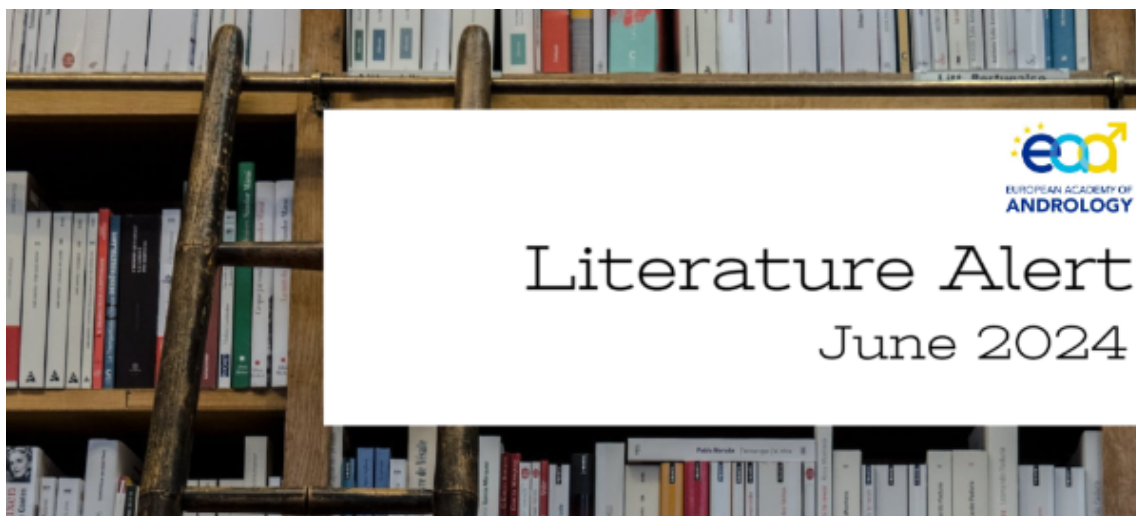




Dear EAA Members,

A new selection of articles published recently in the field of andrology and reproductive biology, several involving the EAA members. We especially highlight the latest special issue of *Andrology*, which is focused on clinical and biological aspects of epididymis. In this edition we have added also a “video corner” for andro-urologists. Other clinical topics include CAH, Klinefelter syndrome, hypogonadism, effect of onco-treatment on spermatogonia, orchialgia, PIEZO-ICSI and health of transgender people. The translational/basic topics are very exciting (3 published in *Nature!*): epigenetic inheritance transferred by epididymal sperm, evolution of sex chromosome in apes, WNT/ β -catenin signalling in early human embryo, genital vibrotactile sensors, testis organoids, and more.

Special Issue of *Andrology*, July 2024

[Vol. 12 \(5\): Special Issue: The Clinic and Biology of the Epididymis](#)

Issue Edited by: A. Meinhardt, T. Berger, R. Middendorff

Editorial: <https://doi.org/10.1111/andr.13651>

The issue contains 10 articles from the “von Behring-Röntgen-Symposium on the Epididymis” held in Giessen, Germany, in 2022. Two excellent articles, one clinical and one basic, are highlighted in this alert (*see below*). In addition to the epididymis articles, several regular articles are included in the July issue, most of these already highlighted in previous alerts.



Clinical andrology and epidemiology

Patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency are treated with glucocorticoid replacement therapy, often with supraphysiologic dosing.

Co-treatment with Crinecerfont, an oral corticotropin-releasing factor type 1 receptor antagonist resulted in a greater than placebo decrease in the mean daily glucocorticoid dose.



The NEW ENGLAND
JOURNAL of MEDICINE

Auchus RJ, Hamidi O, Pivonello R, Bancos I, Russo G, Witchel SF, Isidori AM, Rodien P, Srirangalingam U, Kiefer FW, Falhammar H, Merke DP, Reisch N, Sarafoglou K, Cutler GB Jr, Sturgeon J, Roberts E, Lin VH, Chan JL, Farber RH; CAHtalyst Adult Trial Investigators. Phase 3 Trial of Crinecerfont in Adult Congenital

Why do some but not all patients with Klinefelter syndrome have focally preserved tubules with spermatogenesis? DNA ploidy and the expression of XIST was examined in testis samples from Klinefelter patients at different ages. The results suggest that a micro-mosaic loss of the additional X-chromosome, most likely at puberty, is needed for Sertoli cells to mature and to allow focal spermatogenesis.

