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Published in:
Andrology

DOI:
10.1111/andr.12673

Publication date:
2019

ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

OPINION ARTICLE

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Keywords:
male health, male reproduction, epigenetics, assisted reproduction, policy, funding

Received: 29-Apr-2019
Revised: 30-May-2019
Accepted: 3-Jun-2019

doi: 10.1111/andr.12673

The present crisis in male reproductive health: an urgent need for a political, social, and research roadmap

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ABSTRACT

Background: There is a global crisis in male reproductive health. Evidence comes from globally declining sperm counts and increasing male reproductive system abnormalities, such as cryptorchidism, germ cell tumors, and onset of puberty. Male factor infertility occurs in ~40% of couples experiencing infertility. Data demonstrate an association between male infertility and overall health. Associated significant health conditions include diabetes mellitus, metabolic disorders, and cardiovascular disease. Adding to the complexity is that men typically do not seek health care unless there is acute medical need or, as in the case of the infertile couple, the male goes for a reproductive examination and semen analysis. However, 25% of the time a reproductive health examination does not occur. Couples are increasingly utilizing IVF at more advanced ages, and advanced paternal age is associated with increased risk for (i) adverse perinatal outcomes for both offspring and mother; (ii) early child mortality, cancer, and mental health issues. In addition to age, paternal lifestyle factors, such as obesity and smoking, impact not only the male fertility but also the offspring wellness.

Objectives: The purpose of this paper was (i) to spotlight emerging and concerning data on male reproductive health, the relationship(s) between male reproductive and somatic health, and the heritable conditions father can pass to offspring, and (ii) to present a strategic roadmap with the goals of increasing (a) the awareness of men and society on the aforementioned, (b) the participation of men in healthcare seeking, and (c) advocacy to invigorate policy and funding agencies to support increased research into male reproductive biology.

Conclusions: The Male Reproductive Health Initiative (MRHI) is a newly established and rapidly growing global consortium of key opinion leaders in research, medicine, funding and policy agencies, and patient support groups that are moving forward the significant task of accomplishing the goals of the strategic roadmap.

INTRODUCTION

Men's health is globally in crisis and worsening due, in part, to limited healthcare policies, ebbing research funding, and underdeveloped societal awareness and education. Global health care initiatives by the World Health Organization (WHO) and the United Nations (UN) serve as meaningful and representative examples for how policy enactment can act as a catalyst for globally increased social awareness and education to support healthier lives. For example, the WHO announced (September 2018) that over USD$35 billion in financial commitments were made to the "Every Woman Every Child Global Strategy for Women's, Children's and Adolescent's Health" (2016–2030) program. This substantial financial resource has supported a highly successful educational outreach program through which 377 million women, children, and adolescents were reached. The UN's 2030 Sustainable Development Goals (SDG) program is showing steady progress toward achieving SDG 3 on health and well-being by, for example, demonstrating global improvement in nutrition, reducing mortality, and ensuring reproductive health and rights for women and children. The success of these programs helps to reinforce what can also be accomplished for men's health. These initiatives also help to shed light on the presence of a gender gap in healthcare policies and, thus, a need for more gender-inclusive healthcare strategies (Hawkes & Buse, 2013; Rovito *et al.*, 2017). A recent publication (Baker, 2019) provides a comprehensive report on the global state of men's health, and

some factors that contribute to and that are needed to be overcome in order for men's health to improve.

The field of reproductive biology, while a component of, for example, the WHO and UN initiatives, has received less attention in policy, funding, and societal awareness and education than other areas of the health sciences, for example, cancer and cardiovascular disease. In spite of these limitations, researchers have made remarkable progress in gaining a better understanding of female reproduction, diagnosing associated disease states, and developing effective therapies. This paper will specifically focus on the critical state of men's reproductive health and how it is intimately connected with their overall health, how men's reproductive health can impact their female partner and future generations, and it concludes with some current initiatives and recommendations for advancement.

WHY IS MEN'S HEALTH IMPORTANT?

