



EAA Literature Alert Edition August 2021

If you have recently joined EAA - this monthly alert informs our members about recent publications of interest for andrologists and reproductive biologists, with special emphasis on studies performed in the EAA-endorsed centres. You are welcome to share this list with your colleagues and students. If you want to share your recent publication, send a note to the EAA Secretary. Enjoy the reading!

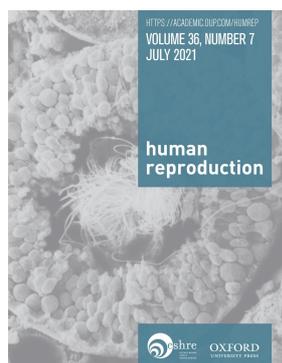
Clinical andrology and epidemiology



A prospective study investigated reproductive factors associated with impairment of general health in a cohort of 899 infertile men over a 10-year follow-up period. A decrease of the overall health status was found in almost 10% of these men, and the most frequent health problems were: cancer, cardio-vascular diseases and diabetes mellitus. Men with non-obstructive azoospermia showed the worst health status impairment and should be strictly followed-up regardless of their fertility status.

Boeri L, Ventimiglia E, Cazzaniga W, Pederzoli F, Fallara G, Pozzi E, Belladelli F, Baudo A, Frego N, Capogrosso P, Alfano M, Montorsi F, Salonia A. Risk of health status worsening in primary infertile men: a prospective 10-year follow-up study. *Andrology* 2021 Aug 9. doi: 10.1111/andr.13090. PMID: 34369670.

<https://onlinelibrary.wiley.com/doi/10.1111/andr.13090>



Some good news! This large Danish register-based study of 9353 young (<30 years of age) male survivors of cancer (any type) showed that even though men diagnosed with cancer in childhood and adolescence have significantly reduced rates of fatherhood, the survival and the fatherhood rates have improved markedly over time.

Sylvest R, Vassard D, Schmidt L, Schmiegelow K, Macklon KT, Forman JL, Pinborg A. Parenthood among men diagnosed with cancer in childhood and early adulthood: trends over time in a Danish national cohort. *Human Reproduction* 2021; 36 (9), 2576-2586, PMID: 34166497

<https://doi.org/10.1093/humrep/deab154>

An interesting study looking at endocrine consequences of sleep loss in men. Sleep restriction alone induced hyperinsulinemia, hyperglycemia, and insulin resistance. Clamping cortisol and testosterone alleviated the development of overall insulin resistance and hyperinsulinemia by 50%. The interplay between cortisol and testosterone may be important as a mechanism by which sleep restriction impairs metabolic health.

Liu PY, Lawrence-Sidebottom D, Piotrowska K, Zhang W, Iranmanesh A, Auchus RJ, Veldhuis JD, Van Dongen HPA.



Clamping Cortisol and Testosterone Mitigates the Development of Insulin Resistance during Sleep Restriction in Men. *J Clin Endocrinol Metab.* 2021: dgab375. doi: 10.1210/clinem/dgab375. Epub ahead of print. PMID: 34043794.

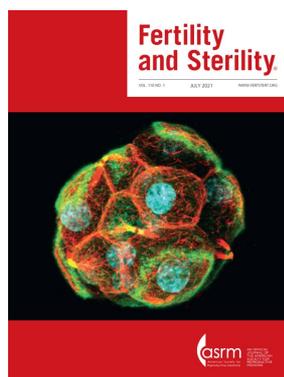
<https://doi.org/10.1210/clinem/dgab375>



This longitudinal cohort study of 2,713 infertile couples from Sweden evaluated how the choice of the first ART treatment type (IVF vs ICSI) affects the live birth rate - if the male partner has a high sperm DNA fragmentation index (DFI). A high sperm DFI predicted a significantly lower cumulative live birth rate if IVF and not ICSI was applied in the first cycle of assisted reproduction.

Vončina SM, Stenqvist A, Bungum M, Schyman T, Giwercman A. Sperm DNA fragmentation index and cumulative live birth rate in a cohort of 2,713 couples undergoing assisted reproduction treatment. *Fertility & Sterility* 2021 Aug 7: S0015-0282(21)00562-8. doi: 10.1016/j.fertnstert.2021.06.049. PMID: 34376283.

