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Current Challenges in Female Veterans' Health

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Abstract

Women in the U.S. military are technically barred from serving in combat specialties, positions, or units; however, since Operation Desert Storm, women have served in forward positions in greater numbers. This increased involvement in combat zones has resulted in exposures to trauma, injury, and a myriad of environmental hazards associated with modern war. Some of these hazards present new health risks specifically relevant to women who have been deployed to or recently returned from Iraq or Afghanistan or both. To address this evolving public health concern, the Society for Women's Health Research (SWHR) convened a 1-day interdisciplinary scientific conference, with speakers and attendees from civilian, military, and veteran settings. The purpose of the conference was to reveal the state-of-the-science on the health of the female veteran and to focus attention on recent advances in biomedical research related to female veterans' health. The following topics were discussed: mental health (posttraumatic stress disorder [PTSD] and depression), urogenital health, musculoskeletal health, and traumatic brain injury (TBI).

Introduction

In July 2011, the Society for Women's Health Research (SWHR) convened a 1-day, interdisciplinary scientific conference on female veterans' health entitled, "What a Difference an X Makes: The State of Women's Health Research. A Focus on Female Veterans." Researchers and medical professionals from academia and the military presented new research findings and shared future perspectives related to the female veteran population. This report focuses on research highlights related to mental health (posttraumatic stress disorder [PTSD] and depression), urogenital health, musculoskeletal health, and traumatic brain injury (TBI).

According to the conference's Keynote Speaker, Betty Moseley-Brown, Ed.D., Associate Director of the Veterans Administration (VA) Center for Women Veterans (CWV), there are nearly 1.84 million living female veterans (8.1%) of the approximately 23 million surviving veterans in the United States, and this number is projected to increase.[1] Further, the number of female veterans enrolled in VA healthcare is expected to double in the next 5 years.[2] The Congressionally mandated CWV is meeting the needs of female veterans by monitoring and coordinating VA programs for women and advocating for a cultural transformation within the military and among civilians to recognize the service and contributions of women in the military.[3] The CWV also strives to connect female veterans to the VA and provide them with essential programs, including employment, suitable housing, child care options, and opportunities for social interaction (B. Moseley-Brown, personal communication). In order to help the VA to better serve and improve health outcomes of the growing female veteran population, future biomedical research must consider the specific needs of this unique population. The following discussions of the latest research in PTSD, depression, urogenital health, musculoskeletal health, and TBI in female veterans emphasize this requirement.

Posttraumatic Stress Disorder

Women and PTSD: Are women veterans different?

PTSD is defined by symptoms that last >1 month and include reexperiencing of a traumatic event, persistent avoidance of stimuli associated with a traumatic event, and numbing of general responsiveness and persistent symptoms of increased arousal, both absent before the traumatic event. Kathryn Magruder, M.P.H., Ph.D., Medical University of South Carolina, stated that PTSD is twice as prevalent in women (10.4%–12.3%) as in men (5.0%–6.0%).[4,5] However, trauma exposure is more common in men than women (61% vs. 51%), and men are more likely to be exposed to multiple traumatic events.[5] Men also experience a wider variety of trauma types (fire, disaster, physical assault, combat, threat with a weapon) compared to women (sexual assault/child abuse). These data present a PTSD paradox: If men have more traumatic experiences, why do women have more PTSD? Dr. Magruder suggested three reasons for this paradox: (1)

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women experience traumas that are higher risk for PTSD, specifically sexual assault/abuse, (2) women have longer duration of PTSD symptoms, and (3) women have stronger reactions to traumatic events.

