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Dear EAA Members,

The second summer edition brings for your consideration several important clinical and basic studies. The keywords helping you decide whether or not this issue is worthy your attention: late-onset hypogonadism – comorbidities and treatment, inhibin B levels throughout life, CAG/GGC repeats in the AR, sperm cryopreservation (incl. a new textbook), sperm DNA fragmentation, penile prosthesis, rising prevalence of cryptorchidism, debate on “fertility industry”, novel gene variants associated with male fertility in humans and mice, DDX4 granules in cancer cells, GARINs and sperm head morphogenesis, diffusion tensor imaging and fiber tractography, AI in andrology, and more.

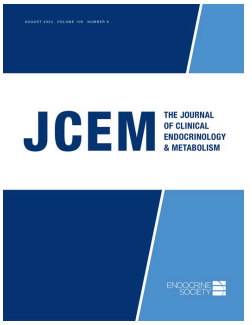
Clinical andrology and epidemiology

Annals of Internal Medicine®

A rigorous meta-analysis done by a group of experts (including EAA Academicians) trying to reconcile the inconsistent findings on the mortality in men with late age hypogonadism.
The conclusion is that only men with low testosterone (T) concentrations <7.4 nmol/l) had a higher risk for all-cause mortality, regardless of LH concentration, while men with T <5.5 nmol/L had high risk of cardiovascular death.

Yeap BB, Marriott RJ, Dwivedi G, Adams RJ, Antonio L, Ballantyne CM, Bauer DC, Bhasin S, Biggs ML, Cawthon PM, Couper DJ, Dobs AS, Flicker L, Handelsman DJ, Hankey GJ, Hannemann A, Haring R, Hsu B, Martin SA, Matsumoto AM, Mellström D, Ohlsson C, O'Neill TW, Orwoll ES, Quartagno M, Shores MM, Steveling A, Tivesten Å, Travison TG, Vanderschueren D, Wittert GA, Wu FCW, Murray K. Associations of Testosterone and Related Hormones With All-Cause and Cardiovascular Mortality and Incident Cardiovascular Disease in Men: Individual Participant Data Meta-analyses. ***Ann Intern Med***. 2024 Jun;177(6):768-781.
https://doi.org/10.7326/m23-2781
Editorial by BD Anawalt: The Relationship of Sex Steroid Hormones and Clinical Outcomes Is Complex https://doi.org/10.7326/M24-0875

This trial determined the effect of testosterone (T) treatment on health-related quality of life (QoL) in >1000 men without pathologic hypogonadism. Weight loss induced by a lifestyle intervention improved QoL and psychosocial function in more domains than the T treatment. The magnitude of weight reduction were predicted by baseline physical function, depressive symptomology, and sense of coherence.



Grossmann M, Robledo KP, Daniel M, Handelsman DJ, Inder WJ, Stuckey BGA, Yeap BB, Ng Tang Fui M, Bracken K, Allan CA, Jesudason D, Zajac JD, Wittert GA. Testosterone Treatment, Weight Loss, and Health-related Quality of Life and Psychosocial Function in Men: A 2-year Randomized Controlled Trial. ***J Clin Endocrinol Metab.*** 2024 Jul 12;109(8):2019-2028.
https://doi.org/10.1210/clinem/dgae085

Androgens affect erythrocyte lifespan. This study showed that hypogonadal men have reduced erythrocyte lifespan, and testosterone treatment improved that transiently, while blood haemoglobin remained elevated for a longer time.



McMartin MC, Savkovic S, Romano A, Lim S, Muir CA, Jayadev V, Conway AJ, Seccombe L, Handelsman DJ. Testosterone and Erythrocyte Lifespan. ***J Clin Endocrinol Metab.*** 2024 Jun 24:dgae434. Epub ahead of print.
https://doi.org/10.1210/clinem/dgae434

To re-examine how AR trinucleotide repeats affect androgen-related traits and disease risks, this study quantified the repeats in UK Biobank (>180 K men). Longer CAG and GGC repeats influenced androgen resistance, elevated circulating testosterone (T) via a feedback loop and played a role in some androgen-targeted tissues. But circulating T level is a more important determinant of androgen action than the repeats.



