. refeições/dia

- *Motilidade*: negativamente influenciada pelo IMC, álcool e cigarro; positivamente influenciada pelo consumo de cereal e frutas


Reproductive BioMedicine Online (2015) 31, 30–38

ELSEVIER

www.sciencedirect.com
www.rbmonline.com

ARTICLE

**The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation**

Daniela Paes Almeida Ferreira Braga [a,*], Gabriela Halpern [a], Amanda S Setti [b], Rita Cássia S Figueira [a], Assumpto Iaconelli Jr [a], Edson Borges Jr [a]

- *2659 embriões – 269 ciclos de ICSI*

***Qualidade embrionária:***

✓ **negativamente** influenciada pelo álcool, cigarro, carne vermelha e perda de peso e,

✓ **positivamente** influenciada pelo consumo de cereais, frutas e peixes

Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes

Fertility and Sterility® Vol. 97, No. 1, January 2012

Daniela Paes de Almeida Ferreira Braga, D.V.M., M.Sc.,[a,b] Gabriela Halpern, M.Sc.,[a] Rita de Cássia S. Figueira, M.Sc.,[a] Amanda S. Setti, B.Sc.,[b] Assumpto Iaconelli Jr., M.D.,[a] and Edson Borges Jr., M.D., Ph.D.[a,b]

# ***Xenobióticos***

- *Carne vermelha e dieta (perda peso)*: impacto negativo na implantação / diminui as chances de gestação

Impacto da orientação nutricional em resultados de ciclos de reprodução assistida

JBRA Assist. Reprod. | V. 17 | nº1 | Jan-Feb / 2013

Nutritional Counseling Impact on Assisted Reproduction Treatment Outcomes

Gabriela Halpern[1], Fátima Aparecida Arantes Sardinha[2], Amanda Setti[3], Assumpto Iaconelli Jr,[4] Edson Borges Jr[5]

- Fertilização (81.0% and 67.1% p = 0.0225)
- Gestação (46.9% and 28.6% p = 0.0396)

➢ ***significativamente maiores nas pacientes que receberam aconselhamento nutricional***

✓ Pacientes que receberam esta orientação tiveram ***2X mais chances de engravidar*** (OR: 2.27, p = 0.0408)

***Concentração***:

- negativamente influenciada pelo IMC e álcool;
- positivamente influenciada pelo consumo de cereal e nº. refeições/dia

***Motilidade***:

- negativamente influenciada pelo IMC, álcool e cigarro;
- positivamente influenciada pelo consumo de cereal e frutas

**TABLE 2**

**Linear regression analysis of eating and social habits that may affect the sperm concentration, sperm motility, and sperm morphology.**

| Response variable | Predictor variable | RC | *P* value |
|---|---|---|---|
| Sperm concentration | Cereals | 15.293 | < .01 |
| | Vegetables | 5.380 | .104 |
| | Legumes | 7.983 | .035 |
| | Fruits | 5.541 | .129 |
| | Meat | −7.776 | .310 |
| | Fish | 2.764 | .441 |
| | Dairy products | 2.834 | .440 |
| | Sweet foods | −4.046 | .089 |
| | Alcoholic drinks | −5.003 | < .01 |
| | Soft drinks | −0.233 | .897 |
| | Coffee | 2.749 | .138 |
| | Exercising | 7.888 | .074 |
| | Weight loss diet | 9.487 | .045 |
| | Smoking | −0.238 | .945 |
| | Meals/d | 5.836 | .046 |
| | BMI | −2.3331 | < .01 |
| Sperm motility | Cereals | 10.974 | < .01 |
| | Vegetables | 9.602 | .436 |
| | Legumes | 2.861 | .444 |
| | Fruits | 7.453 | .028 |
| | Meat | −0.078 | .991 |
| | Fish | 4.091 | .217 |
| | Dairy products | 2.579 | .445 |
| | Sweet foods | 2.568 | .239 |
| | Alcoholic drinks | −8.5592 | < .01 |
| | Soft drinks | 0.595 | .721 |
| | Coffee | −0.109 | .949 |
| | Exercising | 2.861 | .444 |
| | Weight loss diet | −3.848 | .374 |
| | Smoking | −8.003 | .013 |
| | Meals/d | 4.295 | .110 |
| | BMI | −2.7780 | < .01 |
| Sperm morphology | Cereals | 0.749 | .327 |
| | Vegetables | 6.029 | .643 |
| | Legumes | 6.823 | .326 |
| | Fruits | 5.760 | .609 |
| | Meat | −5.829 | .878 |
| | Fish | 6.456 | .564 |
| | Dairy products | 3.765 | .604 |
| | Sweet foods | 1.963 | .421 |
| | Alcoholic drinks | −8.865 | .974 |
| | Soft drinks | 0.934 | .612 |
| | Coffee | −0.312 | .906 |
| | Exercising | 3.164 | .231 |
| | Weight loss diet | −2.484 | .984 |
| | Smoking | −8.003 | .567 |
| | Meals/d | 3.457 | .476 |
| | BMI | −0.876 | .573 |