Dr. Magruder discussed additional studies investigating the interplay among gender, traumatic events, and PTSD in veterans. Studies have demonstrated similar PTSD risk between male and female veterans, but compared to male veterans, female veterans experience fewer combat situations and are exposed to more military sexual trauma (MST).[6,7] It is not known, however, if the rates and types of premilitary trauma differ between male and female veterans or if the currently used trauma exposure scales capture the experience of women differently. Dr. Magruder stressed additional research gaps related to comparisons between female veterans and nonveterans, such as a lack of prevalence data regarding PTSD, rates of sexual harassment/assault, and social support. Prevalence data also are unavailable to indicate differences among populations of female veterans, such as variations in trauma exposures experienced by female veterans in different war eras. In conclusion, Dr. Magruder emphasized the need to continue to be sensitive to gender issues in terms of prevention, detection, and advancing treatment of female veterans.

Stress X gender: What we know and don't know about the neurobiology of PTSD in women

According to Ann Rasmusson, MD, Boston University School of Medicine, even though PTSD prevalence is higher in women in the general population, recent studies have not demonstrated sex differences in risk in the military. In a study of 340 female and 252 male Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans within 1 year of deployment, no sex differences were observed in risk for posttraumatic stress symptoms, mental health functioning, or depression when controlling for combat-related exposure.[8] Despite these findings, Dr. Rasmusson believes that further research should investigate the influence of biologic sex on the neurobiology of PTSD, which could ultimately result in better treatments.

Dr. Rasmusson described studies investigating the role of several neuromodulators of the stress response that may uniquely influence risk, recovery, and comorbidity of PTSD in women. Allopregnanolone and its stereoisomer, pregnanolone (ALLO), are neurohormones synthesized from progesterone in the brain and released from the adrenal glands in response to stress. One study by Dr. Rasmusson et al. examined the levels of progesterone and ALLO in the cerebrospinal fluid (CSF) of healthy women and women with PTSD.[9] During the follicular phase of the menstrual cycle, ALLO levels in women with PTSD were only 40% of levels in healthy controls and were negatively correlated with PTSD and depression symptoms (A. Rasmusson, personal communication). It appeared that there was a block in the conversion of progesterone to ALLO. Consistent with these findings, further pilot data showed that both CSF progesterone and ALLO levels in healthy women increased by 200%–300% between the follicular and luteal phases of the menstrual cycle, as expected, whereas in the pilot subject with PTSD, progesterone increased by 500%–600%, but ALLO levels increased by only about 25%. A more definitive study of ALLO levels across the menstrual cycle in women with PTSD is underway.

Dr. Rasmusson described how sex differences in ALLO modulation may influence PTSD in women and men. The male gonadal hormone testosterone increases gene expression of an enzyme that synthesizes ALLO. A study of male participants in the U.S. Military's Survival, Evasion, Resistance and Escape training (SERE School) found that extreme training stress decreased testosterone.[10] A study is underway to ascertain if ALLO level are also low in men with PTSD. Other studies have examined cortisol output, another stress hormone, in men and women with comorbid PTSD/major depressive disorder (MDD).[11,12] Results demonstrated decreased cortisol output in men but an increase in women with PTSD/MDD. Because ALLO provides negative feedback to the hypothalamic-pituitary-adrenal axis, it is possible that low ALLO levels in women with PTSD/MDD contribute to the high cortisol levels in these women. In other PTSD subpopulations in whom cortisol synthesis may be limited under stress, it is possible that the low cortisol levels may contribute to low ALLO levels. Dr. Rasmusson, therefore, emphasized that the mechanisms underlying the neurobiology of stress and PTSD are highly complex and are likely to exhibit sex differences.

Depression

Sex steroids and affective adaptation in women

Depression is twice as prevalent in women as in men and is a leading cause of disease-related disability in the western world, according to Peter Schmidt, M.D., National Institute of Mental Health (NIMH), National Institutes of Health (NIH). Depression causes increased risk for osteoporosis, cardiovascular disease, metabolic syndrome, dementia, and 50% cardiovascular mortality in postmenopausal women. Lifetime prevalence of unipolar depression in women is higher compared to men (15%–25% vs. 4%–12%). In spite of this, depression still remains undiagnosed and undertreated, and the efficacy of long-term use of selective-serotonin reuptake inhibitors (SSRIs) is disputed.

