



EAA Literature Alert Edition December 2021

This is the last 2021 literature digest for EAA members interested in the latest findings in clinical and basic aspects of andrology. We wish you a great 2022 – with lots of good results and high-impact publications!

Clinical andrology and epidemiology



An exciting review article from one of the founders of the EAA, his group in Copenhagen and international collaborators. The authors critically discussed possible reasons behind the observed decline in childbirth rates and human reproductive health in industrialized regions. The authors hypothesize that the negative trends are partially linked to increasing human exposures to ubiquitously present chemicals originating directly or indirectly from fossil fuels. They call for more interdisciplinary research to elucidate the impact of these chemicals and – if proven – for regulatory action.

Skakkebaek NE, Lindahl-Jacobsen R, Levine H, Andersson AM, Jørgensen N, Main KM, Lidegaard Ø, Priskorn L, Holmboe SA, Bräuner EV, Almstrup K, Franca LR, Znaor A, Kortenkamp A, Hart RJ, Juul A. Environmental factors in declining human fertility. *Nature Reviews Endocrinol.* 2021 Dec 15. Epub ahead of print. PMID: 34912078.

<https://www.nature.com/articles/s41574-021-00598-8>

Comment in The Guardian: <https://www.theguardian.com/society/2021/dec/15/fall-fertility-rates-may-be-linked-fossil-fuel-pollution-finds-study>



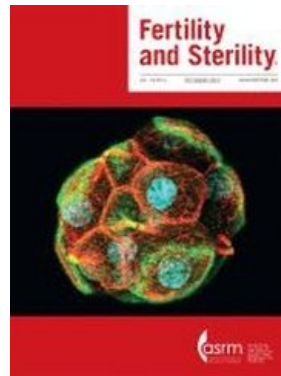
In this meta-analytic review, our Italian colleagues evaluated the existing evidence of the impact of diabetes mellitus type 1 (DM1) on male reproduction. DM1 might impair male fertility and testis functions (endocrine, spermatogenesis), but the evidence is surprisingly limited. More studies are needed, with a complete hormonal, seminal, and ultrasound workup and a longer follow-up of men with DM1.

Facondo P, Lodovico ED, Delbarba A, Anelli V, Pezzaioli LC, Filippini E, Cappelli C, Corona G, Ferlin A. The impact of Diabetes Mellitus type 1 on male fertility: Systematic review and meta-analysis. *Andrology* 2021 Dec 14. Epub ahead of print. PMID: 34904793.
<https://doi.org/10.1111/andr.13140>

(WC), as a proxy for central obesity, was inversely associated with lower sperm concentrations and a decreased probability of achieving a live birth. The authors concluded that increased male WC may be a risk factor for poor outcomes of ART, particularly in couples where the male partner has a normal BMI.

Bian H, Mínguez-Alarcón L, Salas-Huetos A, Bauer D, Williams PL, Souter I, Attaman J, Chavarro JE; EARTH Study Team. Male waist circumference in relation to semen quality and partner infertility treatment outcomes among couples undergoing infertility treatment with assisted reproductive technologies. *Am J Clin Nutrition* 2021 Nov 3:nqab364. Epub ahead of print. PMID: 34734234.

<https://doi.org/10.1093/ajcn/nqab364>



The EARTH Study Team analysed retrospectively male dietary habits in association with fertility outcomes. They found no significant associations between men's adherence to any of the analyzed dietary patterns and their semen quality, the probabilities of implantation, clinical pregnancy, or live birth.

Salas-Huetos A, Mínguez-Alarcón L, Mitsunami M, Arvizu M, Ford JB, Souter I, Yeste M, Chavarro JE; EARTH Study Team. Paternal adherence to healthy dietary patterns in relation to sperm parameters and outcomes of assisted reproductive technologies. *Fertil Steril* published 15 Dec 2021.

[https://www.fertstert.org/article/S0015-0282\(21\)02155-5/fulltext](https://www.fertstert.org/article/S0015-0282(21)02155-5/fulltext)



This study from Japan investigated hormonal profiles and testis biopsy at orchidopexy in boys with cryptorchidism. The authors found low inhibin B/FSH and AMH/FSH ratios in bilateral cryptorchid boys (≤ 24 months at orchidopexy). These low ratios correlated with decreased numbers of germ cells, which may reflect impaired Sertoli cell function and predict a high risk of future infertility.