*Note:* BMI = body mass index; RC = regression coefficient.

*Braga. Lifestyle and assisted reproduction. Fertil Steril 2012.*

## ***Álcool, café, dieta (perda de peso):***

*- impacto negativo na fertilização*

## ***Carne vermelha e dieta (perda peso)*:**

- impacto negativo na implantação
- diminui as chances de gestação

**TABLE 3**

**Linear regression analysis of eating and social habits that may affect the fertilization and implantation rates.**

| Response variable | Predictor variable | RC | *P* value |
|---|---|---|---|
| Fertilization rate | Cereals | 1.151 | .646 |
| | Vegetables | 3.539 | .246 |
| | Legumes | 1.483 | .601 |
| | Fruits | 1.201 | .657 |
| | Meat | −8.096 | .152 |
| | Fish | 5.028 | .164 |
| | Dairy products | 0.715 | .792 |
| | Sweet foods | −1.727 | .339 |
| | Alcoholic drinks | −3.958 | .007 |
| | Soft drinks | −1.471 | .115 |
| | Coffee | −3.963 | .007 |
| | Exercising | 0.681 | .801 |
| | Weight loss diet | −18.046 | .019 |
| | Smoking | −3.540 | .018 |
| | Meals/d | 0.313 | .887 |
| | BMI | 0.2620 | .542 |
| | Female smoking | −4.352 | .043 |
| | Female BMI | 0.575 | .398 |
| Implantation rate | Cereals | 6.555 | .292 |
| | Vegetables | 11.081 | .072 |
| | Legumes | 5.733 | .320 |
| | Fruits | 7.234 | .213 |
| | Meat | −36.2 | .003 |
| | Fish | 4.507 | .446 |
| | Dairy products | 3.061 | .602 |
| | Sweet foods | 3.031 | .428 |
| | Alcoholic drinks | −3.100 | .314 |
| | Soft drinks | −0.541 | .861 |
| | Coffee | −1.269 | .690 |
| | Exercising | 3.833 | .568 |
| | Weight loss diet | −17.43 | .028 |
| | Smoking | −0.713 | .896 |
| | Meals/d | 4.513 | .347 |
| | BMI | 0.8011 | .380 |
| | Female smoking | −2.984 | .543 |
| | Female BMI | −12.43 | .035 |

*Note:* BMI = body mass index; RC = regression coefficient.

