Can Gender Reassignment Surgery Modulate the Risk of Development of Autoimmune Diseases?

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Gender-specific medicine, known also as simply gender medicine, is the study of how the same disorder differs according to sex (i.e., between males and females) and to gender (i.e., men and women) in terms of epidemiology (incidence and prevalence), etiopathogenesis, clinical presentation, preventative and management/therapeutic approaches, and prognosis, as well as the psychological impact and societal burden imposed by the disease itself. Despite its importance, it is generally an overlooked dimension of medicine. The coronavirus disease-2019 (COVID-19) pandemic has shown that adopting a gender-specific perspective is of paramount importance, given the sex- and gender-specific outcomes of the viral outbreak.

Both sex and gender, rather than being opposite endpoints within a rigid dichotomy, can be seen as a spectrum: a continuum ranging from men/masculine to women/feminine. In some cases, sex and gender may not be aligned: in these circumstances, sex or gender reassignment surgery (SRS/GRS), known also as gender-affirmation/confirmation surgery (GAS/GCS), refers to those surgical procedures that, together with clinical/pharmacological treatments (such as hormonal therapy), enable transgender people to affirm their gender identity. This kind of surgery significantly reduces gender dysphoria and rates of suicide and depression as well as improving sexual performance and satisfaction and quality of life [1,2].

Transgender/transsexual individuals have specific healthcare needs, which are often unmet [3]. For this reason, recently, in 2021, the Israeli Health Ministry, recognizing these health needs, released new, updated guidelines aimed at codifying how public health systems, including hospitals, health maintenance organizations (HMOs), and other healthcare facilities should relate to this community.

Elias et al. [4], in their article in this issue of *Israel Medical Association Journal* (*IMAJ*) on chest masculinizing GAS in transgender men, reviewed mastectomies conducted at their center in a sample of 110 female-to-male (FTM) transgender people. The authors proposed a holistic approach to transgender healthcare based on the World Professional Association for Transgender Health (WPATH) standard of care. Last, authors introduced Wolf's classification for FTM transgender mastectomy.

Elias and colleagues filled a major gap in the knowledge of transmasculine chest surgery. Indeed, according to a recent critical appraisal of the scholarly literature [1], while there are many data available about male-to-female (MTF) transgender surgeries [5] less is known about FTM surgical procedures. A systematic review [6] synthesized 22 studies, totaling a sample of 2447 patients undergoing FTM transgender surgery, and noted that further research is warranted to improve patient eligibility criteria and selection, surgical decision making-related processes, and patient-reported outcome measures (PROMs) for different chest surgical approaches. Moreover, some issues like the shape, the size, and the location of the ideal nipple-areolar complex (NAC) are still debated [7]. Elias et al. [4] advanced the field with their series of patients, contributing not only in terms of improved surgical techniques and algorithms but also by addressing the issue from a holistic and integrated lesbian-gay-bisexual-transgender-queer (LGBTQ+) lens.

Transgender medicine represents an emerging, highly multidisciplinary branch of medicine, which is at the intersection of several specializations, ranging from endocrinology to urology/andrology and gynecology [8]. Several aspects are highly understudied and neglected in the current literature, warranting further research. For example, it is known that, while silicone used in breast implants in aesthetic and reconstructive breast surgery for breast augmentation has been considered rela-

tively safe, it has been associated with the possible insurgence of malignancies and autoimmune/autoinflammatory adverse reactions. One of the facets of breast implant illness (BII) is the breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), which is a quite rare peripheral T-cell lymphoma [9]. Silicone incompatibility has been linked with the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) or Shoenfeld's syndrome [9,10]. Watad and colleagues [10] conducted a cross-sectional epidemiological survey, mining the database of the Maccabi Healthcare Services, one of the most important HMOs in Israel. The authors recruited 24,651 silicone breast implant recipients and 98,604 matched breast implant-free women. The adjusted odds-ratio indicating the risk for developing any autoimmune/autoinflammatory rheumatological condition having received a silicone breast implant was 1.22 (95% confidence interval 1.18–1.26). The most statistically robust associations were found for Sjögren's syndrome, systemic sclerosis, and sarcoidosis. However, most data on the risk of autoimmunity following silicone breast implants have come from studies that were conducted in women rather than MTF transgender subjects. The epidemiology of malignancies and autoimmune/autoinflammatory rheumatological disorders in MTF who have undergone breast augmentation is poorly understood. Four cases of BIA-ALCL have been documented in the literature [11]. Concerning autoimmunity and autoinflammation, for example, Campochiaro and co-authors [11] described three clinical cases of systemic sclerosis in MTF under hormonal therapy. Their findings are particularly intriguing because systemic sclerosis is known to be predominant in women, probably due to the role of female hormones in the etiopathogenesis of the disease. The interplay between silicone breast implant and hormonal therapy, in terms of overall risk for developing an oncological/rheumatological disorder, has yet to be fully elucidated.

CONCLUSIONS

There are current knowledge gaps in the field of gender medicine, and the potential impact of gender reassignment surgeries on the risk of developing autoimmunity.

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Capsule

CORONAVIRUS immune imprinting

For severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), immune responses to heterologous variants are influenced by a person's infection history. Healthcare workers (HCWs) may be exposed to several doses and types of antigens, either by natural infection or by vaccination. **Reynolds** and co-authors studied a cohort of UK HCWs followed since March 2020. The immunological profiles of these people depended on how often the subject had encountered an antigen and which variant was involved. Vaccine responses after infection were found to be less effective if the infection involved heterologous spike from a variant virus. Unfortunately, the N501Y spike mutation, found in many variants, seems to induce the regulatory T cell transcription factor FOXP3, indicating that the virus could subvert effective T cell function. Changes to antibody binding between variants also means that serology data using the Wuhan Hu-1 S1 receptor-binding domain sequence may not be a reliable measure of protection.

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