Globally, men on average have a shorter life expectancy as compared to women (69.1 vs. 73.8 years, respectively)—"males across the globe live sicker and die younger than females" (Rovito *et al.*, 2017). Contributing factors include reluctance of men to seek healthcare advice and treatment and, in general, unhealthy lifestyle factors. These are readily correctable factors that could help to erase the live sicker die younger label. The disparity in life expectancy between male and female has tremendous impact not only on the family but also on the economy. In the United States, many hundreds of billions of dollars are spent by federal, non-federal, and employer-supported health plans to support male chronic disease (Brott *et al.*, 2011). Effecting change in male attitude from reluctance to active and regular participation in healthcare seeking would likely result in lower morbidity and mortality and, as a consequence, a very substantial monetary savings to national and global economies. Leone *et al* (2017) conclude "it is in the US economy's best interest, in addition to being the morally correct position, to invest in understanding how to augment men's health through access, participation, and prevention, with access being the linchpin to action."

Economics is not the only benefit to come from men more actively seeking health care. For couples experiencing infertility, the male factors into 40% of the cause of infertility yet very often he lacks a current health and lifestyle profile much less a reproductive health profile. Absence of early diagnosis and treatment for a reproductive health issue or comorbidity can result not only in greater healthcare cost but, importantly, often place the burden of infertility treatment solely upon the woman. Thus, men's health extends beyond just the individual; men's health is very much a women's health issue and a baby-born health concern as well.

WHAT ARE SOME FACTORS THAT INFLUENCE MALE PARTICIPATION IN HEALTH CARE?

Men characteristically fall second to women in seeking health care. Male participation in health care is predominantly influenced by the presence or absence of illness or injury, social norms, and feelings of vulnerability to one's masculinity (Mahalik *et al.*, 2007; Mahalik & Backus Dagirmanjian, 2018). For example, in the event of illness or workplace injury, a man may adopt a "tough it out" attitude in an effort to retain and maintain one's sense of masculinity (Mahalik & Backus Dagirmanjian, 2018). If a man feels that a physical examination might reveal known or hidden illness, he may be reluctant to go because he identifies that as a sign of weakness and contrary to his sense of masculinity. Following along the same hegemonic masculine ideals, a man may feel his masculinity threatened if there is question regarding his fertility.

Social norms can play a positive role in help-seeking if, for example, a partner or family member suggests that the man has a routine physical examination and he sees other men doing the same (Mahalik *et al.*, 2007). This scenario may exist as it relates to a couple's pursuit of a remedy to childlessness through assisted reproduction. The female partner is often said to be the instigator and motivator for the male seeking help to investigate his fertility potential. However, while the examination serves a purpose for fertility evaluation, other pre-existing medical issues may simultaneously be diagnosed for which the man was unaware because of his "caveman" attitude regarding participation in health care. Reassuring, however, is a study by Farrimond (2011), in which middle-class professional men were interviewed for their thoughts and feelings on health, illness, and help-seeking. The results were surprising in that any anticipation of a threat to masculinity as being a deterrent to help-seeking was not revealed. In contrast, the men reflected a "take action" attitude regarding health and healthy lifestyle. Thus, perhaps there is a change emerging regarding male self-awareness that will be promotive of repealing the historic "caveman" attitude of men toward help-seeking. If there is such an evolution, then it is deserving of affirmation and support because there is a global crisis in male reproductive health that demands urgent attention.

THE PRESENT GLOBAL CRISIS IN MALE REPRODUCTIVE HEALTH

A portent of potentially significant male reproductive health issues is the global decline in sperm count being reported in a growing number of scientific reports (Carlsen *et al.*, 1992; Levine *et al.*, 2017). While the studies are retrospective, the consistency in findings between them provides strong indication that sperm counts are changing and trending negatively. These exemplar reports serve as foundation for designing prospective, longitudinal studies to investigate possible cause(s) of the historical decline and to forecast what might be anticipated for the future. In parallel with sperm count, decline is an equally unsettling and persisting upward trend in male reproductive system abnormalities, such as cryptorchidism, germ cell tumors, and onset of puberty (Skakkebaek *et al.*, 2016). Although these conditions are likely to have complex relationships and the causes are far from clear, it is alarming that the data are consistently negative and effectively point in the same direction. It is simply not tenable to ignore these data. If the negative trend in sperm counts and male reproductive system problems has validity, then what might that mean for male fertility as a whole and are there other areas of concern regarding male reproductive health (Skakkebaek *et al.*, 2019)?