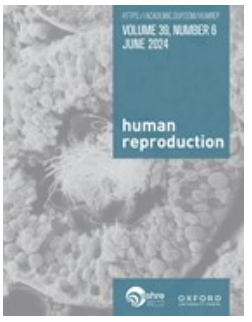
Sasako T, Ilboudo Y, Liang KYH, Chen Y, Yoshiji S, Richards JB. The influence of trinucleotide repeats in the androgen receptor gene on androgen-related traits and diseases. ***J Clin Endocrinol Metab.*** 2024 May 3:dgae302. Epub ahead of print.
https://doi.org/10.1210/clinem/dgae302
Commentary by S. Bhasin (JCEM): https://doi.org/10.1210/clinem/dgae505

Sex- and age-specific reference ranges of serum inhibin B concentrations were established based on samples from 2707 healthy controls (0 to 80 y.), and in 42 males with Klinefelter syndrome (KS). In the KS patients, the decline in inhibin B at puberty underlined the shift in regulation of inhibin B production.



Borelli-Kjær A, Aksglaede L, Jensen RB, Hagen CP, Ljubicic ML, Busch AS, Upners EN, Fischer MB, Jensen TK, Linneberg A, Kårhus LL, Andersson AM, Petersen JH, Juul A, Johannsen TH. Serum Concentrations of Inhibin B in Healthy Females and Males Throughout Life. ***J Clin Endocrinol Metab.*** 2024 Jun 26:dgae439. Epub ahead of print.
https://doi.org/10.1210/clinem/dgae439

Using frozen vs fresh sperm in ICSI resulted in statistically significant decrease in pregnancy rate, live birth rate (LBR) and cumulative LBR. However, the differences are so small that clinically can be overlooked in favour of the many benefits of sperm cryopreservation.



Gil Juliá M, Cozzolino M, Navarro-Gomezlechon A, Hervas I, Mossetti L, Pacheco-Rendón RM, Rivera-Egea R, Garrido N. Assessment of reproductive outcomes of fresh versus cryopreserved ejaculated sperm samples-a retrospective analysis of 44 423 oocyte donation ICSI cycles. ***Hum Reprod.*** 2024 May 9:deae088. Epub ahead of print.
https://doi.org/10.1093/humrep/deae088

This study looked at sperm DNA fragmentation index (DFI) in association with recurrent pregnancy loss (RPL). At referral, sperm DFI, morphology and concentration did not identify RPL couples at risk of another pregnancy loss. Increased baseline DFI was associated with difficulty achieving another pregnancy.



Krog MC, Nielsen JR, Slot A, Hviid KV, Kolte AM, Westergaard D, Bliddal S, Almstrup K, Nielsen HS. Prospective reproductive outcomes according to sperm parameters, including DNA fragmentation, in recurrent pregnancy loss. ***Reprod Biomed Online.*** 2024 Aug;49(2):103773.
https://doi.org/10.1016/j.rbmo.2023.103773

Men with severe oligozoospermia (≤ 1 M/ml), especially those with low testosterone levels, have a dramatically increased chance of becoming azoospermic with time. Sperm banking should be recommended in these cases. Men with a sperm concentration >1 M/ml are not at a high risk of becoming azoospermic.



Karavani G, Kattan MS, Lau S, Lo KC, Grober ED, Mehra VM, Akroof B, Lajkosz K, Jarvi K. Idiopathic secondary azoospermia occurrence in men with oligospermia over time. ***J Assist Reprod Genet***. 2024 Jun 28.
https://doi.org/10.1007/s10815-024-03179-6

A comprehensive meta-analysis, based on 83 studies and >12000 subjects, assessed patient satisfaction after penile prosthesis.
The analysis revealed a high satisfaction rate (average 83%) and a low long-term complication rate (3-5%).

