EUROPEAN ACADEMY OF ANDROLOGY

Literature alert

June 2026

Before the peak summer holiday months in Europe, a good portion of exciting literature to read in your free time. As ever, the latest issue of *Andrology* is highly recommended. Other journals also published good articles, including several of special interest for paediatric andrologists. The main topics of this edition: sex hormones, INSL3, ultrasound localisation microscopy, ICSI, environmental effects on male germ cells (incl. exposure to outdoor heat – very timely!), Klinefelter syndrome, gynecomastia, penile size during development, puberty timing, Y-chromosome loss and cancer, meiosis initiation, epigenetic inheritance, and good methods for testis tissue analysis in andrology labs.

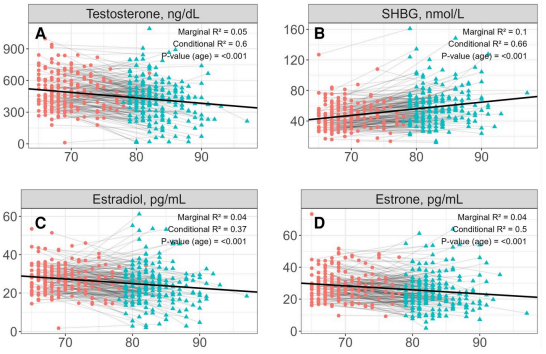
The latest issue of *Andrology*

The July 2026 issue of *Andrology* has been released. The issue opens with the editorial of Wei Yan, the current Editor-in-Chief, who announced the changes and priorities planned for his term, and officially introduced the new Deputy Editor, **Emmanuele A. Jannini**, who started his EAA appointment in January 2026. The issue is very large and contains 30 articles, some of which were highlighted in previous literature alerts.

Two **Editor's picks** of the month are: *Moya-Fernández A. et al. & Matás C.* on extracellular vesicles in pig seminal plasma (https://doi.org/10.1111/andr.70153), and *Yahyavi S.K. et al. & Blomberg Jensen M.* on seminal fluid calcium levels in infertile men (https://doi.org/10.1111/andr.70172).
Browsing through the entire issue is highly recommended!
https://onlinelibrary.wiley.com/toc/20472927/2026/14/5?campaign=woletoc

Clinical andrology and epidemiology

There are limited data about sex hormone levels in men older than 80 y. This longitudinal study examined a large cohort of men aged 78 to 97 y. and found a broad range of total testosterone (T) levels. In around 37% of men the T levels were in a range considered hypogonadal. Gradual declines in mean total T continued in the 8th through 10th decades of life.



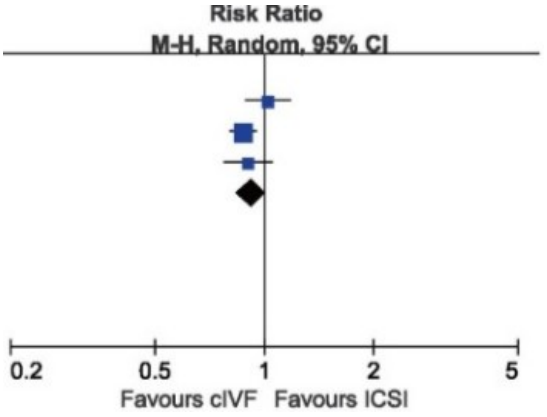
Hills ST, Mansfield TA, Bhasin S, Orwoll ES. Longitudinal Changes in Sex Hormones in a Population of Older Community-dwelling Men. ***J Clin Endocrinol Metab.*** 2026 May 19;111(6):1739-1750, https://doi.org/10.1210/clinem/dgaf652

Ultrasound localisation microscopy (ULM), a new diagnostic method that enables super-resolution mapping of microvascular structure and flow was assessed in this case-control study. The ULM parameters: vessel density, diameter, area and flow-related index, were reduced in azoospermia, distinguished hypogonadotropic hypogonadism treatment groups, and correlated with T and inhibin B. During fertility therapy, ULM parameters detected testicular activation earlier than volume or inhibin B.

