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Infertility

Deafening Silence of Male Infertility

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Think about 6 loved ones of reproductive age in your life. Now imagine that 1 of these 6 individuals is suffering from infertility. Perhaps they feel alone and isolated, unable to discuss their heartbreak with their closest friends, family, and support network. Suffering in silence. In this editorial, we discuss the infertility journey through the lens of the patients, the providers, and the scientists who struggle with infertility each and every day. Our goal is to open a dialogue surrounding infertility, with an emphasis on dismantling the longstanding societal barriers to acknowledging male infertility as a disease. Through education, communication, compassion, and advocacy, together we can all begin to break the deafening silence of male infertility. UROLOGY xx: xxx–xxx, xxxx.

One in Six

Think about 6 loved ones of reproductive age in your life. Have any shared their fertility journey with you? Perhaps a positive pregnancy test happened right away. Or perhaps it took a year, transforming sex into a chore, rife with growing pessimism, and erection problems and disappointments. Perhaps the joy of a positive pregnancy test was replaced with dread as the heartbeat could not be found. Now imagine feeling isolated because "no one talks about these things." Is it possible that 1 of those 6 friends or family members might be suffering in silence?

One in 6 couples will have difficulty conceiving a child, with male-factor infertility contributing to at least half of such cases.[1,2] There is now increasing concern regarding decreasing sperm counts[3] worldwide suggesting that this problem may be growing. While the statistics highlight how common this experience is for couples, the impact of infertility—and male factor infertility in particular—can only be fully appreciated by hearing the individual and collective experiences with this devastating condition.

As providers, we encounter the importance of children in the human experience in many contexts. When an adolescent male presents with testicular torsion, the first question raised is whether having a child could be possible in the future, but do we always acknowledge the gravity of this at 2 AM? When transgender patients present to our clinic for gender affirming care, we discuss potential for biological offspring and the effects of hormones and surgery, but do we truly place ourselves in their shoes? When the fertility journey of a couple ends without a biological child, do we feel comfortable in openly grieving with them? How does the lack of insurance coverage precluding sperm cryopreservation before chemotherapy make us feel—numb…or angry?

In this editorial, first we will hear the patient voices of those who have struggled with infertility. From a surgical sperm extraction with a positive outcome to hearing the devastating phrase "we did not find any sperm." What follows is a glimpse of the pervasiveness and impact of male infertility on mental health, the importance of our environment on fecundity, and the established treatment pathways in place for couples. You will hear the perspective of experts in health policy and access to care, socioeconomic disparities, and gender non-conformity. Lastly, we provide a glimpse into the future of research and experimental technologies to provide hope in treatment options.

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It is these stories that will form the collective voice to shatter the deafening silence of infertility.

"If you think you are unique, you aren't helping the situation"

-Joe (Anonymous Patient)

The appointment a healthy young man schedules with a physician may very realistically be with a reproductive urologist.[4] Male factor contribution is reported in half of the 15% of couples who have fertility difficulties.[5] This setting contextualizes the jarring nature of how a sensitive physician visit and a diagnosis of "infertility" can be a 0-100 miles-an-hour experience.

Joe is a lawyer in Florida diagnosed with male factor infertility who was willing to anonymously share his infertility journey. After being unable to conceive for 5 years, Joe and his wife sought a fertility evaluation, and to their surprise, 2 semen analyses revealed no sperm, and he was referred to a reproductive urologist.

Though he had a strong support system, Joe recounts that his diagnosis was not handed out gently. "You take a few tests, and when the lab assistant calls you and says 'We found zero sperm', you wonder what's the deal? That may not be the best way to put it. I was driving in my car, and then it's "this is the repro lab. You have 0 sperm!"

A physical exam and genetic workup revealed absent vasa deferentia and a cystic fibrosis transmembrane conductance regulator mutation. Joe is one of 0.1% of men who will be diagnosed with congenital bilateral absence of the vas deferens.[6] Men in Joe's position with a normal follicle-stimulating hormone and no testicular abnormalities may elect to undergo sperm retrieval and in vitro fertilization (IVF) to achieve a pregnancy.[7]

The male experience with infertility is varied. Men may choose not to discuss their reproductive treatments with anyone else other than their partner.[8] "I did have family exposure to female infertility with my sister, but nothing on the male side," Joe notes. Joe recounts, "I think that I used humor to cover it up. Deep down it was more about being afraid or being embarrassed. I was afraid and unsure of the future" (Fig. 1).

Active-avoidance coping is a significant predictor of high fertility problem stress. Men who use active-confronting coping strategies, such as asking other people for advice or seeking social support, have a reported lower level of marital stress.[9] "Infertility actually brought us closer together. There was no issue," says Joe. "My wife was great about everything. She was supportive and there were no ill feelings or hostility."

Ultimately, Joe underwent a testicular sperm extraction where tissue was surgically removed from his testicle and processed to provide sperm with eggs retrieved from his wife. He and his wife subsequently had a successful pregnancy through IVF.

Though Joe's experience is not common, it is certainly not unique and serves as a reminder to the importance a male infertility evaluation. There is also a growing body of evidence that indicates male infertility is associated with increased risk of oncologic, cardiovascular, metabolic, and autoimmune disease.[10]

Despite his diagnosis after a half decade of uncertainty, Joe's outlook on infertility remains encouraging, "Don't live on an island. If you think you are unique, you aren't helping the situation you're in. Don't think you're the only person going through it. Keep talking to more experts, and don't give up."