Winge SB, Skakkebaek NE, Aksglaede L, Saritaş G, Rajpert-De Meyts E, Goossens E, Juul A, Almstrup K. Loss of the extra X chromosome rescues Sertoli cell maturation and spermatogenesis in the testis of men with 47,XXY Klinefelter syndrome. *Cell Death & Disease* 2024 *in press*.
<https://doi.org/10.1038/s41419-024-06792-6>



Klinefelter syndrome (KS) is associated with hypergonadotropic hypogonadism and metabolic alterations. This study confirmed a primary role of obesity, insulin resistance and unfavourable lipid profile in causing disturbances of liver function. Evaluation of the liver function should be part of the clinical care in KS men.

Øzdemir CM, Ridder LO, Chang S, Fedder J, Just J, Gravholt CH, Skakkebæk A. Mild liver dysfunction in Klinefelter syndrome is associated with abdominal obesity and elevated lipids but not testosterone treatment. *J Endocrinol Invest*. 2024 May 30.
<https://doi.org/10.1007/s40618-024-02394-3>



Depressive symptoms are common in middle-aged and old men with hypogonadism but late-life-onset, low-grade persistent depressive disorder ('dysthymia') is uncommon. Testosterone replacement is associated with small improvements in mood and energy in hypogonadal men regardless of depressive symptoms.

Bhasin S, Seidman S, Travison TG, Pencina KM, Lincoff AM, Nissen SE, Miller MG, Flevaris P, Li X, Wannemuehler KA, Pope HG. Depressive Syndromes in Men With Hypogonadism in the TRAVERSE Trial: Response to Testosterone-Replacement Therapy. *J Clin Endocrinol Metab*. 2024 Jun 17;109(7):1814-1826.
<https://doi.org/10.1210/clinem/dgae026>



This multi-centre study examined numbers of spermatogonia in testis samples from prepubertal patients undergoing haematopoietic stem cell transplantation (HSCT), with chemotherapy and/or radiation. Results showed that 49% of patients have decreased and 19% severely depleted spermatogonial pool prior to HSCT, especially patients with Fanconi anaemia.

Lahtinen AK, Funke M, Krallmann C, Wyrwoll MJ, Jarisch A, Yang Y, Bjarnason R, Romerius P, Sundin M, Norén-Nyström U, Langenskiöld C, Cremers JF, Kliesch S, Stukenborg JB, Neuhaus N, Jahnukainen K. Decreased spermatogonial numbers in boys with severe haematological diseases. *Br J Haematol*. 2024 May 29.
<https://doi.org/10.1111/bjh.19572>



This study assessed the impact of hematospermia in patients with acute epididymitis and its association with clinical, microbiological, and semen parameters. Self-reported hematospermia is evident in 15% of patients with acute epididymitis. Conversely, none of the patients presenting with isolated hematospermia developed epididymitis within the next 4 weeks.

Dittmar F, Rosellen J, Reiser L, Fritzenwanker M, Hauptmann A, Diemer T, Schuppe HC, Wagenlehner F, Pilatz A. Comprehensive evaluation of hematospermia in patients with acute epididymitis compared to patients with isolated hematospermia. **Andrology**. 2024 Jul;12(5):1001-1011.

<https://doi.org/10.1111/andr.13489>



This multicentric study revealed that about 30% of men with non-obstructive azoospermia (NOA) were eligible for treatment with clomiphene citrate and/or hCG while 37% were potential candidates for aromatase inhibitors, and 17% for both therapies.

Therefore, only a small subset of NOA patients can benefit from medical therapy prior to considering any sperm retrieval procedures.

Pozzi E, Venigalla G, Raymo A, Ila V, Achermann APP, Esteves SC, Salonia A, Ramasamy R. Eligibility for the medical therapy among men with non-obstructive azoospermia-Findings from a multi-centric cross-sectional study. **Andrology**. 2024 May 28.

