



## EAA Literature Alert Edition April 2021

Several exciting articles have been published recently in the field of andrology, reproductive biology and androgenetics, so this collection is bigger than the previous one. Enjoy the reading! You are welcome to share this list with your colleagues and students. If you want to inform EAA members about your latest work, send a note to the [EAA Secretary](#).

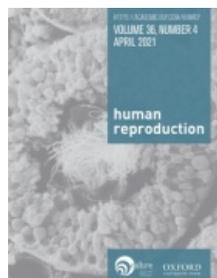
### Clinical andrology and epidemiology



A nice contribution from the EAA Centre in Ghent. Their longitudinal study of 999 healthy men (aged 24-46 years) showed that serum androgen levels start declining early in adult men independently of BMI or lifestyle factors, with a concurrent rise in gonadotropin levels.

Banica T, Verroken C, Reyns T, Mahmoud A, T'Sjoen G, Fiers T, Kaufman JM, Lapauw B. Early Decline of Androgen Levels in Healthy Adult Men: An Effect of Aging Per Se? A Prospective Cohort Study. **J Clin Endocrinol Metab** 2021; 106(4):1074-1083. PMID: 33382411.

<https://doi.org/10.1210/clinem/dgaa915>



The incidence of cryptorchidism requiring surgery has increased in France by 36% in just 13 years (2002–2014)! Importantly, this large study based on the nationwide hospital discharge database identified clustering of the cases, suggestive of shared socio-economic and environmental factors.

Le Moal J, Gorla S, Guillet A, Rigou A, Chesneau J. Time and spatial trends of operated cryptorchidism in France and environmental hypotheses: a nationwide study from 2002 to 2014. **Hum Reprod** 2021 (in press) deaa378. PMID: 33728432.

<https://academic.oup.com/humrep/advance-article/doi/10.1093/humrep/deaa378/6171098?searchresult=1>  
Commentary by Richard M. Sharpe: <https://doi.org/10.1093/humrep/deab051>



A collaborative study looked at the potential impact of in utero exposure to endocrine disruptors and found an association between the mother's occupational exposure to pesticides, phthalates and heavy metals, and a decrease in some semen parameters in their sons in adulthood.

M Istvan, R Rahban, B Dananche, A Senn, E Stettler, L Multigner, S Nef, R Garlantézec. Maternal occupational exposure to endocrine-disrupting chemicals during pregnancy and semen parameters in adulthood: results of a nationwide cross-sectional study among Swiss conscripts. **Hum Reprod** 2021 (in press) deab034

<https://doi.org/10.1093/humrep/deab034>

A multicentre study from Germany, including the EAA Centre in Münster, addressed the impact of the treatment on fertility and the prevalence of testicular adrenal rest tumours (TART) in young



men with congenital adrenal hyperplasia (CAH). They found that TART development is favoured by inadequate long-term hormonal control in CAH, and reduced semen quality may be associated with large TART, probably due to gonadotropin suppression by adrenal androgen excess

Rohayem J, Bäumer LM, Zitzmann M, Fricke-Otto S, Mohnike K, Gohlke B, Reschke F, Jourdan C, Müller HL, Dunstheimer D, Weigel J, Jorch N, Müller-Rosberg E, Lankes E, Gätjen I, Richter-Unruh A, Hauffa BP, Kiesch S, Krumbholz A, Brämwig J. Semen quality and testicular adrenal rest tumour development in 46,XY congenital adrenal hyperplasia: the importance of optimal hormonal replacement. **Eur J Endocrinol** 2021 Apr; 184(4):487-501. PMID: 33524003.

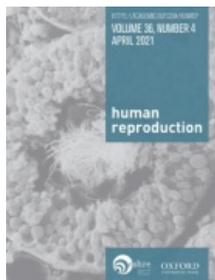
<https://eje.bioscientifica.com/view/journals/eje/184/4/EJE-20-1154.xml>



A study of 121 patients, who had a detailed semen analysis performed before and after surgical correction of varicocele, revealed a significant improvement in several sperm parameters. The greatest improvement was observed in men with ultrasonography varicocele degrees I and II.

Morini D, Spaggiari G, Daolio J, Melli B, Nicoli A, De Feo G, Valli B, Viola D, Garganigo S, Magnani E, Pilia A, Polese A, Colla R, Simoni M, Aguzzoli L, Villani MT, Santi D. Improvement of sperm morphology after surgical varicocele repair. **Andrology** 2021 Apr 7. Epub ahead of print. PMID: 33825345.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/andr.13012>



A retrospective study from the EAA Centre in L'Aquila (Italy) investigated infertile men with and without testicular microlithiasis (TM), and found an association of TM with smaller testis volume and reduced sperm count.

