EUROPEAN ACADEMY OF ANDROLOGY

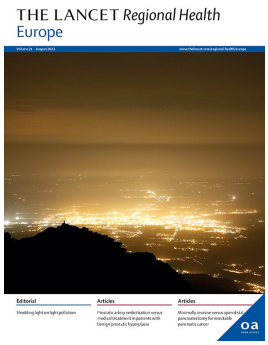
Dear EAA Members,

We encourage you to read the latest issue of *Andrology* (vol. 11, issue 6 https://onlinelibrary.wiley.com/toc/20472927/2023/11/6). Several original studies in this issue have been included in our previous alerts immediately after their publication online but review articles and the editorial concerning the *Andrology Award* is certainly worthy your attention. As usual, we recommend also good publications in other periodicals, covering the following topics: LUTS, testosterone treatment, vit. D treatment, congenital adrenal hyperplasia, maternal smoking and testis cancer, sequence of Y chromosome, TEX genes, mice models for sperm (dys)function and premature ejaculation, CatSper channel modifiers, antiepileptic drugs as endocrine disrupters and more.

Clinical andrology and epidemiology

A summary of the 2023 version of the European Association of Urology guidelines on the management of male LUTS is presented in this paper. The guidelines are based on the articles with the highest certainty evidence selected after a structured literature search (1966 to 2021). The Delphi technique consensus approach was used to develop the recommendations.

Gravas S, Gacci M, Gratzke C, Herrmann TRW, Karavitakis M, Kyriazis I, Malde S, Mamoulakis C, Rieken M, Sakalis VI, Schouten N, Speakman MJ, Tikkinen KAO, Cornu JN. Summary Paper on the 2023 European Association of Urology Guidelines on the Management of Non-neurogenic Male Lower Urinary Tract Symptoms. ***Eur Urol.*** 2023 Aug;84(2):207-222.
https://doi.org/10.1016/j.eururo.2023.04.008



This trial from France suggests that in patients with benign prostatic hyperplasia (BPH) ≥50 ml and LUTS resistant to alpha-blocker monotherapy, prostatic artery embolization (PAE) provides more urinary and sexual symptoms benefit than combined therapy (dutasteride/tamsulosin).

Sapoval M, Thiounn N, et al et, Durand-Zaleski I, Pereira H, Chatellier G; PARTEM study group. Prostatic artery embolisation versus medical treatment in patients with benign prostatic hyperplasia (PARTEM): a randomised, multicentre, open-label, phase 3, superiority trial. ***Lancet Reg Health Eur***. 2023 Jun 26;31:100672.
https://doi.org/10.1016/j.lanepe.2023.10067

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

A randomised controlled trial from Australia examined long-term effects of testosterone undecanoate (T) in >1000 overweight males (50-74 y) with pre-clinical or newly diagnosed diabetes, and how the T effects were mediated. The findings are described in two papers listed below. The authors observed some testosterone dependence and main effects on the body fat.

EJE

Handelsman DJ, Grossmann M, Yeap BB, Stuckey BG, Shankara-Narayana N, Conway AJ, Inder WJ, McLachlan RI, Allan C, Jenkins AJ, Jesudason D, Bracken K, Wittert GA. Long-Term Outcomes of Testosterone Treatment in Men: A T4DM Post-Randomisation Observational Follow-Up Study. ***J Clin Endocrinol Metab***. 2023 Aug 25:dgad485. Epub ahead of print.
https://doi.org/10.1210/clinem/dgad485

Robledo KP, Marschner IC, Handelsman DJ, Bracken K, Stuckey BGA, Yeap BB, Inder W, Grossmann M, Jesudason D,

Allan CA, Wittert G. Mediation analysis of the testosterone treatment effect to prevent type 2 diabetes in the Testosterone for Prevention of Type 2 Diabetes Mellitus trial. ***Eur J Endocrinol.*** 2023 Jul 10;188(7):613-620.
https://doi.org/10.1093/ejendo/lvad074

In a cohort of infertile men, vitamin D + calcium supplementation did not alter sex steroid production, but in vit. D insufficient men this treatment increased testosterone/LH ratio compared with placebo-treated men, suggesting that optimal Leydig cell function depends on adequate vit. D status.

Holt R, Yahyavi SK, Kooij I, Poulsen NN, Juul A, Jørgensen N, Jensen MB. Effects of vitamin D on sex steroids, luteinizing hormone, and testosterone to luteinizing hormone ratio in 307 infertile men. ***Andrology***. 2023 Aug 9. doi: 10.1111/andr.13505. Epub ahead of print.
https://doi.org/10.1111/andr.13505

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Executive function and brain activation were investigated in adolescents with and without Klinefelter syndrome (KS). Males with KS exhibited reduced executive function, associated with severity of pubertal developmental delay, as indexed by lower testosterone and lower testes volume.

