

## Dear EAA Members,

In this issue we are opening a new section on sex-based differences in health and disease, outside the reproductive system. Other topics/keywords: mini-puberty, hypogonadism, AMH, fertility preservation in boys, leukemic cells in prepubertal testis, novel AZF CNVs and Y-linked variants, *RHOXF1* variants in male infertility, *FGFR3* mutations, sperm and zona pellucida (and a new contraception candidate!), activation of SRY/SOX9, glucocorticoid receptor in germ cells, anti-piRNAs, inflammatory response in epididymis, phthalates and blood-testis-barrier, and useful methods for prepubertal testis size measurements and for trans-differentiating human fibroblasts into Sertoli-like cells. Enjoy!

## Clinical andrology and epidemiology

The authors compared polygenic scores of adult total testosterone (T) and SHBG concentrations with longitudinal reproductive hormone values in male infants from the Copenhagen mini-puberty cohort. The findings suggest that the genetic architecture underlying total T and SHBG in adults also associates with hormone concentrations and their trajectories during infancy.

**JCEM** THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Busch AS, Ljubicic ML, Upners EN, Fischer MB, Odronec A, Hagen CP, Juul A. Polygenic Scores for Adult Testosterone and SHBG Levels Are Associated With Reproductive Hormone Levels in Male Infants. *J Clin Endocrinol Metab.* 2024 Feb 27;dgae104. <https://doi.org/10.1210/clinem/dgae104>

To assess efficacy and clinical utility of testosterone therapy in functional hypogonadism, the authors analysed registry data from 650 patients with different types of hypogonadism.

**ANDROLOGY**



The study demonstrated heterogeneous responses, significantly influenced by diagnostic categorization, age, and baseline risk factor profiles.

Zitzmann M, Cremers JF, Krallmann C, Soave A, Kliesch S. Testosterone therapy in men with classical versus functional hypogonadism: results from a controlled 9-years, real-world registry study. *Andrology.* 2024 Mar 15. Epub ahead of print. <https://doi.org/10.1111/andr.13626>

This double-blind study showed that low serum AMH is associated with poor semen quality in infertile men, which implies that AMH may have clinical value during the evaluation of male infertility.

Holt R, Yahyavi SK, Wall-Gremstrup G, Jorsal MJ, Toft FB, Jørgensen N, Juul A, Jensen MB. Low Serum anti-Mullerian Hormone is Linked with Poor Semen Quality in Infertile Men Screened for Participation in an RCT. *Fertil Steril*. 2024 Mar 22:S0015-0282(24)00193-6.

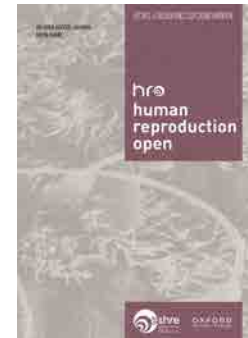
<https://doi.org/10.1016/j.fertnstert.2024.03.018>



16 centres which offer testicular tissue cryopreservation to patients under the age of 18 years (now ORCHID-NET) completed a survey concerning their experience. The growing number of patients (currently 3118 in total) necessitates collaboration between centres to better harmonize clinical and research protocols evaluating tissue function and clinical outcomes in these patients.

Duffin K, Neuhaus N, Andersen CY, Barraud-Lange V, Braye A, Eguizabal C, Feraille A, Ginsberg JP, Gook D, Goossens E, Jahnukainen K, Jayasinghe Y, Keros V, Kliesch S, Lane S, Mulder CL, Orwig KE, van Pelt AMM, Poirot C, Rimmer MP, Rives N, Sadri-Ardekani H, Safrai M, Schlatt S, Stukenborg JB, van de Wetering MD, Wyns C, Mitchell RT. A 20-year overview of fertility preservation in boys: new insights gained through a comprehensive international survey. *Hum Reprod Open*. 2024 Feb 16;2024(2):hoae010.

<https://doi.org/10.1093/hropen/hoae010>



Investigation of prepubertal testis tissue samples in a Belgian cohort of boys diagnosed with leukemia and lymphomas, found contamination with cancer cells in 39%, and all patients had reduced spermatogonia numbers compared to healthy references. The authors call for development of adapted fertility restoration protocols.

Kourta D, Camboni A, Saussoy P, Kanbar M, Poels J, Wyns C. Evaluating testicular tissue for future autotransplantation: focus on cancer cell contamination and presence of spermatogonia in tissue cryobanked for boys diagnosed with a hematological malignancy. *Hum Reprod*. 2024 Mar 1;39(3):486-495.

