EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

The second summer edition brings several important studies, including surgical treatment of LUTS, maternal lifestyle and the reproductive health of their sons, testosterone and sports performance (incl. transgenders), a guideline how to follow patients with testicular cancer after orchiectomy, sperm separation and metabolic evaluation methods, evolution of the human Y chromosome, novel biallelic variants in male infertility, spermatogonial stem cell niche, cannabinoids in fetal life, adverse developmental effects of benzopyren, genistein, paracetamol, and more.

Clinical andrology and epidemiology

This important meta-analysis summarised the evidence from 63 clinical trials on minimally invasive surgical therapies for male lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction. Symptoms and quality of life were similar after prostatic arterial embolisation (PAE), prostatic urethral lift (PUL), water vapour thermal therapy (WVTT) and transurethral resection of the prostate (TURP). TURP had the most clinically significant improvement in flow rate. Comparisons of ejaculatory function favoured WVTT and PUL compared with TURP.

Cornu JN, Zantek P, Burtt G, Martin C, Martin A, Springate C, Chughtai B. Minimally Invasive Treatments for Benign Prostatic Obstruction: A Systematic Review and Network Meta-analysis. ***Eur Urol.*** 2023 Jun;83(6):534-547.
https://doi.org/10.1016/j.eururo.2023.02.028
Authors' commentary: Cornu JN, Chughtai B. https://doi.org/10.1016/j.eururo.2023.06.002

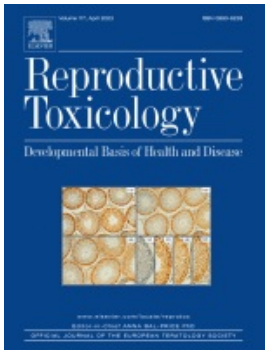
One trial on some of the same surgical therapies, with ejaculatory function as the main outcome, showed that transperineal interstitial laser ablation of the prostate (TPLA) preserved ejaculatory function in 96% of cases in addition to providing significant relief from benign prostatic obstruction.

Bertolo R, Iacovelli V, Cipriani C, Carilli M, Vittori M, Antonucci M, Maiorino F, Signoretti M, Petta F, Travaglia S, Panei M, Bove P. Ejaculatory function following transperineal laser ablation vs TURP for benign prostatic obstruction: a randomized trial. ***BJU Int.*** 2023 Jul;132(1):100-108.
https://doi.org/10.1111/bju.16008

ANDROLOGY

Maternal obesity can affect reproductive health of the offspring, as shown in this study that associated maternal obesity and early weight gain with lower testosterone levels in their adult sons, independently of adulthood abdominal obesity.

Laru J, Pinola P, Ojaniemi M, Korhonen E, Laikari L, Franks S, Piltonen TT, Tapanainen JS, Niinimäki M, Morin-Papunen L. Low testosterone at age 31 associates with maternal obesity and higher body mass index from childhood until age 46: A birth cohort study. ***Andrology***. 2023 Jul 10. Epub ahead of print.
https://doi.org/10.1111/andr.13492

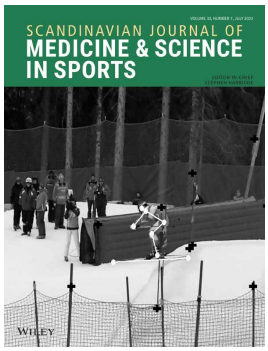


Maternal alcohol intake in early pregnancy was associated with biomarkers of fecundity in adult sons in the FEPOS cohort study (DK). Some small tendencies towards lower semen characteristics and an altered hormone level profile were found in sons of mothers who drank >3 drinks/week or had repeated episodes of binge drinking during pregnancy.

Thomsen AH, Gaml-Sørensen A, Brix N, Tøttenborg SS, Hougaard KS, Ernst A, Arendt LH, Toft G, Bonde JP, Ramlau-Hansen CH. Maternal alcohol intake in early pregnancy and biomarkers of fecundity in adult sons: A cohort study. ***Reprod Toxicol.*** 2023 Aug;119:108396.
https://doi.org/10.1016/j.reprotox.2023.108396

Testosterone-prescribing has markedly increased in recent decades. This study from the USA developed and validated quality measures of care around initiation and monitoring of testosterone prescribing based on the current Endocrine Society guidelines.

Borzecki AM, Conti J, Reisman JI, Vimalananda V, Nagy MW, Paluri R, Linsky AM, McCullough M, Bhasin S, Matsumoto AM, Jasuja GK. Development and Validation of Quality Measures for Testosterone Prescribing. ***J Endocr Soc***. 2023 Jun 14;7(7):bvad075.
https://doi.org/10.1210/jendso/bvad075



Ketone bodies, such as 3-hydroxybutyrate (3-OHB), have been frequently used by athletes to enhance performance and recovery. Surprisingly, in this pilot trial, testosterone levels decreased significantly by 20% after oral 3-OHB, and LH increased. This suggests that 3-OHB may counteract some of the beneficial effects of endurance training.