Kato T, Mizuno K, Matsumoto D, et al, Hayashi Y. Low Serum Inhibin B/Follicle-Stimulating Hormones and Anti-Müllerian Hormone/Follicle-Stimulating Hormones Ratios as Markers of Decreased Germ Cells in Infants with Bilateral Cryptorchidism. *J Urology*. 2021 Nov 26:101097JU00000000000002344. Epub ahead of print. PMID: 34823367.

doi: 10.1097/JU.00000000000002344.

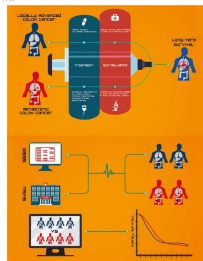
Editorial Comment: Husmann DA. Cryptorchidism: What Are the Risks of Infertility? What Do We Tell the Parents? How Do We Manage the Child? *J Urol* Dec 2021

<https://doi.org/10.1097/JU.00000000000002381>

Volume 10, Number 24

Cancer Medicine

Editor-in-Chief
Gingqi Wei



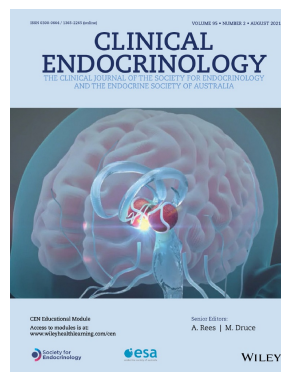
WILEY

Testicular cancer patients are often treated with chemotherapy regimens containing platinum, which can be detected in serum many years after treatment. This Canadian study found that platinum levels were higher in semen than in blood. Semen parameters correlated with time from last cisplatin dosing, with sperm concentration and motility increasing over time. Further study is needed to assess the relationship between platinum persistence in semen and recovery of fertility postchemotherapy.

Malone ER, Lewin J, Li X, Zhang WJ, Lau S, Jarvi K, Hamilton RJ, Hansen AR, Chen EX, Bedard PL. Semen and serum platinum levels in cisplatin-treated survivors of germ cell cancer. *Cancer Med*. 2021 Dec 17. doi: 10.1002/cam4.4480. Epub ahead of print. PMID: 34918879.

<https://onlinelibrary.wiley.com/doi/10.1002/cam4.4480>

Clinical Guidelines

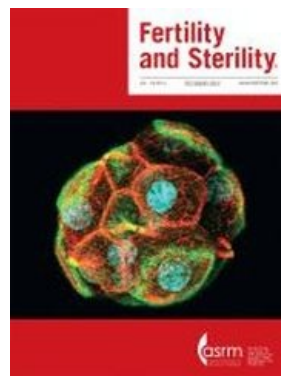


This new guideline on testosterone replacement therapy has been commissioned by the Society for Endocrinology (UK), with several EAA Academicians involved. The new guideline differs from others by multidisciplinary approach and includes expertise from endocrine, primary care, clinical biochemistry, urology, reproductive medicine practices and a patient perspective.

Jayasena C, Anderson RA, Llahana S, Barth J, MacKenzie F, Wilkes S, Smith ND, Sooriakumaran P, Minhas S, Wu FCW, Tomlinson JW, Quinton R. Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism. *Clin Endocrinol* (Oxf). 2021 Nov 22. doi: 10.1111/cen.14633. Epub ahead of print. PMID: 34811785.

<https://onlinelibrary.wiley.com/doi/10.1111/cen.14633>

Debate

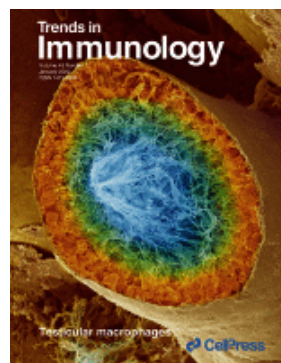


This article is set-up as a pro- and contra- opinion exchange on various aspects of changing trends in semen quality. There are interesting arguments on both sides, so reading the discussion is a thought-stimulating exercise.

Jørgensen N, Lamb DJ, Levine H, Pastuszak AW, Sigalos JT, Swan SH, Eisenberg ML. Are worldwide sperm counts declining? *Fertil Steril*. 2021 Dec;116(6):1457-1463. PMID: 34836581.