<https://doi.org/10.1093/humrep/dead271>



This study explored whether maternal use of nitrosatable drugs, such as penicillins and beta 2-agonists, during pregnancy was associated with biomarkers of male fecundity in their adults sons.

Reassuringly, no harmful influence on the male fecundity of the offspring was found.

Clemmensen PJ, Brix N, Schullehner J, Toft G, Søgaard Tøttenborg S, Sørig Hougaard K, Bjerregaard AA, Halldorsson TI, Olsen SF, Hansen B, Stayner LT, Sigsgaard T, Kolstad H, Bonde JPE, Ramlau-Hansen CH. Maternal use of nitrosatable drugs during pregnancy and adult male reproductive health: A population-based cohort study. *Andrology*. 2024 Mar 15. Epub ahead of print.

<https://doi.org/10.1111/andr.13625>



## Androgenetics

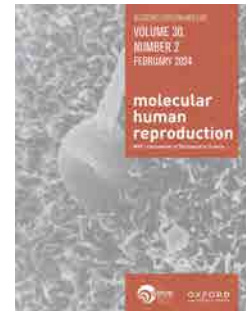
In a cohort of Japanese NOA patients, AZF-linked (Y-chr.) copy number variants (CNVs) were found in more than half (54.8%) or in 31%, if the common in Japan gr/gr deletion was excluded. Novel CNVs included gr/gr triplication. The study identified several other pathogenic variants, and some patients carried rare damaging variants in multiple genes.

Muranishi Y, Kobori Y, et al. Shinohara N, Fukami M. Systematic molecular analyses for 115 karyotypically normal men with isolated non-obstructive



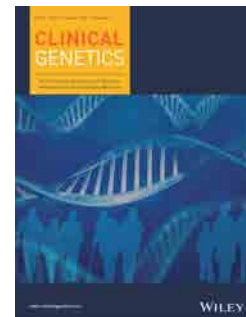
Four hemizygous variants were found in the X-linked *RHOXF1* gene in 4 unrelated cases from a cohort of 1201 infertile Chinese men, incl. one with SCO. Others with oligozoospermia could be treated by ICSI.

Yi S, et al et, Zhang Q. Deleterious variants in X-linked *RHOXF1* cause male infertility with oligo- and azoospermia. *Mol Hum Reprod.* 2024 Feb 1;30(2):gaae002. <https://doi.org/10.1093/molehr/gaae002>



A novel hemizygous nonsense variant of *BCORL1* was identified in a male patient with OAT, and previously in another one with azoospermia, and in a knockout mouse model. *BCORL1* is a transcriptional corepressor and may play a role in spermatogenesis by interacting with SKP1.

Luo C, Chen Z, Meng L, et al et, Tan YQ, Hu TY. A hemizygous loss-of-function variant in *BCORL1* is associated with male infertility and oligoasthenoteratozoospermia. *Clin Genet.* 2024 Feb 11. <https://doi.org/10.1111/cge.14500>



Two studies from Austria analysed *FGFR3* mutations that increase in frequency with age. The first study assessed 10 different *FGFR3* missense substitutions in male germline. 9/10 resulted in a higher activation of the receptor's signalling. In the second study, known *FGFR3* mutations linked to paternal transmission of achondroplasia (ACH) and thanatophoric dysplasia (TDII) were investigated for mutations rates in sperm, revealing distinct behaviors for ACH (G380R) and TDII (K650E) variants.

Moura S, Hartl I, Brumovska V, Calabrese PP, et al et, Tiemann-Boege I. Exploring *FGFR3* Mutations in the Male Germline: Implications for Clonal Germline Expansions and Paternal Age-Related Dysplasias. *Genome Biol Evol.* 2024 Feb 1; 16(2):evae015. <https://doi.org/10.1093/gbe/evae015>



Striedner Y, Arbeithuber B, Moura S, et al et, Tiemann-Boege I. Exploring the Micro-Mosaic Landscape of *FGFR3* Mutations in the Ageing Male Germline and Their Potential Implications in Meiotic Differentiation. *Genes.* 2024 Jan 30; 15(2):191. <https://doi.org/10.3390/genes15020191>



## Case report of the month (more genetics)

This report described a patient with a combined genetic alteration: AZFc deletion of the Y chromosome and TT homozygosity for the -211G>T polymorphism in the *FSHB* gene, presenting with cryptozoospermia and low plasma FSH levels. Treatment with FSH improved his sperm count, to allow cryopreservation and ICSI.

