

## Dear EAA Members,

In the first 2024 issue, a short information for our new members. These monthly alerts highlight the latest noteworthy publications in all aspects of andrology. Original studies from established andrology centres (incl. EAA training Centres), and leading research groups in reproductive biology are prioritised. Preprints and review articles are usually not included, except ground-breaking news, good meta-analyses, or valuable guidelines for clinical education. You are welcome to share the alerts with your students, and if you have a good publication to promote – send a note to the EAA Secretary.

This edition contains a lot of excellent work for your attention! Check out the second edition of *Andrology*, which you can access as EAA members. Keywords for other publications: CatSper channel, sperm DNA fragmentation, hepatitis B virus, ejaculatory abstinence period, ART, Klinefelter syndrome and high-grade aneuploidies, phthalates, late-onset hypogonadism, gynaecomastia, declining semen quality, testicular ageing in non-human primates, gene-splicing in spermatogonia, androgen signalling and genome integrity, PATE factors in epididymis, sperm membranes lipids, peritubular macrophages, basoNuclin 1 and more. If you are interested in ART – scroll to the end to see a new edition of one of the best textbooks on this topic.

## Clinical andrology and epidemiology

The second issue of *Andrology* in 2024 has been released. It contains several very interesting articles (*a few previously highlighted in the EAA alerts*), including; a large study from China on premature ejaculation, meta-analysis on semen quality after oestrogen modulation, telomere length and sperm quality, testosterone levels in obese men and in sons of obese mothers, a summary of immature testis tissue cryopreservation efforts in France, sperm DNA methylation after chemotherapy, a new method to evaluate sperm metabolism, an internet tool for adolescents with varicocele, INSL3 in men with COVID-19, and more.

<https://onlinelibrary.wiley.com/toc/20472927/2024/12/2?campaign=woletoc>



Men with unexplained infertility should be tested for sperm channelopathy before choosing the ART method. The experts in Münster developed a new motility-based test and detected defective CatSper function (caused by variants in CATSPER) among normospermic men who failed IVF. CatSper-deficient sperm were unable to undergo hyperactive motility and to penetrate the egg.

Young S, Schiffer C, Wagner A, Patz J, Potapenko A, Herrmann L, Nordhoff V, Pock T, Krallmann C, Stallmeyer B, Röpke A, Kierzek M, Biagioni C, Wang T, Haalck L, Deuster D, Hansen JN, Wachten D, Risse B, Behre HM, Schlatt S, Kliesch S, Tüttelmann F, Brenker C, Strünker T. Human fertilization in vivo and in vitro requires the CatSper channel to initiate sperm hyperactivation. *J Clin Invest*. 2024 Jan 2;134(1):e173564.

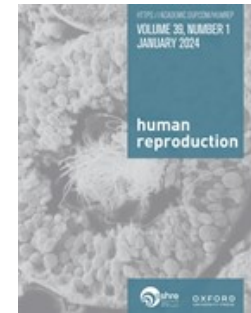
<https://doi.org/10.1172/JCI173564>



The EAA Centre in Florence examined sperm DNA fragmentation (SDF) in male patients with Hodgkin- and non-Hodgkin lymphoma. They followed some patients for 3 years and concluded that the currently advised 2 y. waiting time before attempting fatherhood may not be adequate for all men. SDF is a suggested biomarker to monitor the treatment-induced genotoxic effects on sperm DNA.

Farnetani G, Vannucci M, Fino MG, Cioppi F, Rosta V, Palma M, Tamburrino L, Vinci S, Casamonti E, Degl'Innocenti S, Spinelli M, Abrardo C, Marchiani S, Lotti F, Muratori M, Riera-Escamilla A, Krausz C. Severe sperm DNA fragmentation may persist for up to 3 years after cytotoxic therapy in patients affected by Hodgkin lymphoma and non-Hodgkin lymphoma. *Hum Reprod*. 2024 Jan 4:dead269. Epub ahead of print.

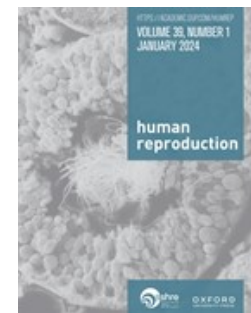
<https://doi.org/10.1093/humrep/dead269>



This large retrospective study examined the impact of hepatitis B virus (HBV) infection on sperm quality and assisted reproductive (ART) outcomes. HBV infection impaired sperm quality but the ART outcomes were not affected, except a lower rate of 2PN-fertilised oocytes. The authors suggest sperm washing before ART.

