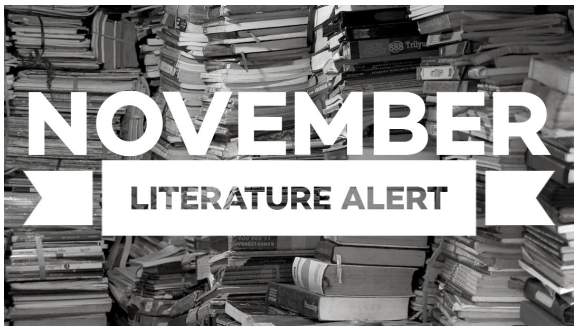


EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

It is our pleasure to share with you the latest EAA literature digest. Andrology-related research is going strong! Keywords for this issue: world-wide sperm count decline, mTESE, INSL3, late effects of testosterone deficiency, oxidation-reduction potential in semen, a novel spermicide, androgen deprivation therapy, robotic prostate biopsy, ART and birth defects, transgender health, post-vasectomy epididymis inflammation, *AR* variants, genetics of male baldness, DSD, early testis development, Sertoli cell, transcriptome of peritubular cells, sperm collection in mice, testotoxicosis and testicular cancer.

Clinical andrology and epidemiology

This analysis reports a decline in sperm count among unselected men from 53 countries, including South/Central America–Asia–Africa. The data suggest that the world-wide decline in sperm quality is continuing in the 21st century at an accelerated pace. Research on the causes of this continuing decline and actions to prevent further disruption of male reproductive health are urgently needed.

Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Jolles M, Pinotti R, Swan SH. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. ***Hum Reprod Update***. 2022 Nov 15:dmac035. Epub ahead of print. PMID: 36377604. https://doi.org/10.1093/humupd/dmac035

The first ever multicentre randomised trial compared the rate of sperm retrieval in men with nonobstructive azoospermia using either percutaneous multiple needle-pass testicular aspiration (TESA) or micro-TESE (mTESE). In direct comparison, the rate was clearly better in patients treated with mTESE rather than TESA: 43% vs 22%, respectively (p=0.02), confirming that the TESA should be abandoned.

Jensen CFS, Ohl DA, Fode M, Jørgensen N, Giwercman A, Bruun NH, Elenkov A, Klajnbard A, Andersen CY, Aksglaede L, Grøndahl ML, Bekker MC, Sønksen J. Microdissection Testicular Sperm Extraction Versus Multiple Needle-pass Percutaneous Testicular Sperm Aspiration in Men with Nonobstructive Azoospermia: A Randomized Clinical Trial. ***Eur Urol***. 2022 Oct;82(4):377-384. PMID: 35599183. https://doi.org/10.1016/j.eururo.2022.04.030

frontiers in Endocrinology

Insulin-like peptide 3 (INSL3) is a constitutive hormone secreted by the mature Leydig cells (LC) and a biomarker for LC functional capacity. Circulating INSL3 was assessed in the European Male Ageing Study (EMAS) cohort and related to the hormone and health profile. The findings suggest that INSL3 could predict co-morbidity in elderly men.

Ivell R, Heng K, Severn K, Antonio L, Bartfai G, Casanueva FF, Huhtaniemi IT, Giwercman A, Maggi M, O'Connor DB, O'Neill TW, Punab M, Rastrelli G, Slowikowska-Hilczer J, Tournoy J, Vanderschueren D, Wu FCW, Anand-Ivell R. The Leydig cell biomarker INSL3 as a predictor of age-related morbidity: Findings from the EMAS cohort. ***Front Endocrinol*** (Lausanne). 2022 Nov 8;13:1016107. PMID: 36425465. https://doi.org/10.3389/fendo.2022.1016107

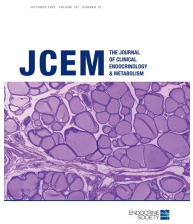
Men with prostate cancer receive adjuvant androgen deprivation therapy (ADT). This study investigated the function of the pituitary-testis axis

following adjuvant ADT. The conclusion was that testosterone deficiency is a common long-term consequence of adjuvant ADT, so the patients must be followed-up systematically.

