EUROPEAN ACADEMY OF ANDROLOGY

Literature alert

February 2023

Dear EAA Members,

We are presenting the latest publications of interest for andrologists with all clinical subspecialties, including urology, endocrinology, fertility medicine, and paediatric andrology as well as for geneticists and basic scientists. Enjoy the reading!

Clinical andrology and epidemiology

First, we recommend reading the March issue of our journal ***Andrology*** – there are several very interesting articles, some already highlighted in the previous alerts. The topics include erectile (dys)function, Klinefelter syndrome, FSH, Peyronie disease, TESE/ICSI, maternal problems and their sons health, testosterone and cardiovascular health, and more.
https://onlinelibrary.wiley.com/toc/20472927/2023/11/3

Fertility and Sterility

Retrospective national cohort study analysed all ICSI cycles performed in the UK over a 10-year period.

The study indicates that reproductive outcomes of ICSI after surgical sperm retrieval (SSR) are comparable to ICSI using ejaculated sperm, and does not support the preferential use of fresh over cryopreserved sperm in SSR-ICSI. Rate of births per SSR-ICSI cycle was higher for cycles using epididymal sperm compared to testicular sperm.

Lewin J, Lukaszewski T, Sangster P, Williamson E, McEleny K, Al Wattar BH, Yasmin E. Reproductive outcomes following surgical sperm retrieval in couples with male factor subfertility: A 10-year retrospective national cohort. ***Fertil Steril***. 2022 Dec 30:S0015-0282(22)02133-1. Epub ahead of print.

https://doi.org/10.1016/j.fertnstert.2022.12.041

Commentary: https://www.fertstert.org/article/S0015-0282(23)00084-5/fulltext

A study from Spain investigated sperm chromatin and ICSI outcomes. Sperm protamination was related to fertilization rates in healthy donors, and the in vitro capacity of sperm to condense their chromatin was linked to blastocyst rates, both associations being more apparent in women <33 years of age.

Ribas-Maynou J, Novo S, Salas-Huetos A, Rovira S, Antich M, Yeste M. Condensation and protamination of sperm chromatin affect ICSI outcomes when gametes from healthy individuals are used. ***Hum Reprod***. 2022 Dec 20:deac261. Epub ahead of print. PMID: 36539233.

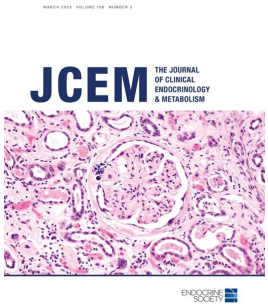
https://doi.org/10.1093/humrep/deac261

An important Swedish study with a surprising finding, in view of the bad reputation the PSA screening had in latest decades. Indeed, PSA test increased the detection of prostate cancer, but starting PSA screening at a younger age – at 50-55 yr - significantly reduced mortality from the disease.

Carlsson SV, Arnsrud Godtman R, Pihl CG, Vickers A, Lilja H, Hugosson J, Månsson M. Young Age on Starting Prostate-specific Antigen Testing Is Associated with a Greater Reduction in Prostate Cancer Mortality: 24-Year Follow-up of the Göteborg Randomized Population-based Prostate Cancer Screening Trial. ***Eur Urol***. 2023 Feb;83(2):103-109.

https://doi.org/10.1016/j.eururo.2022.10.006

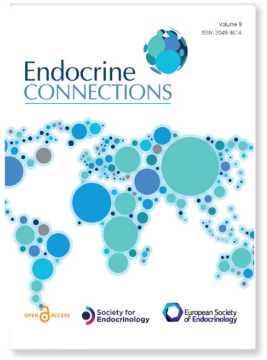
Editorial by Peter C. Albertsen:
https://doi.org/10.1016/j.eururo.2022.10.018



A Danish register-based cohort study of >23,000 males diagnosed with gynecomastia (idiopathic in the majority) found that they had adverse long-term and general health outcomes in comparison with matched controls. Gynecomastia is an important clinical symptom of an underlying disease and a significant predictor of future disease risk.

Uldbjerg CS, Lim YH, Bräuner EV, Juul A. Increased Morbidity in Males Diagnosed with Gynecomastia: A nationwide register-based cohort study. ***J Clin Endocrinol Metab***. 2023 Jan 31:dgad048. Epub ahead of print.

