



Dear EAA Members,

The April edition highlights several interesting publications in all areas of andrology. The recently published special issue of *Andrology* on small RNAs is of interest primarily to basic scientists but clinicians will find several interesting articles, e.g. about miRNAs in the diagnosis of testicular cancer. Trainees and students considering a career in andrology should get familiar with the Handbook of Andrology – a free online book compiled by the American Society of Andrology (*scroll to the end of this alert*). Other topics: growing debate on the global problem of infertility, Klinefelter syndrome, testosterone therapy, occupation and fertility, cryptorchidism, prostate cancer, cannabis and reproductive parameters, DDX3Y (AZFa), new contraception candidate (ARRDC5), Sertoli cell maturation, and more.

Clinical andrology and epidemiology



A large study with a prospective description of the natural history of testicular dysfunction in boys and adults with Klinefelter syndrome. The integrated analysis of clinical, hormonal and ultrasound was associated with Tanner stages of puberty. Quantitative ultrasound score combined with the presence of hypoechoic lesions and microlithiasis can predict a lower circulating testosterone.

Pozza C, Sesti F, Tenuta M, Spaziani M, Tarantino C, Carlomagno F, Minnetti M, Pofi R, Paparella R, Lenzi A, Radicioni A, Isidori AM, Tarani L, Gianfrilli D. Testicular dysfunction in 47, XXY boys: when it all begins. A semi-longitudinal study. *J Clin Endocrinol Metab*. 2023 Apr 12:dgad205. Epub ahead of print.
<https://doi.org/10.1210/clinem/dgad205>

Two articles explored the effects of testosterone replacement therapy (TRT) in men with Klinefelter syndrome (KS) or opioid-induced hypogonadism:



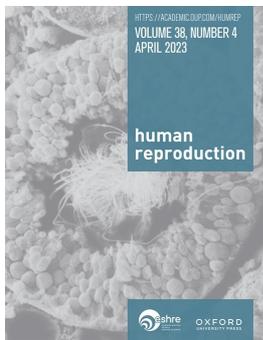
1. A retrospective study found that patients with KS have an unfavorable body composition and an impaired bone mineral status already during childhood and adolescence, and TRT can improve these parameters.

López Krabbe HV, Petersen JH, Asserhøj LL, Johannsen TH, Christiansen P, Jensen RB, Cleemann LH, Hagen C, Priskorn L, Jørgensen N, Main KM, Juul A, Aksglaede L. Reproductive hormones, bone mineral content, body composition and testosterone therapy in boys and adolescents with Klinefelter syndrome. *Endocr Connect*. 2023 Apr 1:EC-23-0031. Epub ahead of print.
<https://doi.org/10.1530/ec-23-0031>

2. A placebo-controlled study investigated men with opioid-induced hypogonadism. TRT augmented anticoagulant regulation through the suppressed tissue factor pathway.

Bøgehav M, Glintborg D, Gram JB, Bladbjerg EM, Andersen MS, Sidelmann JJ. Testosterone therapy increases the anticoagulant potential in men with opioid-induced hypogonadism: a randomized, placebo-controlled study. *Endocr Connect*. 2023 Mar 10;12(4):e220455.
<https://doi.org/10.1530/EC-22-0455>

The latest publication from the Environment and Reproductive Health (EARTH) study looked at occupational factors in male partners in infertile



couples. Interestingly, men working non-daytime/rotating shifts and those with physically demanding jobs had higher sperm concentration and total sperm count, higher estradiol, and total testosterone concentrations.

Mínguez-Alarcón L, Williams PL, Souter I, Ford JB, Ghayda RA, Hauser R, Chavarro JE; Earth Study Team. Occupational factors and markers of testicular function among men attending a fertility center. *Hum Reprod.* 2023 Apr 3;38(4):529-536. <https://doi.org/10.1093/humrep/dead027>



A meta-analysis of the published data on testicular cancer (TC) in adults with a history of surgically corrected congenital cryptorchidism. Selected studies included in total 371,681 patients who underwent orchidopexy and 1786 TC incidents. The association of congenital cryptorchidism with TC risk in adulthood was verified: OR=3.99 [95% CI: 2.80-5.71].

