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EAA Literature Alert
Edition January 2022

With this edition we are opening the 2022 library service to the EAA members, alerting you about new interesting articles in clinical and basic andrology. As in the previous year, the work performed in the EAA-accredited centres will be highlighted. If you want to share your new study with other EAA members, send a note to the EAA Secretary.

Clinical andrology and epidemiology

Annals of Internal Medicine®

The association between testosterone (T) levels and risk for cardiovascular disease in ageing men has been actively studied but the results remain conflicting

This study analysed this association in a large (>200K) cohort men followed for 9 years. The authors found that calculated free T may be associated with risk for major adverse cardiovascular events, and men with lower SHBG concentrations might have higher risk for myocardial infarction but lower risk for ischemic stroke. Taken together the data suggest that a decline in total T levels in men is unlikely to be a major explanation for age-related increase in cardiovascular disease.

Yeap BB, Marriott RJ, Antonio L, Raj S, Dwivedi G, Reid CM, Anawalt BD, Bhasin S, Dobs AS, Handelsman DJ, Hankey GJ, Haring R, Matsumoto AM, Norman PE, O'Neill TW, Ohlsson C, Orwoll ES, Vanderschueren D, Wittert GA, Wu FCW, Murray K. Associations of Serum Testosterone and Sex Hormone-Binding Globulin With Incident Cardiovascular Events in Middle-Aged to Older Men. ***Annals Internal Med.*** 2021 Dec 28. doi: 10.7326/M21-0551. Epub ahead of print. PMID: 34958606.
https://www.acpjournals.org/doi/10.7326/M21-0551
Editorial Comment: https://www.acpjournals.org/doi/10.7326/M21-4777

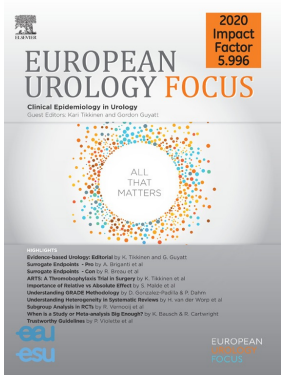
In this study, testosterone (T) levels were correlated with brachial artery flow, and markers of oxidative stress and inflammation in 58 healthy men of different ages. The authors found that men with low T had greater age-associated endothelial dysfunction, related in part to greater oxidative stress and inflammation. They concluded that low T concentrations may contribute to accelerated vascular aging in men.

Babcock MC, DuBose LE, Witten TL, Stauffer BL, Hildreth KL, Schwartz RS, Kohrt WM, Moreau KL. Oxidative Stress and Inflammation Are Associated With Age-Related Endothelial Dysfunction in Men With Low Testosterone. ***J Clin Endocrinol Metab***. 2022 Jan 18;107(2):e500-e514. PMID: 34597384.
https://doi.org/10.1210/clinem/dgab715

“Machine learning” (ML), meaning computer software learning from experience, is increasingly used in medical diagnosis. This study assessed supervised ML-based models for identification of Klinefelter syndrome (KS) among azoospermic patients, and found that these models had better sensitivity and comparable specificity to expert physicians. A new KS Score Calculator has been developed, possibly improving patient care, especially among less experienced medical care providers.

Krenz H, Sansone A, Fujarski M, Krallmann C, Zitzmann M, Dugas M, Kliesch S, Varghese J, Tüttelmann F, Gromoll J. Machine learning based prediction models in male reproductive health: development of a proof-of-concept model for Klinefelter Syndrome in azoospermic patients. ***Andrology.*** 2021 Dec 16. doi: 10.1111/andr.13141. Epub ahead of print. PMID: 34914193.

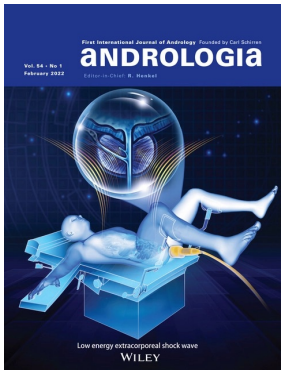
https://onlinelibrary.wiley.com/doi/10.1111/andr.13141



This systematic review summarised evidence-based data concerning the management of lower urinary tract symptoms (LUTS), with focus on β3-adrenoreceptor agonists, anticholinergics and sacral neuromodulation. The authors confirmed the efficacy and safety of vibegron or mirabegron, onabotulinum toxinA, and the risk of dementia associated with long-term use of anticholinergics. Emerging new approaches are transcutaneous devices for tibial nerve stimulation and gene therapy.