<https://doi.org/10.1111/andr.13670>



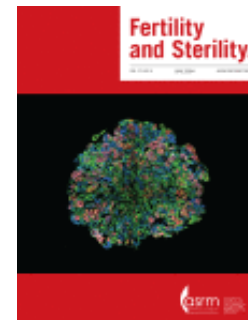
This Australian “sibling split” trial compared the results of PIEZO-intracytoplasmic sperm injection (PIEZO-ICSI) with conventional ICSI. The trial supports the possibility that PIEZO-ICSI improves the fertilization rates, the oocyte degeneration rates, and the blastocyst quality; however, it does not appear to influence the clinical pregnancy or live birth rate per transfer.

Zander-Fox D, Green M, Watson K, Turner R, Bakos HW, Foo J, Pacella-Ince L, Caddy M, McPherson NO, Rombauts L. Improved fertilization, degeneration, and embryo quality rates with PIEZO-intracytoplasmic sperm injection compared with conventional intracytoplasmic sperm injection: a sibling oocyte split multicenter trial. **Fertil Steril**. 2024 Jun;121(6):971-981.

<https://doi.org/10.1016/j.fertnstert.2024.01.028>

Comment by Ebner & Shebi:

<https://www.sciencedirect.com/science/article/pii/S0015028224001080>



Patients with chronic orchialgia are often treated with microscopic denervation of spermatic cord (MSCD) and - in those not interested in fertility - either stripping or ligation of vas deference.

The data showed that both methods are safe and yield similar outcomes with regard to pain resolution.

El-Achkar A, Hammad M, Barham D, Service CA, Patel D, Hsieh TC, Mills J, Kianian R, Eleswarapu S, Ziegelmann M, Smith R, Bryk D, Bernie HL, Egert M, Raheem O, Fendereski K, Gross K, Pastuszak A, Hotaling J, Yafi F. Stripping versus ligation of vas deferens in microscopic denervation of spermatic cord in men with chronic orchialgia: A multicenter study. **Andrology**. 2024 Apr 19. Epub ahead of print.

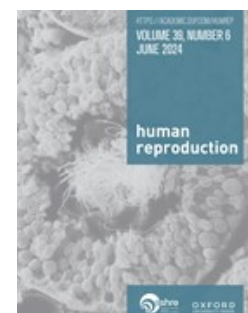
<https://doi.org/10.1111/andr.13650>



Sperm PLCζ abrogation is linked with human male infertility caused by deficient oocyte activation. This study found that PLCζ was required for optimal early embryogenesis. Sperm PLCζ levels below specific thresholds were associated with ineffective embryogenesis and lower pregnancy rates, despite successful fertilization in both mice and humans.

Kashir J, Mistry BV, Rajab MA, BuSaleh L, Abu-Dawud R, Ahmed HA, Alharbi S, Nomikos M, AlHassan S, Coskun S, Assiri AM. The mammalian sperm factor phospholipase C zeta is critical for early embryo division and pregnancy in humans and mice. **Hum Reprod**. 2024 Jun 3;39(6):1256-1274.

<https://doi.org/10.1093/humrep/deae078>



Paracetamol is suggested to be an endocrine disrupter affecting fetal programming of reproductive health. This large cohort study found no clear effect of maternal exposure on biomarkers of fecundity in sons. But it cannot be ruled out that long duration of maternal paracetamol intake might be associated with impaired semen characteristics.

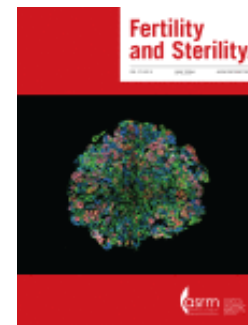
Laursen TQ, Ramlau-Hansen CH, Tøttenborg SS, Liew Z, Toft G, Gaml-Sørensen A, Hougaard KS, Bonde JPE, Ernst A. Maternal intake of paracetamol during pregnancy and biomarkers of male fecundity in young adult sons. **Reprod Toxicol**. 2024 Aug;127:108626. Epub 2024 May 28. <https://doi.org/10.1016/j.reprotox.2024.108626>



Andro-urology video corner

A visual documentation with concurrent commentary of micro-OncoTESE, performed in an azoospermic man previously orchiectomised for seminoma, with multifocal masses in the contralateral testis. The m-OncoTESE performed with the second orchiectomy resulted in the cryopreservation of 200,000 motile sperm for future assisted reproduction.

