

## Dear EAA Members,

The year-end double issue is brimming with new publications relevant to clinical and basic andrologists, including high-impact papers in *Nature*, *Cell Metabolism*, *Nature Genetics*, *JCEM*, *Eur Urol*, *Development*, *FASEB J*, and *Andrology*.

This edition is also the last of the literature alerts that you have been receiving every month over the last four years. This service will need some rethinking – your suggestions are welcome. To my faithful readers – thank you for your encouragement.

Best wishes,

**Ewa Rajpert-De Meyts**  
the EAA Librarian 2021–24

## The latest issue of *Andrology*

I am pleased to announce the latest issue of *Andrology* published in November 2024. The issue contains several articles previously announced in the literature alerts, such as the study of associations between microlithiasis, testis atrophy and germ cell neoplasia in situ, or the methods of measurement of testis size. Below are the “Editor’s picks” but I recommend reading the entire issue.

Vanselow J, Wesenauer C, Eggert A, Sharma A, Becker F. Summer heat during spermatogenesis reduces in vitro blastocyst rates and affects sperm quality of next generation bulls. *Andrology*. 2024 Mar 13.

<https://doi.org/10.1111/andr.13627>

Clemmensen PJ, *et al et.* 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.

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

*Andrology*, Vol. 12, issue 8, pages: 1611-1927,

<https://onlinelibrary.wiley.com/toc/20472927/current>



## Clinical andrology and epidemiology

This international cross-sectional “*Androgens in Men*” study examined 21 sociodemographic, lifestyle, and medical predictors influencing calculated free T (cFT) in >20K men across ages. When interpreting cFT values, the following factors should be considered: age and BMI (most prominent associations), and the presence of diabetes and cancer.

Narinx N, Marriott RJ, Murray K, Adams RJ, Ballantyne CM, Bauer DC, Bhasin S, Biggs ML, Cawthon PM, Couper DJ, Dobs AS, Flicker L, Hankey GJ, Hannemann A, Wilkening R, Martin SA, Matsumoto AM, Ohlsson C, O'Neill TW, Orwoll ES, Shores MM, Steveling A, Travison TG, Wittert GA, Wu FCW, Antonio L, Vanderschueren D, Yeap BB. Sociodemographic, lifestyle, and medical factors associated with calculated free testosterone concentrations in men: individual participant data meta-analyses. *Eur J Endocrinol*. 2024 Oct 29;191(5):523-534.

<https://doi.org/10.1093/ejendo/lvae133>

This work compared global coagulation of hypogonadal men before and after starting testosterone replacement therapy (TRT), and healthy controls (HCs). Hypogonadal men displayed a procoagulant imbalance detected by increased thrombin generation. Short-term TRT did not worsen global coagulation, so the treatment can be safely used in men diagnosed with hypogonadism.

Lanzi V, Indirli R, Tripodi A, Clerici M, Bonomi M, Cangiano B, Petria I, Arosio M, Mantovani G, Ferrante E. Testosterone Therapy Does Not Affect Coagulation in Male Hypogonadism: A Longitudinal Study Based on Thrombin Generation. *J Clin Endocrinol Metab*. 2024 Nov 18;109(12):3186-3195.

<https://doi.org/10.1210/clinem/dgae317>

The effects of weight loss on vitamin D status in men and women with obesity were investigated in this controlled trial. Weight loss induced by a low-calorie diet resulted in an increase in serum 25(OH)D in both women and men, but further weight loss had an additional beneficial impact on vit. D in women but not in men. Men with initial low serum 25(OH)D had also problems with weight loss maintenance.

Holt R, Holt J, Jorsal MJ, Sandsdal RM, Jensen SBK, Byberg S, Juhl CR, Lundgren JR, Janus C, Stallknecht BM, Holst JJ, Juul A, Madsbad S, Jensen MB, Torekov SS. Weight Loss Induces Changes in Vitamin D Status in Women with Obesity but not in Men: a Randomized Clinical Trial. *J Clin Endocrinol Metab*. 2024 Nov 12:dgae775.

<https://doi.org/10.1210/clinem/dgae775>

Serum concentrations of total 25-hydroxy vitamin D (25OHD) are used to determine vitamin D status in clinical practice. This study investigated other parameters: calculated free 25OHD and free 25OHD% (free 25OHD × 100 %/total 25OHD) and found that the latter is better associated with metabolic health markers but not with bone- or calciotropic markers, except parathyroid hormone.

