**Women’s Health in Spaceflight: Life Beyond Low Earth Orbit**

**In “Precision Medicine in Space”**

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**Abstract**

Historically, only 75 women have flown in space and while this inequity has been recently addressed with astronaut candidates about 50% female, research defining female biological responses to spaceflight remain limited. The NASA Artemis Campaign aims to land the first woman on the Moon for purposes of scientific discovery, technology advancement, and learning how to live and work on another world in preparation for human missions to Mars. The need to understand how sex and gender affect a wide range of physiological functions, impacting numerous health outcomes is critical. The purpose of this chapter is to summarize recent findings in women’s health in spaceflight, past studies examining female mammalian responses to spaceflight and highlight the need for additional studies to help reduce risk and enhance countermeasure development specific to female astronauts. The promise of artificial intelligence approaches for advancing the pace of research is discussed with the caveat that, at present, fundamental research on women’s health in space and sex-specificity of response to spaceflight stressors is not sufficiently robust to achieve this goal.

**Introduction**

Over six decades of human spaceflight have significantly advanced our understanding of the distinctive health challenges associated with living and working in space. Spaceflight exposes astronauts to a diverse range of environmental, physical, and psychological stressors, including profound gravitational alterations, continuous galactic cosmic radiation, acceleration and vibration forces during launch, ascent, entry and landing. In addition, the risk of toxic chemical exposures, reduced atmospheric pressure during extravehicular activities (EVAs), altered breathing gas concentrations, and social isolation are also encountered by the spaceflight crew. Since the first life science space mission, it has been documented that spaceflight involves physiological changes in multiple systems across neurological, immunological, ophthalmological, vestibular, cardiovascular, and musculoskeletal systems (1).

On Earth, the past few decades have witnessed a growing emphasis on the physiological and health consequences of sex[[1]](#footnote-1) (2). Further, federal agencies have instituted policies to ensure that men and women are included in clinical trials, and that animal based studies incorporate equal representation of males and females and that findings are evaluated for sex-based differences. Spaceflight research incorporating the variables of sex and gender has not kept pace, as most studies have been necessarily conducted on male astronauts due to the historically low numbers of female astronauts. Despite early attempts to prepare and train women for orbital spaceflight (i.e., the ‘Mercury 13’) (3), thus far, 75 of the 644 people who have orbited the Earth have been women (4). Since 2013, the future of women in space has undergone a pivotal change with NASA Astronaut Corps class selections comprising 40–50% women. Nonetheless, recent biomedical reports remain troubled by insufficient sample sizes, thereby impeding clear understanding of male/female differences in response to spaceflight. Strong evidence for sex specificity in the symptoms, prevalence, age of onset, severity, and health outcomes of common human diseases (1) underscores the value of evaluating biological sex differences and their causal mechanisms. This approach has led to the broad realization that sex is an important factor for consideration with respect to disease management, and prevention.

In 2002, NASA sponsored a workshop entitled ‘‘Sex, Space and Environmental Adaptation: A National Workshop to Define Research Priorities Regarding Sex-Differences in Human Responses to Challenging Environments’’. This workshop provided a comprehensive review of existing data and recommendations to fill gaps in NASA’s knowledge base (5). In response to the 2011 National Academy of Sciences Decadal Survey, “Recapturing a Future for Space Exploration: Life and Physical Sciences for a New Era,” the need to further understand sex differences in response to spaceflight, NASA and the National Space Biomedical Research Institute (NSBRI) commissioned a study that resulted in a workshop and a compendium of six individual manuscripts, a Commentary, and Executive Summary. This body of work entitled “The Impact of Sex and Gender on Adaptation to Space” was published a decade ago in the Journal of Women’s Health (2014). The major findings include the identification of sex-similarities and differences affecting physiological adaptation to spaceflight across six key systems: cardiovascular, immunologic, sensorimotor, musculoskeletal, reproductive, and behavioral processes. Highlights from this effort are that women, compared to men, showed: (1) increased sensitivity to orthostatic intolerance (cardiovascular), (2) mount more profound immune responses (immunologic), (3) have fewer findings concerning for spaceflight-associated neuro-ocular syndrome (SANS) and no bias toward loss of hearing in left ear, (sensorimotor), (4) no sex difference in the large variability observed in bone and muscle loss (musculoskeletal), (5) greater tendency to develop urinary tract infections and struvite kidney stones, rather than calcium oxalate kidney stones (reproductive/urogenital), and (6) demonstrate slight bias towards accuracy as opposed to speed in a vigilance/alertness task (behavioral). Similarities and differences in female and male responses to spaceflight (Figure 1), emphasize the need to increase our investigations of physiological/behavioral effects of spaceflight and to consider the ramifications for human health management in space (6).



