Dear EAA Members,

A new load of published knowledge for clinical and basic andrologist, including the latest issue of our journal *Andrology,* well worth exploring. Topics in this issue: guidelines for management of penile cancer, ultrasound and testicular tumours, microlithiasis in TGCT, non-hormonal drugs in male infertility, sperm DNA fragmentation and ART outcomes, transgender women, ageing men, disrupted piRNA pathways in male infertility, prenatal BPA exposure and autism, voltage-sensing in sperm, testicular organoids, MALDI spectrometry, and more.

Clinical andrology and epidemiology

The September issue of *Andrology* has been already released. The issue contains several interesting articles, some previously highlighted, including sexual dysfunction treatment in China compared to Western countries; experimental models for erectile dysfunction; ICSI using testicular spermatozoa; sperm cryopreservation; hypospadias repair; *TENT5D* variants in teratozoospermia; testosterone replacement therapy. ***Andrology*** Volume 12, Issue 6

The latest clinical practice guidelines for penile cancer, providing recommendations for diagnosis, staging, pathology, treatment and follow-up of patients with penile cancer.
The author group encompasses a multidisciplinary group of experts across Europe. Recommendations are based on available scientific data and the authors' collective expert opinion.

Muneer A, Bandini M, Compérat E, De Meerleer G, Fizazi K, Gietema J, Gillessen S, Kirkham A, Sangar V, Alifrangis C, Powles T; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Penile cancer: ESMO-EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up. ***ESMO Open.*** 2024 Jul;9(7):103481.
https://doi.org/10.1016/j.esmoop.2024.103481

This study investigated parameters helping predicting occurrence of metachronous bilateral testicular germ cell tumours (TGCT).

The ultrasound features were confirmed as risk factors: reduced testicular volume, inhomogeneous echotexture, and microlithiasis. The patients with these features should have extended follow-up beyond the standard 5-year period.

Tenuta M, Mazzotta P, Sesti F, Angelini F, Gelibter AJ, Speranza I, Paoli D, Lombardo F, Anzuini A, Magliocca FM, Franco G, Cortesi E, Santini D, Lenzi A, Gianfrilli D, Isidori AM, Pozza C. Testicular ultrasonographic features predict future risk for bilateral testicular germ cell tumour: A long-term single centre follow-up study. ***Andrology***. 2024 Jul 30.
https://doi.org/10.1111/andr.13704

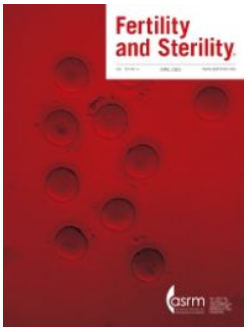
This retrospective study of 130 men with testicular incidentalomas <1 cm (identified by ultrasound and with negative tumour markers) showed that small lesions can be differentiated based on growing parameters, even though overlap exists. An increase of the maximum diameter of about 1 mm in 3 months and 2 mm in 6 months suggests malignancy.

Bertolotto M, Campo I, Freeman S, Lotti F, Huang DY, Rocher L, Dell'Atti L, Valentino M, Pavlica P, Sidhu PS, Derchi LE. Follow-up of non-palpable testicular incidentalomas under 1 cm: does growth rate differentiate malignant and non-malignant lesions? ***Eur Radiol.*** 2024 Jul 30.
https://doi.org/10.1007/s00330-024-10981-4

This meta-analysis compared the effectiveness of non-hormonal pharmacological treatments for men with infertility, based on 14 randomised trials (1342 men). The authors concluded that there is insufficient evidence to support the routine use of clomiphene, tamoxifen, and aromatase inhibitors to optimise semen parameters in men with infertility.

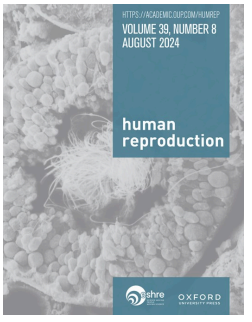
Al Wattar BH, Rimmer MP, Teh JJ, Mackenzie SC, Ammar OF, Croucher C, Anastasiadis E, Gordon P, Pacey A, McEleny K, Sangster P. Pharmacological non-hormonal treatment options for male infertility: a systematic review and network meta-analysis. ***BMC Urol.*** 2024 Jul 29;24(1):158.
https://t.co/LYgde0vWIU

This prospective cohort study of >1500 infertile couples undergoing IVF or ICSI treatment, with focus on pregnancy and perinatal outcomes demonstrated that high sperm DNA fragmentation index was associated with increased odds of preeclampsia and preterm birth.



