



EAA Literature Alert Edition April 2022

We are presenting the latest publications of interest for andrologists of all subspecialties. Enjoy the reading! If you are a new EAA member and would like to share your work with your fellow members – please send a note to the EAA Secretary.

Clinical andrology and epidemiology



This Dutch study investigated the association between pre-conception paternal body mass index (BMI), embryo morphokinetics and in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) outcomes. The data demonstrated that a high paternal BMI was associated with a reduced fertilization rate in IVF/ICSI treatment.

Hoek J, Schoenmakers S, van Duijn L, Willemsen SP, van Marion ES, Laven JSE, Baart EB, Steegers-Theunissen RPM. A higher preconceptional paternal body mass index influences fertilization rate and preimplantation embryo development. *Andrology*. 2022; 10(3):486-494. PMID: 34779151.

<https://onlinelibrary.wiley.com/doi/10.1111/andr.13128>



This systematic review gathered evidence on the pharmacokinetics and safety of subcutaneous testosterone esters (scT) which is an alternative to intramuscular route (imT). The available evidence suggests that scT therapy in doses similar to imT results in comparable mean serum T levels. Clinicians should consider discussing the sc route with their patients because it is easier to self-administer and has the potential to improve patient adherence.

Figueiredo MG, Gagliano-Jucá T, Basaria S. Testosterone Therapy With Subcutaneous Injections: A Safe, Practical, and Reasonable Option. *J Clin Endocrinol Metab (JCEM)*. 2022;107(3):614-626. PMID: 34698352.

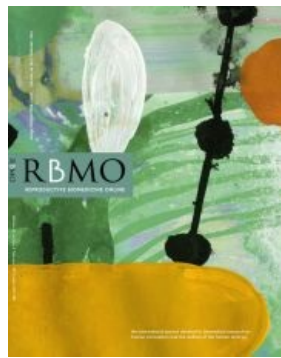
<https://doi.org/10.1210/clinem/dgab772>



This systematic review and meta-analysis evaluated the effectiveness and safety of clomiphene citrate therapy in men with hypogonadism. The authors concluded that clomiphene citrate is effective for improving both biochemical and clinical symptoms of males suffering from hypogonadism. Clomiphene citrate has few reported side effects and good safety aspects.

Huijben M, Lock MTWT, de Kemp VF, de Kort LMO, van Breda HMK. Clomiphene citrate for men with hypogonadism: a systematic review and meta-analysis. *Andrology*. 2022 Mar;10(3):451-469. PMID: 34933414.

<https://onlinelibrary.wiley.com/doi/10.1111/andr.13146>



Which criteria of sperm normality were used after the publication of the WHO 5th edition manual (WHO5), and how did the laboratories perform? The analysis performed in Australia can be extrapolated to other countries. Before the publication of WHO5, at least six different classification criteria were in use. The introduction of WHO5 resulted in the effective adoption of its morphology classification system, with laboratories showing improved between-laboratory variation over time.

Matson P, Kitson M, Zuvela E. Human sperm morphology assessment since 2010: experience of an Australian external quality assurance programme. *Reprod Biomed Online (RBMO)*. 2022; 44(2): 340-348. PMID: 34949537.

[10.1016/j.rbmo.2021.11.005](https://doi.org/10.1016/j.rbmo.2021.11.005)



This study from the EAA centre in Leuven assessed the bone mineral density (BMD) in men treated for paraphilic disorder with androgen deprivation therapy (ADT); cyproterone acetate and/or triptoreline, with or without bisphosphonates. They found that bone loss in ADT is an important side effect. The treatment with bisphosphonates had a positive stabilizing effect on bone density.

De Landtsheer A, Bekaert L, David K, Marcq P, Jeandarme I, Decallonne B, Antonio L, Vanderschueren D. The impact of androgen deprivation therapy on bone mineral density in men treated for paraphilic disorder: A retrospective cohort study. *Andrology*. 2022;10(3):545-550. PMID: 34914863.

<https://doi.org/10.1111/andr.13142>



This observational cohort study (based on data from the UK Biobank) examined associations of serum testosterone and SHBG with incidence of dementia. Lower total testosterone and higher SHBG were independently associated with incident dementia and Alzheimer's disease in older men. The causality remains unexplained.