D'Andrea S, Martorella A, Castellini C, Cordeschi G, Totaro M, Parisi A, Francavilla F, Necozone S, Francavilla S, Barbonetti A. Clinical and seminal parameters associated with testicular microlithiasis and its severity in males from infertile couples. **Hum Reprod** 2021 Mar 18;36(4):891-898. doi: 10.1093/humrep/deaa354. PMID: 33406236.

<https://doi.org/10.1093/humrep/deaa354>



April is testicular cancer awareness month. On this occasion, we highlight an excellent review on the late effects of testicular germ cell cancer. Survivors of this cancer have an increased risk of several comorbidities, including sexual dysfunction. Leydig cell dysfunction is observed in >20% and testosterone substitution is needed in 5-10% of the survivors.

Chovanec M, Lauritsen J, Bandak M, Oing C, Kier GG, Kreiberg M, Rosenkilde J, Wagner T, Bokemeyer C, Daugaard G. Late adverse effects and quality of life in survivors of testicular germ cell tumour. **Nat Rev Urol**. 2021 Apr;18(4):227-245. PMID: 33686290.

<https://www.nature.com/articles/s41585-021-00440-w>

## Androgenetics



A great study from Estonia and the UK, including our colleagues from the EAA Centre in Tartu! They identified a novel structural variant of the Y-chromosome (AZFc region) that predisposes to spermatogenic failure in Northern European populations, especially in ageing men. The paper provides also detailed laboratory protocols and clear guidelines for genetic counselling.

Hallast P, Kibena L, Punab M, Arciero E, Rootsi S, Grigorova M, Flores R, Jobling MA, Poolamets O, Pomm K, Korrovits P, Rull K, Xue Y, Tyler-Smith C, Laan M. A common 1.6 mb Y-chromosomal inversion predisposes to subsequent deletions and severe spermatogenic failure in humans. **Elife**. 2021 Mar 30;10:e65420. PMID: 33781384.

<https://doi.org/10.7554/eLife.65420>

**eLife press release:** 'Structural genetic change may increase risk of male fertility' - <https://elifesciences.org/for-the-press/935def52/structural-genetic-change-may>



Are you confused about the impact of AZFb deletions, and how to identify them? You are not alone. Find the answers in this article from Peter Vogt, 'the father' of the AZF deletion diagnostics, which shows different types of 'classical' and 'non-classical' AZFb deletions

Vogt PH, Bender U, Deibel B, Kiesewetter F, Zimmer J, Strowitzki T. Human AZFb deletions cause distinct testicular pathologies depending on their extensions in Yq11 and the Y haplogroup: new cases and review of literature. **Cell Biosci.** 2021 Mar 25;11(1):60. PMID: 33766143.

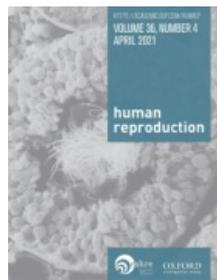
<https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-021-00551-2>



A prospective next-generation sequencing (NSG) study of 293 boys with mild (glandular to penoscrotal) hypospadias identified likely pathogenic variants in 5.5% of patients. Early molecular diagnosis of these patients would help improve follow-up at puberty and medical counselling.

Ea V, Bergougnoux A, Philibert P, Servant-Fauconnet N, Faure A, Breaud J, Gaspari L, Sultan C, Paris F, Kalfa N. How Far Should We Explore Hypospadias? Next-generation Sequencing Applied to a Large Cohort of Hypospadiac Patients. **Eur Urol.** April 2021; 79(4):507-515. PMID: 33468338.

<https://www.sciencedirect.com/science/article/abs/pii/S0302283820310228?via%3Dihub>  
**Editorial by Laurence Baskin: [New Insights into Hypospadias: Next-generation Sequencing Reveals Potential Genetic Factors in Male Urethral Development - ScienceDirect](#)**



According to our colleagues from Münster, the FSHB c.-211G>T polymorphism might result in an impaired response to endogenous or exogenous GnRH stimulation. This finding might contribute to the clinical phenotype of reduced testicular volume and sperm count for patients carrying one or two T alleles.

Sansone A, Schubert M, Tüttelmann F, Krallmann C, Zitzmann M, Kliesch S, Gromoll J. Pituitary response to GnRH stimulation tests in different FSHB-211 G/T genotypes. **Hum Reprod.** 2021 Mar 10:deab033. Epub ahead of print. PMID: 33704441.

<https://academic.oup.com/humrep/advance-article-abstract/doi/10.1093/humrep/deab033/6168018?redirectedFrom=fulltext>

## COVID-19



Italian researchers found a deleterious TLR7 gene variant (X-linked) in 6.3% of relatively young (<60 y) and 2.1% overall male patients severely affected by COVID-19. None of the oligo-asymptomatic control men carried this variant. The patients may benefit from genetic screening and interferon treatment.