Yahyavi SK, Holt R, Jorsal MJ, Árting LB, Eldrup E, Juul A, Jørgensen N, Blomberg Jensen M. Influence of cholecalciferol supplementation on changes in total 25OHD, free 25OHD, and free 25OHD % in relation to calcium, bone, and glucose homeostasis in young, infertile men. *J Steroid Biochem Mol Biol*. 2024 Nov 20;246:106640.

<https://doi.org/10.1016/j.jsbmb.2024.106640>

Human chorionic gonadotropin (hCG) has structural similarities with TSH. The study analysed thyroid complications caused by hCG secretion from testicular germ cell tumours (GCT) and looked for risk factors. Patients with nonseminomas, and hCG-producing choriocarcinoma or embryonal carcinoma are at risk of thyrotoxicosis, so early recognition and treatment are critical.

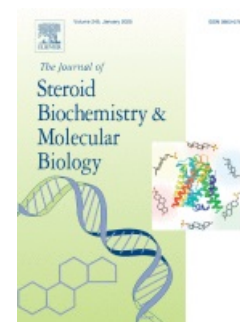
Rohayem J, Idkowiak J, Huss S, Balke T, Schürmann H, Heitkötter B, Wistuba J, Huebner A. Hyperthyroidism induced by paraneoplastic human chorionic



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gonadotropin production from testicular tumours: a retrospective clinical and histopathological study. *Endocr Connect*. 2024 Nov 1;EC-24-0341. Epub ahead of print.  
<https://doi.org/10.1530/ec-24-0341>

A retrospective study examined associations of semen parameters, paternal and maternal age and BMI, with embryological and clinical outcomes in ICSI cycles involving preimplantation genetic testing for aneuploidy (PGT-A).



The results can help counselling infertile couples about their chances of success, taking into account the impact of male partner characteristics, which can be improved before ART.

Mazzilli R, Cimadomo D, Innocenti F, Taggi M, Cermisoni GC, Ginesi S, Dovere L, Albricci L, Guido M, Campitiello MR, Ferrero S, Capalbo A, Vaiarelli A, Ubaldi FM, Ferlin A, Rienzi L, Gennarelli G. A WHO 2021-based comprehensive scheme outlining sperm parameters' associations with IVF outcomes in PGT-A cycles. *Andrology*. 2024 Nov 28. Epub ahead of print.  
<https://doi.org/10.1111/andr.13811>

Neurodevelopmental impairments are common among survivors of extremely preterm birth, particularly in males. This study showed that the HPG axis is activated immediately after birth in extremely preterm infant males, resulting in an androgen pulse occurring several months earlier than during a normal pregnancy. The long-term implications of high androgen exposure during a sensitive neurodevelopmental period warrant further studies.

Nilsson AK, Sjöbom U, Landin A, Andersson MX, Ryberg H, Pivodic A, Löfqvist C, Sävmán K, Poutanen M, Ohlsson C, Hellström A. Postnatal Dysregulation of Androgens in Extremely Preterm Male Infants. *J Endocr Soc*. 2024 Oct 16;8(12):bvae179.  
<https://doi.org/10.1210/jendso/bvae179>



The impact of a recently updated protocol of cytotoxic treatment for boys/adolescents with classical Hodgkin lymphoma on reproductive parameters was investigated in this trial. The semen quality post-treatment was generally poor. The measurements of FSH and inhibin B had a low predictive value.

Drechsel KCE, Broer SL, van Breda HMK, Stoutjesdijk FS, van Dulmen-den Broeder E, Beishuizen A, Wallace WH, Körholz D, Mauz-Körholz C, Hasenclever D, Cepelova M, Uyttebroeck A, Ronceray L, Twisk JWR, Kaspers GJL, Veening MA. Semen analysis and reproductive hormones in boys with classical Hodgkin lymphoma treated according to the EuroNet-PHL-C2 protocol. *Hum Reprod*. 2024 Nov 1;39(11):2411-2422.  
<https://doi.org/10.1093/humrep/deae204>



Sperm banking through ejaculation is not feasible for all transfeminine adolescents due to genital dysphoria and early puberty. This group of transitioning individuals and their parents should consider postponing puberty suppression for fertility preservation via TESE.

Stolk THR, van Mello NM, Meißner A, Huirne JAF, van den Boogaard E. The experience of transfeminine adolescents and their parents regarding fertility preservation via testicular sperm extraction (TESE): a qualitative study. *Hum Reprod*. 2024 Nov 1;39(11):2512-2524.  
<https://doi.org/10.1093/humrep/deae200>



A four-round Delphi study was conducted by 24 experts, representing multiple subspecialties, to obtain consensus on the management of small testicular masses (STM). Testis-sparing surgery or surveillance should be considered in many patients with an STM.



