EAA Literature Alert
Edition June 2021

A new selection of articles published recently in the field of andrology and reproductive biology. In this edition, there is something for everyone, including new studies of male infertility, falling sperm counts, COVID-19 and sperm, reproductive ageing issues, management of LUTS and Klinefelter syndrome, semen microbiome, androgen signalling in prostate cancer, and more. EAA members have contributed to a number of these papers. If you feel that your work should be highlighted in these alerts, send a note to the EAA Secretary.

Clinical andrology and epidemiology

An important international project addressing couple infertility has been formally launched by researchers from EAA Centres in Copenhagen and Malmö. The cohort: ReproUnion Biobank and Infertility Cohort (RUBIC) will include 5000 couples undergoing fertility management. The project will investigate risk factors for infertility and adverse pregnancy outcomes; develop new diagnostic and prognostic biomarkers for fecundity and treatment success, and study health characteristics of infertile people during long-term follow-up.

Priskorn L, Tøttenborg SS, Almstrup K, Andersson AM, Axelsson J, Bräuner EV, Elenkov A, Freiesleben NC, Giwercman YL, Grøndahl ML, Hansen AH, Hansen LS, Henic E, Kitlinski ML, Landersoe SK, Lindh C, Løkkegaard EL, Malm J, Olsen KW, Petersen KU, Schmidt L, Stormlund S, Svendsen PF, Vassard D, Wang NF, Zedeler A, Bhasin S, Chavarro J, Eisenberg ML, Hauser R, Huhtaniemi I, Krawetz SA, Marko-Varga G, Salonia A, Toppari J, Juul A, Jørgensen N, Nielsen HS, Pinborg A, Rylander L, Giwercman A. RUBIC - A binational clinical foundation to study risk factors, life course, and treatment of infertility and infertility-related morbidity. ***Andrology***. 2021 Jun 10. doi: 10.1111/andr.13063. Epub ahead of print. PMID: 34114375.

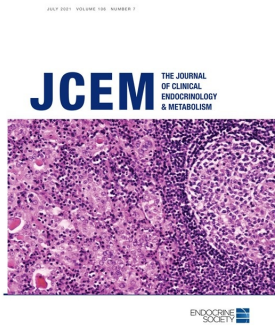
https://onlinelibrary.wiley.com/doi/10.1111/andr.13063

This study investigated possible thresholds for sperm parameters that could predict earlier time-to-conception in couples undergoing fertility evaluation. The authors compared the semen analysis data and the follow-up conception data in a large cohort of men from subfertile couples divided into groups with natural conception or helped with ART. In the overall cohort, a threshold of 50 million total progressive motile sperm count provided the best predictive power to estimate earlier time-to-conception.

Keihani S, Verrilli LE, Zhang C, Presson AP, Hanson HA, Pastuszak AW, Johnstone EB, Hotaling JM. Semen parameter thresholds and time-to-conception in subfertile couples: how high is high enough? ***Human Reproduction***. 2021 Jun 7:deab133. doi: 10.1093/humrep/deab133. Epub ahead of print. PMID: 34097024.

https://academic.oup.com/humrep/advance-article-abstract/doi/10.1093/humrep/deab133/6294420?redirectedFrom=fulltext

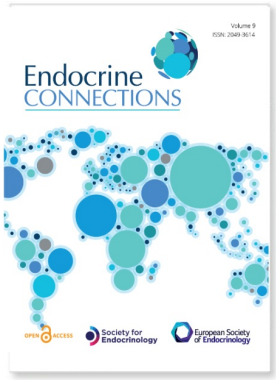
A study from Denmark showing that abuse of



anabolic androgenic steroids (AAS) is not a good idea! Serum INSL3 is reduced years following AAS cessation in men, independently of testosterone, suggesting persistently impaired Leydig cell capacity.

Rasmussen JJ, Albrethsen J, Frandsen MN, Jørgensen N, Juul A, Kistorp C. Serum Insulin-like Factor 3 Levels Are Reduced in Former Androgen Users, Suggesting Impaired Leydig Cell Capacity. ***J. Clin. Endocrinol. Metab.*** 2021 Jun 16;106(7):e2664-e2672. doi: 10.1210/clinem/dgab129. PMID: 33693710.

https://academic.oup.com/jcem/article-abstract/106/7/e2664/6156950?redirectedFrom=fulltext



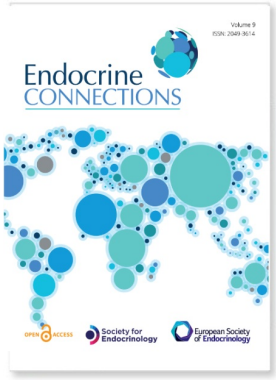
This study based on >6800 injections in 325 patients attempted to define the optimized inter-injection interval of injectable testosterone undecanoate (TU) treatment for hypogonadal and transmen. The optimal injection interval had a median of 12.0 weeks (interquartile range 10.4-12.7 weeks). The interval was significantly influenced by age and body size.

