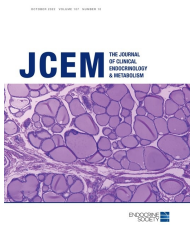
EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

This month's selection of interesting articles across andrology-related fields, includes the following topics: cryptorchidism, semen analysis, Klinefelter syndrome, varicocele, hypothyroidism, metabolism of ICSI-conceived men, Peyronie disease, COVID-19, piRNA-pathway, sperm epigenetics, TART, seminal fluid microbiome, sperm-egg complex, endocrine disrupters, and more.

Clinical andrology and epidemiology



This prospective, longitudinal study compared pubertal hormone levels between boys with and without a history of congenital cryptorchidism. Cryptorchid boys, in particular those with bilateral cryptorchidism who underwent orchiopexy, had altered levels of FSH, Inhibin B and smaller testicular volumes compared with controls.

Rodprasert W, Koskenniemi JJ, Virtanen HE, Sadov S, Perheentupa A, Ollila H, Albrethsen J, Andersson AM, Juul A, Skakkebaek NE, Main KM, Toppari J. Reproductive markers of testicular function and size during puberty in boys with and without a history of cryptorchidism. ***J Clin Endocrinol Metab***. 2022 Sep 8:dgac520. Epub ahead of print. PMID: 36073163.
https://doi.org/10.1210/clinem/dgac520

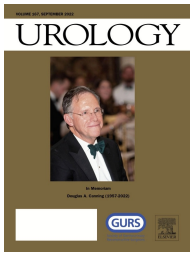
In this population-based prospective study, higher maternal gestational urinary bisphenol and phthalate concentrations were associated with alterations in offspring reproductive development, mainly in boys (earlier puberty and larger testis) but not with the risk of cryptorchidism or hypospadias.

Blaauwendraad SM, Jaddoe VW, Santos S, Kannan K, Dohle GR, Trasande L, Gaillard R. Associations of maternal urinary bisphenol and phthalate concentrations with offspring reproductive development. ***Environ Pollut***. 2022 Sep 15;309:119745. PMID: 35820574.
https://doi.org/10.1210/clinem/dgac520

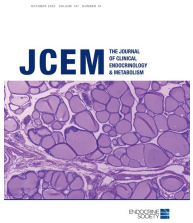
To explore the possible association between varicocele at adolescence and the incidence of testicular cancer at adulthood, a retrospective, population-based study was performed in Israel. No association was found.

Verhovsky G, Giladi M, Tzur D, Afek A, Keinan-Boker L, Derazne E, Kaminsky D, Hoffman A, Erlich T, Neuman T. Varicocele in adolescence and testicular cancer in young adulthood. ***Andrology***. 2022 Sep 6. Epub ahead of print. PMID: 36068656.
https://doi.org/10.1111/andr.13280

Widespread adoption and early usage of home semen analysis may be a cost-effective method of screening for oligospermia and facilitating further evaluation with an andrology specialist.

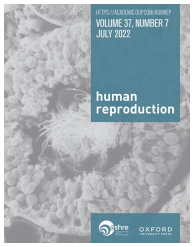


Lai JD, Fantus RJ, Meza JA, Hudnall MT, Pham M, Brannigan RE, Ghomrawi HMK, Halpern JA. Cost-effectiveness of early screening home semen analysis in couples attempting to conceive. ***Urology***. 2022 Sep 14:S0090-4295(22)00776-2. doi: 10.1016/j.urology.2022.06.053. Epub ahead of print. PMID: 36115433.
https://www.goldjournal.net/article/S0090-4295(22)00776-2/fulltext



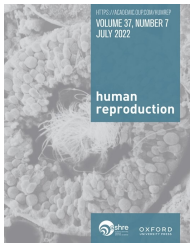
Paternal subclinical hypothyroidism (SCH) can have a detrimental effect on the clinical outcomes of ART. This cross-sectional study examined the sperm DNA fragmentation index (DFI) in men with SCH seeking infertility treatment and found a significant association with the risk of abnormal DFI.

Zhao S, Tang L, Fu J, Yang Z, Su C, Rao M. Subclinical Hypothyroidism and Sperm DNA Fragmentation: A Cross-sectional Study of 5401 Men Seeking Infertility Care. ***J Clin Endocrinol Metab*** 2022; 107(10):e4027-e4036.
https://doi.org/10.1210/clinem/dgac458



The difference in sperm retrieval rate (SRR) in TESE was not significant between the 'Young' (15-22 years old) cohort and the 'Adult' (23-43 years old) cohort of non-mosaic Klinefelter patients recruited prospectively in parallel.

