npj | women's health

Review

https://doi.org/10.1038/s44294-024-00009-z

Understanding how space travel affects the female reproductive system to the Moon and beyond

Begum Mathyk[1] ✉, Anthony N. Imudia[1], Alexander M. Quaas[2], Cihan Halicigil[3], Fathi Karouia[4,5,6,7], Pinar Avci[25], Nicolas G. Nelson[8], Ozlem Guzeloglu-Kayisli[9], Miriah Denbo[9], Lauren M. Sanders[10,11], Ryan T. Scott[10,12], Murat Basar[3], Ana Paula Guevara-Cerdán[13], Michael Strug[14], Brent Monseur[14], Umit A. Kayisli[9], Nathaniel Szewczyk[15], Christopher E. Mason[16,17,18], Steven L. Young[19], Savas Tasoglu[20,21,22,23] ✉, Sylvain V. Costes[10] & Afshin Beheshti[11,24] ✉

As the space industry grows exponentially and aspirations for space travel expand, we are entering a new era where we will very likely become an interplanetary species. Although reproduction is an essential human function and necessary for species survival, we have remarkably little knowledge regarding the impact of space travel on the female reproductive system. The effects of spaceflight on human reproductive potential, fertility, implantation and subsequent pregnancy resulting in a healthy live birth must be considered before planning prolonged spaceflight missions and the colonization of planets. In this review, we explore what is known and what remains to be learned about the effects of space travel on female reproductive endocrinology. We also delve deeper into reproductive endocrinology and discuss normal physiologic mechanisms at the molecular level to have a better understanding of how it may change during spaceflight. The rigors of spaceflight including radiation, gravitational stressors, and circadian rhythm changes could potentially affect ovulation, fertilization, endometrial receptivity, preimplantation embryo development, embryo implantation, placentation, and pregnancy. Thus, we will examine what is known about spaceflight effects on the hypothalamic–pituitary–gonadal (HPG) axis, ovarian folliculogenesis and steroidogenesis, early embryogenesis, endometrial receptivity, and pregnancy. We further discuss the recent advances in reproductive endocrinology and future research platforms. Establishing a better understanding of the effect of space travel on female reproductive health, as well as developing countermeasures to mitigate adverse effects, are decisive components of our species' successful transition to an interplanetary one.

In 1969, Neil Armstrong famously said: "One small step for man, one giant leap for mankind." Now, over 50 years later, the National Aeronautics and Space Administration (NASA) in collaboration with international partners is planning to return to the Moon with Artemis missions to establish a human habitat, land the first female on the Moon, and pave the way for future planetary missions in our solar system. With these early, but giant steps toward becoming an interplanetary species, we can no longer ignore potential reproductive challenges incurred during spaceflight and deep space exploration. Rather, we must identify and overcome (or accept) these challenges. The new NASA decadal survey marks a significant milestone in shaping the future of space research. It highlights the critical importance of understanding female biology in the next decade of NASA's scientific endeavors[1]. The survey underscores the need for dedicated fundamental and applied research efforts to ensure the health, safety, and well-being of women during extended space missions by highlighting the physiologic complexities that female astronauts may face in space.

A full list of affiliations appears at the end of the paper. ✉e-mail: abegum@usf.edu; stasoglu@ku.edu.tr; abehesht@broadinstitute.org

Since the first woman went to space, Valentina Tereshkova in 1963, the number of female astronauts has consistently increased along with the length of the mission. In the last decade, female astronauts went on longer-duration missions, lasting from 6 months to a year, far beyond the technical definition of long-duration flights (>30 days). With this increase in duration, comes longer exposure to the unique hazards and technical challenges of the space environment. Moreover, despite a significant increase in female crew assignments for the past few years, overall representation of women in spaceflight only represents 10% of total crewed missions.

During missions in low Earth orbit (LEO) and beyond, astronauts face identified risks such as space radiation, altered gravitational forces, circadian rhythm changes, isolation, communication delays, and limited health care access. These conditions are associated with oxidative stress, cancer, cardiac dysfunction, immune dysregulation, muscle atrophy, bone loss, limited nutrition, sleep disorders, and mood changes[2]. The "space exposome" is a unifying term, combining these space-related risk factors with individual factors such as age, gender, lifestyle, and genetics[3]. In the following sections, we will be discussing space-related risk factors and their impact on the female reproductive system. We provide insight on the physiology of reproductive endocrinology and possible pathophysiology that may occur during spaceflight based on current data.

Radiation exposure during spaceflight

One of the most studied space-related risk factors is exposure to ionizing radiation, which has been considered the main limiting factor for exploration class missions[4]. The geomagnetic field of the Earth primarily serves as a shield for life on our planet against charged particles present in galactic cosmic radiation[5]. Astronauts are considered as special radiation workers due to the unique space radiation environments of LEO and beyond[6]. NASA's radiation exposure limits are set to maintain a 3% risk of exposure-induced death (REID) for cancer, using a 95% confidence level to address uncertainties in risk predictions[7]. This limit is based on age and sex-specific cancer risk assessments. This standard impose more lenient restrictions on men and older astronauts, whose cancer mortality risk attributable to radiation is presumed to be lower[8]. The National Academies released a report in 2021 that encouraged NASA to proceed with a universal standard corresponding to an estimated 3% cancer mortality risk increase for a 35-year-old female astronaut[4]. In early 2022, NASA adopted this new standard, limiting all astronauts to 600 mSv of radiation for their entire career[9].

Unlike exposures to radiation on Earth, space radiation contains high-energy charged particles, including ions from solar flares (solar particle events; SPE) and galactic cosmic rays (GCR) from interstellar sources[10]. Aboard the International Space Station (ISS) in LEO, astronauts also encounter increased exposure to high-energy particles, particularly when the ISS passes through the South Atlantic Anomaly (SAA) with doses peaking several hundred μGy/min[11]. The SAA anomaly is a region where the Earth's inner Van Allen Belt, which traps charged particles, comes closest to the Earth's surface. Consequently, the ISS's passage through this area results in heightened radiation levels. Therefore, the effective dose of galactic cosmic radiation for individuals on aircraft, is affected by factors like altitude, geographic location, the Earth's magnetic field, and solar activity[12]. Cumulative exposures may be expected to be higher for crews of commercial spaceflight companies than airlines[13]. For example, total exposures aboard the ISS fluctuate around an equivalent 5–20 μGy per hour[14], compared to an estimated 3.0–6.6 μGy per hour aboard international flights[15].

The primary radiation risks for spaceflight crew beyond LEO are threefold: (1) Constant exposure to low-dose, low-energy solar wind; (2) Acute, sporadic, and somewhat unpredictable exposure to high-energy protons from Solar Particle Events (SPEs), originating from solar flares and Coronal Mass Ejections (CMEs); (3) Chronic low-dose exposure to high-energy Galactic Cosmic Rays (GCRs). GCRs include protons, helium ions, and heavier energetic elemental nuclei (HZE particles) accelerated by various celestial phenomena outside our solar system[16]. Notably, during solar minimum periods, SPEs become rarer, but the chronic dose rates from GCRs are about twice as high[14]. The intravehicular space radiation environment is further complicated by spallation, in which GCR collides with materials and triggers a cascade of nuclear fragmentation events that result in a shower of lower-energy ions and neutrons. As such, shielding cannot prevent exposure to GCR or the products of spallation[5]. The SPE that may threaten crew safety are mostly protons with kinetic energies of 50–300 MeV at high fluence. Exposure to SPE radiation decreases with thicker shielding, but contribution to generation of secondary neutrons from interaction with the shielding can increase exposure to radiation and it can pose a higher threat during extra-vehicular activities (EVA)[17].

A distinction is made between sparsely ionizing (or low-linear energy transfer; low- LET) and densely ionizing (or high-LET) radiation. The LET of a particle is defined as the average energy deposited along its path per unit length, expressed in kiloelectron volts per micrometer (keV μm^{-1}). Electromagnetic (photon) radiation, including X- and γ-rays, is considered low-LET because it deposits energy less densely along its track, depositing energy uniformly in the tissue. In contrast, α-particles and heavier energetic ions, which are critical components of the GCR, are densely ionizing (high-LET) because they deposit the majority of their energy along their linear trajectory[18] and can cause more complex DNA damage[19] and clustering of DNA double-strand breaks clustering[20].

The proportion of GCR in space radiation will differ between the LEO and beyond-LEO environments, as well as the Martian surface[21]. The estimated total radiation dose received during a Mars mission, which typically includes 6 months of travel each way and an 18-month surface stay, is expected to result in a cumulative dose equivalent that is significantly lower than 1000 mGy[22,23]. This number is probably an under-estimation based on the recent radiation dosimeter readings during the cruise phase of the Mars Curiosity mission, which reported trans-Earth-Mars exposures of up to 1.8 mGy/day[24] or ~660 mGy for a 1-year travel alone, but could exceed 1200 mGy depending on trajectory, time of the mission, and stage of the solar cycle[25]. The total dose is also subject to change based on local conditions and extreme events such as solar flares.

The effect of radiation on female reproductive organs

Ionizing radiation damages DNA either directly or indirectly through reactive oxygen and nitrogen species[10]. The effects of acute radiation exposure can persist for years, as exemplified with high-LET radiation by persistent oxidative stress, lipid peroxidation, and mitochondrial dysfunction in the murine intestine one year after ^{56}Fe irradiation[26]. In turn, mitochondrial dysfunction and oxidative stress have been implicated in several diseases of the reproductive system as well as spaceflight pathologies[27,28]. For example, reactive oxygen species cause human endometrial endothelial cell apoptosis, thereby contributing to the pathogenesis of progestin contraceptive-mediated abnormal uterine bleeding[29]. Radiation exposure is also an independent risk factor for future cancer, and its potential association with gynecologic cancers during spaceflight has recently been reviewed[30]. Historically, most radiation studies have focused on the effects of acute radiation exposure, but recent efforts have also shifted to understanding the carcinogenic and tissue effects of chronic low-dose high-LET radiation, i.e., GCR[31].

Our knowledge on the effects of radiation on the human body is largely derived from survivors of childhood cancer or atomic bombs, but there are important distinctions between clinical and environmental exposures. In external beam radiotherapy, high doses of targeted radiation are delivered to a specific anatomical region in discrete fractions. To suppress native bone marrow for stem cell transplantation, some patients receive total-body irradiation at a lower dose than radiotherapy but significantly higher than medical imaging. Regardless of dose and dose rate, these are all relatively brief, controlled exposures. On the other hand, environmental radiation results in more chronic, whole-body exposure, so one must be cautious when attempting to extrapolate data from one context to the other.

Radiation therapy has short and long-term reproductive toxicities that vary by total radiation dose as well as dose rate and radiation type (Table 1). Oocytes are exquisitely radiosensitive[32], and radiotherapy is a known risk factor for primary ovarian insufficiency (POI) and premature menopause. Twelve-week-old C57BL/6J female mice, exposed to charged iron and

Table 1 | Radiation effects on female reproductive function[171]

Sex	Dose, Gy	Effect
Female*		
All ages	1.25–1.5	Amenorrhea in 50%
	1.7	Temporary sterility lasting 1–3 years
	3.2–6.25	Permanent sterility
Ages 15–40	1.5–2.5	Temporary amenorrhea
	2.5–5	Ovulatory suppression in 40–100% (permanent in 60%)
	5–8	Permanent ovulatory suppression in 40–100%
	> 8	Permanent ovulatory suppression in 100%

*Dose needed to induce ovarian failure is age-dependent.

oxygen particles in separate experiments conducted in the same laboratory, depletion of primordial follicles and estrous cycles irregularities were observed at different rates based on particle type and doses[33–35]. More specifically, the primordial follicle pool decreased by 71% after only 5 cGy of 600 MeV/n ^{18}O (16.5 keV/μm) exposure and was fully depleted following 30 cGy. In contrast, 57% follicle loss was observed after exposure to 5 cGy of 600 MeV/n ^{56}Fe (179 keV/μm)[33]. For the primordial follicle loss, the ED50 was 4.6 cGy and 27.5 cGy for oxygen and iron species, respectively[34], indicating a differential effect based on ion species. These outcomes can be understood through Poisson statistics. Given the reported nuclear area of 113 μm^2, a 5 cGy exposure implies that 88% of nuclei are likely to be hit by an oxygen particle and 18% by an iron particle. For oxygen, it's estimated that 63% of nuclei experienced more than one hit, suggesting that two oxygen traversals might be necessary to destroy a follicle. Conversely, with iron particles, the mere 18% of nuclei hit by at least one particle reflects the higher Linear Energy Transfer (LET) of these particles, which release ~11 times more energy locally. This suggests that even a single traversal by an iron particle is sufficient for follicular destruction. The corresponding Poisson distribution target area for 57% hit by iron is ~500 μm^2, meaning any particle impacting within this radius centered on a cell could be lethal.

In humans, ovarian damage after radiation is also dose- and age-dependent[36] (Table 1). Radiation-induced ovarian insufficiency and subsequent cessation of hormone production can lead to premature menopause and temporary or permanent infertility (Table 1). After radiotherapy, studies showed that an average of 2 Gy radiation can destroy half of human oocytes[37], while POI occurs in 97% of women when exposed to 20.3 Gy at birth, 18.4 Gy at age 10 years and 14.3 Gy at age 30 years[36]. Therefore, a dose of 3.5–20 Gy can result in permanent infertility in women depending on their age (Table 1)[38].

In addition to oocytes being radiosensitive, the larger organs that support fertilization and embryo development also show signs of damage when exposed to radiation. The vagina has mucosal layer, a radiosensitive tissue. Radiotherapy can cause mucosal atrophy and vaginal stenosis, resulting in dyspareunia and vaginal dryness[39]. The uterus is known to be more radioresistant than the ovaries, but changes in cervical length, endometrial thickness, and junctional zone visibility have been reported in colorectal cancer survivors after pelvic radiotherapy[40]. Furthermore, when females are exposed to pelvic irradiation at a young age, their uterine volumes are reported to be decreased in adulthood[41]. Uterine exposure to radiotherapy during childhood also increases the risk of pregnancy complications such as preterm delivery and low birth weight[42]. As for chronic low-dose exposure, one recent study found an association between higher levels of home radon, a radioactive gas, and the incidence of hypertensive disorders in pregnancy[43].