Meng X, Dai X, Huang J, Han T, Liao X, Cheng K, Sun X, Xie Q, Sun P, Zhou X. The influence of male HBV infection on sperm quality, embryonic development, and assisted reproductive outcomes. *Hum Reprod*. 2024 Jan 5;39(1):43-52.

<https://doi.org/10.1093/humrep/dead235>



The ejaculatory abstinence period strongly influences oocyte fertilization in terms of 2PN and 3PN zygote rates, suggesting its impact on sperm functionality. Interestingly, shorter ejaculatory abstinence periods were associated with a higher percentage of usable zygotes.

Cermisoni GC, Minetto S, Marzanati D, Alteri A, Salmeri N, Rabellotti E, Nova A, Salonia A, Pozzi E, Candiani M, Papaleo E, Pagliardini L. Effect of ejaculatory abstinence period on fertilization and clinical outcomes in ICSI cycles: a retrospective analysis. *Reprod Biomed Online*. 2024 Jan;48(1):103401.

<https://doi.org/10.1016/j.rbmo.2023.103401>



The EAA Centre in Rome examined comprehensively the endocrine and metabolic function in a large series of patients with high grade aneuploidies (HGA) and age-matched subjects with Klinefelter syndrome (KS), incl. variants with extra-Xs. They found a “dose-dependent” progressive impairment in steroid producing glands, thyroid function, cardiac structure, and performance.

Spaziani M, Carlomagno F, Tarantino C, Angelini F, Paparella R, Tarani L, Putotto C, Badagliacca R, Pozza C, Isidori AM, Gianfrilli D. From Klinefelter Syndrome to High Grade Aneuploidies: Expanding the Gene-dosage Effect of Supernumerary X Chromosomes. *J Clin Endocrinol Metab.* 2024 Jan 9:dgad730. Epub ahead of print.

<https://doi.org/10.1210/clinem/dgad730>

Exposure to phthalates may have antiandrogenic effects. This study of Korean children aged 10-12 y. suggests that phthalate exposure, especially exposure to the high molecular weight phthalates, was associated with lower T levels and later puberty.

Kim MR, Jung MK, Jee HM, Ha EK, Lee S, Han MY, Yoo EG. The association between phthalate exposure and pubertal development. *Eur J Pediatr.* 2024 Jan 11. Epub ahead of print.

<https://doi.org/10.1007/s00431-023-05416-z>

People are constantly exposed to phthalates (plasticizers), mainly via ingestion, inhalation or intravenous medication administration. This study showed that plateletpheresis results in high levels of phthalate exposure associated with a transient and reversible decrease in sperm motility.

von Ostau NE, Martynov A, Schreiber J. et al. Transient Decrease in Sperm Motility after Plateletpheresis. *Expo Health* (2024) – in press.

<https://doi.org/10.1007/s12403-023-00621-5>

Two *JCEM* articles concerning testosterone treatment in older hypogonadal men:

Within the Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) trials, the effects of TRT on sexual function were evaluated. In men with low libido, TRT for 2 years improved sexual activity, and sexual desire, but not erectile function.

Pencina KM, Travison TG, Cunningham GR, Lincoff AM, Nissen SE, Khera M, Miller MG, Flevaris P, Li X, Wannemuehler K, Bhasin S. Effect of Testosterone Replacement Therapy on Sexual Function and Hypogonadal Symptoms in Men with Hypogonadism. *J Clin Endocrinol Metab.* 2024 Jan 18;109(2):569-580.

<https://doi.org/10.1210/clinem/dgad484>

This controlled study did not show improvement of nonalcoholic fatty liver disease (NAFLD) in older hypogonadal men after 12 months of T vs placebo treatment, as assessed by 3 clinical scores and liver CT for hepatic steatosis.

Lee HS, Han SH, Swerdloff R, Pak Y, Budoff M, Wang C. The Effect of Testosterone Replacement Therapy on Nonalcoholic Fatty Liver Disease in Older Hypogonadal Men. *J Clin Endocrinol Metab.* 2024 Jan 18;109(2):e757-e764.