Renault L, Labrune E, Giscard d'Estaing S, Cuzin B, Lapoirie M, Benchaib M, Lornage J, Soignon G, de Souza A, Dijoud F, Fraison E, Pral-Chatillon L, Bordes A, Sanlaville D, Schluth-Bolard C, Salle B, Ecochard R, Lejeune H, Plotton I. Delaying testicular sperm extraction in 47,XXY Klinefelter patients does not impair the sperm retrieval rate, and AMH levels are higher when TESE is positive. ***Hum Reprod.*** 2022 Sep 16:deac203. doi: 10.1093/humrep/deac203. Epub ahead of print. PMID: 36112034.
https://doi.org/10.1093/humrep/deac203



ICSI-conceived men, compared with spontaneously conceived controls, showed differences in some metabolic parameters including higher resting diastolic blood pressure and HOMA-IR scores, although the metabolic parameters of ICSI- and IVF-conceived singleton men were comparable.

Catford SR, Halliday J, Lewis S, O'Bryan MK, Handelsman DJ, Hart RJ, McBain J, Rombauts L, Amor DJ, Saffery R, McLachlan RI. The metabolic health of young men conceived using intracytoplasmic sperm injection. ***Hum Reprod***. 2022 Sep 27:deac212. Epub ahead of print. PMID: 36166702.

https://doi.org/10.1093/humrep/deac212

Peyronie's disease (PD) has previously been observed to co-aggregate in a small number of first-degree relative pairs (e.g., father-son). This study provided evidence that supports a genetic contribution to at least a subset of PD cases.

Allen-Brady KL, Christensen MB, Sandberg AD, Pastuszak AW. Significant familial clustering of Peyronie's disease in close and distant relatives. ***Andrology***. 2022 Oct;10(7):1361-1367. doi: 10.1111/andr.13223. Epub 2022 Jul 13. PMID: 35770847; PMCID: PMC9481671.

COVID-19

JAMA Network Open

Additional evidence showing that men with hypogonadism who contract COVID-19 are more likely to be hospitalized compared with those with normal testosterone levels.

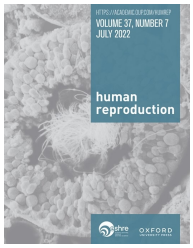
Dhindsa S, Champion C, Deol E, Lui M, Campbell R, Newman J, Yeggalam A, Nadella S, Ahir V, Shrestha E, Kannampallil T, Diwan A. Association of Male Hypogonadism With Risk of Hospitalization for COVID-19. ***JAMA Netw Open***. 2022 Sep 1;5(9):e2229747. PMCID: PMC9440397.
https://doi.org/10.1001/jamanetworkopen.2022.29747

Semen parameters following COVID-19 vaccination (mRNA and viral-vector vaccines) did not display any detrimental effect from vaccination.

Massarotti C, Stigliani S, Maccarini E, Bovis F, Ferraro MF, Gazzo I, Anserini P, Scaruffi P. mRNA and Viral Vector COVID-19 Vaccines Do Not Affect Male Fertility: A Prospective Study. ***World J Mens Health***. 2022 Oct;40(4):561-569. PMID: 36047075.

https://doi.org/10.5534/wjmh.220055

Debate



An important consensus statement voiced by a large group of prominent andrologists from around the globe, including numerous EAA members. They proposed that authors of studies including semen analysis ought to follow standardised laboratory methods (the 6th edition of the WHO Lab Manual for the Examination and Processing of Human Semen, and the ISO 23162:2021) and should use a mandatory checklist.

Björndahl L, Barratt CLR, Mortimer D, Agarwal A, Aitken RJ, Alvarez JG, Aneck-Hahn N, Arver S, Baldi E, Bassas L, Boitrelle F, Bornman R, Carrell DT, Castilla JA, Cerezo Parra G, Check JH, Cuasnicu PS, Darney SP, de Jager C, De Jonge CJ, Drevet JR, Drobnis EZ, Du Plessis SS, Eisenberg ML, Esteves SC, Evgeni EA, Ferlin A, Garrido N, Giwercman A, Goovaerts IGF, Haugen TB, Henkel R, Henningsohn L, Hofmann MC, Hotaling JM, Jedrzejczak P, Jouannet P, Jørgensen N, Kirkman Brown JC, Krausz C, Kurpisz M, Kvist U, Lamb DJ, Levine H, Loveland KL, McLachlan RI, Mahran A, Maree L, Martins da Silva S, Mbizvo MT, Meinhardt A, Menkveld R, Mortimer ST, Moskovtsev S, Muller CH, Munuce MJ, Muratori M, Niederberger C, O'Flaherty C, Oliva R, Ombelet W, Pacey AA, Palladino MA, Ramasamy R, Ramos L, Rives N, Roldan ER, Rothmann S, Sakkas D, Salonia A, Sánchez-Pozo MC, Sapiro R, Schlatt S, Schlegel PN, Schuppe HC, Shah R, Skakkebæk NE, Teerds K, Toskin I, Tournaye H, Turek PJ, van der Horst G, Vazquez-Levin M, Wang C, Wetzels A, Zeginiadou T, Zini A. Standards in semen examination: publishing reproducible and reliable data based on high-quality methodology. ***Hum Reprod***. 2022 Sep 16:deac189. Epub ahead of print. PMID: 36112046.

https://doi.org/10.1093/humrep/deac189

Growing evidence has shown an association between male subfertility and poor general health, but the mechanistic link is not well understood. Our Australian colleagues present a hypothesis that enzymes involved in the lipid oxidation process might provide novel clues and call for more research in this area.

