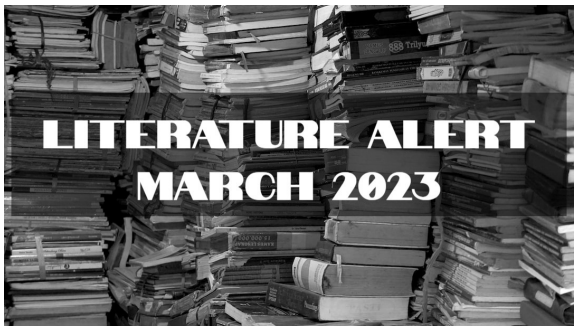
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EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

Enjoy the latest publications of interest for clinical and basic andrologists. Keywords in this edition: sperm DNA fragmentation, testicular cancer, AMH, intratesticular testosterone, penile length, vit. D, HPV infection, testis in COVID-19, hypogonadotropic hypogonadism, *PNLDC1*, *PRUNE2*, DND1, eggs from male cells, paternal alcohol and ART, sperm preparation and ART, androgens and T-cell immuno-protection, sperm tail proteomics, exposures to endocrine disrupters (NSAIDs, phthalates, BPA).

Clinical andrology and epidemiology



Patients with testicular germ cell tumours (TGCT) are currently advised to wait two years post-chemotherapy before seeking natural pregnancy. This study assessed the time needed for the recovery of sperm DNA fragmentation (SDF) and found that 2 y. may not be sufficient for all patients. The analysis of SDF may represent a useful biomarker for pre-conception counselling in cancer survivors.

Farnetani G, Fino MG, Cioppi F, Riera-Escamilla A, Tamburrino L, Vannucci M, Rosta V, Vinci S, Casamonti E, Turki L, Degl'Innocenti S, Spinelli M, Marchiani S, Lotti F, Muratori M, Krausz C. Long-term effect of cytotoxic treatments on sperm DNA fragmentation in patients affected by testicular germ cell tumor. ***Andrology***. 2023 Mar 17. PMID: 36932666.

https://doi.org/10.1111/andr.13429

BMC Medicine

A randomized placebo-controlled clinical trial of infertile men treated with cholecalciferol (+/- calcium) for 150 days, with serum AMH as the main outcome. Low AMH was associated with poor semen quality and lower T/LH ratio, and was not influenced by vit. D supplementation.

Holt R, Yahyavi SK, Kooij I, Andreassen CH, Andersson AM, Juul A, Jørgensen N, Blomberg Jensen M. Low Serum anti-Mullerian Hormone is Associated with Semen Quality in Infertile Men and not Influenced by Vitamin D Supplementation. ***BMC Medicine*** 2023 Feb 28;21(1):79. PMID: 36855109.
https://doi.org/10.1186/s12916-023-02782-1



A follow-up study of 827 young men from the Fetal Programming of Semen Quality (FEPOS) cohort, nested in the Danish National Birth Cohort, found that low maternal vit. D levels were associated with lower testes volume and lower total sperm count in the sons. Vit. D level >75 nmol/L during pregnancy may be beneficial for testis function in adult sons.

Gaml-Sørensen A, Brix N, Hærvig KK, Lindh C, Tøttenborg SS, Hougaard KS, Høyer BB, Ernst A, Arendt LH, Clemmensen PJ, Bonde JPE, Henriksen TB, Toft G, Arah OA, Ramlau-Hansen CH. Maternal vitamin D levels and male reproductive health: a population-based follow-up study. ***Eur J Epidemiol***. 2023 Mar 23. PMID: 36952117.

https://doi.org/10.1007/s10654-023-00987-5

The World Journal of MEN's HEALTH

A study looked at changes in serum 17-hydroxyprogesterone (17-OHP), a surrogate for intratesticular testosterone (ITT) after different

modalities of T replacement therapy (TRT) in 75 hypogonadal men. Short-acting nasal T and other short-acting T formulations may better preserve ITT in men seeking to maintain fertility while on TRT.

Diaz P, Reddy R, Blachman-Braun R, Zucker I, Dullea A, Gonzalez DC, Kresch E, Ramasamy R. Comparison of Intratesticular Testosterone between Men Receiving Nasal, Intramuscular, and Subcutaneous Pellet Testosterone Therapy: Evaluation of Data from Two Single-Center Randomized Clinical Trials. ***World J Mens Health***. 2022 Apr 22. PMID: 35791295. https://doi.org/10.5534/wjmh.210261

biomedicines

The prognostic value of 4 sperm selection techniques before ICSI was compared in 385 infertile couples with the male partner exhibiting teratozoospermia: density gradient centrifugation (DGC), swim-up (SU), DGC-SU and DGC followed by magnetic-activated cell sorting (DGC-MACS). The study confirmed that DGC-MACS gave best outcomes: embryo cleavage, clinical pregnancy and implantation.