Cranial radiotherapy affects the central nervous system, and the hypothalamic–pituitary–gonadal (HPG) axis is the central regulator of reproductive endocrinology (Fig. 1). The pituitary gland secretes follicle-stimulating hormone (FSH) and luteinizing-hormone (LH) along with other crucial hormones such as growth hormone, thyroid stimulating

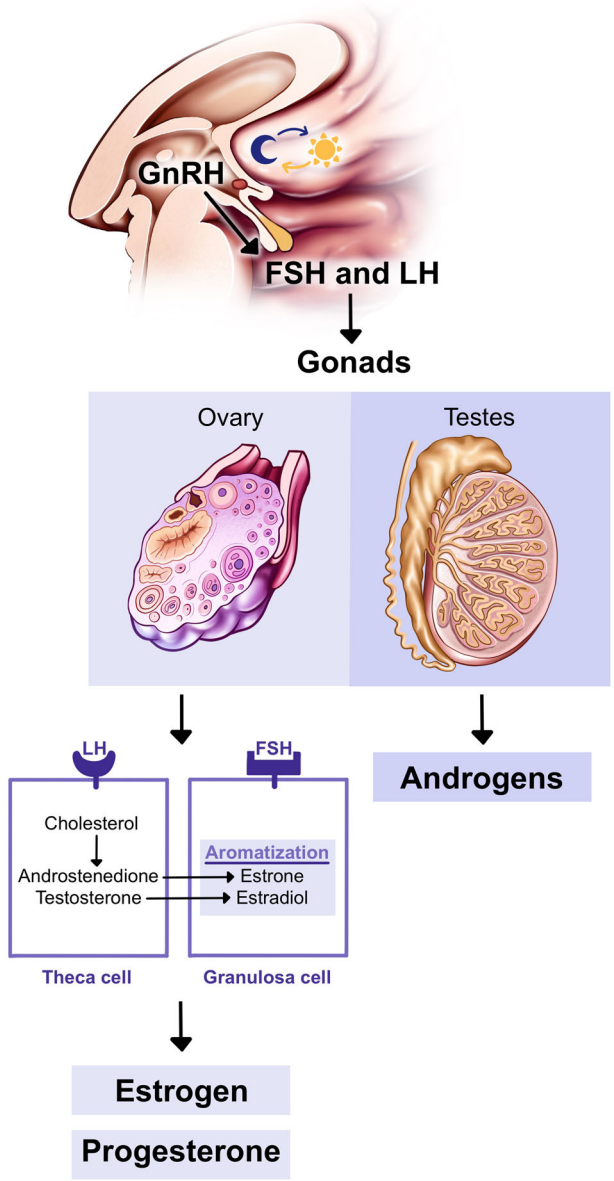

Fig. 1 | The hypothalamic–pituitary–gonadal (HPG) axis. This figure illustrates GnRH secretion, as well as the downstream effects of FSH and LH. It also shows the action of FSH and LH on gonads, and depicts the two-cell, two-gonadotropin model of estrogen synthesis.

hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin, oxytocin, and vasopressin. Pituitary dysfunction has been reported in patients with brain and neck malignancies who underwent radiotherapy[44]. Radiation-induced pituitary dysfunction can be permanent and progressive, with effects dependent on pituitary cell type, radiation dose, age, and sex[45]. Moreover, cranial radiotherapy has been associated with gonadotropin alterations and can cause pubertal delay or precocious puberty[46]. Precocious puberty was reported after the administration of 30 Gy[45].

Lastly, the dose threshold for radiation-induced teratogenesis during pregnancy differs based on the gestational age (Table 2). During early embryogenesis, radiation exposure results in an "all or none" phenomenon, but afterward the occurrence and degree of unwanted effects in the fetus often depend on the gestation and dose received (Table 2).

It is important to reemphasize that radiotherapy entails brief, acute, and targeted exposures at much higher dose rates than those experienced in LEO and beyond. Furthermore, differences in radiation quality can produce different biological responses. The existing research on radiation risks to the

Table 2 | Effects of radiation dose on radiation-induced teratogenesis[172]

Gestational age	Effects	Estimated threshold dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequences "All or none"	50–100 mGy
Organogenesis (2–8 weeks fertilization)	Congenital anomalies (skeleton, eyes, genitals) Growth restriction	200 mGy 200–250 mGy
8–15 weeks	Severe intellectual disability (high risk)† Intellectual deficit Microcephaly	60–310 mGy 25 IQ point loss per 1000 mGy 200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (e.g. radiation therapy for carcinoma of the uterus).
†This is the period for rapid neuronal development and migration.
Reprinted with permission from ref. 172.

female reproductive system primarily relies on therapeutic doses of low-LET (photon) irradiation. However, there is an unmet need in space biology to investigate the consequences of chronic low-dose, high-LET radiation, which is particularly relevant in this context.

Gravitational forces during spaceflight

The difference in gravitational forces in space compared to earth, are another source for adverse health effects. The gravity that humans experience on Earth is about 9.81 m/s^2, defined as 1 g (varies about 1% by location)[47]. However, space travelers are exposed to both reduced and increased gravity forces. In LEO, the forces amount to free fall, resulting in a gravity that is a millionth of that on Earth's surface. In practice, perfect weightless conditions are impossible to attain due to disturbances from drag, vibrations, etc., and so the term microgravity (μg) is used to describe the actual conditions. The suppression of gravitational force, or its strong reduction, is responsible for the following effects: (1) decreased hydrostatic pressure, (2) no weight, (3) no sedimentation, and (4) no natural convection[48]. Those living on the Moon and Mars would experience about 1/6 and 1/3 the amount of gravity on Earth, respectively; while hypergravity of 3–7 times that on Earth can be seen during re-entry[49]. These gravitational alterations have an impact on blood flow, shear stress forces, cytoskeleton, cell adhesion properties, and mechanoreceptors[50,51]. Under microgravity, body fluid is displaced in the cephalad direction, causing 'puffy face syndrome' in astronauts. At the same time, the loss of loading in the lower extremities leads to decreased bone mass, muscle mass, and strength. Change in vascular dynamics under microgravity has been observed. Simulated microgravity in a rat model caused an increase in aorta stiffness[52]. In astronauts, femoral artery intima media thickness increased during 6 months of spaceflight[53]. Similar to the lower extremities, pelvic organs receive blood supply from the aorta and internal iliac arteries. Uterine blood flow is ~100 mL/min, whereas in a uterus in term pregnancy, this flow increases to 700 mL/min, which accounts for nearly 10% of the cardiac output[54]. Currently, we have limited knowledge of how gravitational forces affect pelvic and pituitary portal circulations. Also, we do not know if micro- or hypergravity impact utero-placental blood flow, which is crucial for healthy fetal growth. Therefore, it is important to understand the impact of gravitational forces on reproductive organs and their vascular dynamics. In the following sections, we will discuss gravitational studies focusing on reproductive tissues in more detail.

Reproductive endocrinology and developmental biology for Earth and beyond

To date, various models including mice, rats, salamanders, frogs, fish, and cockroaches have been studied to understand the effects of spaceflight on reproduction[53]. Some of these studies were conducted during actual spaceflights, while others were carried out under simulated microgravity (i.e., parabolic flights, hindlimb suspension and rotating wall vessels)[53]. In 2000, Jennings et al. reviewed the gynecological data and reproductive outcomes in U.S. female astronauts between 1991 and 1997[55]. The success rates for assisted reproductive technology (ART) in astronauts have been low, yet comparable to older patients undergoing ART[55]. Yet as of 2023, there has been no global update on the reproductive outcome data after space travels despite continued participation from female astronauts in space missions. There is a global need for a women's health database that includes clinical, biochemical and omics information for spaceflight. Although literature exists on non-human species, there are still many unknown questions regarding the effects of the space environment beyond LEO on the human reproductive system.

As we navigate the intricate realms of reproductive endocrinology and developmental biology on Earth, this complex system has been marveled over since the beginning of time. Now, as we venture into space, new dimensions to our understanding have begun to unfold. In the next sections, we will review the normal physiology, alongside an exploration of the current space literature available. We will discuss ovarian steroidogenesis and the menstrual cycle elucidating the core processes of reproductive endocrinology. We will explore the circadian rhythm and associated hormonal regulations illuminating chronobiology. Finally, we will examine ovarian folliculogenesis and oocyte maturation while shedding light on ovarian dynamics and the aging process. It is important to note that even with successful oocyte development, the path to successful pregnancy hinges on the pivotal stages of fertilization, implantation, embryo development, and subsequent fetal growth to achieve a healthy live birth. During these complex steps, prenatal conditions shape the trajectory of health across a lifetime, forming the foundation of the Developmental Origins of Health and Disease (DOHaD) Hypothesis[56].

The hypothalamic–pituitary–gonadal (HPG) axis, menstrual cycle, and ovarian steroidogenesis

The HPG axis is the primary regulator of menstrual cycle, ovarian steroidogenesis and folliculogenesis. Pulsatile hypothalamic secretion of gonadotropin-releasing hormone (GnRH) plays an essential role in releasing pituitary gonadotropins (FSH and LH), which, in turn, regulate gonadal function (Fig. 1). Frequency and amplitude of GnRH secretion change in follicular and luteal phases of the menstrual cycle. Thus, a physiologic menstrual cycle requires pulsatile GnRH secretion. Although there are limited data regarding the HPG axis during spaceflight, one study demonstrated lowered serum GnRH, FSH, LH, and testosterone levels in male rats exposed to simulated microgravity[57]. The fluid shift and its impact on the pituitary gland could be an explanation for the reported gonadotropin changes. Cephalad fluid shift due to microgravity has been observed during spaceflight and MRI studies showed increased pituitary deformation and change in cerebrospinal fluid dynamics during spaceflight[58]. Thus, these physiologic adaptations may impact the HPG axis.

The HPG axis controls the menstrual cycle via hormonal feedback loops during menstruation, follicular phase, ovulation, and luteal phase. Menstrual cycle irregularities have been reported in female flight attendants[59,60]. In 1978, the first bed rest study in females investigated gynecological data[61]. In this study, no significant change in the length of the menstrual cycle was noted after 17 days[61]. In rodent studies, data are conflicting regarding the effects of spaceflight on the estrous cycle in female mice during spaceflight[62,63]. A recent study reported possible estrous cycle activity[62], whereas prior STS missions showed smaller ovaries, regression of corpora lutea, and cessation of estrous cycling[64]. Under simulated microgravity, female rodents showed less time in estrous phase[65]. On the other hand, hypergravity exposure extended the diestrus stage of the estrous cycle in rats[66].There is limited data on human cycle variations as most female astronauts taking a form of hormonal contraception[61]. Hormone use has been associated with the risk of venous thromboembolism (VTE) in both pre- and postmenopausal women. Hormonal contraceptive use during

spaceflight and the risk of VTE have been reviewed in another article[67]. It was revealed that women using combined oral contraceptives (COCs) during flight exhibit higher calculated blood viscosity than those not taking COCs[67]. Furthermore, due to the physiological changes during spaceflight, the pharmacokinetics of drugs may be different in space[68]. Currently, we have limited information on the pharmacokinetics of hormonal medications in the space environment. Knowing if the kinetics are different would change dosing and should be explored further.

Sex steroid hormones are essential part of the menstrual cycle. Ovarian steroidogenesis is the main source of sex steroid hormones (e.g., estradiol, progesterone) (Fig. 1). The two-cell two-gonadotropin theory is the main foundation of ovarian steroidogenesis and involves the interaction of theca and granulosa cells. In the ovary, steroidogenesis starts with cholesterol, the precursor of steroid hormones, and LH stimulates theca cells to produce androgens. Androgens then shuttle to granulosa cells and aromatize to estrogens via FSH-induced aromatase. Estrogens play a major role not only in the reproductive system, but also systemically promote bone health, cardiovascular health, immune function, and metabolism[69]. Estrogen deficiency is a known risk factor for decreased bone mineral density and osteoporosis. The bone mineral density is also negatively impacted by mechanical unloading, such as weightlessness experienced during spaceflight and bed rest studies, as well as exposure to radiation[70,71]. Therefore, both estrogen deficiency and spaceflight are independently associated with decreased bone mineral density, and their combined effects may have compounding impacts on bone health. Further, during the menopausal transition and menopause, women experience decreased estradiol levels and its systemic and metabolic consequences such as vasomotor symptoms, sleep disturbances, and changes in cholesterol profile. Currently, there is limited data on how estrogen receptors and signaling are affected by spaceflight in various organs[72]. Our previous study showed gene expression changes in estrogen-linked gene sets during spaceflight across various tissues in both rodent and human samples[72]. We still have limited knowledge on whether spaceflight has an impact on steroid hormone signaling pathways in reproductive tissues. One study showed that ovarian tissue estradiol concentrations of space-flown mice were not significantly different than their ground control counterparts[62]. Although ovarian expression of steroidogenic genes (i.e., *Star*, *Cyp11a1*, *Cyp17a1*, *Cyp19a1*, and *Hsd3b1*) were not significantly different across groups, ovarian progesterone levels were lower in the flight group than the baseline cohort[62]. Simulated microgravity in mouse Sertoli cells results in the upregulation of Cyp19a1, which encodes aromatase[73]. Consequently, this leads to an increase in estradiol production[73]. Ovaries also produce testosterone and androstenedione, which are converted to estradiol and estrone via aromatization, respectively. Ovarian testosterone production is also stimulated by insulin and insulin-like growth factors (IGFs). Although insulin-linked gene expressions are altered during spaceflight in both human and rodent samples[74,75], information is limited on how these genes and related pathways may change in reproductive organs. Ovarian steroidogenesis undergoes modifications throughout a woman's life span. Thus, it is important to understand the stages of a woman's life and the hormonal changes that occur during these stages, starting with puberty and continuing through her reproductive years, perimenopause and postmenopausal periods.

