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Authors: Ravitsky, Vardit, and Kimmins, Sarah

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Forum

The forgotten men: rising rates of male infertility urgently require new approaches for its prevention, diagnosis and treatment

Vardit Ravitsky¹ and Sarah Kimmins^{2,3,*}

¹Department of Social and Preventive Medicine, School of Public Health, University of Montreal, Quebec, Canada

²Department of Pharmacology and Therapeutics, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

and ³Department of Animal Science, Faculty of Agricultural and Environmental Sciences, McGill University, Montreal, Quebec, Canada

Correspondence: E-mail: Sarah.Kimmins@mcgill.ca

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Over the past 40 years, sperm counts worldwide have halved and sperm quality has declined alarmingly with 1 in 20 men currently facing reduced fertility [1]. Potential causes of this male fertility crisis include exposure to environmental endocrine disrupting chemicals (e.g., plasticizers, bisphenol A, and phthalates), rising rates of obesity, and the trend of delayed parenthood. Overall, infertility is on the rise with 1 in 6 couples wishing to conceive being diagnosed as infertile. The use of assisted reproductive technologies (ART) is therefore increasing at a rate of 5–10% per year, due to greater need.

Just over 40 years ago, the first in vitro fertilization (IVF) baby was born, Louise Brown, and as it was then, women continue to be the focus of infertility research and treatment. Despite half of infertility cases involving male factors, men have been largely neglected in terms of research, diagnosis, and treatment. Diagnostic methods for male infertility are based on outdated semen assessment methods that have remained essentially unchanged for the past 50 years. This is surprising given the advancement of molecular and cellular knowledge around sperm function. The primary intervention currently offered to infertile men is intracytoplasmic sperm injection (ICSI). This procedure is non-invasive for the male partner, since sperm is collected through masturbation. However, in order to perform ICSI, the female partner is subject to numerous invasive procedures including: blood tests, hormone injections, surgical ova retrieval, and embryo transfer. Some of these procedures are painful and carry short- and long-term medical risks, such as ovarian hyperstimulation syndrome, stroke, and multiple gestation. Evidence is also emerging regarding the long-term risks of these procedures such as the increased cancer incidence in women and the consequences of ART for the health of offspring [2]. Women are exposed to these risks even when they are fertile, since ICSI or IVF are the only options for their male partners. They thus carry a disproportionate and unjust physical and psychosocial burden in the treatment of infertility. On the backdrop of this ethically challenging reality, the paucity of attention to male infertility, in terms of research

and clinical alternatives, is so scandalous that some have called it an “infringement of basic human rights and dignity” of female partners [3].

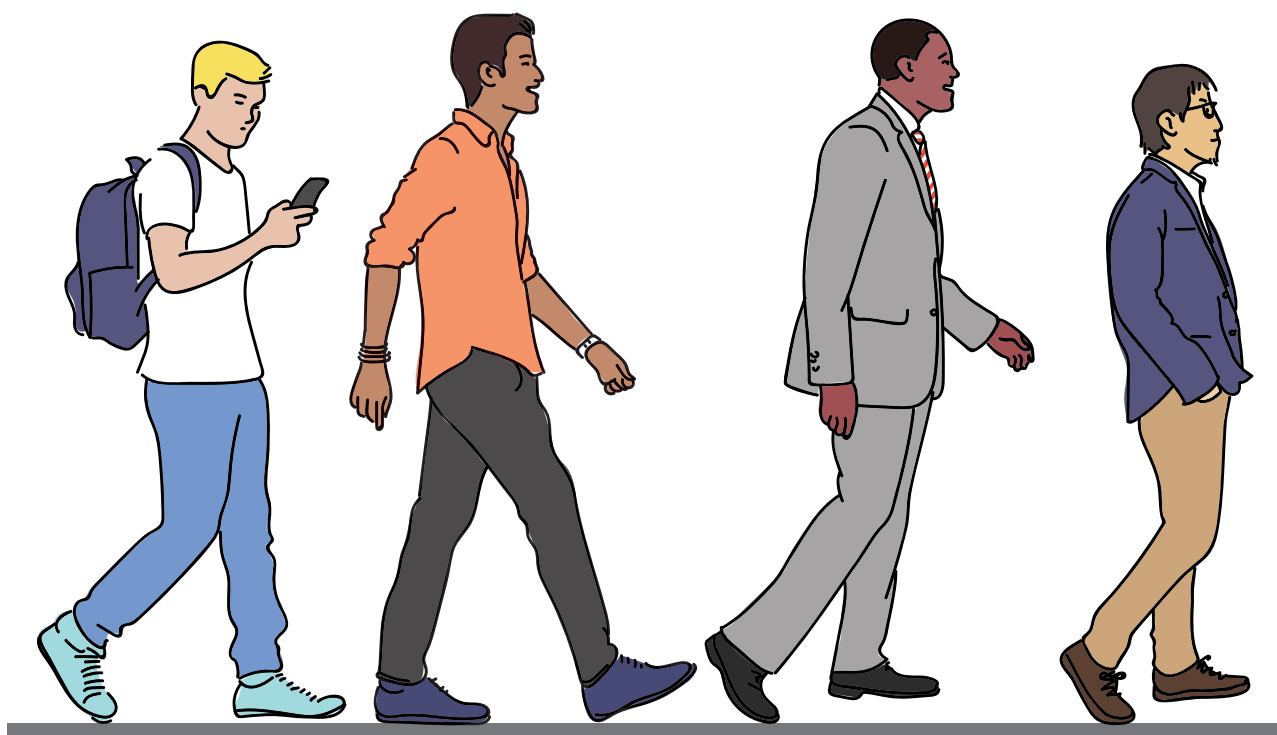
ART is expensive and often not covered by health insurance. Couples undergoing treatments spend upwards of \$30 000 USD and often acquire debt for treatment. About 75% of IVF/ICSI cycles fail, requiring women to go through multiple treatment cycles. Moreover, due to the ongoing and pervasive nature of treatment, women miss numerous days of work and carry a heavy emotional burden when being treated for infertility, with documented elevated rates of stress and depression and even more so in cases of failed treatment.