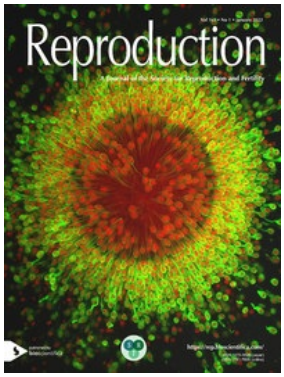
Abreu-Mendes P, Martins-Silva C, Antunes-Lopes T, Cruz F. Treatment of Non-neurogenic Lower Urinary Tract Symptoms-A Review of Key Publications from 2018 Onward. ***Eur Urol Focus.*** 2021 Nov;7(6):1438-1447. doi: 10.1016/j.euf.2020.06.015. PMID: 32624454.

https://www.eu-focus.europeanurology.com/article/S2405-4569(20)30173-5/fulltext



This cover story in *Andrologia* evaluated the clinical efficacy and safety of low-intensity extracorporeal shock wave therapy (Li-ESWT) performed once a week for 4 weeks in 91 patients with prostatitis-like symptoms (PLS). The patients were followed for 16 weeks, with no pronounced undesirable side effect observed.

Jin C, Zhang S, Mo F, et al et Liang C. Efficacy and safety evaluation of low-intensity extracorporeal shock wave therapy on prostatitis-like symptoms: An open-label, single-arm trial. ***Andrologia.*** 2022 Feb;54(1):e14260. PMID: 34585431.
https://doi.org/10.1111/and.14260



Diagnostic tools and treatments for men with sperm dysfunction, other than medically assisted reproduction, are limited. In this review article, the authors discussed current limitations and the rationale for development of high-throughput phenotypic screening platforms for human spermatozoa. The potential advantages are numerous, including the identification of compounds which affect sperm cell function and improved understanding of sperm biology.

Johnston ZC, Gruber FS, Brown SG, Norcross NR, Swedlow J, Gilbert IH, Barratt CLR. High-throughput phenotypic screening of the human spermatozoon. ***Reproduction***. 2021 Dec 27;163(1):R1-R9. PMID: 34882578.
https://doi.org/10.1530/REP-21-0372

COVID-19

A new review article comprehensively covered the epidemiology and pathophysiology of long COVID-19, with focus on neuropsychiatric, cardiovascular, respiratory and endocrine complications and their effects on erectile function. The international group of authors,

including several EAA members, called for more studies of sexual function in COVID-19 long haulers, and suggested that erectile dysfunction could be used as a biomarker for the severity of the long COVID disease.

Sansone A, Mollaioli D, Limoncin E, Ciocca G, Bắc NH, Cao TN, Hou G, Yuan J, Zitzmann M, Giraldi A, Jannini EA. The Sexual Long COVID (SLC): Erectile Dysfunction as a Biomarker of Systemic Complications for COVID-19 Long Haulers. ***Sex Med Rev.*** 2021 Nov 20:S2050-0521(21)00085-8. doi: 10.1016/j.sxmr.2021.11.001. Epub ahead of print. PMID: 34933829.

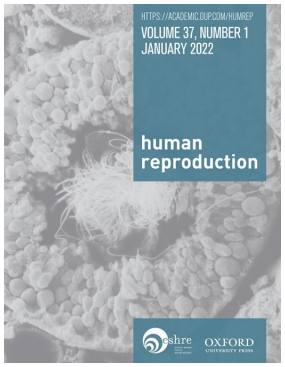
https://www.sciencedirect.com/science/article/pii/S2050052121000858?via%3Dihub

Androgenetics

A new landmark study proving the key role of *de novo* mutations' in severe male infertility! The authors from two large consortia (GEMINI and IMIGC) used trio-based exome sequencing in 185 infertile males and their unaffected parents.