Not the "standard plan," but "our plan"

David and Erica Collins (Patients)

All throughout teenage years and young adulthood, the dream was to always find someone you love, marry them, and then have children when you are ready. Our plan was slightly longer than the "standard dream" in that we wanted to enjoy our marriage for a little while and then start having children. During that time, infertility never crossed our minds.

Our plan was running smoothly; we fell in love, got married, and enjoyed our time as a married couple. When we decided it was time to start trying for children, we were both excited and ready. We tried for over 1 year and still no success. Every chance that came and gone made it increasingly difficult to try each month. It started to add extra stress into our lives.

It was at roughly 13 months where we decided to seek help from a female fertility specialist. They suggested a few tests, including blood work and an hysterosalpingography. The hysterosalpingography determined that one of the fallopian tubes was blocked and needed to be surgically opened. In that moment, we thought we had the answers to our infertility. We were excited and thought that once this tube becomes unblocked, it will happen within the next couple cycles.

Unfortunately, that was not the case. After trying for another 6 months with no success, we decided to do male hormone testing. That blood work showed abnormalities with the hormones that stimulate sperm and testosterone production, resulting in a decrease in both. The female fertility specialist tried a couple medications that he typically prescribes for males, which unfortunately did not help, and we decided to go to a male infertility specialist. At this point, we were almost 2 years into trying to have a child.

Meeting Dr. Vij and hearing her explain some potential reasons for the decline in testosterone and sperm production, gave us a sense of hope but also fear at the same time. Some seemed to be reversible while others did not. After running some more labs, she finally came to a conclusion. "You have Klinefelter's syndrome." There is nothing in life that can prepare you for a diagnosis like that. We were completely shocked and numb. We felt hopeless and angry. Why was this happening? How did we not know? Why us? So many questions were running through our minds. We sat and listened to the doctor's explanation. She informed us that this diagnosis sometimes may lack other warning signs or symptoms other than infertility, low testosterone, and low sperm

Figure 1. Mosaic representing male infertility, with the solitary orange sperm representing men who struggle with this devastating diagnosis.

production. Based on her explanation, it seemed that many men discover they have this syndrome when they struggle to start a family. By the end of our call with Dr Vij, we knew the best option for us to potentially have children together was a microTESE procedure and egg extraction in hopes of finding sperm within the testicles that could be used to fertilize an egg in-vitro. While skeptical at first, we decided that this was our only option, and we were going to do whatever it took for a chance to have a child.

Once the day of surgery came, there was a mix of emotions from hopefulness to negativity, and everything in between. After the surgery, a phone call from the female fertility lab came before we were expecting it, and our hearts sank into our stomachs when we heard the words "we did not find any sperm." Thoughts came running through our minds: Why us? What did we do to deserve this? Are we not meant to be parents? It was one of the hardest things we had to deal with in our lives, like losing a loved one, and we began our journey through the stages of grief.

Six months passed after the microTESE before we finally came to the acceptance stage of grief. It was not easy, and trust us, there was a lot of crying, anger, and disbelief in between. Somehow, we made it through by talking with family and close friends. It is possible to get to acceptance, but you need to be open to talking to each other and those outside of your marriage.

Now we are excited about where our journey will take us. We want to start a family and be parents together, and we are in the process of doing intrauterine insemination (IUI) with a sperm donor. While it is not the "standard plan," we see that it is "our plan," and that is what makes this whole experience special. We are in this together and cannot wait for the potential to be parents.

We will forever be thankful to both Dr Vij and Dr Lundy. If it were not for both, we would not have had the potential to extract sperm or know of the seriousness of low testosterone and how to safely treat it. It is comforting knowing that we have doctors who care about the well-being of both the patient and spouse. We cannot say thank you enough for that.

"As a fertility patient and a male partner, I've made every mistake in the book."

Jake Anderson (Patient and co-founder of Informational Website FertilityIQ)

As male partner in a heterosexual infertile couple, you'd be crazy to complain. You're asked to watch your diet, avoid the jacuzzi, masturbate into a cup, and skip work to help your partner. And yet, the experience as a male factor patient conjures confusion, guilt, and the undying sense you're both responsible for the problem and incapable of being part of the solution.

To start, "your doctor" is not always *your doctor*. Fertility clinics are teaming with a rotation of obstetrics and gynecology (OBGYNs) but seldom-if-ever do you encounter a reproductive urologist. I've heard OBGYNs tell me in the same breath that the semen analysis is both pivotal and meaningless—that it will both impact our treatment decisions and yet have no bearing ("we'll do intracytoplasmic sperm injection (ICSI) regardless").

When your sperm is the culprit, all you want to do is fix the situation. Most doctors preach moderation, but when you think you're the problem, you don't chance it—you cut everything that gives you enjoyment but could be a risk. It's the least you can do, and going without these pales to the sacrifice women make. And yet avoiding the things that make you happy, for months or years, dims the flicker of joy around which you're trying to build a family.

What men *don't* hear is that their infertility is a possible "check engine" light on health. Most doctors move on if the couple conceives. Nobody reflects on why the semen analysis was aberrant or what it might auger. Most men are none the wiser, but for any doctor who takes the Hippocratic oath seriously, this pattern should warrant immense soul searching.

