EUROPEAN ACADEMY OF ANDROLOGY

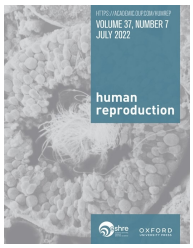
Dear EAA Members,

During the peak vacation season in Europe, your librarian had fun looking for interesting andrology-related studies in reputable scientific journals. As always, original studies are prioritised, with exceptions given to important meta-analyses, clinical guidelines or particularly debated topics. Keywords for this edition: semen analysis, sperm quality, sperm aminopeptidase, sperm mitochondria, testosterone therapy, transgender male, osteoporosis, COVID-19, cannabis, erectile dysfunction, prostatectomy, meiotic arrest, TRIM28, transdifferentiation, protamination, testis proteomics, and more.

Clinical andrology and epidemiology

Four recent publications addressed different aspects of human semen analysis (some in relation to the WHO manuals) and sperm preservation.

A new evidence for substantial diurnal oscillation of human semen parameters, with most parameters reaching a peak between 1100 and 1500 h.
Liu K, et al et Cao J. Diurnal rhythm of human semen quality: analysis of large-scale human sperm bank data and timing-controlled laboratory study. ***Hum Reprod.*** 2022 Jul 30;37(8):1727-1738. PMID: 35690928.
https://doi.org/10.1093/humrep/deac135



The authors demonstrated poor methodological agreement with the 5th ed. of the WHO semen analysis laboratory manual, despite 70% of papers stating that they followed the recommendations.
Vasconcelos AL, Campbell MJ, Barratt CLR, Gellatly SA. Do studies published in two leading reproduction journals between 2011 and 2020 demonstrate that they followed WHO5 recommendations for basic semen analysis? ***Hum Reprod.*** 2022 Aug 10:deac173. Epub ahead of print. PMID: 35947767.
https://doi.org/10.1093/humrep/deac173

Criteria for semen parameters according to the new WHO-2021 manual were compared with the WHO-2010. Overall, WHO-2021 criteria better identify a subgroup of patients with impaired reproductive health.
Boeri L, Fallara G, Pozzi E, Belladelli F, Corsini C, Raffo M, Schifano N, Capogrosso P, d'Arma A, Montorsi F, Salonia A. The impact of different WHO reference criteria for semen analysis in clinical practice: Who will benefit from the new 2021 thresholds for normal semen parameters? ***Andrology*** 2022 Sep;10(6):1134-1142. PMID: 35726049.
https://doi.org/10.1111/andr.13213

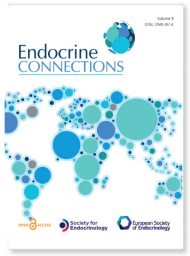
A technical advance for sperm banking in subject with low sperm counts and semen volume. Micro vapour fast freezing is better for these patients than vitrification.
Arciero V, Ammar O, Maggi M, Vignozzi L, Muratori M, Dabizzi S. Vapour fast freezing with low semen volumes can highly improve motility and viability or DNA quality of cryopreserved human spermatozoa. ***Andrology*** 2022 Sep;10(6):1123-1133. PMID: 35712876.
https://doi.org/10.1111/andr.13208

The group in Malmö compared health outcomes in

men who used donated spermatozoa to the ones who became fathers by using own sperm. The data were retrieved from Swedish nationwide register. Fathers who used donor spermatozoa had higher risk for testosterone treatment and dyslipidaemia.

Elenkov A, Zarén P, Sundell B, Lundin L, Giwercman A. Testosterone deficiency and metabolic disturbances in men who fathered a child by use of donated spermatozoa. ***Sci Rep.*** 2022 Aug 24;12(1):14458. PMID: 36002478.
https://doi.org/10.1038/s41598-022-17864-y

A useful systematic review analysed differences between the three most used testosterone preparations in adult men with hypogonadism and transgender males. The authors noted that current recommendations on testosterone treatment appear to be based on data primarily from non-randomized clinical studies and observational studies.



Madsen MC, Heijer MD, Pees C, Biermasz NR, Bakker LEH. Testosterone in men with hypogonadism and transgender males: a systematic review comparing three different preparations. ***Endocr Connect***. 2022 Jul 25;11(8):e220112. PMID: 35904217.
https://doi.org/10.1530/ec-22-0112

Investigators in China observed higher levels of the chemokine CXCL9 in the blood samples of men with subsequent hip fractures compared with controls. No such difference was seen in women.

Phan QT, Chua KY, Jin A, Winkler C, Koh WP. CXCL9 Predicts the Risk of Osteoporotic Hip Fracture in a Prospective Cohort of Chinese Men - A Matched Case-Control Study. ***J Bone Miner Res.*** 2022 Jul 10. Epub ahead of print. PMID: 35810382.
https://doi.org/10.1002/jbmr.4646

New evidence for lower total testosterone levels and altered sperm morphology in white male cannabis users compared to nonusers. No association was found for FSH or LH levels.