The authors identified 29 rare *de novo* mutations, with significant enrichment of loss-of-function and missense mutations in infertile men compared to controls. Among these genes, RBM5, is an essential regulator of male germ cell pre-mRNA splicing and has been previously implicated in male infertility in mice.

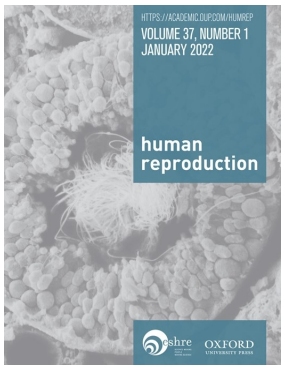
Oud MS, Smits RM, Smith HE, Mastrorosa FK, Holt GS, Houston BJ, de Vries PF, Alobaidi BKS, Batty LE, Ismail H, Greenwood J, Sheth H, Mikulasova A, Astuti GDN, Gilissen C, McEleny K, Turner H, Coxhead J, Cockell S, Braat DDM, Fleischer K, D'Hauwers KWM, Schaafsma E; Genetics of Male Infertility Initiative (GEMINI) consortium, Nagirnaja L, Conrad DF, Friedrich C, Kliesch S, Aston KI, Riera-Escamilla A, Krausz C, Gonzaga-Jauregui C, Santibanez-Koref M, Elliott DJ, Vissers LELM, Tüttelmann F, O'Bryan MK, Ramos L, Xavier MJ, van der Heijden GW, Veltman JA. A de novo paradigm for male infertility. ***Nature Commun*** 2022 Jan 10;13(1):154. PMID: 35013161.
https://www.nature.com/articles/s41467-021-27132-8



This paper, from the Male Reproductive Genomics (MERGE) study, reported biallelic, pathogenic variants in *MSH5* and *MSH4* in six azoospermic men, and in *MSH4* in one woman with POI. The study demonstrated that variants in these genes, which are required for prophase of meiosis I, were associated with meiotic arrest (MeiA), and provided further evidence that MeiA in men and POI in women share the same genetic causes.

Wyrwoll MJ, van Walree ES, Hamer G, Rotte N, Motazacker MM, Meijers-Heijboer H, Alders M, Meißner A, Kaminsky E, Wöste M, Krallmann C, Kliesch S, Hunt TJ, Clark AT, Silber S, Stallmeyer B, Friedrich C, van Pelt AMM, Mathijssen IB, Tüttelmann F. Bi-allelic variants in DNA mismatch repair proteins MutS Homolog MSH4 and MSH5 cause infertility in both sexes. ***Hum Reprod.*** 2021 Dec 27;37(1):178-189. PMID: 34755185.

https://doi.org/10.1093/humrep/deab230



This study from China found rare and novel deleterious gene variants in men with morphological abnormalities of the sperm head or tail defects; *SEPTIN12*, *KIAA1210* and *CHPT1* variants in acrosomal hypoplasia and *CCNB3* in globozoospermia. They also postulated that loss-of-function mutations of *PIWIL4* and *CC2D1B* can contribute to abnormal sperm-head formation. They checked ICSI outcomes and found that the abnormal sperm head may play a significant role in fertilization failure.

Li Y, Wang Y, Wen Y, Zhang T, Wang X, Jiang C, Zheng R, Zhou F, Chen D, Yang Y, Shen Y. Whole-exome sequencing of a cohort of infertile men reveals novel causative genes in teratozoospermia that are chiefly related to sperm head defects. ***Hum Reprod.*** 2021 Dec 27;37(1):152-177. PMID: 34791246.

https://doi.org/10.1093/humrep/deab229

The study used a large cohort of idiopathic infertile men to determine whether an unbiased clustering approach could identify subgroups with different aetiology.

The authors did identify two distinct clusters, with *FSHB* c.-211G>T genotype, FSH, and bi-testicular volume as the strongest segregation markers. They propose that *FSHB* genotyping should be implemented as a routine test in patients with idiopathic infertility.