Abildgaard J, Stroomberg HV, Bang AK, Albrethsen J, Kruuse LS, Juul A, Brasso K, Røder A, Jørgensen N. Pituitary-testis axis dysfunction following adjuvant androgen deprivation therapy. ***Endocr Related Cancer***. 2022 Nov 1:ERC-22-0246. Epub ahead of print. PMID: 36356295.
https://doi.org/10.1530/ERC-22-0246

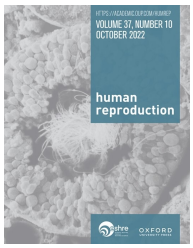
The study from Switzerland showed that robotic-assisted (Mona-Lisa) transperineal biopsy of the prostate is minimally invasive and highly precise, and can spare erectile function without limiting the extent of biopsy and without compromising diagnostic accuracy.

Trotsenko P, Walter M, Engesser CH, Nicola K, Viktor AA, Winkel DJ, Breit HC, Meyer A, Seifert HH, Wetterauer C. The impact of robotic-assisted transperineal biopsy of the prostate on erectile function. ***Andrology***. 2022 Nov 25. Epub ahead of print. PMID: 36427333.
https://doi.org/10.1111/andr.13346



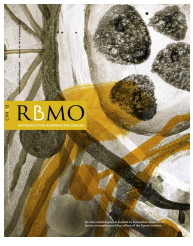
This study showed that after gender affirming treatment with gonadotropin-releasing hormone (GnRH) analogues and testosterone, transgender boys reach a predicted or even slightly taller adult height, especially those who start management at a younger age.

Willemsen LA, Boogers LS, Wiepjes CM, Klink DT, van Trotsenburg ASP, den Heijer M, Hannema SE. Just as tall on testosterone; a neutral to positive effect on adult height of GnRHa and testosterone in trans boys. ***J Clin Endocrinol Metab***. 2022 Oct 3:dgac571. doi: 10.1210/clinem/dgac571. Epub ahead of print. PMID: 36190924.
https://doi.org/10.1210/clinem/dgac571



This population-based cohort study correlated data on thousands of ART children to the birth defect registries to identify major defects diagnosed within the first year of life. The use of ART was associated with increased risks of major non-chromosomal birth defects and potentially with a greater risk for cancer.

Luke B, Brown MB, Wantman E, Schymura MJ, Browne ML, Fisher SC, Forestieri NE, Rao C, Nichols HB, Yazdy MM, Gershman ST, Sacha CR, Williams M, Ethen MK, Canfield MA, Doody KJ, Eisenberg ML, Baker VL, Williams C, Sutcliffe AG, Richard MA, Lupo PJ. The risks of birth defects and childhood cancer with conception by assisted reproductive technology. ***Hum Reprod.*** 2022 Oct 31;37(11):2672-2689. PMID: 36112004.
https://doi.org/10.1093/humrep/deac196



An international team found that seminal oxidation-reduction potential (ORP) was negatively correlated with fertilization rate (r = -0.267; P = 0.0012), blastocyst development rate (r = -0.432; P < 0.0001), implantation/clinical pregnancy (r = -0.305; P = 0.0003) and live births (r = -0.366; P < 0.0001).

Henkel R, Morris A, Vogiatzi P, Saleh R, Sallam H, Boitrelle F, Garrido N, Arafa M, Gül M, Rambhatla A, Maldonado Rosas I, Agarwal A, Leisegang K, Siebert TI. Predictive value of seminal oxidation-reduction potential analysis for reproductive outcomes of ICSI. ***Reprod Biomed Online***. 2022; 45(5) November, PMID: 36055912.
10.1016/j.rbmo.2022.05.010

Debate

Two experts in transgender medicine appeal to medical professionals, including general practitioners, to improve education in this relatively new but rapidly growing field of health care. At the same time, more long-term follow-up research is needed.

T'Sjoen G, Motmans J. Integrating transgender care into mainstream medicine- an essay by Guy T'Sjoen and Joz Motmans. ***BMJ***. 2022 Oct 3;379:o1949. doi: 10.1136/bmj.o1949. PMID: 36191953.
https://doi.org/10.1136/bmj.o1949

Androgenetics

In this large study from Italy, 45 variants in AR gene (incl. 18 novel missense AR variants) were found in 1.6% of men of idiopathic infertile couples, but in 3.4% of subjects with low sperm count and high T levels. The authors suggest AR sequencing as a routine genetic test in cases of idiopathic oligozoospermia with T ≥15.38 nmol/L.