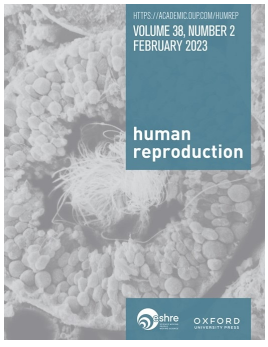
https://doi.org/10.1210/clinem/dgad048



Newborns with congenital hypogonadotropic hypogonadism (CHH) have an impaired activation of the gonadotropic axis, and require substitutive therapy to induce physiological mini-puberty in early infancy. This study compared the injections and pump and found that both methods were effective for testis descent, penile length and testicular hormones.

Avril T, Hennocq Q, Lambert AS, Leger J, Simon D, Martinerie L, Bouvattier C. Gonadotropin administration to mimic minipuberty in hypogonadotropic males: pump or injections? ***Endocr Connect***. 2023 Feb 1:EC-22-0252. Epub ahead of print.

10.1530/EC-22-0252



Two studies dealing with fertility in male cancer survivors. Masliukaite et al. examined boys with CNS and hematological malignancies and found decreased spermatogonial numbers before therapy, which can contribute to persistent infertility later in life. Kitlinski *et al.* did a register-based study and reported that the use of assisted reproduction (especially ICSI) was more frequent in fathers with a history of cancer.

Masliukaite I, Ntemou E, Feijen EAM, van de Wetering M, Meissner A, Soufan AT, Repping S, Kremer LMC, Jahnukainen K, Goossens E, van Pelt AMM. Childhood cancer and hematological disorders negatively affect spermatogonial quantity at diagnosis: a

retrospective study of a male fertility preservation cohort. ***Hum Reprod***. 2023 Jan 27:dead004. Epub ahead of print.

https://doi.org/10.1093/humrep/dead004

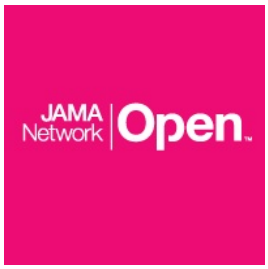
Kitlinski M, Giwercman A, Elenkov A. Paternity through use of assisted reproduction technology in male adult and childhood cancer survivors: a nationwide register study. ***Hum Reprod***. 2023 Feb 11:dead026. Epub ahead of print.

https://doi.org/10.1093/humrep/dead026

Useful clinical guidelines on the management of erectile dysfunction, assembled by the leading experts in Italy, a powerhouse in sexual medicine. The recommendations are based on the GRADE system.

Corona G, Cucinotta D, Di Lorenzo G, Ferlin A, Giagulli VA, Gnessi L, Isidori AM, Maiorino MI, Miserendino P, Murrone A, Pivonello R, Rochira V, Sangiorgi GM, Stagno G, Foresta C, Lenzi A, Maggi M, Jannini EA. The Italian Society of Andrology and Sexual Medicine (SIAMS), along with ten other Italian Scientific Societies, guidelines on the diagnosis and management of erectile dysfunction. ***J Endocrinol Invest***. 2023 Jan 25:1–34. Epub ahead of print.

https://link.springer.com/article/10.1007/s40618-023-02015-5



In this randomized placebo-controlled clinical trial of 32 men with hypoactive sexual desire disorder, kisspeptin administration significantly modulated brain activity in the sexual-processing network, and increased sexual behavior and penile tumescence in response to visual sexual stimuli. Kisspeptin was well-tolerated and no side-effects were reported, which is important for potential drug development.

Mills EG, Ertl N, Wall MB, *et al et* Goldmeier D, Comninos AN, Dhillo WS. Effects of Kisspeptin on Sexual Brain Processing and Penile Tumescence in Men With Hypoactive Sexual Desire Disorder: A Randomized Clinical Trial. ***JAMA Network Open***. 2023 Feb 1;6(2):e2254313.

https://doi.org/10.1001/jamanetworkopen.2022.54313

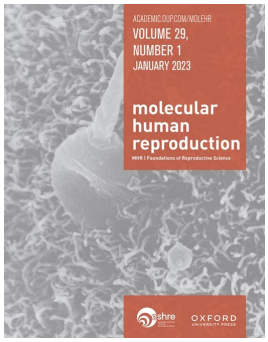
Androgenetics

Using whole-exome sequencing, the authors identified deleterious variants of X-linked SSX1 in six unrelated men with asthenoteratozoospermia. They knocked-down Ssx1 in the testis of three animal models and observed a reduced sperm motility and abnormal morphology. Notably, 3/5 couples treated with ICSI achieved a successful pregnancy.

