



## Dear EAA Members,

We highly recommend the latest special issue of *Andrology* on sperm DNA integrity. There are other special issues in the pipeline, and we would like to encourage you to consider submitting to the next one - on *Genetics of Male Infertility* (Guest Editors: M Laan, D Conrad & KI Aston), see details on the Andrology's webpage: <https://shorturl.at/abiV3>

Other topics in the October issue of this alert: treatment of male obesity-associated hypogonadism, diagnosis of hypogonadism in lymphoma survivors, PSA screening, AMH and TEX101 as sperm retrieval predictors in TESE, treatment of hypergonadotropic hypogonadism, CAH and TART, candidate genes for male infertility, function of PRAMEL1, SRSF2, UTX in mouse spermatogonia, micro-RNAs in testicular tumours, as well as a debate paper on raising rates of male infertility.

## Clinical andrology and epidemiology



All andrologists should read this special issue of ***Andrology***, comprising 15 articles (reviews and original studies) on the important and still controversial topic of DNA integrity in spermatozoa. The following aspects are covered in the special issue: oxidative stress and sperm DNA damage, novel methods of detection, selection of sperm with low levels of DNA damage and management of causes of DNA damage.

<https://onlinelibrary.wiley.com/toc/20472927/2023/11/8>  
Editorial by Guest Editor RJ Aitken:  
<https://doi.org/10.1111/andr.13503>



A controlled clinical trial of an oral aromatase inhibitor, leflutrolole, in treatment of obesity-associated hypogonadotropic hypogonadism (OHH) showed that despite testosterone normalisation and some improvement in sperm parameters in a subset of OHH patients, no benefit was observed on endpoints of sexual dysfunction, cardio-metabolic, or body composition, and there was a reduction in bone mineral density.

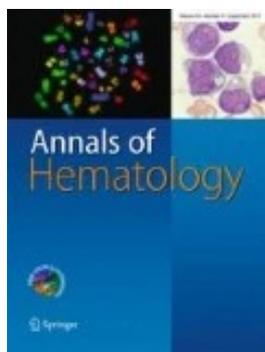
Jones TH, Dobs AS, Randeve H, Moore W, Parkin JM. Leflutrolole in male obesity-associated hypogonadotropic hypogonadism: Ph 2b double-blind randomised controlled trial. *Eur J Endocrinol*. 2023 Sep 1;189(3):297-308. <https://doi.org/10.1093/ejendo/lvad099>



Secondary endpoints from a controlled trial of vit. D3 treatment of infertile men stratified according to the BMI. At baseline, serum 25OHD was significantly lower in overweight or obese men compared with the normal weight men. After vitamin D3 supplementation all men achieved adequate serum 25OHD levels.

Holt R, Jorsal MJ, Yahyavi SK, Qin S, Juul A, Jørgensen N, Blomberg Jensen M. High-dose cholecalciferol supplementation to obese infertile men is sufficient to reach adequate vitamin D status. *Br J Nutr*. 2023 Oct 9:1-16. <https://doi.org/10.1017/s0007114523002222>

Hodgkin lymphoma survivors after intense treatment are at risk for sexual dysfunction and



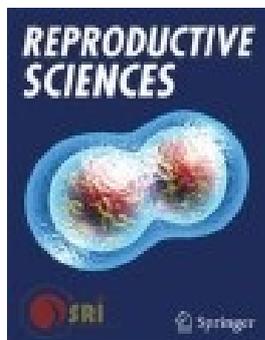
testosterone (T) deficiency necessitating endocrinological attention during follow-up. This study found that measuring only the total T is often insufficient, because 15% survivors had subnormal calculated free T.

