

Dear EAA Members,

The recently held European Congress of Andrology in Barcelona was a great opportunity to get updated on the latest developments in andrology. But literature search remains an indispensable way of learning. This edition introduces a new section 'Methodology' to highlight novel methods specifically useful for translational andrology – an analysis of testis images is the first entry. Keywords for this edition: endocrine disruption during development, male contraception, glucocorticoids and testis function, AFP, sperm aminopeptidase N, WHO semen analysis manual, androgen sensitivity window, DNA breaks in meiosis, sperm DNA degradation after vasectomy, small RNAs, phosphodiesterases (PDEs), and a scrotal case of *fetus in fetu*.

## Clinical andrology and epidemiology



Commonly used polyfluoroalkyl substances (PFAS) are very stable and accumulate in environment.

This Danish-Swedish study found consistent inverse associations between maternal exposure to PFAS during early pregnancy and semen quality in their sons. A disruption of early testis development is the suspected mechanism.

Hærvig KK, Petersen KU, Hougaard KS, Lindh C, Ramlau-Hansen CH, Toft G, Giwercman A, Høyer BB, Flachs EM, Bonde JP, Tøttenborg SS. Maternal Exposure to Per- and Polyfluoroalkyl Substances (PFAS) and Male Reproductive Function in Young Adulthood: Combined Exposure to Seven PFAS. *Environ Health Perspect*. 2022 Oct; 130(10):107001. PMID: 36197086. <https://doi.org/10.1289/ehp10285>

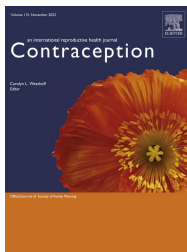


This French study evaluated the acceptability of thermal male contraception (TMC), based on a +2°C increase in testis temperature by a contraceptive underwear. A positive evaluation by most participants, together with the efficacy and reversibility of TMC, should encourage further development of this method.

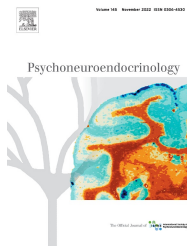
Joubert S, Tcherdukian J, Mieuisset R, Perrin J. Thermal male contraception: A study of users' motivation, experience, and satisfaction. *Andrology*. 2022 Nov;10(8):1500-1510. PMID: 35934916. <https://doi.org/10.1111/andr.13264>

For male partners, abortion may be an opportunity to engage men in contraceptive counselling and when available, offer new male contraceptives. 75% of men would be prepared to use it in the future and if no side effects were reported.

Nguyen BT, Jacobsohn TL. Post-abortion contraception, an opportunity for male



partners and male contraception. *Contraception*. 2022 Nov;115:69-74. PMID: 35870483.  
<https://doi.org/10.1016/j.contraception.2022.07.004>



Associations between hair cortisol and glucocorticoid receptor gene variants were found in this study from the Copenhagen centre, indicating that these SNPs may influence systemic glucocorticoid levels. The potential health effects of such alterations are yet unknown.

Nordkap L, Almstrup K, Priskorn L, Bang AK, Stalder T, Petersen JH, Hansen ÅM, Juul A, Johannsen TH, Jørgensen N. Hair cortisol, glucocorticoid gene receptor polymorphisms, stress, and testicular function. *Psychoneuroendocrinology*. 2022 Sep 24;146:105942. Epub ahead of print. PMID: 36179533.

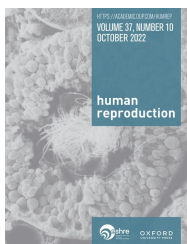
<https://doi.org/10.1016/j.psyneuen.2022.105942>



Alfa-fetoprotein (AFP) is produced mainly during fetal development, and later by testicular tumours. This study reported unexplained high AFP levels in almost 2% of primary infertile patients without a previous history of associated disorders.

Corsini C, Fallara G, Candela L, Raffo M, Pozzi E, Belladelli F, Capogrosso P, Boeri L, Costa A, Schifano N, Cignoli D, Ventimiglia E, D'Arma A, Montorsi F, Salonia A. High serum alpha-fetoprotein levels in primary infertile men. *Andrology*. 2022 Sep 18. Epub ahead of print. PMID: 36116018.

<https://doi.org/10.1111/andr.13297>

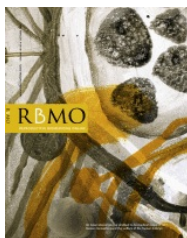


Human sperm aminopeptidase N can be a biomarker for the potential for high-quality embryos, especially when seminal parameters are close to the threshold values. This study showed that the best usable blastocysts were associated with low APN levels in sperm used for ICSI.