Pang KH, Fallara G, Lobo J, Alnajjar HM, Sangar V, von Stempel C, Huang DY, Parnham A, Cazzaniga W, Giganti F, Haider A, Sachdeva A, Albersen M,

Alifrangis C, Bandini M, Castiglione F, De Vries HM, Fankhauser C, Heffernan Ho D, Nicol D, Shamash J, Thomas A, Walkden M, Freeman A, Muneer A; EAU-YAU Penile and Testis Cancer Working Group. Management of Small Testicular Masses: A Delphi Consensus Study. *Eur Urol Oncol*. 2024 Nov 4:S2588-9311(24)00239-6.

<https://doi.org/10.1016/j.euo.2024.10.010>

This study described the relationship between specific testicular histopathologies and the serum concentrations of reproductive hormones and semen quality in 4245 andrological patients.

Heterogeneous spermatogenic arrest was associated with a more severe phenotype than a homogeneous arrest.

Saritas G, Mørup N, Johannsen TH, Juul A, Aksglaede L, Winge SB, Almstrup K. Testicular histopathology and its association with germ cell numbers, serum concentrations of reproductive hormones, and semen quality. *Andrology*, 2024 Nov 21. Epub ahead of print.

<https://doi.org/10.1111/andr.13803>

The incidence, diagnostic age, and surgical volume of hypospadias was assessed in Denmark. Since 1977 the prevalence of diagnosed hypospadias cases significantly increased and peaked in 2007. The diagnostic age decreased, proximal cases were diagnosed earlier, and there were more surgical admissions than distal cases. Approximately 40% of patients (mild cases) did not undergo hypospadias surgery.

Leunbach TL, Berglund A, Ernst A, Hvistendahl GM, Rawashdeh YF, Gravholt CH. Prevalence, Incidence, and Age at Diagnosis of Boys With Hypospadias: A Nationwide Population-Based Epidemiological Study. *J Urol*. 2024 Dec 3,

<https://doi.org/10.1097/ju.0000000000004319>



## Androgenetics

This impressive GWAS meta-analysis combined data for male and female infertility across six cohorts (41,200 cases and 687,005 controls). 21 genetic risk loci for infertility were identified, of which 12 have not been reported for any reproductive condition. The results suggest that while individual genes associated with hormone regulation may be relevant for fertility, there is limited genetic evidence for correlations between reproductive hormones and infertility at the population level.

Venkatesh SS, *et al* et Genes & Health Research Team; Estonian Biobank Research Team; DBDS Genomic Consortium; FinnGen; et Stefansson K, Seminara SB, Chan YM, Laisk T, Lindgren CM. Genome-wide analyses identify 21 infertility loci and over 400 reproductive hormone loci across the allele frequency spectrum. medRxiv [Preprint]. 2024 Mar 20:2024.03.19.24304530. Nature Genet 2024, in press.

<https://doi.org/10.1101/2024.03.19.24304530>

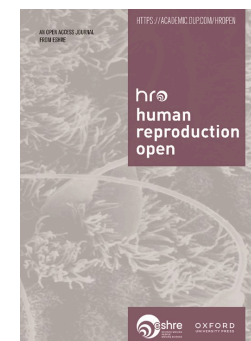
medRxiv  
THE PREPRINT SERVER FOR HEALTH SCIENCES



This multi-centre study employed a hypothesis-driven approach and analysed by GWAS all genetic variants with a reported role in spermatogenesis in 1571 patients with severe spermatogenic failure (SPGF). The findings revealed a novel association between SPGF and the SHOC1 gene and found three novel genes (*PCSK4*, *AP3B1*, and *DLK1*) along with 32 potentially pathogenic rare variants in 30 genes.

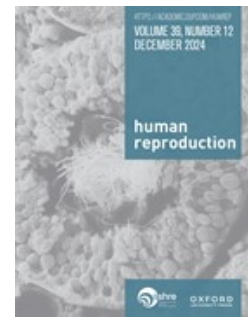
Guzmán-Jiménez A, González-Muñoz S, Cerván-Martín M, Garrido N, *et al.* et Bassas L, Seixas S, Gonçalves J, Lopes AM, Larriba S, Palomino-Morales RJ, Carmona FD, Bossini-Castillo L. A comprehensive study of common and rare genetic variants in spermatogenesis-related loci identifies new risk factors for idiopathic severe spermatogenic failure. *Hum Reprod Open*, 13 Nov 2024 (4), in press.

<https://doi.org/10.1093/hropen/hoae069>



Biallelic mutations in *CALR3* were identified in two infertile men from unrelated families and were shown to cause fertilization failure associated with defective sperm-zona pellucida (ZP) binding.