Foland-Ross LC, Ghasemi E, Wun VL, Aye T, Kowal K, Ross J, Reiss AL. Executive dysfunction in Klinefelter syndrome: associations with brain activation and testicular failure. ***J Clin Endocrinol Metab.*** 2023 Aug 18:dgad487. Epub ahead of print.
https://doi.org/10.1210/clinem/dgad487

Endocrine CONNECTIONS

Males with congenital adrenal hyperplasia (CAH) experience impaired gonadal function and can develop testicular adrenal rest tumours (TART). This study comprehensively examined the reproductive hormone profiles in adult males with CAH and found INSL3 particularly reduced in men with TART.

Johannsen TH, Albrethsen J, Neocleous V, Baronio F, Cools M, Aksglaede L, Jørgensen N, Christiansen P, Toumba M, Fanis P, Ljubicic ML, Juul A. Reduced serum concentrations of biomarkers reflecting Leydig and Sertoli cell function in male patients with congenital adrenal hyperplasia. ***Endocr Connect.*** 2023 Jul 14;12(8):e230073.
https://doi.org/10.1530/ec-23-0073

IJC INTERNATIONAL JOURNAL of CANCER UICC global cancer control

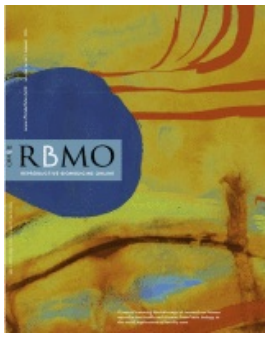
Maternal smoking in pregnancy may increase the risk of testicular germ cell cancer in sons but the evidence is inconclusive. Using cotinine measurements in maternal serum and amniotic fluid as a biomarker for tobacco exposure this prospective study did not provide convincing evidence supporting this hypothesis.

Beck AL, Uldbjerg CS, Lim YH, Coull BA, Sørensen KM, Utko MM, Wilkowski B, Rantakokko P, Bengtsson M, Lindh C, Petersen JH, Skakkebaek NE, Hauser R, Juul A, Bräuner EV. Cotinine concentrations in maternal serum and amniotic fluid during pregnancy and risk of testicular germ cell cancer in the offspring: A prospective nested case-control study. ***Int J Cancer.*** 2023 Aug 21. Epub ahead of print.
https://doi.org/10.1002/ijc.34688

COVID-19

Severe COVID-19 is known to affect testis function. This study followed men mildly affected by SARS-CoV-2 infection (detected in blood but not semen) and found reduced testicular function, including decreased testosterone and INSL3.

Lauritsen MP, Kristensen TL, Bo Hansen C, Schneider UV, Talbot AL, Skytte AB, Petersen JH, Johannsen TH, Zedeler A, Albrethsen J, Juul A, Priskorn L, Jørgensen N, Westh H, Freiesleben NC, Nielsen HS. The impact of acute SARS-CoV-2 on testicular function including insulin-like factor 3 [INSL3] in men with mild COVID-19: A longitudinal study. ***Andrology***. 2023 Jul 8. Epub ahead of print.
https://doi.org/10.1111/andr.13494



SARS-CoV-2 virus was not detected (by RT-PCR) in semen samples from asymptomatic infected individuals. No significant differences in semen volume, concentration, or progressive motility were observed between the last and the subsequent donation. This finding supports the safety of assisted human reproduction treatments in asymptomatic donors.

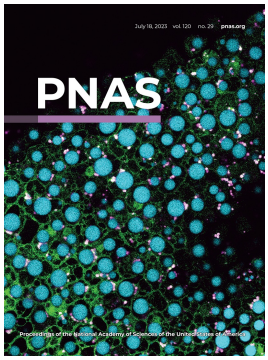
Álvarez-Corral G, Molina M, Castilla JA, Clavero A, Gonzalvo MC, Sampedro A, Bernat N, Caba O. Study of SARS-CoV-2 in semen from asymptomatic donors with presence of virus in nasopharyngeal swab. ***RBMO***, published 30 July 2023. https://doi.org/10.1016/j.rbmo.2023.103321

Androgenetics

Two papers reporting the complete sequence of the human Y chromosome have been published online in Nature. The first was announced in the January edition of this alert as a preprint (Rhie et al. bioRxiv). The work corrected errors in the previous (GRCh38-Y) reference sequence and revealed the complete ampliconic and repetitive structures of *TSPY, DAZ, RBMY* and other protein-coding genes. The second paper (*Hallast et al.*) reported considerable diversity in size and structure, based on the analysis of 43 Y chromosomes spanning >182K years of evolution. The study also fine-mapped the boundaries between the recombining and non-recombining portions of the X and Y chromosomes.

