**Genome and Hormones: Gender Differences in Physiology**

Invited Review: Gender issues related to spaceflight: a NASA perspective

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Harm, Deborah L., Richard T. Jennings, Janice V. Meck, Michael R. Powell, Lakshmi Putcha, Clarence P. Sams, Suzanne M. Schneider, Linda C. Shackelford, Scott M. Smith, and Peggy A. Whitson. Invited Review: Gender issues related to spaceflight: a NASA perspective. **J Appl Physiol** 91: 2374–2383, 2001.— This minireview provides an overview of known and potential gender differences in physiological responses to spaceflight. The paper covers cardiovascular and exercise physiology, barophysiology and decompression sickness, renal stone risk, immunology, neurovestibular and sensorimotor function, nutrition, pharmacotherapeutics, and reproduction. Potential health and functional impacts associated with the various physiological changes during spaceflight are discussed, and areas needing additional research are highlighted. Historically, studies of physiological responses to microgravity have not been aimed at examining gender-specific differences in the astronaut population. Insufficient data exist in most of the discipline areas at this time to draw valid conclusions about gender-specific differences in astronauts, in part due to the small ratio of women to men. The only astronaut health issue for which a large enough data set exists to allow valid conclusions to be drawn about gender differences is orthostatic intolerance following shuttle missions, in which women have a significantly higher incidence of presyncope during stand tests than do men. The most common observation across disciplines is that individual differences in physiological responses within genders are usually as large as, or larger than, differences between genders. Individual characteristics usually outweigh gender differences per se.

**CARDIOVASCULAR PHYSIOLOGY**

Orthostatic intolerance. There is a gender-related difference in the occurrence of postflight orthostatic
intolerance (presyncope during a stand or tilt test) after space shuttle missions (Fig. 1). Presyncope is defined as a sudden dip in systolic blood pressure of \( >25 \) mmHg or in diastolic blood pressure of \( >15 \) mmHg, a sudden and sustained drop in heart rate \( >15 \) beats/min, an absolute heart rate \( <40 \) beats/min for those whose resting absolute heart rates were \( >50 \) beats/min, and absolute systolic blood pressure of \( <70 \) mmHg. In both the database of experimental results and the database of routine postflight medical tests, women had a much greater incidence of presyncope during the postflight stand test (21). Generally, women have lower blood pressure and peripheral vascular resistance and higher heart rates than men. In addition, women respond to cardiovascular stress with greater heart rate increases, whereas men respond primarily with greater increases in vascular resistance. In a previous study designed to examine postflight orthostatic intolerance, the presyncope astronauts (5 women and 3 men) were found to have greater increases in heart rate, greater decrease in blood pressure, and less of an increase in peripheral resistance in response to the postflight stand test than their non-presyncope counterparts (2 women and 19 men). It was suggested that indirect vasodilatory effects of estrogen in premenopausal women may contribute to smaller vasoconstrictive responses in women compared with men during orthostatic stress (21).

Evidence exists in the scientific literature to support the hypothesis that women have less tolerance to upright posture or gravitational stress than men (18, 19, 22). This type of research is currently funded by NASA and the U.S. Navy, organizations that are sensitive to this issue because of their increasing numbers of female pilots. Preliminary data from our laboratory support the hypothesis that women are less able to tolerate upright posture, primarily because of a reduced ability to maintain venous return and cardiac output. Data for long-duration spaceflight are very limited, but the first six American astronauts who flew aboard Mir (almost all of whom were men) had an 85% failure rate during the postflight tilt test. Thus it appears that gender-related differences may be overridden by long-duration flight. More subjects are needed before that determination can be made. However, it is evident that more effective countermeasures must be developed for all crewmembers.

**Ventricular dysrhythmias.** New data suggest that cardiac dysrhythmias may be of greater concern during long-duration than short-duration spaceflight (20). We know of no data from in-flight cardiovascular (Holter) monitoring of women on either shuttle or Mir missions. However, there have been several reports of ventricular dysrhythmias in men. In the general population, men in this age group have a greater risk of ventricular dysrhythmias than women. It would, therefore, be expected that in the astronaut population this would hold true as well (30, 34).