Gao Y, *et al et*, Wu H. *CALR3* defects disrupt sperm-zona pellucida binding in humans: new insights into male factor fertilization failure and relevant clinical therapeutic approaches. *Hum Reprod*. 2024 Nov 1;39(11):2608-2617. <https://doi.org/10.1093/humrep/deae205>



## Basic and translational andrology

This study demonstrated how the extra X chromosome impairs the development of male fetal germ cells (FGC) in Klinefelter syndrome (KS). X chromosomes are not inactivated and the dosage of X-linked genes is excessive in FGCs. Most FGC are arrested at an early stage, with upregulation of pluripotency genes, and the WNT- and TGF- $\beta$  pathways. Interaction of Sertoli cells and FGCs is disrupted and late FGCs do not migrate to the basement membrane. Inhibition of the TGF- $\beta$  pathway may improve the differentiation of KS FGCs.

Lu Y, Qin M, He Q, *et al et*, Yuan P, Qiao J. How the extra X chromosome impairs the development of male fetal germ cells. *Nature*. 2024 Nov;635(8040):960-968. <https://doi.org/10.1038/s41586-024-08104-6>



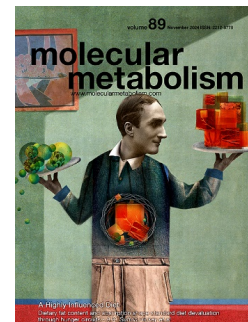
XY mice lacking functional ZNRF3 (anti-WNT factor) exhibit a variable gonadal sex reversal phenotype in the fetal period, with appearance of ovarian tissue. This study used single-cell RNA-seq to examine the transcriptomes of XY *Znrf3*-deficient gonads during early development, and revealed the failure of pre-supporting cells to commit to the Sertoli cell fate and leading to XY granulosa cell development.

Kay RGG, Reeves R, Siggers P, Greenaway S, Mallon AM, Wells S, Koo BK, Mayère C, Nef S, Greenfield A, Simon MM. Gonadal sex reversal at single-cell resolution in *Znrf3*-deficient mice. *Development*. 2024 Dec 1;151(23):dev202707. <https://doi.org/10.1242/dev.202707>



Glycerol-3-phosphate phosphatase (G3PP), a metabolic enzyme, is highly expressed in the testis. This study examined G3PP's role in mouse spermatogenesis, using conditional KO models. Germ cell G3PP deletion affected the structure and function of spermatozoa, likely due to the increased mitochondrial membrane potential and oxidative stress, indicating that G3PP and the glycerol shunt are essential for normal spermatozoa function and male fertility.

Oppong A, Leung YH, Ghosh A, Peyot ML, Paquet M, Morales C, Clarke HJ, Al-Mulla F, Boyer A, Madiraju SRM, Boerboom D, O'Flaherty C, Prentki M. Essential role of germ cell glycerol-3-phosphate phosphatase for sperm health, oxidative stress control and male fertility in mice. *Mol Metab*. 2024 Nov 13:102063. <https://doi.org/10.1016/j.molmet.2024.102063>



Testosterone (T) is produced in the testis by HSD17B3, and an alternate pathway produces DHT from precursors other than T via SRD5A activity. In this study, *Hsd17b3* KO mice with inhibited or ablated *Srd5a1*, surprisingly retained normal testicular T, reproductive tracts and fertility. Another SRD5A enzyme, *Srd5a2*, was markedly increased, and circulating 11-keto-derivative of DHT was elevated, suggesting intra- and extra-gonadal compensatory mechanisms.

Lawrence BM, O'Donnell L, Gannon AL, Smith S, Curley MK, Darbey A, Mackay R, O'Shaughnessy PJ, Smith LB, Rebourcet D. Compensatory mechanisms that maintain androgen production in mice lacking key androgen biosynthetic enzymes. *FASEB J*. 2024 Nov 30;38(22):e70177.

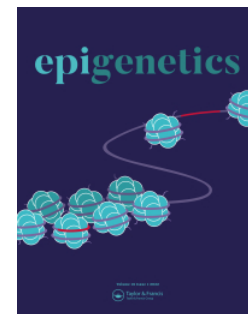
<https://doi.org/10.1096/fj.202402093r>



This study examined changes in the epigenome in fertile and infertile men in correlation with the age-associated changes in semen. The main finding is that variations in the semen methylome associated with aging are linked to inflammatory genes.

Feng J, Rubbi L, Kianian R, Mills JN, Osadchiv V, Sigalos JT, Eleswarapu SV, Pellegrini M. Epigenetic aging of semen is associated with inflammation. *Epigenetics*. 2024 Dec;19(1):2436304.