Liu C, Si W, Tu C, Tian S, *et al et* Ray PF, Tan YQ, Cao Y, Zhang F. Deficiency of primate-specific SSX1 induced asthenoteratozoospermia in infertile men and cynomolgus monkey and tree shrew models. ***Am J Hum Genet***. 2023 Feb 8:S0002-9297(23)00016-2. Epub ahead of print. PMID: 36796361.

https://doi.org/10.1016/j.ajhg.2023.01.016

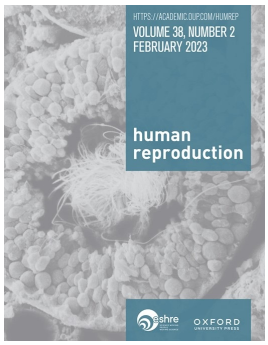
This study found that *WDR87* was highly expressed in the testis of humans and mice, and in the mouse specifically located in the middle piece of the sperm tail, where it interacted with CFAP47. The authors then screened men with multiple morphological abnormalities of the flagella (MMAF) and



found two novel mutations in *CFAP47*.

Liao HQ, Guo ZY, Huang LH, Liu G, Lu JF, Zhang YF, Xing XW. WDR87 interacts with CFAP47 protein in the middle piece of spermatozoa flagella to participate in sperm tail assembly. ***Mol Hum Reprod***. 2022 Dec 28;29(1):gaac042..

https://doi.org/10.1093/molehr/gaac042



Whole exome sequencing analysis of a large consanguineous family identified in 3 brothers a novel homozygous nonsense HORMAD1 variant responsible for nonobstructive azoospermia (NOA) characterized by arrest at primary spermatocyte stage.

Okutman O, Boivin M, Muller J, Charlet-Berguerand N, Viville S. A biallelic loss of function variant in HORMAD1 within a large consanguineous Turkish family is associated with spermatogenic arrest. ***Hum Reprod***. 2023 Feb 1;38(2):306-314.

https://doi.org/10.1093/humrep/deac259

Journal of *Clinical Medicine*

A homozygous pathogenic MCM9 variant (c.394C>T) was identified in three sisters affected by ovarian dysgenesis and premature ovarian insufficiency (POI) and their brother who had normal pubertal development but suffered from non-obstructive azoospermia, with Sertoli cell-only testicular histopathology.

Potorac I, Laterre M, Malaise O, Nechifor V, Fasquelle C, Colleye O, Detrembleur N, Verdin H, Symoens S, De Baere E, Daly AF, Bours V, Pétrossians P, Pintiaux A. The Role of *MCM9* in the Etiology of Sertoli Cell-Only Syndrome and Premature Ovarian Insufficiency***. J Clin Med***. 2023 Jan 28;12(3):990.

https://doi.org/10.3390/jcm12030990

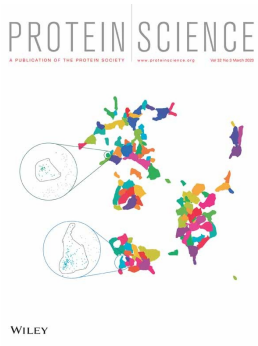
A remarkable study of >1,000 patients with premature ovarian insufficiency (POI). In addition to variants in 59 known POI-causative genes, the study also identified 20 novel POI-associated genes, bringing the total to 23.5% of genetic causes. The novel genes involved in gonadogenesis (*LGR4*, *PRDM1*), and in meiosis (*CPEB1, KASH5, MCMDC2, MEIOSIN, NUP43, RFWD3, SHOC1, SLX4, STRA8*) are likely candidates also for male infertility.

Ke H, Tang S, Guo T, *et al et* Qin Y, Jin L, Chen ZJ. Landscape of pathogenic mutations in premature ovarian insufficiency. ***Nature Medicine***. 2023 Feb 2. Epub ahead of print. PMID: 36732629.

https://doi.org/10.1038/s41591-022-02194-3

A very nice Belgian-Italian study of the molecular mechanisms, including protein structure, behind mutations V770D/A in the androgen receptor (AR), which cause the androgen insensitivity syndrome. The work sheds light on the process of the AR dimerization.