Sex differences in the effects of reproductive steroids on the brain may help explain a woman's greater susceptibility to depression. Whereas much research has been done to investigate the basic physiology behind depression in general, Dr. Schmidt stated that no physiologic research has been done specifically in female veterans. Levels of reproductive steroids fluctuate at hormonal transitions across the female life span, which are critical time points for susceptibility to mood disorders, such as perimenopausal depression and premenstrual dysphoric disorder (PMDD).[13,14] The menopause transition is associated with increased risks of both first-onset and recurrent depression, with episodes clustering during the late menopause transition and early postmenopause. The prevalence of depression in these groups is 20%–30%. In a small study Dr. Schmidt's group conducted at NIMH, estrogen induced remission of depressive symptoms in perimenopausal women with depression.[15] Additional data demonstrated that estrogen withdrawal precipitated depressive symptoms in only those perimenopausal women who had past major or minor depression (within 2–4 years). Dr. Schmidt stressed that a direct link between estrogen loss at the menopause transition and depression has not been firmly demonstrated.

Changes in levels of sex steroids also play a role in PMDD (prevalence 3%–8%), with symptoms occurring in the luteal

phase of the menstrual cycle when progesterone and estrogen levels increase. Interestingly, women who suffer from PMDD do not exhibit abnormal levels of gonadal hormones, again indicating differential susceptibility to gonadal influences on depression among women. Treatments for PMDD may involve SSRIs or therapies that suppress hormonal fluctuations and ovulation. A study using Lupron, a gonadotropin-releasing hormone agonist that suppresses ovarian hormone production, demonstrated reduction in PMDD symptoms and provided evidence for gonadal hormone effects on brain function.[13]

Depression and other mental health conditions among OEF/OIF women veterans

Kristin Mattocks, Ph.D., M.P.H., Yale University, cited three key points regarding female veterans seeking mental healthcare at the VA by referring to data published in the sourcebook entitled *Women Veterans in the Veterans Health Administration*, Volume 1 (December 2010). First, the VA must pay immediate attention to the needs of very young and elderly female veterans and must prepare for an impending large, new cohort of elderly female veterans. Second, between 2000 and 2009, the proportion of female veterans with service-connected disabilities increased. Finally, both men and women have a high frequency rate for mental health visits at the VA, but the rate for women is higher than that of men after age 45. Additional studies demonstrated that OEF/OIF post-deployment (1–6-years window) depression rates were consistently higher among women compared to men.[16,17]

Dr. Mattocks discussed two of her research projects using the Women Veterans Cohort Study (WVCS) launched in 2007. The WVCS plans to (1) assess gender differences in healthcare costs, service use, and health outcomes among OEF/OIF veterans enrolled in VA care and (2) examine pregnancy and mental health among OEF/OIF veterans. The first project involves assembling an administrative cohort (550,849 men, 74,535 women) of OEF/OIF veterans in the Northeast and Midwest. A prospective survey is collecting data on combat exposure, MST, quality of life, non-VA care, reproductive health history, pain, eating behaviors, and so on. The second project is studying pregnancy and mental health conditions among OEF/OIF female veterans. Untreated mental health conditions during pregnancy may lead to poor maternal outcomes (substance abuse, loss of employment, divorce, and suicidal ideation/suicide), poor outcomes in offspring (low birth weight and infant neglect/abuse), and maternal depression. This has been studied extensively, but few studies have focused on female veterans and depression/PTSD during pregnancy. Dr. Mattocks emphasized that studying pregnancy and concomitant mental health problems in the VA is complicated, as contract providers (fee basis) outside the VA provide most prenatal care in the VA. Therefore, little information is available about the quality of prenatal care or the outcomes of pregnancy.

