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EAA Literature Alert
Edition July 2021

A summer selection of newly published articles in the field of andrology and reproductive biology. As before, we especially highlight the work performed in EAA-certified centres. You are welcome to share this list with your students and colleagues. Your feedback and information about good upcoming publications is highly appreciated.

Clinical andrology and epidemiology



Published just before the launch of the 6th Edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen, this multi-centre study critically re-evaluated the reference values from the previous edition. Based on data from more than 3500 subjects from 12 countries, the lower (5th centile) values were similar to the 2010 references: sperm concentration 16 × 106/ml, 30% progressive motility [42% total motility] and 4% normal morphological forms.

Campbell MJ, Lotti F, Baldi E, Schlatt S, Festin MPR, Björndahl L, Toskin I, Barratt CLR. Distribution of semen examination results 2020 - A follow up of data collated for the WHO semen analysis manual 2010. ***Andrology*** 2021; 9(3):817-822. doi: 10.1111/andr.12983. PMID: 33528873.

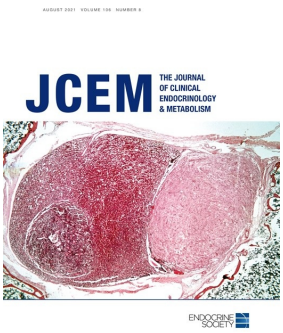
https://onlinelibrary.wiley.com/doi/10.1111/andr.12983



Another re-examination of sperm quality values – this study looked at the thresholds below which the time-to-conception is prolonged in almost 10,000 couples having problems conceiving. In couples evaluated for male infertility, total progressive sperm count (TPMC) of 50 million best differentiated men who were more likely to father a child within 5 years. Higher values of sperm count, concentration and progressive motility beyond the WHO references were still associated with better conception rates and time-to-conception.

Keihani S, Verrilli LE, Zhang C, Presson AP, Hanson HA, Pastuszak AW, Johnstone EB, Hotaling JM. Semen parameter thresholds and time-to-conception in subfertile couples: how high is high enough? ***Human Reproduction*** 2021; 36(8):2121-2133. doi: 10.1093/humrep/deab133. PMID: 34097024.

https://academic.oup.com/humrep/article-abstract/36/8/2121/6294420?redirectedFrom=fulltext



This American study evaluated the skeletal response to testosterone therapy in hypogonadal men with or without type-2 diabetes (T2D). Testosterone therapy resulted in greater improvements in the skeletal health of hypogonadal men with T2D than their nondiabetic counterparts.

Colleluori G, Aguirre L, Napoli N, Qualls C, Villareal DT, Armamento-Villareal R. Testosterone Therapy Effects on Bone Mass and Turnover in Hypogonadal Men with Type 2 Diabetes. ***J Clin Endocrinol Metab***. 2021 Jul 13;106(8):e3058-e3068. doi: 10.1210/clinem/dgab181. PMID: 33735389.

https://academic.oup.com/jcem/article-abstract/106/8/e3058/6178348?redirectedFrom=fulltext



This Swedish register-based study found that men born small for gestational age (SGA) or with low birth weight (LBW) have a lower chance of becoming fathers than men born with normal birth characteristics, especially in an older cohort, with up to 44 years of follow-up.

Liffner S, Bladh M, Nedstrand E, Hammar M, Martinez HR, Sydsjö G. Men born small for gestational age or with low birth weight do not improve their rate of reproduction over time: a Swedish population-based study. ***Fertility & Sterility*** 2021; S0015-0282(21)00431-3. doi: 10.1016/j.fertnstert.2021.05.078. PMID: 34187702.

https://www.fertstert.org/article/S0015-0282(21)00431-3/fulltext



This randomized double-blind study from Copenhagen examined anogenital distance (AGD) in testicular cancer survivors with a mild Leydig cell insufficiency, who were treated with testosterone or placebo for 52 weeks. Men from the general population were included as controls. A shorter AGD was found in TC survivors compared to controls, and it did not change upon testosterone therapy, supporting the hypothesis that reduced AGD is part of the testicular dysgenesis syndrome and may be a marker of disrupted foetal testicular development.