Health effect observed in Space



Health effect observed on Earth

*Figure 1. Key physiological differences between women and men in neural, behavioral, cardiovascular, sensorimotor, musculoskeletal, immune, and reproductive adaptations to human spaceflight. Note that new data acquired since publication may suggest different outcomes than those recognized in 2014. Permissions: JWH and NSBRI/NASA.*

Defining sexually dimorphic biological responses to extended habitation of the deep space environment and the development of sex-appropriate countermeasures for undesirable or adverse health outcomes are critically important for the health and safety of both female and male astronauts. Since the Apollo missions in the 1970s, most spaceflight exposures have occurred in low Earth orbit (LEO), within the protection of Earth’s magnetosphere. Now, with the NASA Artemis program returning to the Moon, and Christina Hammock Koch selected to be the first female astronaut to orbit the moon, it is essential to begin to unravel the differential effects of spaceflight on sex/gender differences. The Artemis campaign will lay the groundwork for subsequent prolonged durations in space with the aim(s) of humans learning how to live and work on another world in advance of future mission to Mars (7). As the NASA Artemis Program will place astronauts beyond protection of the van Allen belt, and expose them to longer and more intense bouts of radiation, obvious concerns exist for radiation induced cancer increases in both sexes. Additionally, the male and female germlines are exquisitely sensitive to radiation effects and reproductive health is a bellwether for an individual’s overall fitness (8). These focus areas are recognized in the recently published National Academy of Sciences (NAS) Thriving in Space: Ensuring the Future of Biological and Physical Sciences Research: A Decadal Survey 2023-2032 (9). In this current report, we intend to highlight the need for comprehensive studies to better understand the impacts of spaceflight on the female reproductive system. This will help reduce risk and enhance countermeasure development specific to female astronauts. Further, we emphasize the need for clinicians and researchers in the space life sciences to consider sex in their approach to diagnosis, treatment, and prevention of adverse health conditions in space as a necessary and fundamental step towards precision medicine in the space program. An individual differences approach is supported by the NASA Twins Study (10).

**Female Gynecologic and Reproductive Health in Space and After Return to Earth**

*Short Term Effects.*

In space, female health considerations focus on both general and reproductive processes, including normal menstrual cycle and the potential for pathological gynecological events (such as endometriosis, ovarian/uterine cancer). On Earth, there are several pharmacological and surgical options and procedures available to prevent and treat gynecological pathology (11). However, during spaceflight, the primary devices available to female astronauts are pharmacological (11–13). Steller et al (11,14) have previously reviewed pre-, in- and post-flight management considerations for reducing gynecological risks in female astronauts. Thorough pre-flight screening is currently the best way to minimize gynecological pathologies in spaceflight. Yet long-duration spaceflight presents new challenges, and much of the impact of the short-term effects of deep space environment on gynecological health remains unknown. The authors emphasize a need for careful consideration of the gynecological risks and potential occurrences of unpredictable pathological events during spaceflight (11,14,15).