Corona G, Santi D, Cocci A, Vena W, Pizzocaro A, Vignozzi L, Isidori AM, Pivonello R, Salonia A, Minhas S, Bettocchi C, Reisman Y, Maggi M. Long-term penile prosthesis couple's satisfaction: A systematic review and meta-analysis. ***Andrology***. 2024 Jul 16. Epub ahead of print.
https://doi.org/10.1111/andr.13696

Data from the national surveillance system in China were analysed and revealed that overall prevalence of cryptorchidism tripled within the study period.
Significant variations were observed across maternal age and residence (urban vs. rural), and geographic regions.

Li W, Chen Z, Xu W, Gao Y, Liu Z, Li Q, Dai L. Prevalence of congenital cryptorchidism in China: A nationwide population-based surveillance study, 2007-2021. ***Andrology***. 2024 Jul 3. Epub ahead of print.
https://doi.org/10.1111/andr.13686

Debate

This editorial raised the important issue of the industry and private clinics pushing procedures used in medically assisted reproduction without scientific evidence, exemplified by two trials published recently in the Lancet.



The Lancet. The fertility industry: profiting from vulnerability. ***Lancet***. 2024 Jul 20;404(10449):215.
https://doi.org/10.1016/s0140-6736(24)01484-3

In infertile couples with non-severe male factor, ICSI did not improve live birth rate compared with conventional IVF, and should not be used routinely in this population.



Wang Y, Li R, Yang R, et al et Huang H, Qiao J. Intracytoplasmic sperm injection versus conventional in-vitro fertilisation for couples with infertility with non-severe male factor: a multicentre, open-label, randomised controlled trial. ***Lancet***. 2024 Mar 9;403(10430):924-934.
https://doi.org/10.1016/s0140-6736(23)02416-9

In women undergoing IVF or ICSI, the use of time-lapse imaging systems for embryo selection does not significantly increase the odds of live birth compared with standard care.



Bhide P, Chan DYL, Lanz D, et al et Perez T, Khan KS, Thangaratinam S. Clinical effectiveness and safety of time-lapse imaging systems for embryo incubation and selection in in-vitro fertilisation treatment (TILT): a multicentre, three-parallel-group, double-blind, randomised controlled trial. ***Lancet***. 2024 Jul 20;404(10449):256-265.
https://doi.org/10.1016/s0140-6736(24)00816-x

Androgenetics

Two articles in *Andrology* coming up in the special issue on genetics:



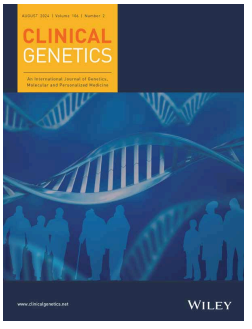
This study found diverse phenotypic consequences of allelic variants that disrupt the AF-2 region of the AR gene in patients with AIS.

Giuliatti S, Benedetti AFF, Ramos RM, Petroli RJ, Domenice S, Mendonca BB, Batista RL. Hydropathic AF-2 variants in the androgen receptor gene among androgen insensitivity patients. ***Andrology***. 2024 Jun 26.
https://doi.org/10.1111/andr.13680

A novel LRRC6 mutation leading to primary ciliary dyskinesia was identified. Further analysis found shortening of sperm flagella, absence of dynein arms, and incomplete mitochondrial sheath in the mid-piece. ICSI successfully induced pregnancy.

Shi S, Tang X, Long S, et al et Qiao S, Lin T. A novel homozygous LRRC6 mutation causes male infertility with asthenozoospermia and primary ciliary dyskinesia in humans. ***Andrology***. 2024 Jun 27.
https://doi.org/10.1111/andr.13685

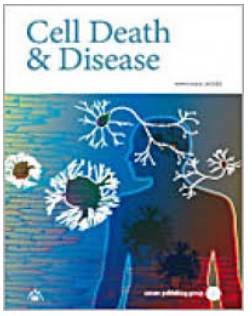
TDRKH is a factor essential for piRNA biogenesis in germ cells. A homozygous variant in *TDRKH* was identified in an Iranian family with NOA, confirming previous observations in a North African cohort. Men carrying *TDRKH* variants and Tdrkh KO mice exhibit spermatogenic arrest, correlating with failed sperm retrieval.