As a fertility patient and a male partner, I've made every mistake in the book. Emotionally, I allowed distance to fester when my wife sought connection. I didn't advocate strongly enough when our clinic misprescribed my wife's medication and she ended up in the emergency room. The list goes on. During this period, I seemed to have only 2 factory settings as a male factor patient: "stubbornly passive" and "recklessly optimistic." The fact I couldn't grasp

the process, terminology, anatomy, or the facts didn't stop me from providing "reassurance" to my wife that probably sounded a lot like "you're overreacting." She wasn't, and to this day I'm disappointed in myself for this.

Here are a few ideas for how doctors can help people like me avoid the pitfalls I foolishly made:

- Insist men attend the first consultation, slow down the education, and avoid terminology. If people can't follow, they'll think their involvement is optional or irrelevant. Neither is true.
- Explain the tests, what they mean, and how that information will be used to improve fertility *and* the health of the man. Don't ignore or forget the latter.
- When it comes to lifestyle, advise moderation rather than cold-turkey abstinence (unless it's smoking). It's helpful if both partners truly absorb this message.
- Discuss counseling. Infertility is about sex, money, and kids—the 3 topics that spawn fights. When couples build a scaffolding of trust and good communication, this process gets easier.

"While caring for our patients is hugely important, so is caring for ourselves, and family expansion is a vital piece of that for me and likely many others."

Mary Samplaski MD (Patient and Reproductive Urologist)

I have always wanted children. But as life unfolded, I was approaching 35 years old, not on the "marriage tract" with anyone, and my urologic career was expanding. One of my first financial investments with a faculty salary was to freeze my eggs. For me, this was an insurance plan of sorts to increase the odds that I would achieve an important life dream to have children.

I froze my eggs twice, at 34 and 35 years old, and I was fortunate to get around 20 eggs/cycle. Egg freezing costs around $10-20,000, roughly 30%-40% of a trainee annual salary, and I would have frozen them sooner if the cost was more approachable as a trainee. Freezing eggs as a professional is also tricky with multiple time-sensitive self-injections, fertility clinic ultrasounds, and blood draws requiring time away from patient care. This is complicated by the sensitive nature of fertility, and I did not feel comfortable sharing with my institutional administrative staff. Despite these challenges, I made it work.

Fast forward 6 years later to when I was married at 41 years old. Interestingly, my husband, who was 45 years old and thus classified as "advanced paternal age," had cryopreserved sperm for medical reasons. Knowing the adverse effects advanced paternal age may have on offspring, we opted to use our cryopreserved gametes from the get-go. People commonly told me "You look so young and take good care of yourself, you'll be fine." But as a 41 year old reproductive urologist, I knew that outward youth did not correlate with inner egg quality.

We proceeded, but unfortunately, our first 3 embryo transfers were unsuccessful. I was very thankful that I had undergone 2 hyperstimulation cycles, since we used a large number of frozen eggs for these failed transfers. Ultimately, per my request, we moved forward with the transfer of 2 mid-grade embryos, which resulted in pregnancies and ultimately the birth of my twins. The emotional toll throughout the year-long process to become pregnant was substantial. It felt as though my entire department and adjunct staff knew about my fertility struggles due to missing so much clinic and operative time. But at the end of the day, all the struggles were worth it. My children are the greatest joys of my life.

I was fortunate to have a positive end (or beginning) to my fertility story. There are several points worth highlighting. First, having a baby is not always as easy or idyllic as one would hope. Second, if you want children and are of advancing maternal age but not ready for a child yet, consider egg freezing. I likely would not have my babies if I had not frozen my eggs. Third, on a global scale, gamete freezing should be made more accessible and especially so for medical professionals and trainees, who often spend their prime reproductive years in patient care. Lastly, there is no perfect time to have a baby—life is always busy—at some point you just have to try, and know that it may not happen immediately, or ever. My babies are the best thing to ever happen to me, the absolute best part of every day, and their smiles light up my life (even through the burnout of medicine that many of us struggle with). Despite my advanced age and the continual fatigue, I would not give them up for anything. While caring for our patients is hugely important, so is caring for ourselves, and family expansion is a vital piece of that.

"It is through these findings that we understand how infertility is not "my problem" or "your problem", it is ours"

Chiara Acquati PhD (Sexual and Reproductive Health Researcher)

While often neglected, there is a growing understanding of the implications male infertility has on psychological, sexual, and relational wellbeing.[11-14] Infertility can lead to increased levels of anxiety, depression, and distress.[15-18] These are often accompanied by feelings of helplessness, frustration, and a sense of loss of control.[19,20] One potential explanation for the negative effects of male infertility is the disruption of traditional gender roles and masculinity.[21,22] Qualitative accounts from men who have shared their experience often describe feeling inadequate, emasculated, and remarked on how these concerns are often associated with a decreased sense of self-esteem and confidence.[22-24] Sexually, infertility is often associated with erectile dysfunction, premature ejaculation, and relationship satisfaction;[25-28] with worse outcomes reported over time[29] and among men experiencing depressive symptomatology.[30] A recent meta-analysis confirmed greater prevalence of sexual dysfunction among infertile men, ranging from 17.8%-61.6%, as well as impaired erectile function, orgasm, and sexual desire.[26]

When working in the context of complex medical issues such as infertility, it is necessary to assume a

relational perspective that accounts for the interdependence between partners.[31-36] Uncertainty, treatment-decision making, demands of care, and the financial burden associated with ongoing fertility treatments can have a pervasive effect on couple relationship, sexual function, and emotional distress.[31,32,34,35,37-40] Some couples will find ways to communicate, engage with each other, problem-solve; but others may experience communication difficulties, lower relationship satisfaction and support, reduced perceived intimacy, estrangement, or even relationship dissolution.[40-42] Emerging evidence on within-dyad interpersonal processes supports that coordinated coping behaviors, support from partner, and emotion regulation strategies are associated with psychological health, sexual function, and relationship functioning,[15,32,34,35,43,44] while self-blame and avoidant coping impair psychological adjustment.[16] It is through these findings that we understand how infertility is not "my problem" or "your problem," it is "our problem."