EBioMedicine
Published by THE LANCET

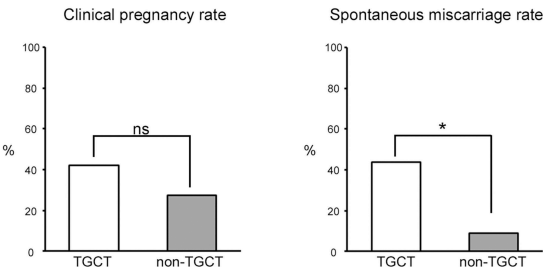
Papanikolaou N, Yan J, Huang B, Davies R, Dunsterville C, De Silva NL, Go C, Grachev P, Luo R, Broughton-Venner J, Minhas S, Bewick G, Dhillo W, Murphy K, Lim A, Tang MX, Jayasena CN. Ultrasound localisation microscopy tracks testicular microvascular adaptations to endocrine function in male infertility. ***EBioMedicine.*** 2026 Jun 18;129:106333. https://doi.org/10.1016/j.ebiom.2026.106333

Does ICSI improve the live birth rate in couples without severe male factor infertility compared to conventional IVF (cIVF)? This multicentre meta-analysis of controlled trials showed no benefit from ICSI over cIVF. Based on current evidence, ICSI should not be routinely recommended for indications other than severe male infertility.



Kayimu K, Berntsen S, *et al. et* Pinborg A, Westergaard D, Mol BW, Nielsen HS, la Cour Freiesleben N, Qiao J, Wang Y. Does intracytoplasmic sperm injection outperform conventional in vitro fertilization in couples without severe male factor infertility? A systematic review and meta-analysis of randomized controlled trials. ***Hum Reprod***. 2026 May22:deag066. https://doi.org/10.1093/humrep/deag066

A small retrospective study found a higher spontaneous miscarriage rate in women who received ICSI from patients with testicular germ cell tumours (TGCT), compared to partners with other cancers. The authors attributed that to chromosomal abnormalities or DNA fragmentation in the sperm of TGCT patients and recommended to use only post-treatment sperm.

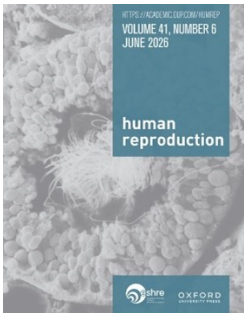


Hamada H, *et al. et,* Tanoshima M, Murase M. Spontaneous miscarriage after intracytoplasmic sperm injection with frozen sperm of patients with testicular germ cell tumour. ***BJU Int***. 2026 Jun 3. https://doi.org/10.1111/bju.70332

This study investigated the effects of fetal or childhood exposures to organochlorine compounds (OC), including PCBs, and PFAS on sperm chromosomal structure in adulthood. The authors found associations of greater OC exposures with sperm chromosomal disomies, suggesting vulnerability of the formation of male germ cells.

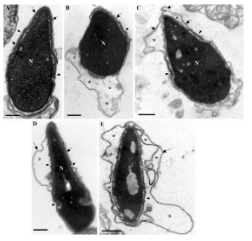
Perry MJ, Meddis A, Young HA, Robbins CR, Budtz-Jørgensen E, Jørgensen N, Halling J, Weihe P, Grandjean P, Petersen MS. In utero and childhood exposure to organochlorines and perfluorinated chemicals in relation to sperm aneuploidy in adulthood. ***Environ Health***. 2026 May 2. https://doi.org/10.1186/s12940-026-01303-w

Can exposure to outdoor heat stress alter age-related changes in sperm DNA methylation? This study reported some associations between exposure to heat conditions during spermatogenesis, particularly during the development window of meiosis I + II, with accelerated sperm epigenetic age.



Nobles C, Canty TP, Mendola P, *et al. et* Pilsner JR. Heat exposure during susceptible windows of spermatogenesis and sperm epigenetic age. ***Hum Reprod***. 2026 Jun 1;41(6):969-980. https://doi.org/10.1093/humrep/deag048

Sperm damage during cryopreservation is well known. This study investigated ultrastructure of rapidly frozen human sperm at two time points and found that cryopreservation caused damage not only to the sperm head membrane, but also to the acrosomal vesicle.