Krenz H, Sansone A, Kliesch S, Gromoll J, Schubert M. FSHB Genotype Identified as a Relevant Diagnostic Parameter Revealed by Cluster Analysis of Men With Idiopathic Infertility. ***Front Endocrinol*** (Lausanne). 2021 Dec 21;12:780403. doi: 10.3389/fendo.2021.780403. PMID: 34992580; PMCID: PMC8725293.
https://www.frontiersin.org/articles/10.3389/fendo.2021.780403/full

Translational and basic andrology

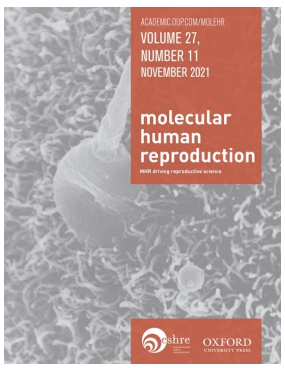
Exciting new data for reproductive biologists interested in germ cell development and epigenetics! This study investigated the dynamics of DNA methylation in mouse primordial germ cells (PGC). The authors showed that following DNA demethylation the gonadal PGC undergo remodelling of repressive histone modifications, resulting in a sex-specific signature, with the Polycomb complex (PRC2) playing a central role in transcriptional control of the hypomethylated germline genome. The genetic loss of Ezh2 led to aberrant transcriptional activation of meiotic prophase, retrotransposon derepression and loss of germ cells in females but not in males.

Huang TC, Wang YF, Vazquez-Ferrer E, Theofel I, Requena CE, Hanna CW, Kelsey G, Hajkova P. Sex-specific chromatin remodelling safeguards transcription in germ cells. ***Nature***. 2021 Dec;600(7890):737-742. PMID: 34880491.
https://www.nature.com/articles/s41586-021-04208-5

This study from the EAA centre in Münster compared the germ cell methylomes of men with cryptozoospermia and men with normal spermatogenesis (obstructive azoospermia).

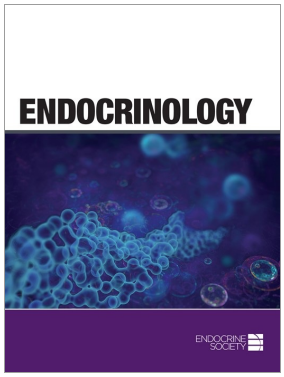
There was no difference in DNA methylation at the whole genome level but the authors detected many differentially methylated regions (DMRs), and 13 DMR-associated genes, which are mainly expressed during meiosis and spermiogenesis.

Di Persio S, Leitão E, Wöste M, Tekath T, Cremers JF, Dugas M, Li X, Zu Hörste GM, Kliesch S, Laurentino S, Neuhaus N, Horsthemke B. Whole-genome methylation analysis of testicular germ cells from cryptozoospermic men points to recurrent and functionally relevant DNA methylation changes. ***Clin Epigenetics*** 2021;13(1):160. doi: 10.1186/s13148-021-01144-z. PMCID: PMC8379757.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8379757/



Brasilian researchers investigated EPPIN (epididymal protease inhibitor), a mammalian conserved sperm-binding protein, which plays a key role in regulating sperm motility after ejaculation via interaction with the seminal plasma protein SEMG1 (semenogelin-1). EPPIN ligands targeting the SEMG1 binding site are under development as male contraceptive drugs. The authors showed that targeting specific epitopes in EPPIN in vitro can inhibit sperm motility and capacitation-associated events.

Silva AAS, Raimundo TRF, Mariani NAP, Kushima H, Avellar MCW, Buffone MG, Paula-Lopes FF, Moura MT, Silva EJR. Dissecting EPPIN protease inhibitor domains in sperm motility and fertilizing ability: repercussions for male contraceptive development. Mol Hum Reprod. 2021 Nov 27;27(12):gaab066. PMID: 34792600.
https://doi.org/10.1093/molehr/gaab066



In this study, international collaborators investigated two INHBB gene variants, previously identified in infertile men, in the mouse models generated using CRISPR/Cas9 technology. Surprisingly, they found that male Inhbb M364T/M364T mutant mice had larger testes compared to wildtype males, and retained normal fertility. Both INHBB variants had a significant disruption of in vitro biosynthesis of activin B.