Burke ND, Nixon B, Roman SD, Schjenken JE, Walters JLH, Aitken RJ, Bromfield EG. Male infertility and somatic health - insights into lipid damage as a mechanistic link. ***Nat Rev Urol.*** 2022 Sep 13. doi: 10.1038/s41585-022-00640-y. Epub ahead of print. PMID: 36100661.
https://doi.org/10.1038/s41585-022-00640-y

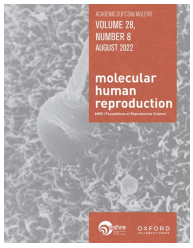
Androgenetics

A new excellent study from the GEMINI Consortium identified rare bi-allelic loss-of-function variants in *FKBP6* in infertile men with spermatogenic arrest at the stage of round spermatids. Small RNA sequencing revealed that loss of FKBP6 severely impacted piRNA levels, supporting a role for FKBP6 in piRNA biogenesis and formation of the synaptonemal complex in humans.

Wyrwoll MJ, Gaasbeek CM, Golubickaite I, Stakaitis R, Oud MS, Nagirnaja L, Dion C, Sindi EB, Leitch HG, Jayasena CN, Sironen A, Dicke AK, Rotte N, Stallmeyer B, Kliesch S, Grangeiro CHP, Araujo TF, Lasko P; Genetics of Male Infertility Initiative (GEMINI) consortium, D'Hauwers K, Smits RM, Ramos L, Xavier MJ, Conrad DF, Almstrup K, Veltman JA, Tüttelmann F, van der Heijden GW. The piRNA-pathway factor FKBP6 is essential for spermatogenesis but dispensable for control of meiotic LINE-1 expression in humans. ***Am J Hum Genet.*** 2022 Sep 16:S0002-9297(22)00405-0. Epub ahead of print. PMID: 36150389.

https://doi.org/10.1016/j.ajhg.2022.09.002

This nice study defined a novel phenotype of an



acrosomal abnormality and characterised the mechanism. A patient with teratozoospermia and bubble-shaped acrosomes was found to carry a variant of actin-like 7A (ACTL7A). Homozygous Actl7a(-) male mice were sterile, and the mutant sperm failed to activate the oocyte. Assisted oocyte activation by calcium ionophore exposure successfully overcame fertilisation failure.

Dai J, Chen Y, Li Q, Zhang T, Zhou Q, Gong F, Lu G, Zheng W, Lin G. Pathogenic variant in ACTL7A causes severe teratozoospermia characterized by bubble-shaped acrosomes and male infertility. ***Mol Hum Reprod***. 2022 Jul 29;28(8):gaac028. PMID: 35863052.

https://doi.org/10.1093/molehr/gaac028

This study aimed to elucidate if copy number variants (CNVs) are associated with non-obstructive azoospermia (NOA) using a-CGH or exome sequencing, with the latter approach judged as more effective. CNVs were not detected more frequently in infertile men compared with controls.

Wyrwoll MJ, Wabschke R, Röpke A, Wöste M, Ruckert C, Perrey S, Rotte N, Hardy J, Astica L, Lupiáñez DG, Wistuba J, Westernströer B, Schlatt S, Berman AJ, Müller AM, Kliesch S, Yatsenko AN, Tüttelmann F, Friedrich C. Analysis of copy number variation in men with non-obstructive azoospermia. ***Andrology***. 2022 Aug 30. doi: 10.1111/andr.13267. Epub ahead of print. PMID: 36041235.

https://doi.org/10.1111/andr.13267

Translational and basic andrology

Testicular adrenal rest tumors (TART) occur in patients with congenital adrenal hyperplasia (CAH). This study found evidence indicating that TART is induced from a progenitor cell into a unique mature adrenal-like cell type, sometimes exhibiting both adrenal and testicular characteristics.