Florou M, Tsilidis KK, Siomou E, Koletsis T, Syrmioti A, Spyridakis I, Kaselas C, Ntzani EE. Orchidopexy for congenital cryptorchidism in childhood and adolescence and testicular cancer in adults: an updated systematic review and meta-analysis of observational studies. *Eur J Pediatr.* 2023 Mar 29. Epub ahead of print. PMID: 36988678. <https://doi.org/10.1007/s00431-023-04947-9>



Good news! A recent systematic review (Seibert et al. *Eur Urol* March 2023) suggested that despite the strong genetic background, some men with prostate cancer can avoid poor (lethal) disease outcomes through a healthy lifestyle. This excellent Swedish-American study confirmed this finding by following 12,411 men with a defined polygenic risk score.

Plym A, Zhang Y, Stopsack KH, Delcoigne B, Wiklund F, Haiman C, Kenfield SA, Kibel AS, Giovannucci E, Penney KL, Mucci LA. A Healthy Lifestyle in Men at Increased Genetic Risk for Prostate Cancer. *Eur Urol.* 2023 Apr;83(4):343-351. <https://doi.org/10.1016/j.eururo.2022.05.008>



The impact of the consumption of tetrahydrocannabinol (THC) and cannabidiol (CBD) on reproductive parameters was assessed in a cohort of young Swiss men. Androgens, estradiol, and SHBG levels were all higher in cannabis users, whereas prolactin and albumin concentrations were lower. Cannabis users had a more basic semen pH and a higher percentage of sperm with progressive motility.

Zufferey F, Buitrago E, Rahban R, Senn A, Stettler E, Rudaz S, Nef S, Donzé N, Thomas A, Rossier MF. Gonadotropin axis and semen quality in young Swiss men after cannabis consumption: Effect of chronicity and modulation by cannabidiol. *Andrology.* 2023 Apr 12. Epub ahead of print. PMID: 37042163. <https://doi.org/10.1111/andr.13440>



This Turkish study investigated the relation between BMI and cell turnover in the testis in patients undergoing m-TESE. BMI had no significant effect on reproductive hormone profile, m-TESE success, apoptosis, and proliferation in testicular tissue in nonobstructive azoospermic men.

Kuntsal E, Kadioğlu A, Şirvancı S. Testicular Apoptosis and Proliferation in Relation to Body Mass Index and m-TESE Success in Nonobstructive Azoospermic Men", *Andrologia*, April 2023, Epub ahead of print. <https://doi.org/10.1155/2023/4720387>

COVID-19

An interesting commentary on the potential damage of spermatogenesis caused by SARS-CoV-2 infection, discussing the publication announced in the March edition of our literature alert (*Basolo et al. JCEM* 2023; <https://doi.org/10.1210/clinem/dgac608>) and other COVID-19 studies.



Pivonello R, de Angelis C, Menafra D, Colao A. Testis-Specific Genes Deregulation in the Testis of COVID-19 Patients: A Potential Driver of Spermatogenesis Disruption? *J Clin Endocrinol Metab.* 2023 Apr 13;108(5):e195-e196. <https://doi.org/10.1210/clinem/dgac730>

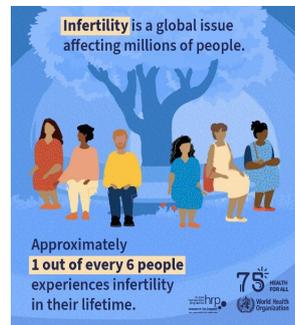
Debate

April saw an important international debate on the importance of human reproduction and the global issue of infertility. *Science* published a special issue on human reproduction with a comment: “Modern medicine has allowed for unprecedented control of reproductive decisions and health, but major limitations remain in both scientific knowledge and healthcare access”. The World Health Organization (WHO) acknowledged that 1 out of 6 people would experience infertility and called for more research, data availability, and reduction of treatment costs.