Endocrine effects of circadian rhythm alterations

Changes in the circadian rhythm may interfere with GnRH signaling and the HPG axis. The HPG axis is closely related to the circadian clock. Humans evolved to live in a 24-h light–dark cycle; however, the day cycle on the ISS is vastly different with the ISS orbiting the Earth every 90 min and will be different on other planets as well. Disruptions in sleep and circadian rhythm have an impact on fertility and pregnancy. Specifically, sleep dysregulation has been associated with menstrual irregularities[76] infertility, miscarriage, fetal growth restriction, preeclampsia, and preterm birth[77,78]. Therefore, it is critical to assess these effects.

In mammals, the circadian system is driven by the suprachiasmatic nucleus (SCN) located in the hypothalamus (Fig. 1). In female rodents, the SCN is necessary for generating the preovulatory surge via GnRH and LH secretion[79]. Both microgravity and hypergravity can alter circadian rhythm and clock genes[80–82], the latter of which are expressed centrally, but also in reproductive organs where they are involved in the regulation of key steroidogenic genes, including *Cyp19a1* and *Hsd3b2*[83,84]. Women who sleep less than 8 h display lower FSH levels, which may indicate functional impairments in GnRH pulsatility and resulting pituitary function due to altered circadian rhythm[85]. In addition, chronic insomnia increases pituitary adrenocorticotropic hormone (ACTH) and cortisol levels, associated with enhanced stress response which may disrupt HPG function[86,87].

Ovarian clock gene expression has been associated with ovarian aging[88]. Ovarian clock genes were downregulated with aging and correlated with Anti-Müllerian hormone (AMH) levels[88]. Insulin is another hormone that is closely related to both circadian rhythm and HPG axis[89]. Insulin resistance has been linked to circadian rhythm changes[90] and was observed in both astronauts and rodents[74,75,91]. Sleep abnormalities such as short sleep duration, chronic insomnia and evening chronotype are all associated with insulin resistance[92]. Insulin signaling plays a role in ovarian physiology and is essential for lipid and glucose transport during ovarian folliculogenesis[93] and impaired insulin signaling is a major disruptor for female infertility[94]. Impaired insulin signaling not only affects nonpregnant women; overt insulin resistance during pregnancy can lead to gestational diabetes and associated neonatal risks including macrosomia, shoulder dystocia, hypoglycemia, and hyperbilirubinemia[95]. In summary, menstrual cycle dynamics are complex and involve ovarian steroidogenesis, recruitment of follicles and folliculogenesis, oocyte maturation during folliculogenesis, cyclic changes in the endometrium, which are coordinated by the HPG axis and feedback loops along with metabolic and cellular changes at the molecular level. This complex system is closely related to the circadian rhythm, involving both central and peripheral clock systems.

Furthermore, circadian rhythm alterations have been implicated in the incidence and biology of human cancers as well as DNA damage repair mechanisms, suggesting that circadian alterations could plausibly affect the rate of radiation-induced carcinogenesis[96]. Further research needs to highlight physiologic and pathophysiologic changes during spaceflight if they interfere with these intricate and interrelated steps.

Ovarian folliculogenesis, oocyte maturation, and aging

Women have a limited number of oocytes throughout their life span. Initially, a female fetus at 20 weeks of gestation possesses a maximum of 6–7 million oocytes. At birth, this number decreases to 1 to 2 million. The count steadily decreases as age advances, reaching around 1000 oocytes at 51 years old. Oocytes are supported by the follicles throughout folliculogenesis, a continuous process that involves follicle recruitment, selection, and eventual ovulation. Ovarian folliculogenesis and intraovarian signaling both play critical roles during oocyte maturation and quality. Hormones, calcium signaling, cytokines, growth factors, and the cytoskeleton are pivotal in this maturation process. Oocyte maturation progress is in synchrony with the ongoing folliculogenesis.

Ovarian folliculogenesis is a continuous process that has both gonadotropin-independent and gonadotropin-dependent phases, regulated by FSH, LH, and intraovarian factors such as AMH, activin, inhibin, growth differentiation factor-9 (GDF-9), bone morphogenic protein-15 (BMP-15), and gap junction proteins[97]. There is an interactive communication between the oocyte and follicle cells (i.e., granulosa cells). This complex system is understudied in the realm of human space biology. The effect of microgravity on rodent oocytes during follicle development has been studied using rotating wall vessels. In simulated microgravity, the arrangement of granulosa cells within follicles was disrupted as more than 50% of cells lost their polarity[98]. In a porcine model, simulated microgravity inhibited the proliferation of granulosa cells and arrested the cell cycle[99]. These changes would hinder cellular communication, thereby impacting folliculogenesis. In female mice, folliculogenesis is disrupted during spaceflight, with the majority of follicles in the flight group exhibiting atresia[64]. AMH is one of the regulatory hormones of folliculogenesis and is secreted by the granulosa cells

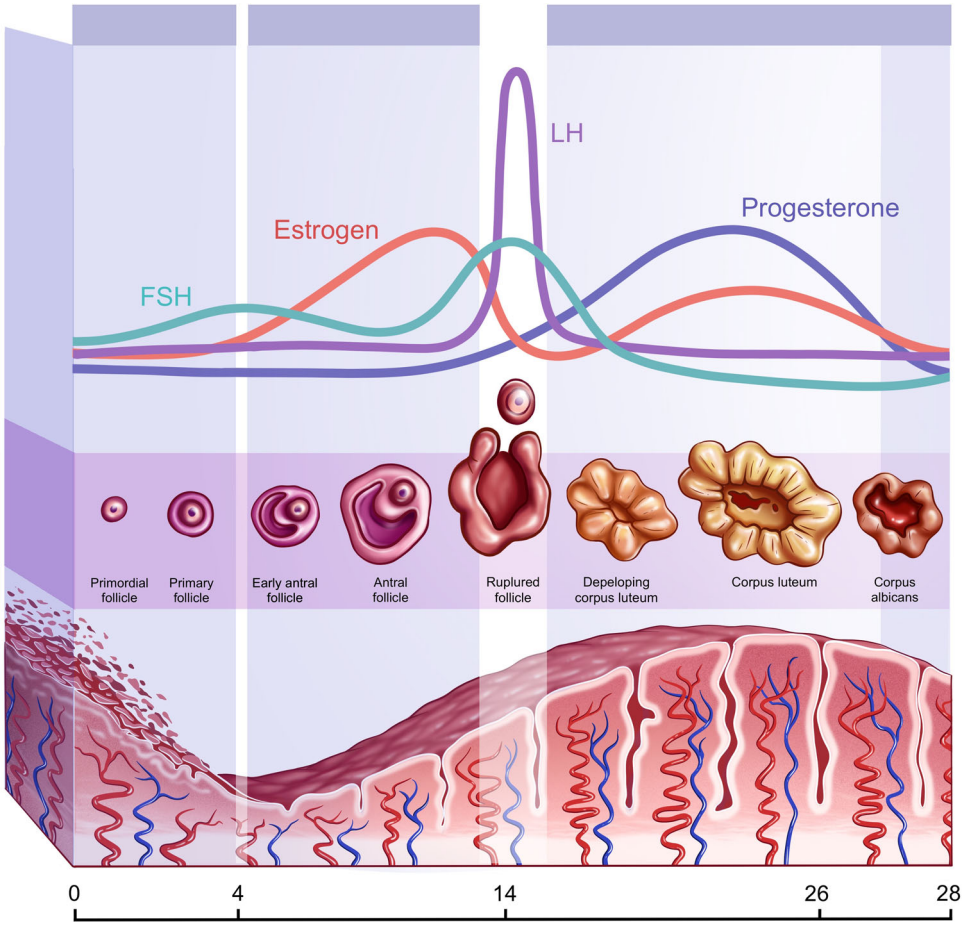

Fig. 2 | Menstrual cycle and follicle development. The endometrial, ovarian cycles are depicted in parallel with hormonal and gonadotropin fluctuations throughout the menstrual cycle.

of developing follicles. A dry immersion study on 12 women, designed to mimic microgravity conditions, revealed variations in serum AMH levels[100]. However, the median AMH levels remained relatively stable before and after immersion[100]. In contrast, inhibin B levels were higher, while LH and progesterone levels were lower post-immersion. Notably, subjects' ages ranged from 22.7 to 40.8 years, which might have contributed to the observed variations. GDF-9 is another paracrine factor which regulates folliculogenesis. Microgravity exposure resulted in decreased number of follicles, and GDF-9 protein expressions along with adverse morphological effects on mice oocytes[101]. These morphological effects included disrupted mitochondria and Golgi, absent microvilli, and the appearance of multilamellar bodies and lipid droplets[101]. In another study, oocyte maturation rates were significantly lower under simulated microgravity (8.9% vs. 73% in μg vs. 1 g) along with disrupted meiotic spindle formation[102]. When exposed to microgravity, mice oocytes exhibited a decrease in the release of the first polar body, indicating further unfavorable effects of microgravity on oocyte maturation[98]. A recent study on human oocytes exposed to simulated microgravity demonstrated notable morphological changes in both mitochondria and smooth endoplasmic reticulum (SER)[103]. Under simulated microgravity, there was a decrease in the number of mitochondria and SER aggregates while mitochondria vesicle complexes increased. In addition, distinctive morphological disparities were observed such as elongated and dumbbell-shaped mitochondria, along with irregular borders and collapsed cristae. These morphological alterations may have implications for metabolism and fertilization. Although murine models are commonly used in reproductive biology research, it is important to highlight that there are physiological differences between mice and humans such as folliculogenesis takes longer in humans. Keep in mind that ovarian folliculogenesis is not a separate physiological process, as it synchronizes with sex steroid-induced changes in the endometrium (Fig. 2).

An important point of distinction is that oocyte maturation and quality are related but different concepts. The oocyte maturation process involves structural and molecular changes including germinal vesicle breakdown, resumption of meiosis to metaphase, segregation of chromosomes, first polar body extrusion, and cytoplasmic maturation, which results in a haploid oocyte that is ready for fertilization. On the other hand, oocyte quality refers to viability and fertilization capacity of the oocyte, which is mainly assessed morphologically via evaluating distinct features such as ooplasmic granularity, perivitelline space, and zona pellucida[104]. Several factors can impact ovarian aging and quality, including age, genetics, and environmental factors (i.e., radiation, reproductive toxins)[105].

As women age, oocyte quality declines and there is an increased risk of aneuploidy. In addition, telomeres at the end of chromosomes shorten with advancing maternal age. With each cell division, telomeres progressively shorten, and cell division stops when they reach a critical length, resulting in cellular senescence. Mitochondrial dysfunction and subsequent oxidative stress may contribute to telomere dysfunction[106]. The connection between aging and spaceflight has been explored in previous studies[107]. In the NASA twin study, telomere length increased during spaceflight and returned to its normal length upon return to Earth, suggesting that space travel might have an impact on the telomeres and telomerase activity[108]. Telomere dynamics was further studied in 11 astronauts who spent a year or less in the International Space Station[106]. Luxton et al. found that irrespective of the mission duration, there was an increase in the telomere length during spaceflight[106]. Upon returning to Earth, a decrease in telomere length was observed resulting in shorter telomeres than their preflight levels[106]. Additional findings were alterations in cell populations and significantly increased chromosomal inversion frequency during and after spaceflight[106]. Based on these findings, the authors proposed that in environments with chronic oxidative stress, a transient telomerase-independent adaptive response via

activation of the Alternative Lengthening of Telomeres pathway may take place in somatic cells[106].

In addition to parental DNA, the oocyte is also responsible for passing down cellular components and genetic materials to the offspring. While nuclear DNA is inherited from both parents, mitochondrial DNA, located in the cytoplasm, is inherited maternally from the oocyte's cytoplasm. Considering that mitochondria is an organelle affected by the conditions during the spaceflight[2,101], it is plausible to assume that spaceflight may also possess a risk to inherited mitochondrial DNA. The mitochondrial dysfunction that occurs in space has implications in instigating long-term health risks associated with the development of mitochondrial and metabolic diseases. Promising techniques involving the transfer of mitochondria, meiotic spindle, and ooplasm have emerged in reproductive endocrinology as potential solutions for specific forms of infertility and for preventing the inheritance of mitochondrial diseases.

The impacts of spaceflight, radiation, and microgravity on ovaries have been summarized in Table 3. In summary, gamete maturation, epigenetics, and aging in space remains an understudied area. Furthermore, there have been reports of epigenetic changes during spaceflight in various organisms[109], but our understanding of potential epigenetic effects on reproductive tissues, gametes, and subsequent embryos remains limited.

Fertilization and embryo development

Fertilization is the fusion of gametes (sperm and oocyte) to form a zygote. Following ovulation, fertilization usually occurs in the ampulla region of the fallopian tube. Successful fertilization requires more than sperm and oocyte interaction. A sperm must undergo physiological changes, a process known as capacitation, to fertilize the oocyte. Capacitated spermatozoa bind to the protective layer of the oocyte (zona pellucida), and after an acrosomal reaction, it penetrates through the oocyte. Once sperm enters the oocyte cytoplasm, maternal and paternal genetic fuses via pronuclear fusion followed by expulsion of the second polar body. Following fertilization, the zygote undergoes a series of cell divisions to proceed with embryo development. After successful cellular divisions, the formed blastocyst reaches the uterine cavity for implantation. The implanted embryo grows inside the uterine cavity. Ectopic pregnancy, seen in 2% of all pregnancies, is a condition in which the embryo implants and grows outside of the uterine cavity. When an ectopic pregnancy ruptures, it can be a life-threatening condition due to bleeding. The ciliary movement in the fallopian tubes aids the transfer of embryo toward the uterus; and it remains unknown if space travel is a risk factor or not for an extrauterine embryo implantation (i.e., ectopic pregnancy) due to altered cell adhesions and fluid dynamics resulting from microgravity.