Micas Pedersen S, Feltoft CL, Nielsen TH, de Nully Brown P, Gang AO, Pedersen LM, Jørgensen N. Men treated with BEACOPP for Hodgkin lymphoma may be at increased risk of testosterone deficiency. *Ann Hematol.* 2023 Oct 23. Epub ahead of print. <https://doi.org/10.1007/s00277-023-05512-y>



This detailed analysis of PSA screening in the Netherlands over 21 years (N= 42376 men, aged 55-74 yr), showed a reduction of metastatic prostate cancer and mortality, resulting in a more favourable harm-benefit ratio of the screening. These data showed that starting screening >70 years is too late, and the repeated screening is essential.

de Vos II, Meertens A, Hogenhout R, Remmers S, Roobol MJ; ERSPC Rotterdam Study Group. A Detailed Evaluation of the Effect of Prostate-specific Antigen-based Screening on Morbidity and Mortality of Prostate Cancer: 21-year Follow-up Results of the Rotterdam Section of the European Randomised Study of Screening for Prostate Cancer. *Eur Urol.* 2023 Oct;84(4):426-434. <https://doi.org/10.1016/j.eururo.2023.03.016>



Based on their centre's analysis of NOA patients who underwent mTESE, the authors found that higher serum AMH levels were associated with failure of sperm retrieval, and constructed a logistic regression model using AMH as a predictor, subsequently validated in a small prospective study.

Zheng Y, Li DM, Jiang XH, Bai HZ, Zhao GC. A Prediction Model of Sperm Retrieval in Males with Idiopathic Non-obstructive Azoospermia for Microdissection Testicular Sperm Extraction. *Reprod Sci.* 2023 Sep 25. Epub ahead of print: <https://doi.org/10.1007/s43032-023-01362-1>



This prospective cross-sectional cohort study found that the preoperative median seminal TEX101 level was significantly higher in men with NOA and varicocele, who had successful seminal sperm recovery, compared with patients without sperm recovery.

Ragab MW, Saad M, Nour Z, Hamed HA, Mostafa T, El-Guindi AM. Seminal TEX101 May Predict Seminal Sperm Recovery after Varicocelectomy in Nonobstructive Azoospermic Patients with Varicocele. *Andrologia* 2023(Sep 21):1-6, <https://doi.org/10.1155/2023/5652572>



A multicentre study examined the association between early glucocorticoid treatment and TART development in 188 male patients with CAH. A delayed CAH diagnosis (> 1yr) and poor disease control in early life was associated with a 2.6 times higher risk of TART diagnosis.

Schröder MAM, et al et Claahsen-van der Grinten HL. Hormonal control during infancy and testicular adrenal rest tumor development in males with congenital adrenal hyperplasia: a retrospective multicenter cohort study. *Eur J Endocrinol.* 2023 Oct 17;189(4):460-468, <https://doi.org/10.1093/ejendo/lvad143>

## Debate

Following the Male Reproductive Health Initiative (MRHI), a group of 26 international experts – including several EAA members – identified the pressing questions spanning the spectrum of

Kimmins S, Anderson RA, Barratt CLR, Behre HM, Catford SR, De Jonge CJ, Delbes G, Eisenberg ML, Garrido N, Houston BJ, Jørgensen N, Krausz C, Lisper A, McLachlan RI, Minhas S, Moss T, Pacey A, Priskorn L, Schlatt S, Trasler J, Trasande L, Tüttelmann F, Vazquez-Levin MH, Veltman JA, Zhang F, O'Bryan MK. Frequency, morbidity and equity - the case for increased research on male fertility. *Nat Rev Urol.* 2023 Oct 12. Epub ahead of print. <https://doi.org/10.1038/s41585-023-00820-4>

## Androgenetics



Balanced chromosomal rearrangements can be used as genomic signposts for identification of candidate genes or genomic loci associated with male infertility. In this study, likely position effects were found in 3 male patients, involving *YIPF5*, *SPATC1L*, and *CAMK2B*. The data also support the existence of other loci for spermatogenesis defects.

David D, Fino J, Oliveira R, Dória S, Morton CC. Balanced chromosomal rearrangements implicate *YIPF5* and *SPATC1L* in non-obstructive oligoasthenozoospermia and oligozoospermia and of a derivative chromosome 22 in recurrent miscarriage. *Gene* 2023 Dec 15;887:147737. <https://doi.org/10.1016/j.gene.2023.147737>



*ESX1* was activated using CRISPRa technology in human seminoma cells-TCam-2, and a network of genes potentially regulated by the *ESX1* gene was determined. *ESX1* is localized in the nucleus of spermatogonia and probably regulates the balance between cell proliferation and differentiation.