Teenage and young adult men are typically perceived as having limited reproductive health care needs that require medical attention. Often it is not until they have grown older, entered into a relationship in which a baby is wanted and are unsuccessful that they seek help to find the cause for the infertility (Sonfield, 2002). Alarmingly, accumulating data have

considerably strengthened an association between male subfertility and somatic health (Jensen *et al.*, 2009; Eisenberg *et al.*, 2015; Eisenberg *et al.*, 2016; Hanson *et al.*, 2017). For example, Latif et al. (2017) examined 4712 men and evidence revealed that impaired semen quality was significantly associated with long-term morbidity. In a subsequent analysis (Latif *et al.*, 2018), they critically showed that this was largely independent of socioeconomic status and lifestyle factors. A related and pertinent conclusion made by Choy & Eisenberg (2018) is "semen quality and male infertility may be fundamental biomarkers of overall health and could serve as harbingers for the development of comorbidity and mortality." Convincingly, a recent systematic literature review (Capogrosso *et al.*, 2018) demonstrated substantial evidence of an association between male infertility and overall health. Associated significant health conditions include testicular cancer, urogenital malignancies, diabetes mellitus, metabolic disorders, and cardiovascular disease. The authors urge that "Physicians should comprehensively assess men presenting for couple infertility" given "their higher risk for developing cancer." Male infertility due to, for example, illness or environmental factors, is emerging as a potential key marker of systemic resilience or lack thereof and, as such, its etiology is an essential component to integrate into the complex, multifactorial paradigm of preventive health care (Scheffer *et al.*, 2018).

THE AGING MALE AND OFFSPRING WELLNESS

With assisted reproductive technologies serving as a fertility safety net, there is an increased trend of couples delaying family-building until later in life. For example, in the United States during the decade from 2003 to 2013 childbirth increased in women aged 35–39, 40–44, and 45–49 by 12%, 19%, and 60%, respectively. During that same time, births to women 30–34 years remained unchanged. For men, during the same time period, paternity in ages 35–39, 40–44, 45–49, and 50–54 increased by 9%, 14%, 16%, and 8%, respectively. These data appear to be consistent with global trends (Cedars, 2015). Ample data are available regarding maternal age-related decline in fertility, associated comorbidities, complications with pregnancy, and risks to the neonate. In contrast, details are only beginning to emerge regarding paternal age-related decline in fertility, profound consequences for male reproductive health, and associated health risks (Simard *et al.*, 2019). In fact, new research papers on the topic are suggestive of a "tip of the iceberg" scenario with the larger unseen contribution of the paternal iceberg looming ominously.

A systematic review and meta-analysis (Johnson *et al.*, 2015) demonstrated an age-associated decrease in traditional semen parameters and, in addition, an increase in sperm DNA fragmentation. For the latter, high levels of DNA fragmentation are associated with reduced fertility and live birthrates. Khandwala et al. (2017) showed that mean paternal age has increased in the United States over the past 44 years from 27.4 to 30.9. These same investigators (2018), in a follow-up study, reviewed health records of over 40 million documented live births in the United States from 2006 to 2016 to evaluate primary perinatal outcome measures data, for example, gestational age, birthweight, and post-partum complications. Maternal perinatal outcomes were also evaluated for gestational diabetes and preeclampsia. The results surprisingly revealed an association between advanced paternal age (45 years and older) at conception with an increased risk of adverse perinatal outcome measures of premature birth, low birthweight, and Apgar scores. Further, the odds of maternal gestational diabetes were over 30% higher in the mothers with the oldest male partner. Collectively, these concerning health outcomes demand large-scale investigations to identify the nature of the age-related decline in semen parameters and, more importantly, how spermatozoa from advanced paternal age fathers contribute to increased risk of adverse perinatal outcomes for both offspring and mothers. It merits emphasis that these paternally driven adverse perinatal outcomes have significant health and financial cost to both the family and the society. As Khandwala and colleagues conclude (2018), in the United States "The cumulative risk over hundreds of thousands of births to older fathers is also likely to be important in terms of both economic burden and overall public health." Extended globally, the influence of the aging father at conception on the many millions of affected neonates and mothers will have a significant public health impact and cause substantial economic strain, and comprehensive data for both categories are urgently needed.