**EXERCISE PHYSIOLOGY**

At the present time, 22% of the active astronaut corps are women (35 of 158) (see Table 1). The average female astronaut is 42 yr old (43 yr for men) and weighs 60.7 kg (81.2 kg for men). In general, the average woman is 10 cm shorter and 13 kg lighter and has 11% more body fat, 8% less muscle mass, 10–14% less hemoglobin mass, and a lower level of aerobic fitness (37) than her male counterpart. These gender differences can be expected to influence exercise capacity and thus the ability to perform specific tasks during spaceflight.

**Aerobic fitness.** The average aerobic fitness, expressed as the maximal oxygen uptake (\( \dot{V} \text{O}_2 \text{max} \)), of adult women is 2.0 l/min, compared with 3.5 l/min for men. When adjusted for differences in body weight, the average \( \dot{V} \text{O}_2 \text{max} \) for women is 40 vs. 50 ml·kg\(^{-1}\)·min\(^{-1}\) for men (37). These differences can be reduced still
the adult man. Upper body strength of the woman is about two-thirds that of the adult woman. This would result in a higher heart rate, higher body temperature, greater stress, and a quicker onset of fatigue during the exercise. These more severe exercise responses may result in a greater number of injuries and less tolerance for a stressful environment. For example, in a study of 124 men and 186 women during basic combat training, the women had a 51% injury rate compared with 27% for the men (27).

The average woman is less active and less fit than the average man. Therefore, when exercise data are normalized for fitness, the gender differences often are greatly reduced. If allowed to work at a similar percentage of their maximal exercise capacity, men and women would have similar cardiovascular and thermoregulatory responses. However, men tend to be faster than women during aerobic events due to their greater muscle strength and the mechanical advantage of their longer arms and legs. Women, on the other hand, tend to have a greater endurance capacity due to a greater reliance on fat metabolism during exercise; thus a glycogen-sparing effect might delay fatigue during long-duration events (58).

The average female astronaut has a peak oxygen uptake (VO_2peak) of 2.19 l/min or 36 ml·kg^{-1}·min^{-1} (see Table 1) when normalized for body weight (3.55 l/min and 44.2 ml·kg^{-1}·min^{-1} for men). These VO_2peak values probably underestimate fitness, however, because the clinical treadmill test used to evaluate astronauts is stopped when subjects reach 85% of their age-predicted maximal heart rate. Actual aerobic capacity is probably ~15% higher than reported, which would increase average female fitness to ~2.5 l/min, or a “very good” fitness for their age, and increase the male value to 4.1 l/min, or an “excellent” level of aerobic fitness (54).

At this time, there is not sufficient data to compare the degree of aerobic deconditioning after spaceflight between men and women. However, in response to bed rest, the relative changes in aerobic capacity are similar between men and women (9), despite the marked differences in absolute values.

**Strength.** There are obvious strength differences between the average man and the average woman. Body strength of the adult woman is about two-thirds that of the adult man. Upper body strength of the woman is ~50% that of the man, whereas lower-body strength is ~70% (37).

Few data exist concerning strength changes in women after spaceflight or bed rest. Regional decreases in muscle volume were similar in two men and two women after 8 days of spaceflight (31). Some reports, however, indicate that women have a greater percentage of slow-twitch muscle fibers than men (40). Slow-twitch muscle fibers appear to be more affected by spaceflight than the fast-twitch fibers (14). If this is the case, then women may be more susceptible to changes in muscle mass and endurance. This hypothesis has yet to be tested. In response to strength training, women and men have a similar proportional increase in lean body mass and strength, yet the total muscle girth of the women is less (37). These consistent differences in muscle mass of men and women are believed to be attributable to the anabolic effect of the 20- to 30-fold greater concentration of testosterone in men.

