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“While there has been an enormous amount of attention focused on geographic disparity, the disparity for women in transplant has been well known, but not well discussed. This is a fixable disparity,” says Sommer Gentry, PhD, professor in the mathematics department at the United States Naval Academy in Annapolis, Maryland, and senior author of a recent paper describing a corrected Model for End-Stage Liver Disease-Serum Na (MELD-Na) score that the authors refer to as the MELD-Na-Shift.¹ By using a simulated liver allocation model to estimate the impact of implementing these corrections, the researchers found that use of MELD-Na-Shift eliminated sex disparity in transplant and mortality rates. “What we are trying to do with allocation of livers is to rescue more people who would otherwise die on the list,” says Dr. Gentry.

While this particular research focuses on livers, the reality is that women are disproportionately dying on all organ waitlists and, in many cases, the causes are specific to the organ.

The Liver

According to Dr. Gentry, the current MELD score underestimates women’s need for a transplant, and Kimberly Brown, MD, associate medical director of the Henry Ford Hospital Transplant Institute in Detroit, and a member of the Organ Procurement and Transplantation Network’s (OPTN) Liver and Intestine Committee, agrees. “The issue primarily comes down to muscle mass, which is related in large part to gender, but also to size,” explains Dr. Brown. Since women tend to have lower muscle mass, they also have lower creatinine levels and lower MELD scores, which places them at a disadvantage on waitlists.

According to Dr. Brown, the Committee is in the process of identifying ways to overcome this flaw in the allocation system. It is unclear whether this will mean giving women extra MELD points or recreating the scoring system, as suggested by Dr. Gentry’s research. However, precedence exists for giving extra MELD points.² The National Liver Review Board gives standardized MELD exceptions based on standardized criteria. These exceptions are intended to standardize what MELD means for any given patient. The effort to optimize the ranking of these exceptions is ongoing.

Once the Committee has decided on an approach to adjust the MELD score to address sex disparity, their recommendation will go to the OPTN board and then out for public comments. Any policy changes would require several months. If the change occurs at this pace, it would be remarkable. According to Dr. Gentry, OPTN has historically taken a conservative approach to making changes in allocation, as reflected in the 20 years it took to address geographic inequity.

KEY POINTS

• The sex disparity in transplant that negatively impacts women warrants more attention than it has received.
• Models suggest that an adapted MELD score can help mitigate sex disparity in liver transplant rates and mortality rates.
• For kidney donation, the real sex disparity lies in living donation because many women have pregnancy-induced incompatibility with spouse donors.
• Women waiting for heart transplants are more likely than men to die on the waitlist, likely because the current allocation system relies primarily on severity of illness.

Unfortunately, addressing the MELD score only solves part of the disparity problem. Women are also disadvantaged by their smaller size, as larger livers cannot be transplanted into smaller bodies. Per Dr. Gentry’s research, the proposed MELD-Na-Shift does not address this problem, which is, Dr. Brown notes, more difficult to address: Any effort to give points to women for their smaller size could theoretically disadvantage men of similar size, as well as pediatric patients.
Dr. Brown raises another aspect of sex disparity that is even more difficult for OPTN to address. "One of the struggles that some of us have is that allocation only works for people who get on the list," she says. "There's a lot of subjectivity when it comes to listing a patient for transplant." The existing sex disparity is revealed by a simple comparison of the higher severity of liver disease in women at listing as opposed to men, and the number of each who get waitlisted.

**The Kidney**

According to Deirdre Sawinski, MD, nephrologist and associate professor of medicine at the Hospital of the University of Pennsylvania (Penn) in Philadelphia, there is less of a sex disparity in waitlisting for kidney transplant than for liver transplant. She says that, in the case of kidney transplantation, the real disparity lies in living donation.

"The vast majority of living donors are women, and they are mostly giving to men," reports Dr. Sawinski. At her transplant center, slightly more women than men get donor referral forms, but, since most living donors are spouses, mothers are at a distinct disadvantage because many have pregnancy-induced incompatibility with spouse donors. While multiparous women are more prone to sensitization, resulting in a reduced number of compatible deceased donors, the effect is most pronounced for living donor kidney transplantation (LDKT). Dr. Sawinski found that these sex-specific differences in sensitization history and histocompatibility reduced the rate of LDKT for women by 30%.

Paired kidney exchange could go a long way toward solving the problem of sex disparity in kidney transplant. In paired kidney exchange, patients with incompatible donors swap kidneys to receive a compatible kidney. Dr. Sawinski found that participation in a paired kidney exchange program eliminated sex-based differences in LDKT. These exchanges, however, happen on a separate registry from the United Network for Organ Sharing (UNOS) National Kidney Registry, and are more expensive than traditional LDKT. Paired kidney exchange also requires additional staffing and additional time to educate donors and recipients. The extra cost must be absorbed by the transplant center, a factor that disincentivizes some centers from participating. Also, many donors and recipients are unaware of the existence of paired kidney exchange.

Incompatible transplant programs can help address the problem of sex disparity. The University of Alabama in Birmingham, for example, has advanced positive crossmatch transplantation following desensitization." This approach not only results in cost savings compared with remaining on dialysis but may represent a reasonable treatment option for sensitized patients—such as women—who would otherwise face extended waiting times and may never be able to achieve compatible transplantation.

**The Heart**

According to Dr. Sawinski, the biggest sex disparity in transplant occurs with hearts. As a kidney expert, she sees firsthand how most heart transplant recipients with kidney disease are men, but it was not until someone showed her the heart transplant waitlist mortality numbers that she fully processed the sex disparity. A 2014 analysis of adult patients in the Scientific Registry of Transplant Recipients found that women who were waitlisted as UNOS status 1A (high-risk patients) were 20% more likely than men to die on the waitlist. This disparity in waitlist survival rates persisted after rigorous multivariable risk adjustment and is of particular concern given the limited number of donor hearts available each year.

The heart transplant allocation system relies primarily on severity of illness and does not distinguish sex, despite known sex differences in cause, cardiac remodeling, response to therapy and prognosis. One solution to the identified sex disparity would be a shift from the current “rule-based” heart transplant allocation system to a “survival model-based” allocation system that would account for sex differences in survival. Another possible solution would be a modification of the heart allocation system to resemble the dynamic lung allocation system, wherein regression models are used to balance sex differences as disease progresses and assign a weight score that can be used to rank patients.

**Solving the Problem**

Dr. Sawinski feels that the transplant community needs to acknowledge the challenge of sex disparity. "Really, it's a problem hiding in plain sight," she says. In June, she co-hosted a virtual meeting entitled "Sex Disparities in Organ Allocation: Leveling the Playing Field" that covered organ-specific contributors to sex-based disparity in transplantation, organ-specific allocation policies, and medical and immunologic solutions to improve access. Dr. Sawinski emphasizes that the solutions to sex disparity in transplant covered in the meeting, and in this article, are not the only solutions, and encourages conversations on the topic to help increase awareness in the field.

"Part of it is recognizing that there is an issue and thinking creatively about how best to support women through the process," she says.

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