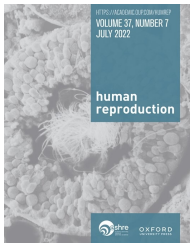
Schröder MAM, Sweep FCGJ, van Herwaarden AE, Mitchell RT, Eliveld J, van Pelt AMM, Rowan AE, Korbie D, Stikkelbroeck NMML, Claahsen-van der Grinten HL, Span PN. Transcriptional comparison of testicular adrenal rest tumors with fetal and adult tissues. ***Eur J Endocrinol***. 2022 Sep 29;187(5):607-615. PMID: 36047744.

https://doi.org/10.1530/eje-22-0143

The Copenhagen group used a novel approach to characterise the microbiome of seminal plasma in men with testicular germ cell tumours (TGCT) and preinvasive GCNIS-only. The study identified several microbial species overrepresented in patients with TGCTs.

Mørup N, Main AM, Jørgensen N, Daugaard G, Juul A, Almstrup K. The seminal plasma microbiome of men with testicular germ cell tumours described by small RNA sequencing. ***Andrology***. 2022 Sep 28. Epub ahead of print. PMID: 36168917.

https://doi.org/10.1111/andr.13305



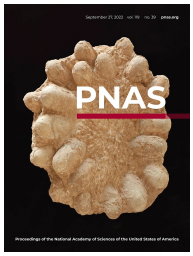
Novel evidence that the metabolic phenotype of prepubertal human spermatogonia is distinct from that of adult spermatogonia. Human PGCs and prepubertal spermatogonia show an enrichment of OXPHOS-associated genes, which is downregulated at the onset of puberty. Similar metabolic changes are detectable in the mouse.

Voigt AL, Dardari R, Su L, Lara NLM, Sinha S, Jaffer A, Munyoki SK, Alpaugh W, Dufour A, Biernaskie J, Orwig KE, Dobrinski I. Metabolic transitions define spermatogonial stem cell maturation. ***Hum Reprod***. 2022 Aug 25;37(9):2095-2112. PMID: 35856882.
https://doi.org/10.1093/humrep/deac157

Gamete fusion is a critical event of mammalian fertilization. Using a novel approach of combinatorial peptide library mimicking synthetic human egg, this study identified a new immunoglobulin super family receptor named MAIA, which interacts with the known IZUMO1/JUNO sperm-egg complex.

Vondrakova J, Frolikova M, Ded L, Cerny J, Postlerova P, Palenikova V, Simonik O, Nahacka Z, Basus K, Valaskova E, Machan R, Pacey A, Holubcova Z, Koubek P, Ezrova Z, Park S, Liu R, Partha R, Clark N, Neuzil J, Ikawa M, Erickson K, Lam KS, Moore H, Komrskova K. MAIA, Fc receptor-like 3, supersedes JUNO as IZUMO1 receptor during human fertilization. ***Sci Adv***. 2022 Sep 9;8(36):eabn0047. doi: PMCID: PMC9451160.

https://doi.org/10.1126/sciadv.abn0047



This study used a *C. elegans* model to explore different states of the repressive mark H3K27me3, and found that sperm alleles without H3K27me3 were sensitive to up-regulation in the offspring tissues, and the up-regulated sperm alleles were further transmitted, demonstrating that H3K27me3 can serve as a transgenerational epigenetic carrier.

Kaneshiro KR, Egelhofer TA, Rechtsteiner A, Cockrum C, Strome S. Sperm-inherited H3K27me3 epialleles are transmitted transgenerationally in cis. ***Proc Natl Acad Sci U S A (PNAS)***. 2022 Oct 4;119(40):e2209471119. Epub 2022 Sep 26. PMID: 36161922.
https://www.pnas.org/doi/abs/10.1073/pnas.2209471119

Some fungicides have anti-androgenic properties. This study reported significant transcriptome changes in the rat perineum and phallus after exposure to triticonazole. Expression changes in external genitalia include both AR and ER target genes.

Draskau MK, Schwartz CL, Evrard B, Lardenois A, Pask A, Chalmel F, Svingen T. The anti-androgenic fungicide triticonazole induces region-specific transcriptional changes in the developing rat perineum and phallus. ***Chemosphere***. 2022 Sep 6;308(Pt 2):136346. Epub ahead of print. PMID: 36084822.
https://doi.org/10.1016/j.chemosphere.2022.136346

Case of the month

An ancient human skeleton was found in the archaeological site in Torre Velha, Portugal. Morphological and genetic analysis indicated a possible diagnosis of Klinefelter’s syndrome.

Roca-Rada X, Tereso S, Rohrlach AB, Brito A, Williams MP, Umbelino C, Curate F, Deveson IW, Souilmi Y, Amorim A, Carvalho PC, Llamas B, Teixeira JC. A 1000-year-old case of Klinefelter's syndrome diagnosed by integrating morphology, osteology, and genetics. ***Lancet*** 2022 Aug 27;400(10353):691-692. PMID: 36030812.

https://doi.org/10.1016/S0140-6736(22)01476-3

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