<https://www.science.org/toc/science/380/664>

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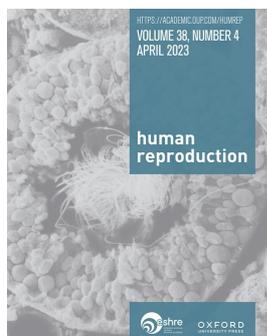
https://www.who.int/health-topics/infertility#tab=tab_1

Androgenetics



Four different likely pathogenic variants in DDX3Y were identified in infertile men, including 3 patients with the testicular Sertoli cell-only phenotype. DDX3Y represents the AZFa key spermatogenic factor and screening for its variants should be included in the diagnostic workflow.

Dicke AK, Pilatz A, Wyrwoll MJ, Punab M, Ruckert C, Nagirnaja L, Aston KI, Conrad DF, Di Persio S, Neuhaus N, Fietz D, Laan M, Stallmeyer B, Tüttelmann F. DDX3Y is likely the key spermatogenic factor in the AZFa region that contributes to human non-obstructive azoospermia. *Commun Biol.* 2023 Mar 31;6(1):350. <https://doi.org/10.1038/s42003-023-04714-4>



The human exome data were screened for various variants in *DND1*. Four heterozygous variants in *DND1* were found in five unrelated patients. The function of these variants was examined in the zebrafish model, confirming a possible role for *DND1* in human male fertility.

Westerich KJ, Reinecke S, Emich J, Wyrwoll MJ, Stallmeyer B, Meyer M, Oud MS, Fietz D, Pilatz A, Kliesch S, Reichman-Fried M, Tarbashevich K, Limon T, Stehling M, Friedrich C, Tüttelmann F, Raz E. Linking human Dead end 1 (*DND1*) variants to male infertility employing zebrafish embryos. *Hum Reprod.* 2023 Apr 3;38(4):655-670. <https://doi.org/10.1093/humrep/dead031>

The Ogata group re-examined the “AGATC” haplotype within *ESR1* in Italian and Japanese cohorts of patients with cryptorchidism and hypospadias. An identical 2,249 bp microdeletion (Δ *ESR1*) was found in both cohorts, confirming its importance as a susceptibility factor. Δ *ESR1* was likely produced in a single ancestral founder of modern humans.



Masunaga Y, Fujisawa Y, Massart F, Spinelli C, Kojima Y, Mizuno K, Hayashi Y, Sasagawa I, Yoshida R, Kato F, Fukami M, Kamatani N, Saito H, Ogata T. Microdeletion at ESR1 Intron 6 (DEL_6_75504) Is a Susceptibility Factor for Cryptorchidism and Hypospadias. *J Clin Endocrinol Metab.* 2023 Apr 3;dgad187. Epub ahead of print. <https://doi.org/10.1210/clinem/dgad187>

Translational and basic andrology



A potential non-hormonal male contraceptive target! This study identified ARRDC5 as an essential regulator of mammalian spermatogenesis, enriched in the testes of mice, pigs, cattle, and humans. Ablation of *Arrdc5* in mice leads to male-specific sterility due to defective spermiogenesis and lack of capacitation in epididymal sperm.