<https://doi.org/10.1210/clinem/dgad511>



This Danish register-based study showed that men diagnosed with gynaecomastia are at higher risk of death, observed mainly in males with a known pre-existing risk factor of gynaecomastia. Causes of death were malignant neoplasms and circulatory, pulmonary and gastrointestinal diseases, e.g. fivefold higher risk of death from liver disease.



Bräuner EV, Uldbjerg C, Lim YH, Beck A, Hueg T, Juul A. Is male gynaecomastia associated with an increased risk of death? A nationwide register-based cohort study. *BMJ Open*. 2024 Jan 16;14(2):e076608. <https://doi.org/10.1136/bmjopen-2023-076608>

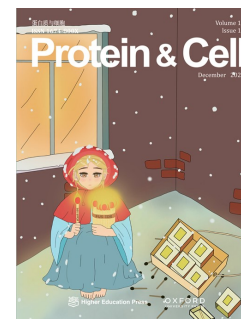
Among sperm donors in Seattle (WA, USA) there was a statistically significant decline in semen quality over time (2008-21) for sperm count, concentration, and progressive motility. Additionally, from 2006 to 2017 there was a significant decline in fertility rate in the same area. Declining sperm parameters likely contributed to the declining fertility rates.



Miller D, Weber A, Loloi J, Reddy R, Ramasamy R. Temporal Trends of Semen Quality and Fertility Rates Over the Course of a Decade: Data From King County, Washington. *Urology*. 2024 Jan;183:93-99. <https://doi.org/10.1016/j.urology.2023.07.042>

## Basic and translational andrology

A remarkable resource for researchers interested in aging of the testis! This study used single-cell transcriptomics of the non-human primate testis to prepare an atlas, with numerous mechanistic pathways resolved. Sertoli cell was identified as the cell type most susceptible to aging, and downregulation of the WT1 pathway as one of the key mechanisms.



Huang D, Zuo Y, Zhang C, Sun G, Jing Y, Lei J, Ma S, Sun S, Lu H, Cai Y, Zhang W, Gao F, Peng Xiang A, Belmonte JCI, Liu GH, Qu J, Wang S. A single-nucleus transcriptomic atlas of primate testicular aging reveals exhaustion of the spermatogonial stem cell reservoir and loss of Sertoli cell homeostasis. *Protein & Cell*. 2023 Dec 1;14(12):888-907. <https://doi.org/10.1093/procel/pwac057>

This interesting study revealed an interaction between the androgen signalling and genomic integrity via innate immune response activation, based on the proteome analysis in a series of DSD patients (incl. AIS) and men with idiopathic NOA. The authors proposed that AR expression induced DNA damage, innate immune response and increased gonadal tissue degeneration.



Zimmer J, Mueller L, Frank-Herrmann P, Rehnitz J, Dietrich JE, Bettendorf M, Strowitzki T, Krivega M. Low androgen signaling rescues genome integrity with innate immune response by reducing fertility in humans. *Cell Death Dis*. 2024 Jan 11;15(1):30. <https://doi.org/10.1038/s41419-023-06397-5>

Two good articles in eLife concerning biology of germ cells.

Sexual dimorphism in transcriptomic responsiveness to glucocorticoids was revealed in a mouse model. In the male but not female germline, dexamethasone treatment led to GR-mediated alternative splicing.



Cincotta SA, Richardson N, Foecke MH, Laird DJ. Differential susceptibility of male and female germ cells to glucocorticoid-mediated signaling. *ELife*. 2024 Jan 16;12:RP90164.



SRSF1 is essential for gene expression and splicing in mouse spermatogonial stem cells (SSC). SRSF1 interacts with RNA splicing-related proteins and *Srsf1* cKO mice display Sertoli-cell-only pattern.

Sun L, Lv Z, Chen *et al.* et Liu J. Splicing factor SRSF1 is essential for homing of precursor spermatogonial stem cells in mice. *ELife*. 2024 Jan 25;12:RP89316.

<https://doi.org/10.7554/eLife.89316.4>

Sperm proteins undergo post-translational modifications during sperm transit through the epididymis. This study explored this using several KO mice, and showed that multiple *Pate* genes are enriched in caput epididymis and function to ensure male fertility in mice.