*Braga. Lifestyle and assisted reproduction. Fertil Steril 2012.*

**TABLE 4**

**Binary regression analysis of eating and social habits that may affect the pregnancy and miscarriage outcome.**

| Response variable | Predictor variable | OR | 95% CI | *P* value |
|---|---|---|---|---|
| Pregnancy | Cereals | 1.59 | 0.73–2.48 | .259 |
| | Vegetables | 1.67 | 0.87–4.32 | .398 |
| | Legumes | 1.93 | 0.33–2.47 | .107 |
| | Fruits | 0.62 | 0.28–1.35 | .230 |
| | Meat | 0.06 | 0.06–0.7 | .042 |
| | Fish | 0.81 | 0.36–1.81 | .605 |
| | Dairy products | 0.71 | 0.33–1.55 | .393 |
| | Sweet foods | 1.06 | 0.63–1.77 | .838 |
| | Alcoholic drinks | 1.02 | 0.69–1.50 | .936 |
| | Soft drinks | 0.93 | 0.62–1.39 | .737 |
| | Coffee | 0.83 | 0.54–1.26 | .380 |
| | Exercising | 1.69 | 0.86–2.70 | .341 |
| | Weight loss diet | 0.21 | 0.01–1.19 | .011 |
| | Smoking | 0.86 | 0.38–1.93 | .706 |
| | Meals/d | 1.23 | 0.64–2.35 | .540 |
| | BMI | 1.04 | 0.92–1.17 | .579 |
| | Female smoking | 1.02 | 0.88–2.02 | .484 |
| | Female BMI | 0.43 | 0.25–1.13 | .027 |
| Miscarriage | Cereals | 1.02 | 0.91–1.12 | .674 |
| | Vegetables | 1.43 | 0.83–1.84 | .763 |
| | Legumes | 0.89 | 0.63–1.16 | .549 |
| | Fruits | 1.23 | 0.87–2.24 | .976 |
| | Meat | 0.85 | 0.43–1.16 | .267 |
| | Fish | 1.21 | 0.68–1.48 | .293 |
| | Dairy products | 1.09 | 0.97–1.16 | .653 |
| | Sweet foods | 0.78 | 0.65–1.18 | .784 |
| | Alcoholic drinks | 0.98 | 0.89–1.12 | .736 |
| | Soft drinks | 1.02 | 0.97–1.24 | .540 |
| | Coffee | 1.01 | 0.89–1.12 | .182 |
| | Exercising | 1.08 | 0.97–1.21 | .943 |
| | Weight loss diet | 0.98 | 0.78–1.32 | .432 |
| | Smoking | 0.85 | 0.65–1.74 | .273 |
| | Meals/d | 1.23 | 0.56–1.98 | .187 |
| | BMI | 1.13 | 0.93–1.65 | .298 |
| | Female smoking | 1.02 | 0.96–1.67 | .476 |
| | Female BMI | 0.96 | 0.79–1.34 | .354 |

*Note:* BMI = body mass index; CI = confidence interval; OR = odds ratio.

*Braga. Lifestyle and assisted reproduction. Fertil Steril 2012.*

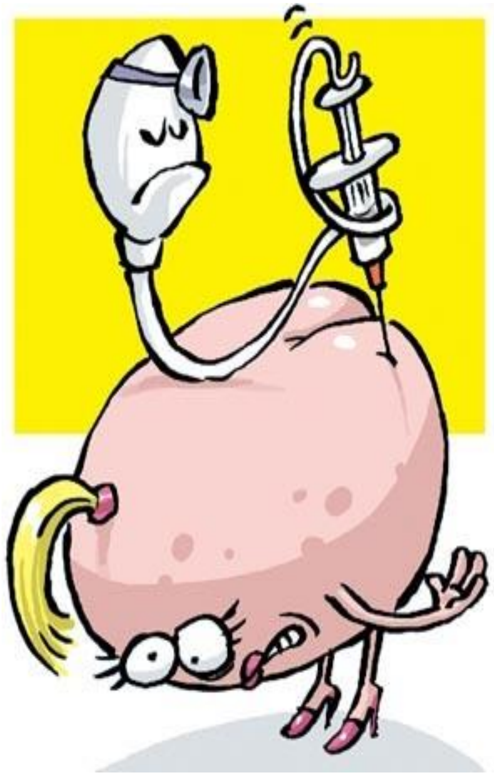
## Linear regression analyses' results for the influence of paternal lifestyle factors on semen quality (n=965)

| | Cigarette smoking | | Alcohol consumption | |
|---|---|---|---|---|
| | B | P | B | p |
| **Semen volume** | -0.417 | 0.047 | -0.1363 | 0.592 |
| **Sperm count/mL** | -7.363 | 0.014 | -12.527 | 0.040 |
| **Total sperm count** | -4.43 | 0.023 | -34.91 | 0.156 |
| **Total sperm motility** | 2.316 | 0.347 | 0.342 | 0.895 |
| **Progressive sperm motility** | -0.369 | 0.887 | 2.547 | 0.240 |
| **TMSC** | - 1.38 | 0.045 | -16.33 | 0.278 |
| **Sperm morphology** | -0.0563 | 0.779 | 0.3751 | 0.180 |
| **SDF** | 0.014 | 0.033 | 5.833 | 0.002 |

