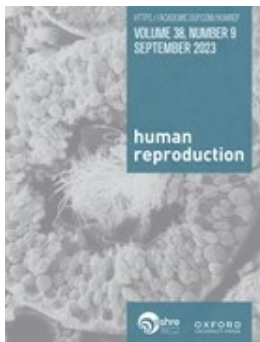


Dear EAA Members,

The November selection of noteworthy articles published recently in the field of andrology. There is something of interest for everyone, including fertility preservation, Klinefelter syndrome, ICSI in men with flagellar defects, infertility and general health, health of transgender persons, testicular cancer, testosterone in COVID-19, environment and sperm counts, APHRODITE criteria, novel gene variants in male infertility, and exciting basic science articles on sex determination, PIWI proteins, and on sperm biology, including a unique ion exchanger.

## Clinical andrology and epidemiology



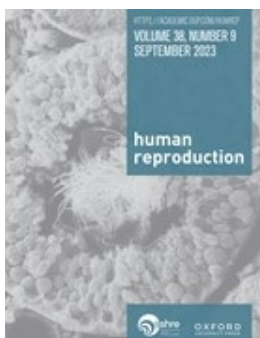
Cryopreserved testicular tissue samples from 79 (pre)pubertal boys with cancer were examined histologically to elucidate the effects of the primary diagnosis and/or chemotherapy on the numbers of spermatogonia. The study confirmed a negative effect of the alkylating agents, and showed a cumulative deleterious effect of vincristine in combination with alkylating agents.

Feraille A, Liard A, Rives N, Bubenheim M, Barbotin AL, Giscard d'Estaing S, Mirallié S, Ancelle A, Roux C, Brugnon F, Daudin M, Schneider P, Dumont L, Rondonino C. Impact of low- or moderate-risk gonadotoxic chemotherapy prior to testicular tissue freezing on spermatogonia quantity in human (pre)pubertal testicular tissue. *Hum Reprod.* 2023 Sep 7:dead161; 38(Nov):2105-18. <https://doi.org/10.1093/humrep/dead161>



Men with Klinefelter syndrome (KS) have an increased risk of thrombosis, especially if overweight. Testosterone-replacement therapy in KS has potential for alleviating the prothrombotic phenotype, in particular by reducing body fat and fibrinogen.

Chang S, Just J, Skakkebaek A, Johannsen EB, Fedder J, Gravholt CH, Münster AB. Testosterone replacement therapy in Klinefelter syndrome - follow-up study associating hemostasis and RNA expression. *J Clin Endocrinol Metab.* 2023 Nov 14:dgad658. Epub ahead of print. <https://doi.org/10.1210/clinem/dgad658>



In men with Klinefelter syndrome (KS), a distinct gene expression pattern within microvascular-associated cells suggests excessive endothelial cell activation, and disorganized vessel formation, with the presence of immature vessels, and pro-inflammatory responses.

Johannsen EB, Skakkebaek A, Kalucka JM, Fedder J, Gravholt CH, Just J. The testicular microvasculature in Klinefelter syndrome is immature with compromised integrity and characterized by excessive inflammatory cross-talk. *Hum Reprod.* 2023 Oct 31:dead224. Epub ahead of print. <https://doi.org/10.1093/humrep/dead224>

Ultrastructural flagellar defects are a rare cause of male infertility, often associated with an underlying genetic cause. Data from France on the chances of success in ICSI of these patients are reassuring:



cumulative pregnancy rates ranged from 29.0 to 43.3%, and cumulative live birth rates were 24.6-36.7%.

Boursier A, Boudry A, Mitchell V, Loyens A, Rives N, Moerman A, Thomas L, Escudier E, Toure A, Whitfield M, Coutton C, Martinez G, Ray PF, Kherraf ZE, Viville S, Legendre M, Smol T, Robin G, Barbotin AL. Results and perinatal outcomes from 189 ICSI cycles of couples with asthenozoospermic men and flagellar defects assessed by transmission electron microscopy. *Reprod Biomed Online (RBMO)*. 2023 Nov;47(5):103328.

<https://doi.org/10.1016/j.rbmo.2023.103328>



This register-based cohort study in Danish transgender persons (N>3800) revealed increased odds ratio for mental health disorders in transgenders compared to controls, which remained elevated throughout follow up, especially in persons assigned male at birth (AMAB).

Glintborg D, Møller JK, Rubin KH, Lidgaard Ø, T'Sjoen G, Larsen Mjø, Hilden M, Andersen MS. Gender-affirming treatment and mental health diagnoses in Danish transgender persons: a nationwide register-based cohort study. *Eur J Endocrinol*. 2023 Sep 1;189(3):336-345.