**Performance of extravehicular activity.** The 50% less upper body strength of the average woman would put her at a disadvantage in performing vigorous upper body work, such as certain extravehicular activity (EVA) tasks. Upper body exercise elicits a VO_2 peak that is ~70% of the whole body VO_2 max. In addition, upper body exercise is generally more stressful than lower-body exercise at a given power output, having a greater oxygen cost and producing a higher heart rate and blood pressure response (51). The average metabolic cost to crewmembers of EVA in the pressurized U.S. EVA suit is ~0.8 l/min (62), and the metabolic cost with the Russian EVA suit is ~40% greater (3). Therefore, for the average female astronaut, EVA work in the U.S. suit would represent approximately a 44% aerobic intensity (0.8/1.8 l/min upper body VO_2 peak), and this work would have to be sustained for up to 6–8 h. (This is assuming that her upper body aerobic capacity is 70% of 2.5 l/min VO_2 max and that no deconditioning has occurred during the flight.) Women, with less upper body strength and a lower VO_2 max, may be more susceptible to fatigue and risk of injury from muscle strains. Careful selection of the crewmembers for given EVA tasks with appropriate task planning and selection of tools are necessary to minimize fatigue during EVA.

**Emergency egress.** During emergency egress, rapid ambulation while wearing the launch and entry suit (LES) requires a high level of aerobic capacity and leg muscle strength. The LES consists of an outer water-impermeable shell, a liquid cooling garment, and an inflatable antigravity garment to protect against orthostatic intolerance. In ground-based simulations of

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**Table 1. Anthropometric data for American astronauts**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Group</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>VO_2peak, l/min</th>
<th>VO_2peak, ml·kg^{-1}·min^{-1}</th>
<th>Body Fat, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, active as of August 2001</td>
<td>22.3</td>
<td>42 ± 6</td>
<td>166 ± 5</td>
<td>60.7 ± 8.5</td>
<td>2.19 ± 0.48</td>
<td>36.5 ± 7.0</td>
<td>20.8 ± 4.5</td>
</tr>
<tr>
<td>Men, active as of August 2001</td>
<td>77.7</td>
<td>43 ± 6</td>
<td>180 ± 25</td>
<td>88.6 ± 8.8</td>
<td>3.55 ± 0.63 (121)</td>
<td>44.2 ± 7.1 (121)</td>
<td>17.8 ± 6.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 35 women and 122 men, unless indicated otherwise in parentheses.
walking in the 26-kg LES, the average metabolic cost for 12 men was 2.0 l/min without G-suit inflation, increasing to 2.5 l/min with the G-suit inflated to 1.5 psi (7). Four of twelve men could not complete the 5-min walk, even without the deconditioning effect of spaceflight. Leg fatigue was considered to be at least part of the reason for their failure, since all the men could complete the task without G-suit inflation. Because of their smaller body weight, lower absolute aerobic capacity, and weaker leg strength, women may be at greater risk of failure while performing an emergency egress, although this is yet to be tested.

BAROPHYSIOLOGY AND DECOMPRESSION SICKNESS

Decompression sickness (DCS) results from the formation of a gas phase in body tissues after a change in pressure. The magnitude of the problem depends on the degree of exposure, usually measured as the magnitude of the pressure change, and the type of tissue in which gas bubbles form. The greatest pressure changes result in the largest volume of separated gas phase, and nerve tissue is the locus of the most severe problems. Death is the worst possible outcome and has occurred in numerous unfortunate cases over the 150 years that pressure has been used in an occupational setting (5). Historically, most cases have arisen in deep-sea diving and tunnel work where compressed air was employed, but numerous events have occurred in aviation. Mitigation of DCS is critical for the safety of both men and women astronauts performing EVA. Fortunately, no incidences of DCS have been associated with the 62 EVAs to date, 7 of which were performed by women astronauts.

It is important to avoid the occurrence of DCS as much as possible while at the same time use the fewest consumables and shortest oxygen prebreath duration commensurate with efficacy. To accomplish this, it is necessary to understand the physiological and biophysical processes involved and any gender differences that may be present.

Gender differences in DCS have been identified and related to such characteristics as thermal stability, upper body strength, and characteristics of the reproductive system, but many of these play a role only in deep-sea and scuba diving (8). Data do not indicate that women are at increased risk for hypobaric DCS. Our primary concern for women crewmembers performing EVA is the potential for increased risk of DCS during menses, as it has been shown that the incidence of DCS is greatest then (8). This might be related to tissue fluid shifts affecting gas uptake and elimination. Because calcium loss increases in microgravity, the possibility of a gender-specific increased risk of dysbaric osteonecrosis should be investigated.

Gender differences in DCS risk are of considerable importance in the space program, and further ground-based research is needed to understand the risk factors. In the spaceflight environment, reduced stress on the musculoskeletal system may play a role in the risk of DCS, and this can be modeled with some degree of fidelity in the laboratory.