Stenqvist A, Bungum M, Pinborg AB, Bogstad J, Englund AL, Grøndahl ML, Zedeler A, Hansson SR, Giwercman A. High Sperm DNA Fragmentation Index is associated with an increased risk of preeclampsia following assisted reproduction treatment. ***Fertil Steril.*** 2024 Aug 7:S0015-0282(24)01939-3.
https://doi.org/10.1016/j.fertnstert.2024.08.316

This study evaluated semen quality of sperm donors in four banks in Denmark (> 6700 young men). The motile sperm concentration and total sperm count declined by 22% from 2019 to 2022. The period coincided with COVID19 lockdowns, so the authors hypothesised that these changes were the result of changes in the lifestyles.



Lassen E, Pacey A, Skytte AB, Montgomerie R. Recent decline in sperm motility among donor candidates at a sperm bank in Denmark. ***Hum Reprod.*** 2024 Aug 1;39(8):1618-1627.
https://doi.org/10.1093/humrep/deae115

Transgender women who undergo gender-affirming hormone therapy to suppress testosterone had no evidence of non-calcified coronary plaque or advanced coronary stenosis.

Lake JE, Feng H, Hyatt AN, Miao H, Debroy P, Funderburg N, Ailstock K, Dobs A, Haberlen S, Magnani JW, Margolick JB, McGowan K, Palella FJ, Witt MD, Bhasin S, Budoff MJ, Post WS, Brown TT. Transgender Women With Suppressed Testosterone Display Lower Burden of Coronary Disease Than Matched Cisgender Men. ***J Endocr Soc.*** 2024; 8(8):bvae120. https://doi.org/10.1210/jendso/bvae120

This retrospective cross-sectional study included data from all US births from 2011 to 2022 to evaluate the impact of advanced paternal age on perinatal outcomes. Older fatherhood was associated with increased ART use, first-time maternal births, adverse perinatal outcomes, and altered sex ratio.

Ha AS, Scott M, Zhang CA, Li S, Langroudi AP, Glover F, Basran S, Del Giudice F, Shaw GM, Eisenberg ML. Sociodemographic Trends and Perinatal Outcomes in Fathers 50 Years and Older. ***JAMA Netw Open.*** 2024 Aug 1;7(8):e2425269. https://doi.org/10.1001/jamanetworkopen.2024.25269
Commentary by Lipshultz LJ & Stocks BT: JAMA Netw Open. 2024;7(8):e2428062. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2821817

Characteristics of men with much younger partners was analysed in this study.
Such men have often more children, higher testosterone levels, a histrionic personality and a higher risk for major cardiovascular events.

Sparano C, Rastrelli G, Corona G, Vignozzi L, Vignoli D, Maggi M. Age disparity in couples and the sexual and general health of the male partner. Andrology. 2024 Aug 19. https://doi.org/10.1111/andr.13738

Male disorders outside reproduction

Male sex, early life chemical exposure and the brain aromatase enzyme have been implicated in autism spectrum disorder (ASD). In this study, higher prenatal maternal bisphenol A (BPA) levels were associated with ASD diagnosis in boys with low aromatase pathway activity, caused by high methylation of the brain CYP19A1 promoter. Male mice exposed to BPA prenatally had similar phenotype that may be reversible through postnatal 10HDA (an estrogenic fatty acid) treatment.

Symeonides C, Vacy K, Thomson S, et al et BIS Investigator Group; Ponsonby AL, Boon WC. Male autism spectrum disorder is linked to brain aromatase disruption by prenatal BPA in multimodal investigations and 10HDA ameliorates the related mouse phenotype. ***Nat Commun.*** 2024 Aug 7;15(1):6367. https://doi.org/10.1038/s41467-024-48897-8

Androgenetics

The latest study made possible by the International Male Infertility Genomics Consortium (IMIGC). The collaborators detected biallelic variants in 14 different piRNA pathway genes (incl. PIWIL1, GTSF1, GPAT2, MAEL, TDRD1, DDX439) in 39 infertile men. The genomic data were backed by careful phenotypic evaluation. Disruption of piRNA pathways is a major cause of human spermatogenic failure.