Giassetti MI, Miao D, Law NC, Oatley MJ, Park J, Robinson LD, Maddison LA, Bernhardt ML, Oatley JM. ARRDC5 expression is conserved in mammalian testes and required for normal sperm morphogenesis. *Nature Commun.* 2023 Apr 17;14(1):2111. <https://doi.org/10.1038/s41467-023-37735-y>



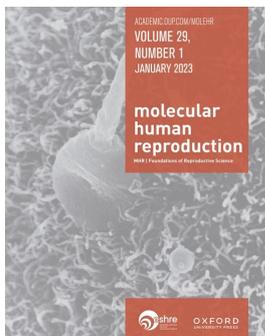
We are pleased to announce a special Issue on **Small RNAs in Andrology:**

Andrology, Volume 11, Issue 4, May 2023, pp: 621-782

The issue contains 14 articles. The introductory editorial by Kristian Almstrup nicely sets up the scene and summarises the main findings in the original studies:

“Small RNAs in andrology: Small messengers with large perspectives”

<https://doi.org/10.1111/andr.13417>



More about small RNAs. tRNAs can be cleaved into active fragments (tRFs), which in germ cells are one of the mechanisms of epigenetic inheritance. In opioid users, the tRF fragments of Gly-GCC tRNA were altered in spermatocytes, and differential expression of a group of small nucleolar RNAs (snoRNAs) was found in semen-derived exosomes.

Gornalusse G, Spengler RM, Sandford E, Kim Y, Levy C, Tewari M, Hladik F, Vojtech L. Men who inject opioids exhibit altered tRNA-Gly-GCC isoforms in semen. *Mol Hum Reprod.* 2023 Feb 28;29(3):gaad003.

<https://doi.org/10.1093/molehr/gaad003>

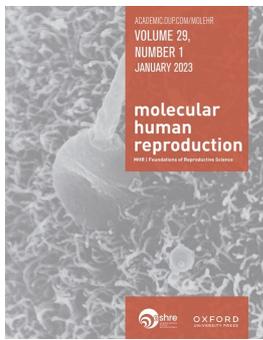


Mating shuts down the 2-methoxyestradiol (2ME) nongenomic pathway that accelerates oviductal egg transport in the rat. This study shows that sperm cells, but not vaginocervical stimulation, utilize TNF- α to shut down this 2ME nongenomic pathway.

Oróstica, M. L., Reuquen, P., Guajardo-Correa, E., Parada-Bustamante, A., Cardenas, H., & Orihuela, P. A. (2023). Sperm utilize tumor necrosis factor alpha to shut down a 2-methoxyestradiol nongenomic pathway that accelerates oviductal egg transport in the rat. *Reproduction*, 165(4), 383-393, 2023.

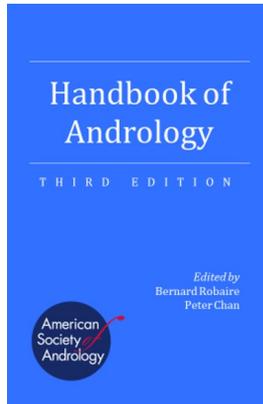
<https://doi.org/10.1530/REP-22-0289>

The maturation of spermatogonial stem cell (SSC) niche was analyzed by combined ‘omics’ technologies. The analysis revealed changes in the transcriptomes of Sertoli cells indicative of niche maturation at 11 years of age in humans and at 8 weeks of age in pigs. This coincided with the morphological and subsequently metabolic maturation of SSCs.



A L Voigt, R Dardari, N L M Lara, T He, H Steele, A Dufour, K E Orwig, I Dobrinski. Multiomics approach to profiling Sertoli cell maturation during development of the spermatogonial stem cell niche. *Mol Hum Reprod*, Volume 29, Issue 3, March 2023, gaad004, <https://doi.org/10.1093/molehr/gaad004>

Book of the month



Handbook of Andrology 3rd Edition, edited by B. Robaire & P. Chan, 2023.

This popular publication is the initiative of the American Society of Andrology. The handbook is addressed to students and trainees at the beginning of their careers. The handbook covers nearly all aspects of clinical andrology and male reproductive biology. The 3rd edition contains 64 chapters written by recognized experts, mainly from North America. Each chapter can be browsed and downloaded separately. The access is free and open for everybody!

Online book:

<https://andrologysociety.org/andrology-handbook/>

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