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EAA Literature Alert
Edition April 2022

This edition comprises a selection of recent noteworthy articles of interest for andrologists and reproductive biologists. Recent publications of the EAA Training Centres are especially highlighted. If you want to share your work with other EAA members using this platform, send a note to the EAA Secretary.

Clinical andrology and epidemiology

The latest publication from the multicentre European Male Ageing Study (EMAS). The authors evaluated the interrelationships between sex steroids and sexual symptoms with all-cause mortality in men aged 40-79. The study found that sexual symptoms, in particular erectile dysfunction, predict all-cause mortality independently of sex steroids and can be an early warning sign of a poor health status.

Antonio L, Wu FCW, Moors H, Matheï C, Huhtaniemi IT, Rastrelli G, Dejaeger M, O'Neill TW, Pye SR, Forti G, Maggi M, Casanueva FF, Slowikowska-Hilczer J, Punab M, Tournoy J, Vanderschueren D; EMAS Study Group. Erectile dysfunction predicts mortality in middle-aged and older men independent of their sex steroid status. ***Age Ageing.*** 2022 Apr 1;51(4):afac094. PMID: 35429269. https://doi.org/10.1093/ageing/afac094

The latest paper from the “Testosterone Trials” (USA). The authors determined the relative contributions of steroid hormones to the observed effects of testosterone (T) treatment in older hypogonadal men. Change in estradiol level was the best predictor of the changes in volumetric bone mineral density, sexual desire, hemoglobin and HDL cholesterol. Consideration of T, estradiol, and DHT together offers a superior prediction of treatment response in older hypogonadal men than T alone.

Stephens-Shields AJ, Snyder PJ, Ellenberg SS, Taylor L, Bhasin S. Relation of Testosterone, Dihydrotestosterone, and Estradiol With Changes in Outcomes Measures in the Testosterone Trials. ***J Clin Endocrinol Metab (JCEM)***. 2022;107(5):1257-1269. PMID: 35041751; https://doi.org/10.1210/clinem/dgac028

Annals of Internal Medicine®

Diabetes medications can have glucose-independent effects on the male reproductive system.

This prospective registry-based cohort Danish-American study evaluated the risk for birth defects in offspring of fathers with diabetes. The study found that preconception paternal metformin treatment was associated with an increased risk of genital birth defects in boys.

Wensink MJ, Lu Y, Tian L, Shaw GM, Rizzi S, Jensen TK, Mathiesen ER, Skakkebæk NE, Lindahl-Jacobsen R, Eisenberg ML. Preconception Antidiabetic Drugs in Men and Birth Defects in Offspring: A Nationwide Cohort Study. ***Ann Intern Med.*** 2022 Mar 29. Epub ahead of print. PMID: 35344380.
https://www.acpjournals.org/doi/10.7326/M21-4389

The same group as above examined the Danish birth cohort for the effect of neurological and psychiatric medication used by the fathers on birth deffects in children. They found that paternal use of antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, selective serotonin reuptake inhibitors and benzodiazepine-derived anxiolytics was generally safe with regard to birth defects.

Wensink M, Lu Y, Tian L, Jensen TK, Skakkebæk NE, Lindahl-Jacobsen R, Eisenberg M. Nervous system drugs taken by future fathers and birth defects in offspring: a prospective registry-based cohort study. ***BMJ Open*** 2022 Mar 30;12(3):e053946. PMID: 35354621. https://doi.org/10.1136/bmjopen-2021-053946

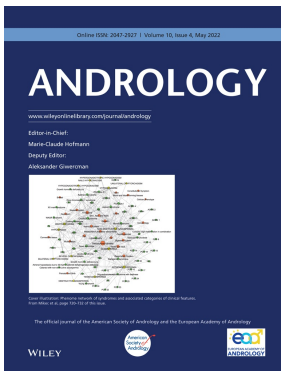
This multicentre review article described the pathogens responsible for male genital tract infections and their association with leukocytospermia as well as the diagnostic tests available to identify seminal leukocytes.

The role of leukocytospermia in male infertility and its management is important and ought to be investigated and treated if detected as part of optimal male infertility management.