A major decision female astronauts must make is which of the various menstrual management options that are available on Earth to use during spaceflight. Many, but not all, opt for medically induced amenorrhea with hormonal supplementation. In addition to menstrual management, these methods are also important to prevent pregnancy during spaceflight. The majority of female astronauts that have elected to use hormonal contraception use continuous combined (estrogen and progestin) oral contraceptives (COCs), or a levonorgestrel intrauterine device (11,16–18). Counseling regarding the risks, benefits, and alternatives of the various methods is nuanced both on Earth and in space, as the choice for the various hormonal modalities (or use of no method) have varying effects on menses, risk of abnormal uterine bleeding, ovarian cyst production, bone mineral density, risk of venous thromboembolism (VTE), and risks of breast, uterine, and ovarian cancer (11,16,17). It remains unclear if these risks are exasperated in spaceflight. In an article by Jain et al, data on female astronauts who flew short and long duration missions between 2000 and 2014 showed no large changes in VTE risk factors after spaceflight regardless of contraceptive use (18). However, recently, an astronaut with no family or personal history of VTE, developed a non-clinical internal jugular vein thrombus during approximately 2 months into an International Space Station mission that was incidentally noted during a research study (19–21). In response to this event, Zwart et al examined the biochemistry data from 65 astronauts for associations with COCs use and serum albumin levels. They found female astronauts who used combined oral contraceptives had lower concentrations of serum albumin and higher concentrations of transferrin (an important protein for clotting response cascade) than female astronauts who were not taking the contraceptives as well as male astronauts. Hypoalbuminemia is a known risk factor for VTE in overtly healthy populations (22) and may be a contributing factor to an increased risk of VTE during spaceflight in addition to the risks of gravitational unloading and stasis (19).

Additionally, the effectiveness of hormonal contraceptives to induce amenorrhea during spaceflight are not fully understood, and there is minimal data robustly evaluating the effectiveness in space or on Earth beyond 12 months as amenorrhea has never been a purposefully engineered endpoint of utilizing contraceptives and, rather, a fortuitous side effect (16). With upcoming spaceflight missions beyond LEO, and a Mars mission estimated to have a duration of about three years, it is necessary to understand the potential risks and benefits to allow female astronauts to make the best decisions for their health.

*Long Term Effects.*

In addition to risks during and immediately following spaceflight, the long-term effects on female health upon return to Earth are equally important to consider. There remains a paucity of data on the effects of spaceflight, including galactic cosmic radiation and altered gravity, on subsequent gonadal function, fertility, and fecundity (11,23–25). This is of synergistic concern with advancing maternal age for female astronauts, as they often delay parity until after training and post-flight. Using the calculated radiosensitivity of the human oocyte, Wallace, et al. created a model to estimate the number of surviving oocytes after a known radiotherapy dose exposure (26). Based on this data, it is hypothesized that a Mars mission may reduce a female astronauts ovarian reserve by about 50% and shorten the time interval to menopause (27). However, not only is GCR different from therapeutic radiation in a variety of ways, but this article did not account for the effects of other stressors such as altered gravity. Thus, results from terrestrial studies should always be carefully contextualized when using them for generating hypotheses of spaceflight effects.

**Animal Studies in Space**

For centuries, scientists have used animal models to understand various aspects of human biology. These animals, including female animals, have been sent to space since the 1940s and include dogs, cats, monkeys, apes, rodents, reptiles, fish, amphibians, and many types of invertebrates. However, many of these launches were to investigate survivability and the overall effects of space travel. For studying the specific effects of spaceflight on female health, currently, rodents are the only mammalian model qualified to fly on ISS. Rodent research models have been fundamental and irreplaceable to the continued advancement of basic biology and medicine without endangering the health of human subjects. Scientists can utilize rodent models in controlled environments to employ intricate experimental protocols to collect data that are difficult, even impossible, to collect in human subjects. Rodents are excellent surrogates for extrapolating to humans the consequences of long duration spaceflight on growth, development, reproduction, multigenerational reproductive fitness, and aging throughout the lifecycle (28).

Evidence has shown that female mice on-orbit for 37 days and dissected in microgravity (thus, eliminating re-entry stressors) experience normal estrous cycles (29). Though, when paired male and female rats were flown on the 1979 COSMOS 1129 spaceflight for 18.5-days (sufficient to mate 2-3 times) and returned to Earth, no pregnancies were observed (23,30)*.* However, as the control mice on Earth also didn’t become pregnant in that study, extraneous concerns such as habitat design have also been hypothesized to interfere. In 1982, Cosmos-1514 carried 10 pregnant female rats into LEO on day 13-20 of rats 22-day gestation period. Upon return to Earth, offspring showed no obvious deficits in typical behaviors but showed unusual responsiveness in a rotation test (31).