<https://doi.org/10.1016/j.fertnstert.2021.06.049>



Paternal age has an effect on pregnancy outcomes in assisted reproduction according to two recent studies. In the Mc Carter et al. study, which controlled for oocyte quality by using paired recipients from the same donor and the same stimulation cycle, increased paternal age (median 48 y) had a negative effect on pregnancy rates. Marsidi et al. found that paternal age ≥ 46 years was associated with a lower likelihood of pregnancy and live birth among couples undergoing IVF. However, the negative effect of paternal age was most notable among women aged ≥ 35 years, highlighting the importance of the maternal age.

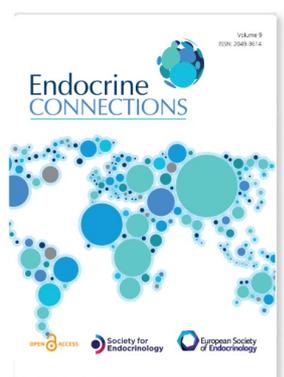
McCarter K, Setton R, Chung A, An A, Rosenwaks Z, Spandorfer S. Is increasing paternal age negatively associated with donor oocyte recipient success? A paired analysis using sibling oocytes. *Fertility & Sterility* 2021 Aug;116(2):373-379. doi: 10.1016/j.fertnstert.2021.03.037. PMID: 33926719.

[https://www.fertstert.org/article/S0015-0282\(21\)00242-9/fulltext](https://www.fertstert.org/article/S0015-0282(21)00242-9/fulltext)

Marsidi AM, Kipling LM, Kawwass JF, Mehta A. Influence of paternal age on assisted reproductive technology cycles and perinatal outcomes. *Fertility & Sterility* 2021 Aug;116(2):380-387. doi: 10.1016/j.fertnstert.2021.03.033. PMID: 33910758.

[https://www.fertstert.org/article/S0015-0282\(21\)00238-7/fulltext](https://www.fertstert.org/article/S0015-0282(21)00238-7/fulltext)

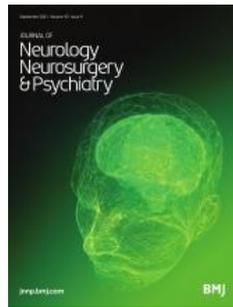
Comment by Ginsburg ES, George JS: [Older but not wiser: the impact of increasing paternal age on donor oocyte recipient success.](#)



A prospective observational study defined the optimized inter-injection interval of testosterone undecanoate (TU) in 325 men undergoing testosterone replacement therapy for pathological hypogonadism or masculinization of female-to-male transgender. Optimal intervals between TU injections after individual titration resulted in the approved 12-week interval in 70% of patients, with only minor influence body size but not of serum LH, FSH, and SHBG. Individually optimized inter-injection interval did not differ between men with primary or secondary hypogonadism or transmen.

Shankara Narayana N, Ly LP, Jayadev V, Fennell C, Savkovic S, Conway AJ, Handelsman DJ. Optimal injection interval for testosterone undecanoate treatment of hypogonadal

and transgender men. *Endocrine Connections* 2021; 10(7):758-766. doi: 10.1530/EC-21-0109. PMID: 34137730. <https://ec.bioscientifica.com/view/journals/ec/10/7/EC-21-0109.xml>



Important news if you treat transwomen (genetic males undergoing feminising hormone therapy) or patients with prostate cancer with cyproterone acetate (CPA), which has anti-androgen and pro-progestin properties. This large cohort study from Denmark compared patients exposed to CPA and found a significantly increased risk of meningioma with the adjusted hazard ratio of 7.0 for low cumulative doses and 19.2 for high cumulative doses, in comparison to non-users.

Mikkelsen AP, Greiber IK, Scheller NM, Hilden M, Lidgaard Ø. Cyproterone acetate and risk of meningioma: a nationwide cohort study. *J Neurol Neurosurg Psychiatry*. 2021 Jun 29:jnnp-2021-326138. doi: 10.1136/jnnp-2021-326138. PMID: 34187864.