Helsen C, Rocca MS, Nguyen TT, Eerlings R, Lee XY, De



Block S, Vinanzi C, Di Millo F, Giagulli V, Voet A, Ferlin A, Claessens F. Study of novel androgen receptor V770 variant in androgen insensitivity syndrome patients reveals the transitional state of the androgen receptor ligand binding domain homodimer. ***Protein Sci***. 2023 Feb 20:e4599. Epub ahead of print.

https://doi.org/10.1002/pro.4599

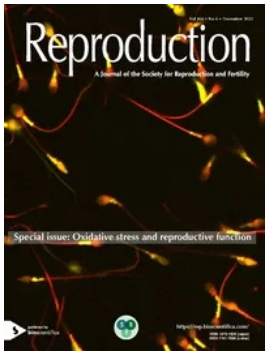
Translational and basic andrology

A possible break-through in the work on male contraception, targeting soluble adenylyl cyclase (sAC), which is essential for sperm motility and maturation!

This study shows that a single dose of a safe, acutely-acting sAC inhibitor with long residence time renders male mice temporarily infertile. The findings provide an in vivo proof-of-concept for an on-demand pharmacological contraception for men.

Balbach M, Rossetti T, Ferreira J, Ghanem L, Ritagliati C, Myers RW, Huggins DJ, Steegborn C, Miranda IC, Meinke PT, Buck J, Levin LR. On-demand male contraception via acute inhibition of soluble adenylyl cyclase. ***Nature Commun***. 2023 Feb 14;14(1):637.

https://doi.org/10.1038/s41467-023-36119-6



This study reported that STRA8/MEIOSIN activates the transcription factors A-MYB and TCFL5, which together reprogram gene expression after spermatogonia enter into meiosis. The pathway is conserved in rhesus macaque. TCFL5 promotes the transcription of meiosis genes, mRNA turnover, miR-34/449 production, meiotic exit, and spermiogenesis. *Tcfl5em1/em1* mutants are sterile, and spermatogenesis arrests at the mid- or late-pachytene stage of meiosis.

Cecchini K, Biasini A, Yu T, Säflund M, Mou H, Arif A, Eghbali A, Colpan C, Gainetdinov I, de Rooij DG, Weng Z, Zamore PD, Özata DM. The transcription factor TCFL5 responds to A-MYB to elaborate the male meiotic program in mice. ***Reproduction.*** 2023 Jan 4;165(2):183-196.

https://doi.org/10.1530/rep-22-0355

Adenosine deaminase domain containing 2 (ADAD2) is a testis-specific protein indispensable for the male reproduction in mice. This study showed that ADAD2 functions in piRNA biogenesis in spermatocytes, in collaboration with RNF17 and other RNA-binding proteins.

Lu Y, Nagamori I, Kobayashi H, Kojima-Kita K, Shirane K, Chang HY, Nishimura T, Koyano T, Yu Z, Castañeda JM, Matsuyama M, Kuramochi-Miyagawa S, Matzuk MM, Ikawa M. ADAD2 functions in spermiogenesis and piRNA biogenesis in mice. ***Andrology***. 2023 Jan 25. Epub ahead of print.

https://doi.org/10.1111/andr.13400

Two studies examined the consequences of prenatal exposures to phthalates, ubiquitous chemicals used to make plastics more durable. The studies raise concern concerning long-term effects to endocrine disrupters.

1. A longitudinal mother-child cohort study from Denmark examined 100 young men (18-20 y.) whose mothers during pregnancy had phthalate metabolites measured in serum. Higher maternal phthalate exposure was associated with higher LH and lower total and free T/LH ratios in the sons.

Henriksen LS, Frederiksen H, Jørgensen N, Juul A, Skakkebæk NE, Toppari J, Petersen JH, Main KM. Maternal phthalate exposure during pregnancy and testis function of young adult sons. ***Sci Total Environ***. 2023 Jan 31;871:161914. Epub ahead of print. https://doi.org/10.1016/j.scitotenv.2023.161914

2. In a study in mice, the researchers found that paternal phthalate (DCHP) exposure led to high insulin resistance and impaired insulin signaling in F1 offspring, and similar but weaker effects persisted in F2 offspring. The researchers used a novel PANDORA-seq method that showed DCHP exposure can lead to small-RNA changes in sperm.