Over 10 years later, pregnant rats were flown again on two NASA and National Institutes of Health jointly sponsored payloads on the Space Shuttle. On the Rodent 1 (NIH.R1) and Rodent 2 (NIH.R2) missions, 10 rat dams were launched at the approximate midpoint of pregnancy and were in space for 11 and 9 days, respectively. Upon return to Earth before parturition, the flight dams that were allowed to labor displayed twice the number of lordosis contractions (predominant labor contraction type in rats), yet labor duration and maternal care during parturition remained qualitatively and quantitatively comparable to ground controls (32). For the offspring, spaceflight did not seem to interfere with developmental milestones or the establishment of normal hind paw placement patterns during walking, however, organogenesis was already complete before the fetuses were subject to the stressors of space (33). However, the flight offspring did exhibit disruption of vestibular mediated responses (34) and altered organization and function of the vestibular system (35), indicating that during in utero development these systems may have been altered by microgravity.

In 2014, NASA launched the Rodent Research Hardware System or Rodent Habitat to conduct long duration rodent studies. This unit evolved from the Animal Enclosure Module that was the workhorse of Shuttle Era rodent experimentation. The ISS Rodent Habitat continues to be used for all NASA supported Rodent Research missions. In contrast to decades of ground-based studies focused on males, many of these spaceflight rodent studies utilize female animals for advantages they confer, primarily their amicable group housing social interactions and smaller size. Interestingly, however, the aims of these studies were not to investigate the impact of spaceflight specifically on females and these studies did not take into consideration the impact on estrous cycle, nor consider it as a covariable. Many of the organ systems that are negatively impacted by spaceflight and decline during aging are also regulated by estrogen signaling like the CNS, musculoskeletal, cardiovascular, immune, among others. For example, in the skeletal system, bone remodeling is intimately tied to sex steroid hormones and their activated receptors (36,37). In females, estrogen receptor alpha regulates growth plate closure, cessation of periosteal and endosteal bone growth, and cessation of cancellous bone resorption, reviewed by (36). In these prior bone loss investigations, where estrogen is of known critical importance, whether the mice had normal estrous cycles, constant estrous (elevated estrogen), or constant diestrous (reduced estrogen) was not considered. A recent analysis of post-mortem vaginal wall tissue from the RR-1 validation mission, indicates that estrous cyclicity of female mice is likely occurring as evidenced by multiple estrous cycle stages being observed in mice euthanized in space (29). This work paved the way for the upcoming RR-20 mission (flown in 2023) to address whether females in-flight can ovulate, produce normal levels of ovarian steroids, and elicit normal steroidal actions in recipient tissues such as brain, uterus, bone, and muscle.

In November 2023, the NASA Rodent Research (RR)-20 mission was flown to investigate the effects of spaceflight on female fertility and fecundity. Young (12-week-old) nulliparous female mice were flown on ISS for 42 days, then bred with proven breeder male mice upon return to Earth. The findings expected from this landmark experiment will provide new and vital information regarding post-flight fertility, conception, and offspring development including epigenetic transmission. Pre-conception stress in either parent may impact germ cells, thereby influencing offspring development across generations. This study will inform intergenerational transmission of spaceflight exposure effects in which F1 female germ cells, but not F2 germ cells, will have experienced spaceflight. Although findings are not yet available, this study comprises a major advance in the acquisition of data furthering understanding of reproductive health and spaceflight.

Two innovative reproductive and developmental studies have been previously conducted by other space agencies (38,39). A JAXA study, showed that after 35 days on orbit and subsequent return to Earth, sperm harvested from males exposed to 0g or 1g (via chronic centrifugation) were successful in fertilizing and siring healthy offspring (39). Subsequently, the Chinese Space Administration (38) launched preimplantation mouse embryos aboard a SJ-10 recoverable satellite. The study demonstrated that embryo development continued during short-term spaceflight, but the rate of blastocyst formation and blastocyst quality were compromised. Embryonic cells contained severe DNA damage and the DNA was globally hypomethylated and presented with a unique set of differentially methylated regions. These initial studies emphasize our need to complete more robust experimentally designed studies of early mammalian development where combined effects of microgravity and GCR exposure can be properly analyzed.