Graziani A, Merico M, Grande G, Di Mambro A, Vinanzi C, Rocca MS, Selice R, Ferlin A. A cryptozoospermic infertile male with Y chromosome AZFc microdeletion and low FSH levels due to a simultaneous polymorphism in the *FSHB* gene: a case report. *Hum Reprod.* 2024 Mar 1;39(3):504-508. <https://doi.org/10.1093/humrep/dead277>

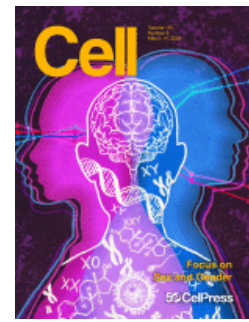


## Sex-based differences outside reproduction

Autoimmune diseases disproportionately affect females more than males. XIST is expressed only in females to inactivate one of the two X chromosomes. This study showed in mice that the Xist ribonucleoprotein (RNP) complex is an important driver of sex-biased autoimmunity. Xist expression in males worsened pathology in lupus and reprogrammed T and B cell to resemble wild-type females.

Dou DR, Zhao Y, Belk JA, Zhao Y, Casey KM, Chen DC, Li R, Yu B, Srinivasan S, Abe BT, Kraft K, Hellström C, Sjöberg R, Chang S, Feng A, Goldman DW, Shah AA, Petri M, Chung LS, Fiorentino DF, Lundberg EK, Wutz A, Utz PJ, Chang HY. Xist ribonucleoproteins promote female sex-biased autoimmunity. *Cell*. 2024 Feb 1;187(3):733-749.e16.

<https://doi.org/10.1016/j.cell.2023.12.037>



Sensitivity to anaesthesia appears to be sex-dependent and is bidirectionally modulated by testosterone. Castration increases anaesthetic resistance but oophorectomy has no effect. Hypothalamic wiring plays also a key role: there are fewer active neurons in the ventral hypothalamic sleep-promoting regions in females than in males.

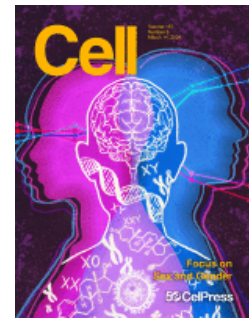
Wasilczuk AZ, Rinehart C, Aggarwal A, Stone ME, Mashour GA, Avidan MS, Kelz MB, Proekt A; ReCCognition Study Group. Hormonal basis of sex differences in anesthetic sensitivity. *Proc Natl Acad Sci USA*. 2024 Jan 16;121(3):e2312913120. <https://doi.org/10.1073/pnas.2312913120>



## Translational and basic andrology

After fertilization of an egg by a single sperm, zona pellucida (ZP) hardens to block polyspermy. The mechanism is explained in this excellent study in mice. Cleavage of ZP2 triggers its oligomerization, with protofilaments: type I (ZP3) and type II (ZP1/ZP2/ZP4) extensively cross-linking, making the egg coat rigid and impenetrable to sperm. To learn more, come to the ECA2024 in Stockholm to hear the opening lecture!

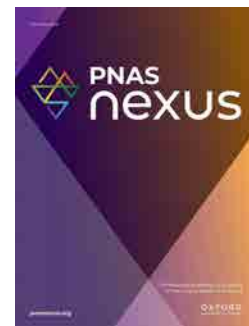
Nishio S, Emori C, Wiseman B, Fahrenkamp D, Dioguardi E, Zamora-Caballero S, Bokhove M, Han L, Stsiapanava A, Algarra B, Lu Y, Kodani M, Bainbridge RE, Komondor KM, Carlson AE, Landreh M, de Sanctis D, Yasumasu S, Ikawa M, Jovine L. ZP2 cleavage blocks polyspermy by modulating the architecture of the egg coat. *Cell*. 2024 Mar 14;187(6):1440-1459.e24. <https://doi.org/10.1016/j.cell.2024.02.013>



Sperm head shape is important for sperm-zona pellucida (ZP) penetration. This study showed that loss of the mouse TEX46 protein causes male sterility primarily due to abnormal sperm head formation and secondary effects on sperm motility. TEX46 is a putative contraceptive target in men.