The pervasive impact of male infertility on mental health, sexual function, and couple relationship emphasizes the need for accessible, timely, and reliable support.[45-49] Given the impact of infertility on the couple relationship and sexual health outcomes of patients and partners, interventions such as communication and coping skills training, intimacy-enhancing programs, and sex therapy can be offered to enhance couples' coping strategies, intimacy, and expand sexual repertoires.[21,45,48,50-52] Additionally, evidence has demonstrated that a variety of approaches are better able to address different needs. Support groups, peer-mentors, and online forums are options for coping with stress and understanding the shared experience of others, while one-on-one consultations with mental health providers have been endorsed by dyads for relationship issues.[53] *Ehealth* approaches are also emerging as feasible options.[54,55] However, the literature has also highlighted differing conclusions about the contribution of psychological interventions, potential aspects of risk among online communities and websites, and the need for an integrated multidisciplinary approach.[45,47,56-58] A recent systematic review and meta-analysis[38] has demonstrated that psychosocial interventions contribute only to small improvements in distress and modest results on conception, indicating that future research is needed to refine available interventions to unique sources of stress, men and partners' preferences, and the experiences of individuals and dyads underrepresented in research,[59] while addressing barriers affecting timely referral to care.[60,61]

"The decline in semen quality over the past 50 years is so universal and rapid that it cannot have a genetic basis but must be environmentally induced"

Audrey Gaskins ScD (Reproductive Epidemiologist)

Sperm counts have halved in the past 50 years among men globally.[3] The decline in semen quality is so universal and rapid that it cannot have a genetic basis but instead must be environmental. Studies of identical twins further suggest that genetic factors may only explain around 5% of male subfertility, whereas unique environmental factors explain around 95%.[62] Taken together, this emphasizes the potential importance of environmental factors such as obesity, diet, smoking, and toxicants on male fertility.

Body Weight

A large systematic review on male adiposity and reproductive health found that men who were overweight or obese (based in a BMI ≥ 25 kg/m^2) had reduced semen quality parameters and disruption of many key reproductive hormones compared to normal weight men.[63] Several studies also indicate that there is a lower probability of clinical pregnancy and live birth for overweight and obese men vs normal weight men following assisted reproductive technologies (ART).[64] The literature, however, is still undetermined on to what degree male obesity impairs natural conception rates[65-67] or whether weight loss[68,69] or bariatric surgery[70] improves male fertility.

Diet

A robust literature of observational studies has found an association between higher adherence to a healthy diet, characterized by higher intakes of seafood, whole grains, vegetables and fruits, and nuts and lower intakes of processed meats, refined grains, and sugar-sweetened beverages, and improved semen quality.[71,72] This association was further confirmed in 2 randomized-controlled trials showing that consumption of a Mediterranean diet for 4-6 months improved semen quality compared to a low-fat diet or national dietary guidelines.[73,74] However, the few studies on dietary patterns and clinical outcomes of ART have failed to show any benefit[75,76] and no studies have evaluated the link between male dietary patterns and time to pregnancy.

Supplements

Several meta-analyses have been published on male antioxidant supplement intake in relation to semen parameters and pregnancy outcomes.[77,78] In general, the studies have found that antioxidants, most notably L-Carnitine, coenzyme-Q10, and ω-3 fatty acids, are associated with small improvements in sperm concentration, motility, and semen volume vs placebo but none had a significant effect on pregnancy rates.

Smoking

There is substantial evidence that cigarette smoking decreases the quantity and quality of sperm but less strong evidence for a relation with time to pregnancy or outcomes of ART.[79] In a meta-analysis, cigarette smoking was associated with reduced sperm count, motility, and morphology.[80] There is also emerging evidence that smoking cessation may positively impact sperm concentration, semen volume, and total sperm

count.[81] Nevertheless, the majority of studies that have evaluated male partner smoking and ART outcomes found no relation.[82-85] Among couples trying to conceive without medical assistance, there is stronger evidence of an association between male smoking and delayed conception.[86,87] Finally, there is suggestive evidence that cannabis and (to an even lesser extent) e-cigarettes may negatively impact male fertility,[88,89] although additional research is warranted.