<https://doi.org/10.1093/ejendo/lvad119>



This survey-based retrospective study of 222 respondents, reported that men with anxiety had lower final total motile sperm counts during IVF compared to men without anxiety; however, there were no differences in live birth rates.

Walker Z, Hernandez J, Lanes A, Srouji SS, Ginsburg E, Kathrins M. The effects of male anxiety and depression on IVF outcomes. *Hum Reprod*. 2023 Sep 10;dead179, 38 (11): 2119-27.

<https://doi.org/10.1093/humrep/dead179>



High maternal pre-pregnancy BMI (overweight or obesity) was associated in this study with an altered reproductive hormone profile in young adult sons - higher levels of oestradiol, LH, and free androgen index (FAI) and lower levels of SHBG.

Gaml-Sørensen A, Thomsen AH, Tøttenborg SS, Brix N, Hougaard KS, Toft G, Håberg SE, Myrskylä M, Bonde JP, Ramlau-Hansen CH. Maternal pre-pregnancy BMI and reproductive health in adult sons: a study in the Danish National Birth Cohort. *Hum Reprod*. 2023 Nov 3;dead230.

<https://doi.org/10.1093/humrep/dead230>



A new meta-analysis of 20 studies (N=1,774 men) adds to the growing evidence of the negative impact of insecticides on sperm concentration. Despite moderate data quality, the evidence warrants reducing exposure to some insecticides to prevent continued reproductive harm.

Ellis LB, Molina K, Robbins CR, Freisthler M, Sgargi D, Mandrioli D, Perry MJ. Adult Organophosphate and Carbamate Insecticide Exposure and Sperm Concentration: A Systematic Review and Meta-Analysis of the Epidemiological Evidence. *Environ Health Perspect*. 2023 Nov;131(11):116001. 2023 Nov 15.

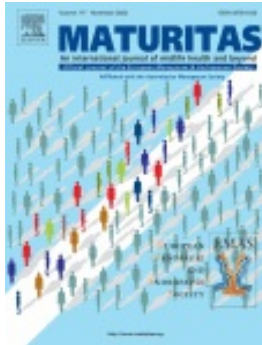
<https://doi.org/10.1289/EHP12678>

Studies of mobile phones and semen quality keep coming back. This population-based study suggests that higher mobile phone use is associated with lower sperm counts but not with other sperm parameters. To solve the controversy, prospective studies with better exposure assessment are needed.

Rahban R, Senn A, Nef S, Rössli M. Association between self-reported mobile phone use and the semen quality of young men. *Fertil Steril*. 2023 Dec;120(6):1181-1192. Epub 2023 Nov 1. <https://doi.org/10.1016/j.fertnstert.2023.09.009>



View of 2023/2023



For the latest recommendations on the testosterone replacement therapy (TRT) in older men – see the 2023 update of the 2015 EMAS statement that was prepared to account for the new research on late-onset hypogonadism.

Kanakis GA, Pofi R, Goulis DG, Isidori AM, Armeni E, Erel CT, Fistonich I, Hillard T, Hirschberg AL, Meczekalski B, Mendoza N, Mueck AO, Simoncini T, Stute P, van Dijken D, Rees M, Lambrinoudaki I. EMAS position statement: Testosterone replacement therapy in older men. *Maturitas*. 2023 Dec;178:107854. <https://doi.org/10.1016/j.maturitas.2023.107854>

## Debate



The APHRODITE classification proposes a novel stratification system for infertile patients with various forms of testicular dysfunction, for whom fertility may improve after hormonal therapy. The criteria would facilitate communication among clinicians, researchers and patients. The authors (including several EAA Academicians) propose the criteria as a basis for future trials of hormonal treatment of male infertility.

Esteves SC, Humaidan P, Ubaldi FM, Alviggi C, Antonio L, Barratt CLR, Behre HM, Jørgensen N, Pacey A, Simoni M, Santi D. APHRODITE criteria: Addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function, *Reprod BioMedicine Online (RBMO)* 2023, in press. <https://doi.org/10.1016/j.rbmo.2023.103647>

## COVID-19

ANDROLOGY



To investigate the independent role of SARS-CoV-2 infection in reducing circulating total testosterone (tT) levels in men, this retrospective study compared patients with different types of severe respiratory illness and found lower tT levels in men with COVID-19 compared to those without.

