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N-of-1 Policymaking — Tragedy, Trade-offs, and the Demise of Morcellation

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When Ms. B., a 28-year-old black woman, noticed last spring that she looked pregnant, she assumed she was just deconditioned after a long winter and a stressful job transition. But her annual gynecologic exam revealed several uterine fibroids, one of them 12 cm long on the outside of the uterus. She soon developed debilitating abdominal pain and one night presented to the emergency department thinking she had appendicitis. She didn't, but her fibroids were so large that on abdominal CT, her appendix could not be visualized.

The lifetime prevalence of uterine fibroids is over 80% among black women and nearly 70% among white women.[1] When fibroids become symptomatic, there are surgical and nonsurgical treatment options. The position of Ms. B.'s fibroids, however, was likely to impede conception and pregnancy, and she wanted to start a family. Told that she needed a surgical myomectomy, which meant 6 to 8 weeks of recovery, she asked for other options.

Until recently, there were two approaches to surgical myomectomy and hysterectomy: an open approach through an abdominal or vaginal incision in which fibroids, the uterus, or both are removed intact, and a minimally invasive approach performed laparoscopically and requiring the mincing of tissue, or morcellation, to allow removal through much smaller incisions. For nearly a century, morcellation, necessary in several gynecologic surgeries, was accomplished with a scalpel. Beginning in the mid-1990s, it could be done more efficiently and effectively with a tool called a power morcellator.

THE RISK

Practice changed after 2013, when Amy Reed, a 40-year-old anesthesiologist and mother of six, underwent a hysterectomy with intraoperative morcellation for presumptively benign uterine fibroids at Boston's Brigham and Women's Hospital (where I have since joined the faculty). The masses turned out to contain foci of leiomyosarcoma (LMS), a rare, aggressive cancer that has a 5-year survival rate of 63% when diagnosed at stage I.[2] Reed's LMS was stage IV, so her likelihood of surviving 5 years was only about 14%.[2] There is a known risk of disseminating cancer during the surgical manipulation of a tumor, but the risk in women undergoing laparoscopic treatment for uterine fibroids was considered minuscule — about 1 in 10,000, which probably simply reflects the tumors' overall incidence.[3]

Almost immediately, Reed's husband, Hooman Noorchashm, then a cardiac surgery fellow, launched a campaign to ban morcellators. The *Wall Street Journal* picked up the story in December 2013 and published an article series that was a finalist for a Pulitzer Prize.[4] The Food and Drug Administration (FDA) undertook a review to quantify the risk of disseminating occult uterine cancers that cannot be reliably detected preoperatively. The resultant safety communication, issued in April 2014, suggested that among women undergoing surgery for presumptively benign fibroids, 1 in 352 had uterine sarcoma and 1 in 498 had LMS.[5] Six months later, the FDA issued a black-box warning and stated that morcellation was contraindicated in perimenopausal or postmenopausal women and in "candidates for en bloc tissue removal" — a category that, strictly speaking, encompasses all women.[6]

Several experts argued that these risk estimates were too high[7] and that it was riskier to expose 100,000 or so women per year to open procedures rather than laparoscopic ones.[8] Since the rarity of LMS precludes a randomized trial, however, risk estimates had to be based primar-

ily on retrospective case series of varying rigor. Some studies were poorly stratified for risk factors such as age, and others spanned decades during which diagnostic criteria for LMS had changed.

Although the FDA couldn't control the quality of the data available, it was criticized for its choice of studies to analyze — for falsely lowering the denominator, by using the search term "uterine cancer" to identify studies and so excluding any in which no cancer was diagnosed, and for elevating the numerator, by including some cases in which morcellation probably wouldn't have been offered. Indeed, another meta-analysis found 1 case of LMS per 8300 surgeries, an order of magnitude lower than the FDA's figure.[9]

But perhaps no risk estimate would have been low enough to counter the chilling effect of Reed's widely publicized story. Many institutions banned morcellation. Johnson and Johnson, the largest manufacturer of morcellators, pulled its product from the market, and the FBI is reportedly investigating whether the company knew about the risk. Some insurers stopped covering the procedure or began requiring prior authorization. Several lawsuits are pending. And the Government Accountability Office is looking into accusations that the FDA responded slowly and exercised inadequate caution.

OPTIONS AND TRADE-OFFS

The laparoscopic approach was once considered to be superior to the open one, which carries a risk of death estimated at 1 in 1000 to 1 in 2500.[3] Minimally invasive approaches mean less pain and blood loss, fewer venous thromboembolisms and surgical-site infections, faster recovery, and better cosmesis. These benefits are heightened among women with obesity and diabetes, a growing subgroup of patients needing fibroid surgery. Although there are other surgical options, such as a vaginal hysterectomy or a minilaparotomy involving a midsize incision, we don't know how they compare with the standard approaches, particularly for higher-risk patients or for those who value faster recovery.