Although microgravity's effect on zygote migration to the uterus has not been studied, fertilization reactions in simulated microgravity and spaceflight have been investigated. Studies in the clinostat, a ground-based model to mimic microgravity, showed that the process of fertilization in vitro is not sensitive to the gravitational vector[110]. In the Micro-11 mission, human and bull sperms were sent to ISS to study capacitation and motility[111,112]. Critical motility parameters necessary for sperm capacitation and fertility, such as progressive motility, curvilinear velocity, and appearance of hyperactivated sperm were negatively compromised during spaceflight compared to ground controls[112]. Acrosome reaction rates were decreased in human and bovine sperm during spaceflight. Finally, significant sperm DNA damage was observed in flight as compared to ground controls[113]. The DNA fragmentation index (DFI%) was higher in spaceflight samples compared to ground controls at both 0 min and 60 minutes activation (0 min: FL = 19.3 ± 2.6% vs. GC = 8 ± 1.4%; 60 mins: FL = 32.7 ± 1.7% vs. GC = 12 ± 1.6%)[113]. In a recent study, mice were kept under microgravity (MG) conditions on the ISS for 35 days. The spermatozoa from artificial gravity (AG) and MG mice showed comparable fertilization rates in vitro to ground control (GC) males. Moreover, when the fertilized eggs were transferred to pseudopregnant females, there were no significant differences in the number of delivered pups among GC, AG, and MG spermatozoa. The growth rates and fecundity of the offspring were also similar across all groups[113]. This was followed up by another study which extended the duration of spaceflight[114]. Despite variations in the number of fertilized oocytes based on strain and duration of flight, most of the freeze-dried sperm demonstrated successful fertilization[114]. In another study, fertilization occurred under MG; however, embryo growth was impaired, and the birth rate was lower compared to 1 g controls[115]. Successful fertilization of gametes and transmission of genetic material to subsequent generations are crucial for the continuation of generations. To investigate epigenetic alterations in spaceflight and their transmission to future generations, Yoshida et al. evaluated the effects of 35 days of spaceflight on germ cells of male mice[116].They observed changes in ATF7 activation, a transcription factor, in the testis as well as microRNA expression profiles in spermatozoa. Male offspring from these sperm samples demonstrated increased levels of DNA replication-related genes (i.e., *Mcm* genes)[116]. The potential reversibility of these spaceflight-induced stress-related epigenetic alterations remains to be explored. Further, space-flown sperm, used in the F1 progeny production, changed liver gene expressions in the next generation. In a separate study, long-term stay in space did not cause any DNA damage in freeze-dried sperm stored at the ISS for periods ranging from 9 months to 5 years and 10 months[117]. However, it is worth mentioning that inside the nucleus and cytoplasm, freeze-dried sperm lacks water molecules that are critical for free radical generation, and when compared to fresh sperm they entail higher resistance to radiation[117]. Another important aim of the study was to assess the fertilization potential of freeze-dried spermatozoa preserved in space. Although the fertilization failure rate was within the normal range, the average rate varied between different preservation periods in space[117]. The blastocyst quality was similar between those fertilized with spermatozoa obtained from ground control groups and those preserved in space and many of those resulted in birth of an offspring[117]. It is however important to emphasize here that some of the offspring from the latter group had a shorter life span despite having normal global gene expression profiles, normal reproductive potential, and producing second- and third-generation offspring without any abnormalities. Although some of these results are encouraging, transgenerational studies in space are limited and further studies are warranted.

A successful fertilization is not the only step toward pregnancy; proper embryo development required as well. The zygote undergoes multiple divisions (mitosis) to form an organized blastocyst during its transition from the fallopian tube to the uterus. Five to six days after fertilization, the embryo reaches the blastocyst stage, hatches out of its zona pellucida and begins the implantation process. Preimplantation embryo development in space has been studied in rodent models under both simulated gravity and during spaceflight. Fertilization of oocytes could be achieved under simulated microgravity (μg); however, morula and subsequent blastocyst formation (30% vs. 57%, μg vs. 1 g) and birth rates (5% vs. 21%, μg vs. 1 g) were significantly reduced compared to control groups[110,115]. A reduction in blastocyst rate (34.3% vs. 60.2%) was seen in actual spaceflight studies versus the GC group. The decreased blastocyst rate was associated with reduced blastocyst quality, a decreased number of cells, and increased DNA damage[118], possibly attributable to microgravity's known effects on cell cycle regulation and progression[119,120]. This assumption may further be supported by the observed induction of pSANK (stress-activated protein kinase) expression and cell cycle arrest in mouse embryos under simulated microgravity[121]. The mechanisms of disruption of cell cycle progression may include long noncoding RNA (lncRNA) expression changes that regulate pathways pertaining to protein transport, and cortical cytoskeleton functions that can affect migration of the pronucleus[122]. Furthermore, embryonic stem cells (ESCs) play a pivotal role during embryogenesis and organogenesis. They originate from the inner cell mass of the embryo, possess pluripotency, and differentiate into three primary germ layers: ectoderm, mesoderm, and endoderm. Each of these germ layers gives rise to specific tissues and organs. Research has indicated that exposure to microgravity changes the expression of genes involved in ESC differentiation and signaling pathways[123]. The cellular differentiation of trophectoderm and inner cell mass were also hindered in space-flown mice embryos[118]. The embryos

Table 3 | The impact of spaceflight, radiation, and gravitational changes on reproductive tissues

Year	Reference	Study type	Tissue	Findings
1985	Megory et al.[173]	Ground-based hypergravity	Plasma (rat)	Hypergravity at 3.14 g of exposure induced prolactin surge
2004	Tou et al.[174]	Ground-based simulated microgravity	Ovary (rat)	Rats exposed to hindlimb suspension showed lengthened estrous cycles due to prolonged diestrus
2011	Wu et al.[102]	Ground-based simulated microgravity	Oocytes (mouse)	Decreased rate of oocyte maturation (8.9% vs. 73%, μg vs. 1 g); disrupted meiotic spindle organization; abnormal γ-Tubulin location; cytoplasmic blebbing
2012	Holets et al.[64]	Spaceflight space shuttle	Ovary Uterus (mouse)	Ovary: smaller ovaries and fewer corpora lutea and atretic follicles suggesting cycling cessation; loss of ovulation Uterus: estrogen receptor alpha and beta mRNA levels lower in the flight group. Lower expressions of Lactoferrin mRNA
2013	Forsman and Nier[175]	Spaceflight space shuttle	Uterus (mouse)	Thicker mucin layer of the uterus in the flight group
2016	Mishra et al.[33]	Ground-based radiation	Ovary (mouse)	Charged iron particles, highly induced H2AX phosphorylation, lipid peroxidation, protein nitration, and apoptosis; dose-dependent depletion in the primordial follicles; increased serum FSH and LH; premature ovarian insufficiency
2016	Zhang et al.[101]	Ground-based simulated microgravity	Oocytes (mouse)	Decreased follicle survival and density; decreased GDF-9 expression; abnormal oocyte structure; vacuolated mitochondria without cristae, lipid droplets, and multilamellar bodies
2018	Mishra et al.[34]	Ground-based radiation	Ovary (mouse)	Charged oxygen particles, Dose-dependent increase in DNA double-strand breaks, oxidative lipid damage, and apoptosis. Dose-dependent decrease in primordial, primary, and secondary follicles; complete absence of follicles at 50 cGy; increased serum FSH and LH; premature ovarian insufficiency
2021	Hong et al.[62]	Spaceflight ISS	Ovary (mouse)	No significant change in the whole No significant change in whole ovarian tissue estradiol levels, steroidogenic gene expression, and ESR1, ESR2, LHCGR, GDF-9 expressions Ovarian progesterone levels are lower in flight and habitat groups compared to the baseline group.
2021	Dai Tx et al.[99]	Ground-based simulated microgravity	Granulosa cells (porcine)	Decrease proliferation of porcine granulosa cells; Increased ratio of cells in G0/G1 vs. S and G2/M phase, inducing arrest; Cyclin D1, cdk4, cdk6 downregulation; granulosa cell morphology changes: rhomboid and pebble-like shape
2023	Cheng et al.[98]	Ground-based simulated microgravity	Oocytes (mouse)	Decreased quality of oocytes; decreased oocyte secreted factors (i.e., GDF-9); decreased first polar body release in oocytes; higher ROS (DCF intensity); disrupted granulosa cell organization and polarity (projections/microvilli)
2019	Cho et al.[129]	Ground-based simulated microgravity	Uterus endometrial stromal cells (human)	Decreased proliferation and migration; decreased Akt phosphorylation; decreased MMP2 and FOXO3a expression; impaired decidualization (cAMP)
2023	Miglietta et al.[103]	Ground-based simulated microgravity	Oocytes (human)	Structural abnormalities: decreased aggregates between mitochondria and smooth endoplasmic reticulum, large MV complexes; asymmetric expansion of perivitelline space, altered organelle localization, cortical granules, thicker zona pellucida

from both space-flown and ground-irradiated mice not only showed decreased rates of blastocyst but also demonstrated changes in their DNA methylation profiles[118]. Space-flown mice embryos displayed a reduction in DNA methylation density. The low- and high-methylation Differentially Methylated Regions (DMR) were enriched in various biological processes, including histone modification, response to radiation, chromosome regulation, and embryo development[118]. Furthermore, when two-cell embryos were irradiated with Cs-137 gamma rays their DNA methylation levels decreased, correlating with increased doses of radiation. These effects were particularly robust after exposure to 2 mGy. In addition, when irradiated blastocysts were transferred to females, lower birth rates were observed in proportion to the radiation dose[118]. Based on current guidelines, the effects of radiation doses on human embryogenesis and organogenesis are also reviewed in Table 2. These studies raise significant questions about the effects of spaceflight on the ability of normal embryo development but also on the epigenetic regulation of expressed DNA, as alluded to earlier. The impacts of spaceflight, radiation, and microgravity on mouse embryo development have been summarized in Table 4.

In recent years, private companies and institutional researchers have been working towards understanding embryo development in the LEO to elucidate some of these questions. Embryo development is a dynamic process that involves changing the culture medium and monitoring developmental steps. Thawing and freezing of samples are often required during embryo research. On Earth, at IVF centers, embryos are vitrified and kept at −196 °C via liquid nitrogen, which is not available on the ISS. In 2022, Wakayama et al. developed a mouse embryo culture device, which allows astronauts to thaw and freeze samples without directly contacting the embryos using a high-osmolarity vitrification method to keep samples at −80 °C. Their method yielded a 90% embryo recovery rate and 80% of the samples reached blastocyst[124]. Future studies are needed to compare these results with human embryo samples donated for research.

Endometrium and endometrial receptivity

An euploid embryo with a high implantation potential and a receptive endometrium are prerequisites for pregnancy. Successful implantation requires embryo-endometrial synchrony, which is only possible during the "window of implantation" (WOI). In humans, this optimal window occurs 7–10 days after ovulation; in mice, it is 4 days post coitus. As aforementioned, upon fertilization of the oocyte, a zygote undergoes cellular divisions to form a blastocyst. Apposition of the blastocyst to endometrium starts the implantation process (Figs. 3A, B and). Following adequate hormonal preparation of the endometrium, the main steps of implantation are apposition, adhesion, and invasion; all regulated by cytokines, growth factors, immune cells, cell adhesion molecules, and hormones (Fig. 3B). Immune cells play essential roles not only during implantation but subsequently also in spiral artery remodeling, a process pivotal for placentation and pregnancy[125]. In this context, immune dysregulation observed during spaceflight[126], and recent studies from the Inspiration 4 mission demonstrating sex-specific alterations in immune cells raise questions regarding successful implantation and endometrial receptivity[127].

The endometrium is composed of dynamically changing proportions of different cell types, including glandular and luminal epithelium, stroma, endothelium, and bone marrow-derived immune cells[128]. A critical step in the establishment of pregnancy is stromal cell decidualization; a profound alteration in stromal cell structure and function that is dependent on the action of sex hormones, primarily progesterone. Decidualization regulates the maternal immune response for fetal allograft acceptance, promotes vascular remodeling to establish maternofetal communication and acts as a biosensor of embryo quality to prevent implantation of genetically abnormal embryos[125]. Using an in vitro decidualization model, simulated microgravity impaired decidualization, in part by impairing FOXO3a and AKT signaling[129]. Furthermore, in the mouse uterus, both alpha and beta estrogen receptors were downregulated during spaceflight compared to ground controls (Table 3)[64]. Similarly, lactoferrin is an estrogen-responsive protein in mouse uterine epithelial cells[130] and its mRNA expression levels decreased during spaceflight[64]. McMaster et al. showed that neutrophils, recruited by estradiol, were also a source of lactoferrin in the pre-implantation mice uterus[130].These findings further highlight the intricate interplay between the immune system and hormones, both of which may be impacted during spaceflight. Prior studies have shown systemic immune dysregulation during spaceflight[126], but little is known about the effects of spaceflight on endometrial specific changes in immunity, and reproductive immunology.

Mechanoreceptors, whose signaling is modified under microgravity, are important for embryo implantation and dysfunctional mechanoreceptors may be involved in pregnancy complications, such as preeclampsia[131,132]. In summary, endometrium and reproductive immunology including maternal immune tolerance are understudied areas in space biology. Understanding the cyclic menstrual changes including proliferation and decidualization of the endometrium is also important in nonpregnant women as imbalance between estrogen and progesterone's effect on endometrium can lead to abnormal uterine bleeding.

Pregnancy and developmental origins of health and disease hypothesis

Pregnancy is a complex process that involves physiological changes and adaptations in multiple organ systems to support the developing fetus. Cardiovascular, respiratory, genitourinary, gastrointestinal, endocrine, hematologic, and immune system changes are some of the examples that occur during this adaptation. Further, some conditions are also unique to pregnancy such as preeclampsia, gestational diabetes, and placental abnormalities. Thus far, to the best of our knowledge, there is no report of human conception during spaceflight. Various reproductive experiments on vertebrates and invertebrates such as cockroaches, fish, frogs, mice, and rats have been performed to understand how spaceflight affects fertilization and reproductive functions, with mixed results, which are summarized thoroughly in another review and rodent ones outlined below[133]. During the Cosmos mission in the 1980s, female and male rats were allowed to mate in space without monitoring[134]. Pregnancy resorption was demonstrated in 2 out of 5 female rats after landing[134]. Following this study, pregnant rats were flown to space to observe the effects of microgravity on parturition and litter size. One study reported prolonged labor in the flight group[135], but others reported no significant changes in labor duration[136]. Variances in uterine contraction patterns were observed in space shuttle flights, such as increased lordosis[136]. Reduced progesterone secretion was detected in luteal cells isolated from the corpus luteum of pregnant rats[137]. In general, offspring from space-flown mice showed decreased birth weight[135,136]. In the 1990s, Medaka fish were the first reported vertebrate species to successfully mate in space during a 15-day mission[138]. The hatching rate and primordial germ cells formed in space were normal compared to controls[138]. Although these fish and invertebrate results are promising, humans have more complex biology and physiology. Therefore, uncertainty remains around the feasibility and safety of human conception, gestation, and labor in space. The impacts of spaceflight, radiation, and microgravity on rodent pregnancy have been summarized in Table 5.

