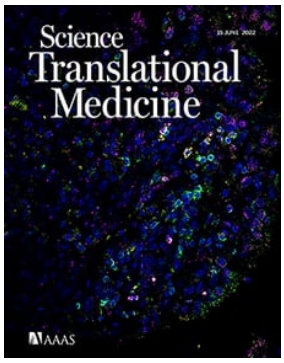
EAA Literature Alert
Edition June 2022

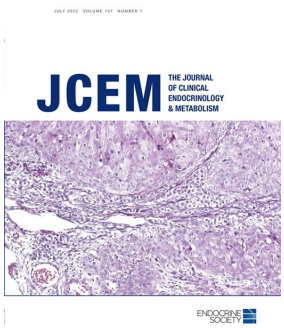
In this edition, we feature several good studies on various aspects of clinical and basic andrology, with priority on the new publications from the EAA-certified centres. Main keywords for your attention: PDE5 inhibitors, AMH, INSL3, TRUS, hypogonadotrophic hypogonadism, premature ejaculation, non-obstructive azoospermia, diagnostic genes, testicular cancer, Sertoli cells, rete testis origin, hyaluronic acid, CatSper, sperm proteins, endocrine-disrupting chemicals, hypospadias surgery.

Clinical andrology and epidemiology



Exciting results of this double-blind, randomized, placebo-controlled trial demonstrated positive effects of treatment with PDE5 inhibitor (tadalafil) in patients with diabetic cardiomyopathy, but with interesting sex differences. The authors observed much better cardiac remodelling outcomes in men than in women, even though some biochemical effects in circulation (changes if miR-199-5p and Klotho levels) occurred in both sexes.

Pofi R, Giannetta E, Feola T, Galea N, Barbagallo F, Campolo F, Badagliacca R, Barbano B, Ciolina F, Defeudis G, Filardi T, Sesti F, Minnetti M, Vizza CD, Pasqualetti P, Caboni P, Carbone I, Francone M, Catalano C, Pozzilli P, Lenzi A, Venneri MA, Gianfrilli D, Isidori AM. Sex-specific effects of daily tadalafil on diabetic heart kinetics in RECOGITO, a randomized, double-blind, placebo-controlled trial. ***Science Transl Med***. 2022 Jun 15;14(649):eabl8503. doi: 10.1126/scitranslmed.abl8503. Epub 2022 Jun 15. PMID: 35704597.
https://doi-org.ep.fjernadgang.kb.dk/10.1126/scitranslmed.abl8503



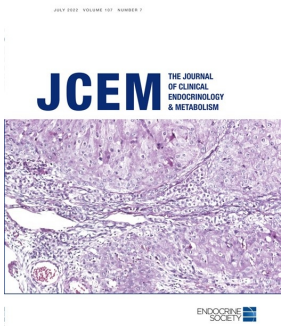
This single-centre French study established the reference ranges for serum AMH and AMH/testosterone ratio in adult males. Serum AMH positively correlated with inhibin B and sperm concentration and negatively with age, FSH, and progressive sperm motility. The authors also showed that AMH type II receptor is expressed in human spermatozoa and in pituitary gonadotrophic cells.

Benderradji H, Barbotin AL, Leroy-Billiard M, Prasivoravong J, Marcelli F, Decanter C, Robin G, Mitchell V, Rigot JM, Bongiovanni A, Sauve F, Buée L, Maurage CA, Cartigny M, Villers A, Prevot V, Catteau-Jonard S, Sergeant N, Giacobini P, Pigny P, Leroy C. Defining Reference Ranges for Serum Anti-Müllerian Hormone on a Large Cohort of Normozoospermic Adult Men Highlights New Potential Physiological Functions of AMH on FSH Secretion and Sperm Motility. ***J Clin Endocrinol Metab***. 2022 Jun 16;107(7):1878-1887. PMID: 35396994.
https://doi.org/10.1210/clinem/dgac218

The latest publication from the EAA multicentre study on the characteristics of the reproductive

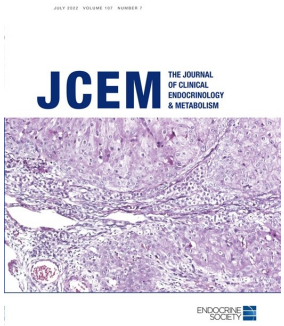
tract ultrasound parameters of healthy fertile men. This study evaluated the transrectal ultrasound (TRUS) and reported characteristics and reference ranges for the prostate and seminal vesicles.