Marriott RJ, Murray K, Flicker L, Hankey GJ, Matsumoto AM, Dwivedi G, Antonio L, Almeida OP, Bhasin S, Dobs AS, Handelsman DJ, Haring R, O'Neill TW, Ohlsson C, Orwoll ES, Vanderschueren D, Wittert GA, Wu FCW, Yeap BB. Lower serum testosterone concentrations are associated with a higher incidence of dementia in men: The UK Biobank prospective cohort study. *Alzheimers Dement*. 2022 Jan 3. Epub ahead of print. PMID: 34978125.

<https://doi.org/10.1002/alz.12529>



The risk of erectile dysfunction (ED) was reported to be increased in men with obstructive sleep apnea (OSA). This study from Taiwan performed a retrospective nationwide study of the effect of OSA treatment on ED. The authors found that surgical treatments lowered the risk for developing ED by 21%.

Hwang JH, Ong HL, Chen YC. Surgical treatments for obstructive sleep apnea decrease the risk of erectile dysfunction: A nationwide cohort study. *Andrology*. 2022 Mar;10(3):477-485. PMID: 34748688.

<https://onlinelibrary.wiley.com/doi/10.1111/andr.13126>

This meta-analysis evaluated the published evidence (260 articles) regarding the treatment of undescended testis (UDT) in children. The authors recommend avoiding pre-operative imaging and hormonal therapy except in specific circumstances, and to perform orchiopexy before one year of age to improve fertility outlook and lessen testicular cancer risk. They also discussed



advantages/disadvantages of various orchiopexy techniques.

Gates RL, Shelton J, Diefenbach KA, Arnold M, St Peter SD, Renaud EJ, Slidell MB, Sømme S, Valusek P, Villalona GA, McAteer JP, Beres AL, Baerg J, Rentea RM, Kelley-Quon L, Kawaguchi AL, Hu YY, Miniati D, Ricca R, Baird R. Management of the undescended testis in children: An American pediatric surgical association outcomes and evidence based practice committee systematic review. *J Pediatr Surg*. 2022 doi: 10.1016/j.jpedsurg.2022.01.003. Epub ahead of print. PMID: 35151498.

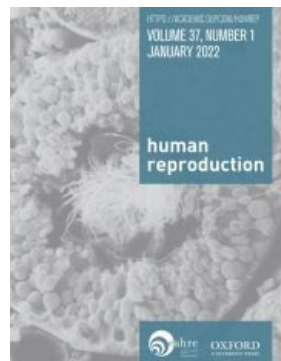
[https://www.jpedsurg.org/article/S0022-3468\(22\)00041-0/fulltext](https://www.jpedsurg.org/article/S0022-3468(22)00041-0/fulltext)



For paediatricians - a good systematic review on congenital micropenis, which can be a marker for a wide range of endocrine conditions, in particular androgen deficiency in fetal life. A group of international experts review the epidemiology and pathogenesis and give advice how to diagnose micropenis and what are the treatment options.

Stancampiano MR, Suzuki K, O'Toole S, Russo G, Yamada G, Faisal Ahmed S. Congenital Micropenis: Etiology And Management. *J Endocr Soc (JES)*. 2021;6(2):bvab172. doi: 10.1210/jendso/bvab172. PMID: 35036822.

COVID-19



A cohort trial looking for the presence of SARS-CoV-2 in residual material samples including semen, follicular fluid, vaginal secretions and ovarian medulla collected during ART procedures during the second pandemic wave. Reassuringly, no viral RNA was detected in these samples, even in patients with positive nasopharyngeal swabs. The results suggested that no additional measures to prevent staff or cross-patient contamination need to be implemented in the IVF and andrology laboratories.

Keily K, Pening D, Diaz Vidal P, Devos M, Dechene J, Op de Beeck A, Botteaux A, Janssens S, Van den Abbeel E, Goldrat O, Delbaere A, Demeestere I. Risk of contamination of semen, vaginal secretions, follicular fluid and ovarian medulla with SARS-CoV-2 in patients undergoing ART. *Hum Reprod*. 2022, 28;37(2):235-241. doi: 10.1093/humrep/deab255. PMID: 34741508.

