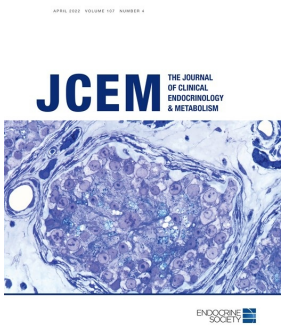
EAA Literature Alert
Edition March 2022

This edition will be of particular interest for paediatric or developmental andrologists but the selection features articles looking at male health in any age. The keywords for your attention: male sex determination, hypospadias, minipuberty, sex hormones, obesity, standardisation of semen analysis, sperm DNA fragmentation, ageing, prostatic urethral lift, erectile dysfunction, paracetamol, X-linked infertility, meiosis, and more.

Clinical andrology and epidemiology

This elegant study from the UK provided evidence that hypospadias is a risk factor for cardiovascular dysfunction in males. Boys with hypospadias have evidence of hypercontractility and impaired vasodilation secondary to increased Rho kinase activation and oxidative stress. This leads to raised systolic blood pressure in adolescence and increased risk of admission to hospital for arrhythmia, hypertension and heart failure in adulthood.

Lucas-Herald AK, Montezano AC, Alves-Lopes R, Haddow L, Alimussina M, O'Toole S, Flett M, Lee B, Amjad SB, Steven M, Brooksbank K, McCallum L, Delles C, Padmanabhan S, Ahmed SF, Touyz RM. Vascular dysfunction and increased cardiovascular risk in hypospadias. ***Eur Heart J***. 2022 Mar 17:ehac112. Epub ahead of print. PMID: 35296881.
https://doi.org/10.1093/eurheartj/ehac112



Two excellent prospective studies from the centre in Copenhagen provided novel data on the physiology and biological importance of minipuberty. The first study demonstrated sequential dynamics of the reproductive hormone profile in male infants; with androgens and INSL3 (secreted by Leydig cells) peaking before Sertoli cell hormones Inhibin B and AMH. The second study found that serum testosterone concentration in infancy was positively associated with adult total sperm count. Other reproductive parameters also correlated between infancy and adulthood, suggesting that a male's reproductive setpoint starts shortly after birth and persists until adulthood.

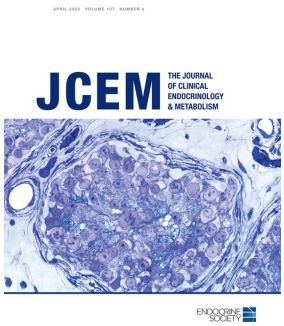
Busch AS, Ljubicic ML, Upners EN, Fischer MB, Raket LL, Frederiksen H, Albrethsen J, Johannsen TH, Hagen CP, Juul A. Dynamic changes of reproductive hormones in male minipuberty: Temporal dissociation of Leydig- and Sertoli-cell activity. ***J Clin Endocrinol Metab***. 2022 Feb 28:dgac115. PMID: 35225342.
https://doi.org/10.1210/clinem/dgac115

Henriksen L, Petersen JH, Skakkebæk NE, Jørgensen N, Virtanen HE, Priskorn L, Juul A, Toppari J, Main KM. Serum testosterone levels in three-month-old boys predict their semen quality as young adults. ***J Clin Endocrinol Metab (JCEM)*** 2022 Mar 22:dgac173. PMID: 35323957.
https://doi.org/10.1210/clinem/dgac173

This study from the EAA-accredited centre in Copenhagen found no significant association

between anogenital distance (AGD) and male factor infertility, and in proven fertile men their time to pregnancy (TTP). The authors concluded that the clinical application of AGD as a predictor of fertility and fecundity is limited.

Madvig F, Pedersen MK, Urhoj SK, Bräuner EV, Jørgensen N, Priskorn L. Anogenital distance, male factor infertility and time to pregnancy. ***Andrology***. 2022 Feb 17. Epub ahead of print. PMID: 35178873. https://doi.org/10.1111/andr.13161



In this cross-sectional study, a team from France found decreased circulating Sertoli and Leydig cell hormone levels in overweight-obese adolescent boys. The disturbances included lower median inhibin B, testosterone (T) and AMH levels. In multiple regression analyses, fat mass percentage was a negative predictor of T, while estradiol and total bone mineral density Z-score were negative predictors of inhibin B.