Gianzo M, Urizar-Arenaza I, Muñoa-Hoyos I, Labaka G, Larreategui Z, Garrido N, Irazusta J, Subirán N. Sperm aminopeptidase N identifies the potential for high-quality blastocysts and viable embryos in oocyte-donation cycles. *Hum Reprod*. 2022 Sep 30;37(10):2246-2254. PMID: 35984316.

<https://doi.org/10.1093/humrep/deac170>

## COVID-19

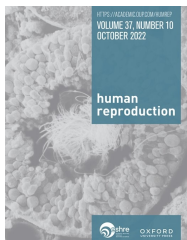


This study aimed to validate SARS-CoV-2 detection in semen. The SARS-CoV-2 genome was effectively detected by multiplex real-time PCR, regardless of semen quality or the media used to freeze spermatozoa. This validated RT-PCR assay is useful to ensure protection against viral contamination in the cryobanking process.

Chabrolles H, Pons-Rejraji H, Chaput L, Brebion A, Flot M, Pereira B, Brugnon F, Henquell C. Validation of a SARS-CoV-2 RT-PCR assay: a requirement to evaluate viral contamination in human semen. *Reprod Biomed Online (RBMO)*. 2022 Sep 6;S1472-6483(22)00684-8. Epub ahead of print. PMID: 36270932.  
<https://doi.org/10.1016/j.rbmo.2022.09.004>

## Debate

Discussion on the usefulness of the latest edition of the WHO semen analysis manual continues. This paper critically evaluated the methodological approach used to define the reference population.



The authors argue that the current WHO distribution of semen examination results is not ideal for interpreting male fertility.

Paffoni A, Somigliana E, Boeri L, Viganò P. The statistical foundation of the reference population for semen analysis included in the sixth edition of the WHO manual: a critical reappraisal of the evidence. *Hum Reprod*. 2022 Sep 30;37(10):2237-2245. PMID: 35849333.  
<https://doi.org/10.1093/humrep/deac161>

## Androgenetics



Chromosome segregation into gametes depends on Spo11-induced DNA double-strand breaks (DSBs). This basic study showed in *C. elegans* that meiotic DSBs are formed throughout the pachytene stage, and the DSBs formed at later meiotic stages are essential to generate crossovers, under control of EXO-1 and DNA-2.

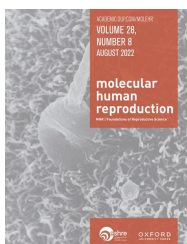
Hicks T, Trivedi S, Eppert M, Bowman R, Tian H, Dafalla A, Crahan C, Smolikove S, Silva N. Continuous double-strand break induction and their differential processing sustain chiasma formation during *Caenorhabditis elegans* meiosis. *Cell Reports* 2022 Sep 27;40(13):111403. PMID: 36170820.  
<https://doi.org/10.1016/j.celrep.2022.111403>

## Translational and basic andrology

### BMC Medicine

Collaboration between the Copenhagen centre and a group at MRC in Edinburgh resulted in the identification of a window of androgen sensitivity in the human testis. Inhibitors of androgen action used in ex vivo cultured fetal testis caused effects only within the period of 7-14 gestational weeks.

Lundgaard Riis M, Matilonyte G, Nielsen JE, Melau C, Greenald D, Juul Hare K, Langhoff Thuesen L, Dreisler E, Aaboe K, Brenøe PT, Andersson AM, Albrethsen J, Frederiksen H, Rajpert-De Meyts E, Juul A, Mitchell RT, Jørgensen A. Identification of a window of androgen sensitivity for somatic cell function in human fetal testis cultured ex vivo. *BMC Med*. 2022 Oct 20;20(1):399. PMID: 36266662.  
<https://doi.org/10.1186/s12916-022-02602-y>



After vasectomy, accumulating sperm is eliminated by granulomas. Based on studies in mice, the authors suggest that sperm chromatin fragmentation in the toroid linker regions is a mechanism activated in vas deferens to degrade sperm DNA when they cannot be ejaculated.

Ribas-Maynou J, Nguyen H, Valle R, Wu H, Yeste M, Ward WS. Sperm degradation after vasectomy follows a sperm chromatin fragmentation-dependent mechanism causing DNA breaks in the toroid linker regions. *Mol Hum Reprod*. 2022 Aug 29;29(9):gaac029. PMID: 35929777.  
<https://doi.org/10.1093/molehr/gaac029>



A group of expert authors in the UK undertook global small ncRNA sequencing in malignant germ cell tumours (GCTs). The study confirmed previous miRNA observations (high expression of miR-371~373 and miR-302/367 clusters), but also demonstrated global piRNA dysregulation in malignant gonadal GCTs.

