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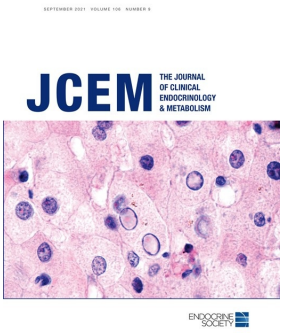
EAA Literature Alert
Edition September 2021

Clinical andrology and epidemiology



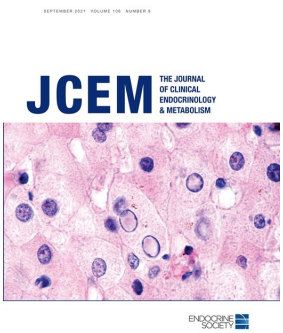
Testicular venous blood flow is altered in Klinefelter syndrome (KS) and independently predicts peripheral release of testosterone (T)! This study from the EAA Centre in Rome followed on previous experimental studies suggesting abnormalities in testicular microcirculation in KS. The authors investigated this aspect in KS patients by contrast-enhanced ultrasonography and correlated vascular parameters with endocrine function. They found slower testicular perfusion kinetics in KS men than in age-matched controls. Faster testicular blood flow was associated with higher circulating T levels.

Carlomagno F, Pozza C, Tenuta M, Pofi R, Tarani L, Sesti F, Minnetti M, Gianfrilli D, Isidori AM. Testicular microvascular flow is altered in Klinefelter syndrome and predicts circulating testosterone. ***J Clin Endocrinol Metab***. 2021 Aug 18:dgab605. Epub ahead of print. PMID: 34407199. https://doi.org/10.1210/clinem/dgab605).

Using a retrospective analysis of electronic health records in a single tertiary-care andrological centre, the authors identified clinical and biological variables that may have a predictive value for the diagnosis of congenital unilateral absence of vas deferens (CUAVD) in male partners of infertile couples. History of cryptorchidism, semen volume, fructose and α-glucosidase were identified as relevant and independent predictors.

Brusq C, Mieusset R, Hamdi SM. Development of a multivariable prediction model for congenital unilateral absence of the vas deferens in male partners of infertile couples. ***Andrology*** 2021. First published: 12 September 2021

https://doi.org/10.1111/andr.13106



High-dose vitamin D supplementation can have beneficial effects on glucose homeostasis and HDL cholesterol levels in infertile men, as shown in this double-blinded, randomized clinical trial from the Centre in Copenhagen. Men receiving vitamin D supplementation (1,400 IU cholecalciferol + 500 mg of calcium daily) had 13% lower fasting serum insulin concentrations, 19% lower HOMA-IR and higher high-density lipoprotein (HDL) cholesterol levels compared with the placebo-treated group.

Holt R, Holm Pedersen J, Dinsdale E, Knop FK, Juul A, Jørgensen N, Blomberg Jensen M.

Vitamin D supplementation improves fasting insulin levels and HDL cholesterol in infertile men. ***J Clin Endocrinol Metab***. 2021; dgab667. Epub ahead of print. PMID: 34508607
https://doi.org/10.1210/clinem/dgab667

This study investigated the relationship between androgen status, inflammatory acute phase factors and blood lipid profile in a group of 149 normal men. The authors found that the serum levels of T, fT, and the fT/C ratio were inversely correlated with the CRP, AAG, and FER concentrations independently of age and blood lipids, but depending on BMI. They concluded that a low serum T concentration may promote low grade inflammatory processes through a reduced inhibition of inflammatory cytokine synthesis, which leads to enhanced acute phase protein production.

Grandys M, Majerczak J, Zapart-Bukowska J, Duda K, Kulpa JK, Zoladz JA. Lowered Serum Testosterone Concentration Is Associated With Enhanced Inflammation and Worsened Lipid Profile in Men. ***Frontiers Endocrinol.***, 9 September 2021 |
https://doi.org/10.3389/fendo.2021.735638

This interesting study of 25 infertile men with multiple morphological abnormalities of the flagellum (MMAF) demonstrated that despite occasional technical difficulties, ICSI outcomes (pregnancies) for couples with MMAF do not differ from those of other infertile couples, irrespective of the genetic defect.