Noda T, Shinohara H, Kobayashi S, Taira A, Oura S, Duritahala, Tokuyasu M, Araki K, Ikawa M. Multiple genes in the Pate5-13 genomic region contribute to ADAM3 processing. *Biol Reprod*. 2024 Jan 13:ioae008.

<https://doi.org/10.1093/biolre/ioae008>

This study performed a lipidomic analysis of human sperm membranes and found differences between fertile and infertile men, and identified a lipid cluster that was associated with semen parameters.



International Journal of  
*Molecular Sciences*

Di Nisio A, De Toni L, Sabovic I, Vignoli A, Tenori L, Dall'Acqua S, Sut S, La Vignera S, Condorelli RA, Giacone F, Ferlin A, Foresta C, Garolla A. Lipidomic Profile of Human Sperm Membrane Identifies a Clustering of Lipids Associated with Semen Quality and Function. *Int J Mol Sci*. 2023 Dec 25;25(1):297.

<https://doi.org/10.3390/ijms25010297>

Peritubular macrophages (PTM $\phi$ ) aggregate near the spermatogonial stem cell niche, and they rapidly increase in numbers after phthalate (MEHP) exposure in peripubertal but not adult rats, revealing age differences in sensitivity.

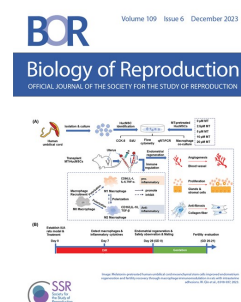
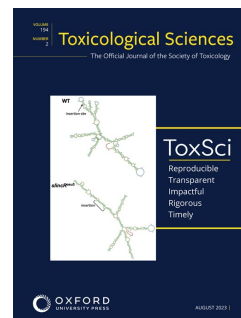
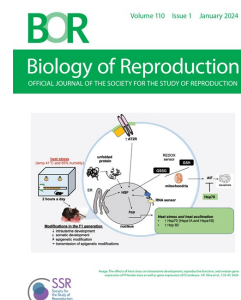
Fang X, Tiwary R, Nguyen VP, Richburg JH. Responses of Peritubular Macrophages and the Testis Transcriptome Profiles of Peripubertal and Adult Rodents Exposed to an Acute Dose of MEHP. *Toxicol Sci*. 2023 Dec 19:kfad128.

<https://doi.org/10.1093/toxsci/kfad128>

Basonuclin 1 (BNC1) is a zinc finger transcription factor expressed in proliferative epithelia and germ cells, and a mutation was found in a cluster of females with premature ovarian insufficiency. This study examined the (patho)physiology of BNC1 in male mice.

Ni F, Wang F, *et al.* et Zhang D. BNC1 deficiency induces mitochondrial dysfunction-triggered spermatogonia apoptosis through the CREB/SIRT1/FOXO3 pathway: the therapeutic potential of nicotinamide riboside and metformin. *Biol Reprod*. 2023 Dec 11:ioad168.

<https://doi.org/10.1093/biolre/iodad168>



# Textbook of Assisted Reproductive Techniques, 6<sup>th</sup> Ed.

**Volume 1: Laboratory Perspectives**

**Volume 2: Clinical Perspectives**

**Editors: D.K. Gardner, A. Weissman, C.M. Howles, Z. Shoham**

The revised 6<sup>th</sup> edition of one of the reference books for fertility clinics using ART, especially IVF. New topics: digitalization, quality control in the cloud, AI in gamete and embryo selection, microfluidics, gene editing, precision medicine in the IVF clinic, the use of GnRH agonists and the efficiency of IVF, immunology in ART, POSEIDON stratification of 'low prognosis' patients in ART, fertility options for transgender and nonbinary individuals, and more.

75 chapters

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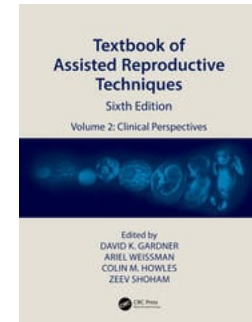
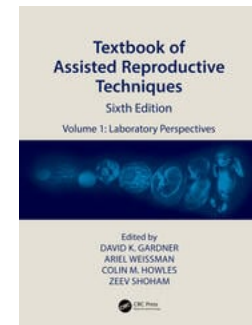
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