While the mechanisms underlying labor are only partially understood, some of the known molecular components have been studied in spaceflight. Connexins are gap junction proteins responsible for allowing coordinated contractions of the myometrium during labor and their expression increases at term. Connexin 43 is a critical gap junction protein expressed in the human and rat uterus and regulated by sex steroids[139–141]. One study demonstrated reduced myometrial connexin 43 during spaceflight, raising a potential concern about its effects on labor[142]. Another important component of uterine contraction is the secretion and action of oxytocin. Oxytocin is synthesized in the hypothalamus and released into the bloodstream by axons projecting from the hypothalamus to the posterior pituitary. Oxytocin plays a key role during labor, postpartum, and lactation. It causes uterine contractions in labor and is used as a medication to augment both labor and prevent postpartum hemorrhage. Gravitational and circadian rhythm changes may alter oxytocin synthesis and/or release. During a 14-day

Table 4 | The impact of spaceflight, radiation, and simulated microgravity on mouse embryo development

Year	Reference	Study type	Tissue	Findings
1998	Schenker and Forkheim[176]	Spaceflight space shuttle	Embryo (mouse)	Two-cell stage embryos not developed
2000	Kojima et al.[110]	Ground-based simulated microgravity	Embryo (mouse)	Decreased number of mice embryos reaching the morula and blastocyst stages after 96 h in clinostat
2008	Ma et al.[177]	Spaceflight SJ-8 satellite	Embryo (mouse)	No blastocysts development
2009	Wakayama et al.[115]	Ground-based simulated microgravity	Embryo oocyte (mouse)	84% of mouse oocytes fertilized; decreased blastocyst stage (30% vs. 57% μg vs. 1 g); low birth rate (5% vs. 21% μg vs. 1 g)
2009	Wang et al.[121]	Ground-based simulated microgravity	Embryos (mouse)	Cell cycle arrest; microgravity is most lethal at the 8-cell stage; increased levels of pSANK (stress-activated protein kinase)
2011	Wang et al.[178]	Ground-based simulated microgravity	Embryonic stem cells (mouse)	Reduced number of cells; decreased adhesion rate; delayed DNA repair; increased apoptosis
2018	Acharya et al.[179]	Parabolic flight	Embryonic stem cells (mouse)	Downregulation of cell cycle and proliferation-related genes in undifferentiated ESCs
2018	Lei et al.[180]	Spaceflight TZ-1 Cargo Spacecraft	Embryonic stem cells (mouse)	Inhibition of terminal differentiation of embryoid bodies
2019	Feng et al.[122]	Ground-based simulated microgravity	Embryo (zygote, mouse)	Long noncoding RNAs (lncRNAs) in mouse pronucleus; 52 lncRNAs differentially expressed pertaining to protein transport, catalytic activity, cytoskeleton; Negative effects on pronuclear migration: stopped at pronuclear stage disturbed tubulin protein
2020	Lei et al.[118]	Spaceflight Chinese SJ-10 Satellite	Embryo (mouse)	Reduced rate of blastocyst (34.3% vs. 60.2% μg vs. 1 g); decreased number of cells in the blastocyst; cellular differentiation affected by altered expressions of Oct4 and Cdx2 in cell populations; increased DNA damage (γ H2AX) and DNA repair (XRCC1); Decreased methylation density in space-flown blastocyst
2020	Lei et al.[118]	Ground-based radiation	Embryo (2-cell stage, mouse)	Low-dose gamma radiation, dose-dependent decrease in the percentage of blastocyst development (58.4% blastocyst at 0.5 mGy, 45.6% blastocyst at 2 mGy). Decrease in DNA methylation in embryos at 2 mGy; dose-dependent decreased in live birth rates (Table 5).
2020	Lei et al.[118]	Ground-based simulated microgravity	Embryo (mouse)	No statistically significant difference: in the rate of blastocyst development after 64 h of exposure to simulated microgravity (65% vs. 72.9%, μg vs. 1 g); DNA damage and DNA methylations

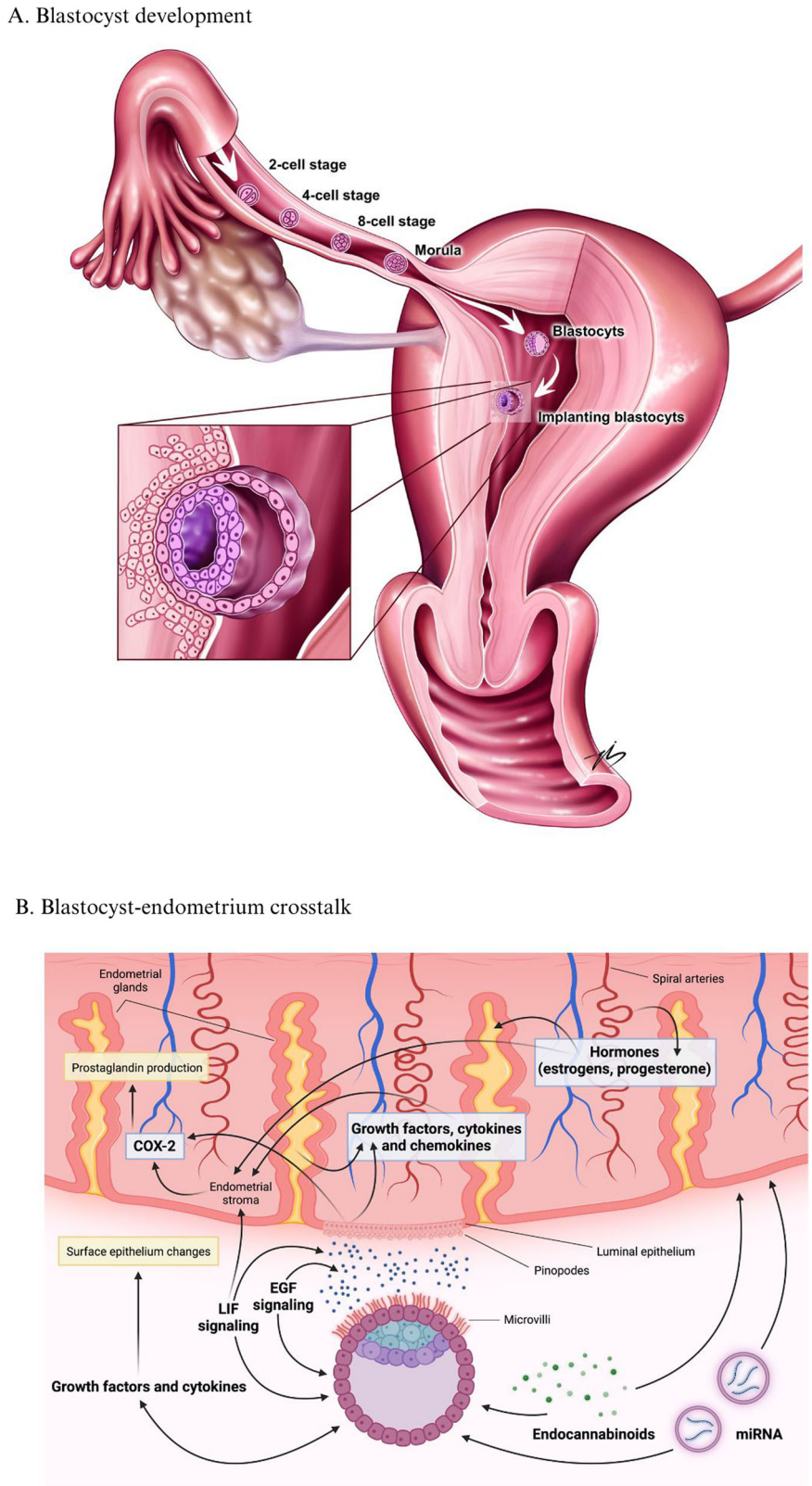

Fig. 3 | Blastocyst development and blastocyst–endometrium crosstalk. A Blastocyst development. This figure illustrates the stages of blastocyst development. **B** Blastocyst–endometrium crosstalk. This figure displays a preimplantation blastocyst and the signaling factors between the endometrium and blastocyst.

mission, rats flown to space showed a 27% reduction in pituitary oxytocin and vasopressin levels[143]. In another study, prepubertal female rats were flown to space for 16 days and then 18 weeks after landing, vasopressin levels returned to normal, but oxytocin levels were still reduced compared to the control group[144]. Oxytocin is also decreased when rats are exposed to hypergravity[145]. Oxytocin has extrauterine roles beyond its uterine functions, including potential effects on bone building and mood[146]. Oxytocin is also known as a social bonding hormone. Social isolation and prolonged living in a confined environment are features of spaceflight that may alter vasopressin, oxytocin, and serotonin receptor binding in a sex-dependent manner[147]. Not only the effects of microgravity but also hypergravity were examined using centrifugation methods to mimic the launch

Table 5 | The impact of spaceflight, radiation, and gravitational changes on rodent pregnancies

Year	Reference	Study type	Tissue	Findings
1967	Oyama et al.[181]	Ground-based hypergravity	Pregnancy (rat)	Rats can mate and deliver at 2.5 g and 3.6 g (2 months of acclimation to centrifugation before mating); decreased rate of pregnancy with increasing gravity and no pregnancy at 4.7 g; increased neonatal mortality
1982	Serova et al.[134]	Spaceflight COSMOS 1129 satellite	Uterus (rat)	Unmonitored mission, inconclusive whether signs of early pregnancy with resorption or cycle disturbances
1984	Serova et al.[182]	Spaceflight space shuttle	Uterus Pregnancy (rat)	Decreased placental weight, lengthened labor. Lower birth weight; increased perinatal mortality
1984	Megory et al.[183]	Ground-based hypergravity	Pituitary, plasma Pregnancy/postpartum (rat)	The number of fetuses decreased with increasing gravity; Pituitary prolactin (PRL) was lower in the hypergravity group, but it increased postpartum; Plasma PRL was lower in the hypergravity group and continued to decrease in postpartum. Above 3 g exposure resulted lethal effects on fetus and newborns
1988	Moore et al.[184]	Ground-based hypergravity	Pregnancy Bone (mouse)	No pregnancy at 3.5 g; decreased fetal weights and reduced ossification in long bones of fetuses
1997	Burden et al.[185]	Spaceflight space shuttle	Pituitary Ovary Postpartum (rat)	Postpartum: increase of plasma FSH concentration and decrease of pituitary LH content No significant change on pituitary/ovarian mass postpartum
1997	Wong et al.[186]	Spaceflight space shuttle	Neonate Rat	D9–D20 gestation in space; increased perinatal morbidity in offsprings, similar birth weights
1998	Burden et al.[187]	Spaceflight space shuttle	Uterus Pregnancy (rat)	D11–20 gestation in space; 37% decrease in myometrial smooth muscle volume; decreased pup mass at birth
1999	Burden et al.[142]	Spaceflight space shuttle	Uterus Pregnancy (rat)	D11–20 gestation in space; decreased connexin 43 in myometrium thought to alter the synchronization and coordination of contractions during labor
2000	Ronca and Alberts[136]	Spaceflight space shuttle	Labor contractions (pregnancy, rat)	Increased lordosis contractions; labor duration and birth weight nonsignificant after 9 or 11 days of spaceflight
2002	Yang et al.[188]	Ground-based simulated microgravity	Corpus luteum cells Pregnancy (Rat)	D8 pregnant rate luteal cells exposed to microgravity; decreased levels of progesterone and increased apoptosis
2002	Baer et al.[145]	Ground-based hypergravity	Plasma Pregnancy/Postpartum (rat)	Exposure to hypergravity D11-postnatal D10; oxytocin decreased in dams and prolactin was unchanged
2012	Casey et al.[80]	Ground-based hypergravity	Pregnancy Lactation (rat)	Exposure to 2 g during pregnancy and lactation (GD11- early lactation). Did not affect labor; increased perinatal morbidity; lower weight. Prolactin, corticosterone, insulin levels and receptor expressions altered by hypergravity. Change in circadian rhythm and expression of clock genes in mammary gland and liver.
2015	Casey et al.[189]	Spaceflight & ground-based hypergravity	Pregnancy Mammary gland (rat)	D11–D20 gestation in space, spaceflight affected lipid metabolism-related gene expressions in the mammary gland during late pregnancy. Both spaceflight and hypergravity altered the genes linked to metabolism and immune response in the mammary gland
2020	Steller et al.[190]	Ground-based radiation	Pregnancy (mouse)	Low-dose neutron irradiation, increased in early resorption rate, decreased placental weight. No differences in birth length, birth weight and anomaly rate.
2020	Lei et al.[118]	Ground-based radiation	Pregnancy (mouse)	Low-dose gamma radiation, irradiated embryos transferred into pseudopregnant females; dose-dependent decrease in live birth rate (21% at 0.5 mGy vs. 7.4% at 2 mGy)

and re-entry phases. Exposure of pregnant rats to hypergravity showed unfavorable effects in terms of decrease in pregnancy rates and increased neonatal mortality[148]. On earth, pregnancy is considered a contraindication for extreme environments, like those with high pressure and temperatures, such as scuba diving. In terms of human data, a review published in 2000 outlined pregnancy after spaceflight[55]. The mean maternal age at the time of delivery for women who have been in space was 40. The mean age of the six women who had spontaneous miscarriage after spaceflight was 41. The advanced maternal age observed in the female astronaut cohort could be the result of career prioritization rather than a direct effect of spaceflight. This data also represents the cohort from shuttle missions, which had shorter durations compared to current missions.