Lotti F, Frizza F, Balercia G, Barbonetti A, Behre HM, Calogero AE, Cremers JF, Francavilla F, Isidori AM, Kliesch S, La Vignera S, Lenzi A, Marcou M, Pilatz A, Poolamets O, Punab M, Godoy MFP, Quintian C, Rajmil O, Salvio G, Shaeer O, Weidner W, Maseroli E, Cipriani S, Baldi E, Degl'Innocenti S, Danza G, Caldini AL, Terreni A, Boni L, Krausz C, Maggi M. The European Academy of Andrology (EAA) ultrasound study on healthy, fertile men: Prostate-vesicular transrectal ultrasound reference ranges and associations with clinical, seminal and biochemical characteristics. ***Andrology.*** 2022 Jun 23. doi: 10.1111/andr.13217. Epub ahead of print. PMID: 35735741.
https://doi.org/10.1111/andr.1321



How to treat adolescent boys with hypogonadotrophic hypogonadism? This multicentre trial demonstrated good results of treatment with corifollitropin alfa (CFA) alone for 12 weeks followed by CFA combined with hCG for 52 weeks, which induced testicular growth accompanied by pubertal progression, increased testosterone and a pubertal growth spurt.

Shankar RR, Shah S, Joeng HK, Mendizabal G, DiBello JR, Guan Y, Stegmann BJ, Nieschlag E, Behre HM, Swerdloff RS, Fox MC, Kaufman KD. Corifollitropin Alfa Combined With Human Chorionic Gonadotropin in Adolescent Boys With Hypogonadotropic Hypogonadism. ***J Clin Endocrinol Metab.*** 2022 Jun 16;107(7):2036-2046. PMID: 35275602.
https://doi.org/10.1210/clinem/dgac145



The natural history and reproductive status of men with congenital hypogonadotrophic hypogonadism (CHH) or with lesional acquired HH (AHH) was compared in this large French study. The AHH patients had later onset and less severe phenotype than the men with CHH. The age at diagnosis is a predictor of the reproductive phenotype in AHH.

Maione L, Sarfati J, Gonfroy-Leymarie C, Salenave S, Brailly-Tabard S, Chanson P, Trabado S, Kaiser UB, Young J. Reproductive Phenotypes in Men With Acquired or Congenital Hypogonadotropic Hypogonadism: A Comparative Study. ***J Clin Endocrinol Metab.*** 2022 Jun 16;107(7):e2812-e2824. PMID: 35358314.
https://doi.org/10.1210/clinem/dgac194

This clinical trial assessed the effects of sperm selection prior to ICSI using hyaluronic acid (HA) binding. Interestingly, older women randomized to the sperm bound to immobilized HA had the same live birth rates as younger women, most likely a result of better avoidance of sperm with damaged DNA.

West R, Coomarasamy A, Frew L, Hutton R, Kirkman-Brown J, Lawlor M, Lewis S, Partanen R, Payne-Dwyer A, Román-Montañana C, Torabi F, Tsagdi S, Miller D. Sperm selection with hyaluronic acid improved live birth outcomes among older couples and was connected to sperm DNA quality, potentially affecting all treatment outcomes. ***Hum Reprod.*** 2022; 37(6):1106-1125. PMID: 35459947.
https://doi.org/10.1093/humrep/deac058

The authors characterized cellular content and morphology in undilated tubules in men with different histological types of non-obstructive

azoospermia (NOA) who failed surgical sperm retrieval.

They found evidence of immaturity (increased AMH expression) and increased DNA damage in Sertoli cells in these tubules.

Jensen CFS, Wang D, Mamsen LS, Giwercman A, Jørgensen N, Fode M, Ohl D, Dong L, Hildorf SE, Pors SE, Fedder J, Ntemou E, Andersen CY, Sønksen J. Sertoli and Germ Cells Within Atrophic Seminiferous Tubules of Men With Non-Obstructive Azoospermia. ***Front Endocrinol*** 2022 Jun 2;13:825904. PMID: 35721721. https://doi.org/10.3389/fendo.2022.825904

Patients with lifelong premature ejaculation (LPE) can have a depressive disorder. In this study, a nomogram to discern LPE patients with low risks of PHQ-9^{+} was established. The nomogram can increase the positivity of depression screening and may improve the therapeutic outcomes of those in the low-risk group.