BONE MINERAL DENSITY

Bone mineral density (BMD) losses of women during 17 wk of bed rest (n = 6) and during 4–6 mo of spaceflight (n = 2) have been similar to bone losses of men (23). Recovery of BMD after spaceflight has not been complete in all crewmembers. If this trend of failure to recover bone continues, then crewmembers could be at greater risk for osteoporotic fracture as they age. Due to gender differences in longevity and in rate of bone loss during their 40s and 50s, women are at greater risk for fracture with aging. BMD losses that are not recovered after spaceflight can lower the age at which astronauts are at high risk for fracture as bone loss occurs with aging. Because of gender differences, a larger percentage of women than men are expected, during their projected lifetime, to be in a high-risk category due to spaceflight sequelae.

One of the countermeasures tested in bed rest was intense resistive exercise. The countermeasure has been fully successful in preventing bone loss in the calcaneus and increasing spinal BMD of the five men and four women tested. The femoral trochanter exhibited losses that appeared to be biomechanically influenced. There were no gender-related differences in the BMD response to 17 wk of bed rest with resistive exercise. In addition, there were no differences in one-repetition-maximum strength gains between the two groups. However, the upper-extremity strength (bench press) of the women was less than that of the men initially; therefore, the bench press gains were a larger percentage of the initial value for the women.

Overall, the skeletal response to spaceflight, bed rest, and bed rest with resistive exercise has shown no differences related to gender.

RENAI STONE FORMATION

Renal stone disease is a common medical problem for both men and women, affecting 1–5% of the population throughout the world. Men suffer from calcium-containing stones more than twice as often as women. Differences in urinary chemistry may account for this discrepancy, due to the greater urinary excretion of calcium, oxalate, and uric acid by men (46). However, women are at increased risk of forming struvite stones (magnesium ammonium phosphate) because of urinary tract infections.

The formation of a renal stone is probably the result of a combination of epidemiological and multiple urinary abnormalities. Men 30–50 yr of age are most affected by renal stones, whereas women in their 30s are most affected, with a second peak of stone formation between the ages of 50 and 55, corresponding to the postmenopausal increase in urinary calcium (46). This age range also represents the prime spaceflight years for astronauts. Occupation and environment may influence renal stone development, as shown by a higher incidence rate in hot, humid environments.
These factors may negatively impact the risk of renal stone formation during spaceflight in the humid shuttle or International Space Station environment, especially during EVAs. Diet also plays a role in the risk of stone development. Diets high in protein, calcium, oxalate, and sodium increase the urinary concentration of the stone-forming salts and promote the development of renal stones. In-flight shuttle foods are high in sodium, and increased sodium intake has been linked to augmented calcium excretion (61). In a normal non-stone-forming population, urine volume may be the most critical variable in reducing renal stone formation in both men and women. Decreased dietary fluid intake results in smaller urine volume, increasing the concentration of the stone-forming salts.

Data collected from female astronauts (n = 37) in NASA's renal stone risk assessment program have shown trends that are similar to data from male astronauts (Table 2). Postflight shuttle data have shown increased urinary calcium excretion by women after flight, although to a lesser degree than by male astronauts, and decreased urinary volume and citrate values. The postflight renal stone risk indexes for female astronauts show higher risks than the preflight indexes, but the risks are not as great as those for male astronauts. Overall, there is no evidence for gender-specific risks for renal stone formation during spaceflight. Both men and women are at increased risk for stones, and, although the types of stones may differ, individual differences significantly outweigh gender effects. In addition, the data described here may not reflect the urinary chemistry during flight and may be influenced by the readaptation to gravity after landing.

NASA astronauts have experienced 14 renal stone episodes, including multiple events experienced by one female crewmember. The increased risk of renal stone formation resulting from exposure to microgravity may be further exacerbated during long-duration stays on the International Space Station or a mission to Mars. The risks of forming a stone are great enough to warrant additional investigation.

The risk of urinary calculus formation has been shown to be associated with identified variables of calcium metabolism (absorption, excretion, and so forth). The potential change in stone risk in perimenopausal women exposed to long-duration spaceflight, due to hormone-induced changes in bone mineral metabolism, is not known. Studies of differences in muscle mass, gravitational loading of bone, calcium kinetics, and urinary calculus formation risk in perimenopausal or older female astronauts need to be performed collaboratively during extended-duration spaceflight.