Belladelli F, Fallara G, Pozzi E, Corsini C, Cilio S, Raffo M, d'Arma A, Boeri L, Capogrosso P, Eisenberg M, Montorsi F, Salonia A. Effects of recreational cannabis on testicular function in primary infertile men. ***Andrology*** 2022; 10(6):1172-1180. PMID: 35868833.
https://doi.org/10.1111/andr.13235

C-reactive protein (CRP), a marker of inflammation, may be related to erectile dysfunction. This meta-analysis (of 12 studies) showed that CRP levels were significantly higher in patients with erectile dysfunction than the controls, and decreased after first-line PDE5i treatment.

Liu G, Zhang Y, Zhang W, Wu X, Jiang H, Huang H, Zhang X. Novel predictive risk factor for erectile dysfunction: Serum high-sensitivity C-reactive protein. ***Andrology*** 2022; 10(6):1096-1106. doi: 10.1111/andr.13206. PMID: 35713296.
https://doi.org/10.1111/andr.13206

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We informed EAA members last year about this survey addressed to men with infertility, developed by the Male Reproductive Health Initiative (MRHI) and the Fertility Europe.
Now the data are out and have revealed men's feelings about their infertility, and their awareness of resources for peer support and information. The authors highlighted significant gaps in the provision of male reproductive health care and offered recommendations on how to address the problem(s).

De Jonge CJ, Gellatly SA, Vazquez-Levin MH, Barratt CLR, Rautakallio-Hokkanen S. Male attitudes towards infertility: Results from a global questionnaire. ***W J Mens Health*** 2022;40:e56, published Aug 16, 2022.
https://doi.org/10.5534/wjmh.220099

A national case-control study in England and Wales showed that risk of breast cancer in men was associated with male-origin infertility (OR = 2.03,

95% CI 1.18-3.49). The reason is not clear and needs investigation.

Swerdlow AJ, Bruce C, Cooke R, Coulson P, Jones ME. Infertility and risk of breast cancer in men: a national case-control study in England and Wales. ***Breast Cancer Res.*** 2022; 24(1):29. PMID: 35578306.
https://doi.org/10.1186/s13058-022-01517-z

COVID-19

All clinicians interested in the impact of COVID-19 on male reproductive function and health should read the latest issue of Andrology, which contains the 4th batch of articles dedicated to this subject: https://onlinelibrary.wiley.com/toc/20472927/2022/10/6

The list below comprises only the studies that have not been announced in previous alerts:

Gat I, et al et Baum M. Covid-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. ***Andrology*** 2022; 10(6):1016-1022.
Olana S, et al et Faggiano A. 4BNT162b2 mRNA COVID-19 vaccine and semen: What do we know? ***Andrology*** 2022; 10(6):1023-1029.
Morselli S, et al et Gacci M. Male reproductive system inflammation after healing from coronavirus disease 2019. ***Andrology*** 2022; 10(6):1030-1037.
Apaydin T, et al et Iliksu Gozu H. The association of free testosterone levels with coronavirus disease 2019. ***Andrology*** 2022; 10(6):1038-1046.
Enikeev D, et al et Glybochko P. Prospective two-arm study of the testicular function in patients with COVID-19. ***Andrology*** 2022; 10(6):1047-1056.

Debate

Human sperm production is widely believed to be declining over time, but evidence from the scientific literature is sometimes contradictory. This thorough analysis performed by French colleagues (incl. the late Bernard Jégou) shows that the available data do not allow to conclude that human semen quality is deteriorating worldwide but a trend is observed in some areas. The authors call for prospective studies, preferably in combination with assessment of the male exposome.

Auger J, Eustache F, Chevrier C, Jégou B. Spatiotemporal trends in human semen quality. ***Nat Rev Urol***. 2022 Aug 17:1–30. Epub ahead of print. PMID: 35978007.
https://www.nature.com/articles/s41585-022-00626-w

Case story of the month

The first robot-assisted radical prostatectomies (RARPs) performed in Europe (Belgium) with the new Hugo RAS system (Medtronic) are described in this article (gracing the cover). The five patients underwent RARP ± lymph node dissection, with the median operative time of 170 min and the median console time of 120 min. The study proves the safety and feasibility of RARP with the Hugo RAS system and provides relevant data that may be of help to early adopters of this platform.

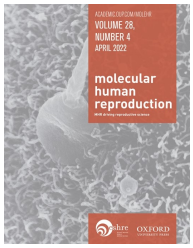
Bravi CA, Paciotti M, Sarchi L, Mottaran A, Nocera L, Farinha R, De Backer P, Vinckier MH, De Naeyer G, D'Hondt F, De Groote R, Mottrie A. Robot-assisted Radical Prostatectomy with the Novel Hugo Robotic System: Initial Experience and Optimal Surgical Set-up at a Tertiary Referral Robotic Center. ***Eur Urol.*** 2022 Aug; 82(2):233-237. PMID: 35568597.
https://doi.org/10.1016/j.eururo.2022.04.029

Androgenetics

This study from Poznan (Poland) using the whole genome sequencing approach identified novel potential candidate NOA-associated genes (incl. novel variants of *TKTL1, IGSF1, ZFPM2, VCX3A*) in 29 out of 39 azoospermic males, including 5 of 6 patients subjected previously to whole exome sequencing, which did not disclose potentially causative variants.