Shankara Narayana N, Ly LP, Jayadev V, Fennell C, Savkovic S, Conway AJ, Handelsman DJ. Optimal injection interval for testosterone undecanoate treatment of hypogonadal and transgender men. ***Endocrine Connections*** 2021 Jun 1:EC-21-0109.R2. doi: 10.1530/EC-21-0109. PMID: 34137730.

https://ec.bioscientifica.com/view/journals/ec/aop/ec-21-0109/ec-21-0109.xml

What is the best mode of hormonal treatment of men with Klinefelter syndrome? This Danish retrospective study evaluated testosterone replacement therapy (TRT) by injection, transdermally or none. Irrespective of the route of administration, TRT affected androgen-responsive variables similarly in KS men. Clinicians should be encouraged to seek the route of administration resulting in the highest degree of adhesion to treatment based on individual patient preferences.

Apiraa Kabilan, Anne Skakkebæk, Simon Chang, Claus H Gravholt, Evaluation of the Efficacy of Transdermal and Injection Testosterone Therapy in Klinefelter Syndrome: A Real-Life Study, ***Journal of the Endocrine Society (JAS)***, June 2021, 5 (6), bvab062, doi.org/10.1210/jendso/bvab062.



Concentrations of estradiol, estrone and testosterone (T) are higher in elderly men than in women. Men with higher BMI had lower T, lower precursors (except pregnenolone) and SHBG but higher estrone levels. This was shown in a prospective Swedish study of a cohort of healthy 70-year-old men and women. The paper provided also LC-MS/MS-based concentrations of endogenous adrenal and sex steroids in this age group.

Penell JC, Kushnir MM, Lind L, Bergquist J, Bergquist J, Lind PM, Naessen T. Concentrations of nine endogenous steroid hormones in 70-year-old men and women. ***Endocrine Connections*** 2021 May 13;10(5):511-520. doi: 10.1530/EC-21-0045. PMID: 33878730.

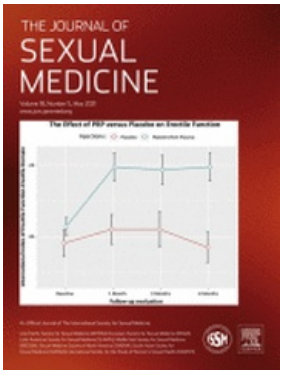
https://ec.bioscientifica.com/view/journals/ec/10/5/EC-21-0045.xml

Some help how to manage the male lower urinary tract symptoms (LUTS), especially in older men. The authors reviewed and evaluated the quality of evidence (according to GRADE guidelines) regarding the values, preferences, and expectations of men towards the investigation and treatment (conservative, pharmacological, and surgical) of LUTS. Men preferred conservative and

less risky treatment options that have fewer sexual side effects and are primarily effective at improving urgency incontinence and nocturia.

Malde S, Umbach R, Wheeler JR, Lytvyn L, Cornu JN, Gacci M, Gratzke C, Herrmann TRW, Mamoulakis C, Rieken M, Speakman MJ, Gravas S, Drake MJ, Guyatt GH, Tikkinen KAO. A Systematic Review of Patients' Values, Preferences, and Expectations for the Diagnosis and Treatment of Male Lower Urinary Tract Symptoms. ***European Urology*** 2021;79(6): 796-809. doi: 10.1016/j.eururo.2020.12.019. PMID: 33461781.

https://www.sciencedirect.com/science/article/abs/pii/S0302283821002499?via%3Dihub
Editors' Commentary:
https://www.sciencedirect.com/science/article/abs/pii/S0302283821002499?via%3Dihub
Commentary by Nunzio et al: Male Lower Urinary Tract Symptoms and Benign Prostatic Obstruction: What Do Patients Want? - ScienceDirect



A study from the European Male Aging Study (EMAS) Consortium, with contribution of several EAA Academicians, addressed a rarely studied problem of shorter than desired ejaculation latency (rapid ejaculation, RE) and its related distress among middle-aged and older men (>2800, age 40-79). The study was based on self-reported sexual function questionnaire and found that RE is a frequent condition (>30%) but causing only mild stress.