Villota CK, Hou SW, Judge C, Eggener S, Paner G, Raheem OA. Ex-vivo microscopic oncotesticular sperm extraction: step-by-step surgical technique at time of radical orchiectomy. **Fertil Steril**. 2024 Jun;121(6):1069-1071. <https://doi.org/10.1016/j.fertnstert.2024.02.037>
Video: <https://youtu.be/BvtWtmwywLQ>
SC Honig: Editorial: Ex vivo onco-testis microdissection **Fertil Steril**. 2024 Jun;121(6): 970



An insightful commentary on the challenges and priorities of the past and present research on transgender individuals. The authors argue that previous neuroscientific studies had too much focus on the biological basis for transgender identity, forgetting the societal factors. More emphasis ought to be on research questions that are likely to enhance the health of the transgender and nonbinary people.

Kennis M, Staicu R, Dewitte M, T'Sjoen G, Sack AT, Duecker F. Heed lessons from past studies involving transgender people: first, do no harm. **Nature**. 2024 May;629(8014):998-1000. <https://doi.org/10.1038/d41586-024-01521-7>

Debate



Basic and translational andrology

Exciting new evidence supporting the importance of paternal health at conception for offspring metabolism through a novel mechanism of father-to-offspring transfer of mitochondrial RNAs by sperm at fertilization. This study showed in mice that acute high-fat diet can change sncRNA pool, especially mt-rsRNA in epididymal spermatozoa. The findings suggest a link between the profiles of mitochondrial RNAs in the father's sperm and the metabolic traits of the son.

Tomar A, Gomez-Velazquez M, Gerlini R, Comas-Armangué G, Makharadze L, Kolbe T, Boersma A, Dahlhoff M, Burgstaller JP, Lassi M, Darr J, Toppari J, Virtanen H, Kühnapfel A, Scholz M, Landgraf K, Kiess W, Vogel M, Gailus-Durner V, Fuchs H, Marschall S, Hrabě de Angelis M, Kotaja N, Körner A, Teperino R. Epigenetic inheritance of diet-induced and sperm-borne mitochondrial RNAs. **Nature**. 2024 Jun;630(8017):720-727. <https://doi.org/10.1038/s41586-024-07472-3>
Comment: Cai C, Chen Q. Father's diet influences son's metabolic health



Sequences of sex chromosomes were assembled in apes (bonobo, chimpanzee, gorilla, orangutan and gibbon), using the methodology developed for the telomere-to-telomere human genome assembly. The Y chromosomes in apes vary in size and have high levels of structural rearrangements and multi-copy families. Thus, the Y chromosome exhibits dynamic evolution, whereas the X chromosome is more stable.

Makova KD, Pickett BD, Harris RS, Hartley GA, Cechova M, Pal K, et al et, Eichler EE, Phillippy AM. The complete sequence and comparative analysis of ape sex chromosomes. *Nature*. 2024 Jun;630(8016):401-411.
<https://doi.org/10.1038/s41586-024-07473-2>



The function of epsilon tubulin (TUBE1) was investigated in mice using a spermatogenesis model. TUBE1 was shown to be essential for the function of multiple complex microtubule arrays, including the meiotic spindle, axoneme and manchette, and in its absence leads to loss of germ cells and male sterility.

Stathatos GG, Merriner DJ, O'Connor AE, Zenker J, Dunleavy JE, O'Bryan MK. Epsilon tubulin is an essential determinant of microtubule-based structures in male germ cells. *EMBO Rep*. 2024 Jun;25(6):2722-2742.
<https://doi.org/10.1038/s44319-024-00159-w>



What are the consequences of dysregulating the WNT/ β -catenin signalling pathway in the supporting cell lineage during sex-specific human fetal gonad development? This study in an ex vivo organ culture model demonstrated that disturbing the signaling balance in early fetal testes severely disrupted seminiferous cord structures and somatic cell function, and caused germ cell loss.