# Linear regression analyses' results for the association between paternal lifestyle factors and ICSI outcomes (n=233)

| | Cigarette smoking | | Alcohol consumption | |
|---|---|---|---|---|
| | B | p | B | p |
| **Fertilisation rate** | -1.349 | 0.039 | -3.617 | 0.041 |
| **High-quality embryos (day 3)** | 4.383 | 0.450 | 9.559 | 0.166 |
| **Blastocyst formation rate** | -14.244 | 0.025 | -34.801 | 0.042 |
| **Implantation rate** | 5.384 | 0.451 | -0.770 | 0.190 |


## Medicações de uso comum



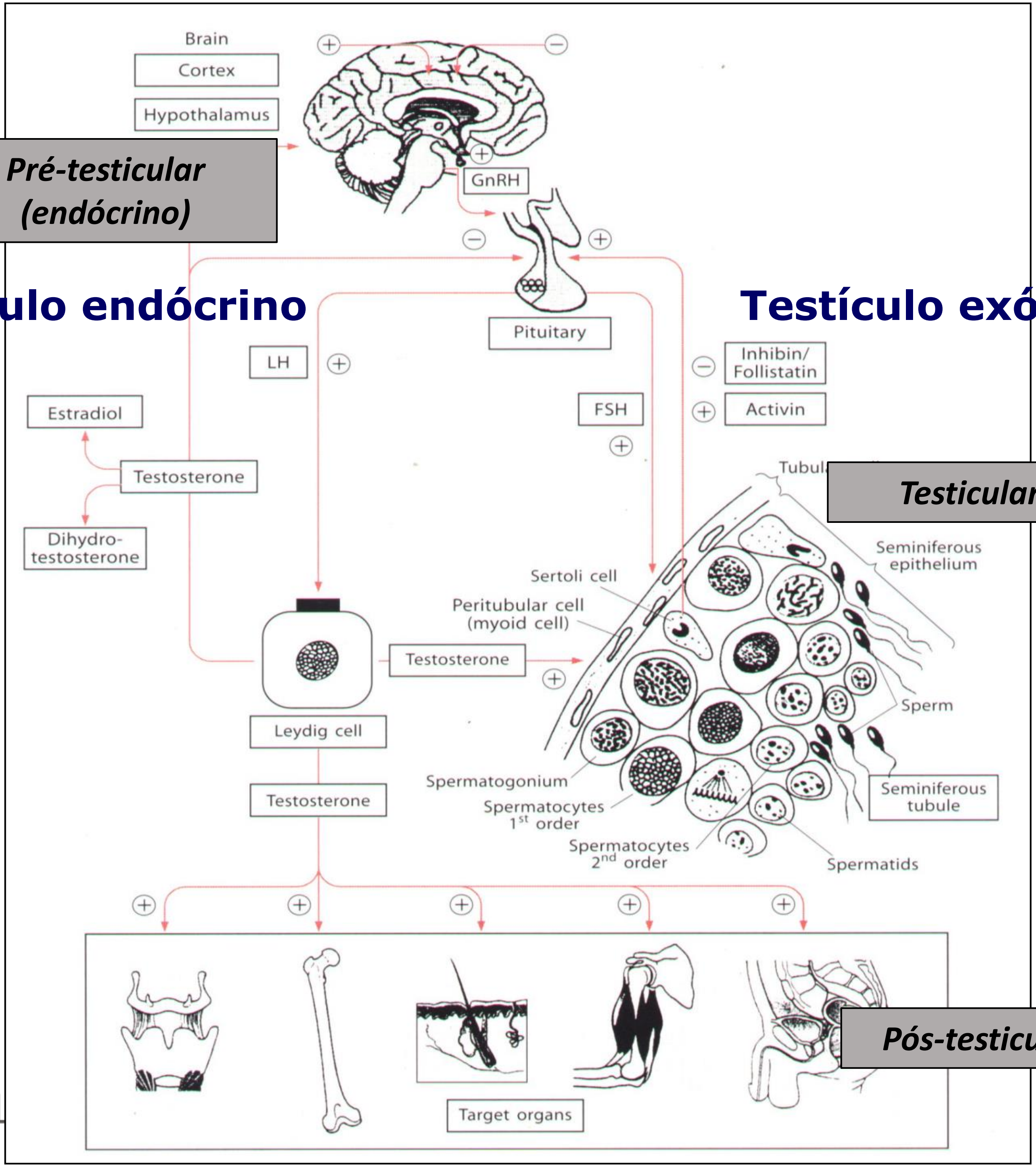
Testículo endócrino

Testículo exócrino

Pré-testicular (endócrino)

Testicular

Pós-testicular



## *DANO PRÉ-TESTICULAR*

*ação sobre eixo hipotalâmico-hipofisário*