Corona G, Rastrelli G, Bartfai G, Casanueva FF, Giwercman A, Antonio L, Slowikowska J, Tournoy J, Punab M, Huhtaniemi IT, Vanderschueren D, O'Neill TW, Wu FCW, Maggi M. Self-Reported Shorter Than Desired Ejaculation Latency and Related Distress-Prevalence and Clinical Correlates: Results From the European Male Ageing Study. ***Journal of Sexual Medicine*** 2021; 18(5):908-919. doi: 10.1016/j.jsxm.2021.01.187. PMID: 33820727.

https://www.jsm.jsexmed.org/article/S1743-6095(21)00241-1/fulltext

More evidence supporting the world-wide decline of semen quality! The systematic meta-analysis reported significant decreases in sperm concentration and total sperm count in 327,373 healthy Chinese men between 1981 and 2019, indicating a serious reproductive health warning.

Mo-Qi Lv, Pan Ge, Jian Zhang, Yan-Qi Yang, Liang Zhou, Dang-Xia Zhou. Temporal trends in semen concentration and count among 327 373 Chinese healthy men from 1981 to 2019: a systematic review. ***Human Reproduction***, July 2021, 36 (7): 1751–1775. DOI: 10.1093/humrep/deab124. PMID: 34046659

https://academic.oup.com/humrep/article-abstract/36/7/1751/6287234?redirectedFrom=fulltext

A cross-sectional study aiming to evaluate semen quality in association with maternal occupational exposure to potential endocrine disrupters during pregnancy was carried out among Swiss conscripts between 2005 and 2017. Associations were found for maternal exposure to pesticides, phthalates and heavy metals (all OR between 1.8 and 2.2). The study confirms that pregnant women should be informed of potential occupational hazard that could impair their son's fertility.

M Istvan, R Rahban, B Dananche, A Senn, E Stettler, L Multigner, S Nef, R Garlantézec. Maternal occupational exposure to endocrine-disrupting chemicals during pregnancy and semen parameters in adulthood: results of a nationwide cross-sectional study among Swiss conscripts. ***Human Reproduction***, July 2021, 36 (7), 1948–1958, doi.org/10.1093/humrep/deab034

COVID-19

A prospective cross-sectional multi-centre Italian study of semen quality in 43 sexually active men who recovered from COVID-19. SARS-CoV-2 could be detected in saliva, urine, and semen in a small percentage of these men. One-quarter of men demonstrated oligo-crypto-azoospermia indicating that an assessment of semen quality should be recommended for men of reproductive age who are affected by COVID-19.

Gacci M, Coppi M, Baldi E, Sebastianelli A, Zaccaro C, Morselli S, Pecoraro A, Manera A, Nicoletti R, Liaci A, Bisegna C, Gemma L, Giancane S, Pollini S, Antonelli A, Lagi F, Marchiani S, Dabizzi S, Degl'Innocenti S, Annunziato F, Maggi M, Vignozzi L, Bartoloni A, Rossolini GM, Serni S. Semen impairment and occurrence of SARS-CoV-2 virus in semen after recovery from COVID-19. ***Human Reproduction*** 2021 May 17;36(6):1520-1529. doi: 10.1093/humrep/deab026. PMID: 33522572

https://academic.oup.com/humrep/article/36/6/1520/6125160

JAMA
The Journal of the American Medical Association

COVID-19 vaccination does not harm your sperm! In this small but reassuring study of 45 volunteers who received 2 doses of either Pfizer-BioNTech or Moderna vaccines, sperm concentrations were not significantly altered and actually slightly increased in most participants.

Gonzalez DC, Nassau DE, Khodamoradi K, Ibrahim E, Blachman-Braun R, Ory J, Ramasamy R. Sperm Parameters Before and After COVID-19 mRNA Vaccination. ***JAMA*** 2021, Jun 17. doi: 10.1001/jama.2021.9976. Epub ahead of print. PMID: 34137808.

Comment on CNN:
https://edition.cnn.com/2021/06/17/health/sperm-count-covid-vaccine-wellness/index.html

JAMA Network | Open

Yet another cohort study found that lower serum testosterone concentrations and higher estradiol to testosterone ratios were associated with COVID-19 severity and circulating inflammatory cytokine concentrations in men but not in women. Transcriptional profiling of circulating mononuclear cells revealed upregulation of hormone signaling pathways in patients requiring intensive care vs those with milder disease. But caution should be practiced with approaches that antagonize testosterone signaling or supplement estrogen to treat men with severe COVID-19.