Liu J, Shi J, Hernandez R, Li X, Konchadi P, Miyake Y, Chen Q, Zhou T, Zhou C. Paternal phthalate exposure-elicited offspring metabolic disorders are associated with altered sperm small RNAs in mice. ***Environment Int,*** 2023; 172: 107769. 10.1016/j.envint.2023.107769

The authors investigated the gonads from five 46,XY individuals with defects in androgen synthesis or action, and found an exclusive expression of HSD17B3 in Sertoli cells, suggesting an androgen-dependent differentiation defect.

Al-Sharkawi M, Calonga-Solís V, Dressler FF, Busch H, Hiort O, Werner R. Persistence of foetal testicular features in patients with defective androgen signalling. ***Eur J Endocrinol***. 2023 Jan 10;188(1):lvad007.

https://doi.org/10.1093/ejendo/lvad007

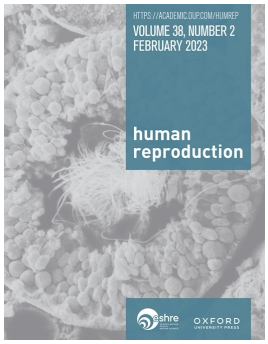
bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

A remarkable preprint with important new data concerning the early development of adrenal cortex and gonads. The study provided a single-cell transcriptomic atlas of early mouse adrenogonadal development including 52 cell types. Surprisingly, gonadal and adrenal fates show distinct molecular signatures upon *Nr5a1* induction indicating the two tissues are specified independently.

Y Neirijnck, P Sararols, F Kuhne, C Mayere, S Nef... - ***bioRxiv***, 2023
Single-cell transcriptomic profiling redefines the origin and specification of early adrenogonadal progenitors

Methodology

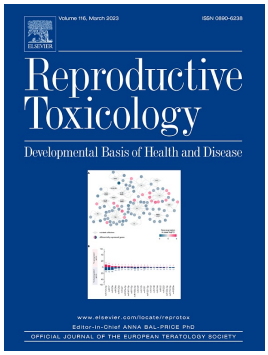
The finding that the sperm membrane can reflect alterations in DNA integrity, prompted a novel method for sperm preparation prior



to assisted reproductive procedures. Immunomagnetic cell sorting for ELSPBP1(-) sperm fraction reduced the level of sperm DNA fragmentation (SDF).

Belardin LB, Antoniassi MP, Camargo M, Intasqui P, Bertolla RP. Separating the chaff from the wheat: antibody-based removal of DNA-fragmented sperm. ***Hum Reprod***. 2023 Feb 1;38(2):204-215.

https://doi.org/10.1093/humrep/deac260

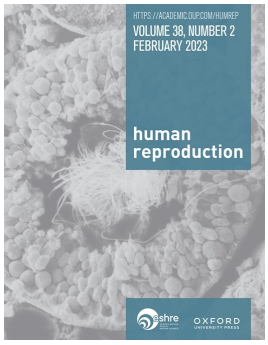


This article from Brazil presents a standardized protocol for assessing simultaneously sperm plasma membrane integrity, acrosomal status, mitochondrial potential, and superoxide anion production using a flow cytometry technique.

de Lima Rosa J, de Paula Freitas Dell'Aqua C, de Souza FF, Missassi G, Kempinas WG. Multiple flow cytometry analysis for assessing human sperm functional characteristics. ***Reprod Toxicol***. 2023 Feb 18:108353.

https://doi.org/10.1016/j.reprotox.2023.108353

Case of the month



Management of transmen is challenging. The authors presented two cases of transmen who were on testosterone prior to- and throughout ovarian stimulation. They discuss current clinical practice and provide rationale for this therapy.

Moravek MB, Dixon M, Pena SM, Obedin-Maliver J. Management of testosterone around ovarian stimulation in transmasculine patients: challenging common practices to meet patient needs-2 case reports. ***Hum Reprod***. 2023 Jan 16:dead003. Epub ahead of print.

https://doi.org/10.1093/humrep/dead003

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