#ESHREjc live edition report: “The forgotten Y” - advanced paternal age from a global health perspective

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This is a pre-copyedited, author-produced version of an article accepted for publication in Human Reproduction following peer review. The version of record Massarotti, C. et al. (2021) '#ESHREjc live edition report: ‘the forgotten Y’–advanced paternal age from a global health perspective', Human Reproduction 37(1), pp. 195-197 is available online at: https://doi.org/10.1093/humrep/deab241.
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Running Title: #ESHREjc live 2021

Keywords: ESHREjc, Journal club, male reproductive health, advanced paternal age
The 2021 live edition of the ESHRE Journal Club (held during the 37th ESHRE annual meeting) revolved around a topic too often side-lined in infertility research and practice: male fertility. Indeed, in some societies, infertility is assumed to be entirely a woman’s fault considering her central role in childbearing. This view carries a social stigma in many countries and can lead to rejection and suboptimal treatments for infertile couples (Thoma et al., 2021).

While it is a consensus that approximately half of infertility cases are related to a male factor (Agarwal et al., 2021), its actual global burden is yet to be defined. Moreover, our knowledge of both causes and treatments of male infertility still has vast gaps and the related funds are scarce (Barratt et al., 2021). Thus, research filling these gaps is much needed, especially if it can be translated into better counselling in clinical practice, preventative actions for the general population and raised awareness through education.

The main theme of the ESHRE 2021 live Journal Club centred around the impact of advanced paternal age (APA) on assisted reproductive technologies (ART) outcomes (Fig. 1). Both, fertility decline and adverse impact of advanced maternal age (AMA) on pregnancy and perinatal health outcomes are well-documented in clinical and basic science settings. As a result of this well-established link between AMA and poor reproductive outcomes, fertility clinics, national health services and legislators have set female age cut-offs for ART treatment (Calhaz-Jorge et al., 2020). While the public is aware of the effect of AMA on fecundity and reproductive outcomes, the clinical significance of APA for perinatal health, its transgenerational effects and impact on ART outcomes remain poorly understood (Bertoncelli Tanaka et al., 2019).
The Journal Club discussion focused on the study by van Opstal and colleagues and set out to shed light on the imperative question regarding the effects of male age on embryo growth and quality in couples undergoing IVF (van Opstal et al., 2021). This prospective longitudinal study conducted at Leuven University Fertility Centre followed 87 IVF couples from pre-pregnancy to live birth, analysing growth and quality parameters of 1057 embryos. The authors concluded that the probability of obtaining an optimal embryo (8-blastomere stage embryo at day 3) was inversely associated with male age, which remained significant after adjusting for female age as well as male and female BMI amongst other confounders. Interestingly, the study cohort presented with idiopathic male infertility (i.e. normal semen parameters) and most male patients were overweight (BMI 26.7). The authors conclude that the findings warrant further research into male age and its impact on embryo growth, embryo quality and ART outcomes, with a specific focus on the role of the sperm epigenome.

To encourage a varied and engaging discussion, the ESHRE live 2021 Journal Club hosted first author Jolien van Opstal, editor-in-chief Prof. Cornelius Lambalk, Dr Ian Askew (Director of the Department of Reproductive Health and Research at WHO), as well as Prof. Christopher Barratt (Head of the Reproductive Medicine Group at the University of Dundee, Scotland, UK; Coordinator of the Global Initiative on Male Reproductive Health) and Dr Sarah Martins Da Silva (Senior lecturer in Reproductive Medicine at the University of Dundee, Scotland, UK) as part of the expert panel. Engaging discussions were aided by challenging questions from the audience, resulting in a variety of comments ranging from detailed analysis of statistical methods to big-picture debates of family-planning and global health. It was highlighted that decades of data on in vivo conception have shown that semen analysis has a strong diagnostic and prognostic value for conception in the lower range of semen concentration (<5 million/ml) (Publicover and Barratt, 2011). The effects of APA on male
fecundity and reproductive outcomes are predominantly studied in relation to male patient baseline diagnostic parameters (such as reproductive hormones, semen quality and DNA integrity). However, the impact of APA on neonatal and long-term health outcomes of offspring conceived either through ART or natural conception are not well investigated. Elucidating the impact of APA is inherently more challenging than that of AMA since changes in sperm production and quality occur gradually, and often variably, without clear cut-offs such as menopause in women. Recent guidelines suggest that there is no clear definition of APA. Indeed, the general lack of well-designed prospective studies examining the impact of APA on ART outcomes was a key focus of the ESHRE 2021 live Journal Club discussion. Some studies suggest a longer time to conception with APA as well as lower IVF success rates and higher miscarriage rates (Kaarouch et al., 2018; Nguyen et al., 2019). There is also evidence of APA affecting the next generation, including congenital abnormalities and chromosomal disorders (Yang et al., 2007; Green et al., 2010) as well as autism and schizophrenia (Shlegel et al., 2021). In addition to these clinical disadvantages, APA has been associated with lower evolutionary fitness (Arslan et al., 2017). Patient counselling should incorporate the effects of APA on sperm quality and quantity, fertility and sexual function, health of offspring and the unclear association with ART success.

ESHRE 2021 live Journal Club participants agreed that progress is being made in the area of male fertility: research such as the discussed paper continue to add to our evidence base. A recent review by Campbell et al. has revisited published semen analysis results since 2010 and reassures that the upcoming 6th edition of the WHO manual for semen analysis (WHO, 2021) includes a larger dataset and is more geographically inclusive (Campbell et al. 2020). This study further shows similar distribution in reference values of semen parameters for the fertile man (Campbell et al., 2021). Nonetheless, more high-quality research data is required to
strategise a robust pipeline for clinical management of male fertility diagnosis and treatment.

This remains a great challenge since funding for male reproductive health is a global issue with only <1% of medical research budget spent on this area (Barratt et al., 2021). Critically, the importance of educating men to protect their reproductive health earlier in life was raised. Indeed, all ESHRE live 2021 Journal Club participants highlighted the need of a stronger focus on male reproductive health in public awareness generation. To be effective, this message should be scientifically sound, understandable, high volume, embedded in formal education programmes, but also shared on all media channels (social media included).

The main take-home message of the ESHRE live 2021 Journal Club was the consequence to this need: there is still much work to do (both inside research laboratories and fertility clinics and in the general society) to guarantee the best possible reproductive outcome to each individual - including those with a Y chromosome. Studies such as the featured work by van Opstal and colleagues, as well as discussions by interdisciplinary experts in a variety of forums, will be critical in this mission.
Data Availability

No datasets were generated or analysed in the current manuscript.

Acknowledgements

The Authors thank Dr Ian Askew, Jolien Van Opstal, the author of the discussed paper, and Prof. Cornelis Lambalk for their invaluable contribution in commenting and contextualising the topic, and all the participants of the ESHRE 2021 live Journal Club. The ESHRE Journal Club editorial team is grateful to ESHRE executive committee and to ESHRE communications for supporting the project.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The members of the #ESHREjc editorial teams organise and moderate the journal club as volunteers and do not receive any compensation.

Conflicts of interest

All authors declare no conflict of interest.
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Figures

**Figure 1.** Overall Discussions’ Summary