In addition to adverse perinatal outcomes associated with increased paternal age at conception, there is also accumulating evidence for health risk to the adolescent. Urhoj *et al* (2014) evaluated Danish registry birth and death data from 1978 to 2009 to address the question of whether advanced paternal age has an influence on offspring mortality. The results of their investigation showed an increased risk for <5-year-old child mortality when the paternal age was >40 years. The cause of increased death, for example, congenital malformations and malignancies, while not significantly linked to advanced paternal age could have been caused by point mutations due to advanced paternal age. Thus, this plausible cause–effect mortality outcome merits much greater investigation. The same research team investigated the effect of paternal age at conception on offspring childhood cancer (Urhoj *et al.*, 2017). The Danish registry was evaluated for children born between 1978 and 2010 for specific childhood cancers. Their results revealed that advanced paternal age (>45 years) was associated with greater risk of <15-year-old children developing acute lymphoblastic leukemia. No other types of cancers were significantly associated with advanced paternal age.

Oldereid et al. (2018) published results from a recent systematic review and meta-analysis investigating paternal age on neonatal and pediatric outcomes. Overall, they concluded that paternal age-associated increases in offspring serious adverse outcomes were modest. However, after evaluating three previous meta-analyses and 19 original investigations they found, based on moderate certainty of evidence, that advanced paternal age, for example, >40 years, is "probably associated" with both autism/ASD and schizophrenia. The reason for this association is not specifically known but causative or contributing factors are thought to be genomic, non-genomic (epigenetic), and environmental.

The age-related, time of conception influence of the paternal gamete on offspring bears closer investigation. First, a child will have de novo point mutations not found in either parent. More than 80% of these de novo mutations are paternal in origin (see, de Ligt *et al.*, 2013). In contrast, maternal de novo single nucleotide mutations are transmitted to offspring at a much lower frequency. The differences between male and female

gametogenesis that contribute to de novo mutations become distinctly divergent with increasing parental age (Goldmann *et al.*, 2016). As father age-at-conception (20–40 years age) increases so de novo single nucleotide mutations in the DNA carried by his spermatozoa and they are passed to his offspring at a rate of ~4% per year (Kong *et al.*, 2012). Critically, as father age-at-conception increases so then does the risk of a deleterious mutation being inherited by offspring that could lead to ASD and schizophrenia.

Arslan et al. (2017) hypothesized, based on evolutionary genetic history, that children born to older fathers would have decreased survival and be less likely to have offspring. To investigate their hypothesis, the authors evaluated three pre-industrial western populations and found evidence for a paternal age effect on both decreased offspring survival and decreased ability of surviving offspring to reproduce, that is, reduced reproductive fitness. They concluded that paternally driven de novo single nucleotide mutations "reduce offspring fitness across populations and time periods." In fact, the paternal age-associated reduction in offspring reproductive fitness might be a critical contributing factor to the globally declining sperm count that has been trending over the past several decades. One parameter unable to be investigated is the potential contribution of epigenetic mutations to offspring outcomes. However, in that regard, evidence is accumulating for paternally driven, transgenerational genomic imprinting and epigenetic alterations in offspring.