Priskorn L, Kreiberg M, Bandak M, Lauritsen J, Daugaard G, Petersen JH, Aksglaede L, Juul A, Jørgensen N. Testicular cancer survivors have shorter anogenital distance that is not increased by 1 year of testosterone replacement therapy. ***Human Reproduction*** 2021 Jul 5:deab162. doi: 10.1093/humrep/deab162. Epub ahead of print. PMID: 34223605.

https://doi.org/10.1093/humrep/deab162



A Danish register-based study evaluated paternity in 4,846 testicular cancer (TC) survivors after currently used treatment modalities (surveillance; BEP chemotherapy; BEP + retroperitoneal surgery; abdominal radiotherapy). The 20 years predicted chance of fatherhood for a 30-year-old man was 39.7% in TC patients compared to 42.5 % in the normal population. The chance of fatherhood was decreased after BEP and BEP + surgery, but not after radiotherapy or surveillance. The risk of needing ART to obtain fatherhood was increased after all treatment modalities.

Bandak M, Jensen A, Dehlendorff C, Lauritsen J, Kreiberg M, Wagner T, Rosenvilde J, Daugaard G. Paternity After Treatment for Testicular Germ Cell Cancer: A Danish Nationwide Population-Based Cohort Study. ***J Natl Cancer Inst.*** 2021 Jun 28:djab130. doi: 10.1093/jnci/djab130. Epub ahead of print. PMID: 34180995.

https://doi.org/10.1093/jnci/djab130

Useful information for the colleagues performing intrauterine insemination (IUI): The IUI outcome was not affected by the time interval between the end of sperm preparation in the lab, and its injection into the uterine cavity. Extended waiting up to 3 hours for insemination did not have any detrimental effect, regardless if partner or donor sperm was used.

Stein A, Altman E, Rotlevi M, Doitsh A, Ben-Haroush A, Wertheimer A, Eizenhamer Y, Schohat T, Shufaro Y. Does the



time interval from the end of sperm processing to intrauterine insemination (lab-to-uterus time) affect treatment outcome? ***Andrology***. 2021 Jul 10. doi: 10.1111/andr.13079. PMID: 34245222.

https://onlinelibrary.wiley.com/doi/abs/10.1111/andr.13079



This study attempted to determine whether the histological seminiferous tubules pattern could predict the sperm retrieval rate in patients with non-obstructive azoospermia undergoing salvage microdissection testicular sperm extraction after failed conventional testicular sperm extraction. The authors confirmed that testis histology is a reliable predictor, except the early maturation arrest.

Caroppo E, Castiglioni F, Campagna C, Colpi EM, Piatti E, Gazzano G, Colpi GM. Intrasurgical parameters associated with successful sperm retrieval in patients with non-obstructive azoospermia undergoing salvage microdissection testicular sperm extraction. ***Andrology***. 2021 Jul 21. doi: 10.1111/andr.13082. PMID: 34289247.

https://onlinelibrary.wiley.com/doi/10.1111/andr.13082

COVID-19



One should check testosterone in all men treated for COVID-19. This study found an independent association between SARS-CoV-2 infection status and secondary hypogonadism already at hospital admission, with lower testosterone levels predicting the most severe clinical outcomes.

Salonia A, Pontillo M, Capogrosso P, Gregori S, Tassara M, Boeri L, Carenzi C, Abbate C, Cignoli D, Ferrara AM, Cazzaniga W, Rowe I, Ramirez GA, Tresoldi C, Mushtaq J, Locatelli M, Santoleri L, Castagna A, Zangrillo A, De Cobelli F, Tresoldi M, Landoni G, Rovere-Querini P, Ciceri F, Montorsi F. Severely low testosterone in males with COVID-19: A case-control study. ***Andrology*** 2021 Jul;9(4):1043-1052. doi: 10.1111/andr.12993. PMID: 33635589.

https://onlinelibrary.wiley.com/doi/10.1111/andr.12993



COVID-19 can seriously damage the testicles. This study revealed that patients who died of COVID-19 had a combination of orchitis, vascular changes, basal membrane thickening, Leydig and Sertoli cell scarcity, and reduced spermatogenesis, which can be expected in all severely affected men.