Rhie A, Nurk S, Cechova M, Hoyt SJ, Taylor DJ, et al et Eichler EE, O'Neill RJ, Schatz MC, Miga KH, Makova KD, Phillippy AM. The complete sequence of a human Y chromosome. ***Nature***. 2023 Aug 23. Epub ahead of print. https://doi.org/10.1038/s41586-023-06457-y

Hallast P, Ebert P, Loftus M, et al et Human Genome Structural Variation Consortium (HGSVC); et O'Neill RJ, Korbel JO, Tyler-Smith C, Eichler EE, Shi X, Beck CR, Marschall T, Konkel MK, Lee C. Assembly of 43 human Y chromosomes reveals extensive complexity and variation. ***Nature***. 2023 Aug 23. Epub ahead of print. https://doi.org/10.1038/s41586-023-06425-6



Missense variants in fertility-related genes (*ANKRD31, BRDT, DMC1, EXO1, FKBP6, MCM9, M1AP, MEI1, MSH4, SEPT12*) were functionally evaluated using genome-edited mouse models. The study emphasized the need for alternative and efficient validation models for more accurate variant description to either pathogenic or benign categories.

Ding X, Singh P, Schimenti K, Tran TN, Fragoza R, Hardy J, Orwig KE, Olszewska M, Kurpisz MK, Yatsenko AN, Conrad DF, Yu H, Schimenti JC. In vivo versus in silico assessment of potentially pathogenic missense variants in human reproductive genes. ***Proc Natl Acad Sci USA (PNAS)***. 2023 Jul 25;120(30):e2219925120. https://doi.org/10.1073/pnas.2219925120

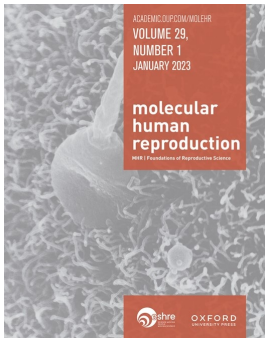
This comprehensive study carefully re-analysed variants in X-linked TEX genes in the context of male infertility (in 1305 men), including KD modelling in Drosophila. Some novel variants associated with azoospermia were identified, while several others can no longer be considered a monogenic cause of infertility.

Sieper MH, Gaikwad AS, Fros M, Weber P, Di Persio S, Oud MS, Kliesch S, Neuhaus N, Stallmeyer B, Tüttelmann F,

Wyrwoll MJ. Scrutinizing the human TEX genes in the context of human male infertility. ***Andrology***. 2023 Aug 18. https://doi.org/10.1111/andr.13511

The authors investigated Italian couples with pure male idiopathic infertility by applying variant prioritization to whole exome sequencing. Twelve monogenic cases (12.1%) were identified in the cohort, suggesting that this approach can uncover a considerable number of Mendelian causes of infertility even in a small cohort of patients.

Quarantani G, Sorgente A, Alfano M, Pipitone GB, Boeri L, Pozzi E, Belladelli F, Pederzoli F, Ferrara AM, Montorsi F, Moles A, Carrera P, Salonia A, Casari G. Whole exome data prioritization unveils the hidden weight of Mendelian causes of male infertility. A report from the first Italian cohort. ***PLoS One.*** 2023 Aug 4;18(8):e0288336. https://doi.org/10.1371/journal.pone.0288336



A frameshift variant in *IQCN* (previously identified as essential for spermatid manchette formation, PMID: 36321563) was found in three infertile brothers with abnormal spermatozoa. Male *Iqcn-/-* mice exhibited a similar phenotype.

Wang Y, et al et Zhang D. Loss-of-function mutations in IQCN cause male infertility in humans and mice owing to total fertilization failure. ***Mol Hum Reprod.*** 2023 Jun 30;29(7):gaad018. https://doi.org/10.1093/molehr/gaad018

Translational and basic andrology

In a vasectomised mouse model for obstructive azoospermia epididymal morphology was abnormal and retrieved sperm had poor motility and low fertilization ability in vitro. The identified mechanisms included differences in the expression of key proteins for sperm maturation (AGT, ROPN1, NPC2, PROM1) and modified sperm phosphorylation.