BEYOND THE MALE GENOME

The sperm epigenome is uniquely complex (Immler, 2018) and susceptible to environmentally associated modification (Schagdarsurengin & Steger, 2016) in part because there are various points in the development that the epigenome is susceptible to modification, that is, paternal embryonic development, spermatogenesis, and offspring early embryonic development (Gold *et al.*, 2018). At each time point, the internal and external environments appear to have a major influence on how the epigenome is modified (Soubry *et al.*, 2014). For example, sperm DNA methylation patterns have recently been shown to predict paternal age with a high degree of accuracy (Jenkins *et al.*, 2018). Preliminary data suggest that environmental factors, such as smoking, may alter DNA methylation patterns to an age beyond actual chronologic age. As the database grows using this unique sperm DNA methylation model (Jenkins *et al.*, 2018), it will be important to learn how lifestyle, that is, environmental factors, may artificially age a man's spermatozoa and, in consequence, how it may impact the gestating fetus, neonate, and child.

Paternal age, smoking, obesity, and other life factors such as pollution have been implicated as influencing the development and wellness of offspring (Soubry *et al.*, 2014). The worldwide incidence of obesity has increased almost threefold since 1975 (WHO, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Data show that obesity can cause or exacerbate male infertility (Campbell *et al.*, 2015; Craig *et al.*, 2017) and the epigenetic signatures of obese men are markedly different than lean men (Donkin *et al.*, 2016). Alarming is that paternal obesity is associated with (i) increased body fat in prepubertal offspring (Figueroa-Colon *et al.*, 2000), (ii) increased risk of offspring developing autism spectrum disorder (Murphy, 2014; Suren *et al.*, 2014), and on a molecular level, (iii) influences the methylation pattern of specific loci of imprinting genes in offspring (Soubry *et al.*, 2013; Soubry *et al.*, 2015). Lastly, preliminary data suggest that the epigenetic profile of morbidly obese men is dramatically altered following bariatric surgery and in regions of the central nervous system attributed with control of appetite (Donkin *et al.*, 2016). To date, there are no published data on wellness and development of offspring resulting from fathers who underwent bariatric surgery.

Cigarette smoking is recognized as a modifiable global health issue that contributes to chronic illness and premature death in half of those that smoke (WHO, https://www.who.int/en/news-room/fact-sheets/detail/tobacco). Smoking is also considered as a male fertility risk factor. A recent paper reported data after a comprehensive literature review on paternal smoking and impact on offspring (Beal *et al.*, 2017). In slightly more than half of studies reviewed, no significant impairment in traditional semen parameters was detected due to smoking. In contrast, the remainder of studies (~40%) found evidence of modest impairment in one or more semen parameters and especially as the number of per day cigarettes smoked increased. Other studies showed that for couples in which the male smokes the odds of pregnancy after 6 months are lower than a non-smoking group. For those couples where the man is a heavy smoker, the odds of pregnancy after 12 months is lower than the non-smoking cohort. In couples with known subfertility, male smoking contributes to a 44% reduction in pregnancy rate after in vitro fertilization. Smoking has perhaps its greatest negative impact on genome integrity where 70% of publications reviewed reported some level of smoking-related damage to the genome, for example, increased DNA fragmentation and aneuploidy. One small study reported that paternal smoking 6 months prior to conception was "four times more likely to pass tandem repeat minisatellite mutations to their children than non-smokers" (Linschooten *et al.*, 2013). Lastly, results from four meta-analyses convincingly demonstrate that paternal preconception smoking significantly increases cancer risk in offspring (Beal *et al.*, 2017).