Capogrosso P, Bertini A, Pontillo M, Ferrara AM, Cotelessa A, Carezzi C, Ramirez GA, Tresoldi C, Locatelli M, Castagna A, De Cobelli F, Tresoldi M, Zangrillo A, Landoni G, Rovere-Querini P, Ciceri F, Montorsi F, Monti G, Salonia A. Is SARS-CoV-2-induced disease a decisive factor influencing testosterone in males? Findings from a case-control ex post facto study. *Andrology*. 2023 Nov 20. Epub ahead of print. <https://doi.org/10.1111/andr.13558>

## Androgenetics

A significant improvement in the assessment of genetic risk scores (GRSs) for prostate cancer. This large multi-ancestry GWAS of thousands of patients and controls identified 187 novel risk variants for prostate cancer, allowing effective risk stratification across ancestry groups.

Wang A, Shen J, Rodriguez AA, et al et Conti DV, Haiman CA. Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants. *Nat Genet*. 2023 Nov 9. Epub ahead of print. <https://doi.org/10.1038/s41588-023-01534-4>



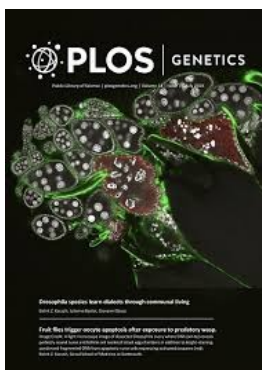
Whole-exome sequencing was performed to identify genetic changes potentially causative of teratozoospermia. *AGTPBP1* missense changes were identified in two patients with severe sperm head and tail defects. Further work characterised the role of *AGTPBP1* in deglutamation, which is crucial for sperm formation.

Lin YH, Wang YY, Lai TH, Teng JL, Lin CW, Ke CC, Yu IS, Lee HL, Chan CC, Tung CH, Conrad DF, O'Bryan MK, Lin YH. Deleterious genetic changes in *AGTPBP1* result in teratozoospermia with sperm head and flagella defects. *J Cell Mol Med.* 2023 Nov 8. <https://onlinelibrary.wiley.com/doi/10.1111/jcmm.18031>



A new homozygous variant in *PNLDC1* was identified in a patient (Han Chinese) with OAT. The spermatozoa had an increased disomy rate, abnormal morphology (microcephaly, head tapering or globozoospermia) and partially or completely lacked the acrosome.

Zhao SY, Meng LL, Du ZL, Tan YQ, He WB, Wang X. A novel loss-of-function variant in *PNLDC1* inducing oligo-asthenoteratozoospermia and male infertility. *Asian J Androl.* 2023 Sep-Oct; 25(5): 643-645. <https://doi.org/10.4103/aja20233>



PIWI proteins and their associated piRNAs act to silence transposons and promote gametogenesis. This study looked for the effects of conserved RG motifs and found that a conserved RG motif in MIWI is indispensable for piRNA biogenesis and male fertility.

Wei C, Jing J, Yan X, Mann JM, Geng R, Xie H, Demireva EY, Hess RA, Ding D, Chen C. MIWI N-terminal RG motif promotes efficient pachytene piRNA production and spermatogenesis independent of LINE1 transposon silencing. *PLoS Genet.* 2023 Nov 13;19(11):e1011031. Epub ahead of print. <https://doi.org/10.1371/journal.pgen.1011031>



*PICK1* is involved in the transport of preacrosomal vesicles in germ cells.

This study identified infertile men with *PICK1* deletions and found in studies in vitro that the vesicle-related secretory function of Sertoli cells was impaired.

Jin, J., Li, K., Du, Y. et al. Multi-omics study identifies that *PICK1* deficiency causes male infertility by inhibiting vesicle trafficking in Sertoli cells. *Reprod Biol Endocrinol* 21, 114 (2023). <https://doi.org/10.1186/s12958-023-01163-w>

*ACTL7B* is a highly conserved testis-specific actin-related protein, expressed in spermatids. This study found that male *Actl7b*<sup>-/-</sup> mice were infertile and had severe spermatid defects. Mechanistic work identified an interaction between *ACTL7B* and the LC8 dynein light chains, suggesting exploring this pathway in infertile men.

Merges GE, Arévalo L, Kovacevic A, Lohanadan K, de Rooij DG, Simon C, Jokwitz M, Witke W, Schorle H. *Actl7b* deficiency leads to mislocalization of LC8 type dynein light

## Development



chains and disruption of murine spermatogenesis. *Development*. 2023 Nov 1;150(21):dev201593. <https://doi.org/10.1242/dev.201593>

## Translational and basic andrology



Mammalian sex determination depends on the differentiation of the supporting lineage of the gonads into Sertoli or pregranulosa cells. This study identified -KTS, a major, alternatively spliced WT1 isoform as a key determinant of female sex determination, which antagonizes *Sry* expression. In XY mouse embryos. Increased expression of this isoform resulted in male-to-female sex reversal.