Results from the WVCS pregnancy project demonstrated that compared to nonpregnant veterans, veterans with a pregnancy were more likely to be younger, Hispanic, unmarried, less educated, enlisted service members rather than officers, and active duty service members rather than members of the Guard or Reserves.[18] Interestingly, veterans with a pregnancy were twice as likely to receive a mental health diagnosis during pregnancy compared to nonpregnant veterans. Most of these pregnant veterans experienced mental health conditions before pregnancy. Dr. Mattocks discussed the implications of her study, which are (1) many OEF/OIF female veterans suffer from significant mental health problems, and it is unclear if these are a direct result of combat/trauma exposure, (2) patterns of VA and non-VA care among OEF/OIF female veterans, including use of VA and private mental healthcare during pregnancy, are not well understood, (3) coordination between VA and private obstetric and mental health systems is crucial, and (4) private providers should inquire about veteran status, ask about combat/trauma exposure, and screen for mental health conditions, including PTSD.

Urogenital Health

Pelvic floor disorders in female veterans

Christine Sears, M.D., Walter Reed National Military Medical Center, discussed urogenital health disorders (urinary tract infections [UTIs], pelvic organ prolapse [POP], urinary incontinence [UI], and bladder pain syndrome [BPS]) and how the military environment may expose women to higher risk for these conditions. One study determined the UTI prevalence in veterans to be 4.3% in women and 1.7% in men.[19] Women in active duty are often exposed to conditions that may increase their risk of UTI, such as poor hygiene, decreased access to care and bathrooms, postponed urination, and fluid restriction, and data from a study of 841 deployed women reported that 18.4% experienced UTI during deployment.[20]

POP is defined as the descent of the bladder, uterus, and rectum as a result of weakening of the muscles and connective tissue within the pelvic floor. Risk factors for POP include age, number of vaginal and multiple deliveries, high birth weight deliveries, chronic cough, obesity, genetic susceptibility, and manual labor.[21] POP may be a concern for women in the military, as strenuous activity, including basic and paratrooper training, could increase risk above that caused by general risk factors. Dr. Sears presented data from an observational study of 116 women at the United States Military Academy (USMA), where 50% of the women exhibited some loss of pelvic support after training.[22] A follow-up study revealed a significant correlation between paratrooper training and worsening pelvic support and prolapse.[23] Although this particular study implicates strenuous military training on the future pelvic health of female veterans, additional studies are needed.

Dr. Sears stressed that areas for future study also include addressing the long-term effects of strenuous military activity and other high impact exposures on UI. UI, which is leakage of urine, is defined as stress incontinence (caused by coughing, sneezing, laughing, jumping, and exercise) or urge incontinence (feeling the need to urinate). According to Dr. Sears, a study of over 3.5 million users of VA healthcare services reported prevalence of primary diagnosis UI to be 2.2% in women and 0.5% in men.[19] Dr. Sears referred to the USMA study data that demonstrated 19% of the women had UI, which was more commonly associated with running as the aerobic activity.[22] Finally, BPS is a chronic condition that causes pain with filling of the urinary bladder and severely impacts quality of life. A study of VA users from 1999 to 2002

found that women were almost twice as likely as men to suffer from BPS.[24] Interestingly, the prevalence of BPS and other urologic health conditions in this veteran population increased during this time period, emphasizing the need for future research.

Musculoskeletal Health

Female casualties of Operations Enduring Freedom and Iraqi Freedom

CPT Jessica Cross Rivera, M.D., San Antonio Medical Center and U.S. Army Institute of Surgical Research, provided four statements on current casualty data: (1) the rate of survival after combat injury is higher in OEF/OIF compared to the Vietnam War and World War II, (2) most (54%) of the OEF/OIF injuries are orthopaedic in nature and cause most of the long-term disability, (3) women experience more nonbattle injuries than men, and (4) women with battle injuries have higher mortality than men. Combat musculoskeletal injuries to the extremity were caused most often by explosions and were associated with disabilities and degenerative arthritis, which ranks as the most common unfitting condition and cause of long-term disability for combat-injured service members.[25–27]