Fallerini C, Daga S, Mantovani S, Benetti E, Picchiotti N, Francisci D, Paciosi F, Schiaroli E, Baldassarri M, Fava F, Palmieri M, Ludovisi S, Castelli F, Quiros-Roldan E, Vaghi M, Rusconi S, Siano M, Bandini M, Spiga O, Capitani K, Furini S, Mari F; GEN-COVID Multicenter Study, Renieri A, Mondelli MU, Frullanti E. Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study. **Elife** 2021 Mar. PMID: 33650967.

<https://elifesciences.org/articles/67569>

**eLife press release:** <https://elifesciences.org/for-the-press/bf984a3a/rare-genetic-variant-puts-some-younger-men-at-risk-of-severe-covid-19>



A small prospective study revealed that SARS-CoV-2 infection can affect total sperm count in the ejaculate in the acute setting. Viral RNA was not detected in semen.

Best JC, Kuchakulla M, Khodamoradi K, Lima TFN, Frech FS, Achua J, Rosete O, Mora B, Arora H, Ibrahim E, Ramasamy R. Evaluation of SARS-CoV-2 in Human Semen and Effect on Total Sperm Number: A Prospective Observational Study. **World J Mens Health.** 2021 (in press). PMID: 33663031.

<https://wjmh.org/DOIx.php?id=10.5534/wjmh.200192>

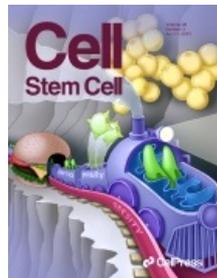


In this preliminary study, the prevalence of erectile dysfunction, measured with the Sexual Health Inventory for Men, was higher in the COVID-positive men (28% vs. 9.33%;  $p = 0.027$ ). It remains to be determined whether erectile dysfunction is a risk factor for developing COVID-19 or is occurring as consequence of COVID-19.

Sansone A, Mollaioli D, Ciocca G, Colonnello E, Limoncin E, Balercia G, Jannini EA. "Mask up to keep it up": Preliminary evidence of the association between erectile dysfunction and COVID-19. **Andrology**. 2021 Mar 20. Epub ahead of print. PMID: 33742540.

<https://onlinelibrary.wiley.com/doi/10.1111/andr.13003>

## Basic and translational andrology



A new insight into the fate of transplanted germ cells in a mouse model. The authors found that only a small fraction of spermatogonia persist and regenerate over the long term, and the rest are lost through differentiation and cell death. Importantly, they showed that repopulation efficiency can be increased, and the fertility of infertile hosts restored, if differentiation is transiently suppressed by inhibiting retinoic acid synthesis.

Nakamura Y, Jörg DJ, Kon Y, Simons BD, Yoshida S. Transient suppression of transplanted spermatogonial stem cell differentiation restores fertility in mice. **Cell Stem Cell** 2021 Apr 8:S1934-5909(21)00122-3. Epub ahead of print. PMID: 33848470.

[https://www.cell.com/cell-stem-cell/fulltext/S1934-5909\(21\)00122-3](https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(21)00122-3)



Not strictly andrology but a very exciting advancement in the modelling of the early human embryo! In vitro-forming blastoids were reported by four teams independently. Two articles in Nature described models of human blastocysts developed from pluripotent stem cells (Yu et al. from China and USA) or reprogrammed fibroblasts (Liu et al. from Australia and USA). Two bioRxiv preprints (not yet peer-reviewed) (Sozen et al. from the USA and UK, and Fan et al. from China) also used reprogrammed human cells. The 'human blastoids'/iBlastoids closely resemble human blastocysts; have an inner cell mass-like structure, a blastocoel-like cavity and a trophectoderm-like outer layer. The blastoids give rise to pluripotent and trophoblast stem cells, and can further develop into peri-implantation embryo-like structures in vitro.

Yu L, Wei Y, Duan J, Schmitz DA, Sakurai M, Wang L, Wang K, Zhao S, Hon GC, Wu J. Blastocyst-like structures generated from human pluripotent stem cells. **Nature**. 2021 Mar; 591(7851):620-626. PMID: 33731924.

<https://www.nature.com/articles/s41586-021-03356-y>

Liu X, Tan JP, Schröder J, Aberkane A, Ouyang JF, Mohenska M, Lim SM, Sun YBY, Chen J, Sun G, Zhou Y, Poppe D, Lister R, Clark AT, Rackham OJL, Zenker J, Polo JM. Modelling human blastocysts by reprogramming fibroblasts into iBlastoids. **Nature**. 2021 Mar; 591(7851):627-632. PMID: 33731926.