Ferreux L, Bourdon M, Chargui A, Schmitt A, Stouvenel L, Lorès P, Ray P, Lousqui J, Pocate-Cheriet K, Santulli P, Dulioust E, Toure A, Patrat C. Genetic diagnosis, sperm phenotype and ICSI outcome in case of severe asthenozoospermia with multiple morphological abnormalities of the flagellum, ***Human Reproduction***, 2021; September 16, deab200.

https://doi.org/10.1093/humrep/deab200

Addiction to pornography can have physical effects. This study investigated pornography use in relation to reproductive parameters among 568 male college students in China. 95.9% participants reported masturbation experience when using pornography. Earlier pornography use was found to be associated with lower serum prolactin, FSH, progesterone, and lower sperm counts. Higher frequency of pornography use was associated with lower serum estrogen.

Cui Z, Mo M, Chen Q, Wang X, Yang H, Zhou N, Sun L, Liu J, Ao L, Cao J. Pornography Use Could Lead to Addiction and Was Associated With Reproductive Hormone Levels and Semen Quality: A Report From the MARHCS Study in China. Frontiers Endocrinol. 10 September 2021
https://doi.org/10.3389/fendo.2021.736384

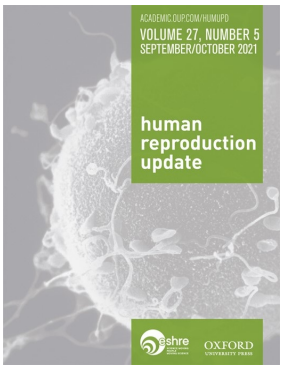
Clinical Guidelines

Updated summaries of the EAU guidelines on male sexual dysfunction and on male infertility were published in September by the EAU Working Group on Male Sexual and Reproductive Health. The guidelines summarised the most recent findings, including advances in areas of controversy in male infertility, and advise urologists in terms of diagnosis and treatment, reflecting the multidisciplinary nature of andrological management.

Salonia A, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, Cocci A, Corona G, Dimitropoulos K, Gül M, Hatzichristodoulou G, Jones TH, Kadioglu A, Martínez Salamanca JI, Milenkovic U, Modgil V, Russo GI, Serefoglu EC, Tharakan T, Verze P, Minhas S; EAU Working Group on Male Sexual and Reproductive Health. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: Male Sexual Dysfunction. ***European Urology*** 2021; 80(3):333-357. PMID: 34183196.
https://www.sciencedirect.com/science/article/abs/pii/S0302283821018133?via%3Dihub

Minhas S, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, Cocci A, Corona G, Dimitropoulos K, Gül M, Hatzichristodoulou G, Jones TH, Kadioglu A, Martínez Salamanca JI, Milenkovic U, Modgil V, Russo GI, Serefoglu EC, Tharakan T, Verze P, Salonia A; EAU Working Group on Male Sexual and Reproductive Health. European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility. ***European Urology*** 2021 Sep 9:S0302-2838(21)01982-5. doi: 10.1016/j.eururo.2021.08.014. PMID: 34511305.
https://doi.org/10.1016/j.eururo.2021.08.014

Androgenetics



We highlighted a preprint of this paper in the May edition. Now this systematic review study from two international consortia conducting research in genetics of male infertility (IMIGC and GEMINI) has been published in a journal. They gathered and curated all available evidence for monogenic causes of male infertility and identified 120 genes that were linked to 104 infertility phenotypes. These results may help to design relevant 'gene panels' and improve genetic testing in male infertility.