Environmental factors, toxins, and pollutants are important factors to consider for reproductive health, pregnancy, and prenatal development. The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that environmental factors during early development of life can have a profound and long-lasting impact on an individual's health as well as susceptibility to diseases later in life. Exposure to environmental stressors and adverse nutritional conditions before or during pregnancy was shown to result in intergenerational and transgenerational epigenetic inheritance; a non-DNA sequence-based inheritance of a modified phenotype across generations[149]. This type of inheritance occurs through alterations in the pattern of gene expression by mechanisms such as DNA methylation, histone modification, and small RNA transmission[149]. Supporting this notion, a study conducted by Pembrey et al. demonstrated an anecdote of a paternal grandfather's food supply was associated with mortality risk ratios of grandsons but not granddaughters, demonstrating a transgenerational but also sex-specific response[150]. Moreover, a series of studies utilizing rats as subjects demonstrated that susceptibility to diabetes and obesity was increased when rats were undernourished in utero for 50 generations, whereas nutrient recuperation for the subsequent two generations was not sufficient to reverse the resulting metabolic profile and epigenetic alterations, nor to mitigate the risks of developing obesity and diabetes[151]. Thus, optimization of nutrition and maternal weight is crucial during pregnancy, including prioritizing a balanced diet and appropriate vitamin intake to support fetal development. Prepregnancy counseling and screening is

important to prevent certain comorbidities[152]. For instance, folic acid supplementation should be encouraged to prevent neural tube defects, and checking for iron and vitamin D deficiencies to provide appropriate supplementation is recommended. Dietary needs and caloric intake recommendations of pregnant and lactating women differ significantly from those of nonpregnant women and also vary per trimester and postpartum[153]. It is also important to note that 30 min of daily exercise is recommended, which could be a unique challenge in anti-gravity conditions. There are other routine recommended screenings throughout pregnancy such as ultrasound for fetal anatomy, gestational diabetes, sexually transmitted disease, and Rh status screening. All these above factors could present unique challenges, especially considering limited availability to bring medical and laboratory equipment, as well as limited nutritional resources in the space environment compared to Earth.

In summary, both direct and indirect space-related factors could affect the ability to conceive and pregnancy at various stages. It is important to consider and further investigate the influence of these factors before embarking on the idea of pregnancy in space.

Unintended pregnancy

Most female astronauts opt to use contraceptive methods[154]. Even with perfect adherence to contraceptive methods, the risk of pregnancy is not eliminated[155]. For instance, unplanned pregnancy rates in the first year of oral contraceptives is 9% with typical use, whereas it is 0.3% with perfect use[155]. One of the main causes of oral contraceptive failure is adherence. In addition, oral contraceptives are metabolized by the liver via the cytochrome p450 system. Certain antiseizure medications and antibiotics such as carbamazepine, phenytoin, and rifampin induce the p450 system which may increase oral contraception metabolism and decrease their efficacy. Prolonged diarrhea and vomiting are other conditions that may interfere with the absorption of contraceptive pills. Space adaptation syndrome (space sickness) is a subtype of motion sickness that presents with nausea and vomiting. It can be seen in 60–80% of space travelers in the first days of gravitational changes[156]. A space traveler who is on oral contraceptive pills and experiencing severe space sickness syndrome needs to be aware of possible absorption interference. There is also a risk of oral contraception failure after bariatric surgery, thus a space traveler with a history of bariatric surgery should be aware of effective contraceptive methods.

Another consideration is the risk of thrombosis, which differs depending on the type of contraceptive. The risk of thromboembolism is increased in combined oral contraceptive users as 3–9 in 10,000 women[157]. The Virchow's triad is the main foundation underlying thrombus formation: vascular/endothelial injury, stasis, and hypercoagulability. Incidental occlusive internal jugular vein thrombosis was diagnosed in one of the ISS crew members during a mission[158]. Thus, before prescribing oral contraceptives, it is important to have a discussion with space travelers about their specific underlying risk factors and potential aggravating factors such as prolonged immobility or inherited thrombophilia. An alternative to contraceptive pills is the use of long-lasting progestin-only contraceptives, which can be used highly effectively in averting unwanted pregnancies from months to 8 years, and safe in women in whom estrogen-containing formulations are contraindicated. Thus, contraceptive methods should be individualized as their advantages and contraindications may vary.

Even with the more invasive contraceptive methods such as vasectomy and tubal sterilization, there is a slight possibility of unintended pregnancy. Failure rate (post-procedure pregnancy rate) depends on the method of tubal occlusion chosen. For instance, women who underwent postpartum salpingectomy have pregnancy rates of 6.3 and 7.5 per 1000 procedures at 5 years and 10 years, respectively[159]. On the other hand, for males who underwent vasectomy, the pregnancy rate is 11.3 per 1000 procedures at 5 years[159]. It is worth noting that some methods are not immediately effective and may require use of an additional method. For example, most men become azoospermic 3 to 6 months after the vasectomy procedure. While the number of commercial spaceflights and the emergence of space tourism is on the rise, we remain uncertain about the safety and feasibility of human conception in the space environment. Additionally, even if a successful and safe conception occurs, pregnancy outcomes in space remain uncharted territory. Therefore, as mentioned earlier, to prevent unintended pregnancies, space travelers should consult their obstetrician-gynecologist providers regarding contraception options, preflight pregnancy tests and precautions against unintended conception should also be addressed during these consultations.

Looking to the future of space biology

Cutting-edge research in gravitational biology and biomedical engineering is centered on experimental cell studies and explores tissue engineering in a space environment, including the 3D organoids. Organoids can be used for understanding tissue structure and function, hormonal regulations, early developmental biology research, disease models, and drug testing[160]. A few examples include mice bioprosthetic ovaries created by 3D-printed microporous hydrogel scaffolds[161] and a microfluidic platform supported ovary for hormone production[162].

Advancements in technology also had an impact on surgical techniques. Currently, robotic-assisted surgery is commonly performed with a surgeon controlling the robotic arms from a console. The use of robotic-assisted surgery in space has been reviewed in another article[163]. Communication delay and its impact on team performance is an important concept for remote tasks and telesurgery. For example, at the greatest distance, ~24 min of communication latency is expected between Earth and Mars[163]. In the future, during space travel, with the advent of smart surgery glasses that can transmit intraoperative content[164] and improvements in haptic feedback[165] telesurgery may be utilized for the management of gynecologic emergencies such as ovarian torsion, cyst rupture or for a ruptured ectopic pregnancy.

Another development in the field of medical robotics is swimmable micro-robots or nanobots[166]. These are robotic devices designed to navigate and perform tasks inside the human body and they have the potential to enable remote-controlled minimal invasive procedures as well as targeted drug delivery. Although they are still in the research phase, they show great promise for the future of diagnosing and treating medical conditions.

While significant scientific achievements are occurring worldwide, it is also important to establish ground-based tools and methods for replicating microgravity. Thus far, traditionally hindlimb suspension and rotating wall vessels have been utilized to mimic microgravity[167]. Magnetic levitation approach by utilizing anti-Helmholtz configuration of magnets via diamagnetophoresis has been proposed and validated to simulate the microgravity conditions[168]. This approach allows reduction (if not full elimination) of one continuous force field (i.e., gravitation field) by another continuous force field (i.e., magnetic field). The biocompatible environment mimicking the weightlessness condition was achieved by utilizing gadolinium (Gd) solutions (i.e., FDA-approved MRI contrast agent), shown to be nontoxic, iso-osmolar to human blood cells[169]. The same platform enables levitated cells within capillary to be exposed to a low-intensity laser beam via microscope. For instance, an earlier study showed that, at the UV-irradiated area of levitated RBCs, lymphocytes, and PMNs, cells raised their equilibration heights. Instantly after UV stimulation was shut down, cells returned to their starting heights, while RBCs equilibrated at a lower height than its starting height, possibly suggesting that intracellular, UV-induced ROS raised the magnetic susceptibility of RBCs[169]. These studies can be expanded to monitor several cellular activities affecting female reproductive health in the presence of microgravity and/or irradiation and have implications for longer missions to Mars and advanced precision medicine[170]. Novel spatiotemporal monitoring of human cells, followed by nucleic acid and protein analyses, will pave the way for studies in distinctive signaling mechanisms that appear only during microgravity settings.

Conclusion

The relationship between spaceflight and reproduction is an emerging area of research that is necessary as an increasing number of humans venture into space. Hormones necessary for reproduction also play an important role in

other organ systems. Sex differences involving tissue response to space-associated risk factors and multi-organ analysis are also crucial areas to be investigated during spaceflight. With so little data on spaceflight and its effect on endocrine signaling, ovulation, reproduction, cryopreservation of gametes and/or embryos or other fertilization preservation actions will be important to astronaut well-being.

Some of the obvious limitations on reproductive space research include inconsistent duration of spaceflights, different age and strain of animals, lack of data in menstruating species (e.g., humans, apes, and Old-World monkeys) and human models. We also do not have information on how space travel will affect women with gynecological issues such as diminished ovarian reserve, polycystic ovarian syndrome (PCOS), endometriosis, and uterine fibroids. Moreover, as we are slowly transitioning from governmental led crewed activities in low Earth orbit by highly selected and trained career astronauts to more commercially led missions by the general public, future studies are needed to explore the unanswered aspects of mammalian reproduction in space so that results can be interpreted, and information can be used to achieve safe space travel and colonization.

Received: 15 October 2023; Accepted: 31 January 2024;
Published online: 11 June 2024

References

1. Thriving in Space: Ensuring the Future of Biological and Physical Sciences Research: A Decadal Survey for 2023-2032. *National Academies of Sciences, Engineering, and Medicine, Sciences* (2023).
2. Afshinnekoo, E. et al. Fundamental biological features of spaceflight: advancing the field to enable deep-space exploration. *Cell* **184**, 6002 (2021).
3. Patel, Z. S. et al. Red risks for a journey to the red planet: the highest priority human health risks for a mission to Mars. *NPJ Microgravity* **6**, 33 (2020).
4. Space Radiation and Astronaut Health: Managing and Communicating Cancer Risks. *The National Academies Press* (2021).
5. Zeitlin, C. & La Tessa, C. The role of nuclear fragmentation in particle therapy and space radiation protection. *Front. Oncol.* **6**, 65 (2016).
6. Space Radiation: An Important Concern for Human Spaceflight. Space Radiation Analysis Group, Johnson Space Center. https://srag.jsc.nasa.gov/spaceradiation/why/why.cfm
7. Cucinotta, F. A. Space radiation risks for astronauts on multiple International Space Station missions. *PLoS ONE* **9**, e96099 (2014).
8. Locke, P. A. & Weil, M. M. Personalized cancer risk assessments for space radiation exposures. *Front. Oncol.* **6**, 38 (2016).
9. *NASA Space Flight Human-System Standard Volume 1 Crew Health.* NASA-STD-3001, Vol 1 Rev B (NASA, 2022).
10. Beheshti, A. et al. Genomic changes driven by radiation-induced DNA damage and microgravity in human cells. *Int. J. Mol. Sci.* (2021).
11. Meier, M. M. et al. Impact of the South Atlantic Anomaly on radiation exposure at flight altitudes during solar minimum. *Sci. Rep.* **13**, 9348 (2023).
12. Federal Aviation Administration. *CARI-7 and CARI-7A (2021)* https://www.faa.gov/data_research/research/med_humanfacs/aeromedical/radiobiology/cari7
13. Scheibler, C. et al. Cancer risks from cosmic radiation exposure in flight: a review. *Front. Public Health* **10**, 947068 (2022).
14. The RadLab Portal and the RadLab Data API. NASA. https://visualization.osdr.nasa.gov/radlab/gui/data-overview/ (2024).
15. Bottollier-Depois, J. F. et al. Assessing exposure to cosmic radiation during long-haul flights. *Radiat. Res.* **153**, 526–532 (2000).
16. Papadopoulos, A. et al. Space radiation quality factor for Galactic Cosmic Rays and typical space mission scenarios using a microdosimetric approach. *Radiat. Environ. Biophys.* **62**, 221–234 (2023).
17. Trovati, S. et al. Human exposure to space radiation: role of primary and secondary particles. *Radiat. Prot. Dosimetry* **122**, 362–366 (2006).
18. Neumaier, T. et al. Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells. *Proc. Natl. Acad. Sci. USA* **109**, 443–448 (2012).
19. Jones, J., Karouia F., Cristea, O., Casey, R. & Popov, D. Ionizing Radiation as a Carcinogen, In *Comprehensive Toxicology*, Vol. 3rd, (ed McQueen, C.) 183–225 (Elsevier, 2018).
20. Vadhavkar, N. et al. Combinatorial DNA damage pairing model based on X-ray-induced foci predicts the dose and LET dependence of cell death in human breast cells. *Radiat. Res.* **182**, 273–281 (2014).
21. Clowdsley, M. S. et al. Neutron environments on the Martian surface. *Phys. Med.* **17**, 94–96 (2001).
22. Hassler, D. M. et al. Mars' surface radiation environment measured with the Mars Science Laboratory's Curiosity rover. *Science* **343**, 1244797 (2014).
23. Zeitlin, C. et al. Measurements of energetic particle radiation in transit to Mars on the Mars Science Laboratory. *Science* **340**, 1080–1084 (2013).
24. Zeitlin, C. et al. Measurements of radiation quality factor on Mars with the Mars Science Laboratory Radiation Assessment Detector. *Life Sci. Space Res.* **22**, 89–97 (2019).
25. Nelson, G. A. Space radiation and human exposures, a primer. *Radiat. Res.* **185**, 349–358 (2016).
26. Datta, K., Suman, S., Kallakury, B. V. & Fornace, A. J. Exposure to heavy ion radiation induces persistent oxidative stress in mouse intestine. *PLoS ONE* **7**, e42224 (2012).
27. Kim, J. & Seli, E. Mitochondria as a biomarker for IVF outcome. *Reproduction* **157**, R235–R242 (2019).
28. May-Panloup, P. et al. Ovarian ageing: the role of mitochondria in oocytes and follicles. *Hum. Reprod. Update* **22**, 725–743 (2016).
29. Guzeloglu-Kayisli, O. et al. Long-acting progestin-only contraceptives enhance human endometrial stromal cell expressed neuronal pentraxin-1 and reactive oxygen species to promote endothelial cell apoptosis. *J. Clin. Endocrinol. Metab.* **99**, E1957–E1966 (2014).
30. Drago-Ferrante, R. et al. Extraterrestrial gynecology: could spaceflight increase the risk of developing cancer in female astronauts? An updated review. *Int. J. Mol. Sci.* (2022).
31. Shin, E. et al. Organ-specific effects of low dose radiation exposure: a comprehensive review. *Front. Genet.* **11**, 566244 (2020).
32. Adriaens, I., Smitz, J. & Jacquet, P. The current knowledge on radiosensitivity of ovarian follicle development stages. *Hum. Reprod. Update* **15**, 359–377 (2009).
33. Mishra, B., Ortiz, L. & Luderer, U. Charged iron particles, components of space radiation, destroy ovarian follicles. *Hum. Reprod.* **31**, 1816–1826 (2016).
34. Mishra, B., Ripperdan, R., Ortiz, L. & Luderer, U. Very low doses of heavy oxygen ion radiation induce premature ovarian failure. *Reproduction* **154**, 123–133 (2017).
35. Mishra, B., Lawson, G. W., Ripperdan, R., Ortiz, L. & Luderer, U. Charged-iron-particles found in galactic cosmic rays are potent inducers of epithelial ovarian tumors. *Radiat. Res.* **190**, 142–150 (2018).
36. Wallace, W. H., Thomson, A. B., Saran, F. & Kelsey, T. W. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int. J. Radiat. Oncol. Biol. Phys.* **62**, 738–744 (2005).
37. Wallace, W. H., Thomson, A. B. & Kelsey, T. W. The radiosensitivity of the human oocyte. *Hum. Reprod.* **18**, 117–121 (2003).
38. Ogilvy-Stuart, A. L. & Shalet, S. M. Effect of radiation on the human reproductive system. *Environ. Health Perspect.* **101**, 109–116 (1993).
39. Jensen, P. T. & Froeding, L. P. Pelvic radiotherapy and sexual function in women. *Transl. Androl. Urol.* **4**, 186–205 (2015).