**IMMUNOLOGY**

Alterations in the immune system have been shown to occur along with the physiological changes associated with spaceflight (32, 59). Altered white blood cell subpopulations, decreased proliferation of immune cells, and altered production of immunoregulatory molecules have been documented immediately after landing. Other studies have demonstrated a reduced in vivo cell-mediated immunity during spaceflight. Overall, these data suggest that a dysregulation of the immune system occurs in some individuals and that these changes may increase the risks of infection, increase the reactivation of latent viruses, and potentially alter immune surveillance and the incidence of autoimmune disease or tumorigenesis. As the space program moves to longer missions on the International Space Station.

**Table 2. Urinary biochemistry of male and female astronauts before and after space shuttle flights**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preflight  Postflight</td>
<td>Preflight  Postflight</td>
<td>Warp</td>
</tr>
<tr>
<td>Total volume, l/day</td>
<td>1.99 (0.07) 1.95 (1.02)</td>
<td>2.12 (0.21) 1.83 (0.15)</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>5.99 (0.03) 5.63 (0.39)</td>
<td>6.15 (0.07) 6.03 (0.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium, mg/day</td>
<td>202.3 (6.2) 254.6 (7.7)</td>
<td>117.3 (10.6) 152.0 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphate, mg/day</td>
<td>1,080.8 (30.4) 926.9 (21.4)</td>
<td>730.5 (39.6) 587.6 (38.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxalate, mg/day</td>
<td>36.7 (0.81) 36.2 (0.9)</td>
<td>40.3 (5.9) 34.3 (4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium, mg/day</td>
<td>161.4 (4.14) 122.8 (4.16)</td>
<td>134.2 (9.1) 60.6 (6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium, mmol/day</td>
<td>67.9 (1.5) 54.4 (1.3)</td>
<td>54.9 (3.2) 42.0 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Magnesium, meq/day</td>
<td>117.8 (2.8) 103.8 (2.6)</td>
<td>93.1 (4.9) 81.3 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Citrate, meq/day</td>
<td>765.3 (19.0) 623.0 (21.2)</td>
<td>722.0 (46.0) 539.8 (41.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sulfate, mmol/day</td>
<td>23.1 (0.5) 26.7 (0.6)</td>
<td>16.5 (0.7) 16.2 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid, mg/day</td>
<td>663.7 (13.4) 597.3 (16.9)</td>
<td>521.6 (29.2) 455.0 (21.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine, mg/day</td>
<td>1,783.1 (23.4) 1,885.8 (31.0)</td>
<td>1,135.4 (44.5) 1,119.0 (50.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Urinary relative supersaturation**

|                        | Men                | Women               | P     |
| Calcium oxalate        | 1.72 (0.07) 2.42 (0.09) | 1.10 (0.13) 1.81 (0.22) | <0.001 |
| Brushte                | 1.44 (0.08) 1.00 (0.07) | 0.74 (0.10) 0.94 (0.15) | NS    |
| Sodium urate           | 2.80 (0.16) 1.56 (0.09) | 2.09 (0.30) 1.01 (0.06) | <0.001 |
| Struvite               | 2.10 (0.43) 0.43 (0.11) | 1.75 (0.43) 1.42 (0.40) | NS    |
| Uric acid saturation   | 2.05 (0.11) 2.88 (0.12) | 1.24 (0.17) 1.60 (0.24) | NS    |

Values are means ± SE before and immediately after flight. For men (preflight), n = 240 (except n = 239 for oxalate and calcium oxalate); for men (postflight), n = 239 (except n = 238 for oxalate and calcium). For women (preflight and postflight), n = 37. Urinary relative supersaturation values >2.0 for calcium oxalate, brushte, sodium urate, and uric acid and values >1.5 for struvite indicate an increased risk for renal stone development. Paired t-test was used for statistical analysis.

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and exploration missions, the importance of the observed immune system changes will increase dramatically. Further assessment of immune status will be required to determine whether the changes observed present significantly altered risks to the spacecraft crew.