Gao S, Chen Z, Shi J, Chen Z, Yun D, Li X, Wu X, Sun F. Sperm immotility is associated with epididymis metabolism disorder in mice under obstructive azoospermia. ***FASEB J.*** 2023 Aug;37(8):e23081. https://doi.org/10.1096/fj.202201862rr

Alanine substitution in protamine 1 (P1(K49A)) decreases sperm motility and male fertility and leads to premature male pronuclear decompaction, altered DNA replication, and embryonic arrest in mice, suggesting that protamine non-arginine residues are essential for reproductive fitness.

Moritz L, Schon SB, Rabbani M, Sheng Y, Agrawal R, Glass-Klaiber J, Sultan C, Camarillo JM, Clements J, Baldwin MR, Diehl AG, Boyle AP, O'Brien PJ, Ragunathan K, Hu YC, Kelleher NL, Nandakumar J, Li JZ, Orwig KE, Redding S, Hammoud SS. Sperm chromatin structure and reproductive fitness are altered by substitution of a single amino acid in mouse protamine 1. ***Nat Struct Mol Biol.*** 2023 Jul 17. https://doi.org/10.1038/s41594-023-01033-4

cells

Osmoregulation in sperm involves aquaglyceroporins, a subclass of aquaporins (AQPs). This study found that AQP7 mediated glycerol permeability and affected sperm motility.

Ribeiro JC, Bernardino RL, Gonçalves A, Barros A, Calamita G, Alves MG, Oliveira PF. Aquaporin-7-Mediated Glycerol Permeability Is Linked to Human Sperm Motility in

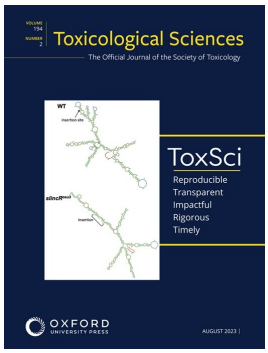
Asthenozoospermia and during Sperm Capacitation. ***Cells***. 2023 Aug 5;12(15):2003.
https://doi.org/10.3390/cells12152003

The Swiss research team developed a high-throughput screening assay to measure changes in $[Ca^{2+}]_i$ in human sperm and screened 1,280 approved and off-patent drugs including 90 steroids from the Prestwick chemical library. Several potent steroids could modulate the activity of CatSper.

Wehrli L, Galdadas I, Voirol L, Smieško M, Cambet Y, Jaquet V, Guerrier S, Gervasio FL, Nef S, Rahban R. The action of physiological and synthetic steroids on the calcium channel CatSper in human sperm. ***Front Cell Dev Biol.*** 2023 Jul 20;11:1221578.
https://doi.org/10.3389/fcell.2023.1221578

This study from Australia examined the effects of increased Activin A on spermatogonial stem cells (SSC) in Inha KO mice, which develop gonadal stromal cell tumours as adults. They found that the tumours create a microenvironment that supports self-renewal of SSC but not differentiation.

Whiley PAF, Nathaniel B, Stanton PG, Hobbs RM, Loveland KL. Spermatogonial fate in mice with increased activin A bioactivity and testicular somatic cell tumours. ***Front Cell Dev Biol.*** 2023 Jul 26;11:1237273.
https://doi.org/10.3389/fcell.2023.1237273



Valproic acid (VPA), an antiepileptic and anti-migraine drug, can have adverse effects on the male reproductive system. The results of this French study show that VPA and other antiepileptic drugs can behave as endocrine disruptors for the human fetal testis ex vivo.

Lesné L, Desdoits-Lethimonier C, Hug E, Costet N, Raffenne L, Toupin M, Evrard B, Kugathas I, Lavoué V, Chalmel F, Jégou B, Mazaud-Guittot S. Antiepileptic drugs are endocrine disruptors for the human fetal testis ex vivo. ***Toxicol Sci.*** 2023 Jul 28:kfad076.
https://doi.org/10.1093/toxsci/kfad076

Using a rat model, this study found that upregulation of dopamine D4 receptor would enhance the dapoxetine effect in premature ejaculation treatment.

Gao P, Liu X, Zhu T, Gao R, Gao J, Zhang Y, Jiang H, Huang H, Zhang X. Vital function of DRD4 in dapoxetine medicated premature ejaculation treatment. ***Andrology***. 2023 Sep;11(6):1175-1187.
https://doi.org/10.1111/andr.13390

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