Amiri-Yekta A, Sen S, Hazane-Puch F, Tebbakh C, Roux-Buisson N, Cazin C, Thierry-Mieg N, Bouras A, Mohammad Ali SG, Hosseini SH, Goodarzian M, Gourabi H, Ray PF, Kherraf ZE. Whole genome sequencing identifies a homozygous splicing variant in TDRKH segregating with non-obstructive azoospermia in an Iranian family. ***Clin Genet***. 2024 Jul 2.
https://doi.org/10.1111/cge.14584

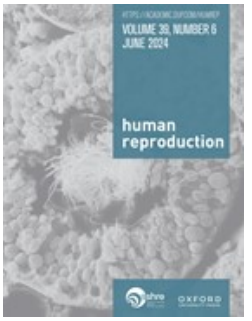
Basic and translational andrology

Variants in AXDND1 were identified in infertile men with oligo- or azoospermia. In this study, a KO mouse model revealed that *Axdnd1*$^{-/-}$ males were sterile following one round of histologically replete spermatogenesis, suggesting a role for AXDND1 in spermatogonial maintenance. In addition, sperm were immotile due to abnormal axoneme structure.



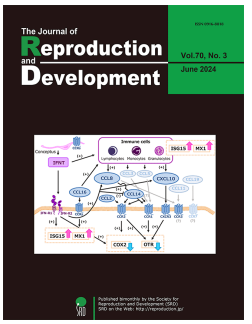
Houston BJ, Nguyen J, Merriner DJ, O'Connor AE, Lopes AM, Nagirnaja L, Friedrich C, Kliesch S, Tüttelmann F, Aston KI, Conrad DF, Hobbs RM, Dunleavy JEM, O'Bryan MK. AXDND1 is required to balance spermatogonial commitment and for sperm tail formation in mice and humans. ***Cell Death Dis.*** 2024 Jul 12;15(7):499.
https://doi.org/10.1038/s41419-024-06874-5

Sequencing of infertile men and fertile controls identified *TEX13B* as a potential candidate infertility gene. In this study, the authors produced a Tex13b KO mouse and conditional overexpression system in GC-1 spg cells, and concluded that TEX13B regulates male germ cell differentiation by metabolic reprogramming.



Kumar U, Sudhakar DVS, Kumar N, Moitra A, Kale HT, Jha RK, Rawat S, Verma G, Gupta NJ, Deenadayal M, Tolani AD, Raychaudhuri S, Chandra Shekar P, Thangaraj K. TEX13B is essential for metabolic reprogramming during germ cell differentiation. Hum Reprod. 2024 May 13:deae094. Epub ahead of print.
https://doi.org/10.1093/humrep/deae094

This study found that *Kdm4dl* mutant mice developed normally but were subfertile because of impaired sperm motility. The absence of Kdm4d was associated with an altered distribution of H3K9me3 in round spermatids. KDM4D is also expressed in the human testes, warranting studies in infertile men.



Xu Z, Fujimoto Y, Sakamoto M, Ito D, Ikawa M, Ishiuchi T. Kdm4d mutant mice show impaired sperm motility and subfertility. ***J Reprod Dev***. 2024 Jul 22. Epub ahead of print.
https://doi.org/10.1262/jrd.2024-039

Cancer cells often express germ-cell-specific genes ectopically. This excellent study showed that the germ-granule-resembling DDX4 granules control gene expression and promote malignant and invasive properties of cancer cells. The occurrence of DDX4 granules is associated with poor survival in patients with some tumours, including prostate cancer.