Environmental Toxicants

In general, there tends to be more robust evidence linking male exposure to persistent organic pollutants—specifically organochlorine pesticides, brominated flame retardants, polychlorinated organic compounds, and per- and polyfluoroalkyl substances—to lower semen quality[90]; however, there is very little evidence for associations between male exposure to persistent organic pollutants and couple-based fertility endpoints such as time to pregnancy.[91] Evidence is suggestive, but inconsistent, for an association between non-persistent endocrine disrupting chemicals, such as bisphenol A, phthalates, and parabens, and lower semen quality.[92,93] The most recent review and meta-analysis on air pollution and male fertility (which included 11 studies with over 60,000 men) concluded that higher exposure to ambient certain types of air pollutants were associated with significantly lower sperm concentration, count, and motility.[94]

"A shared understanding of what each type of provider offers and how it fits into the treatment pathway allows for synergistic counseling, outcomes, and patient satisfaction"

Pietro Bortoletto MD (Reproductive Endocrinologist)

It is often the case that a new diagnosis of male factor infertility is being made by a reproductive endocrinologist (REI). The interpretation and counseling of abnormal semen analysis is nuanced and critical to a male patient's acceptance of further testing or referral to a male infertility specialist for treatment. Casual disregard for "borderline parameters" or overinterpretation of results set the stage for mistrust or fear when assisted reproduction does not perform as expected. Additionally, sharing news of newly identified azoospermia or failed fertilization may contribute to significant distress to patients and their partners that may often hamper further counseling efforts by others. To facilitate the best clinical outcome, it is essential that the REI has a good working relationship with their male infertility counterparts. A shared understanding of what each type of provider offers and how it fits into the treatment pathway allows for synergistic counseling, outcomes, and patient satisfaction.

For this model to become a reality, male infertility specialists must share with their REI colleagues what should prompt a referral. This may be lab driven, in the case of semen analysis parameters, or may be based on symptoms, such as erectile dysfunction. Second, an open line of communication between both parties must be established beyond the consultation note. Finally, a shared vision for how to prioritize reproductive goals without missing the parallel opportunity for early diagnosis and intervention will allow goals of all parties involved to be optimized.

"This knowledge about the substantial out of-pocket costs for infertility treatment should be a rallying call for providers … who are devoted to helping couples struggling with infertility"

Juan Andino MD MBA (Reproductive Urologist)

Despite American Society for Reproductive Medicine (ASRM)/American Urological Association (AUA) guideline recommendations that both partners in a couple should receive an infertility evaluation, only 8%-9% of men undergo an evaluation[95,96]. Responses from the National Survey for Family Growth between 2011 and 2017 also suggest that an additional 5% of men who self-reported as infertile had never used infertility services.[96]

Infertile patients in the United States of America are significantly impacted by the costs of care. In a 2022 Kaiser Family Foundation survey of over 2300 patients, 40% of adults had delayed or foregone medical care in the last year due to cost,[97] and 47% of insured adults still said they found it very/somewhat difficult to afford health care costs. These proportions were even higher in Black (60%) and Hispanic (65%) adults as well as patients whose household income was < $40,000 (69%). Costs of care are a significant concern impacting patients and families regardless of insurance status and disparities and across sociodemographic characteristics.

While infertility is classified as a disease by many organizations, most insurance plans in the United States do not cover the evaluation and management of infertility conditions.[98] This lack of coverage places significant financial burden on patients and their families[6] and risks impacting their health, not only by preventing family building efforts, but by missing significant medical pathology including testicular cancer, hypertension, diabetes, hyperlipidemia, and heart disease.[99,100]

At the federal level, efforts from ASRM and RESOLVE have helped achieve coverage of evaluation and some treatment options for active-duty service members (TRICARE) since 2012 and improvement in infertility evaluation and treatment coverage for retired serve members (Veterans Affairs) in 2016 and 2018.[101] However, coverage for assistive-reproductive technologies remains tied to whether patients have service-connected injuries. At the state level, 19 states have infertility coverage laws that require commercial insurance companies to either cover or offer infertility treatments (Table 1).[102] The details of the laws at the state level, however, are critical, and offering but not actually covering these

Table 1. States with infertility benefits.

State	Infertility Insurance Laws	IVF Insurance Laws	Fertility Preservation Laws
Arkansas	x	x	
California	x		x
Colorado	x	x	x
Connecticut	x	x	x
Delaware	x	x	x
Hawaii	x	x	
Illinois	x	x	x
Louisiana	x		
Maryland	x	x	x
Massachusetts	x	x	
Montana	x		
New Hampshire	x	x	x
New Jersey	x	x	x
New York	x	x	x
Ohio	x		
Rhode Island	x	x	x
Texas	x		
Utah	x	x	
West Virginia	x		

From "Infertility coverage by state," by RESOLVE, 2022 (https://resolve.org/what-are-my-options/insurance-coverage/infertility-coverage-state/).

services remains an issue. Recently, California SB 600 was signed into law requiring all commercial plans to offer fertility preservation for patients who will undergo medical treatments that can result in iatrogenic infertility. However, many couples and patients are not counseled that in many of these cases, assisted-reproductive technologies like IVF or ICSI will be required to achieve a family with cryopreserved sperm, eggs, or both. This year in California, SB 729 was introduced by Senators Menjivar and Weiner with support from ASRM, Society for the Study of Male Reproduction, and Society for Male Reproduction and Urology to address this gap in care coverage and ensure coverage for future fertility treatments including IVF.[103] Finally, employers themselves have identified that fertility benefits can help recruit and retain employees. Between 2016 and 2018, there was a 15% increase in offering of IVF coverage in organizations with >20,000 employees.[98] In a poll of workers considering a career change reported in *Fortune*, 45% of respondents rated fertility benefits as an important component when considering a new job.[104] These numbers highlight the importance of fertility for our patients.

Knowledge about the substantial out-of-pocket costs for infertility treatment should be a rallying call for providers who are devoted to helping couples struggling with infertility. Male fertility specialists are continually collecting data at and across institutions and leveraging health services research to understand how local, state, and national policies impact our patients. Health advocacy efforts through the American Urological Association, Resolve (ASRM's legislative arm), and other state and national organizations can then share real patient stories, combined with data from those who provide fertility services to influence health policy for the benefit of our patients.