[Modelling human blastocysts by reprogramming fibroblasts into iBlastoids | Nature](#)



Sozen B, Jorgensen V, Zhu M, Cui T & Zernicka-Goetz M. Reconstructing human early embryogenesis in vitro with pluripotent stem cells. Reconstructing human early embryogenesis in vitro with pluripotent stem cells. **Preprint at bioRxiv**.

<https://doi.org/10.1101/2021.03.12.435175> (2021).

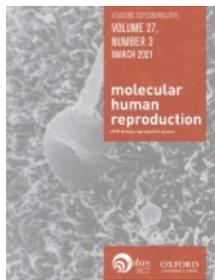
Fan Y, Min Z-Y, Alsolami S, Ma Z-L, Zhong K, Pei W-D, Zhang P-Y, Kang X-J, Zhang Y-Y, Zhu X-Y, Qiao J, Li M, Yu Y. Generation of human blastocyst-like structures from pluripotent stem cells. **Preprint at bioRxiv**.

<https://doi.org/10.1101/2021.03.09.434313> (2021).

**Commentary:** [First complete model of the human embryo \(nature.com\)](#)

**Commentary:** [Lab-grown structures mimic human embryo's earliest stage yet \(nature.com\)](#)

This translational study from Münster demonstrated a novel mechanism of infertility, associated with ciliopathy but distinct from primary defects of sperm motility. The authors examined

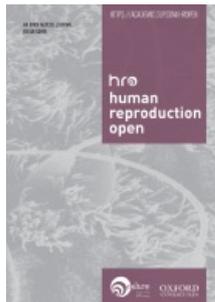


mice and human patients with deficiency or loss of function of axonemal motor protein DNAH5 (disturbing ciliary motility of efferent ducts) and found reduced sperm counts and dilatations of the epididymal head but normal sperm motility.

Apra I, Nöthe-Menchen T, Dougherty GW, Raidt J, Loges NT, Kaiser T, Wallmeier J, Olbrich H, Strünker T, Kliesch S, Pennekamp P, Omran H. Motility of efferent duct cilia aids passage of sperm cells through the male reproductive system. **Mol Hum Reprod**. 2021 Feb 27;27(3):gaab009. PMID: 33561200.

<https://doi.org/10.1093/molehr/gaab009>

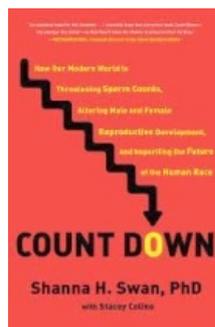
## Male health - general aspects and popular reading



A mission statement from the Male Reproductive Health Initiative (MHRl); an open, international consortium of people concerned by the growing problem of male infertility. This initiative is supported by the EAA and ESHRE.

Barratt CLR, De Jonge CJ, Anderson RA, Eisenberg ML, Garrido N, Rautakallio Hokkanen S, Krausz C, Kimmins S, O'Bryan MK, Pacey AA, Tüttelmann F, Veltman JA. A global approach to addressing the policy, research and social challenges of male reproductive health, **Human Reproduction Open**, Volume 2021 (1), hoab009

<https://doi.org/10.1093/hropen/hoab009>



A highly praised and engrossing book on “how our modern world is threatening sperm counts, altering male and female reproductive health and imperiling the future of the human race”, written by a renowned reproductive epidemiologist.

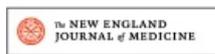
“**Count Down**” by **Shanna Swan, PhD** (with Stacey Colino), Scribner (an imprint of Simon & Schuster Inc.), ISBN 978-1-9821-1366-7, ISBN 978-1-9821-1368-1 (ebook)

**Comment by Erin Brockovich (the Guardian):**

<https://www.theguardian.com/commentisfree/2021/mar/18/toxic-chemicals-health-humanity-erin-brockovich>

**How to order:** <https://www.simonandschuster.com/books/Count-Down/Shanna-H-Swan/9781982113667>

## Case report of the month



A complete hydatidiform mole (CHM) developed in a woman who had undergone intrauterine implantation of a blastocyst obtained through in vitro injection of a presumed round spermatid (ROSI) into her oocyte. It is likely that a spermatogonium, rather than a round spermatid, was inadvertently selected for the procedure. The CHM developed into gestational trophoblastic neoplasia, which resolved after chemotherapy.

Usui H, Shozu M. Spermatogonium-Derived Complete Hydatidiform Mole. **N Engl J Med**. 2021 Mar 11; 384(10):936-943. PMID: 33704938.

[https://www.nejm.org/doi/10.1056/NEJMoa2005756?url\\_ver=Z39.88-2003&rft\\_id=ori:rid:crossref.org&rft\\_dat=cr\\_pub%20%20pubmed](https://www.nejm.org/doi/10.1056/NEJMoa2005756?url_ver=Z39.88-2003&rft_id=ori:rid:crossref.org&rft_dat=cr_pub%20%20pubmed)

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