Malcher A, Graczyk Z, Bauer H, Stokowy T, Berman A, Smolibowski M, Blaszczyk D, Jedrzejczak P, Yatsenko AN, Kurpisz M. *ESX1* gene as a potential candidate responsible for male infertility in nonobstructive azoospermia. *Sci Rep.* 2023 Oct 2;13(1):16563. <https://doi.org/10.1038/s41598-023-43854-9>

## Basic and translational andrology

### Development



A study using mouse KO models looked at the function of a cancer-testis antigen, *PRAMEL1*. *Pramel1* deficiency led to an increased fecundity in juvenile males and decreased fecundity in mature males. The findings suggest that *PRAMEL1* fine-tunes RA signalling, playing a key role in the proper establishment of the first and subsequent rounds of spermatogenesis.

Yang M, Ma W, Oatley J, Liu WS. Mouse *Pramel1* regulates spermatogonial development by inhibiting retinoic acid signaling during spermatogenesis. *Development.* 2023 Nov 1;150(21):dev201907. <https://doi.org/10.1242/dev.201907>

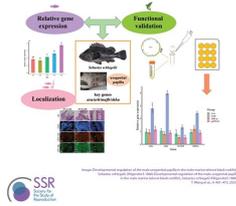
### BMC Biology

The function of serine/arginine-rich splicing factor 2 (*SRSF2*, aka *SC35*) was investigated in mice KO models. Male germ cell-specific deletion of *Srsf2* caused complete infertility and defective spermatogenesis by disruption of meiosis initiation in spermatogonia. *SRSF2* affected alternative splicing of *Stra8*, *Stag3* and *Atr*.

Lei WL, Du Z, *et al* et Qian WP, Sun QY. *SRSF2* is required for mRNA splicing during spermatogenesis. *BMC Biol.* 2023 Oct 23;21(1):231. <https://doi.org/10.1186/s12915-023-01736-6>

Lysine demethylase 6a (*KDM6A*, *UTX*) is transiently expressed in mouse in late spermatogonia and early meiotic prophase. *Kdm6a* KO males do not have defects in fertility, but hundreds of genes are deregulated, highlighting *KDM6A* as a transcriptional activator important for intergenerational safeguarding gene regulatory state.

Walters BW, Rainsford SR, Heuer RA, Dias N, Huang X, de Rooij D, Lesch BJ. *KDM6A/UTX* promotes spermatogenic gene



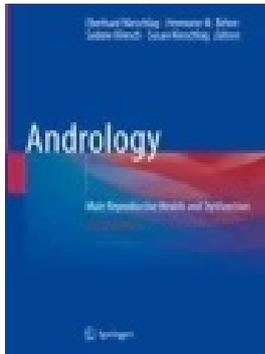
expression across generations and is not required for male fertility. *Biol Reprod.* 2023 Oct 20:ioad141. <https://doi.org/10.1093/biolre/ioad141>



MiR-371~373 and miR-302/367 cluster are over-expressed in malignant germ cell tumours (GCTs). Targeting of these microRNAs in malignant GCTs using locked nucleic acid (LNA)-DNA inhibition demonstrated their functional significance, with cell cycle disruption and growth inhibition.

Bailey S, Ferrareso M, et al et Murray MJ. Targeting oncogenic microRNAs from the miR-371~373 and miR-302/367 clusters in malignant germ cell tumours causes growth inhibition through cell cycle disruption. *Br J Cancer.* 2023 Oct 3. Epub ahead of print. <https://doi.org/10.1038/s41416-023-02453-1>

## Book of the month



**"Andrology"** Male Reproductive Health and Dysfunction.  
**Editors:** E. Nieschlag, H. M. Behre, S. Kliesch, S. Nieschlag

The new edition of this excellent textbook contains 50 chapters and covers practically all aspects of andrology, from relevant scientific base to the clinical management. A must for all andrologists, andro-urologists, endocrinologists and specialists in fertility treatment.

4th Edition, 2023, available in English and German ("Andrologie"), as hardcover or e-book: <https://link.springer.com/book/10.1007/978-3-031-31574-9>

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