<https://doi.org/10.1080/15592294.2024.2436304>



The pig is an important animal model and a livestock species. This study characterised the single-cell transcriptomic profiles of pig testes from fetal stage to adulthood, and compared with humans and mice. Among novel findings: early onset of porcine meiosis shortly after birth, a distinct subtype of porcine spermatogonia, and persistent proliferating progenitors for myoid cells.

Wang, X., Wang, Y., Wang, Y. *et al.* et Zhao, J. Single-cell transcriptomic and cross-species comparison analyses reveal distinct molecular changes of porcine testes during puberty. *Commun Biol* 7, 1478 (2024).

<https://doi.org/10.1038/s42003-024-07163-9>



The effects of blocking ROS1, a sperm maturation-promoting factor in epididymis, were investigated in mice. The study revealed that the ROS1 inhibition by lorlatinib suppressed sperm maturation and male fertility reversibly, suggestive of a potential contraceptive exploration.

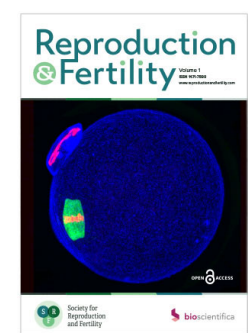
Oyama Y, Shimada K, Miyata H, Iida-Norita R, Emori C, Kamoshita M, Oura S, Katayama R, Matzuk MM, Ikawa M. Inhibition of ROS1 activity with lorlatinib reversibly suppresses fertility in male mice. *Andrology*. 2024 Nov 20. <https://doi.org/10.1111/andr.13808>



The interaction of seminal fluid extracellular vesicles (SFEVs) with human spermatozoa was explored in this *in vitro* study. Functional analyses suggest that, aside from subtle effects on sperm motility, the encapsulated SFEV cargo may be destined for targets other than sperm, likely the female reproductive tract.

Tamessar CT, Anderson AL, Bromfield EG, Trigg NA, Parameswaran S, Stanger SJ, Weidenhofer J, Zhang HM, Robertson SA, Sharkey DJ, Nixon B, Schjenken JE. The efficacy and functional consequences of interactions between human spermatozoa and seminal fluid extracellular vesicles. *Reprod Fertil*. 2024 Oct 4;5(4):e230088.

<https://doi.org/10.1530/raf-23-0088>



## Methodology

A call for improvement of semen cryopreservation protocols, based on the analysis of the consequences of sperm storage in liquid



nitrogen performed by an experienced team at the the EAA Centre in Florence.

The data indicated that freezing/thawing procedures can alter sperm chromatin structure. The length of storage in liquid nitrogen appears to progressively affect sperm parameters.

Tamburrino L, Traini G, Ragosta ME, Dabizzi S, Vezzani S, Scarpa F, Vignozzi L, Baldi E, Marchiani S. Semen cryopreservation and storage in liquid nitrogen: Impact on chromatin compaction. *Andrology*. 2024 Nov 29. Epub ahead of print.

<https://doi.org/10.1111/andr.13806>

## Case of the month

A healthy father of 3 children underwent elective vasectomy. Despite confirmed azoospermia, his wife conceived 119 days post-vasectomy, and paternity testing confirmed he was the father. This early failure was likely caused by the transient release of sperm stored in the seminal vesicles or vas deferens. The time from vasectomy to functional azoospermia is not known, which is the reason for counseling about the risks of rare unexpected failures.

Bernardes T, Wu TY, Greves CC, Carlan S. Documented Paternity Despite Azoospermia Post-vasectomy. *Cureus*. 2024 Oct 29;16(10):e72619.

<https://doi.org/10.7759/cureus.72619>



## Book of the month

### **Biomarkers of Oxidative Stress:**

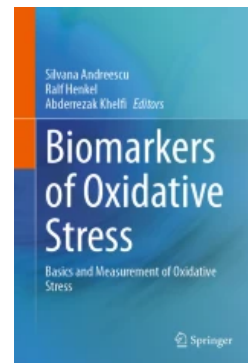
Basics and Measurement of Oxidative Stress

**Editors:** Silvana Andreescu, Ralf Henkel, Abderrezak Khelifi

The book describes in detail the reactivity of radicals and ROS, and provides an overview of the role of ROS in physiology and disease. The 23 chapters present the state-of-the-art methods and techniques that any investigator working in the oxidative/reductive stress field needs to access.

**Publisher:** Springer Cham 2024

<https://doi.org/10.1007/978-3-031-60738-7>



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