Sharma R, Gupta S, Agarwal A, Henkel R, Finelli R, Parekh N, Saleh R, Arafa M, Ko E, Zini A, Tadros N, Shah R, Ambar RF, Elbardisi H, Sengupta P, Martinez M, Boitrelle F, Simopoulou M, Vogiatzi P, Gosalvez J, Kavoussi P, Kandil H, Palani A, Peña MR, Rajmil O, Busetto GM, Anagnostopoulou C, Micic S, Alves MG, Rocco L, Mostafa T, Alvarez JG, Jindal S, Sallam HN, Rosas IM, Lewis SEM, AlSaid S, Altan M, Park HJ, Ramsay J, Parekattil S, Sabbaghian M, Tremellen K, Khalafalla K, Durairajanayagam D, Colpi GM. Relevance of Leukocytospermia and Semen Culture and Its True Place in Diagnosing and Treating Male Infertility. ***World J Mens Heal*****th**. 2022 Apr;40(2):191-207. PMID: 34169683. https://doi.org/10.5534/wjmh.210063

April is Testicular Cancer Awareness Month. This study grouping oncologists and andrologists (from the EAA Training Centre in Copenhagen) examined the effects of testosterone replacement therapy (TRT) in testicular cancer survivors with mild Leydig cell insufficiency. Compared to placebo, TRT did not improve anxiety, depression, sexual function, fatigue, or overall quality of life. Hence, in this group of survivors TRT should not be routinely used.

EG Højer, M Kreiberg, C Dehlendorff, N Jørgensen, Juul A, Lauritsen J, Wagner T, Rosenvilde JJ, Daugaard G, Bandak M. Effect of testosterone replacement therapy on quality of life and sexual function in testicular cancer survivors with mild Leydig cell insufficiency: Results from a randomized double-blind trial. ***Clin Genit Cancer*** 1 April 2022. Epub ahead of print. https://doi.org/10.1016/j.clgc.2022.03.012



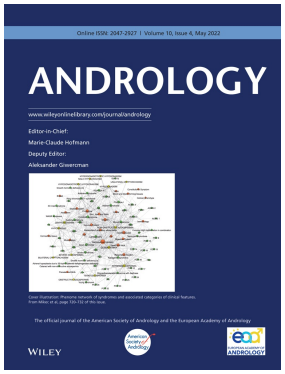
This study evaluated the efficacy and safety of a novel oral testosterone undecanoate (TLANDO) therapy for the treatment of hypogonadism. TLANDO restored testosterone levels to the normal range in the majority of patients. This new therapy can provide an option for no-titration oral testosterone replacement therapy (TRT) and has the potential to improve patient compliance in TRT.

DelConte A, Papangkorn K, Kim K, Bruno BJ, Chidambaram N, Khera M, Goldstein I, Kohler TS, Miner M, Dobs AS, Patel MV. A new oral testosterone (TLANDO) treatment regimen without dose titration requirement for male hypogonadism. ***Andrology*****.** 2022 May;10(4):669-676. PMID: 34994093. https://doi.org/10.1111/andr.13153

Hypersexual disorder (HD) involves excessive, persistent sexual behaviors. The authors hypothesized that oxytocin may play a role in the pathophysiology of HD with compensatory actions to cortisol. They found higher oxytocin plasma levels in hypersexual men compared with

controls, thus oxytocin holds promise as a potential HD biomarker. The hyperactive oxytocinergic system may be a compensatory mechanism to attenuate hyperactive stress.

Flanagan J, Chatzittofis A, Boström ADE, Hallberg J, Öberg KG, Arver S, Jokinen J. High Plasma Oxytocin Levels in Men With Hypersexual Disorder. ***J Clin Endocrinol Metab (JCEM)*** 2022;107(5):e1816-e1822. PMID: 35108393.



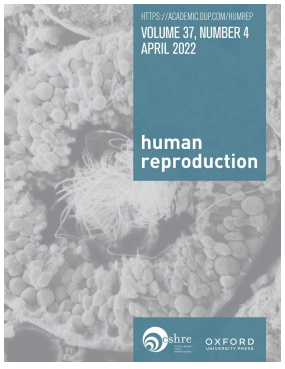
This study from Ancona (Italy) found that hyperhomocysteinemia is highly prevalent in patients with vasculogenic erectile dysfunction. Homocysteine levels correlated with velocimetric parameters assessed by basal penile duplex ultrasound, confirming the role of hyperhomocysteinemia in the genesis of erectile dysfunction of arterial origin.