In lieu of dedicated spaceflight developmental studies, utilization of terrestrial analogs continues. One emerging analog for studying GCR is NASA’s Neutron Irradiator/Vivarium Facility at Colorado State University (40). In addition to the National Space Radiation Laboratory’s (NSRL) ability to study fractionated doses of protons and heavy ions, this facility is unique as animals can be exposed to a near-continuous low dose-rate Californium-252 neutron source that can simulate similar daily exposures in deep space, the Moon, or Mars. Not only are neutrons charged particles like protons and heavy ions that have high-linear energy transfer (LET), but neutrons are also clinically relevant in spaceflight given that secondary neutron irradiation occurs when those protons and heavy ions impact the hull of a spacecraft, structure, or human body. The first reproductive study to utilize this new center randomized 80 female mice to a near-continuous Cf252 exposure at a dose rate of 1 mGy/day versus terrestrial background pan-pregnancy. While this simulated Mars exposure led to increased resorptions in mice pregnancy, it was overall reassuring that it did not affect fetal growth and viability in a mammalian model that shares a similar hemochorial placenta to humans (41). Furthermore, there were no significant differences noted in placental signaling studies and minimal effects on gene expression in the placenta. Studies utilizing this analog for studies on ovarian function and fertility are commencing.

**Cancer Risk**

As spaceflight is associated with a number of stressors, particular radiation, cancer risk is a significant health concern for both sexes (42). Terrestrially, women have a higher incidence of radiation-induced cancers than men, and this is largely driven by lung, thyroid, breast, and ovarian cancers (43). Reynolds et. al. compared cancer incidence rates, cancer-specific mortality rates, and cancer case-fatality ratios in US astronaut cohort from April 1959 through 31 December 2017 to the US general population. Overall, cancer incidence and mortality were slightly lower than expected from national rates, except melanoma, where the increase in incidence was consistent with that observed in aircraft pilots, suggesting this may not be due to astronaut-specific exposure (44). In this cohort, 14.8% were female astronauts and contributed a small proportion of the follow-up time for ages between ages 25 and 75, with no female astronauts in age groups greater than 75 years (44). Due to the relatively small number of female astronauts exposed to long-duration spaceflight it is currently difficult to reliably determine the risks related to gynecological cancers (43).

**Applications of Artificial Intelligence to Spaceflight Effects on Women’s Health**

In recent years,artificial intelligence (AI), defined as the ability of machines to learn and display intelligence, has undergone rapid expansion and application in biomedicine (45). Advances in machine learning algorithms, development and availability of robust datasets, and enhancements in computer technology have contributed significantly to recent innovations. Major categories of AI methods widely used in medical applications include: (a) machine learning (ML), a subset of AI focused on pattern detection from large, complex datasets allows for clustering of patient features and prediction of disease outcomes by analyzing structured data derived from medical imaging and genetic information; (b) natural language processing (NLP) that converts the raw, unstructured clinical data (e.g., electronic medical records) into structured data that can be read and analyzed using ML techniques, and (c) robotic surgery.

Women’s health on Earth is already reaping immense benefits from AI approaches. AI is exerting positive influence(s) on the clinical assessment of breast pathologies (46) and gynecological imaging for cancer detection (47,48). Further, AI is emerging as an effective supplementary method for assessing female reproductive function via AI-assisted ultrasound to monitor follicles, determine endometrial receptivity, and predict the pregnancy outcome of in vitro fertilization and embryo transfer (IVF-ET) (49).  For assisted reproduction applications, accurately predicting the outcome of an IVF cycle has yet to be achieved because morphological assessment of embryos is the traditional subjective method for evaluating embryo quality and selecting which embryo to transfer. This is due to inter- and intra-observer variability, often resulting in less-than-optimal IVF success rates. However, multiple embryo transfer, commonly used to improve embryo viability can result in high-risk multiple pregnancies. Recent studies investigating the use of AI as an unbiased, automated approach to embryo assessment is a highly promising tool to help improve IVF outcomes (50). The potential value of digital health datasets to support the testing, use, and evaluation of AI in the in fields of nursing and midwifery is a topic of growing interest (51). From the pre-clinical research perspective, the rodent estrus cycle is of significant interest owing to its role in modulating a broad range of biological functions from gene expression to behavior. The cycle is typically divided into four stages, each characterized by distinct hormone concentration profiles. However difficulties associated with repeatedly sampling of plasma steroid hormones from rodents, the primary method for classifying estrous stage is manual identification of vaginal epithelial cell types, which extremely time- and labor-intensive and variable, even amongst expert investigators. Deep learning approaches (e.g., the "EstrousNet" algorithm) are proving to be highly efficient in achieving expert classification accuracy (52).