Rocca MS, Minervini G, Vinanzi C, Bottacin A, Lia F, Foresta C, Pennuto M, Ferlin A. Mutational screening of androgen receptor gene in 8224 men of infertile couples. ***J Clin Endocrinol Metab*** 2022 Nov 17:dgac671. Epub ahead of print. PMID: 36394509.
https://doi.org/10.1210/clinem/dgac671

A novel model for genetic prediction of male pattern baldness (MPB) is presented, based on 117 SNP predictors tested among 187,435 European subjects.

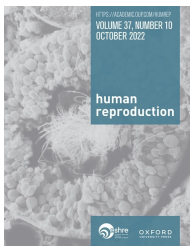
Chen Y, Hysi P, Maj C, Heilmann-Heimbach S, Spector TD, Liu F, Kayser M. Genetic prediction of male pattern baldness based on large independent datasets. ***Eur J Hum Genet***. 2022 Nov 7. Epub ahead of print. PMID: 36336714.
https://doi.org/10.1038/s41431-022-01201-y

frontiers in Genetics

In this study, whole exome sequencing was performed in a cohort of 125 individuals with DSD, detecting etiology in almost 50% of patients, all with 46,XY.
Remarkably 11.5% of the 46,XY DSD group carried pathogenic/likely pathogenic variants in more than one gene. Variants in the *AR*, *HSD17B3*, *NR5A1* and *SRD5A2* genes were the most common causes of DSD.

Zidoune H, Ladjouze A, Chellat-Rezgoune D, Boukri A, Dib SA, Nouri N, Tebibel M, Sifi K, Abadi N, Satta D, Benelmadani Y, Bignon-Topalovic J, El-Zaiat-Munsch M, Bashamboo A, McElreavey K. Novel Genomic Variants, Atypical Phenotypes and Evidence of a Digenic/Oligogenic Contribution to Disorders/Differences of Sex Development in a Large North African Cohort. ***Front Genet***. 2022 Aug 30;13:900574. PMID: 36110220.
https://doi.org/10.3389/fgene.2022.900574

Translational and basic andrology



An engineered cathelicidin antimicrobial peptide, 17BIPHE2, was a very effective spermicide in a mouse model in vivo and for human sperm in vitro, as well as a microbicide. It is a promising candidate for a vaginal multipurpose prevention technology agent.

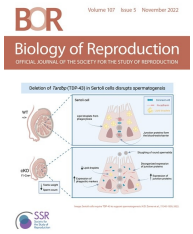
Lee SG, Kiattiburut W, Khongkha T, Schinkel SCB, Lunn Y, Decker AP, Mohammadi A, Vera-Cruz A, Misra A, Angel JB, Anderson DJ, Baker M, Kaul R, Wang G, Tanphaichitr N. 17BIPHE2, an engineered cathelicidin antimicrobial peptide with low susceptibility to proteases, is an effective spermicide and microbicide against Neisseria gonorrhoeae. ***Hum Reprod***. 2022 Oct 31;37(11):2503-2517. PMID: 36053257.
https://doi.org/10.1093/humrep/deac188

eLife

This work demonstrates a role for DLC3/Cv-c in male gonadogenesis and highlights a novel StART domain mediated function required to organize the gonadal mesoderm and to maintain its interaction with the germ cells during testis development.

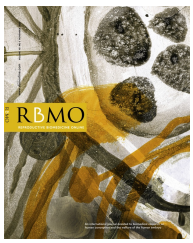
Sotillos S, von der Decken I, Domenech Mercadé I, Srinivasan S, Sirokha D, Livshits L, Vanni S, Nef S, Biason-Lauber A, Rodríguez Gutiérrez D, Castelli-Gair Hombría J. Human DLC3 and Drosophila Cv-c function in testis development: using a model organism to analyse variations in sex development. ***eLife*** 2022, 11:e82343.
https://doi.org/10.7554/eLife.82343

TAR DNA binding protein (TDP-43) is a transcription



factor and RNA-binding protein ubiquitously expressed, including Sertoli and germ cells. The current study (*featured on the cover of BOR*) reported failure of spermatogenesis and male subfertility caused by conditional knockout of TDP-43 in mouse Sertoli cells.