"It is well known that underrepresented minorities suffer from disparities in urological care, and male infertility is no exception"

Denise Asafu-Adjei MD MPH (Reproductive Urologist)

Infertility is a well-recognized disease that affects millions of people around the world. Despite the fact that infertility plagues males and females across the socioeconomic spectrum, male factor infertility continues to be poorly recognized. Male factor infertility affects approximately 6% of men in the United States, with different rates reported around the world.[105] There are various health care disparities that have contributed to the trends we have seen in male infertility care.

Male infertility continues to be stigmatized among males around the world, with strong beliefs about ties to masculinity and societal status. Any issues of fertility typically start with a magnified lens on the female. These differences in gender thoughts about infertility have unfortunately spilled over into legislation. Reproductive health legislation still largely indicates and favors females, often without mentioning males in fertility care. Similarly, insurance companies have followed suit and largely do not offer male fertility services, placing further financial strain on people trying to build their families.[106] This strain is amplified among males with fertility issues. Organizations, such as the ASRM, have been longtime champions of legislative efforts, but we continue to be far behind legislative efforts that are in place for female fertility.

The urological workforce also contributes to disparities in male fertility care. There continues to be a major shortage of urologists in the United States and around the world. Currently, there are approximately 4 urologists per 100,000 Americans.[107] There are also fewer urology trainees pursuing fellowship training in male infertility. In 2021, the AUA reported that only 3.1% of graduating trainees pursued fellowship training in male infertility, perhaps from a lack of exposure during residency. Finally, the urological workforce continues to lack racial and gender diversity that parallels the U.S. population and society. Although there are several concerted efforts in place to improve diversity in urology, patients still lack a truly diverse set of reproductive urology workforce.

It is well known that under-represented minorities (URMs) suffer from disparities in urological care and male infertility is no exception.[108,109] There are biases inherent in care delivery among physicians and urologists as well as institutionalized racism which contributes significantly to disparities in male infertility care. An underappreciated component is that stemming from the painful history in the United States of direct attacks on Black male fertility. The infamous Tuskegee Study resulted in the sterilization of many African American

men. These truths still ring true among many Black and URM families today and the inadvertent effect has been widespread distrust for the medical profession. Additionally, until about the 1990s, there were also sanctioned government sterilization programs for males and females which targeted URMs, the physically and/or mentally handicapped, and institutionalized persons.[110]

These harsh realities have posed major barriers to URMs seeking care for infertility. Furthermore, treatment options, such as sperm donors, are also wrought with disparities due to the lack of and scarcity of diverse donors in sperm banks.[111] Most users of donor sperm continue to be White, high-earning, college-educated individuals.[111] Therefore, fertility has been a unique subject in the disparities dialog and the acknowledgment of this somber sterilization history is important as we seek to shift the paradigm of how we equitably deliver care across races and ethnicities.

In conclusion, major health disparities plague the male infertility space: racial disparities, gender disparities, and workforce disparities. These all adversely impact how males seek care for this disease and how reproductive urologists and other physicians can deliver care. Although we are working toward achieving equity, the tide is shifting! More males are recognizing their roles in fertility care. With continued widespread education and advocacy across professional and special interest organizations, we can and will close the gap in male infertility care.

"As an infertility scientist, a transgender* patient, and a person, I challenge the fertility community to embark on a journey to reset the decades of habits surrounding gender in your daily life, language, and practice"

Ava Adler (Reproductive Research Scientist)

*While I am transgender, I am one gender diverse person writing to honor the larger transgender community. While many use "transgender" as an umbrella term, I chose to use the terms "transgender or nonbinary" or "gender diverse" in this piece, as this is language that best reflects how I see myself. Gender at its basis is a spectrum and a personal choice.

This piece is a call to action for the fertility community to evolve in language and approach to create a more inclusive environment for its patients.

While some people treat sex and gender as synonyms, these 2 concepts can be in conflict in the connections drawn between reproductive anatomy and the gendered assumptions attached to them. Sex is a label assigned at birth according to medical factors such as genital appearance. Gender, on the other hand, is a social and cultural construct built upon norms, behaviors, and historical roles. It is personal. It is subjective. It exists along a dynamic continuum. To reject gender conformity is not simply to ignore the rigid self-selection boxes on official documents; it is to embrace one's inner self, independent of the expectations and assumptions made by others.

The outdated gender binary system hinders all health care professionals from seeing their patients in their totality. When I share that I am transgender, I often feel the eyes of acquaintances and strangers alike inspecting me for evidence, disassembling and reassembling my silhouette, and categorizing me rather than seeing me. My experience is not unique among trans and nonbinary community.

For transgender or nonbinary patients and physicians alike, the concept of fertility may be the most cognitively dissonant aspect of medicine. It is rife with stigma and demands a unique form of intimacy and trust between provider and patient. And yet, few aspects of medicine are as rigidly binary—at present, egg and sperm must still come together for reproduction. Fertility doctors have an obligation to discuss the medical facts surrounding the very organs that represent the binary sexual construct that gender diverse patients may feel trapped by. Simultaneously, they must build bridges of empathy and kindness to collectively accomplish unique reproductive goals. Achieving such goals requires that both parties can trust that each will hold a place of mutual respect.