Olotu O, Koskenniemi AR, Ma L, Paramonov V, Laasanen S, Louramo E, Bourgery M, Lehtiniemi T, Laasanen S, Rivero-Müller A, Löyttyniemi E, Sahlgren C, Westermarck J, Ventelä S, Visakorpi T, Poutanen M, Vainio P, Mäkelä JA, Kotaja N. Germline-specific RNA helicase DDX4 forms cytoplasmic granules in cancer cells and promotes tumor growth. ***Cell Rep.*** 2024 Jul 3;43(7):114430.
https://doi.org/10.1016/j.celrep.2024.114430

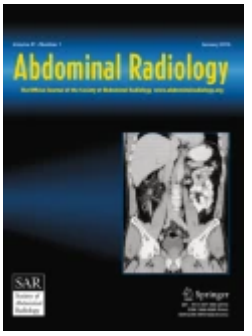
Golgi-associated proteins GARIN1A/1B are important for acrosome biogenesis in mice. This study looked at the effects of KO of other GARINs and found that GARINs assure correct sperm head morphogenesis, and some members of the GARIN family function distinctively in male fertility.



Wang H, Iida-Norita R, Mashiko D, Pham AH, Miyata H, Ikawa M. Golgi associated RAB2 interactor protein family contributes to murine male fertility to various extents by assuring correct morphogenesis of sperm heads. ***PLoS Genet.*** 2024 Jun 27;20(6):e1011337.
https://doi.org/10.1371/journal.pgen.1011337

Methodology

The authors assessed the utility of 3.0 T Diffusion Tensor Imaging (DTI) and Fiber Tractography (FT) of the testes in the work-up of nonobstructive azoospermia, and found that this imaging was helpful to distinguish Sertoli-cell-only from spermatogenic arrests.



Pappa O, Astrakas L, Anagnostou N, Bougia CK, Maliakas V, Sofikitis N, Argyropoulou MI, Tsili AC. 3.0 T diffusion tensor imaging and fiber tractography of the testes in nonobstructive azoospermia. ***Abdom Radiol (NY)***. 2024 Jun 28.
https://doi.org/10.1007/s00261-024-04457-8

Two studies explored artificial intelligence (AI) tools in andrology:

1. A proof-of-concept study showed that AI-aided image analysis tool can improve sperm search times in testis tissue samples, thus reducing physical strain and fatigue on embryologists.



Goss DM, Vasilescu SA, Vasilescu PA, Cooke S, Kim SH, Sacks GP, Gardner DK, Warkiani ME. Evaluation of an artificial intelligence-facilitated sperm detection tool in azoospermic samples for use in ICSI. ***Reprod Biomed Online.*** 2024; 49(1):103910.

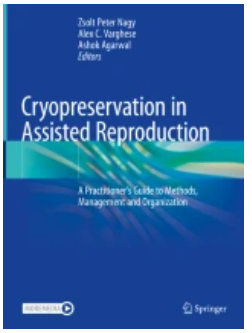
2. The accuracy of ChatGPT4.0 was tested in a large number of clinical queries used in managing male infertility. The information was judged as reliable and guideline-based, helping clinicians and supporting patient education.



Gokmen O, Gurbuz T, Devranoglu B, Karaman MI. Artificial intelligence and clinical guidance in male reproductive health: ChatGPT4.0's AUA/ASRM guideline compliance evaluation. ***Andrology***. 2024 Jul 17.
https://doi.org/10.1111/andr.13693

Book of the Month

Cryopreservation in Assisted Reproduction
A Practitioner's Guide to Methods, Management and Organization
Editors: Zsolt Peter Nagy, Alex C. Varghese, Ashok Agarwal



The book contains 59 chapters and provides a comprehensive overview of the basics of cryobiological processes and a technically detailed presentation on all aspects of cryopreservation of reproductive cells and tissues, including sperm and testis tissue.
DOI https://doi.org/10.1007/978-3-031-58214-1
eBook ISBN978-3-031-58214-1
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