- *Hormônios exógenos, antiandrogênios, GnRH agonistas*
- *Antiepiléticos*
- *Antipsicóticos*
- *Inibidores da captação da serotonina*
- *Antidepressivos tricíclicos*
- *Opióides*
- *Glicocorticóides*
- *Espironolactona*
- *Cetoconazol*
- *Cimetidina*

# DANO TESTICULAR

- *Sulfassalazina, metotrexate, infliximab*
- *Nitrofurantoína, eritromicina / gentamicina, tetraciclina*
- *Bactrim, ofloxacim, doxicilina (menor efeito)*
- *Colcichina*
- *Bloqueadores do canal de cálcio*
- *Agentes quimioterápicos (agentes alquilantes > efeito que os antimetabólicos)*

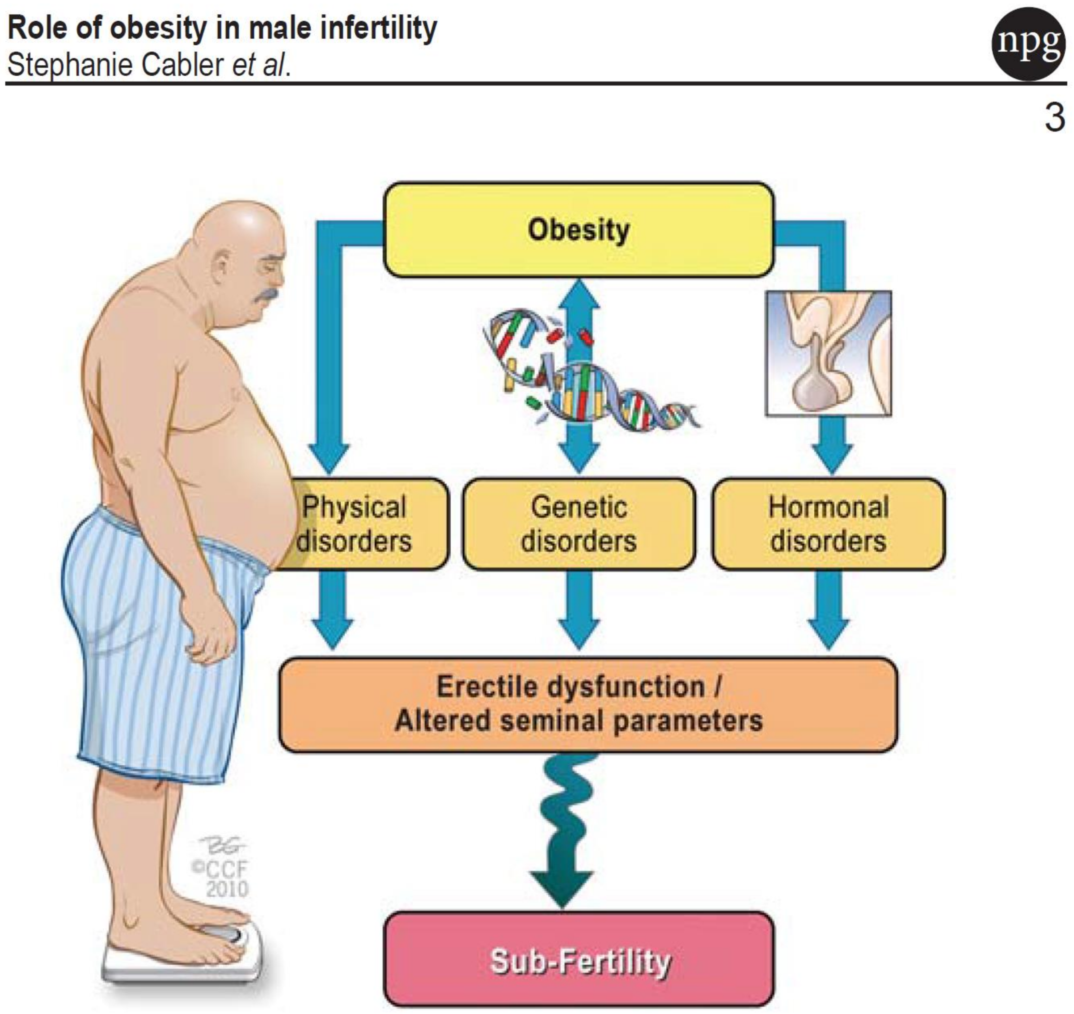
# DANO PÓS-TESTICULAR
## ação na função sexual