Salvio G, Ciarloni A, Cordoni S, Cutini M, Muti ND, Finocchi F, Firmani F, Giovannini L, Perrone M, Balercia G. Homocysteine levels correlate with velocimetric parameters in patients with erectile dysfunction undergoing penile duplex ultrasound. ***Andrology*** 2022 May;10(4):733-739. PMID: 35224883. https://doi.org/10.1111/andr.13169

Androgenetics

This pilot study investigated *de novo* mutations (DNMs) in 53 children born after assisted or natural conception, and found that the method of conception did not have an effect on the number of mutations per genome in offspring. Given the role that DNMs play in disease risk, this negative result is good news for IVF and ICSI-TESE born children.

Smits RM, Xavier MJ, Oud MS, Astuti GDN, Meijerink AM, de Vries PF, Holt GS, Alobaidi BKS, Batty LE, Khazeeva G, Sablauskas K, Vissers LELM, Gilissen C, Fleischer K, Braat DDM, Ramos L, Veltman JA. De novo mutations in children born after medical assisted reproduction. ***Hum Reprod.*** 2022 Apr 12:deac068. doi: 10.1093/humrep/deac068. Epub ahead of print. PMID: 35413117. https://doi.org/10.1093/humrep/deac068



In this cohort study, 26 men with NOA and maturation arrest (MA) at spermatocyte stage diagnosed after TESE were investigated by SGH and WES. Deleterious homozygous or compound heterozygous variants (*TEX11, MEI1, PSMC3IP, FANCM, CTCFL, C11ORF80, EXO1*) were identified in 50% of the cohort (100% of the consanguineous patients). The authors concluded that WES could help as a predictive test of a negative outcome of a recurrent TESE in patients with MA.

Ghieh F, Barbotin AL, Swierkowski-Blanchard N, Leroy C, Fortemps J, et al et Vialard F. Whole-exome sequencing in patients with maturation arrest: a potential additional diagnostic tool for prevention of recurrent negative testicular sperm extraction outcomes. ***Hum Reprod.*** 2022 Apr 12:deac057. doi: 10.1093/humrep/deac057. Epub ahead of print. PMID: 35413094.

https://doi.org/10.1093/humrep/deac057

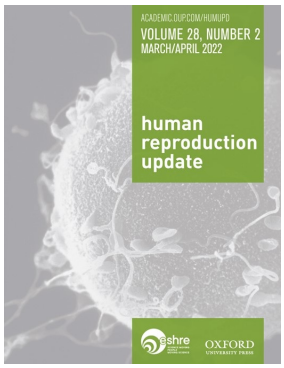
The authors (from the EAA Centre in Münster) performed a GWAS in a cohort of men with idiopathic/unexplained infertility, and looked for variants with association to FSH values. Imputation revealed a polymorphic FSHB genomic region at 11p.14.1 which accounted for up to 4 – 6% variance in FSH level. One of the identified SNPs was associated with lowered FSH and decreased spermatogenesis.

Schubert M, Pérez Lanuza L, Wöste M, Dugas M, Carmona FD, Palomino-Morales RJ, Rassam Y, Heilmann-Heimbach S, Tüttelmann F, Kliesch S, Gromoll J. A GWAS in idiopathic/unexplained infertile men detects a genomic region determining Follicle-stimulating hormone levels. ***J Clin Endocrinol Metab (JCEM)*** 2022 Mar 19:dgac165. doi: Epub ahead of print. PMID: 35305013.
https://doi.org/10.1210/clinem/dgac165

Cell-free nucleic acids in serum have been considered diagnostic markers for a range of diseases. This study screened cfs-mRNA (*AKAP1, BOLL, TCP11, SETX*) for utility to predict successful sperm retrieval (SR) in men with non-obstructive azoospermia (NOA). Significantly higher levels of BOLL cfs-mRNA ($p < 0.0001$) were detected in infertile men with maturation arrest.

Dai Y, Kong X, Yao C, Xiong C, Li Z, Li H. Multi-stage screening cell-free seminal mRNAs to diagnose completion of meiosis and predict testicular sperm retrieval in men with non-obstructive azoospermia. ***Andrology*** 2022 May;10(4):749-757. PMID: 35266640.
https://doi.org/10.1111/andr.13173

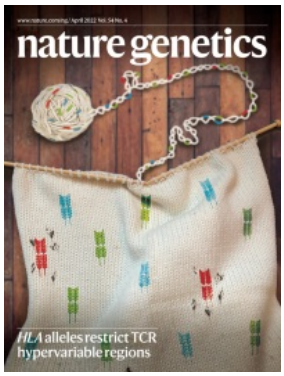
Debate / Food for thought



This review describes the systematic differences between IVF and coitus in selection pressures on reproducing cells, individuals and populations. The authors argue that IVF facilitates the redirection of resources away from reproduction in humans. Hence, IVF sets the evolutionary stage for a human species increasingly reliant on technological means of reproduction.