This respect begins with changing social and long-held habits, such as the misuse of pronouns. Misusing pronouns often prevents a patient from feeling seen and correcting this may not be a priority for some providers. To these providers, I pose some numbers. The 2015 US Transgender survey,[112] which surveyed 27,715 respondents, showed 33% of respondents had at least 1 negative experience related to being transgender, and 23% reported not seeking the health care they needed from fear of being mistreated. A study based in Canada[113] found a 66% reduction in suicide ideation for the transgender population when providers used proper pronouns and provided a hospitable environment.

As an infertility scientist, a transgender patient, and a person, I challenge the fertility community to reset the decades of habits surrounding gender in your daily life, language, and practice. Name your pronouns first when introducing yourself to all patients, not just those you assume may offer pronouns themselves. Embrace gender as fluid, and do not hesitate to revisit the conversation regularly with patients to see if anything has changed. Cultivate a space where patients do not feel forced to interact with their health through a gender-specific lens. Give patients the opportunity to share what language they use about their bodies. Be emboldened to discuss cryopreservation with your transgender and nonbinary patients, recognizing the limited knowledge on the impact of gender-affirming care practices on fertility. Accept that you will make mistakes, and you will learn from them. Try not to apologize but rather correct yourself if you stumble. When you apologize for misgendering your patient, recognize that it puts them in the awkward position of feeling socially compelled to provide a degree of reassurance—of caring for *you*, their health care provider, in their moment of vulnerability. Seeing people in their humanity above all else will move

mountains in relieving the stress of navigating the nuances of gender diverse medical care.

Every person, regardless of their gender, has a unique journey in how their body moves through the world and how they want to be seen and heard, addressed, and respected. Language is the first step in evolving medicine to treat all patients, but more specifically, to treat transgender and nonbinary patients more comprehensively. The fertility field has the opportunity to embrace gender diverse patients and build a future where we patients are afforded the same opportunities to create the families and futures of our dreams.

"There are several experimental technologies in the research pipeline that may provide fertile hope to patients with nonobstructive azoospermia."

Kyle E. Orwig PhD (Male Reproductive Scientist)

Spermatogenesis is dependent on a population of spermatogonial stem cells (SSCs) that maintain continuous sperm production in post-pubertal males and produces more than 40 million sperm in a single ejaculate from fertile men. Nonobstructive azoospermia (NOA, no sperm in the ejaculate) is the most severe form of male infertility and there are few treatment options. There are several experimental technologies in the research pipeline that may provide fertile hope to patients with NOA.

Medically induced (iatrogenic) NOA

Medical treatments for cancer, bone marrow transplantation, gender dysphoria and others, can cause NOA. The only fertility preservation option available to prepubertal patients who are not yet producing sperm is to cryopreserve immature testicular tissues (containing SSCs). Thousands of patients have cryopreserved their immature testicular tissues with the expectation that those tissues or cells can be thawed in the future and matured to produce sperm. SSC transplantation[114,115] and testicular tissue grafting[116] are 2 mature in vivo technologies that have been replicated in numerous animal models (reviewed in[117]), including nonhuman primates[118,119] and may be ready for the human clinic. However, there are challenges that may limit application in some patients. Testicular biopsies from young patients may contain only a few SSCs, limiting regenerative potential. Autologous transplantation may not be safe for patients with testicular cancer or leukemia. Transgender patients may not want to experience male puberty that would be required to mature their tissues inside their bodies. Methods to expand human SSC numbers in culture,[120] remove malignant contamination,[121,122] and/or mature testicular tissues,[123] *ex vivo*, are in early stages of development.

Genetic NOA

Half of NOA is idiopathic (unexplained) and genetic mutations are the likely culprit in many of those cases.[124] Affordable whole genome or whole exome sequencing makes it possible to discover genetic causes of NOA in patients[125] and develop diagnostic screens or gene therapies. Consider a man with a germ cell mutation that causes NOA with maturation arrest (testes contain germ cells, including SSCs, but maturation to sperm in blocked). In theory, it would be possible to obtain SSCs from his testes; use CRISPR/Cas9 gene editing to correct the mutation in cultured SSCs; and transplant the gene-corrected SSCs back into the testis of the patient to regenerate spermatogenesis. The proof in principle for this approach is already established in mice.[126-128] While the research community works on the technical challenges of germline gene editing in patients, the ethical, legal, and social implications are actively debated in the world community.[129]

Sertoli Cell Only

The patient scenarios described above require functional SSCs. Those approaches would not be applicable to NOA patients with a true Sertoli cell only phenotype. *In vitro* gametogenesis is an early-stage technology that could produce sperm in people who do not have sperm or SSCs. Briefly, any cell in a patient's body could be reprogrammed to induced pluripotent stem cells that could then be differentiated to germ cells. Pioneering research has demonstrated that induced pluripotent stem cells can be differentiated into primordial germ cell-like cells (embryonic precursors of SSCs) that can either be transplanted to regenerate spermatogenesis in the patient testes[130] or differentiated to transplantable SSC-like cells[131] or fertilization competent spermatid-like cells,[131,132] in vitro. These approaches are established in mice but have not been replicated in other species.

CONCLUSION

It only takes one.

One sperm and 1 egg to create something truly magnificent.

One phone call to the reproductive endocrinology team to coordinate care in a complex couple.

One offer to speak with a mental health professional when recurrent pregnancy losses become too difficult to bear.