Duarte-Neto AN, Teixeira TA, Caldini EG, Kanamura CT, Gomes-Gouvêa MS, Dos Santos ABG, Monteiro RAA, Pinho JRR, Mauad T, da Silva LFF, Saldiva PHN, Dolhnikoff M, Leite KRM, Hallak J. Testicular pathology in fatal COVID-19: A descriptive autopsy study. ***Andrology*** 2021 Jul 1. doi: 10.1111/andr.13073. PMID: 34196475.

https://onlinelibrary.wiley.com/doi/10.1111/andr.13073

Androgenetics



A new, important publication from the International Testis Cancer Consortium (TECAC), with the participation of several EAA Academicians. In total, 10,156 testicular germ cell tumor (TGCT) cases and 179,683 controls were examined in the largest genome-wide association study of TGCT. This meta-analysis identified 22 novel markers,

raising disease heritability to 44%. Men with a polygenic risk score in the 95th percentile have nearly a 7-fold increased risk of TGCT compared to men with median scores. Novel findings emphasize the interconnected nature of two known pathways that promote TGCT susceptibility: male germ cell development within its somatic niche and regulation of chromosomal division and structure.

Pluta J, Pyle LC, Nead KT, Wilf R, Li M, Mitra N, Weathers B, D'Andrea K, Almstrup K, Anson-Cartwright L, Benitez J, Brown CD, Chanock S, Chen C, Cortessis VK, Ferlin A, Foresta C, Gamulin M, Gietema JA, Grasso C, Greene MH, Grotmol T, Hamilton RJ, Haugen TB, Hauser R, Hildebrandt MAT, Johnson ME, Karlsson R, Kiemeney LA, Lessel D, Lothe RA, Loud JT, Loveday C, Martin-Gimeno P, Meijer C, Nsengimana J, Quinn DI, Rafnar T, Ramdas S, Richiardi L, Skotheim RI, Stefansson K, Turnbull C, Vaughn DJ, Wiklund F, Wu X, Yang D, Zheng T, Wells AD, Grant SFA, Rajpert-De Meyts E, Schwartz SM, Bishop DT, McGlynn KA, Kanetsky PA, Nathanson KL; Testicular Cancer Consortium. Identification of 22 susceptibility loci associated with testicular germ cell tumors. ***Nature Communications*** 2021 Jul 23;12(1):4487. doi: 10.1038/s41467-021-24334-y. PMID: 34301922.

https://onlinelibrary.wiley.com/doi/10.1111/andr.13073



The authors conducted whole-exome sequencing in a cohort of 150 Han Chinese men with asthenoteratozoospermia, and identified two novel hemizygous mutations in USP26, an X-linked gene preferentially expressed in the testis and encoding a deubiquitinating enzyme. Men with these *USP26* variants showed a highly aberrant morphology and ultrastructure of the sperm heads and flagella, but could be treated with ICSI.

Liu C, Shen Y, Shen Q, Zhang W, Wang J, Tang S, Wu H, Tian S, Cong J, He X, Jin L, Zhang F, Jiang X, Cao Y. Novel Mutations in X-Linked, USP26-Induced Asthenoteratozoospermia and Male Infertility. ***Cells***. 2021; 10(7):1594. PMID: 34202084

https://www.mdpi.com/2073-4409/10/7/1594

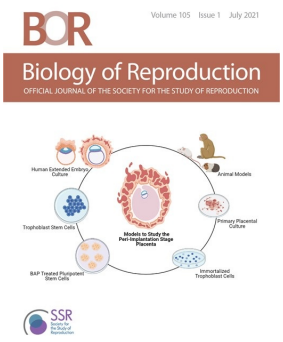
Translational and basic andrology



The authors compared the transcriptomes of fetal (FLC) and adult (ALC) mouse Leydig cell populations and found significant variations in expression profiles, revealing a dual regulation of steroidogenesis. The androstenedione synthesis by FLCs is stimulated by LH, CRH and ACTH, whereas the testosterone synthesis by ALCs is dependent exclusively on LH.