Hanevik HI, Hessen DO. IVF and human evolution. ***Hum Reprod Update***. 2022 Mar 31:dmac014. Epub ahead of print. PMID: 35355060.
https://doi.org/10.1093/humupd/dmac014

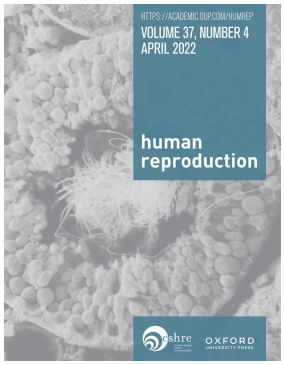
Translational and basic andrology



DNA methyltransferase is essential for spermatogenesis. This study found that in *Dnmt3A-/-* mice, spermatogonial stem cell (SSCs) can only self-renew and are not able to differentiate. The findings highlight a key function of the epigenetic programming on SSC commitment to differentiation and progress of spermatogenesis.

Dura M, Teissandier A, Armand M, Barau J, Lapoujade C, Fouchet P, Bonneville L, Schulz M, Weber M, Baudrin LG, Lameiras S, Bourc'his D. DNMT3A-dependent DNA methylation is required for spermatogonial stem cells to commit to spermatogenesis. ***Nat Genet.*** 2022 Apr;54(4):469-480. PMID: 35410378.
https://www.nature.com/articles/s41588-022-01040-z

An interesting French study showing that normal spermatozoa not only have a lower mitochondrial DNA (mtDNA) copy number but also more DNA



rearrangements than spermatozoa of men with severe oligoasthenozoospermia. The findings suggest that sperm mtDNA rearrangements are not necessarily associated with mitochondrial dysfunction and male infertility.

Boguenet M, Desquiret-Dumas V, Goudenège D, Bris C, Boucret L, Blanchet O, Procaccio V, Bouet PE, Reynier P, May-Panloup P. Mitochondrial DNA content reduction in the most fertile spermatozoa is accompanied by increased mitochondrial DNA rearrangement. ***Hum Reprod.*** 2022; 37(4):669-679. PMID: 35150574. https://doi.org/10.1093/humrep/deac024

This study investigated the association between mitochondrial DNA copy number (mtDNAcn) and semen quality in a large cohort of healthy male sperm donors. The data showed that mtDNAcn was inversely associated with semen quality in a dose-dependent manner. Sperm mtDNAcn may serve as a useful predictor of human semen characteristics.

Sun B, Hou J, Ye YX, Chen HG, Duan P, Chen YJ, Xiong CL, Wang YX, Pan A. Sperm mitochondrial DNA copy number in relation to semen quality: A cross-sectional study of 1164 potential sperm donors. ***BJOG.*** 2022 Mar 11. Epub ahead of print. PMID: 35274799. https://doi.org/10.1111/1471-0528.17139

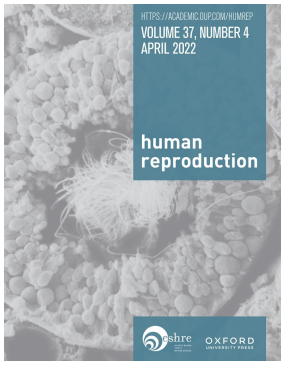
The nuclear hormone receptors SF1 (NR5A1) and LRH1 (NR5A2) are close paralogs but in the testis only SF1 role has been defined. This study found that in the mouse, Lrh1, like Sf1, is an essential regulator of testis development. It is required in Sertoli cells for their proliferation, maintenance of the blood-testis barrier, and to support spermatogenesis. In the germ line, Lrh1 is required for initial maintenance of functional spermatogonia, but over time its lack is reversible.