<https://academic.oup.com/humrep/article/37/2/235/6422543>



This article presents the results of a survey on safety protocols during the COVID-19 pandemic among semen banks accredited by the EAA and SIAMS. Most centres relied on a questionnaire, about half requested a negative test before cryopreservation, and few banks used a quarantine- or a dedicated tank in case of infection.

SARS-CoV-2 mRNA test in semen was done only in one semen bank in Florence. The authors recommended improving safety measures and using safe devices for sample handling and storage.

Marchiani S, Dabizzi S, Degl'Innocenti S, Fino MG, Torcia MG, Paoli D, Lombardo F, Ciccone N, Pollini S, Rossolini GM, Vignozzi L, Krausz C, Baldi E. Safety issues in semen banks during the COVID-19 pandemic: data from a European survey. *J Endocrinol Invest*. 2022 Jan 25:1-8. Epub ahead of print. PMID: 35075607.

<https://link.springer.com/article/10.1007/s40618-021-01728-9>

Androgenetics

One more study demonstrating close connection



between regulation of synaptonemal complex (SC) in male and female meiosis. Using whole exome sequencing, the authors investigated SC gene variations in 1030 patients with premature ovarian insufficiency (POI) and 400 patients with nonobstructive azoospermia (NOA). They identified novel pathogenic variants of *C14ORF39* and *SYCE1*.

Hou D, Yao C, Xu B, Luo W, Ke H, Li Z, Qin Y, Guo T. Variations of C14ORF39 and SYCE1 Identified in Idiopathic Premature Ovarian Insufficiency and Nonobstructive Azoospermia. *J Clin Endocrinol Metab. (JCEM)* 2022 Feb 17;107(3):724-734. PMID: 34718620.

<https://doi.org/10.1210/clinem/dgab777>



In this study, several *CFAP61* variants encoding cilia- and flagella-associated protein 61 were found in 11 Pakistani infertile patients with multiple morphological abnormalities of the flagella (MMAF), confirmed by transmission electron microscopy.

Ma A, Zeb A, Ali I, Zhao D, Khan A, Zhang B, Zhou J, Khan R, Zhang H, Zhang Y, Khan I, Shah W, Ali H, Javed AR, Ma H, Shi Q. Biallelic Variants in CFAP61 Cause Multiple Morphological Abnormalities of the Flagella and Male Infertility. *Front Cell Dev Biol.* 2022 Jan 31;9:803818. PMID: 35174165.

<https://doi.org/10.3389/fcell.2021.803818>



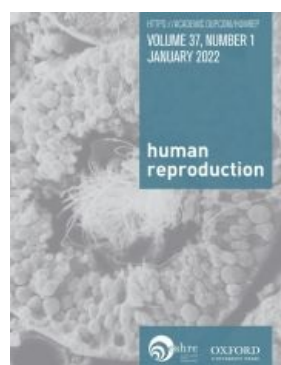
International Journal of
Molecular Sciences

This review discusses the available literature to explore possible novel functions related to competing endogenous RNA (ceRNA) activity of lncRNAs produced by the X-inactivation centre (e.g. XIST), beyond their role in dosage compensation, with implications for emerging gender-biased functions and pathological mechanisms.

Siniscalchi C, Di Palo A, Russo A, Potenza N. The lncRNAs at X Chromosome Inactivation Center: Not Just a Matter of Sex Dosage Compensation. *Int J Mol Sci.* 2022 Jan 6;23(2):611. PMID: 35054794.

<https://www.mdpi.com/1422-0067/23/2/611>

Debate on fertility decline



This comprehensive opinion article discusses the reasons behind a decline in human fertility rates. The author presented a picture of many factors affecting fertility and fecundity simultaneously, including education and emancipation of women, adverse environmental factors, reduced selection pressure on high fertility genes and retention of poor fertility genes, all "colluding to drive our species into an infertility trap". Interesting and thought-provoking article.