Dhindsa S, Zhang N, McPhaul MJ, Wu Z, Ghoshal AK, Erlich EC, Mani K, Randolph GJ, Edwards JR, Mudd PA, Diwan A. Association of Circulating Sex Hormones with Inflammation and Disease Severity in Patients with COVID-19. ***JAMA Network Open***. 2021; 4(5):e2111398. doi: 10.1001/jamanetworkopen.2021.11398. PMID: 34032853.

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780135

Commentary: https://medicalxpress.com/news/2021-05-men-testosterone-high-severe-covid-.html

Androgenetics

The outcome of ICSI was studied in patients with azoospermia or severe oligozoospermia and AZFc deletions. Compared with the control group, the AZFc deletion group exhibited poorer ICSI outcome, with significantly lower clinical pregnancy rate, fertilization rate and cumulative live birth delivery rate. The patients with AZFc deletion should be informed that they have reduced opportunities to be biological fathers.

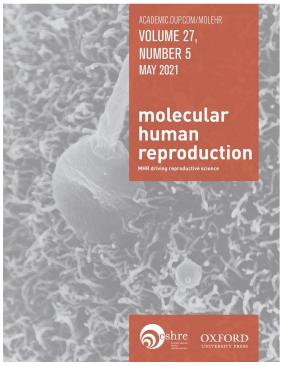
Zhang L, Mao JM, Li M, Lian Y, Lin SL, Chen LX, Yan LY, Qiao J, Liu P. Poor intracytoplasmic sperm injection outcome in infertile males with Azoospermia Factor c microdeletions. ***Fertility & Sterility*** 2021 Jul;116(1):96-104. doi: 10.1016/j.fertnstert.2021.01.025. PMID: 33745721.

https://www.fertstert.org/article/S0015-0282(21)00046-7/fulltext

This study investigated by exome sequencing 21 patients with severe sperm motility disorders, from Argentina and Australia. In 10 patients (48%), pathogenic variants were identified in known sperm assembly genes: *CFAP43/44/58, QRICH2, DNAH1/H6*. In addition, the study identified variants in the novel human candidate sperm motility genes: *DNAH12, DRC1, MDC1, PACRG, SSPL2C* and *TPTE2*.

Oud MS, Houston BJ, Volozonoka L, Mastrorosa FK, Holt GS, Alobaidi BKS, deVries PF, Astuti G, Ramos L, Mclachlan RI, O'Bryan MK, Veltman JA, Chemes HE, Sheth H. Exome sequencing reveals variants in known and novel candidate genes for severe sperm motility disorders. ***Human Reproduction*** 2021 Jun 5:deab099. doi: 10.1093/humrep/deab099. PMID: 34089056.

https://academic.oup.com/humrep/advance-article/doi/10.1093/humrep/deab099/6292397



A model explaining how acephalic spermatozoa in men with SUN5 mutations ‘lose their heads’ is proposed in this study: SUN5, Nesprin3, and ODF1 may form a 'triplet' structure at sperm neck. Loss of SUN5 disrupts this structure rendering the head-tail junction fragile.

Zhang D, Huang WJ, Chen GY, Dong LH, Tang Y, Zhang H, Li QQ, Mei XY, Wang ZH, Lan FH. Pathogenesis of acephalic spermatozoa syndrome caused by SUN5 variant. ***Molecular Human Reproduction*** 2021; 27(5):gaab028. doi: 10.1093/molehr/gaab028. PMID: 33848337.

https://doi.org/10.1093/molehr/gaab028

frontiers in Cell and Developmental Biology

The role of *TRIM71* in mammalian germ cell embryonic development was studied in a germline-specific conditional *TRIM71* knockout mouse. Male KO mice displayed a Sertoli cell-only (SCO) phenotype, already apparent at birth. Exome sequencing analysis identified several *TRIM71* variants in a cohort of infertile men.

Torres-Fernández LA, Emich J, Port Y, Mitschka S, Wöste M, Schneider S, Fietz D, Oud MS, Di Persio S, Neuhaus N, Kliesch S, Hölzel M, Schorle H, Friedrich C, Tüttelmann F, Kolanus W. *TRIM71* Deficiency Causes Germ Cell Loss During Mouse Embryogenesis and Is Associated With Human Male Infertility. ***Frontiers Cell. Dev. Biology*** 2021 May 13; 9:658966. doi: 10.3389/fcell.2021.658966. PMID: 34055789.

https://www.frontiersin.org/articles/10.3389/fcell.2021.658966/full

Translational and basic andrology

“Sneaky’ sperm particles hitchhike around the body” (according to a science journalist). A multicentre collaboration between Australian and European researchers (incl. EAA Academicians) found that germ cell-derived and sperm-specific proteins, including multiple cancer-testis antigens (CTA) are deposited by the Sertoli cells of the mouse and human seminiferous tubules into testicular interstitial fluid that is "outside" the blood-testis barrier. Sperm-specific CTA are significantly decreased in testicular fluid from infertile men. The results suggest that these antigens can possibly be blood-based markers useful in the management of male infertility.