Rerat S, Amsellem-Jager J, L'hour MC, Bouhours-Nouet N, Donzeau A, Rouleau S, Levaillant L, Emeriau F, Moal V, Boux de Casson F, Lahlou N, Coutant R. Lower Circulating Sertoli and Leydig Cell Hormone Levels During Puberty in Obese Boys: A Cross-sectional Study. ***J Clin Endocrinol Metab (JCEM)*** 2022 Mar 24; 107(4):e1568-e1576. PMID: 34918072. 10.1210/clinem/dgab845

This study evaluated the changes in sex hormones following bariatric surgery in obese adolescents, most of them (73%) with subnormal free testosterone (T) concentrations. Bariatric surgery resulted in the loss of about one-third of body weight within 2 years and led to a robust increase in T concentrations. Participants who later regained weight had a decline in their T concentrations.

Dhindsa S, Ghanim H, Jenkins T, Inge TH, Harmon CM, Ghoshal A, Wu Z, McPhaul MJ, Saad F, Dandona P. High prevalence of subnormal testosterone in obese adolescent males: reversal with bariatric surgery. ***Eur J Endocrinol.*** 2022; 186(3):319-327. PMID: 35007209. https://eje.bioscientifica.com/view/journals/eje/186/3/EJE-21-0545.xml

This placebo-controlled randomized clinical trial from Australia investigated the rate, extent, and determinants of reproductive hormone recovery after stopping 2 year-long treatments with injectable testosterone undecanoate (TU). Full reproductive hormone recovery was slow and progressive over 15 months. Persistent proportionate reduction in serum SHBG and T reflected lasting exogenous T effects on hepatic SHBG secretion rather than androgen deficiency.

Handelsman DJ, Desai R, Conway AJ, Shankara-Narayana N, Stuckey BGA, Inder WJ, Grossmann M, Yeap BB, Jesudason D, Ly LP, Bracken K, Wittert GA. Recovery of male reproductive endocrine function after ceasing prolonged testosterone undecanoate injections. ***Eur J Endocrinol.*** 2022; 186(3):307-318. PMID: 35000898. https://eje.bioscientifica.com/view/journals/eje/186/3/EJE-21-0608.xml

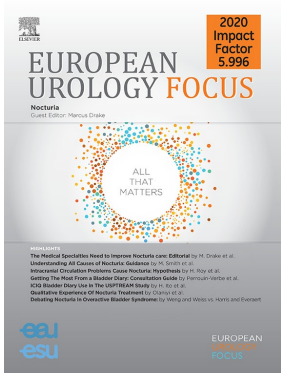
A set of four articles published back-to-back in Fertility & Sterility provided a historical context on the examination of human semen, explained the standardisation, quality control process, and methodological changes in the 6th edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen, with an outlook on emerging research in reproductive testing.

Wang C, Mbizvo M, Festin MP, Björndahl L, Toskin I; *et al.* Evolution of the WHO "Semen" processing manual from the first (1980) to the sixth edition (2021). ***Fertil Steril.*** 2022; 117(2):237-245. PMCID: PMC8842884.

Björndahl L, Kirkman Brown J; *et al.* The sixth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen: ensuring quality and standardization in basic examination of human ejaculates. ***Fertil Steril.*** 2022; 117(2):246-251. PMID: 34986984.

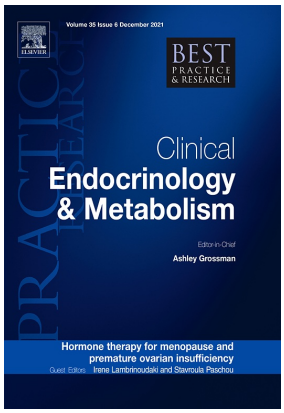
Baldi E, Gallagher MT, Krasnyak S, Kirkman-Brown J; *et al.* Extended semen examinations in the sixth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen: contributing to the understanding of the function of the male reproductive system. ***Fertil Steril.*** 2022; 117(2):252-257. PMID: 34986981.