Coelho S, Oliveira E, Fonseca Cardoso M, Lobo Xavier S, Barros A, Marques CJ, Sousa M. Quantitative prospective experimental study on time-dependent ultrastructural changes in human spermatozoa after cryopreservation. ***Tissue Cell.*** 2026 Jun 8;103:103684. https://doi.org/10.1016/j.tice.2026.103684

Two international meta-analyses gathered available data on the fetal and childhood penile length, which reflects masculinisation of the reproductive system. The fetal study provided a practical nomogram for measurements from 14 to 40 weeks of gestation. The second study analysed penile length from 1 week to 10 years, indicating a large variability but also a possible decrease of the penile size over the last two decades.

O'Hagan LA, Deshpande A, Cho YH, Teoh M, Mirjalili A, Blanc T, Taghavi K. Nomogram of fetal penile length during pregnancy: A systematic review. ***J Pediatr Urol***. 2026 Feb; 22(1):105693. https://doi.org/10.1016/j.jpurol.2025.12.009

Negri F, Belladelli F, Zhang CA, Stinson J, Langroudi AP, Basran SS, Chen AL, Pozzi E, Cheng Y-S, Giudice FD, Montorsi F, Salonia A, Eisenberg ML. Paediatric penile length: a systematic review and meta-analysis. ***BJU Int***. 14 June 2026, https://doi.org/10.1111/bju.70356

In this controlled trial, circulating insulin-like peptide 3 (INSL3) were examined in boys with constitutional delay of growth and puberty treated with *i.m.* testosterone (T) or oral aromatase inhibitor letrozole (Lz) for 3 months. Exogenous T was found to suppresses transiently INSL3 via gonadotropin inhibition in early puberty.

Raivio T, Tanner M, Vaaralahti K, Hero M, Miettinen PJ, Varimo T. Transient gonadotropin suppression by exogenous testosterone decreases INSL3 in early puberty in boys with constitutional delay of growth and puberty. ***J Endocr Soc***. 2026 May 30;10(7):bvag123. https://doi.org/10.1210/jendso/bvag123

This study found that earlier pubertal development in males (testicular enlargement) was associated with higher insulin and insulin resistance at the age of 26 years when compared to the late/average puberty onset group.
In females, early puberty was associated with higher BMI and waist circumference.

Nummela S, Pahkala K, Karppinen S, Toppari J, Raitakari O, Viikari J, Rönnemaa T, Niinikoski H. Pubertal Timing Associates with Cardiometabolic Markers During Puberty and in Young Adulthood. ***Acta Paediatr***. 2026 May 29. https://doi.org/10.1111/apa.70624.

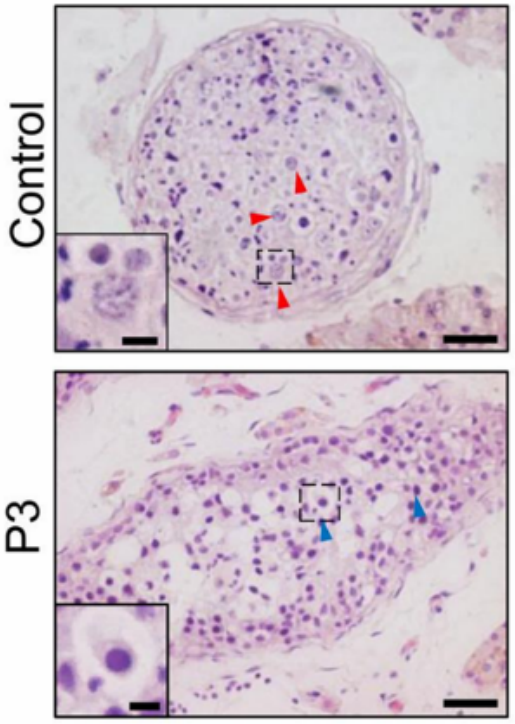
Recent Italian guidelines on the management of gynecomastia, co-authored by several EAA members, contain carefully evidenced clinical recommendations, which will be useful for andrologists also in other countries.