Svart M, Nielsen MM, Rittig N, Hansen M, Møller N, Gravholt CH. Oral 3-hydroxybuturate ingestion acutely lowers circulating testosterone concentrations in healthy young males. ***Scand J Med Sci Sports.*** 2023 Jun 28. Epub ahead of print.
https://doi.org/10.1111/sms.14441

This article describes the sex-based dichotomy in testosterone and the implications for sex-based differences in individual sports performance, including factors that relate to athletic performance for transgender individuals, and areas of future investigation.

Nokoff NJ, Senefeld J, Krausz C, Hunter S, Joyner M. Sex Differences in Athletic Performance: Perspectives on Transgender Athletes. ***Exerc Sport Sci Rev***. 2023 Jul 1;51(3):85-95.
https://doi.org/10.1249/jes.0000000000000317

How to follow patients with testicular cancer? This article reviewed 46 articles on follow-up strategies for clinical stage 1, and 6 clinical practice guidelines, including 4 guidelines published by urological scientific associations and 2 guidelines published by medical oncology associations.

Chavarriaga J, Bobrowski A, Hamilton RJ. Guideline of Guidelines: Follow-up After Orchiectomy for Clinical Stage I Testicular Cancer. ***BJU Int.*** 2023 Jul 6. Epub ahead of print.
https://doi.org/10.1111/bju.16111

Methodology

Reproduction & Fertility

Determining the optimal technique for isolating spermatozoa post-thaw is vital for assisted reproduction. In this paper, three isolation techniques were compared for their ability to separate ideal sperm from semen and media following cryopreservation. The electrophoretic

isolation exhibited significantly lower levels of DNA fragmentation.

Hungerford AJ, Bakos HW, Aitken RJ. Analysis of sperm separation protocols for isolating cryopreserved human spermatozoa. ***Reprod Fertil.*** 2023 May 2;4(2):e220133. https://doi.org/10.1530/raf-22-0133

ANDROLOGY

Human sperm oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), were measured using the Seahorse flux analyser, providing information on sperm oxidative and glycolytic metabolism, potentially useful for diagnostic purposes.

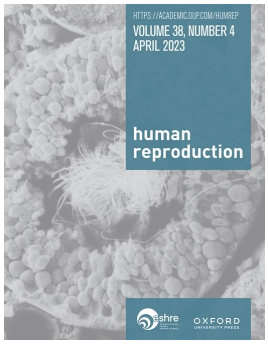
Freitas-Martins A, Sousa MI, Cristo MI, Ramalho-Santos J, Amaral S. Metabolic characterization of human sperm cells using the Seahorse metabolic flux analyzer. ***Andrology***. 2023 Jun 25. Epub ahead of print. https://doi.org/10.1111/andr.13486

Androgenetics

nature COMMUNICATIONS

A large number of de novo copy number mutations in chromosome Y palindromes was found in Islandic men but these mutations are lost faster than expected. Testing did not identify significant associations with diverse traits (including infertility), suggesting that palindrome copy number variation on the Y chromosome has little impact on human phenotype diversity.

Lucotte EA, Guðmundsdóttir VB, Jensen JM, Skov L, Macià MC, Almstrup K, Schierup MH, Helgason A, Stefansson K. Characterizing the evolution and phenotypic impact of ampliconic Y chromosome regions. ***Nature Commun***. 2023 Jul 6;14(1):3990. https://doi.org/10.1038/s41467-023-39644-6



Two studies on biallelic genetic variants causing male infertility published in Human Reproduction:
A likely causal relationship between KCTD19 (a transcriptional regulator of meiotic progression) and male infertility was found in this study, which also provided evidence for poor ICSI outcomes in men with biallelic *KCTD19* variants.

Wang W, Su L, et al et Tan YQ. Biallelic variants in KCTD19 associated with male factor infertility and oligoasthenoteratozoospermia. ***Hum Reprod.*** 2023 Jul 5;38(7):1399-1411. https://doi.org/10.1093/humrep/dead095

Deficiency in IQCN causes sperm flagellar assembly defects and male infertility. The sperm from the affected men showed an irregular structure of the flagellum, which resulted in abnormal CASA parameters.
Li Q, Wang Y, et al et Dai J. Biallelic variants in IQCN cause sperm flagellar assembly defects and male infertility. ***Hum Reprod.*** 2023 Jul 5;38(7):1390-1398. https://doi.org/10.1093/humrep/dead079

PLOS

NR5A1/SF-1 (Steroidogenic factor-1) variants may cause differences of sex development (DSD) but also may be found in healthy carriers. DSD individuals with the NR5A1/SF-1 p.Gly146Ala gene variant (confirmed as benign) always harbour an additional gene mutation.