<http://dx.doi.org/10.1136/jnnp-2021-326138>
(preprint: <https://www.medrxiv.org/content/10.1101/2020.12.29.20248395v1>)

Androgenetics



An important contribution from GEMINI Consortium, which performed exome sequencing of constitutive DNA from 924 men with nonobstructive azoospermia (NOA).

Mutations in PNLDC1 were identified in 4 patients of Middle Eastern descent, who had a spermatogenic arrest with round spermatids of type Sa as the most advanced stage. The mechanistic part of the study, led by researchers from Copenhagen, found disruption of pachytene piRNAs-processing proteins PIWIL1, PIWIL4, MYBL1, and TDRKH. The study demonstrated a direct effect of faulty piRNA processing on meiosis and spermatogenesis in men, ultimately leading to male infertility.

Nagirnaja L, Mørup N, Nielsen JE, Stakaitis R, Golubickaite I, Oud MS, Winge SB, Carvalho F, Aston KI, Khani F, van der Heijden GW, Marques CJ, Skakkebaek NE, Rajpert-De Meyts E, Schlegel PN, Jørgensen N, Veltman JA, Lopes AM, Conrad DF, Almstrup K. Variant PNLDC1, Defective piRNA Processing, and Azoospermia. *N Engl J Med*. 2021; 385(8):707-719. doi: 10.1056/NEJMoa2028973. PMID: 34347949.

https://www.nejm.org/doi/full/10.1056/NEJMoa2028973?query=featured_home

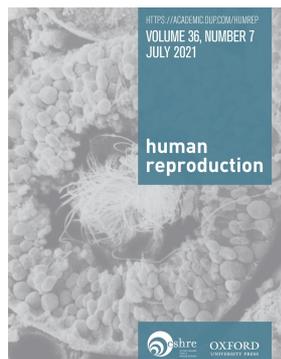


This study investigated mechanisms preventing premature acrosomal reaction (AR) during sperm capacitation. The authors showed that GIV/Girdin (*CCDC88A*), a guanine nucleotide-exchange modulator for trimeric GTPases, is rapidly phosphorylated in spermatozoa, in two compartmentalised signalling programs.

In the sperm tail, GIV enhances sperm motility and survival, whereas in the head it inhibits cAMP surge and premature AR. GIV transcripts are downregulated in the testis and semen of infertile men, suggesting a novel cause of infertility.

Reynoso S, Castillo V, Katkar GD, Lopez-Sanchez I, Taheri S, Espinoza C, Rohena C, Sahoo D, Gagneux P, Ghosh P. GIV/Girdin, a non-receptor modulator for Gai/s, regulates spatiotemporal signaling during sperm capacitation and is required for male fertility. *eLife* 2021 Aug 19;10:e69160. doi: 10.7554/eLife.69160. PMID: 34409938.

<https://elifesciences.org/articles/69160>



A homozygous nonsense variant in the SPACA1 gene (NM_030960.2: c.53G>A; p. Trp18*) was identified in two brothers with globozoospermia (in a consanguineous family). The phenotype was very similar to that of Spaca1 gene-disrupted mice. The study expanded the spectrum of causative genes for globozoospermia, explored the pathogenesis of globozoospermia caused by SPACA1 deficiency, and provided evidence for ICSI treatment outcomes in the affected patients.

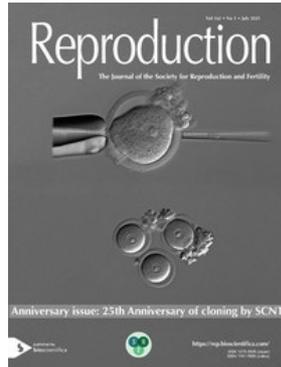
Chen P, Saiyin H, Shi R, Liu B, Han X, Gao Y, Ye X, Zhang X, Sun Y. Loss of SPACA1 function causes autosomal recessive globozoospermia by damaging the acrosome-acroplaxome complex. *Human Reproduction*, 2021; 36 (9): 2587-2596. PMID: 34172998.