[https://www.fertstert.org/article/S0015-0282\(21\)02154-3/fulltext](https://www.fertstert.org/article/S0015-0282(21)02154-3/fulltext)

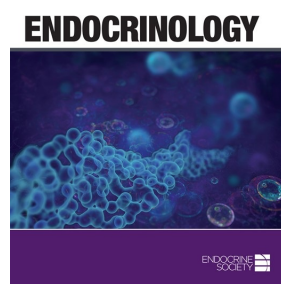
Translational and basic andrology



If you want to learn what is the origin and function of testicular macrophages, under the steady-state and inflammatory conditions – read this excellent review from the world-leading group in Giessen (also an EAA-Training Centre). The review is featured on the cover.

Meinhardt A, Dejucq-Rainsford N, Bhushan S. Testicular macrophages: development and function in health and disease. *Trends Immunol*. 2021 Nov 27:S1471-4906(21)00239-8. PMID: 34848166.

<https://doi.org/10.1016/j.it.2021.11.003>



The human testis can be infected by viruses, which may variably induce orchitis and impair testicular functions. This study examined the effects of viral RNA and DNA sensor signaling pathways on mouse testis. The Zika virus induced high levels of TNF- α and impaired blood-testis barrier and testosterone production, whereas Herpes simplex virus type 2 induced antiviral responses but did not impair the cell functions.

Wang Q, Wang F, Chen R, Liu W, Gao N, An J, Chen Y, Wu H, Han D. Differential Effects of Viral Nucleic Acid Sensor Signaling Pathways on Testicular Sertoli and Leydig Cells. *Endocrinology* 2021 Dec 1; 162(12):bqab180. PMID: 34453520.

doi: 10.1210/endo/bqab180

Androgen deprivation therapy (ADT) is one of the first lines of treatment in prostate cancer. Paradoxically, tumour growth can be inhibited in some patients by supraphysiologic levels of testosterone. This study investigated the mechanisms and showed that supraphysiologic



testosterone induces two parallel autophagy-mediated processes, ferritinophagy and nucleophagy, which then activate immune signaling pathways in prostate cancer.

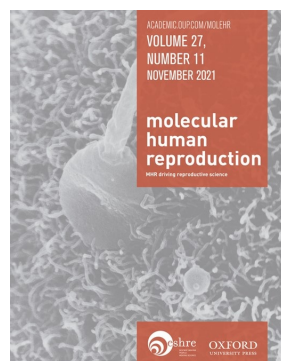
Kumar R, Mendonca J, Owoyemi O, Boyapati K, Thomas N, Kanacharoen S, Coffey M, Topiwala D, Gomes C, Ozbek B, Jones T, Rosen M, Dong L, Wiens S, Brennen WN, Isaacs JT, De Marzo AM, Markowski MC, Antonarakis ES, Qian DZ, Pienta KJ, Pardoll DM, Carducci MA, Denmeade SR, Kachhap SK. Supraphysiological testosterone induces ferroptosis and activates immune pathways through nucleophagy in prostate cancer. *Cancer Research* Dec 2021, doi: 10.1158/0008-5472.CAN-20-3607. <https://cancerres.aacrjournals.org/content/81/23/5948.long>



Melanoma occurs more frequently and has worse prognosis in males compared with females. This study showed that testosterone promotes melanoma by activating a zinc transporter ZIP9 (SLC39A9), which can be blocked by androgen receptor inhibitors that are currently approved only for prostate cancer.

Aguirre-Portolés C, Payne R, Trautz A, Foskett JK, Natale CA, Seykora JT, Ridky TW. ZIP9 is a Druggable Determinant of Sex Differences in Melanoma. *Cancer Research* 2021 December, doi: 10.1158/0008-5472.CAN-21-0982.

<https://cancerres.aacrjournals.org/content/81/23/5991>.



This study showed that the human zygote inherits from the sperm a basal body enriched with centrosomal proteins, establishing the first functional centrosome of the new organism. This centrosome contributes to the robustness of the early cell divisions, ensuring the early steps of embryogenesis and successful compaction.

Amargant F, Pujol A, Ferrer-Vaquer A, Durban M, Martínez M, Vassena R, Vernos I. The human sperm basal body is a complex centrosome important for embryo preimplantation development, *Molecular Human Reproduction* 2021; 27(11), gaab062

<https://doi.org/10.1093/molehr/gaab062>



This study examined metabolic pathways that regulate sperm capacitation. The authors found that human sperm can remain motile for several hours under starvation due to mitochondrial use of endogenous metabolites but hyperactivation is inhibited. Full motility and capacitation can be reversed by adding nutrients, suggesting that this treatment might be used to modulate human sperm fertilizing ability in vitro.