Stallmeyer B, Bühlmann C, Stakaitis R, Dicke AK, Ghieh F, Meier L, Zoch A, MacKenzie MacLeod D, Steingröver J, Okutman Ö, Fietz D, Pilatz A, Riera-Escamilla A, Xavier MJ, Ruckert C, Di Persio S, Neuhaus N, Gurbuz AS,

Şalvarci A, Le May N, McEleny K, Friedrich C, van der Heijden G, Wyrwoll MJ, Kliesch S, Veltman JA, Krausz C, Viville S, Conrad DF, O'Carroll D, Tüttelmann F. Inherited defects of piRNA biogenesis cause transposon de-repression, impaired spermatogenesis, and human male infertility. ***Nat Commun.*** 2024 Aug 9;15(1):6637.
https://doi.org/10.1038/s41467-024-50930-9

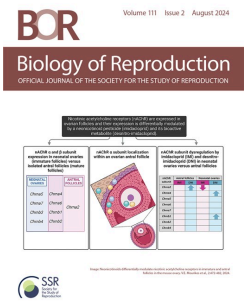
Some de novo mutations (DNMs) are positively selected in the testes of ageing men ("selfish" mutations) and can cause paternal origin disorders. This study demonstrated the selfish nature of the SMAD4 DNMs causing Myhre syndrome (MYHRS), a rare multisystem connective tissue disorder. Pathogenic variants of SMAD4 accumulate in sperm and exhibit a positive correlation with man's age.

Wood KA, Tong RS, Motta M, Cordeddu V, Scimone ER, Bush SJ, Maxwell DW, Giannoulatou E, Caputo V, Traversa A, Mancini C, Ferrero GB, Benedicenti F, Grammatico P, Melis D, Steindl K, Brunetti-Pierri N, Trevisson E, Wilkie AO, Lin AE, Cormier-Daire V, Twigg SR, Tartaglia M, Goriely A. SMAD4 mutations causing Myhre syndrome are under positive selection in the male germline. ***Am J Hum Genet.*** 2024 Jul 30:S0002-9297(24)00250-7.
https://doi.org/10.1016/j.ajhg.2024.07.006

NR2F2/COUP-TFII is required for the development of the steroidogenic lineages in gonads. Pathogenic variants in *NR2F2* can cause testis formation in 46,XX individuals. This study reported an *NR2F2* variant in a 46,XY under-masculinized boy with primary hypogonadism. In vitro studies indicated that the mutant protein affected the NR5A1/SF1-mediated activation of the *LHB* and *INSL3* promoters.

Wankanit S, Zidoune H, Bignon-Topalovic J, Schlick L, Houzelstein D, Fusée L, Boukri A, Nouri N, McElreavey K, Bashamboo A, Elzaiat M. Evidence for NR2F2/COUP-TFII involvement in human testis development. ***Sci Rep.*** 2024 Aug 1;14(1):17869.
https://doi.org/10.1038/s41598-024-68860-3

Translational and basic andrology



More than 1000 genes are predominantly expressed in the testis or are testis-specific. Not all are needed for fertility. This study just eliminated 18 good candidates for (mouse) male infertility.

Eighteen genes primarily expressed in the testis are not required for male fertility in mice
Kaito Yamamoto, Yuki Hiradate, Masahito Ikawa
Biology of Reproduction, ioae119, https://doi.org/10.1093/biolre/ioae119
Published: 06 August 2024

Voltage-sensing phosphatase (VSP) generates a specialized phosphoinositide environment in mammalian sperm flagellum. This study found that VSP is activated during mouse sperm maturation through voltage sensing, indicating that electric signals in immature spermatozoa are essential.

Kawai T, Morioka S, et al et Sasaki T, Okamura Y. The significance of electrical signals in maturing spermatozoa for phosphoinositide regulation through voltage-sensing phosphatase. ***Nature Commun.*** 2024 Aug 24;15(1):7289.
https://doi.org/10.1038/s41467-024-51755-2

The authors generated MYCBPAP knockout mice and found disruption of centrosome-nuclear envelope docking, causing abnormal flagellar biogenesis and infertility. Fertility could be restored by transgenesis with human MYCBPAP. Interactome analyses unveiled binding partners of MYCBPAP including central apparatus proteins CFAP65 and CFAP70, and centrosome-associated proteins such as CCP110.