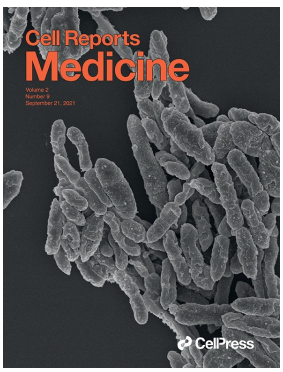
Houston BJ, Riera-Escamilla A, Wyrwoll MJ, Salas-Huetos A, Xavier MJ, Nagirnaja L, Friedrich C, Conrad DF, Aston KI, Krausz C, Tüttelmann F, O'Bryan MK, Veltman JA, Oud MS. A systematic review of the validated monogenic causes of human male infertility: 2020 update and a discussion of emerging gene-disease relationships. ***Human Reproduction Update***, 2021; dmab030
https://doi.org/10.1093/humupd/dmab030

frontiers in Genetics

This study investigated incomplete penetrance in two Tunisian families with hypogonadotropic hypogonadism (HH) and Kallmann syndrome (KS), in which some members were unaffected despite carrying homozygous mutations in the *PROKR2* gene. The authors identified pathogenic combinations involving additional genes; *CCDC141*, *DUSP6* and *SEMA7A*. The findings confirmed that homozygous loss-of-function genetic variations are insufficient to cause KS, and that oligogenism is most likely the main transmission mode involved in congenital HH.

Mkaouar R, Abdallah LCB, Naouali C, Lahbib S, Turki Z, Elouej S, Bouyacoub Y, Somai M, McElreavey K, Bashamboo A, Abdelhak S, Messaoud O. Oligogenic Inheritance Underlying Incomplete Penetrance of PROKR2 Mutations in Hypogonadotropic Hypogonadism. ***Frontiers in Genetics*** 2021; 12:1366.
https://www.frontiersin.org/articles/10.3389/fgene.2021.665174/full

Basic and translational studies



This excellent translational study from the Münster Centre explored the regulation of human germ cell function in cryptozoospermia using single-cell RNA sequencing. They found increased numbers of the most undifferentiated spermatogonia (PIWIL4^{+}), fewer Adark spermatogonia, changes in spermatogonial chromatin structure, and downregulation of the EGR4-regulated chromatin-associated transcriptional repressor UTF1.

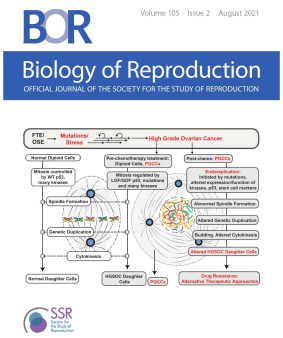
Di Persio S, Tekath T, Siebert-Kuss LM, Cremers JF, Wistuba J, Li X, zu Hörste GM, Drexler HCA, Wyrwoll M, Tüttelmann F, Dugas M, Kliesch S, Schlatt S, Laurentino S, Neuhaus N. Single-cell RNA-seq unravels alterations of the human spermatogonial stem cell compartment in patients with impaired spermatogenesis. ***Cell Reports Medicine***, 2: 100395, September 21, 2021
https://doi.org/10.1016/j.xcrm.2021.100395

This Swiss-German-Danish collaborative study investigated if serotonin uptake inhibitors (SSRI), which have off-target actions on Ca2+, Na+ and K+ channels in somatic cells, would affect Ca2+

channels in sperm. Using kinetic Ca2+ fluorimetry and patch-clamp recordings, they found that antidepressant Sertraline (e.g. Zoloft) inhibits CatSper and affects human sperm function *in vitro*.