One reminder to consider fertility preservation for the shell-shocked patient hearing the word "cancer" for the very first time.

One discussion about fertility side effects before starting fertility-altering medications.

One moment of honesty to share an infertility struggle with a colleague who may be secretly experiencing the very same challenge.

One empathetic acknowledgment of how failing to conceive transforms physical pleasure for couples into a monthly reminder of perceived inadequacy.

One brief pause to ensure the right pronouns are being used and acknowledge that gender identity, sexuality, and reproductive biology are not the same.

One moment of self-reflection to acknowledge that each ethnic culture has its own unique and sometimes negative connotation of the health care system spanning generations.

To the medical professionals: It only takes one voice to break the deafening silence of male infertility. Will it be yours?

To those of all ages, all genders, all ethnic backgrounds, all sexual orientations, and walking along all paths on the fertility journey: If you are struggling, please know that you are not alone. Others are experiencing the same sadness, frustration, anger, and countless other emotions that you are feeling. There are options. There is help. Above all, there is hope.

Declaration of Competing Interest

Jake Anderson: Owner, FertilityIQ. The other authors declare no conflict of interest.

General Infertility Resources (The authors and journal are not responsible for the content listed below)

Academy of Adoption and Assisted Reproduction Attorneys Charitable Trust.

Academy of Adoption and Assisted Reproduction Attorneys formed the Family Formation Charitable Trust based on the belief that no person should be denied the ability to build their families through adoption or assisted reproduction due to financial hardship and that children in foster care seeking permanent placement and the adults who seek to adopt them should have additional assistance available to them.

https://adoptionart.org/charitable-trust/.

AGC Scholarships

AGC is a nonprofit group committed to providing both advocacy and scholarships for those struggling with infertility in the United States.

https://agcscholarships.org/about-agc/.

Baby Quest Foundation

Baby Quest was born from 1 young woman's struggles to have a child. With the high costs of assisted reproduction, a solution to infertility is often out of reach, allowing financial need to prevent many from becoming parents. Baby Quest has grown 1 grant, 1 IVF, 1 new baby at a time.

https://babyquestfoundation.org/our-recipients/.

Fertility Within Reach

Fertility within Reach's mission is to increase access to fertility treatment and fertility preservation with aims to alleviate emotional, physical, and financial stresses as individuals strive to build their family.

https://www.fertilitywithinreach.org/.

FertilityIQ

A couple who experienced infertility that made a resource to help other patients experiencing infertility to have good access to information. They have a section highlighting grants and charities to help support IVF.

https://www.fertilityiq.com/topics/fertilityiq-data-and-notes/free-ivf-grants-and-charities.

Gay Parenting Assistance Program

Men Having Babies created The Gay Parenting Assistance Program as part of their mission to make building a family more affordable for gay prospective parents that need financial assistance for their surrogacy journey.

https://menhavingbabies.org/assistance/.

Gay Parents To Be

Informational resource and a starting point for LGBTQ parenting that has listed grants and charities to help patients through the process of family building using assisted reproductive technology or adoption.

https://www.gayparentstobe.com/financial/grants-charities/.

Gift of Parenthood

Founded by Teresa Barbosa in 2019, Gift of Parenthood is a non-profit driven by a simple mission—to help families and individuals overcome infertility through education, awareness, and fertility assistance grants. We provide grants to couples and individuals at least 4 times a year.

https://giftofparenthood.org/grant-giveaways/.

Resolve

The website of the National Infertility Association offers education, advocacy, and information about fertility preservation in addition to a database of support groups.

http://resolve.org.

Oncofertility Resources

Alliance for Fertility Preservation

Advocacy group that helps craft legislation for state mandated coverage of fertility preservation care.

https://www.allianceforfertilitypreservation.org/.

American Cancer Society

Offers materials about sexual health and fertility issues commonly experienced by people with cancer and their partners. A section on male fertility and sexual health in males is available.

https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects.html.

Cancer Support Community

Discussion community centered on intimacy, sex, and fertility issues.

https://www.cancersupportcommunity.org/article/intimacy-sex-and-fertility-issues.

Cancer.net

Comprehensive information for people with cancer, families, and caregivers from the American Society of Clinical Oncology.

https://www.cancer.net/navigating-cancer-care/dating-sex-and-reproduction/fertility-concerns-and-preservation-men.

LIVESTRONG Fertility

Offers education and information to cancer patients regarding fertility risks as well as referrals to access fertility preservation discounts.

https://www.livestrong.org/what-we-do/program/fertility.

National Cancer Institute

Offers information about changes to the body during and after treatment, dating after cancer, changes in sexual desire and activity, and fertility.

https://www.cancer.gov/about-cancer/treatment/side-effects/fertility-men.

Team Maggie

Provides financial assistance to young women and men cancer survivors for the purpose of preserving eggs and sperm.

https://www.teammaggiesdream.org/.

Oncofertility Consortium

Offers a telephone support hotline, education, and clinic/center search options for people with cancer coping with infertility or potential loss of fertility because of cancer treatments.

https://oncofertility.msu.edu.

http://savemyfertility.org.

Surviving and Moving forward Fund

Provides scholarships to young adult cancer survivors for a wide range of cancer associated costs—they offer 2 categories of family building grants: storage of eggs, embryos, or sperm and expenses for fertility procedures such as testing, IUI, IVF, gestational carrier, adoption.

https://expectmiraclesfoundation.org/samfund/.

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