Lundgaard Riis M, Delpouve G, Nielsen JE, Melau C, Langhoff Thuesen L, Juul Hare K, Dreisler E, Aaboe K, Tutein Brenøe P, Albrethsen J, Frederiksen H, Juul A, Giacobini P, Jørgensen A. Inhibition of WNT/ β -catenin signalling during sex-specific gonadal differentiation is essential for normal human fetal testis development. *Cell Commun Signal*. 2024 Jun 15;22(1):330.
<https://doi.org/10.1186/s12964-024-01704-9>



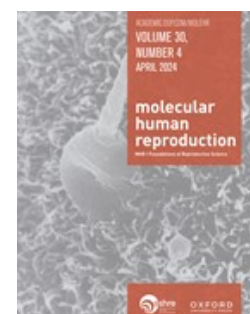
The identity of cells within the human efferent ducts (EDs) and caput epididymis cells was studied by single-cell RNA sequencing, in primary tissues and in culture and organoid models. The findings suggest that EDs are lined with a transitional epithelium, which is able to stretch and contract, consistent with its primary role in seminal fluid resorption and sperm concentration.

Leir SH, Paranjapye A, Harris A. Functional genomics of the human epididymis: Further characterization of efferent ducts and model systems by single-cell RNA sequencing analysis. *Andrology*. 2024 Jul;12(5):991-1000.
<https://doi.org/10.1111/andr.13477>



Changes in the endometrial transcriptomic profile were investigated after vaginal application of seminal plasma or placebo 2 days after HCG-triggered ovulation. The gene set enrichment analysis showed a positive enrichment of several pathways but no significant differences between the two groups. Similar studies were conducted in pigs and mice or in vitro using human endometrial cells.

Catalini L, Burton M, Egeberg DL, Eskildsen TV, Thomassen M, Fedder J. In vivo effect of vaginal seminal plasma application on the human endometrial transcriptome: a randomized controlled trial. *Mol Hum Reprod*. 2024 Mar 28;30(5):gaee017.
<https://doi.org/10.1093/molehr/gaae017>



The Krause corpuscles were proposed more than a century ago to be responsible for detecting touch in genital organs. This study in mice thoroughly examined the structure and location of the corpuscles, and confirmed that they are specialised genital sensory structures at nerve endings, and are triggered by low-frequency vibrations.

Qi L, Iskols M, Greenberg RS, Xiao JY, Handler A, Liberles SD, Ginty DD. Krause corpuscles are genital vibrotactile sensors for sexual behaviours. *Nature*. 2024 Jun 19. Epub ahead of print.
<https://doi.org/10.1038/s41586-024-07528-4>



Methodology

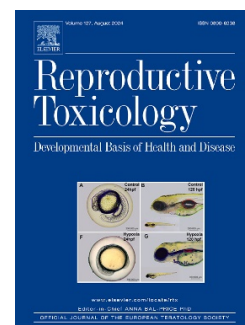
A database called the Reproductive Chemical Database (RCDB) was developed to facilitate research on chemicals in reproductive biology in human and mouse (<https://yu.life.sjtu.edu.cn/ChenLab/RCDB>). The database is based on literature data extraction and precise protein target prediction methodologies.

Cao, Y., Tian, G.G., Hong, X. et al. Reproductive chemical database: a curated database of chemicals that modulate protein targets regulating important reproductive biological processes. *Cell Biosci* 14, 73 (2024).
<https://doi.org/10.1186/s13578-024-01261-1>
[Download citation](#)



An immature porcine testis organoid system was validated for its suitability as an in vitro platform for endocrine toxicology tests. The model appears to be especially good for studying Sertoli cell maturation and formation of the blood-testis barrier.

Cham TC, Ibtisham F, Al-Dissi A, Honaramooz A. An in vitro testicular organoid model for the study of testis morphogenesis, somatic cell maturation, endocrine function, and toxicological assessment of endocrine disruptors. *Reprod Toxicol*. 2024 Jun 17:108645. Epub ahead of print.
<https://doi.org/10.1016/j.reprotox.2024.108645>



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