That's why Ms. B. felt stuck. Her insurance plan would leave much of her recovery time uncompensated, and though she realized an occult cancer couldn't be ruled out preoperatively, she had no high-risk features. She believed the benefits of the laparoscopic approach outweighed the risk that surgeons would "tear up what they think are fibroids and spread cancer through my body." She proposed signing a waiver stating that she understood. When I spoke to her, she offered to start a petition. "I'd do anything," she said, "for my body, for my health. I just want the choice."

From a policy perspective, the FDA has a mandate to keep the public safe, but medical products are associated with two types of risk: that caused by using the products and that caused by preventing their use. In making regulatory decisions, the FDA considers both, but political pressure focuses more on the former than the latter. "In all our FDA history," noted former FDA commissioner Alexander Schmidt, "I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them."[10]

The morcellation controversy highlights this precautionary pressure, given that there may be greater population benefits and lesser risks from continuing than from discontinuing morcellator use. A recently published decision tree comparing outcomes for a hypothetical cohort of 100,000 women with presumptively benign fibroids undergoing either a laparoscopic procedure requiring morcellation or an abdominal hysterectomy showed there would be fewer deaths overall (98 versus 103) with morcellation, though more deaths from LMS (32 versus 12) with the laparoscopic approach. The laparoscopic group would have more vaginal cuff dehiscence but fewer venous thromboembolisms, wound infections, and incisional hernias — and would gain more quality-adjusted life-years.[8] Such an analysis can't provide definitive answers, but it offers a framework for considering population-level trade-offs.

THE POWER OF TRAGEDY

Yet disproportionate focus on harms caused by use rather than nonuse is common. In 2004, for instance, the FDA placed a black-box warning on antidepressants for pediatric and adolescent use because of concern that they increased the risk of suicidality, although untreated depression probably poses equal or greater risk.[11] Media stories

about adolescents harmed by these medications had frightened parents and physicians. Since then, untreated depression has increased among both adolescents and adults, and some data suggest that adolescent suicide rates have also increased.[12]

The tendency to focus on eliminating an immediate harm while failing to consider potentially greater harms caused by that reaction is heightened by the power of tragic stories. Major policy and behavioral shifts often arise from visible tragedies. Residents' duty-hour limits, for instance, sprang from the death of Libby Zion, which was attributed to resident fatigue; the death of Jesse Gelsinger during a gene-therapy trial led to an abrupt cessation of such research, delaying potential therapeutic benefits by years.

Not all anecdote-driven policies are misguided, but since we can't know in advance every consequence a regulation will have, it's worth considering how anecdote can skew risk perception, leading to estimates of the likelihood of outcomes based on how easy they are to imagine. At the individual level, such "availability bias" helps explain why we might hesitate to use anticoagulation therapy in a patient at risk for thromboembolism if we've just cared for a similar patient who had a rare bleeding complication. At a broader level, a tragedy that focuses attention on a potential harm may lead to reactive behaviors or policies that ultimately pose more danger than the original threat. After 9/11, for instance, there was a sharp uptick in deaths from car accidents: many Americans, afraid to fly, traveled by car instead, although the latter carries a far greater risk of death.[13]

In the case of morcellation, availability exaggerated the risk of LMS. Media coverage featured the faces of women dying of LMS, ravaged by chemotherapy, flanked in photos by their husbands and young children. Meanwhile, the benefits of morcellation are largely invisible and thus "unavailable." Who sees the women who undergo a minimally invasive procedure, recover quickly, and avoid losing income? What does a pulmonary embolus, a wound infection, or a hemorrhage that didn't happen look like? You can't post pictures of these nonevents on social media. But their nonoccurrence is why we ought to be celebrating.

The FDA recognizes stories' power to inform regulatory demands, and it carefully considers patient testimony; but as William Maisel, deputy director for science and chief scientist at the FDA Center for Devices and Radiological Health, emphasized, "In the end we come back to the data." In light of the poor data on the risks of morcellation and the existence of alternative approaches, it's hard to justify anything but extreme caution. Moreover, the FDA warning theoretically leaves the procedure available to patients who could benefit most, while better evidence is sought to clarify the comparative risks and safety of morcellation and its alternatives, such as morcellating fibroids in a contained bag.

But no matter how effectively the FDA separates reason from emotion in making decisions, its actions may ultimately carry less weight than the public outrage that catalyzes them. A less cautionary FDA stance on morcellation might not have tempered the tragedy's fallout. And although gathering prospective data on comparative risk is imperative, disgust over exposing women to an aggressive cancer with a barbaric-sounding tool is hard to overcome with evidence, no matter how low the risk of disseminating cancer is proven to be. Thus, although science may better define morcellation's trade-offs, at the core of this debate is an ideological divide that science not only is unable to address but may paradoxically widen. How do you use data to clarify tough trade-offs when the most compelling narratives paint evidence-based reasoning itself as anathema?