Bibi R, Jahan S, Afsar T, Almajwal A, Hammadeh ME, Amor H, Abusharha A, Razak S. Analyzing the Differential Impact of Semen Preparation Methods on the Outcomes of Assisted Reproductive Techniques. ***Biomedicines***. 2023 Feb 6;11(2):467. PMID: 3683100 https://doi.org/10.3390/biomedicines11020467



This retrospective case-control study found that prevalence of human papilloma virus (HPV) infection of sperm (established by PCR) was approx. 1/5 patients and was associated with a significantly higher risk of recurrent pregnancy loss (RPL) in affected couples.

Busnelli A, Garolla A, Tersigni C, Parodi V, Inversetti A, Levi-Setti PE, Scambia G, Di Simone N. Sperm human papillomavirus infection and risk of idiopathic recurrent pregnancy loss: insights from a multicenter case-control study. ***Fertil Steril***. 2023 Mar;119(3):410-418.

https://doi.org/10.1016/j.fertnstert.2022.12.002



A cohort study addressing the desire for children was conducted as part of the Dutch Childhood Cancer Survivor Study LATER. The percentage of men who had an unfulfilled desire for children remained significantly higher among cancer survivors compared with their siblings.

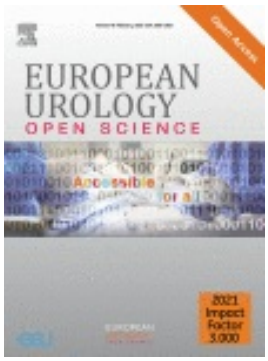
Claessens JJM, Penson A, Bronkhorst EM, Kremer LCM, van Dulmen-den Broeder E, van der Heiden-van der Loo M, Tissing WJE, van der Pal HJH, Blijlevens NMA, van den Heuvel-Eibrink MM, Versluys AB, Bresters D, Ronckers CM, Walraven I, Beerendonk CCM, Loonen JJ; Dutch LATER Study Group. Desire for children among male survivors of childhood cancer: A DCCSS LATER study. ***Cancer***. 2023 Mar 7. PMID: 36881488.

https://doi.org/10.1002/cncr.34685

The World Journal of MEN's HEALTH

This meta-analysis found that the average erect (but not flaccid) penis length has increased by 24% over the past three decades across the world. The authors suggested investigation of potential causes.

Belladelli F, Del Giudice F, Glover F, Mulloy E, Muncey W, Basran S, Fallara G, Pozzi E, Montorsi F, Salonia A, Eisenberg ML. Worldwide Temporal Trends in Penile Length: A Systematic Review and Meta-Analysis. ***World J Mens Health***. 2023 Feb 15. PMID: 36792094. https://doi.org/10.5534/wjmh.220203



This register-based study from Austria found an increase in the incidence rate of testicular germ cell tumours (TGCTs) from 4.1 in 1983 to 8.7 per 100 000 in 2018, with a steep rise in the period 1983-97, and stable high levels thereafter. The overall incidence was highest in men aged 30–40 yr.

Brönimann S, Mun DH, Hackl M, Yang L, Shariat SF, Waldhoer T. Increase and Plateauing of Testicular Cancer Incidence in Austria-A Time Trend Analysis of the Past Four Decades. ***Eur Urol Open Sci***. 2023 Feb 6;49:104-109. PMID: 36874603. https://doi.org/10.1016/j.euros.2023.01.005

COVID-19



SARS-CoV-2 infection of testicular cells was detected in 9/24 (37%) of lethal COVID-19 cases. The infection was associated with activation of interferon pathways and downregulation of testis-specific genes involved in spermatogenesis.

Basolo A, Poma AM, Macerola E, Bonuccelli D, Proietti A, Salvetti A, Vignali P, Torregrossa L, Evangelisti L, Sparavelli R, Giannini R, Ugolini C, Basolo F, Santini F, Toniolo A. Autopsy Study of Testicles in COVID-19: Upregulation of Immune-Related Genes and Downregulation of Testis-Specific Genes. ***J Clin Endocrinol Metab***. 2023 Mar 10;108(4):950-961.

https://doi.org/10.1210/clinem/dgac608

Androgenetics



The correlation between genotypic severity with pubertal and neuroendocrine phenotypes was examined in 242 adult men with isolated hypogonadotropic hypogonadism (IHH). The most severe reproductive phenotypes were found in patients with protein-truncating ANOS1 mutations. Partial puberty and LH greater >2.10 IU/L were predictors of pulsatile LH secretion.