At present, there is no indication that spaceflight alters the immune system in a gender-specific manner, although the small number of female subjects evaluated makes such an analysis difficult. Gender-specific differences in immune responses have been documented in a variety of clinical situations. Women express a generally elevated immune response and a higher incidence of autoimmune disease compared with men. Differences in cytokine balance and immune responses are also observed during the menstrual cycle, which can have a clinically significant impact on expression of disease (e.g., asthma) (1). Further analysis of gender differences correlating rigorous immune tests and validated clinical outcomes must be carried out in ground-based investigations before detailed analysis of in-flight gender-based responses can be performed.

NEUROVESTIBULAR AND SENSORIMOTOR FUNCTION

The major areas of concern with regard to spaceflight effects on neurovestibular and sensorimotor function are posture and locomotor control, gaze stabilization, spatial orientation, space motion sickness (SMS), and vestibular influence on cardiovascular control mechanisms. Disturbances in neurovestibular and sensorimotor function can result in degraded performance of operational tasks on orbit, inability to perform emergency egress, and impairments in performing normal daily activities for varying periods after landing. The magnitude of these disturbances increases as a function of flight duration. Hence, for long-duration missions, changes in neurovestibular and sensorimotor functions may pose health concerns for an extended period after landing. Data from Russian studies indicate that some of the changes may be permanent, although this has not been confirmed, nor has their functional significance been determined (I. Koslovskaya, personal communication).

In general, large individual differences in gaze, posture and locomotor control, spatial orientation, and SMS have been observed during flight and when comparing pre- and postflight data. These differences can be attributed to a number of factors, including differences in control strategies, adaptation rates, training and experience (as for pilots vs. mission specialists), perceptual styles, and gender (13, 35, 49, 53). For most of the areas of concern in this discipline, the number of women astronauts studied to date is far too small and the number of factors contributing to individual differences is too large to draw valid conclusions about gender-specific differences.

With only a few exceptions, the ground-based scientific and medical literature offers no evidence that significant or functionally important gender-specific differences exist in neurovestibular and sensorimotor functions. Reports in the literature suggest gender differences do exist in cognitive performance and visual spatial abilities. However, these are highly controversial and the results are equivocal. Even in studies in which such gender differences have been found, they account for a very small percentage of the variance in the population (33). Finally, some reports in the literature suggest that women are somewhat more susceptible to motion sickness than men. However, these reports indicate that gender differences in susceptibility to motion sickness may be more a function of the type of provocative stimulus than of gender per se. Earlier published reports on gender differences in SMS showed that the incidence in women was 38% compared with 70% in men (10), which would suggest that female astronauts are less susceptible to SMS than their male counterparts. However, a more recent report indicates that male and female astronauts are equally affected by SMS (26).

NUTRITION

The nutritional requirements for spaceflight (29, 42) have been based on interpretation of findings from actual spaceflight and weightlessness analog studies and on extrapolation of extensive terrestrial nutrition information (38, 39, 43). Little information is available regarding nutrient requirements during spaceflight, and even less is available regarding gender differences in requirements. Whereas energy requirements are based on both gender and body size, only a few examples of gender-specific nutrient issues exist.

Iron. In Earth-based populations, clear gender differences exist with regard to iron metabolism and requirements. Specifically, because of menstrual blood loss, women have a higher dietary iron requirement than men. Iron metabolism and hematology are altered in men and women during weightlessness, when the circulating red blood cell mass is decreased 10–15% compared with preflight values (2). This reduction in red blood cell mass occurs despite adequate iron stores and tissue iron availability. Iron overload is a concern for extended-duration spaceflight, based on the concept that iron is an oxidant and might damage tissue (17, 24, 41), either alone or in conjunction with radiation exposure. Women may actually be at less risk of iron overload than men because they typically have lower iron stores than men. The dietary iron requirements for spaceflight have been defined as <10 mg/day for both men and women, in the interest of avoiding iron excess. Unfortunately, no data exist on flight gender differences in iron metabolism or on dietary iron absorption by men or women during spaceflight.

Calcium. Bone loss, calcium homeostasis, and osteoporosis are obvious nutrition-related concerns for women’s health on Earth as well as during spaceflight. Unfortunately, few or no data exist regarding gender differences in bone and calcium metabolism during flight. A calcium kinetics experiment has been flown on some Mir flights (55), albeit with male subjects only.
Additional data is needed for both male and female subjects to provide information about changes in calcium metabolism during the first days of weightlessness.