- ***Tratamento dos distúrbios urinários***
  - *Inibidores da 5 alfaredutase (finasterida, dutasterida)*
  - *Alfa-bloqueadores (tansulosina, alfuzosina, doxasozina)*

- ***Anti-hipertensivos***
  - *Antagonista beta-adrenérgico (propranolol, metoprolol, carvedilol)*
  - *Diuréticos tiazídicos (clortalidona)*

- ***Medicamentos psicoterápicos***
  - *Antipsicóticos, antidepressivos tricíclicos, inibidores da recaptação da serotonina, inibidores na MAO, fenotiazídicos, lítio*

# Peso




**Physical mechanims:**

- *endothelial dysfunction*
- *reduced testosterone levels*
- *hypogonadism and ED*

**Hormonal:**

*decreased Leydig cell T secretion*

**Testicular disruptions:**

- *increases sperm DNA damage,*
- *decreases sperm mitochondrial activity,*
- *induces seminal oxidative stress,*
- *impairs blastocyst development,*
- *reduces pregnancy outcome,*

*or increases miscarriage following ART*

Human Reproduction Update Advance Access published December 12, 2012
Human Reproduction Update, Vol.0, No.0 pp. 1–11, 2012
doi:10.1093/humupd/dms050
human reproduction update

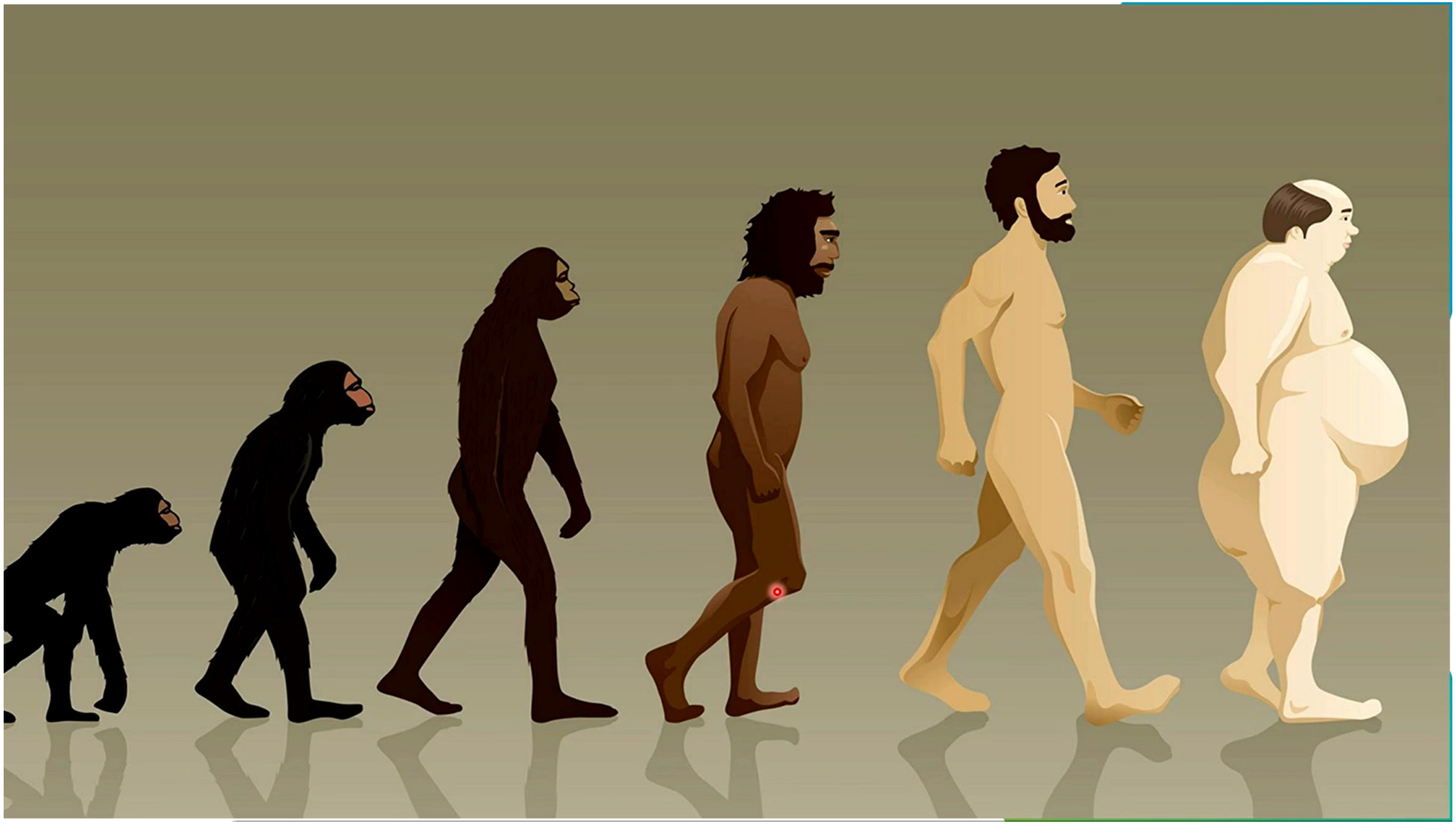
# BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis

N. Sermondade[1,2], C. Faure[1,2], L. Fezeu[2], A.G. Shayeb[3], J.P. Bonde[4], T.K. Jensen[5], M. Van Wely[6], J. Cao[7], A.C. Martini[8], M. Eskandar[9], J.E. Chavarro[10,11], S. Koloszar[12], J.M. Twigt[13], C.H. Ramlau-Hansen[14], E. Borges Jr[15], F. Lotti[16], R.P.M. Steegers-Theunissen[13], B. Zorn[17], A.J. Polotsky[18], S. La Vignera[19], B. Eskenazi[20], K. Tremellen[21], E.V. Magnusdottir[22], I. Fejes[23], S. Hercberg[2,24], R. Lévy[1,2†], and S. Czernichow[25,26,*†]

- 21 studies, meta-analysis: 13,077 men from the general population and attending fertility clinics
- Investigate the impact of BMI on sperm count

**Compared with normal weight men, the odds ratio for oligozoospermia or azoospermia :**

- Underweight: OR= 1,15 (0,93-1,43)
- Overweight: OR= 1,11 (1,01-1,21)
- Obese: OR= 1,28 (1,06-1,55)
- Morbidly obese: OR= 2,04 (1,59-2,62)



## 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.

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)."

Strongest form of autism!!