Dwyer AA, Stamou MI, Anghel E, Hornstein S, Chen D, Salnikov KB, McDonald IR, Plummer L, Seminara SB, Balasubramanian R. Reproductive Phenotypes and Genotypes in Men With IHH. ***J Clin Endocrinol Metab***. 2023 Mar 10;108(4):897-908. PMID: 36268624.

https://doi.org/10.1210/clinem/dgac615



PRUNE2, a target protein-coding gene variant, harbours the PCA3 locus, which is an antisense intronic long noncoding (lnc)RNA. This paper reports pathogenic germline variants in *PRUNE2* in patients with early-onset or familial prostate cancer, representing a novel prostate cancer predisposition gene.

Cardoso M, Maia S, Brandão A, Sahasrabudhe R, Lott P, Belter N, Carvajal-Carmona LG, Paulo P, Teixeira MR. Exome sequencing of affected duos and trios uncovers *PRUNE2* as a novel prostate cancer predisposition gene. ***Br J Cancer*** 128, 1077–1085 (2023), PMID: 36564567

https://doi.org/10.1038/s41416-022-02125-6



This study identified a Chinese patient with OAT caused by a homozygous nonsense variant (c.142C>T, p.Gln48Ter) of *PNLDC1* as determined by WES. The patient presented with spermatocyte apoptosis, abnormal morphology of the sperm head, and an increased disomy rate of chromosomes.

Zhao SY, Meng LL, Du ZL, Tan YQ, He WB, Wang X. A novel loss-of-function variant in *PNLDC1* inducing oligo-astheno-teratozoospermia and male infertility. ***Asian J Androl***. 2023 Mar 21. PMID: 36960498.

https://doi.org/10.4103/aja20233

Translational and basic andrology



Japanese researchers made functional eggs from mouse male cells! They induced male pluripotent cells, selected the cells that lost the Y- and duplicated the X-chromosome, and manipulated them to develop as oocytes to fertilise with mature sperm. The survival rate of embryos was low (7/630), but those that developed were normal and fertile. This experiment is a proof-of-concept with potentially important applications, including treating infertility but any medical application in humans is a long way ahead.

Murakami K, Hamazaki N, Hamada N, Nagamatsu G, Okamoto I, Ohta H, Nosaka Y, Ishikura Y, Kitajima TS, Semba Y, Kunisaki Y, Arai F, Akashi K, Saitou M, Kato K, Hayashi K. Generation of functional oocytes from male mice in vitro. ***Nature***. 2023 Mar 15. Epub ahead of print. PMID: 36922585.

https://doi.org/10.1038/s41586-023-05834-x

Comment: Ledford H, Kozlov M. The mice with two dads: scientists create eggs from male cells. ***Nature.*** 2023 Mar;615(7952):379-380. https://doi.org/10.1038/d41586-023-00717-7



This previously announced preprint has now been published after peer-review. The study provided a single-cell transcriptomic atlas of early mouse adreno-gonadal development including 52 cell types. Surprisingly, gonadal and adrenal fates showed distinct molecular signatures upon *Nr5a1* induction indicating the two tissues are specified independently.

Neirijnck Y, Sararols P, Kühne F, Mayère C, Weerasinghe Arachchige LC, Regard V, Nef S, Schedl A. Single-cell transcriptomic profiling redefines the origin and specification of early adrenogonadal progenitors. ***Cell Rep***. 2023 Feb 28;42(3):112191. PMID: 36862551.

https://doi.org/10.1016/j.celrep.2023.112191



Dnd1 is a RNA-binding protein, essential for germ cells identity. Using a mouse line carrying a GFP-tag on endogenous *Dnd1* ($DND1^{GFP}$), this study discovered distinct populations of male germ cells (GCs) expressing high and low levels of DND1 during late gestation. GCs expressing high levels of DND1 are more likely to express transcripts for genes associated with the transition to pro-spermatogonial fate.

Ruthig VA, Hatkevich T, Hardy J, Friedersdorf MB, Mayère C, Nef S, Keene JD, Capel B. The RNA binding protein DND1 is elevated in a subpopulation of pro-spermatogonia and targets chromatin modifiers and translational machinery during late gestation. ***PLoS Genet***. 2023 Mar 1;19(3):e1010656. PMID: 36857387.

https://doi.org/10.1371/journal.pgen.1010656



This study revealed a novel mechanism contributing to sex differences in cancer. Androgen signalling suppressed T-cell immunity against cancer in male mice via AR-mediated over-expression of USP18, which activated NF-κB in antitumor T cells. Reduction of testosterone synthesis enhanced the antitumor activity of T cells in male mice and improved the efficacy of anti–PD-1 immunotherapy.