PHARMACOTHERAPEUTICS

Gender-related differences are known to exist with respect to clinical efficacy and adverse effects of drug treatment (60). There is a general consensus among clinical pharmacologists that pharmacokinetics and pharmacodynamics in women are different from those in men (64). Gender differences in gastrointestinal physiology and hepatic metabolism may contribute to differences in drug dynamics. In addition, hormonal changes during the menstrual cycle, renal blood flow, and body composition also play roles in gender-specific drug disposition (4). These gender-related physiological differences could greatly impact the therapeutic efficacy of drugs on Earth and in space. Currently, very little is known about pharmacokinetics and pharmacodynamics in space. Understanding discrete gender differences in the pharmacokinetics and pharmacodynamics of drugs is important for pharmacotherapeutics in space, particularly for long-duration missions, which will probably present a greater variety of conditions requiring pharmacotherapy than short-duration missions.

Gastrointestinal physiology and hepatic metabolism. Gender differences in gastrointestinal physiology and hepatic metabolizing enzyme systems may adversely affect drug absorption, bioavailability, metabolism, and elimination in women. Women have altered bile composition, slower intestinal transit time, and higher gastric pH than men (16). During the first few days of spaceflight, there is a high incidence of SMS accompanied by decreased gastrointestinal motility (10). The combination of initial slower intestinal transit time and decreased gastrointestinal motility associated with SMS may adversely affect absorption and bioavailability of orally ingested medications more in female than in male astronauts. Clinically significant gender differences have been reported for drug elimination processes; these were predominantly linked to the gender-specific expression of metabolic enzyme systems (4). Differences between men and women in hepatic phase I and phase II metabolism have an important influence on drug metabolism. Men have higher levels of certain metabolizing enzyme isoforms, whereas women have higher activity levels of different isoforms (4). These differences in drug metabolism may partially account for the higher incidence of adverse reactions to drugs in women than in men.

Hormonal changes. Menstrual cycle hormonal changes can also influence drug absorption, distribution, metabolism, and elimination (28), and oral contraceptive use can interfere with the metabolism of many drugs (25). Due to the absolute preclusion of pregnancy in space, many female astronauts choose oral contraceptives during the training period, and most continue to use them while on orbit. Changes in the renal, cardiovascular, hematological, and immune systems during menstruation are well known, and these physiological changes could influence the pharmacokinetics and pharmacodynamics of drugs by altering such variables as protein binding and volume of distribution of drugs, which could significantly worsen disease severity.

The gender differences in physiology described above could greatly impact the therapeutic efficacy of drugs. Moreover, the manifestation of physiological adaptations to spaceflight would most likely exacerbate these gender-related differences in pharmacokinetics and pharmacodynamics of medications used during spaceflight, which will affect therapeutics in space. Therefore, space pharmacotherapeutic research must focus on understanding how gender differences in physiological adaptation to microgravity affect pharmacotherapy in space and on whether significant advantages would accrue to implementing gender-specific pharmacotherapeutic protocols for treatment of medical conditions in space.

REPRODUCTION

Several reproductive medical issues that pertain to astronauts warrant further clinical investigation, including the following: 1) the effect of spaceflight on normal menstrual functioning, 2) the role of gravity in menstrual efflux and retrograde (intra-abdominal) menstruation, and 3) the effect of space radiation on the future childbearing capacity of both men and women.

Normal menstrual function. Because space shuttle flights are considerably shorter than the average menstrual cycle length, no on-orbit studies have been done to determine the impact of microgravity on normal hypothalamic/pituitary/ovarian axis function. The primary concern is that anovulation might occur, resulting in continuous estrogen exposure, endometrial hyperplasia, and possibly menorrhagia. Second, there is some concern that hypothalamic amenorrhea and reduced estrogen levels could occur. The reason for concern is that the exercise necessary for long-term cardiovascular and musculoskeletal fitness may be strenuous enough to cause hypothalamic-induced hypogonadism with reduced serum estrogen levels. The combined effect of hypoestrogenemia and spaceflight-related calcium loss could lead to increased osteoporosis risk (13, 35, 49, 53). Were this to occur, oral contraceptive or hormone replacement therapy has been shown to control the risk. An additional advantage of hormonal therapy is the ability to eliminate menstruation altogether.