Martinez de Lapiscina I, Kouri C, et al et, Flück CE. Genetic reanalysis of patients with a difference of sex development carrying the NR5A1/SF-1 variant p.Gly146Ala has discovered other likely disease-causing variations. ***PLoS One.*** 2023 Jul 11;18(7):e0287515. https://doi.org/10.1371/journal.pone.0287515

Translational and basic andrology

Two excellent studies using transcriptomics to shed light on the regulation of spermatogonial stem cell (SSC) niche and induction of meiosis. The first study found that pleiotrophin regulates mouse SSC through syndecan receptors, and the spatial re-distribution of inflammation-related pathways underlies diabetes-induced testicular injury. The second study indicated that retinoic acid induces meiosis partially by downregulating their nutrient transporter genes (Slc family) via Stra8, which

induces H3K27 deacetylation of these genes.

1. Rajachandran S, Zhang X, et al et Nagano M, Orwig KE, Chen H. Dissecting the spermatogonial stem cell niche using spatial transcriptomics. ***Cell Rep.*** 2023 Jul 1;42(7):112737. https://doi.org/10.1016/j.celrep.2023.112737

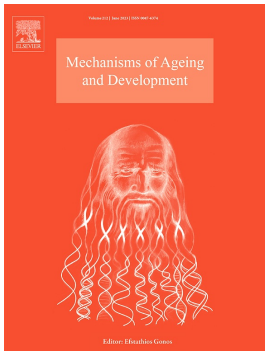
2. Zhang X, Liu Y, et al et Orwig KE, Wang N. Transcriptional metabolic reprogramming implements meiotic fate decision in mouse testicular germ cells. ***Cell Rep.*** 2023 Jul 4;42(7):112749. https://doi.org/10.1016/j.celrep.2023.112749

BMC Medicine

The presence of the functional endocannabinoid system demonstrated in the human fetal testis!

Ex vivo exposure of first trimester testes to cannabinoids altered hormone secretion, and the expression of genes involved in steroid synthesis and toxic substance response, highlighting the potential risks of cannabis consumption by pregnant women.

Dochez-Arnault J, Desdoits-Lethimonier C, Matias I, Evrard B, Lagarrigue M, Toupin M, Lardenois A, Chalmel F, Mazaud-Guittot S, Dejucq-Rainsford N, Gely-Pernot A. Expression of the endocannabinoid system and response to cannabinoid components by the human fetal testis. ***BMC Med.*** 2023 Jul 11;21(1):219.
http://dx.doi.org/10.1186/s12916-023-02916-5



Cannabis (marijuana) use in pregnancy has been increasing. Prenatal exposure of mice to a CB2 agonist, JWH-133, had a sex-specific impact on their germ cell development: in males a delay of germ cell differentiation was observed, coinciding with an enrichment of H3K27me3.

Zucchi A, Innocenzi E, Onorato A, Dolci S, Colopi A, Balistreri CR, Grimaldi P. Prenatal exposure to CB2 receptors agonist differentially impacts male and female germ cells via histone modification. ***Mech Ageing Dev.*** 2023 Jul;213:111840. doi: 10.1016/j.mad.2023.111840. Epub 2023 Jun 28. PMID: 37385302
https://doi.org/10.1016/j.mad.2023.111840

The F2 generation of rat males indirectly exposed (F1 - via germ cells) to benzo(a)pyrene (BaP, a product of coal burning and cigarette smoke), exhibited a decrease in anogenital distance, fertility potential, testosterone levels, and sperm quality, together with affected histomorphology of the testis and epididymis.

Jorge BC, Stein J, Reis ACC, Bueno JN, Paschoalini BR, da Silva Moreira S, de Matos Manoel B, Arena AC. Paternal low-dose benzo(a)pyrene exposure in rats impairs sexual development and fertility of the paternal lineage in F2 generation: A transgenerational study. ***Toxicology***. 2023 Jun 25:153585. Epub ahead of print.
https://doi.org/10.1016/j.tox.2023.153585

cells

Using two models of immature rodent Sertoli cells, this study showed that phytoestrogen Genistein and analgesic acetaminophen (APAP) disrupt their function and development in vitro.

Gene expression studies identified p53, TNF, and TGF-β signaling pathways as main targets.

Corpuz-Hilsabeck M, Mohajer N, Culty M. Dysregulation of Immature Sertoli Cell Functions by Exposure to Acetaminophen and Genistein in Rodent Cell Models. ***Cells***. 2023; 12(13):1804.
https://doi.org/10.3390/cells12131804

Case report of the month

ANDROLOGY

This interesting study profiled longitudinally DNA methylation in frozen sperm from a testicular cancer patient before and up to 2 years after BEP chemotherapy. Numerous epigenetic modifications of the paternal genome were found, some with potentially deleterious effects on the offspring.

Neyroud AS, Rolland AD, Lecuyer G, Evrard B, Alary N, Dejucq-Rainsford N, Bujan L, Ravel C, Chalmel F. Sperm DNA methylation dynamics after chemotherapy: a longitudinal study of a patient with testicular germ cell tumor treatment. ***Andrology***. 2023 Jun 24. doi: 10.1111/andr.13485. Epub ahead of print.
https://doi.org/10.1111/andr.13485