Zomer HD, Osuru HP, Chebolu A, Rayl JM, Timken M, Reddi PP. Sertoli cells require TDP-43 to support spermatogenesis†. ***Biol Reprod***. 2022 Nov 14;107(5):1345-1359. PMID: 35986894.
https://doi.org/10.1093/biolre/ioac165



A small histological study visualising nicely disorganisation of microtubule structure of Sertoli cells in patients with non-obstructive azoospermia (NOA).

Wu X, Yun D, Sang M, et al et Cheng CY. Defects of microtubule cytoskeletal organization in NOA human testes. ***Reprod Biol Endocrinol***. 2022 Nov 3;20(1):154. PMID: 36329464.
10.1186/s12958-022-01026-w

SCIENTIFIC REPORTS

This study evaluated the effects of neonatal corticosterone (CORT) administration (a proxy of stress) on the male reproductive system in mice and found a significant induction of p27 expression in Sertoli cells, which terminated their proliferation, leading to decreased Sertoli cell number.

Miyaso H, Takano K, Nagahori K, Li ZL, Kawata S, Kuramasu M, Ogawa Y, Yoshioka H, Matsuno Y, Yokota S, Itoh M. Neonatal corticosterone administration increases p27-positive Sertoli cell number and decreases Sertoli cell number in the testes of mice at prepuberty. ***Sci Rep***. 2022 Nov 12;12(1):19402. doi: 10.1038/s41598-022-23695-8. PMID: 36371473; PMCID: PMC9653474.
https://doi.org/10.1038/s41598-022-23695-8

cells

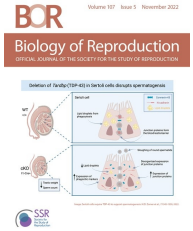
This study employed single-cell RNA sequencing of cultured human testicular peritubular cells (HTPCs), demonstrating their classification as testicular smooth muscle cells.
Among novel findings was the ability of HTPCs to produce retinoic acid.

Liebich A, Schmid N, Koupourtidou C, Herrmann C, Dietrich KG, Welter H, Ninkovic J, Mayerhofer A. The Molecular Signature of Human Testicular Peritubular Cells Revealed by Single-Cell Analysis. ***Cells***. 2022 Nov 19;11(22):3685. PMID: 36429113.
10.3390/cells11223685

This study from Canada examined pro-inflammatory P2Y14 in the epididymis following vasectomy. The data indicates that vasectomy-induced spermatozoa congestion may lead to an inflamed-prone local environment characterized by potential activation of P2Y14 and recruitment of immune cells in the epididymis.

Belardin LB, Légaré C, Sullivan R, Belleannée C, Breton S. Expression of the pro-inflammatory P2Y14 receptor in the non-vasectomized and vasectomized human epididymis. ***Andrology***. 2022 Nov;10(8):1522-1539. PMID: 36029226.
https://doi.org/10.1111/andr.13284

Methodology



This study describes a new approach for in vivo collection of sperm in the mouse via direct puncture of the epididymis. The technique is easy and allows the animal to recover and maintain its fertility, making it possible to carry long-term and time-course experiments under different treatments or conditions while maintaining the spermatogenic niche in vivo.

Val GM, Muñoz-Robledano P, Caler AJ, Morante J. A Method for Multiple Sampling Mouse Sperm in Vivo. ***Biol Reprod***. 2022 Oct 29:ioac194. doi: 10.1093/biolre/ioac194. Epub ahead of print. PMID: 36308433.
https://doi.org/10.1093/biolre/ioac194

Case of the month

Six males (3 father-son pairs) with familial male-limited precocious puberty (FMPP) caused by activating LH receptor (LHCGR) pathogenic variants are described. Two fathers had testicular germ cell tumours (TGCT). The authors collected all published similar cases and suggested prolonged patient monitoring from mid-puberty onward including periodic testicular ultrasound investigation in patients with *LHCGR* mutations.

Kooij CD, Mavinkurve-Groothuis AMC, Kremer Hovinga ICL, Looijenga LHJ, Rinne T, Giltay JC, de Kort LMO, Klijn AJ, de Krijger RR, Verrijn Stuart AA. Familial Male-limited Precocious Puberty (FMPP) and Testicular Germ Cell Tumors. ***J Clin Endocrinol Metab***. 2022 Nov 23;107(11):3035-3044. PMID: 36071555.
https://doi.org/10.1210/clinem/dgac516