Assisted reproduction using the technique of in vitro fertilization (IVF) is a multi-billion dollar global industry that has been responsible for the birth of many millions of babies that might not otherwise have been born. Male infertility is diagnosed in approximately 40% of couples suffering from infertility. Complicating matters is the estimation that in the United States almost 25% of males in an infertile couple do not undergo a male reproduction evaluation (Eisenberg *et al.*, 2013). A recent meta-analysis demonstrated that male infertility is associated with impaired DNA methylation patterns (Santi *et al.*, 2017). In more severe forms of male infertility, for example, obstructive and non-obstructive azoospermia, a technique called intracytoplasmic sperm injection (ICSI) is used to inject into the oocyte a single spermatozoon judged by the ICSI operator as demonstrating vitality and appearing normally shaped. Alarmingly, there is an association between offspring conceived using IVF-ICSI and imprinting disorders, such as Beckwith–Wiedemann and Angelman syndromes (Monk *et al.*, 2019). While the aforementioned IVF-ICSI-associated imprinting disorder outcomes require additional confirming or refuting large data studies, results from a recent systematic review (Catford et al., 2018) of long-term follow-up of offspring conceived through IVF-ICSI point in a similar direction for possibly both genomic and non-genomic (epigenetic) impacts on neonatal well-being, for example,

metabolic disorders and general health morbidities. Highlighted in Catford et al. (2017) and in a previous systematic review by the same group (Catford et al., 2017) is the critical need for more comparable large datasets from high-quality studies in order to draw strong-evidence conclusions.

In contrast to diagnosed male infertility, approximately 20–30% of men evaluated for (in)fertility will have no definitive diagnosis, termed idiopathic infertility. A recent case–control study reported an association between aberrant methylation of imprinted genes and idiopathic infertility (Tang *et al.*, 2018). However, no follow-up on offspring born has been reported. Therefore, a reasonable possibility exists that an unknown percentage of children born to fathers without a fertility diagnosis may have occult paternally transmitted imprinting errors—and these children may in turn transmit the errors to their future offspring (Champroux *et al.*, 2018).

CURRENT INITIATIVES AND RECOMMENDATIONS

Beginning in late adolescence, for example, post puberty, male medical examinations become much less frequent and occur primarily because of acute-care need (Marcell *et al.*, 2011). The US National Institutes of Health's MedlinePlus encyclopedia topic for patients on health screenings for men ages 18–39, while advocating for physical examination every 1–2 years, does not include a male reproductive health assessment and recommends against performing testicular self-examination (Review Date 5/12/2018, https://medlineplus.gov/ency/article/007464.htm). Given the increasingly cementing link between somatic and reproductive health, we propose a new male preventive healthcare paradigm for early teens and young adults, embraced by healthcare funders, that (i) ensures continuity of medical care from adolescence through early adulthood, when men are at their most medically vulnerable due, in part, to infrequency of surveillance, and (ii) a campaign that reinforces an annual physical examination combined with a reproductive health examination that includes semen analysis. To facilitate and encourage male participation in healthcare seeking, Miner *et al.* (2018) advocate for integrated health centers for men that provide comprehensive service and support for a man's physical and mental health needs.

Modernization is required not only of the healthcare system but also of the healthcare funders as well, for example, private insurance and national health programs. Healthcare funders need convincing evidence that there is a financial benefit by including the monitoring of male reproductive health, analogous to what is offered for women, as part of an overall preventive medicine program. By supporting such a paradigm shift, there will likely be an increase in early detection of potentially chronic or life-threatening disease states that can be mitigated through lifestyle modification and, as a result, a decrease in payor expense from otherwise high cost (potentially) curative medical intervention, for example, surgery, chemotherapy, and radiotherapy. This seems rather simple if one considers the exorbitant costs associated with cancer treatments or chronic disease as opposed to early detection through routine examination. The financial cost of the current scenario versus the proposed male reproductive preventive health program requires immediate investigation to make determinations regarding benefit or not of the latter proposed program. Until male-lifetime preventive healthcare programs become globally entrenched, the consequences from the status quo will be that the "live sicker and die younger" label will continue to apply.