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

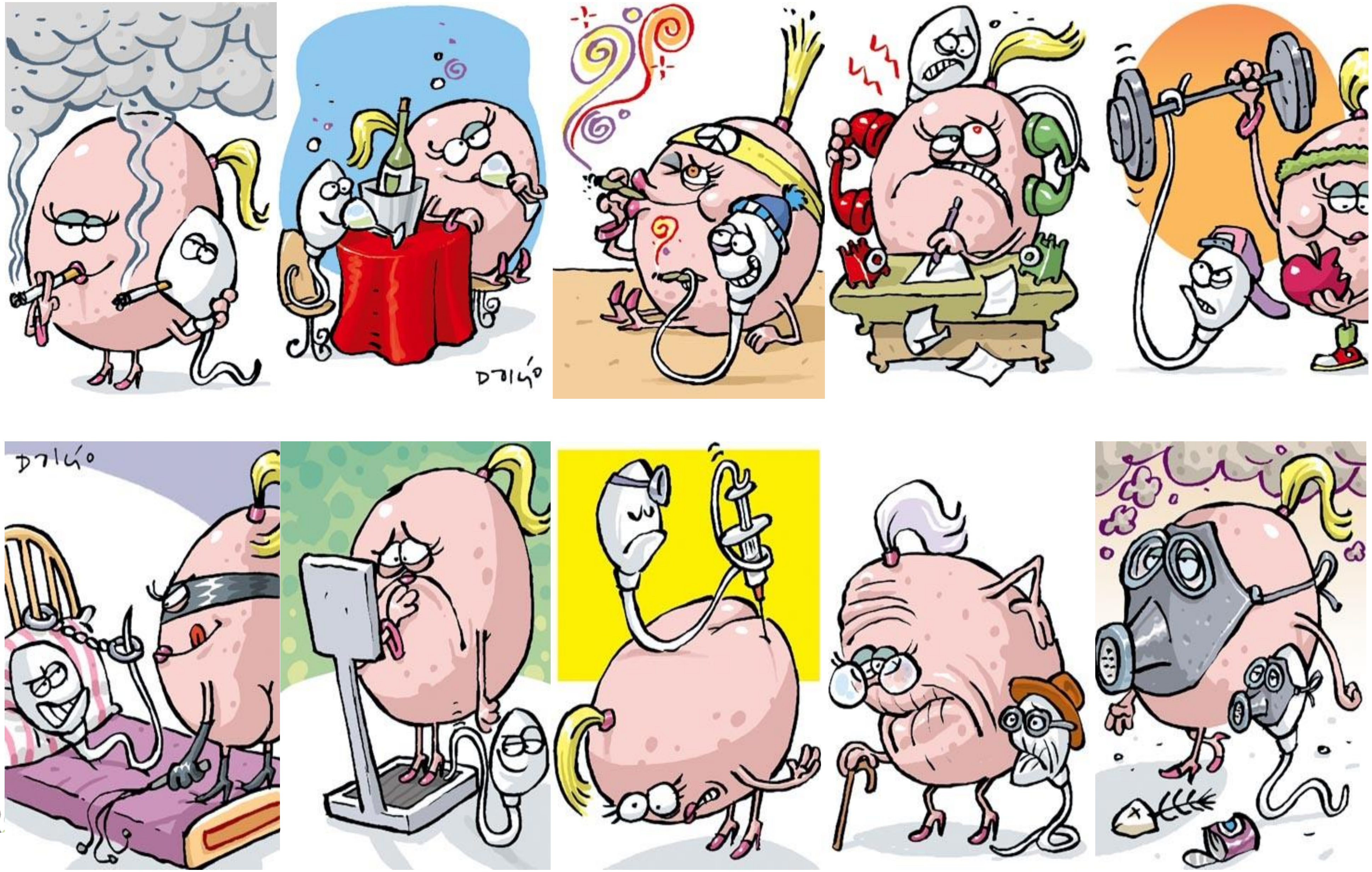
# Sperm DNA methylation epimutation biomarker for paternal offspring autism susceptibility

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 ou dos ancestrais no início da vida que alteram a epigenética da linhagem germinativa*

- *Componente molecular da etiologia do TEA.*

# Ten Commandments to preserve your fertility



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# Obrigado!


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