40. Milgrom, S. A. et al. Acute effects of pelvic irradiation on the adult uterus revealed by dynamic contrast-enhanced MRI. *Br. J. Radiol.* **86**, 20130334 (2013).
41. Larsen, E. C. et al. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet. Gynecol. Scand.* **83**, 96–102 (2004).
42. Van de Loo, L. E. X. M. et al. Uterine function, pregnancy complications, and pregnancy outcomes among female childhood cancer survivors. *Fertil. Steril.* **111**, 372–380 (2019).
43. Papatheodorou, S. et al. Residential radon exposure and hypertensive disorders of pregnancy in Massachusetts, USA: a cohort study. *Environ. Int.* **146**, 106285 (2021).
44. VanKoevering, K. K. et al. Pituitary dysfunction after radiation for anterior skull base malignancies: incidence and screening. *J. Neurol. Surg. B Skull Base* **81**, 75–81 (2020).
45. Darzy, K. H. & Shalet, S. M. Hypopituitarism following radiotherapy. *Pituitary* **12**, 40–50 (2009).
46. Roth, C., Lakomek, M., Schmidberger, H. & Jarry, H. Cranial irradiation induces premature activation of the gonadotropin-releasing-hormone. *Klin. Padiatr.* **213**, 239–243 (2001).
47. Gallagher, M., Torok, A., Klaas, J. & Ferrè, E. R. Gravity prior in human behaviour: a perceptual or semantic phenomenon? *Exp. Brain Res.* **238**, 1957–1962 (2020).
48. Karouia, F., Peyvan, K. & Pohorille, A. Toward biotechnology in space: High-throughput instruments for in situ biological research beyond Earth. *Biotechnol. Adv.* **35**, 905–932 (2017).
49. Williams DR. A crewed mission to Mars. NASA Goddard Space Flight Center. https://nssdc.gsfc.nasa.gov/planetary/mars/marsprof.html (2015).
50. Lin, X. et al. The impact of spaceflight and simulated microgravity on cell adhesion. *Int. J. Mol. Sci.*(2020).
51. Najrana, T. & Sanchez-Esteban, J. Mechanotransduction as an adaptation to gravity. *Front. Pediatr.* **4**, 140 (2016).
52. Tuday, E. C., Nyhan, D., Shoukas, A. A. & Berkowitz, D. E. Simulated microgravity-induced aortic remodeling. *J. Appl. Physiol.* **106**, 2002–2008 (2009).
53. Arbeille, P., Provost, R. & Zuj, K. Carotid and femoral artery intima-media thickness during 6 months of spaceflight. *Aerosp. Med. Hum. Perform.* **87**, 449–453 (2016).
54. Page, S. & Rollins M. Physiology and Pharmacology of Obstetrics Anesthesia. In *Pharmacology and Physiology for Anesthesia Foundations and Clinical Application* (eds Hemmings, H. C. & Egan, T. D.) 2nd Ed., pp 732–751 (Elsevier, 2019).
55. Jennings, R. T. & Baker, E. S. Gynecological and reproductive issues for women in space: a review. *Obstet. Gynecol. Surv.* **55**, 109–116 (2000).
56. Gillman, M. W. Developmental origins of health and disease. *New Engl. J. Med.* **353**, 1848–1850 (2005).
57. Moustafa, A. Hindlimb unloading-induced reproductive suppression via downregulation of hypothalamic Kiss-1 expression in adult male rats. *Reprod. Biol. Endocrinol.* **19**, 37 (2021).
58. Kramer, L. A. et al. Intracranial effects of microgravity: a prospective longitudinal MRI study. *Radiology* **295**, 640–648 (2020).
59. Lauria, L., Ballard, T. J., Caldora, M., Mazzanti, C. & Verdecchia, A. Reproductive disorders and pregnancy outcomes among female flight attendants. *Aviat. Space Environ. Med.* **77**, 533–539 (2006).
60. Radowicka, M., Pietrzak, B. & Wielgoś, M. Assessment of the occurrence of menstrual disorders in female flight attendants—preliminary report and literature review. *Neuro Endocrinol. Lett.* **34**, 809–813 (2013).
61. Sandler, H. & Winters, D. *Physiological Responses of Women to Simulated Weightlessness. A Review of the Significant Findings of the First Female Bed Rest Study* (NASA SP-340, 1978).
62. Hong, X. et al. Effects of spaceflight aboard the International Space Station on mouse estrous cycle and ovarian gene expression. *NPJ Microgravity* **7**, 11 (2021).
63. Ronca, A. E. et al. Effects of sex and gender on adaptations to space: reproductive health. *J. Womens Health* **23**, 967–974 (2014).
64. Holets, L. M., Gupta, V., Roby, K. F. & Tash, J. S. Spaceflight Inhibits Ovarian Follicle Development, Induces Down Regulation of Estrogen Receptor Alpha, and Alters Metabolic Pathways and Gene Expression in Mouse Uterus. *Biol. Reprod.* **87**, 18 (2012).
65. Rosa-Caldwell, M. E. et al. The oestrous cycle and skeletal muscle atrophy: investigations in rodent models of muscle loss. *Exp. Physiol.* **106**, 2472–2488 (2021).
66. Megory, E., Konikoff, F., Ishay, J. S. & Lelyveld, J. Hypergravity: its effect on the estrous cycle and hormonal levels in female rats. *Life Sci. Space Res.* **17**, 213–218 (1979).
67. Zwart, S. R., Auñón-Chancellor, S. M., Heer, M., Melin, M. M. & Smith, S. M. Albumin, oral contraceptives, and venous thromboembolism risk in astronauts. *J. Appl. Physiol.* **132**, 1232–1239 (2022).
68. Eyal, S. & Derendorf, H. Medications in space: in search of a pharmacologist's guide to the galaxy. *Pharm. Res.* **36**, 148 (2019).
69. Davis, S. R. et al. Menopause. *Nat. Rev. Dis. Primers* **1**, 15004 (2015).
70. Stavnichuk, M., Mikolajewicz, N., Corlett, T., Morris, M. & Komarova, S. V. A systematic review and meta-analysis of bone loss in space travelers. *NPJ Microgravity* **6**, 13 (2020).
71. Lloyd, S. A. et al. Effect of proton irradiation followed by hindlimb unloading on bone in mature mice: a model of long-duration spaceflight. *Bone* **51**, 756–764 (2012).
72. Aydogan Mathyk, B., Alvarado, F., Young, S., Beheshti, A. & Quaas, A. Effects of Spaceflight on Estrogen Receptor Expression and Signaling. *Scientific Papers Presented at the 70th Annual Meeting of the Pacific Coast Reproductive Society March 23-27, 2022. Fertility and Sterility.* Vol 118, e21 (2022).
73. Cirelli, E. et al. Effect of microgravity on aromatase expression in sertoli cells. *Sci. Rep.* **7**, 3469 (2017).
74. Aydogan Mathyk, B., Alvarado, F., Young, S., Quaas, A. & Beheshti, A. Expression of insulin resistance related genes during spaceflight. *Fertility Sterility* **116**, E107 (2021).
75. Mathyk, B. et al. Spaceflight induces changes in gene expression profiles linked to insulin and estrogen. *Commun. Biol*. https://doi.org/10.1038/s42003-023-05213-2 (2024).
76. Baker, F. C. & Driver, H. S. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med.* **8**, 613–622 (2007).
77. Kloss, J. D., Perlis, M. L., Zamzow, J. A., Culnan, E. J. & Gracia, C. R. Sleep, sleep disturbance, and fertility in women. *Sleep Med. Rev.* **22**, 78–87 (2015).
78. Caetano, G. et al. Impact of sleep on female and male reproductive functions: a systematic review. *Fertil. Steril.* **115**, 715–731 (2021).
79. Wiegand, S. J. & Terasawa, E. Discrete lesions reveal functional heterogeneity of suprachiasmatic structures in regulation of gonadotropin secretion in the female rat. *Neuroendocrinology* **34**, 395–404 (1982).
80. Casey, T. et al. Hypergravity disruption of homeorhetic adaptations to lactation in rat dams include changes in circadian clocks. *Biol. Open* **1**, 570–581 (2012).
81. Ranieri, D., Cucina, A., Bizzarri, M., Alimandi, M. & Torrisi, M. R. Microgravity influences circadian clock oscillation in human keratinocytes. *FEBS Open Bio* **5**, 717–723 (2015).
82. Fujita, S. I., Rutter, L., Ong, Q. & Muratani, M. Integrated RNA-seq analysis indicates asynchrony in clock genes between tissues under spaceflight. *Life* (2020).
83. Wang, L. et al. NR1D1 targeting CYP19A1 inhibits estrogen synthesis in ovarian granulosa cells. *Theriogenology* **180**, 17–29 (2022).