O'Donnell L, Rebourcet D, Dagley LF, Sgaier R, Infusini G, O'Shaughnessy PJ, Chalmel F, Fietz D, Weidner W, Legrand JMD, Hobbs RM, McLachlan RI, Webb AI, Pilatz A, Diemer T, Smith LB, Stanton PG. Sperm proteins and cancer-testis antigens are released by the seminiferous tubules in mice and men. ***FASEB J.*** 2021; 35(3):e21397. doi: 10.1096/fj.202002484R. PMID: 33565176.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7898903/

Commentary: https://www.newcastle.edu.au/newsroom/featured/sneaky-sperm-particles

This pilot study compared the taxonomic and functional profiles of the gut, semen, and urine microbiomes of 25 infertile and 12 healthy fertile men. The authors identified a diverse semen microbiome and modest changes in infertile men, with anaerobes over-represented in the semen of men with a varicocele. Metagenomics data identified alterations in the S-adenosyl-L-methionine cycle, which may play a role in the pathogenesis of infertility.

Lundy SD, Sangwan N, Parekh NV, Selvam MKP, Gupta S, McCaffrey P, Bessoff K, Vala A, Agarwal A, Sabanegh ES, Vij SC, Eng C. Functional and Taxonomic Dysbiosis of the Gut, Urine, and Semen Microbiomes in Male Infertility. ***European Urology*** 2021; 79(6):826-836. doi: 10.1016/j.eururo.2021.01.014. PMID: 33573862.

Functional and Taxonomic Dysbiosis of the Gut, Urine, and Semen Microbiomes in Male Infertility - European Urology
Commentary: The Microbiome of Male Infertility: Paving the Road Ahead - ScienceDirect

A new way to calculate age-dependent 'fertility index' by standardized measures (Z-score values) of spermatogonial quantity in tissue samples from boys with cancer and young men with Klinefelter syndrome was proposed. The cells were identified by morphology and germ cell-specific markers (MAGEA4 and/or DDX4). The Z-score values allowed for the quantification of genetic and cancer treatment-related effects on testicular tissue stored for fertility preservation, facilitating their use for patient counseling.

Funke M, Yang Y, Lahtinen A, Benninghoven-Frey K, Kliesch S, Neuhaus N, Stukenborg JB, Jahnukainen K. Z-scores for comparative analyses of spermatogonial numbers throughout human development. ***Fertility & Sterility*** 2021 May 8: S0015-0282(21)00304-6. doi: 10.1016/j.fertnstert.2021.04.019. PMID: 33975728.

https://www.fertstert.org/article/S0015-0282(21)00304-6/fulltext

In the adult mouse, spermatogonial differentiation is coordinated by pulses of retinoic acid (RA), presumably acting via retinoic acid receptor gamma (RARG). The authors of this study found that RARG alone is insufficient to initiate a spermatogonial response to RA and suggested that differential RXRA expression may discriminate responding cells.

Suzuki S, McCarrey JR, Hermann BP. Differential RA responsiveness among subsets of mouse late progenitor spermatogonia. ***Reproduction***. 2021 May 5;161(6):645-655. doi: 10.1530/REP-21-0031. PMID: 33835049.

https://rep.bioscientifica.com/view/journals/rep/161/6/REP-21-0031.xml

nature COMMUNICATIONS

A new mechanism for how androgen regulates communication within prostate cancer cells discovered! The authors found components of an androgen signaling axis that uses a writer and reader of ADP-ribosylation to regulate protein-protein interactions and AR activity. A key ADP-ribosylation regulated pathway is mediated by an enzyme, PARP7, involved in important cellular functions, including DNA repair.

Yang CS, Jividen K, Kamata T, Dworak N, Oostdyk L, Remlein B, Pourfarjam Y, Kim IK, Du KP, Abbas T, Sherman NE, Wotton D, Paschal BM. Androgen signaling uses a writer and a reader of ADP-ribosylation to regulate protein complex assembly. ***Nature Communications*** 2021 May;12(1):2705. doi: 10.1038/s41467-021-23055-6. PMID: 33976187.

https://www.nature.com/articles/s41467-021-23055-6
Commentary: https://www.news-medical.net/news/20210521/New-study-may-lead-to-better-treatments-for-prostate-ovarian-and-breast-cancers.aspx

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