Barratt CLR, Wang C, Baldi E, Toskin I, Kiarie J, Lamb DJ; *et al.* What advances may the future bring to the diagnosis, treatment, and care of male sexual and reproductive health? ***Fertil Steril.*** 2022; 117(2):258-267. PMCID: PMC8877074.
https://www.fertstert.org/issue/S0015-0282(21)X0016-7



This article is an evidence-based guide on the indications for sperm DNA fragmentation (SDF) testing for testicular sperm extraction (TESE) in non-azoospermic men, prepared by the EAU Working Panel on Male Sexual and Reproductive Health, including several EAA Academicians. The Panel recommended performing SDF testing in couples with recurrent pregnancy loss and men with unexplained infertility but did not advocate the routine use of TESE-ICSI in men with raised SDF outside of clinical trials.

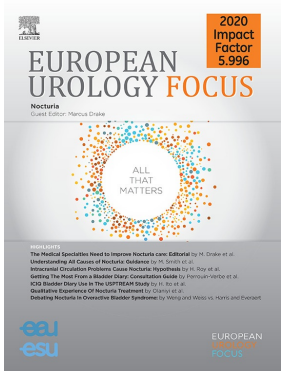
Tharakan T, Bettocchi C, Carvalho J, Corona G, Jones TH, Kadioglu A, Salamanca JIM, Serefoglu EC, Verze P, Salonia A, Minhas S; EAU Working Panel on Male Sexual Reproductive Health. European Association of Urology Guidelines Panel on Male Sexual and Reproductive Health: A Clinical Consultation Guide on the Indications for Performing Sperm DNA Fragmentation Testing in Men with Infertility and Testicular Sperm Extraction in Nonazoospermic Men. ***Eur Urol Focus.*** 2022; 8(1):339-350. PMID: 33422457.
https://www.eu-focus.europeanurology.com/article/S2405-4569(20)30319-9/fulltext



Two experts and Honorary EAA Academicians summarised key points of the pathogenesis and diagnosis of the ageing-related decline of testosterone in men, termed functional hypogonadism. They indicated that this condition is not common and is detectable in about 2% of community-dwelling men aged 40-80 years.

Huhtaniemi IT, Wu FCW. Ageing male (part I): Pathophysiology and diagnosis of functional hypogonadism. ***Best Pract Res Clin Endocrinol Metab.*** 2022 Feb 11:101622. Epub ahead of print. PMID: 35210191.

This article focused on the treatment of sexual dysfunction in patients with benign prostatic hyperplasia (BPH). The authors concluded that prostatic urethral lift (PUL) offers safe and effective relief of lower urinary tract symptoms (LUTS) while preserving sexual function. In many patients PUL was superior to daily medical therapy of doxazosin or finasteride alone or in



combination.

Roehrborn CG, Rukstalis DB. Prostatic Urethral Lift Versus Medical Therapy: Examining the Impact on Sexual Function in Men with Benign Prostatic Hyperplasia. ***Eur Urol Focus.*** 2022; 8(1):217-227. PMID: 33436276. https://www.eu-focus.europeanurology.com/article/S2405-4569(20)30315-1/pdf

The recognition of the pathogenesis of erectile dysfunction is essential to identify the appropriate management. This study from the Modena Andrology Unit (Italy) showed that the combination of intracavernosal injection test with late penile erections evaluation was able to diagnose psychological erectile dysfunction with high sensitivity and specificity. The authors provided good advice on how to indirectly identify also the patients in need of evaluation of vascular health.

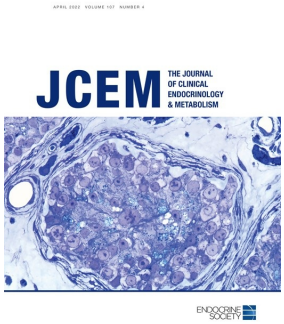
Santi D, Spaggiari G, Simoni M, Granata ARM. Accurate and time-saving, two-step intracavernosal injection procedure to diagnose psychological erectile dysfunction. ***Andrology*** 2022 Mar 13. Epub ahead of print. PMID: 35279959. https://doi.org/10.1111/andr.13175

COVID-19

This randomized phase 2 clinical trial (COVIDENZA) evaluated the effect of antiandrogens on SARS-CoV-2 infection in hospitalized COVID-19 patients. The authors also conducted a population-based retrospective study of 7894 SARS-CoV-2-positive prostate cancer patients and an experimental study in cultured primary lung cells. The results do not support a therapeutic effect of enzalutamide or preventive effects of bicalutamide or ADT in COVID-19. Thus, these antiandrogens should not be used as prevention or treatment for COVID-19.