Hou G, Gao M, Zheng Y, Hou N, Zhang S, Sun J, Jannini TB, Zhang L, Dun X, Wang F, Jannini EA, Yuan J. Nomogram for stratifying patients with lifelong premature ejaculation before using the PHQ-9: An observational study. ***Eur J Clin Invest.*** 2022 May 6:e13809. Epub ahead of print. PMID: 35514259. https://doi.org/10.1111/eci.13809

Androgenetics

The Münster Center performed exome sequencing in 647 crypto- and azoospermic men, analysed genes with previously reported clinical validity, and strictly assessed variants according to clinical guidelines. They found informative variants in 1 of 12 men, increasing the number of diagnostic genes to 21. The authors call for applying this approach in routine clinical workup.

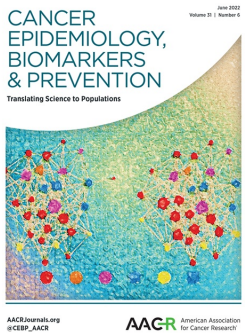
Wyrwoll MJ, Köckerling N, Vockel M, Dicke AK, Rotte N, Pohl E, Emich J, Wöste M, Ruckert C, Wabschke R, Seggewiss J, Ledig S, Tewes AC, Stratis Y, Cremers JF, Wistuba J, Krallmann C, Kliesch S, Röpke A, Stallmeyer B, Friedrich C, Tüttelmann F. Genetic Architecture of Azoospermia-Time to Advance the Standard of Care. ***Eur Urol.*** 2022 Jun 8:S0302-2838(22)02384-3. Epub ahead of print. PMID: 35690514. https://doi.org/10.1016/j.eururo.2022.05.011

The study evaluated the effects of the common genetic variation of *KATNAL1* in a large and well-characterized cohort of men with spermatogenic failure. Specific allelic combinations of *KATNAL1* polymorphisms may confer risk for male infertility by favouring the overrepresentation of a short non-functional transcript isoform in the testis.

Cerván-Martín M, Bossini-Castillo L, Guzmán-Jiménez A, Rivera-Egea R, Garrido N, Lujan S, Romeu G, Santos-Ribeiro S, Group I, Group LC, Castilla JA, Gonzalvo MC, Clavero A, Maldonado V, Vicente FJ, Burgos M, Jiménez R, González-Muñoz S, Sánchez-Curbelo J, López-Rodrigo O, Pereira-Caetano I, Marques PI, Carvalho F, Barros A, Bassas L, Seixas S, Gonçalves J, Larriba S, Lopes AM, Palomino-Morales RJ, Carmona FD. Common genetic variation in KATNAL1 non-coding regions is involved in the susceptibility to severe phenotypes of male infertility. ***Andrology.*** 2022 Jun 25. doi: 10.1111/andr.13221. Epub ahead of print. PMID: 35752927. https://doi.org/10.1111/andr.13221

Novel heterozygous deletions within *SYCE1* were identified in two infertile Chinese men, with NOA and meiotic arrest.

Huang Y, Tian R, Xu J, et al et Yao C. Novel copy number variations within *SYCE1* caused meiotic arrest and non-obstructive azoospermia. ***BMC Med Genomics***. 2022; 15(1):137. PMID: 35718780.
https://doi.org/10.1186/s12920-022-01288-8



The latest publication from the Testicular Cancer Consortium (TECAC), with participation of several EAA members. The authors evaluated the association between SNPs from 28 DNA methylation-related genes and TGCT risk. They found a positive risk association (with seminoma) of SNPs mapping within MTHFR, three of which are associated with MTHFR enzymatic activity or expression level in testis tissue.

Grasso C, Popovic M, Isaevska E, Lazzarato F, Fiano V, Zugna D, Pluta J, Weathers B, D'Andrea K, Almstrup K, Anson-Cartwright L, Bishop DT, Chanock SJ, Chen C, Cortessis VK, Dalgaard MD, Daneshmand S, Ferlin A, Foresta C, Frone MN, Gamulin M, Gietema JA, Greene MH, Grotmol T, Hamilton RJ, Haugen TB, Hauser R, Karlsson R, Kiemeney LA, Lessel D, Lista P, Lothe RA, Loveday C, Meijer C, Nead KT, Nsengimana J, Skotheim RI, Turnbull C, Vaughn DJ, Wiklund F, Zheng T, Zitella A, Schwartz SM, McGlynn KA, Kanetsky PA, Nathanson KL, Richiardi L. Association study between polymorphisms in DNA methylation-related genes and testicular germ cell tumor risk. ***Cancer Epidemiol Biomarkers Prev.*** 2022 Jun 14:cebp.0123.2022-2-12 14:42:56.847. Epub ahead of print. PMID: 35700037.
https://doi.org/10.1158/1055-9965.epi-22-0123

A good systematic review on the potential of cell-free DNA (cfDNA) in management of patients with testicular germ cell tumours (TGCT). The authors from the Centre in Zagreb identified potential challenges of this approach and proposed a focus on cfDNA methylation analysis.