Menstrual efflux and retrograde menstruation. Many women normally experience some retrograde intra-abdominal bleeding during menses. Because of the effects of gravity, the blood products and cellular debris usually stay confined to the pelvis. The development of endometriosis is multifaceted, but exposure of the pelvic peritoneum to menstrual blood products is thought to be the primary cause of its development (36, 50, 52,
56, 63). Endometriosis is also primarily a pelvic problem in part because gravity keeps the menstrual products confined to the pelvis. Although medical debriefing data from shuttle flights have not supported concern that retrograde menstruation increases during spaceflight, the role of gravity in menstruation should be investigated to determine whether retrograde menstruation is increased and how peritoneal fluid is distributed. In addition, radiation exposure at varying doses has been associated with the development of endometriosis in certain primate species (15, 63). It will be prudent to follow female crewmembers longitudinally to determine whether spaceflight changes the incidence, location, or severity of endometriosis.

Effect of space radiation. Radiation concerns for women and men are generally similar except for exposure of the gonads and breast and thyroid tissue. Although the radiation exposure levels found in long-duration spaceflight may present an infertility problem for men, this is not likely for the more radiation-resistant ovary (57). However, the effect of space-based radiation on the chromosomes of oocytes is of considerable importance to women who may desire future pregnancies. Compared with women, men are at considerably increased short-term risk from damage to gametes. However, the effect of neutrons, high-energy particles, and other radiation from space needs to be assessed for both men and women on prolonged missions so that they can make informed decisions regarding cryopreservation of gametes before flight. The participation of women in spaceflight piques the interest of the public in issues relating to pregnancy and fertility in space. However, the radiation levels associated with spaceflight in low Earth orbit or deep space preclude pregnancies at this time. The National Council on Radiation Protection and Measurements guidelines limit radiation exposure to 500 mrem for an entire pregnancy and to only 50 mrem per month. The International Commission on Radiological Protection guidelines are more restrictive. On the International Space Station, radiation exposure to a pregnancy may approach 35,000 mrem or more (11, 12, 32a, 44, 45, 47, 48, 65). Radiation exposure on the International Space Station varies with altitude, solar cycle, and location of the astronaut in the space station. Thus, during a 9-mo pregnancy, exposure could range from 10,500 to 36,000 mrem, depending on the altitude of the station and the solar cycle. Moreover, these numbers could be 30% lower or 30% higher depending on where the astronaut spends their time onboard the station.

SUMMARY

In summary, the only astronaut health issue for which a large enough data set exists to allow valid conclusions to be drawn about gender-specific differences is postflight orthostatic intolerance. Female shuttle astronauts have a significantly higher incidence of presyncope during postflight stand tests than do male astronauts. However, the first American astronauts who flew aboard Mir (almost all of whom were men) had an 85% failure rate during the postflight tilt test. Thus it is expected that gender-related differences will not be apparent on long-duration missions. Other gender-specific issues that are likely to have functional or operational impacts for astronauts on long-duration missions include ventricular dysrhythmias, bone and calcium changes associated with osteoporosis, menstrual function, and radiation effects on gametes. Although gender differences in aerobic capacity and muscle strength are not considered health issues per se, ground-based data suggest that women may be more susceptible to fatigue and injury, particularly during more strenuous tasks. Finally, an emerging body of evidence suggests that there are gender-specific differences in clinical efficacy and adverse effects of drug treatment (pharmacotherapeutics). Understanding these differences is likely to become more important for long-duration International Space Station and exploration missions.

Insufficient data exist in most of the discipline areas at the present time to draw valid conclusions about gender-specific differences in astronauts or to determine their impact on the health of male and female astronauts. One of the reasons for this is that the relatively small size of the female astronaut population compared with the male astronaut population generally precludes having sufficient statistical power to draw valid conclusions about gender differences. In addition, individual differences in physiological responses within genders are usually as large or, larger than, differences between genders, so individual characteristics usually outweigh gender differences per se. Finally, data concerning gender differences in physiology for the Earth-bound population is somewhat limited.

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