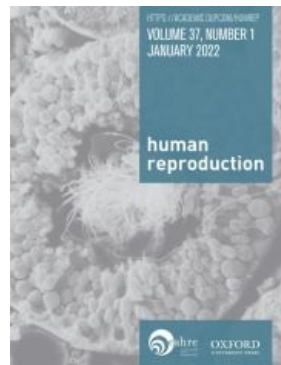
Aitken RJ. The changing tide of human fertility. *Hum. Reprod.* 2022, Jan 25, Epub ahead of print.

<https://doi.org/10.1093/humrep/deac011>

Translational and basic andrology

The authors developed a high-throughput screening platform, which identified a large number of compounds that enhanced human sperm motility. Dose-response experiments in vitro confirmed the enhancing effect on sperm motility. Major identified targets were phosphodiesterase inhibitors, in particular PDE10A inhibitors as well as GABA signalling. The authors made the results of screening available for researchers.

Gruber FS, Johnston ZC, Norcross NR, Georgiou I, Wilson



C, Read KD, Gilbert IH, Swedlow JR, Martins da Silva S, Barratt CLR. Compounds enhancing human sperm motility identified using a high-throughput phenotypic screening platform. **Hum Reprod.** 2022 Jan 20:deac007. Epub ahead of print. PMID: 35048946.

<https://doi.org/10.1093/humrep/deac007>



This study characterized the phenotype of mutant mice devoid of *Cep250/C-Nap1*, a gene encoding for a docking protein for fibers linking centrioles. The *Cep250*^{-/-} mice presented with male infertility due to a reduction in the spermatogonial pool and the meiotic blockade.

The authors propose a specific requirement of centrosome cohesion in the male germline, with a crucial role of CEP250.

Floriot S, Bellutti L, Castille J, Moison P, Messiaen S, Passet B, Boulanger L, Boukadiri A, Tourpin S, Beauvallet C, Vilotte M, Riviere J, Péchoux C, Bertaud M, Vilotte JL, Livera G. CEP250 is Required for Maintaining Centrosome Cohesion in the Germline and Fertility in Male Mice. **Front Cell Dev Biol.** 2022 Jan 19;9:754054. PMID: 35127699.

<https://doi.org/10.3389/fcell.2021.754054>



In this study from Hungary, the authors presented a new quantitative computer-based histomorphometric-mathematical image analysis methodology for the analysis of testicular tissue in the rat model. The results are promising and can be hopefully adapted to further automation and use in human tissue.

Sziva RE, Ács J, Tőkés A-M, Korsós-Novák Á, Nádasy GL, Ács N, Horváth PG, Szabó A, Ke H, Horváth EM, Kopa Z, Várbíró S. Accurate Quantitative Histomorphometric-Mathematical Image Analysis Methodology of Rodent Testicular Tissue and Its Possible Future Research Perspectives in Andrology and Reproductive Medicine. **Life.** 2022; 12(2):189.

<https://doi.org/10.3390/life12020189>



A blood test for monitoring pregnancy complications! Molecular diagnostics based on sequencing of plasma nucleic acids has been increasing in different fields of medicine. The authors of this study reported that plasma cell-free RNA profiling is suitable for comprehensive molecular monitoring of pregnancy progression for both healthy and complicated pregnancies such as preeclampsia.

Rasmussen M, Reddy M, Nolan R, Camunas-Soler J, Khodursky A, Scheller NM, Cantonwine DE, Engelbrechtsen L, Mi JD, Dutta A, Brundage T, Siddiqui F, Thao M, Gee EPS, La J, Baruch-Gravett C, Santillan MK, Deb S, Ame SM, Ali SM, Adkins M, DePristo MA, Lee M, Namsaraev E, Gybel-Brask DJ, Skibsted L, Litch JA, Santillan DA, Sazawal S, Tribe RM, Roberts JM, Jain M, Høgdall E, Holzman C, Quake SR, Elovitz MA, McElrath TF. RNA profiles reveal signatures of future health and disease in pregnancy. **Nature.** 2022 Jan;601(7893):422-427. PMID: 34987224.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8770117/>

Editorial comment by Shook & Edlow: <https://www.nature.com/articles/d41586-021-03801-y>

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