The advent of AI plays a promising role in future long-duration spaceflight missions, particularly in the areas of female physiology, women’s health, and sex differences in space. Further, similar to Earth-based models, building robust AI algorithms for space medicine requires large datasets for proper training. However, crew medical data is constrained by sample size, and often difficult to collect, thus biomedical datasets tend to be small and limited, particularly for females. Waisberg et al. (53) has identified restricted size of astronaut medical datasets is currently the largest barrier for training machine learning algorithms in the spaceflight environment. While traditional AI algorithms rely on AI model training and testing of data collected in same venue, they suggest an alternate approach. “Transfer learning” employs existing large terrestrial training and target datasets related to the domain of interest (space) as a potential segue to the successful application of AI and ML in the field of Space Medicine.

**Current Challenges**

The greatest challenges with determining the effects of long-term spaceflight on female health is that the sample size of female astronauts is still relatively small, and we are not yet robustly tracking gynecologic and reproductive outcomes. Because there is a lack of data segregated by sex/gender in order to keep the sample size high enough for outcomes data amongst all astronauts, there is an inability to achieve the statistical power necessary to determine sex-based similarities and differences. There has also not been momentum historically to perform individual differences assessments and some reticence to track gynecologic outcomes that could affect mission selection.

While rodents can be used as a suitable model to obtain crucial information, there are still major limitations of small mammalian models and there are few rodent studies reporting sex-specific response to spaceflight stressors. A detailed research roadmap and relevant high-priority spaceflight experiments were previously generated in the NASA Rodent Mark III Habitat Workshop (54) and subsequent White Paper (23), including knowledge gaps in fertility, pregnancy and parturition, neonatal development and weaning, development of key sensorimotor systems, and, importantly, lifespan and multigenerational studies. These reports noted that, for successful multigenerational studies of rodents in space to commence, significant knowledge gaps related to impacts of long-term space flight on reproductive health of both males and females must be addressed. Further, multiple habitats with differing capabilities must be developed and validated to meet requirements for successful breeding, birthing, and nursing, maturation, and aging.

**Summary, Conclusions and Future Directions**

Future studies must investigate female-specific effects of spaceflight, particularly with regards to ovarian function and fertility, alteration of menses and abnormal uterine bleeding, immunosuppression, and impact on microbiomes as they relate to genitourinary infection risk, bone mineral density, ovarian cyst production and torsion risk, gynecologic and breast cancer risk, and how exogenous hormones can affect all of these risks. Continuing selection of female astronauts for space missions in numbers that are comparable to men will help ameliorate the experimental limitations related to small numbers of female astronauts. This approach will help pave the way for much-needed side-by-side experimental studies of humans. Further, it will be important to encourage and facilitate the participation of more female and male subjects in both ground and flight research studies. While animal research studies focus on deep space multi-stressors have begun to employ experimental designs directly comparing males and females (55,56), more of these side-by-side studies are needed to properly assess unique responses of women and men of spaceflight hazards anticipated beyond Low Earth Orbit. Systematic experimental assessment of individual differences in both human and animal studies, with particular attention to sex and gender, will be critical to developing a precision medicine approach for crew. Augmentation of the field utilizing AI approaches will requires a far more robust database than currently exists.

**Major Takeaways**

Much is still unknown on the effects of spaceflight on female astronaut health, especially long-duration missions. Increasing the body of data on women’s health and sex differences in space will be critical to advancing the application of artificial intelligence approaches.

Artificial intelligence approaches may provide a powerful tool for advancing the scope and pace of women’s health research in space, with the caveat that, at present, fundamental work in this field including the female-male sex-specificity of physiological responses to the spaceflight environment is not yet sufficiently mature to achieve this goal.

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1. 1In the 2001 Institute of Medicine report ‘‘Does Sex Matter,’’1 ‘‘sex’’ was first defined as the classification of male or female according to an individual’s genetics and ‘‘gender’’ refers to a person’s self-representation as male or female based upon social interactions. This classification holds today. [↑](#footnote-ref-1)