Fujihara Y, Miyata H, Abbasi F, Larasati T, Nozawa K, Yu Z, Ikawa M, Matzuk MM. Tex46 knockout male mice are sterile secondary to sperm head malformations and failure to penetrate through the zona pellucida. *PNAS Nexus*. 2024 Mar 12;3(3):pgae108.

<https://doi.org/10.1093/pnasnexus/pgae108>



Mammalian male development requires activity of SRY and SOX9. This study showed in mice that two redundant SOX/SRY binding sites within Enh13 are needed for proper Sox9 expression and male development.

Ridnik M, Abberbock E, Alipov V, Lhermann SZ, Kaufman S, Lubman M, Poulat F, Gonen N. Two redundant transcription factor binding sites in a single enhancer are essential for mammalian sex determination. *Nucleic Acids Res*. 2024 Mar 18:gkae178. <https://doi.org/10.1093/nar/gkae178>



The glucocorticoid receptor (GR) is expressed in the mouse germ line; in fetal oocytes as well as the perinatal and adult spermatogonia. But only the male germ cells are susceptible to GR signalling, specifically by regulating RNA splicing within the spermatogonia. The work suggests a sexually dimorphic function for GR in the germ line.



Cincotta SA, Richardson N, Foecke MH, Laird DJ. Differential susceptibility of male and female germ cells to glucocorticoid-mediated signaling. *eLife*. 2024 Jan 16; 12:RP90164. <https://doi.org/10.7554/elife.90164>

The Piwi/Piwi-interacting RNA (piRNA) pathway protects genome integrity in animal germ lines. This study found that worms lacking PARN-1 accumulate a new class of small RNAs, which are antisense to piRNAs and termed anti-piRNAs

Pastore B, Hertz HL, Tang W. Pre-piRNA trimming safeguards piRNAs against erroneous targeting by RNA-dependent RNA polymerase. *Cell Reports* 2024 Feb 27;43(2):113692. Free Full Text From Publisher. <https://doi.org/10.1101/2023.09.26.559619>



This study investigated induced epididymitis in mice and dynamic modulation of TLR4 and TLR2/TLR6 signaling pathways by bacterial-derived antigens.

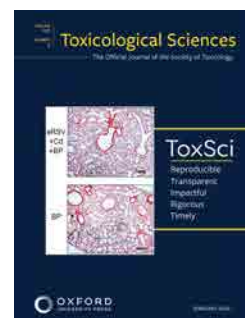
Differential activation of these pathways may contribute to fine-tuning inflammatory responses along the epididymis.



Andrade AD, Almeida PGC, Mariani NAP, Santos NCM, Camargo IA, Martini PV, Kushima H, Ai D, Avellar MCW, Meinhardt A, Pleuger C, Silva EJR. Regional modulation of toll-like receptor signaling pathway genes in acute epididymitis in mice. *Andrology*. 2024 Mar 18. Epub ahead of print. <https://doi.org/10.1111/andr.13630>

Acute exposure to a phthalate MEHP during puberty in rats causes functional but reversible disruption of blood-testis barrier (BTB). Disruption of the BTB may allow for the leakage of germ cell antigens and peritubular macrophages to replenish the lost germ cells by stimulating spermatogenesis.

Tiway R, Richburg JH. Mono-(2-ethylhexyl) phthalate (MEHP) reversibly disrupts the blood-testis barrier (BTB) in pubertal rats. *Toxicol Sci*. 2024, 197: (2) 147–54. <https://doi.org/10.1093/toxsci/kfad116>



## Methodology

This useful for paediatric andrologists study provides reference values for pubertal testicular volume measured with a ruler, in comparison with measurements by an orchidometer and ultrasonography.



Koskela M, Virtanen HE, Rodprasert W, JahnuKainen K, Toppari J, Koskenniemi JJ. Pubertal testicular volume references for ruler, orchidometer, and ultrasonography measurements based on a longitudinal follow-up. *Andrology*. 2024 Mar 14. Epub ahead of print. <https://doi.org/10.1111/andr.13629>

How to trans-differentiate patient fibroblasts into Sertoli cells? This article describes the method and provides a model system for studying patients with variants of unknown significance.

Parivesh, A., Délot, E., Reyes, A. et al. Reprogramming skin fibroblasts into Sertoli cells: a patient-specific tool to understand effects of genetic variants on gonadal development. *Biol Sex Differ* 15, 24 (2024) <https://doi.org/10.1186/s13293-024-00599-y>

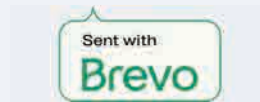


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