<https://doi.org/10.1093/humrep/deab144>

This whole-exome sequencing study of 34 patients with acephalic spermatozoa syndrome identified pathogenic variants in the X-linked gene, *ACTRT1*, in two patients. *Actrt1*-knockout mice exhibited a similar acephalic spermatozoa phenotype. The patients in this study conceived children through artificial insemination.

Sha Y, Liu W, Li L, Serafimovski M, Isachenko V, Li Y, Chen J, Zhao B, Wang Y, Wei X. Pathogenic Variants in ACTRT1 Cause Acephalic Spermatozoa Syndrome. *Frontiers Cell Dev Biol.* 2021 Aug 6;9:676246. doi: 10.3389/fcell.2021.676246. PMID: 34422805. <https://doi.org/10.3389/fcell.2021.676246>

Translational and basic studies



Immature mouse fetal Sertoli cells can undergo sufficient maturation in the adult testis to become functional. The authors transplanted mouse fetal testicular cells into a Sertoli-depleted adult testis and found that donor E12.5-E16.5 Sertoli cells colonized adult seminiferous tubules and supported host spermatogenesis for 2 months after transplantation. This model will help to investigate the potential of iPS-derived Sertoli cells to colonize, undergo maturation, and support spermatogenesis within the testis environment.

Yokonishi T, Capel B. Differentiation of fetal Sertoli cells in the adult testis. *Reproduction* 2021; 162(2):141-147. doi: 10.1530/REP-21-0106. PMID: 34085952.

<https://rep.bioscientifica.com/view/journals/rep/162/2/REP-21-0106.xml?rskey=nITmtM&result=8>

The authors of this interesting study reported that albumin is required to activate human voltage-gated proton channels (hHv1) in sperm and neutrophils. This does not happen in semen because the albumin concentration is too low, but hHv1 is activated in uterine fluid, allowing capacitation, the acrosomal reaction, and oocyte fertilization.

Zhao R, Dai H, Arias RJ, De Blas GA, Orta G, Pavarotti MA, Shen R, Perozo E, Mayorga LS, Darszon A, Goldstein SAN. Direct activation of the proton channel by albumin leads to human sperm capacitation and sustained release of inflammatory mediators by neutrophils. *Nature Commun.* 2021;12(1):3855. doi: 10.1038/s41467-021-24145-1. PMID: 34158477.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8219737>

The authors of this study (from Münster) investigated the action of seminal and follicular fluid, and individual prostaglandins and steroids on the sperm from donors and *CATSPER2*-deficient patients that lack functional CatSper channels.

They showed that any of the reproductive steroids and prostaglandins evokes a rapid Ca^{2+} increase that invariably rests on Ca^{2+} influx *via* CatSper, and that Zn^{2+} suppresses this action, possibly preventing premature activation of CatSper in the ejaculate. The findings indicate that human CatSper is a promiscuous chemosensor that enables sperm to probe the varying hormonal microenvironment prevailing at different stages during their journey across the female genital tract.

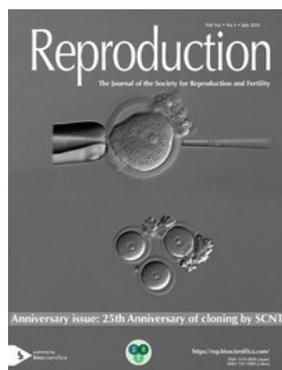
Jeschke JK, Biagioni C, Schierling T, Wagner IV, Börgel F, Schepmann D, Schüring A, Kulle AE, Holterhus PM, von Wolff M, Wunsch B, Nordhoff V, Strünker T, Brenker C. The Action of Reproductive Fluids and Contained Steroids, Prostaglandins, and Zn^{2+} on CatSper Ca^{2+} Channels in Human Sperm. *Frontiers Cell Dev Biol.* 2021; 9:699554. doi: 10.3389/fcell.2021.699554. PMID: 34381781. <https://www.frontiersin.org/articles/10.3389/fcell.2021.699554/full>

Here, the Australian team used a high spatiotemporal sperm imaging system to characterize the function of cysteine-rich secretory proteins (CRISPs) in sperm motility.