Laidlaw S, Alonso-Crisostomo L, Bailey S, Saini HK, Molnár A, Nicholson JC, Enright AJ, Scarpini CG, Rahbari R, Coleman N, Murray MJ; on behalf the Children's Cancer and Leukaemia Group. Small non-coding RNA sequencing reveals global dysregulation of piwi-interacting RNA (piRNA) expression in gonadal malignant germ cell tumours. *Andrology*. 2022 Oct 17. Epub ahead of print. PMID: 36254403.  
<https://doi.org/10.1111/andr.13312>

The findings of this study suggest that the higher expression of miRNA-19a/b-3p or the lower expression of target genes are associated with oligoasthenozoospermia and male infertility, probably through influencing basic semen parameters.

Abu-Halima M, Becker LS, Ayes BM, Meese E. MicroRNA-targeting in male infertility: Sperm microRNA-19a/b-3p and its spermatogenesis related transcripts content in men with oligoasthenozoospermia. *Front Cell Dev Biol.* 2022 Sep 21;10:973849. doi: 10.3389/fcell.2022.973849. PMID: 36211460. <https://doi.org/10.3389/fcell.2022.973849>



Human peritubular cells (HTPCs) express the glucocorticoid receptor (GR), hence this study examined the consequences of dexamethasone in cultured HTPCs, and found novel effects, specifically in extracellular matrix and the immunological state of the testis.

Stepanov YK, Speidel JD, Herrmann C, Schmid N, Behr R, Köhn FM, Stöckl JB, Pickl U, Trottmann M, Fröhlich T, Mayerhofer A, Welter H. Profound effects of Dexamethasone on the immunological state, synthesis and secretion capacity of human testicular peritubular cells. *Cells.* 2022 Oct 9;11(19):3164. PMID: 36231125. <https://doi.org/10.3390/cells11193164>

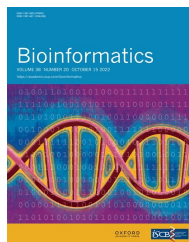


cAMP/PKA and phosphodiesterases (PDEs) are the regulators of endocrine tissue function.

This study demonstrated that human testis expresses PDE8A and PDE8B isoforms, and suggested that PDE8A is involved in the maturation of human sperm, while PDE8B can be involved in Leydig cell transformation.

Campolo F, Capponi C, Tarsitano MG, Tenuta M, Pozza C, Gianfrilli D, Magliocca F, Venneri MA, Vicini E, Lenzi A, Isidori AM, Barbagallo F. cAMP-specific phosphodiesterase 8A and 8B isoforms are differentially expressed in human testis and Leydig cell tumor. *Front Endocrinol (Lausanne).* 2022 Oct 7;13:1010924. PMID: 36277728. [10.3389/fendo.2022.1010924](https://doi.org/10.3389/fendo.2022.1010924)

## Methodology



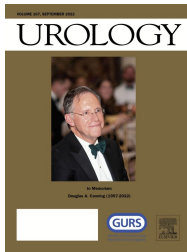
The authors developed software for Analysis of Testis Images with Neural Networks (SATINN), an automated analysis of immunofluorescence images from mouse testis. This approach uses residual learning to accurately classify nuclei from seminiferous tubules into 7 distinct cell types, and to categorise tubules into one of 12 distinct stages.

The classifiers can be used to describe pathology and for analysis of testis histology. The source code and a SATINN standalone application with graphic-user interface are available: <http://github.com/conradlab/SATINN>.

Yang R, Stendahl A, Vigh-Conrad KA, Held M, Lima AC, Conrad DF. SATINN: An automated neural network-based classification of testicular sections allows for high-throughput histopathology of mouse mutants. *Bioinformatics* 2022 Oct 10;btac673. Epub ahead of print. PMID: 36214638. <https://doi.org/10.1093/bioinformatics/btac673>

## Case of the month

*Fetus in fetu* is a rare phenomenon of infancy, and the pathogenesis is not well understood. The majority of these are found in the retroperitoneum. The authors present the diagnosis and management of an exceedingly rare case of *fetus in fetu* in the scrotum of a newborn male including



radiologic imaging and pathologic examination.

Heitman EA, Thomas JC, Maller VV, Zhang J, Gleason JM. Scrotal Fetus in Fetu in a Newborn: A Rare Case Report. *Urology*. 2022; 166:241-245. PMID: 35643112. [10.1016/j.urology.2022.05.016](https://doi.org/10.1016/j.urology.2022.05.016)

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