According to CPT Cross Rivera, casualties in women serving in OEF/OIF or overseas contingency operations account for < 2% of all casualties, and of these, 61% are nonbattle injuries.[28] Compared to the nearly equal mortality rates of wounded soldiers in Iraq (14% women vs. 12% men), a striking 36% fatality rate exists for female casualties in Afghanistan compared to 17% in men.[28] The reason for the fatality disparity by deployment region and gender, as well as the types of combat exposures most likely to cause fatal injuries in female soldiers, is unknown. More research related to the female soldier's response to injury is necessary, including acute physiologic reactions, exposure and evacuation, root cause of mortality, rehabilitation differences, and long-term disability outcomes.

Developing technologies for the wounded warrior

Barbara Boyan, Ph.D., Georgia Institute of Technology, emphasized the need for advances in technology specifically for the wounded warrior. Wounds sustained by military personnel during deployment are highly complex, involving multiple tissues, such as skin, muscle, nerve, vasculature, tendons, ligaments, and bone. The unique nature of injuries suffered in modern combat zones poses new challenges for biomedical engineers, as the nature of these wounds is not commonly experienced in civilian trauma. In a study of service members from OEF/OIF, the majority of combat injuries were to the extremities (54%) and head and neck (29%).[27] Although studies on cartilage damage and reconstruction in the knee in civilian populations are extensive, Dr. Boyan stated that research has not focused on the nose and trachea, which are important areas of cartilage damage in soldiers. Researchers must understand differences in the healing processes of a variety of body regions to improve outcomes in all wounded service members.

In addition, new technologies to treat combat injuries must incorporate the study of sex differences; however, most technologies for treating wounds were designed and tested using male animal models. Dr. Boyan stated that sex differences have been demonstrated *in vitro* in bone cells (e.g., male cells respond better to vitamin D) and in tissue grafting (e.g., female cells respond better to surface design approaches), which indicate a potential influence of sex on healing and regeneration. Therefore, the long-term outcomes of regenerative strategies may be influenced by sex, and technologies must be responsive to sex-based differences accordingly for optimum results. The sex-based effects observed in the cited studies highlight the need to closely evaluate sex differences in the evolution and application of new technologies.

Dr. Boyan focused on efforts of the Center for Advanced Bioengineering for Soldier Survivability (CABSS), which was established by Congress to address the crucial need for regenerative medicine related to combat injuries.[29] In collaboration with the Georgia Institute of Technology, CABSS develops new treatments tailored specifically for wounded warriors. One goal of CABSS is to develop enabling technologies for intraoperative and percutaneous delivery of musculoskeletal stem cells for treatment of bone and cartilage injuries to the extremities, head, and neck. Further, CABSS has established animal models that mimic injury of composite tissue, which closely mirrors battlefield wounds. CABSS is developing new technologies for bone and facial reconstruction, making stems cells clinically useful, and translating basic science to commercially available treatments that provide better outcomes to wounded military personnel.[30]

Traumatic Brain Injury

Traumatic brain injury: Same or different?

TBI covers a spectrum of injury severity and is categorized as mild (brief period of cerebral dysfunction followed by a relatively rapid improvement in condition), moderate (manifested by longer periods of cerebral dysfunction often with more noticeable posttraumatic signs and symptoms), and severe and penetrating (often requiring prolonged hospitalizations, with a less predictable long-term recovery). According to Kimberly Meyer, ACNP-BC, CNRN, Defense and Veterans Brain Injury Center and University of Louisville Hospital, TBI severity distribution between the military and civilian population is similar, and mild TBI is by far the largest percentage of injury severity in both sexes. Men sustain the majority of TBIs, and there are few published studies on TBI in women in the military. Of the 81,850 cases reported in 2010 by the Armed Forces Health Surveillance Center, 12% (9,732) of the cases were women with a TBI diagnosis. Ms. Meyer emphasized that when discussing the impact of TBI on female veterans, it is important to consider that (1) the differences in blast and blunt trauma may play a role in treatment paradigms and recovery and (2) emerging literature suggests that gender differences may play a role in recovery.