Pozza C, Selice R, Barbonetti A, Hasenmajer V, Lotti F, Menafra D, Pasquali D, Sansone A, Isidori AM, Rochira V. Management of gynecomastia in adolescence and adults: the clinical practice guidelines from the Italian Society of Andrology and Sexual Medicine (SIAMS). ***J Endocrinol Invest***. 2026 Jun 8. Epub ahead of print.
https://doi.org/10.1007/s40618-026-02915-2

For those interested in Klinefelter's syndrome (KS), this useful scoping review identified and examined the content of existing registries collecting data on KS patients. There is only one KS-specific registry (KING in Italy) known worldwide, so there is a need for the development of further KS-specific registries.

Stephenson F, Morris A, Arulkkumaran N, Lorenzo A, Mehta S, Cotton A, Yap T. Mapping the current landscape of Klinefelter Syndrome registries: a scoping review. ***BMJ Open***. 2026 Jun 4;16(6):e107451. https://doi.org/10.1136/bmjopen-2025-107451

Androgenetics



YTH N6-methyladenosine RNA binding protein C2 (YTHDC2) is essential in the mitotic to meiotic transition in germ cells. This study reported biallelic pathogenic missense variants in *YTHDC2* in 4 infertile men (2 different consanguineous families), with azoospermia and early meiotic arrest. Mechanistic investigations revealed a failure to silence the mitotic program upon meiotic entry.

Zhi A, Li M, Zubair M, Abbas M, *et al. et* Zhang H, Shi Q. Novel variants in YTHDC2 cause non-obstructive azoospermia by disrupting the mitotic-to-meiotic transition in humans and mice. ***Hum Reprod***. 2026 Jun 5:deag086. Epub ahead of print. https://doi.org/10.1093/humrep/deag086

We rarely highlight review articles, but this one can be of interest for andrologists, as it summarizes current knowledge concerning the association of loss of the Y chromosome (LOY) and poor outcomes in multiple cancer types. The authors discuss studies demonstrating the direct effects of LOY on immune surveillance, DNA repair, metabolism and tumour immune microenvironment. Whether LOY is a causal, cooperative or passenger event remains unresolved, however LOY could be a potential biomarker for cancer risk and precision therapy.

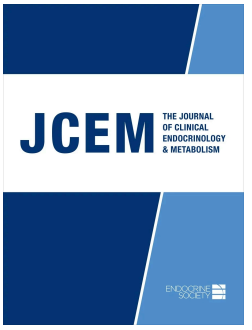
Abdel-Hafiz HA, Hoelzen L, Theodorescu D. Beyond sex determination: the Y chromosome in male cancers. ***Nat Rev Cancer***. 2026 May 21. Epub ahead of print. https://doi.org/10.1038/s41568-026-00935-x

Translational and basic andrology

Single-cell transcriptome analysis of fetal testis tissue from Klinefelter syndrome (KS) found two clusters of KS Sertoli cells, with and w/o XIST expression, the latter with increased G2/M ratio. Fetal KS Leydig cells showed increased proliferation and delayed differentiation with upregulated MAPK signaling pathway and X-linked EIF1AX, which was partially rescued by inhibition of the MAPK pathway.

Yan T, Chen G, *et al. et* Cheng Q, Guo X. Single-cell analysis of fetal testis reveals dysfunction of human Leydig cells in Klinefelter syndrome. ***J Clin Invest***. 2026 Jun 9:e201124. https://doi.org/10.1172/jci201124

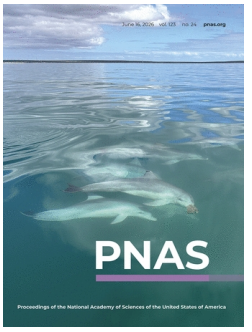
Testosterone replacement therapy (TRT) is used to treat hypogonadal Klinefelter men. This pilot study investigated the TRT effects on skeletal muscle by single-nucleus RNA-seq. TRT was associated with a shift toward a more pro-regenerative skeletal muscle transcriptional environment, though only partially mitigating some of the adverse effects of long-standing hypogonadism and KS.