Gregoire EP, De Cian MC, Migale R, Perea-Gomez A, Schaub S, Bellido-Carreras N, Stévant I, Mayère C, Neirijnck Y, Loubat A, Rivaud P, Sopena ML, Lachambre S, Linssen MM, Hohenstein P, Lovell-Badge R, Nef S, Chalmel F, Schedl A, Chaboissier MC. The -KTS splice variant of WT1 is essential for ovarian determination in mice. *Science*. 2023 Nov 3;382(6670):600-606. <https://doi.org/10.1126/science.add8831>



Two back-to-back articles on the structure of sea urchin SpSLC9C1, a sperm-specific  $\text{Na}^+/\text{H}^+$  exchanger uniquely activated by membrane voltage. This transporter is essential for CatSper  $\text{Ca}^{+2+}$  channel activation, and for sperm motility and fertilization. Both studies used cryo-electron microscopy and revealed unusual configuration of SpSLC9C1 domains in the absence and presence of cAMP ligands. The findings can potentially be exploited for the development of new on-demand contraceptives.

Yeo H, Mehta V, Gulati A, Drew D. Structure and electromechanical coupling of a voltage-gated  $\text{Na}^+/\text{H}^+$  exchanger. *Nature*. 2023 Nov;623(7985):193-201. <https://doi.org/10.1038/s41586-023-06518-2>  
Kalienkova V, Peter MF, Rheinberger J, Paulino C. Structures of a sperm-specific solute carrier gated by voltage and cAMP. *Nature*. 2023 Nov;623(7985):202-209. <https://doi.org/10.1038/s41586-023-06629-w>  
**Commentary:** An ion transporter in sperm that has features of a channel. *Nature*. 2023 Nov;623(7985):38-40. <https://doi.org/10.1038/d41586-023-03154-8>



Uniparental inheritance of mitochondrial DNA (mtDNA) is an evolutionary trait found in nearly all eukaryotes but in many species, including humans, the sperm mitochondria are introduced to the oocyte during fertilization and must be eliminated. This elegant study explains how this process occurs in human germ cells.

Lee W, Zamudio-Ochoa A, Buchel G, Podlesniy P, Marti Gutierrez N, Puigròs M, Calderon A, Tang HY, Li L, Mikhailchenko A, Koski A, Trullas R, Mitalipov S, Temiakov D. Molecular basis for maternal inheritance of human mitochondrial DNA. *Nature Genet*. 2023 Oct;55(10):1632-1639. <https://doi.org/10.1038/s41588-023-01505-9>  
**Commentary:** Mechanism of sperm mtDNA elimination. *Nat Rev Mol Cell Biol*. 2023 Oct 19. <https://doi.org/10.1038/s41580-023-00679-8>

This study explored the role of the hypoxia-inducible transcription factor EPAS1 in the mouse testis and found that EPAS1 is required for spermatogonial stem cell (SSC) function in regenerative conditions, e.g. post-chemotherapy. These findings can potentially facilitate optimisation of in vitro culture conditions for infertility treatment pipelines using SSCs, including paediatric cancer survivors.

Bernstein I.R., Nixon B., Lyons J.M., Damyanova K.B., De Oliveira C.S., Mabotuwana N.S., Stanger S.J., Kaiko G.E., Ying T.H., Oatley J.M., Skillen N.M., Lochrin A.J., Peters J.L., Lord, T.



The hypoxia inducible factor EPAS1 is required for spermatogonial stem cell function in regenerative conditions, *ISCIENCE* (2023).  
<https://doi.org/10.1016/j.isci.2023.108424>

## Methodology



A new robust LC-HRMS methodology is presented for identification of environmental contaminants in semen, enabling quantitative analysis of >2000 chemicals, including plastic additives, PFAS, flame retardants, surfactants, and insecticides. The methodology can be used in large-scale cohort studies.

Sánchez-Resino E, Marquès M, Gutiérrez-Martín D, Restrepo-Montes E, Martínez MA, Salas-Huetos A, Babio N, Salas-Salvadó J, Gil-Solsona R, Gago-Ferrero P. Exploring the Occurrence of Organic Contaminants in Human Semen through an Innovative LC-HRMS-Based Methodology Suitable for Target and Nontarget Analysis. *Environ Sci Technol*. 2023 Nov 7. Epub ahead of print.  
<https://pubs.acs.org/doi/10.1021/acs.est.3c04347>

## European Academy of Andrology

Office: Szent István Krt. 7., 1055, Budapest, Hungary

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