To secure the proposed paradigm shift in male heath care requires the demand not only from men but also from society as a whole. We assert that men, their families, and society, by and large, are naïve to the significance of the "canary in the coalmine" scenario presented by declining sperm counts and, even more, by the sentinel role that male reproductive health appears to have for overall somatic health. If men, their partners, and families are made more aware that routine male reproductive health assessment can provide early detection of potential chronic illness, disease, and cancer, then men may feel more inclined to participate in a preventive healthcare program. Modern social media formats, educational systems, and the medical community are the necessary voices to raise societal awareness of the critical issues at hand. Some examples of annual social programs to help raise awareness of male reproductive health are as follows: for June, in the United States, is "Men's Health Month" (http://www.menshealthmonth.org) and, internationally, "Men's Health Week" (http://www.menshealthmonth.org/imhw/imhw.html), and, in November, is the international male health awareness program of Movember (www.movember.com). Healthy Male (http://www.healthymale.org.au) is an Australian government-funded program that provides information and resources to raise awareness about male reproductive health and associated chronic disease. The Australian government recently reinforced their commitment to male reproductive health by awarding substantial funding for the diagnosis of male infertility and for Andrology Australia, $3.8M and $3M, respectively.

Women make ~80% of family healthcare decisions (Miner *et al.*, 2018), including those of her male partner. Increased awareness by both men and women of male reproductive health issues can positively affect the future of not only the man's health but also the health of the woman and their future children's health. "Men's health is family health" (Miner *et al.*, 2018). Lastly, by increasing family and social awareness there is the ripe opportunity to globally impact the future of men's health. Yet, social transformation is only part of the equation.

The evidence necessary to convince the healthcare system and payors comes from scientific and clinical research, and therein lays part of the problem. The use of ICSI in ART, where only a single spermatozoon is required per egg, has contributed to a diminished, more digitized role, that is, presence/absence of spermatozoa, for the semen analysis. The role for clinical interpretation of sperm numbers and quality of motion in therapeutic decision-making has seemingly taken a back seat to a culture of "DNA only" required. It merits highlighting that ICSI is not a therapy. More critically, the ever-expanding "ICSI-all" approach removes the equally shared burden of infertility treatment from the couple and places it squarely, and wrongly, on the shoulders of the woman alone. Specifically, she becomes potentially and unnecessarily exposed to greater health and emotional risk. This increasingly common and costly scenario serves as but one example of a treatment regimen that could be lessened if healthcare providers had better diagnostic and therapeutic tools for guiding male infertility evaluations. The tools required are derived from research that translates from benchtop to bedside.

Although not entirely responsible, an additional impact of ICSI has been to diminish, due to a perceived lessened need, research funding to investigate sperm functional attributes and

requirements for fertilization (Barratt *et al.*, 2018). This is a critical lapse for a number of reasons (see Barratt *et al.*, 2017). First, there is the basic human desire to learn more about how we humans come to be. Second, by enhancing our knowledge regarding sperm attributes that are essential for fertilization the greater the opportunities for developing better diagnostic tools for infertility detection and therapeutic intervention. Third, on the reverse side of the same coin, better understanding of sperm function leads to a greater ability to develop more specific and highly effective reversible male contraceptive agents. This brief correspondence should provide clear and convincing evidence to motivate funding agencies to refocus and reallocate funds to stimulate and support greater investigation into male reproductive health.

SUMMARY

This paper has presented evidence that there is a present and growing global crisis in male reproductive health. Numerous scientific publications report that chronic illness, disease, and premature death in men are linked to their reproductive health. Further, emerging data demonstrate that the wellness of the female partner, their offspring, and grand-offspring all have connections to partner/father reproductive health. These male-borne health issues are increasing at an alarming rate.

The Male Reproductive Health Initiative (MRHI) is a newly established and rapidly growing consortium of key opinion leaders in research, medicine, funding and policy agencies, and patient support groups. The goals of the MRHI are to raise the awareness of society, policy and funding agencies, and others to (i) the significance of male reproductive health, (ii) the connection with overall male health and illness, (iii) the role the male has in the health and wellness of his offspring and the next generation, and (iv) help alleviate the significant burden that is currently carried by his female partner when seeking diagnosis and treatment for infertility. If action is not taken, and swiftly, then men will continue to die younger, suffer longer with chronic disease and will, unwittingly, continue to pass their potentially altered genomic and epigenomic signatures to future generations. Men's health is global community health!

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