Agrimson KS, Minkina A, Sadowski D, Wheeler A, Murphy MW, Gearhart MD, Bardwell VJ, Zarkower D. Lrh1 can help reprogram sexual cell fate and is required for Sertoli cell development and spermatogenesis in the mouse testis. ***PLoS Genet***. 2022 Feb 22;18(2):e1010088. PMID: 35192609. https://doi.org/10.1371/journal.pgen.1010088

This study from the EAA Centre in Lodz (Poland) found increased *GPER* expression in Sertoli cells in testis biopsies of azoospermic men.

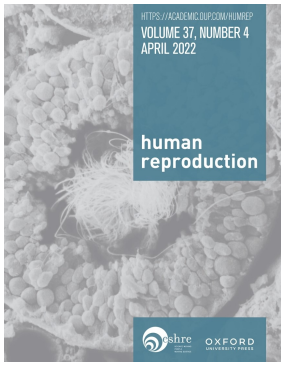
This increased expression correlated positively with the transcriptional level of *AMH,* as well as FSH serum levels. The data highlighted impaired Sertoli cell maturity/function in patients with primary spermatogenic failure.

Walczak-Jędrzejowska R, Forma E, Oszukowska E, Bryś M, Marchlewska K, Kula K, Słowikowska-Hilczer J. Expression of G-Protein-Coupled Estrogen Receptor (*GPER*) in Whole Testicular Tissue and Laser-Capture Microdissected Testicular Compartments of Men with Normal and Aberrant Spermatogenesis. ***Biology*** (Basel). 2022 Feb 26;11(3):373. PMID: 35336747. https://doi.org/10.3390/biology11030373



The authors of this elegant study demonstrated that human and mouse sperm acquire epididymal proteins through epididymosomes. They validated and characterised the epididymal origin of four sperm proteins (SLC27A2, EDDM3B, KRT19 and WFDC8). They also showed that epididymosomes interact with sperm in vitro.

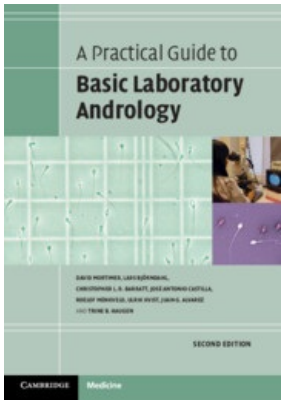
Barrachina F, Battistone MA, Castillo J, Mallofré C, Jodar M, Breton S, Oliva R. Sperm acquire epididymis-derived proteins through epididymosomes. ***Hum Reprod.*** 2022; 37(4):651-668. PMID: 35137089. https://doi.org/10.1093/humrep/deac015



This study from Chile found that human spermatozoa subjected to oxidative stress (OS) activate an autophagic response and its blockage results in increased oxidative damage and cell death. Detection of autophagy activation in sperm cells *ex vivo* could be included in semen analysis as a marker of OS, especially in men displaying high levels of seminal ROS.

Uribe P, Meriño J, Matus CE, Schulz M, Zambrano F, Villegas JV, Conejeros I, Taubert A, Hermosilla C, Sánchez R. Autophagy is activated in human spermatozoa subjected to oxidative stress and its inhibition impairs sperm quality and promotes cell death. ***Hum Reprod.*** 2022; 37(4):680-695. PMID: 35137097. https://doi.org/10.1093/humrep/deac021

Book of the month



This high quality handbook has been revised and updated. The book contains 13 chapters covering the procedures that are undertaken in andrology and ART labs. Each chapter contains an overview of the subject and a detailed protocol of the laboratory procedures. The book is a "must have" for scientists and technicians involved in andrological diagnostics.

Mortimer D, Björndahl L, Barratt CLR, Castilla JA, Menkveld R, Kvist U, Alvarez JG, Haugen T. **A Practical Guide to Basic Laboratory Andrology. *Second Edition.***
Publisher: Cambridge University Press
Print publication year: 2022
Online ISBN: 9781009181648
https://doi.org/10.1017/9781009181648

Case report of the month

The unusual case story of philosopher Pierre Abelard (1079-1142) opens a new series "Andrology and humanities" in our journal, *Andrology*. The authors discuss historical evidence suggesting that Abelard was the victim of penectomy rather than castration.

Sansone A, Jannini TB, Dolci S, Jannini EA. Castration and emasculation in the Middle Age. The andrological conundrum of Peter Abelard. ***Andrology*** 2022 Mar 30. Epub ahead of print. PMID: 35355434. https://doi.org/10.1111/andr.13180

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