Sararols P, Stévant I, Neirijnck Y, Rebourcet D, Darbey A, Curley MK, Kühne F, Dermitzakis E, Smith LB, Nef S. Specific Transcriptomic Signatures and Dual Regulation of Steroidogenesis Between Fetal and Adult Mouse Leydig Cells. ***Front Cell Dev Biol.*** 2021 Jun 28;9:695546. doi: 10.3389/fcell.2021.695546. PMID: 34262907.

https://doi.org/10.3389/fcell.2021.695546



To provide new information into the mechanism of action of COUP-TFII in Leydig cells, the authors performed microarray analyses of COUP-TFII-depleted MA-10 Leydig cells, identifying 262 differentially expressed genes. Many of the differentially expressed genes are known to be involved in lipid biosynthesis, lipid metabolism, male gonad development, and steroidogenesis, providing new evidence that strengthens an important role of COUP-TFII in steroidogenesis, androgen homeostasis, cellular defense and differentiation in mouse Leydig cells.

Mehanovic S, Mendoza-Villarroel RE, Mattos K, Talbot P, Viger RS, Tremblay JJ. Identification of novel genes and pathways regulated by the orphan nuclear receptor COUP-TFII in mouse MA-10 Leydig cells. ***Biology of Reproduction*** 2021 Jul 5:ioab131. doi: 10.1093/biolre/ioab131. Epub ahead of print. PMID: 34225363.

https://doi.org/10.1093/biolre/ioab131

This study looked at the effects of the androgen receptor blocking by flutamide in the rat testis tissue. An expected increase in steroidogenesis and corresponding intratesticular sex steroid hormone levels was accompanied by elevated

transcription of *Drp1* and *Mfn2* genes and multiplication of Leydig cell mitochondria. The findings highlight the importance of mitochondrial homeostasis in the steroidogenic function of Leydig cells.

Brzoskwinia, M., Pardyak, L., Kaminska, A., Tworzydlo, W., Hejmej, A., Marek, S., Bilinski S.M. & Bilinska, B. Flutamide treatment reveals a relationship between steroidogenic activity of Leydig cells and ultrastructure of their mitochondria. ***Scientific Reports*** 11, 13772 (2021).

https://www.nature.com/articles/s41598-021-93292-8



To investigate cross-talk between germ cell tumour cells and Sertoli cells (SC), the authors (including EAA Academicians) established a coculture model of adult human SCs and a seminoma cell line TCam-2, in which they showed progressive changes of expression profiles in both cell types. They proposed that germ cell neoplasia in situ cells (GCNIS) can induce dedifferentiation of Sertoli cells rather than the alternative idea of GCNIS originating in undifferentiated tubules unable to support maturation of gonocytes.

Fink C, Baal N, Wilhelm J, Sarode P, Weigel R, Schumacher V, Nettersheim D, Schorle H, Schröck C, Bergmann M, Kliesch S, Kressin M, Savai R. On the origin of germ cell neoplasia in situ: Dedifferentiation of human adult Sertoli cells in cross talk with seminoma cells in vitro. ***Neoplasia.*** 2021; 23(7):731-742. doi: 10.1016/j.neo.2021.05.008. PMID: 34153645.

https://www.sciencedirect.com/science/article/pii/S1476558621000336?via%3Dihub

A case report of the month

A 26-year-old patient with complete androgen-insensitivity syndrome (CAIS), who underwent gonadectomy, reported a significant decrease in libido, which was improved with testosterone treatment but not with estradiol. The molecular characterization revealed that this patient carried a previously unidentified mutation in the androgen receptor – p.Glu2_Met190del (c.2T>C). This unique CAIS case raises intriguing questions regarding the relative roles of testosterone and estrogen in libido, and the potential non-genomic actions of androgens.

arino L, Messina A, S Acierno J, Phan-Hug F, J Niederländer N, Santoni F, La Rosa S, Pitteloud N. Testosterone-induced increase in libido in a patient with a loss-of-function mutation in the AR gene. ***Endocrinol Diabetes Metab Case Rep.*** 2021 Jun 1;2021:21-0031. doi: 10.1530/EDM-21-0031. PMID: 34152287.

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