THE AVAILABILITY CASCADE

In 1992, faced with numerous anecdotes but limited data, the FDA banned the use of silicone breast implants for cosmetic purposes. Concerns first arose in the mid-1980s, when some cases of implant-associated autoimmune disease were reported. Given that about 1 million American women had received implants, about 10,000 of them would have developed autoimmune disease by chance alone.[14] But it seemed plausible that this foreign, "unnatural" substance could be toxic. When Dow Corning, the largest implant manufacturer, was accused of withholding knowledge of an increased risk of autoimmune disease, the narrative trifecta was complete: greedy corporation, vulnerable women, and self-

anointed "experts" who broadcast the purported harms, condemning anyone willing to propagate those harms as immoral.

None of the data collected in the 14 years between the moratorium and the FDA's 2006 approval of the implants for augmentation purposes supported the allegation that they caused autoimmune disease. But scientific reality mattered little to the media, the plaintiffs' attorneys, and the thousands of American women with implants, half of whom registered for the $4.25 billion class-action settlement with Dow Corning.[14] Many alarmed women also sought to have their implants removed. How did this unproven risk gain such traction?

The chain of events typified what Cass Sunstein and Timur Kuran call "an availability cascade," a phenomenon whereby stories inform public perceptions and anyone challenging those perceptions is vilified.[15] Media coverage featuring women describing how their lives were undone convinced many people that implants cause disease. The influence of such anecdote-driven representations of risk is as much social as cognitive: while people proclaiming the intolerability of the purported risk become heroes, those questioning its existence or magnitude are branded as heartless, so many people with a more accurate understanding of risk remain silent.

Availability cascades often depend on "availability entrepreneurs" who claim the moral high ground and exploit reporters eager to break stories of transgression. Public Citizen's Sidney Wolfe, for example, argued that the use of breast implants, which he claimed cause cancer, was one of the "worst examples of commercial exploitation of women as sex objects,"[16] and CBS's Connie Chung condemned the FDA for allowing "unsuspecting" women to be harmed.[14] Similarly, Sidney Zion told the story of his daughter's death at the hands of tired residents, convincing the public that it was morally reprehensible to allow residents to work such long hours. Afterward, anyone questioning the link between resident fatigue and patient harm was perceived as indifferent to patient safety.

The morcellation controversy has been perpetuated by an availability cascade, with Noorchashm, among others, casting the issue as a moral one. He argues that morcellation is a crime against women, reflecting medicine's corruption by industry greed. He has accused researchers who investigate morcellation's trade-offs of being criminally negligent and compared research examining the procedure's cost-effectiveness with the Nazis' euthanasia practices.[17]

Noorchashm admits he's crossed "professional boundaries" but argues that good behavior would be ineffective, so he has to "use a sledgehammer."[18] It's hard not to feel compassion for him and his family, and some of his points seem reasonable and resonant. For instance, he argues that informed consent merely fosters an "illusion of autonomy," which primarily protects physicians from lawsuits. He emphasizes the inadequacy of postmarketing surveillance, driven by underregulated efforts to collect data on rare harms. Moreover, he says he's been transformed by the tragedy, abandoning a promising surgical career for a mission of offering comfort to people undone by illness.

In the face of that mission, it seems cruel to argue for the benefits of morcellation while Reed fights for her life. It may also be disingenuous: What would the average physician advise a friend who was considering the procedure? Many nongynecologist physicians shudder at descriptions of the procedure — is there some message worth heeding in that reflex response? Yet whatever fear morcellation elicits, women may suffer more from its disuse. As Amanda Fader, a Johns Hopkins gynecologic oncologist, pointed out, in this reactionary climate, it's critical to recognize that one can have compassion and "leave emotion out of the equation."

Yet our capacity to speak science to emotion seems to be collapsing. As our patient-safety focus intensifies and physicians' behavior is publicly dissected, a story that goes viral has outsized power. Questioning narratives that portray the victimization of the innocent seems monstrous. The very forces that have created infinite outlets for expressing our views have paradoxically raised the stakes for offering controversial ones. Policy debates often degenerate, their crux shifting from "Do this solution's benefits outweigh its risks?" to "Are you good or evil?"

Noorchashm insists that it's unethical to consider morcellation's majority benefit when some individual patients may face such serious adverse consequences. But such reasoning could easily apply to giving ACE inhibitors to patients with

heart failure or tamoxifen to patients with breast cancer. Whether benefits outweigh risks is a value judgment, but evaluating such trade-offs is our job. Taken to their logical conclusion, arguments against assuming small risks in pursuit of larger social benefit imply that we're ethically obligated never to do anything.

To recognize that some women may benefit from morcellation is not to dismiss the pain of those it has harmed. But society suffers when there's no rational debate. Autonomy implies the right to choose something you want as well as the right to refuse something you don't. As negligent as it would be to fail to inform women like Ms. B. about risks, it is equally negligent to suggest that anything we do is free of trade-offs.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

Dr. Rosenbaum is a national correspondent for the *Journal*.

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