Welén K, Rosendal E, Gisslén M, Lenman A, Freyhult E, Fonseca-Rodríguez O, Bremell D, Stranne J, Balkhed ÅÖ, Niward K, Repo J, Robinsson D, Henningsson AJ, Styrke J, Angelin M, Lindquist E, Allard A, Becker M, Rudolfsson S, Buckland R, Carlsson CT, Bjartell A, Nilsson AC, Ahlm C, Connolly AF, Överby AK, Josefsson A. A Phase 2 Trial of the Effect of Antiandrogen Therapy on COVID-19 Outcome: No Evidence of Benefit, Supported by Epidemiology and In Vitro Data. ***Eur Urol.*** 2022; 81(3):285-293. PMID: 34980495.

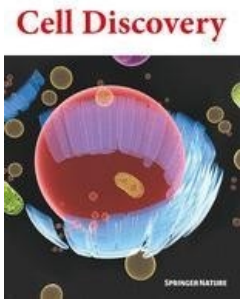
General male health issues



Abdominal aortic aneurysms (AAA) occur predominantly in males. This Swedish study addressed the hypothesis that sex hormones could be responsible for this association. The authors evaluated hormone profiles using a high-performance LC-MS assay and found an association between lower progesterone and estradiol levels and an increased risk of AAA in men, independently of known risk factors.

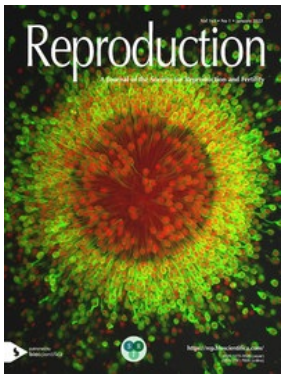
Ohlsson C, Langenskiöld M, Smidfelt K, Poutanen M, Ryberg H, Norlén AK, Nordanstig J, Bergström G, Tivesten Å. Low Progesterone and Low Estradiol Levels Associate With Abdominal Aortic Aneurysms in Men. ***J Clin Endocrinol Metab (JCEM)*** 2022 Mar 24;107(4):e1413-e1425. PMID: 34865072. https://doi.org/10.1210/clinem/dgab867

Androgenetics



This study identified a hemizygous stop-gain mutation of *TENT5D* in a man with primary infertility (OAT). In *Tent5d*-mutated mice, spermatids did not develop normally but male mice could be treated by cell sorting and round spermatid injection (ROSI). The authors suggested that TENT5D is a noncanonical poly(A) polymerase important for the stability of mRNAs during spermatogenesis.

Cong J, Yang Y, Wang X, Shen Y, Qi HT, Liu C, Tang S, Wu S, Tian S, Zhou Y, He X, Wang L, Liu MF, Zhang F. Deficiency of X-linked TENT5D causes male infertility by disrupting the mRNA stability during spermatogenesis. ***Cell Discovery*** 2022 Mar 8;8(1):23. PMID: 35256600. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901658/



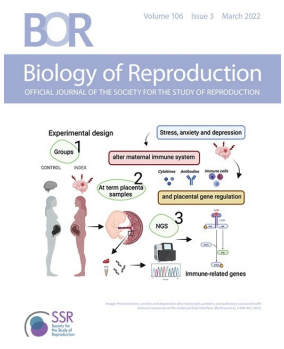
Multiple aspects of spermatogenesis are controlled by chromatin remodellers. This study showed that the severity of male subfertility in Cecr2GT/Del males was dependent on age. The authors identified inappropriately high expression of X chromosome genes in Cecr2GT/Del testes, likely caused by a failure of meiotic sex chromosome inactivation.