However, the emotional burden of infertility is not borne by women alone. Men suffer the painful and isolating effects of infertility as well: “*here I am finding out that I am unable to pass on my genetics and the biologist in me says ‘you are worthless, you have no purpose of living’*. I was on the verge of suicide for a while.” [4]. In the past male infertility has been heavily stigmatized. This is gradually changing. Men desire a more inclusive process in the fertility clinic and welcome better methods of preventing, diagnosing, and treating their infertility. But while male fertility is declining, little to no research is being translated into meaningful clinical interventions. To improve the treatment of male infertility, in-depth assays for the assessment of sperm quality are required that link with clinical outcomes. Ideally, the use of such robust and validated tests would not only improve outcomes for couples but would also reduce the unjust burden on women.

Additional research targeting lifestyle factors that can impact fertility are urgently needed. Sperm quality and quantity are directly linked to morbidity and mortality and can be predictive of men’s overall health. Incorporating sperm screens into primary care check-ups is therefore advisable. Sperm tests should be performed at an early age, to inform men about their fertility potential and allow them to adopt lifestyle changes to abrogate a fertility crisis. Much ink has been spilled in recent years regarding “social egg freezing” as a

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1. TEENAGER

General education regarding healthy living should refer to positive impact of good habits on future fertility. In 'sex-ed' classes, boys should receive information on lifestyle factors that can impact their fertility and potentially the health of their future kids.



2. YOUNG ADULT

General practitioners should discuss fertility with young men and offer sperm analysis by an andrology lab to establish baseline fertility.

Key messages:

- Factors that negatively impact health (such as obesity and smoking) also impact fertility
- Men have a 'biological clock' too! Male fertility is reduced later in life
- If you are considering an occupation that involves hazardous exposures (firefighter, farmer, armed forces), consider sperm freezing to preserve your fertility



3. CONSIDERING PARENTHOOD

Time to optimize sperm quality! It takes 3 months to make sperm. If men are considering starting a family, they should be advised to address lifestyle factors that harm fertility and future offspring health (e.g. hot tubs, smoking, recreational drugs, alcohol, BMI) prior to conception. GP should offer sperm analysis by an andrology lab to establish baseline fertility.



4. MIDDLE-AGE

Sperm quality and quantity begin to decline significantly after the age of 40 for all men. For some, this decline can be a marker of poor overall health as well, or an indicator of a medical condition, such as cardiovascular disease

Clinicians should discuss the impact of age on fertility and raise issues such as increased time to conception for men >40, higher miscarriage rates, and increased risk for offspring, such as autism and schizophrenia.



Figure 1. Fertility education and information from boys to men.

means to tackle the female biological clock and level the reproductive playing field [5]. However, robust evidence shows plummeting sperm counts and declining sperm quality in men after the age of 40. In addition, increased DNA damage and mutation rate in older men augment the risk of complex disease in offspring, such as schizophrenia, autism, and childhood cancer. Occupations are also hazardous to fertility in men such as the heavy exposure to flame retardants of firefighters and the health risks associated with service in the armed forces. Men in high-risk to fertility professions are not informed of the hazards of their occupations to their reproductive health until it is too late. It is therefore relevant and timely to consider "social sperm freezing" as well.

Educational tools and public health campaigns are urgently needed, to inform men and their partners about environmental and behavioral risks to their fertility and how lifestyle changes can improve sperm quality. Information about reproductive health and fertility must be responsibly and widely disseminated to boys and men beginning in school sex education programs and throughout their adult lives. This will lead to increased understanding of the crucial role they can play in taking preventive measures, preserving their fertility, and promoting the health of their future children. We have summarized how we envision men's health across the reproductive lifespan incorporating information on fertility (Figure 1).

It is time to promote a culture that puts as much emphasis on male as on female reproductive health. It is time to put the forgotten men center stage in preconception education and in the development of better methods to diagnose and treat infertility.

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