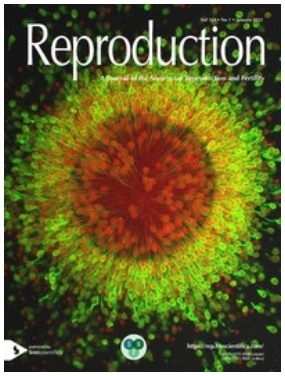
Krasic J, Skara L, Bojanac AK, Ulamec M, Jezek D, Kulis T, Sincic N. The utility of cfDNA in TGCT patient management: a systematic review. ***Ther Adv Med Oncol.*** 2022 May 25;14:17588359221090365. PMID: 35656387.
10.1177/17588359221090365

Translational and basic andrology

This excellent study discovered a previously uncharacterized supporting-like cells (SLCs) in the developing bipotential mouse gonads. SLC progenitors are localized at the interface with the mesonephros and initially co-express *Wnt4* and *Sox9*. SLC progressively acquire a more Sertoli- or pregranulosa-like identity and contribute to the formation of the rete testis and rete ovarii, with WNT4 acting as the master regulator for the rete testis.

Mayère C, Regard V, Perea-Gomez A, Bunce C, Neirijnck Y, Djari C, Bellido-Carreras N, Sararols P, Reeves R, Greenaway S, Simon M, Siggers P, Condrea D, Kühne F, Gantar I, Tang F, Stévant I, Batti L, Ghyselinck NB, Wilhelm D, Greenfield A, Capel B, Chaboissier MC, Nef S. Origin, specification and differentiation of a rare supporting-like lineage in the developing mouse gonad. ***Science Adv.*** 2022 May 27;8(21):eabm0972. doi: 10.1126/sciadv.abm0972. PMID: 35613264.
https://doi.org/10.1126/sciadv.abm0972

Insulin-like 3 (INSL3), a Leydig cell hormone is essential for testis descent during foetal life and bone metabolism in adults. This study reported that COUP-TFII and SF1 functionally cooperate on the Insl3 promoter from various species, providing new mechanistic insights into the regulation of Insl3 gene expression in Leydig cells.



Di-Luoffo M, Pierre KJ, Robert NM, Girard MJ, Tremblay JJ. The nuclear receptors SF1 and COUP-TFII cooperate on the Insl3 promoter in Leydig cells. ***Reproduction.*** 2022 Jun 1:REP-22-0109. doi: 10.1530/REP-22-0109. Epub ahead of print. PMID: 35666805.
https://doi.org/10.1530/rep-22-0109

nature COMMUNICATIONS

This elegant study revealed a dimeric structure of CatSper channels in mouse and human sperm flagella by cryo-electron tomography, and analysed molecular interactions between and within the dimers. Loss of *Efcab9* disrupted the channel structure and sperm motility.

Zhao Y, Wang H, Wiesehoefer C, Shah NB, Reetz E, Hwang JY, Huang X, Wang TE, Lishko PV, Davies KM, Wennemuth G, Nicastro D, Chung JJ. 3D structure and in situ arrangements of CatSper channel in the sperm flagellum. ***Nature Commun.*** 2022 Jun 17;13(1):3439. PMID: 35715406.
https://doi.org/10.1038/s41467-022-31050-8

The first risk assessment concerning exposures of Danish men to mixtures of 9 chemicals associated with deterioration of semen quality. The study identified bisphenols A, S, F, polychlorinated dioxins and the phthalate DEHP as drivers of mixture risks. Dedicated efforts towards lowering exposures to these substances are necessary to mitigate risks.

Kortenkamp A, Scholze M, Ermler S, Priskorn L, Jørgensen N, Andersson AM, Frederiksen H. Combined exposures to bisphenols, polychlorinated dioxins, paracetamol, and phthalates as drivers of deteriorating semen quality. ***Environment Int.*** 2022 Jun 2:107322. Epub ahead of print. PMID: 35691715.
https://doi.org/10.1016/j.envint.2022.107322

The authors observed a dysregulation of histone acetylation (H4ac) in the cells of the seminiferous tubules adjacent to testicular tumours of different aetiology. No comparable alterations were observed in patients with disrupted spermatogenesis, suggesting that there could be a potential paracrine effect of the tumour.