Ms. Meyer mentioned that several studies have looked at gender differences and their impact on mortality after TBI in civilians, but results have been inconsistent. For example, Yeung et al., found no gender differences in mortality in Asian and Australian subpopulations, whereas Dischinger et al. reported that women > age 55 had higher mortality than men following isolated, severe TBI.[31,32] Gender differences in symptom type during long-term TBI recovery have been documented, but studies differ on which gender has better outcomes.[33–35] Except for visual memory, which may be

better in women, similar cognitive outcome was observed in men and women with TBI[36]; however, men were found to have higher risk for developing dementia after TBI.[37] Regarding rehabilitation, older women fared better than men, had shorter length of rehabilitation stay, and had increased use of home health services.[38] Ms. Meyer stressed that gender differences studies may have variable results because of selection bias, sample size, and injury severity; therefore, scientifically rigorous studies are needed.

Hidden in plain sight: How sex differences led us to a treatment for traumatic brain injury

According to Donald Stein, Ph.D., Emory University, an estimated 1.4 million TBIs per year are diagnosed in the United States alone, resulting in 50,000 deaths annually. At least 5.3 million Americans have long-term/lifelong disability due to TBI. In 2004, the economic burden (medical and indirect costs due to loss of productivity) of TBI was estimated at $60 billion. Dr. Stein provided data from the Trauma Registry, U.S. Army Institute of Surgical Research, which reported that at Walter Reed Army Medical Center, 28% of the evacuated injured military personnel from Iraq and Afghanistan who had sustained hostile fire injuries had TBI.

Dr. Stein emphasized that there currently is no treatment to stop loss of brain cells postinjury. Dr. Stein believes that TBI is one of the toughest problems in medicine because the injury to the brain (and destruction of brain cells) is immediate following trauma, and the many complicated biochemical processes after injury continue to destroy brain cells and affect multiple organ systems from days to weeks postinjury. The potential use of progesterone as a TBI therapy was based on three crucial early observations by Dr. Stein: (1) anecdotal reports suggested women recover better from stroke and trauma than do men, (2) the specific estrous cycle phase at the time of brain injury in female rats affected outcomes, and (3) female rats high in progesterone at the time of injury had better outcomes than animals high in estrogen when the brain damage was inflicted. Further, exogenous progesterone treatment significantly reduced cerebral edema in female and male animals and improved functional recovery in cognitive/sensory tasks and motor performance. As Dr. Stein explained, progesterone is naturally present in brains of both sexes, dramatically reduces brain swelling, has potent anti-inflammatory and anti-oxidant properties, and stimulates growth factor expression in response to injury. A successful phase 2 clinical trial, ProTECT II, for brain injury showed a lower mortality rate in the progesterone treatment group compared to placebo over a 30-day period. [39] These results were corroborated by an independent clinical trial in China,[40] and two phase 3 trials are currently ongoing. Thus, progesterone may be an ideal TBI therapy, and further studies into the amount and timing of delivery are required.

Conclusions

Although women are technically barred from serving in combat, since Operation Desert Storm, women have been deployed to forward positions in greater numbers. This increased involvement in combat zones and the associated risk from exposure to trauma, injury, and environmental hazards present new health consequences for woman that must be addressed for both actively serving women and female veterans. Considering that the female segment of the military continues to increase, female veterans' health must be situated at the forefront of the biomedical research and health policy agendas. Biomedical research in veterans that incorporates the study of sex and gender differences will translate to better health outcomes for female veterans and will help the Department of Veterans Affairs to better serve the needs of female veterans. Access to gender-appropriate care and an advanced understanding of the unique health needs of the female veteran are essential. Improved outreach should continue to raise further awareness among the female veterans seeking healthcare and also interest researchers to pursue areas within their work that include studies relevant to female veterans.

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