Zhang X, Cheng L, Gao C, *et al et*, Zhou P. Androgen Signaling Contributes to Sex Differences in Cancer by Inhibiting NF-κB Activation in T Cells and Suppressing Antitumor Immunity. ***Cancer Res***. 2023 Mar 15;83(6):906-921.

10.1158/0008-5472.CAN-22-2405



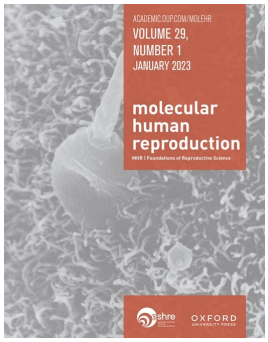
This study quantified the proteomic profile of sperm tails in asthenozoospermic men and controls using TMT-LC–MS/MS. Overall, >400 differentially expressed proteins were identified, and the main pathways were mitochondrial-related energy production, oxidative phosphorylation (OXPHOS), citric acid cycle (CAC) and stress response.

Mirshahvaladi S, Topraggaleh TR, Bucak MN, Rahimizadeh P, Shahverdi A. Quantitative proteomics of sperm tail in asthenozoospermic patients: exploring the molecular pathways affecting sperm motility. ***Cell Tissue Res***. 2023 Feb 27. Epub ahead of print.

https://doi.org/10.1007/s00441-023-03744-y

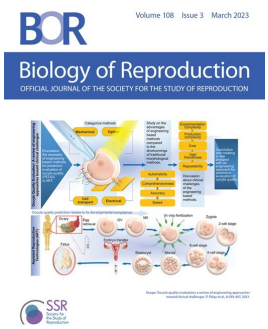
It was found in a mouse model that preconception paternal alcohol abuse reduced IVF embryo survival and pregnancy success rates in a dose-dependent manner. Paternal alcohol exposure disrupted embryonic expression of regulators of trophectoderm stem cell growth and placental patterning.

Roach AN, Zimmel KN, Thomas KN, Basel A, Bhadsavle SS, Golding MC. Preconception paternal alcohol exposure decreases IVF embryo survival and pregnancy success rates in a mouse model. ***Mol Hum Reprod***. 2023 Jan



31;29(2):gaad002. PMID: 36637195.

https://doi.org/10.1093/molehr/gaad002



The authors compared the effects of known endocrine disrupting chemicals (DEHP, BDE47, BPA) with those of their replacements using fetal rat testis organ culture. The studies show that some replacement chemicals can affect testicular function, while others appear to show little toxicity in this model.

Tardif S, Rwigemera A, Letourneau N, Robaire B, Delbes G. Reproductive toxicity of emerging plasticizers, flame-retardants and bisphenols, using culture of the rat fetal testis. ***Biol Reprod***. 2023 Feb 13:ioad018. PMID: 36780129.

https://doi.org/10.1093/biolre/ioad018

International Journal of *Molecular Sciences*

Non-steroidal anti-inflammatory drugs (NSAIDs) and 17α-ethinyl-estradiol (EE2) are endocrine-disrupting pharmaceuticals. This study found that exposure to mixtures of ibuprofens, diclofenac and EE2, delayed male puberty and accelerated female puberty. In post-pubertal testes and ovaries, maturation of the different gonad cell types was altered, and some of these modifications persisted to F2 generation.

Philibert P, Déjardin S, Girard M, Durix Q, Gonzalez A-A, Mialhe X, Tardat M, Poulat F, Boizet-Bonhoure B. Cocktails of NSAIDs and 17α Ethinylestradiol at Environmentally Relevant Doses in Drinking Water Alter Puberty Onset in Mice Intergenerationally. ***Int. J. Mol. Sci***. 2023, 24(6), 5890.
https://doi.org/10.3390/ijms24065890

Methodology



A more efficient sperm DNA fragmentation method would be valuable in andrology laboratories. This study examined 620 semen samples, comparing a conventional Halosperm® G2 assay (G2) with a novel LensHooke® R10 assay combined with X12 PRO analysis. The latter analysis system is faster, more objective, and provides standardization for sperm DNA fragmentation.

Hsu CT, Lee CI, Huang CC, Wang TE, Chang HC, Chang LS, Lee MS. Development and integration of LensHooke® R10 for automatic and standardized diagnosis for sperm DNA fragmentation. ***Andrology***. 2023 Mar 3. PMID: 36869577.

https://doi.org/10.1111/andr.13419

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