Wang H, Kobayashi H, Shimada K, Oura S, Oyama Y, Kitakaze H, Noda T, Yabuta N, Miyata H, Ikawa M. MYCBPAP is a central apparatus protein required for centrosome-nuclear envelope docking and sperm tail biogenesis in mice. ***J Cell Sci.*** 2024 Aug 2:jcs.261962.
https://doi.org/10.1242/jcs.261962

This study investigated the mechanism behind microlithiasis associated with TGCT, and suggests that microcalcifications may arise secondary to local alterations in mineral homeostasis. Impaired Sertoli cell function and reduced levels of mineralization-inhibitors due to high alkaline phosphatase activity in GCNIS and TGCTs facilitate osteogenic-like cell differentiation and deposition of hydroxyapatite.

Boisen IM, Knudsen NK, Nielsen JE, Kooij I, Bagger ML, Kaludjerovic J, O'Shaughnessy PJ, Andrews PW, Ide N, Toft BG, Juul A, Mehmedbasic A, Jørgensen A, Smith LB, Norman RW, Rajpert-De Meyts E, Lanske B, Blomberg Jensen M. Changes in local mineral homeostasis facilitate the formation of benign and malignant testicular microcalcifications. ***eLife*** 2024, 13:RP95545,
https://doi.org/10.7554/eLife.95545.1

This study characterized the epigenetic and transcriptomic response to bisphenol S (BPS) of a variety of induced cell types, including Sertoli-, granulosa- and germ cells. Interestingly, following BPS exposure, a prevalence of epimutations may transcend epigenetic reprogramming even though most individual epimutations are not conserved.

Jake D Lehle, Yu-Huey Lin, Amanda Gomez, Laura Chavez, John R McCarrey. Endocrine disruptor-induced epimutagenesis in vitro: Insight into molecular mechanisms. ***eLife*** 2024, 13:RP93975
https://doi.org/10.7554/eLife.93975.3

Organoids hold promise as a clinical tool to restore fertility using testis tissue biopsies stored before cytotoxic treatment. This multi-centre study showed that organoid formation from testicular tissue collected from childhood cancer patients positively correlated with SOX9 expression in Sertoli cells, which in turn negatively correlated with previous exposure to alkylating chemotherapy.

Cui Y, Harteveld F, Ba Omar HAM, Yang Y, Bjarnason R, Romerius P, Sundin M, Norén Nyström U, Langenskiöld C, Vogt H, Henningsohn L, Frisk P, Vepsäläinen K, Petersen C, Mitchell RT, Guo J, Alves-Lopes JP, Jahnukainen K, Stukenborg JB. Prior exposure to alkylating agents negatively impacts testicular organoid formation in cells obtained from childhood cancer patients. ***Hum Reprod Open.*** 2024 Aug 13;2024(3):hoae049.
https://doi.org/10.1093/hropen/hoae049

Testicular organoids were constructed from cryopreserved human testes tissue from XY and Klinefelter (XXY) prepubertal patients. Testosterone secretion, upregulation of postmeiotic germ cell markers and some haploid cells were detected in the in vitro differentiated organoids.

Galdon G, Zarandi NP, Deebel NA, Zhang S, Cornett O, Lyalin D, Pettenati MJ, Lue Y, Wang C, Swerdloff R, Shupe TD, Bishop C, Stogner K, Kogan SJ, Howards S, Atala A, Sadri-Ardekani H. In Vitro Generation of Haploid Germ Cells from Human XY and XXY Immature Testes in a 3D Organoid System. ***Bioengineering*** (Basel). 2024 Jul 3;11(7):677.
https://doi.org/10.3390/bioengineering11070677

Methods

This study presents a refined approach to construct prepubertal testicular organoids, using agarose microwells. These organoids are scalable and flexible for exploring therapies and chemical screening.

Richer G, Goyvaerts C, Marchandise L, Vanhaecke T, Goossens E, Baert Y. Spermatogenesis in mouse testicular organoids with testis-specific architecture, improved germ cell survival and testosterone production. ***Biofabrication***. 2024 Aug 14;16(4).
https://doi.org/10.1088/1758-5090/ad618f

MALDI imaging mass spectrometry was used to determine the local distribution of phospholipids, plasmalogens and phosphatidylethanolamines in human testicular samples with Sertoli-cell-only syndrome.
This method could be useful for diagnosis and sperm extraction during microTESE.

Sulc A, Czétány P, Máté G, Balló A, Semjén D, Szántó Á, Márk L. MALDI Imaging Mass Spectrometry Reveals Lipid Alterations in Physiological and Sertoli Cell-Only Syndrome Human Testicular Tissue Sections. ***Int J Mol Sci***. 2024 Jul 31;25(15):8358.
https://doi.org/10.3390/ijms25158358

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