Malcher A, Stokowy T, Berman A, Olszewska M, Jedrzejczak P, Sielski D, Nowakowski A, Rozwadowska N, Yatsenko AN, Kurpisz M. Whole genome sequencing identifies new candidate genes for nonobstructive azoospermia. ***Andrology*** 2022 Aug 25. Epub ahead of print. PMID: 36017582.
https://doi.org/10.1111/andr.13269

KASH5 is a component of the LINC complex that regulates meiotic prophase I in mouse spermatocytes. In this study, novel heterozygous variants in human *KASH5* were identified in a patient with NOA and meiotic arrest and in his infertile sister. Kash5 knockout mouse displayed similar phenotypes.



Yang C, Lin X*, et al et,* Yao C. Novel bi-allelic variants in KASH5 are associated with meiotic arrest and non-obstructive azoospermia. ***Mol Hum Reprod***. 2022; 28(7), PMID: 35674372.
https://doi.org/10.1093/molehr/gaac021

Defining the transition from benign to malignant tissue is fundamental to improving early diagnosis of cancer. The authors used spatially resolved transcriptomics to study genome integrity using an organ-wide approach focused on the prostate, and described previously unidentified clonal relationship within tumours and in nearby benign tissue.

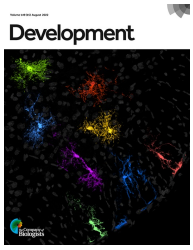
Erickson A, He M, Berglund E, *et al et* Lamb AD, Lundeberg J. Spatially resolved clonal copy number alterations in benign and malignant tissue. ***Nature*** 2022 Aug; 608(7922):360-367. PMID: 35948708.
https://doi.org/10.1038/s41586-022-05023-2

Translational and basic andrology

This exciting study shows that TRIM28 (in addition to previously known FOXL2) is required to prevent female-to-male sex reversal of the mouse ovary after birth. Upon loss of *Trim28*, ovarian granulosa cells transdifferentiate to Sertoli cells through an intermediate cell type. The role of TRIM28 depends on its E3-SUMO ligase activity.

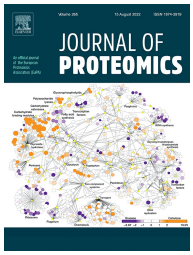
Rossitto M, Déjardin S, Rands CM, Le Gras S, Migale R, Rafiee MR, Neirijnck Y, Pruvost A, Nguyen AL, Bossis G, Cammas F, Le Gallic L, Wilhelm D, Lovell-Badge R, Boizet-Bonhoure B, Nef S, Poulat F. TRIM28-dependent SUMOylation protects the adult ovary from activation of the testicular pathway. ***Nat Commun*** 2022 Jul 29; 13(1):4412. PMID: 35906245.

Analysis of protamine 1-deficient mice revealed that homozygous males are infertile, whereas heterozygous ($Prm1^{+/-}$) males are subfertile, with *Prm1* deficiency leading to defective chromatin compaction and sperm damage.



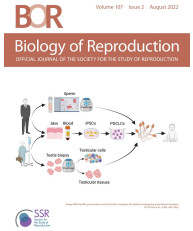
Merges GE, Meier I, Schneider S, Kruse A, Fröbius AC, Kirfel G, Steger K, Arévalo L, Schorle H. Loss of Prm1 leads to defective chromatin protamination, impaired PRM2 processing, reduced sperm motility and subfertility in male mice. ***Development*** 2022; 149(12):dev200330. PMID: 35608054.
https://doi.org/10.1242/dev.200330

Using a comparative proteomics approach on testis tissue this study identified several pathways associated with azoospermia and a number of testis-specific and germ cell-specific proteins that have the potential to pinpoint the type of spermatogenesis failure. Gene expression analysis of 6 genes (H1-6, RANBP1, TKTL2, TKTL1, H2BC1, ACTL7B) confirmed the proteomics results.



Davalieva K, Rusevski A, Velkov M, Noveski P, Kubelka-Sabit K, Filipovski V, Plaseski T, Dimovski A, Plaseska-Karanfilska D. Comparative proteomics analysis of human FFPE testicular tissues reveals new candidate biomarkers for distinction among azoospermia types and subtypes. ***J Proteomics***. 2022 Jul 29:104686. PMID: 35914715.
https://doi.org/10.1016/j.jprot.2022.104686

This well-designed study demonstrated the interactions of TBC1D21 with ACTB, TPM3, SPATA19, and VDAC3 to regulate the architecture of the mouse sperm midpiece. The findings suggest that TBC1D21 is a scaffold protein required for the organization and stabilization of the mitochondrial sheath structure.



Chen Y, *et al et* Yin C. TBC1D21 is an essential factor for sperm mitochondrial sheath assembly and male fertility. ***Biol Reprod***. 2022 Aug 9;107(2):619-634. PMID: 35403672.
https://doi.org/10.1093/biolre/ioac069

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