Marín-Briggiler CI, Luque GM, Gervasi MG, Oscoz-Susino N, Sierra JM, Mondillo C, Salicioni AM, Krapf D, Visconti PE, Buffone MG. Human Sperm Remain Motile After a Temporary Energy Restriction but do Not Undergo Capacitation-Related Events. *Frontiers Cell Dev Biol.* 2021 Nov 12;9:777086. doi: 10.3389/fcell.2021.777086. PMID: 34869380; PMCID: PMC8633110.

<https://www.frontiersin.org/articles/10.3389/fcell.2021.777086/full>

Vitamin D is also a player in reproductive function. This study examined in testis and epididymis (mice and human) the spatial expression of several vitamin D receptor (VDR)-regulated factors involved in calcium transport. In humans, calcium concentration in semen was associated with sperm motility and morphology.

Boisen IM, Nielsen JE, Verlinden L, Lorenzen M, Holt R,



Pinborg A, Andreassen CH, Juul A, Lanske B, Carmeliet G, Blomberg Jensen M. Calcium transport in male reproduction is possibly influenced by vitamin D and CaSR. *J Endocrinol*. 2021 Nov 5;251(3):207-222. doi: 10.1530/JOE-20-0321. PMID: 34612843. <https://joe.bioscientifica.com/view/journals/joe/251/3/JOE-20-0321.xml>

Androgenetics



Two articles from China reported novel mutations in *ARMC2* and *CCDC39*, associated with morphological abnormalities in the human sperm flagella and infertility.

Khan I, Dil S, Zhang H, et al et Ma H, Shi Q. A novel stop-gain mutation in *ARMC2* is associated with multiple morphological abnormalities of the sperm flagella. *Reprod Biomed Online*. 2021 Nov;43(5):913-919. PMID: 34493464. [https://www.rbmojournal.com/article/S1472-6483\(21\)00364-3/fulltext](https://www.rbmojournal.com/article/S1472-6483(21)00364-3/fulltext)

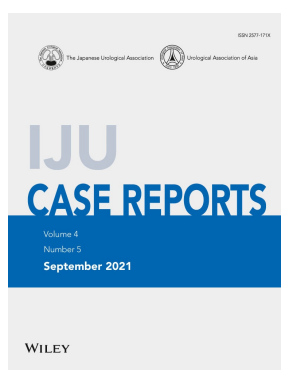
Chen D, Liang Y, Li J, Zhang X, Zheng R, Wang X, Zhang H, Shen Y. A novel *CCDC39* mutation causes multiple morphological abnormalities of the flagella in a primary ciliary dyskinesia patient. *Reprod Biomed Online*. 2021 Nov;43(5):920-930. PMID: 34674941. [https://www.rbmojournal.com/article/S1472-6483\(21\)00345-X/fulltext](https://www.rbmojournal.com/article/S1472-6483(21)00345-X/fulltext)



This study performed a detailed characterization of the gene that encodes long intergenic non-protein-coding RNA 01016 (*LINC01016*, also known as *LncRNA1195*), which is conserved among nonhuman primates and highly expressed in the testis. Human *LINC01016* is a multiexon gene, processed through differential exon usage with differentially expressed isoforms in cervical, testicular, and uterine normal tissues and cancers.

Ramos EI, Yang B, Vasquez YM, Lin KY, Choudhari R, Gadad SS. Characterization of the Testis-specific *LINC01016* Gene Reveals Isoform-specific Roles in Controlling Biological Processes. *J Endocr Soc (JES)*. 2021 Sep 27;5(11):bvab153. PMID: 34703959. <https://doi.org/10.1210/jendso/bvab153>

Case report of the month



A reminder that histology of the tissue taken during micro-TESE should be carefully evaluated. This report described a 35-year-old man orchiectomised because of a seminoma in his right testis, followed by a relapse in the left inguinal lymph node, requiring chemotherapy. He had a history of micro-TESE undertaken 6 years earlier, and a pathology analysis of the stored sample identified germ cell neoplasia in situ in the right testis.

Shimizu, N, Naiki, T, Kobayashi, D, et al. Testicular seminoma arising from infertile testes 6 years after microdissection testicular sperm extraction. *IJU Case Rep*. 2021 <https://doi.org/10.1002/iju5.12391>

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