Rahban R, Rehfeld A, Schiffer C, Brenker C, Egeberg Palme DL, Wang T, Lorenz J, Almstrup K, Skakkebaek NE, Strünker T, Nef S. The antidepressant Sertraline inhibits CatSper Ca2+ channels in human sperm. ***Human Reproduction*** 2021; 36 (10): 2638–2648. doi: 10.1093/humrep/deab190. PMID: 34486673.

https://academic.oup.com/humrep/advance-article/doi/10.1093/humrep/deab190/6364849



This study sought to uncover how Sertoli cells are regulated in the testis environment via germ cell crosstalk in the mouse. By comparing transcriptomes, the authors found two major clusters of Sertoli cells in stages VII-VIII of the seminiferous epithelium and a cluster for all other stages. In germ cell-deficient testes, the Sertoli cell transcriptome cycling was disturbed and resulted in a state unique from either of those seen in normal environment.

Gewiss RL, Law NC, Helsel RA, Shelden EA, Griswold MG. Two distinct Sertoli cell states are regulated via germ cell crosstalk, ***Biology of Reproduction***, 2021; ioab160

https://doi.org/10.1093/biolre/ioab160

This study explored the potential role of different aquaporins (AQPs) during in vitro sperm capacitation using AQP inhibitors. The findings showed that AQPs have a key role in preserving sperm motility and the maintenance of lipid membrane architecture during capacitation and/or the acrosome reaction.

Delgado-Bermúdez A, Recuero S, Llavanera M, Mateo-Otero Y, Sandu A, Barranco I, Ribas-Maynou J, Yeste M. Aquaporins Are Essential to Maintain Motility and Membrane Lipid Architecture During Mammalian Sperm Capacitation. ***Frontiers in Cell & Developmental Biology*** | www.frontiersin.org 1September 2021 | Volume 9 | Article 656438
https://doi.org/10.3389/fcell.2021.656438

Onco-andrology

September is **Prostate Cancer Awareness Month** in many countries. We highlight here a study demonstrating different recovery patterns of hormonal profiles after treatment with a gonadotropin-releasing hormone (GnRH) antagonist (*degarelix*) and GnRH agonists (*leuprorelin acetate* or *goserelin acetate*) used in short-term (12 weeks) neoadjuvant androgen deprivation therapy (ADT) for localized prostate cancer. The choice between these drugs matters and may have a clinical impact depending on the primary objective of ADT.

Sasaki H, Miki K, Tashiro K, Mori K, Urabe F, Fukuokaya W, Kimura T, Sato S, Takahashi H, Aoki M, Egawa S. Differences in sex hormone recovery profile after cessation of 12-week gonadotropin-releasing hormone antagonist versus agonist therapy. ***Andrology***. 2021 Sep 12. doi: 10.1111/andr.13107. Epub ahead of print. PMID: 34510814.
https://doi.org/10.1111/andr.13107

Case reports of the month

Clinicians commonly encounter older men who present with functional hypogonadism, but without evidence of organic hypothalamic-pituitary-testicular axis pathology. Whether, and when, testosterone therapy should be offered to such men remains uncertain and controversial. In this debate, two experts addressed this controversy, framed around a typical clinical case, and provided two opposing points of view on the role of testosterone treatment in older men with functional hypogonadism.

Grossmann M, Jones TH. Functional hypogonadism in middle-aged and older men: testosterone treatment or not? ***Eur J Endocrinol***. 2021; 185(3):D1-D9. doi: 10.1530/EJE-21-0362. PMID: 34260411.

https://eje.bioscientifica.com/view/journals/eje/185/3/EJE-21-0362.xml

It is essential to perform ultrasound examination in all boys with suspected scrotal mass. This paper reports two siblings (14 y. and 24 y.) with congenital adrenal hyperplasia (CAH) and compound mutations (one novel) in the gene encoding 3β-2HSD. Their story illustrates how delayed diagnosis and poor compliance with hormone therapy caused giant testicular adrenal rest tumours (TARTs) requiring surgery.

Yu L, Chen P, Zhu W. et al. Case Report: clinical experience of bilateral giant pediatric testicular adrenal rest tumors with 3 Beta-Hydroxysteroid Dehydrogenase-2 family history. ***BMC Pediatr*** 21, 405 (2021).
https://doi.org/10.1186/s12887-021-02883-x

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