Norton KA, Humphreys R, Weatherill C, Duong K, Nguyen VV, Kommadath A, Niri F, Stothard P, McDermid HE. Subfertility in young male mice mutant for chromatin remodeller CECR2. Reproduction 2022; 163(2):69-83. doi: 10.1530/REP-19-0507. PMID: 34904570. https://rep.bioscientifica.com/view/journals/rep/163/2/REP-19-0507.xml

Translational and basic andrology

This Canadian study examined the role of FAM172A and CHD7 in male sex determination. A partial loss of either *Fam172a* or *Chd7* led to dysregulation of transcription and alternative splicing in fetal pre-Sertoli cells, including direct impacts on Sry and alternative splicing of the WNT effector genes *Lef1* and *Tcf7l2*. These molecular defects were also associated with the abnormal morphology of seminiferous tubules in postnatal testes.

Bélanger C, Cardinal T, Leduc E, Viger RS, Pilon N. CHARGE syndrome-associated proteins FAM172A and CHD7 influence male sex determination and differentiation through transcriptional and alternative splicing mechanisms. ***FASEB J.*** 2022; 36(3):e22176. PMID: 35129866. https://doi.org/10.1096/fj.202100837RR



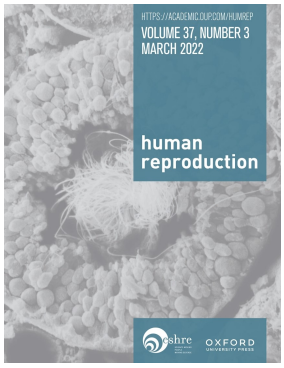
This study explored a possible role in spermatogonia of the NFI family, implicated in stem cell biology. Surprisingly, the analysis of NFIX expression revealed expression in spermatocytes. Nfix-null mice had spermatocytes with structural defects in the synaptonemal complex and unrepaired DNA double-strand breaks, suggesting the requirement for NFIX in correct meiotic progression during the first wave of spermatogenesis.

Davila RA, Spiller C, Harkins D, Harvey T, Jordan PW, Gronostajski RM, Piper M, Bowles J. Deletion of NFIX results in defective progression through meiosis within

the mouse testis. ***Biol Reprod.*** 2022 Mar 3:ioac049. Epub ahead of print. PMID: 35243487.

This study investigated in the mouse model, the consequences of intrauterine hyponutrition, which in humans is regarded as a risk factor for testicular dysgenesis syndrome (TDS). The results imply that reduced fetal testosterone production is the primary underlying factor for the development of TDS in intrauterine hyponutrition.

Fujisawa Y, Ono H, Konno A, Yao I, Itoh H, Baba T, Morohashi K, Katoh-Fukui Y, Miyado M, Fukami M, Ogata T. Intrauterine Hyponutrition Reduces Fetal Testosterone Production and Postnatal Sperm Count in the Mouse. ***J Endocr Soc (JES)*** 2022 Feb 15;6(4):bvac022. PMID: 35265782.
https://doi.org/10.1210/jendso/bvac022



This study from Copenhagen found that a metabolite of commonly used analgesic paracetamol reaches seminal plasma. One of its metabolites, N-arachidonoyl phenolamine (AM404), produced via fatty acid amide hydrolase (FAAH) present in human sperm, can interfere with sperm Ca^{2+}signalling and function through a suggested CatSper channel-dependent action.

Rehfeld A, Frederiksen H, Rasmussen RH, David A, Chaker J, Nielsen BS, Nielsen JE, Juul A, Skakkebæk NE, Kristensen DM. Human sperm cells can form paracetamol metabolite AM404 that directly interferes with sperm calcium signalling and function through a CatSper-dependent mechanism. ***Hum Reprod.*** 2022 Mar 8 Epub ahead of print. PMID: 35259261.
https://doi.org/10.1093/humrep/deac042

frontiers in Cell and Developmental Biology

IZUMO1 is a sperm protein essential for sperm-egg fusion in mammals. In this study, *Izumo1* KO male rats (but not mice) were found to be infertile, because spermatozoa failed to bind to the oolemma.

Matsumura T, Noda T, Satouh Y, Morohoshi A, Yuri S, Ogawa M, Lu Y, Isotani A, Ikawa M. Sperm IZUMO1 Is Required for Binding Preceding Fusion With Oolemma in Mice and Rats. ***Front Cell Dev Biol.*** 2022 ;9:810118. PMID: 35096839.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8790511/

EAA Secretary
rajpertdemeyts.EAA@gmail.com

European Academy of Andrology
www.andrologyacademy.net
office@andrologyacademy.net