Barrachina F, de la Iglesia A, Jodar M, Soler-Ventura A, Mallofré C, Rodriguez-Carunchio L, Goudarzi A, Corral JM, Ballescà JL, Castillo J, Oliva R. Histone H4 acetylation is dysregulated in active seminiferous tubules adjacent to testicular tumours. ***Hum Reprod.*** 2022 Jun 9:deac130. Epub ahead of print. PMID: 35678707.
https://doi.org/10.1093/humrep/deac130

frontiers in Cell and Developmental Biology

Mammalian germ cells produce small regulatory RNAs called PIWI-interacting RNAs (piRNAs). This study compared piRNAs present in male germ cells at different stages and identified three distinct groups: prospermatogonial, early, and late clusters, with longer PIWIL1-type piRNAs

produced earlier, and shorter PIWIL2-type piRNAs remaining for a longer period, than previously thought.

Kawase M, Ichiyanagi K. The Expression Dynamics of piRNAs Derived From Male Germline piRNA Clusters and Retrotransposons. ***Front Cell Dev Biol.*** 2022 May 11;10:868746. PMID: 35646920.

This study investigated the membrane integrity and fusion proteins in spermatozoa from men in couples experiencing total fertilisation failure. The results indicate that acrosomal exocytosis, IZUMO1 and SPESP1 expression in spermatozoa could play a crucial role in achieving fertilisation during IVF.

Enoiu SI, Nygaard MB, Bungum M, Ziebe S, Petersen MR, Almstrup K. Expression of membrane fusion proteins in spermatozoa and total fertilisation failure during in vitro fertilisation. ***Andrology***. 2022 Jun 21. Epub ahead of print. PMID: 35727923.
https://doi.org/10.1111/andr.13215

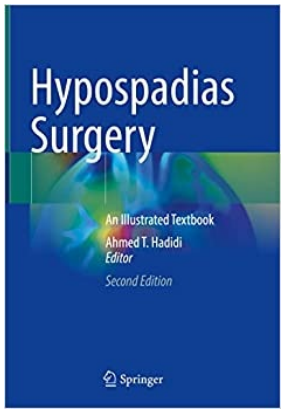
frontiers in Endocrinology

A high-resolution mass spectrometry-based proteomic approach was used to describe alterations of the sperm proteome in secondary male hypogonadism.

Some of the differential sperm proteins (Prosaposin, SMOC-1, SERPINA5, SPANXB1, GSG1, ELSPBP1, fibronectin, 5-oxoprolinase, AKAP3, AKAP4, HYDIN, ROPN1B, ß-Microseminoprotein, Protein S100-A8) could represent new targets for the design of infertility treatments due to androgen deficiency.

Grande G, Barrachina F, Soler-Ventura A, Jodar M, Mancini F, Marana R, Chiloiro S, Pontecorvi A, Oliva R, Milardi D. The Role of Testosterone in Spermatogenesis: Lessons From Proteome Profiling of Human Spermatozoa in Testosterone Deficiency. ***Front Endocrinol*** 2022 May 19;13:852661. PMID: 35663320.
https://doi.org/10.3389/fendo.2022.852661

Books



Hypospadias Surgery. An Illustrated Textbook (Second Edition)
Editor and main Author: Ahmed T. Hadidi (Germany)

The textbook contains comprehensive information on hypospadias surgery and complications by world pioneers in the field (42 authors from 19 countries), with an historical perspective on its evolution. There are 90 chapters, which in addition to surgery cover embryology and pathogenesis, epidemiology, genetics, clinical follow-up and complications, including sexual function and psychological problems. The book is richly illustrated (>600 figures) and is a good practical guide for urologists (incl. paediatric), plastic surgeons, andrologists and specialists in sexual health disorders.

Bibliographic Information
- Book Title: Hypospadias Surgery
- Book Subtitle: An Illustrated Textbook
- DOI: https://doi.org/10.1007/978-3-030-94248-9
- Publisher: Springer Cham (Springer Nature Switzerland AG 2022)
- eBook Packages: Medicine, Medicine (R0)
- Hardcover ISBN: 978-3-030-94247-2
- eBook ISBN: 978-3-030-94248-9

EAA Secretary
rajpertdemeyts.EAA@gmail.com

office@androlog yacademy.net