Houston BJ, O'Connor AE, Wang D, Goodchild G, Merriner DJ, Luan H, Conrad DF, Nagirnaja L, Aston KI, Kliesch S, Wyrwoll MJ, Friedrich C, Tüttelmann F, Harrison C, O'Bryan MK, Walton K. Human INHBB gene variant (c.1079T>C:p.Met360Thr) alters testis germ cell content, but does not impact fertility in mice. ***Endocrinology*** 2022 Jan 12:bqab269. doi: 10.1210/endocr/bqab269. Epub ahead of print. PMID: 35022746.

https://doi.org/10.1210/endocr/bqab269

SCIENTIFIC REPORTS

The effect of obesity on the testis architecture and adult spermatogenesis was investigated in the low-density lipoprotein receptor knock-out Leiden (Ldlr−/−.Leiden) mice, treated with high-fat diet (HFD). The authors found an aberrant intra-tubular organisation and alterations in the spermatogenic cycle, in crucial stages VII and VII.

Komninos D, Ramos L, van der Heijden GW, Morrison MC, Kleemann R, van Herwaarden AE, Kiliaan AJ, Arnoldussen IAC. High fat diet-induced obesity prolongs critical stages of the spermatogenic cycle in a Ldlr-/-.Leiden mouse model. ***Scientific Reports*** 2022 Jan 11;12(1):430. doi: 10.1038/s41598-021-04069-y. PMID: 35017550.
https://www.nature.com/articles/s41598-021-04069-y

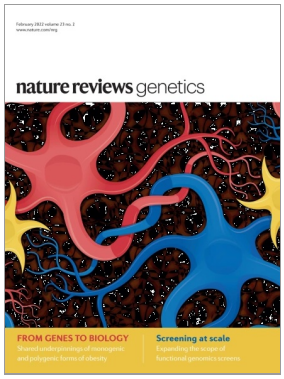
International Journal of *Molecular Sciences*

In this study, isolated testicular cells from XXY prepubertal mice were cultured and characterized.

The team demonstrated that spermatogonial stem cells (SSC) could be propagated in co-culture with somatic cells for up to 120 days. DNA FISH showed the presence of XXY spermatogonia at the beginning and a variety of propagated XY, XX, and XXY spermatogonia at the end of the culture, indicating that an extra sex chromosome was lost during SSC culture.

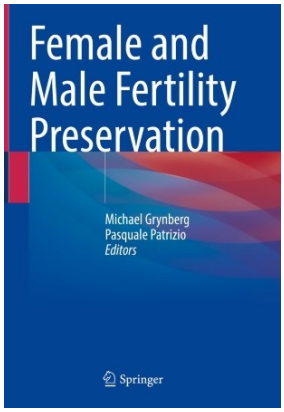
Galdon G, Deebel NA, Zarandi NP, Pettenati MJ, Kogan S, Wang C, Swerdloff RS, Atala A, Lue Y, Sadri-Ardekani H. In Vitro Propagation of XXY Undifferentiated Mouse Spermatogonia: Model for Fertility Preservation in Klinefelter Syndrome Patients. ***Int J Mol Sci***. 2022; 23(1):173.
https://www.mdpi.com/1422-0067/23/1/173

A good review of RNA communication between the germline and soma. The authors discussed inter- and transgenerational effects of environmental conditions, which changed the understanding of how external signals are sensed by the germline epigenome. They focused on the intercellular RNA trafficking from nurse cells or somatic tissues to developing gametes in different species. This aspect is understudied in human testis biology.



Conine CC, Rando OJ. Soma-to-germline RNA communication. ***Nature Rev Genet.*** 2022 Feb;23(2):73-88. PMID: 34545247.
https://www.nature.com/articles/s41576-021-00412-1

Books



This book discusses in detail all major aspects of fertility preservation in women and men, explains the fertility problems in specific diseases, and highlights currently available techniques. The authors are well-known experts in the field. The male fertility part contains 11 chapters, incl. sperm preservation, treatment of infertility, Klinefelter syndrome, tissue preservation in boys with cancer, testis-sparing surgery and more. Four additional chapters deal with general aspects pertaining to both sexes.

Female and Male Fertility Preservation. **Editors: Michael Grynberg (France) and Pasquale Patrizio (USA)**, 47 chapters, 658 pages, 122 illustrations. Springer Nature Switzerland AG 2022.
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DOI: https://doi.org/10.1007/978-3-030-47767-7

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