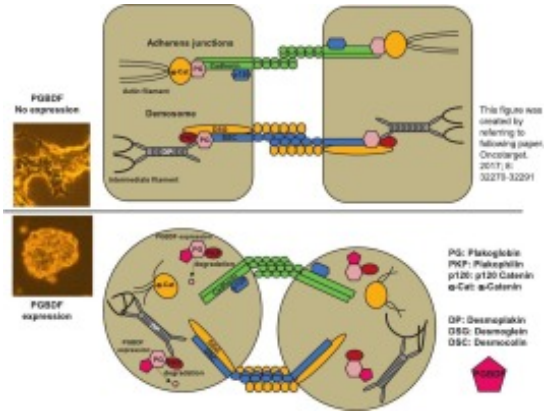
Hasselholm EB, Ridder LO, Schou AN, Wang J, Farup J, Lin L, Just J, Gravholt CH. Single nucleus RNA sequencing reveals testosterone replacement therapy-associated multicellular remodelling of skeletal muscle in hypogonadal men with Klinefelter Syndrome. ***J Clin Endocrinol Metab***. 2026 Jun 17:dgag240.

https://doi.org/10.1210/clinem/dgag240

This translational study added new evidence concerning epigenetic inheritance in males. The authors showed that mature murine sperm are devoid of mitochondrial DNA (mtDNA), precluding mtDNA-dependent transcription, and that mtRNAs found in sperm originate during spermatogenesis. Testicular sperm transmitted diet-induced metabolic traits as efficiently as epididymal sperm.



Wang Z, Yamauchi Y, Chen S, Zheng H, Ward MA, Yan W. Testicular origin of epigenetic inheritance independent of sperm mitochondrial DNA and epididymal exposure. ***Proc Natl Acad Sci USA***. 2026 Jun 16;123(24):e2611096123. https://doi.org/10.1073/pnas.2611096123

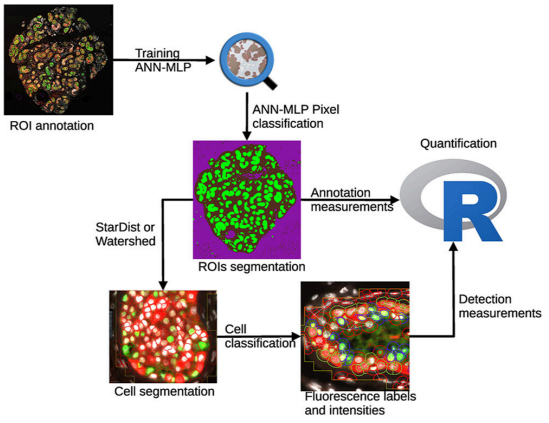


The gene product of C17orf50, earlier known as highly expressed in testes, was identified in this study as a Plakoglobin (PG)-binding protein and named PGBDF. The protein promotes PG's ubiquitination and degradation, likely downstream from GSK3β and Wnt signalling. PGBDF localizes predominantly to interstitial regions.

Yamashita M, *et al. et* Ishiguro K, Konishi H. Identification and characterization of a novel Plakoglobin-binding protein highly expressed in the testes. ***Biochim Biophys Acta Mol Cell Res***. 2026 Jun 11: 120170. https://doi.org/10.1016/j.bbamcr.2026.120170

Andrology lab

A new standardised method for analysis and cell quantification of immunofluorescent mages of human and mouse testicular tissues using existing software QuPath, StarDist and Watershed image transformation. The analysis is more precise and significantly faster at segmenting tubules and quantifying cells than previous manual annotation methods.



Gadd AJR, Sanou I, Brain E, Davies J, Liugaila A, Duffin K, Stefansdottir A, Mitchell RT. Machine learning and automation methods for the segmentation, classification and quantification of testicular tissue sections. ***Reprod Fertil.*** 2026 May 29;7(2):RAF250210. https://doi.org/10.1530/raf-25-0210

For basic scientists a detailed protocol instructing step-by step (with videos!) how to dissect, culture and analyse fetal mouse gonads for short-term screening with signaling modulators. Downstream procedures for phenotypic assessment are also described.

Estermann MA, Rodriguez KF, Hunnicutt J, Yao HH. Protocol for ex vivo mouse paired single-gonad screening platform for phenotypical characterization. ***STAR Protoc***. 2026 Jun 10; 7(2):104628. https://doi.org/10.1016/j.xpro.2026.104628