Each of CRISP1, CRISP2, and CRISP4 acted independently to optimize sperm

flagellum waveform and sperm velocity. The data suggest that CRISPs are the targets of positive Darwinian evolution.

Gaikwad AS, Nandagiri A, Potter DL, Nosrati R, O'Connor AE, Jadhav S, Soria J, Prabhakar R, O'Bryan MK. CRISPs Function to Boost Sperm Power Output and Motility. **Frontiers Cell Dev Biol.** 2021 Aug 5;9:693258. doi: 10.3389/fcell.2021.693258. PMID: 34422816; PMCID: PMC8374954. <https://doi.org/10.3389/fcell.2021.693258>



The authors followed on their previous finding that mice lacking CEP164 in multiciliated cells show a significant loss of multicilia in the trachea, oviduct, and ependyma, and males are sterile. In this study they found that in CEP164^{fl/fl} mice multicilia were not detectable in the efferent ducts, causing severe sperm aggregation and agglutination, dilatation of seminiferous tubules and rete testis, and ultimately leading to male infertility.

Hoque M, Chen D, Hess RA, Li FQ, Takemaru KI. CEP164 is essential for efferent duct multiciliogenesis and male fertility. **Reproduction.** 2021; 162(2):129-139. doi: 10.1530/REP-21-0042. PMID: 34085951.

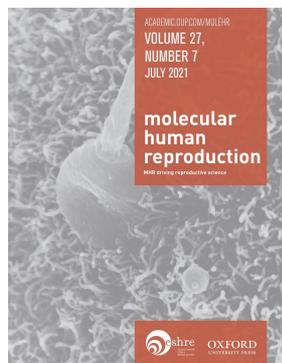
<https://rep.bioscientifica.com/view/journals/rep/162/2/REP-21-0042.xml>



Testicular adrenal rest tumors (TART) occur in males with classic 21-hydroxylase deficiency (21OHD). This study investigated steroidogenesis and found that in patients with 21OHD, TART produce 11 α C19 steroids, but in different proportions than the adrenals. The results suggest the 11-hydroxylation of testosterone by TART, and that this metabolism is ACTH-sensitive.

Schröder MAM, Turcu AF, O'Day P, van Herwaarden AE, Span PN, Auchus RJ, Sweep FCGJ, Claahsen-van der Grinten HL. Production of 11-oxygenated androgens by testicular adrenal rest tumors. **J Clin Endocrinol Metab** 2021 Aug 14:dgab598. doi: 10.1210/clinem/dgab598. Epub ahead of print. PMID: 34390337.

<https://academic.oup.com/jcem/advance-article/doi/10.1210/clinem/dgab598/6352403>



The authors hypothesized that ATP metabolites may contribute to cytokine production by human testicular peritubular cells (HTPCs). They showed that active ENTPD1 and NT5E and three adenosine receptors were present in HTPCs. *In vitro* experiments indicated an overall pro-inflammatory action of adenosine in the mouse testis. If transferable to the *in vivo* situation, interference with adenosine receptors could reduce inflammatory events in the testis, possibly providing a new avenue for treatment of sterile inflammation in male subfertility and infertility.

Missel A, Walenta L, Eubler K, Mundt N, Heikelä H, Pickl U, Trottmann M, Popper B, Poutanen M, Strauss L, Köhn FM, Kunz L, Spehr M, Mayerhofer A. Testicular adenosine acts as a pro-inflammatory molecule: role of testicular peritubular cells. **Molecular Human Reproduction** 2021; 27(7):gaab037. doi: 10.1093/molehr/gaab037. PMID: 33993290.

<https://academic.oup.com/molehr/article-abstract/27/7/gaab037/6276438?redirectedFrom=fulltext>

Meeting proceedings

If you missed the latest virtual ESHRE meeting you can catch up with what your colleagues are currently working on, while browsing through this supplement. The abstracts are written using the well-known 'long' Human Reproduction style, hence, they are very informative. Numerous abstracts have been contributed by EAA members.

https://academic.oup.com/humrep/issue/36/Supplement_1

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