84. Pavlovic, M. V., Marinkovic, D. Z., Andric, S. A. & Kostic, T. S. The cost of the circadian desynchrony on the Leydig cell function. *Sci. Rep.* **12**, 15520 (2022).
85. Touzet, S., Rabilloud, M., Boehringer, H., Barranco, E. & Ecochard, R. Relationship between sleep and secretion of gonadotropin and ovarian hormones in women with normal cycles. *Fertil. Steril.* **77**, 738–744 (2002).
86. Vgontzas, A. N. et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J. Clin. Endocrinol. Metab.* **86**, 3787–3794 (2001).
87. Breen, K. M. & Mellon, P. L. Influence of stress-induced intermediates on gonadotropin gene expression in gonadotrope cells. *Mol. Cell Endocrinol.* **385**, 71–77 (2014).
88. Jiang, Z. et al. Aging attenuates the ovarian circadian rhythm. *J. Assist. Reprod. Genet.* **38**, 33–40 (2021).
89. Werdermann, M. et al. Insulin and obesity transform hypothalamic-pituitary-adrenal axis stemness and function in a hyperactive state. *Mol. Metab.* **43**, 101112 (2021).
90. Oosterman, J. E., Wopereis, S. & Kalsbeek, A. The circadian clock, shift work, and tissue-specific insulin resistance. *Endocrinology* (2020).
91. Hughson, R. L. et al. Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. *Am. J. Physiol. Heart Circ. Physiol.* **310**, H628–638, (2016).
92. St-Onge, M. P. et al. The interrelationship between sleep, diet, and glucose metabolism. *Sleep Med. Rev* **69**, 101788 (2023).
93. Dupont, J. & Scaramuzzi, R. J. Insulin signalling and glucose transport in the ovary and ovarian function during the ovarian cycle. *Biochem. J.* **473**, 1483–1501 (2016).
94. Silvestris, E., de Pergola, G., Rosania, R. & Loverro, G. Obesity as disruptor of the female fertility. *Reprod. Biol. Endocrinol.* **16**, 22 (2018).
95. Caughey A. B. ACOG Practice Bulletin No. 180: Gestational Diabetes Mellitus. American College of Obstetricians and Gynecologists. *Obstet. Gynecol.* **130**, e17–e37. https://journals.lww.com/greenjournal/fulltext/2017/07000/practice_bulletin_no__180__gestational_diabetes.51.aspx (2017).
96. Fekry, B. & Eckel-Mahan, K. The circadian clock and cancer: links between circadian disruption and disease Pathology. *J. Biochem.* **171**, 477–486 (2022).
97. Orisaka, M. et al. The role of pituitary gonadotropins and intraovarian regulators in follicle development: a mini-review. *Reprod. Med. Biol.* **20**, 169–175 (2021).
98. Cheng, K. et al. Simulated microgravity reduces quality of ovarian follicles and oocytes by disrupting communications of follicle cells. *NPJ Microgravity* **9**, 7 (2023).
99. Dai, T. X. et al. Simulated microgravity induces the proliferative inhibition and morphological changes in porcine granulosa cells. *Curr. Issues Mol. Biol.* **43**, 2210–2219 (2021).
100. Gorbacheva, E. Y. et al. The state of the organs of the female reproductive system after a 5-day "dry" immersion. *Int. J. Mol. Sci.* (2023).
101. Zhang, S. et al. Simulated microgravity using a rotary culture system compromises the in vitro development of mouse preantral follicles. *PLoS ONE* **11**, e0151062 (2016).
102. Wu, C. et al. Simulated microgravity compromises mouse oocyte maturation by disrupting meiotic spindle organization and inducing cytoplasmic blebbing. *PLoS ONE* **6**, e22214 (2011).
103. Miglietta, S. et al. Effects of simulated microgravity in vitro on human metaphase II oocytes: an electron microscopy-based study. *Cells* (2023).
104. Lemseffer, Y., Terret, M. E., Campillo, C. & Labrune, E. Methods for assessing oocyte quality: a review of literature. *Biomedicines* (2022).
105. Ferreira, A. F., Soares, M., Almeida-Santos, T., Ramalho-Santos, J. & Sousa, A. P. Aging and oocyte competence: a molecular cell perspective. *WIREs Mech. Dis.* **15**, e1613 (2023).
106. Luxton, J. J. et al. Telomere length dynamics and DNA damage responses associated with long-duration spaceflight. *Cell Rep.* **33**, 108457 (2020).
107. Capri, M. et al. Long-term human spaceflight and inflammaging: does it promote aging? *Ageing Res Rev* **87**, 101909 (2023).
108. Garrett-Bakelman, F. E. et al. The NASA twins study: a multidimensional analysis of a year-long human spaceflight. *Science* (2019).
109. Zhou, M., Sng, N. J., LeFrois, C. E., Paul, A. L. & Ferl, R. J. Epigenomics in an extraterrestrial environment: organ-specific alteration of DNA methylation and gene expression elicited by spaceflight in *Arabidopsis thaliana*. *BMC Genomics* **20**, 205 (2019).
110. Kojima, Y. et al. Effects of simulated microgravity on mammalian fertilization and preimplantation embryonic development in vitro. *Fertil. Steril.* **74**, 1142–1147 (2000).
111. Tash, J. et al. *Fertilization-critical Motility and Acrosome Reaction of Human and Bovine Sperm are Negatively Impacted by Spaceflight on the ISS* (ASGSR, 2020).
112. Mitra, A. et al. *Impact of Spaceflight Radiationand Microgravity on DNA Integrity and Fertility Risk of Human and Bovine Sperm on the ISS* (ASGSR, 2020).
113. Matsumura, T. et al. Male mice, caged in the International Space Station for 35 days, sire healthy offspring. *Sci. Rep.* **9**, 13733 (2019).
114. Mahase, E. Three FDA advisory panel members resign over approval of Alzheimer's drug. *BMJ* **373**, n1503 (2021).
115. Wakayama, S. et al. Detrimental effects of microgravity on mouse preimplantation development in vitro. *PLoS ONE* **4**, e6753 (2009).
116. Yoshida, K. et al. Intergenerational effect of short-term spaceflight in mice. *iScience* **24**, 102773 (2021).
117. Wakayama, S. et al. Evaluating the long-term effect of space radiation on the reproductive normality of mammalian sperm preserved on the International Space Station. *Sci. Adv.* (2021).
118. Lei, X. et al. Development of mouse preimplantation embryos in space. *Natl. Sci. Rev.* **7**, 1437–1446 (2020).
119. Ho, CNQ. et al. Simulated microgravity inhibits the proliferation of chang liver cells by attenuation of the major cell cycle regulators and cytoskeletal proteins. *Int. J. Mol. Sci*. (2021).
120. Kamal, K. Y., Herranz, R., van Loon, J. J. W. A. & Medina, F. J. Simulated microgravity, Mars gravity, and 2g hypergravity affect cell cycle regulation, ribosome biogenesis, and epigenetics in Arabidopsis cell cultures. *Sci. Rep.* **8**, 6424 (2018).
121. Wang, Y. et al. A major effect of simulated microgravity on several stages of preimplantation mouse development is lethality associated with elevated phosphorylated SAPK/JNK. *Reprod. Sci.* **16**, 947–959 (2009).
122. Feng, M. et al. Differential expression profiles of long non-coding RNAs during the mouse pronuclear stage under normal gravity and simulated microgravity. *Mol. Med. Rep.* **19**, 155–164 (2019).
123. Li, F., Ye, Y., Lei, X. & Zhang, W. Effects of microgravity on early embryonic development and embryonic stem cell differentiation: phenotypic characterization and potential mechanisms. *Front. Cell Dev. Biol* **9**, 797167 (2021).
124. Wakayama, S. et al. Development of a new device for manipulating frozen mouse 2-cell embryos on the International Space Station. *PLoS ONE* **17**, e0270781 (2022).
125. Schatz, F., Guzeloglu-Kayisli, O., Arlier, S., Kayisli, U. A. & Lockwood, C. J. The role of decidual cells in uterine hemostasis, menstruation, inflammation, adverse pregnancy outcomes and abnormal uterine bleeding. *Hum. Reprod. Update* **22**, 497–515 (2016).

126. Crucian, B. E. et al. Immune system dysregulation during spaceflight: potential countermeasures for deep space exploration missions. *Front. Immunol.* **9**, 1437 (2018).
127. Kim, J. K. et al. Single-cell multi-ome and immune profiles of the Inspiration4 crew reveal cell-type, sex, and microbiome-specific responses to spaceflight. *Nat. Commun*. https://doi.org/10.1038/s41467-024-49211-2 (2024).
128. Abuwala, N. & Tal, R. Endometrial stem cells: origin, biological function, and therapeutic applications for reproductive disorders. *Curr. Opin. Obstet. Gynecol.* **33**, 232–240 (2021).
129. Cho, H. J. et al. Microgravity inhibits decidualization via decreasing Akt activity and FOXO3a expression in human endometrial stromal cells. *Sci. Rep.* **9**, 12094 (2019).
130. McMaster, M. T., Teng, C. T., Dey, S. K. & Andrews, G. K. Lactoferrin in the mouse uterus: analyses of the preimplantation period and regulation by ovarian steroids. *Mol. Endocrinol.* **6**, 101–111 (1992).
131. Hennes, A. et al. Functional expression of the mechanosensitive PIEZO1 channel in primary endometrial epithelial cells and endometrial organoids. *Sci. Rep.* **9**, 1779 (2019).
132. Arishe, O. O., Ebeigbe, A. B. & Webb, R. C. Mechanotransduction and uterine blood flow in preeclampsia: the role of mechanosensing piezo 1 ion channels. *Am. J. Hypertens.* **33**, 1–9 (2020).
133. Proshchina, A. et al. Reproduction and the early development of vertebrates in space: problems, results, opportunities. *Life* (2021).
134. Serova, L. V. & Denisova, L. A. The effect of weightlessness on the reproductive function of mammals. *Physiologist* **25**, S9–S12 (1982).
135. Serova L, D. L., Makeev, V. & Chelnaya, N. The effect of microgravity on prenatal development of mammals. *Physiologist.* **27**, 107–110 (1984).
136. Ronca, A. E. & Alberts, J. R. Physiology of a microgravity environment selected contribution: effects of spaceflight during pregnancy on labor and birth at 1 G. *J. Appl. Physiol.* **89**, 849–854 (2000). discussion 848.
137. Bhat, G. K., Yang, H. & Sridaran, R. Simulated conditions of microgravity suppress progesterone production by luteal cells of the pregnant rat. *J. Gravit. Physiol.* **8**, 57–66 (2001).
138. Ijiri, K. Development of space-fertilized eggs and formation of primordial germ cells in the embryos of Medaka fish. *Adv. Space Res.* **21**, 1155–1158 (1998).
139. Nadeem, L., Shynlova, O., Mesiano, S. & Lye, S. Progesterone via its type-A receptor promotes myometrial gap junction coupling. *Sci. Rep.* **7**, 13357 (2017).
140. Lye, S. J., Nicholson, B. J., Mascarenhas, M., MacKenzie, L. & Petrocelli, T. Increased expression of connexin-43 in the rat myometrium during labor is associated with an increase in the plasma estrogen:progesterone ratio. *Endocrinology* **132**, 2380–2386 (1993).
141. Kamal, D. A. M., Ibrahim, S. F. & Mokhtar, M. H. Effects of testosterone on the expression of connexin 26 and connexin 43 in the uterus of rats during early pregnancy. *In Vivo* **34**, 1863–1870 (2020).
142. Burden, H. W., Zary, J. & Alberts, J. R. Effects of space flight on the immunohistochemical demonstration of connexin 26 and connexin 43 in the postpartum uterus of rats. *J. Reprod. Fertil.* **116**, 229–234 (1999).
143. Keil, L., Evans, J., Grindeland, R. & Krasnov, I. Pituitary oxytocin and vasopressin content of rats flown on COSMOS 2044. *J. Appl. Physiol.* **73**, 166S–168S (1992).
144. García-Ovejero, D., Trejo, J. L., Ciriza, I., Walton, K. D. & García-Segura, L. M. Space flight affects magnocellular supraoptic neurons of young prepuberal rats: transient and permanent effects. *Brain Res. Dev. Brain Res.* **130**, 191–205 (2001).
145. Baer, L. A., Wade, C. E. & Ronca, A. E. Effects of hypergravity exposure on plasma oxytocin concentration in pregnant and lactating rat dams. *J. Gravit. Physiol.* **9**, P205–P206 (2002).
146. Colaianni, G. et al. Bone marrow oxytocin mediates the anabolic action of estrogen on the skeleton. *J. Biol. Chem.* **287**, 29159–29167 (2012).
147. Ross, A. P. et al. Sex-dependent effects of social isolation on the regulation of arginine-vasopressin (AVP) V1a, oxytocin (OT) and serotonin (5HT) 1a receptor binding and aggression. *Horm. Behav.* **116**, 104578 (2019).
148. Lintault, L. M. et al. In a hypergravity environment neonatal survival is adversely affected by alterations in dam tissue metabolism rather than reduced food intake. *J. Appl. Physiol.* **102**, 2186–2193 (2007).
149. Perez, M. F. & Lehner, B. Intergenerational and transgenerational epigenetic inheritance in animals. *Nat. Cell Biol.* **21**, 143–151 (2019).
150. Pembrey, M. E. et al. Sex-specific, male-line transgenerational responses in humans. *Eur. J. Hum. Genet.* **14**, 159–166 (2006).
151. Hardikar, A. A. et al. Multigenerational undernutrition increases susceptibility to obesity and diabetes that is not reversed after dietary recuperation. *Cell Metab.* **22**, 312–319 (2015).
152. ACOG Committee Opinion No. 762: Prepregnancy counseling. American College of Obstetricians and Gynecologists. *Obstet. Gynecol.* **133**, e78–e89 (2019).
153. Kominiarek, M. A. & Rajan, P. Nutrition recommendations in pregnancy and lactation. *Med. Clin. North Am.* **100**, 1199–1215 (2016).
154. Jain, V. & Wotring, V. E. Medically induced amenorrhea in female astronauts. *NPJ Microgravity* **2**, 16008 (2016).
155. Trussell, J. Contraceptive failure in the United States. *Contraception* **83**, 397–404 (2011).
156. Heer, M. & Paloski, W. H. Space motion sickness: incidence, etiology, and countermeasures. *Auton. Neurosci.* **129**, 77–79 (2006).
157. Jang, Y. S., Lee, E. S. & Kim, Y. K. Venous thromboembolism associated with combined oral contraceptive use: a single-institution experience. *Obstet. Gynecol. Sci.* **64**, 337–344 (2021).
158. Marshall-Goebel, K. et al. Assessment of jugular venous blood flow stasis and thrombosis during spaceflight. *JAMA Netw. Open* **2**, e1915011 (2019).
159. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 208: benefits and risks of sterilization. *Obstet. Gynecol.* **133**, e194–e207 (2019).
160. Hibaoui, Y. & Feki, A. Organoid models of human endometrial development and disease. *Front. Cell Dev. Biol.* **8**, 84 (2020).
161. Laronda, M. M. et al. A bioprosthetic ovary created using 3D printed microporous scaffolds restores ovarian function in sterilized mice. *Nat. Commun.* **8**, 15261 (2017).
162. Xiao, S. et al. A microfluidic culture model of the human reproductive tract and 28-day menstrual cycle. *Nat. Commun.* **8**, 14584 (2017).
163. Pantalone, D. et al. Robot-assisted surgery in space: pros and cons. A review from the surgeon's point of view. *NPJ Microgravity* **7**, 56 (2021).
164. Hiranaka, T. et al. The use of smart glasses for surgical video streaming. *Surg. Innov.* **24**, 151–154 (2017).
165. El Rassi, I. & El Rassi, J. M. A review of haptic feedback in tele-operated robotic surgery. *J. Med. Eng. Technol.* **44**, 247–254 (2020).
166. Sitti, M. Miniature soft robots—road to the clinic. *Nat. Rev. Mater.* **3**, 74–75 (2018).
167. Zhang, Y. et al. NASA's ground-based microgravity simulation facility. *Methods Mol. Biol.* **2368**, 281–299 (2022).
168. Sarabi, M. R., Yetisen, A. K. & Tasoglu, S. Magnetic levitation for space exploration. *Trends Biotechnol.* **40**, 915–917 (2022).
169. Tasoglu, S. et al. Levitational image cytometry with temporal resolution. *Adv. Mater.* **27**, 3901–3908 (2015).
170. Nangle, S. N. et al. The case for biotech on Mars. *Nat. Biotechnol.* **38**, 401–407 (2020).

171. Jones, J., Karouia, F., Pinsky, L. & Cristea, O. Radiation and Radiation Disorders. In *Principles of Clinical Medicine for Space Flight* (eds Barratt, M. R., Baker, E. S. & Pool, S. L.) 39–108 (Springer, 2019).
172. Patel, S. J., Reede, D. L., Katz, D. S., Subramaniam, R. & Amorosa, J. K. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. *Radiographics* **27**, 1705–1722 (2007).
173. Megory, E. & Oyama, J. Hypergravity induced prolactin surge in female rats. *Aviat. Space Environ. Med.* **56**, 415–418 (1985).
174. Tou, J. C., Grindeland, R. E. & Wade, C. E. Effects of diet and exposure to hindlimb suspension on estrous cycling in Sprague-Dawley rats. *Am. J. Physiol. Endocrinol. Metab.* **286**, E425–433, (2004).
175. Forsman, A. & Nier, A. The effects of spaceflight on mucin production in the mouse uterus. *Gravit. Space Res.* **1**, 20–28 (2013).
176. Schenker, E. & Forkheim, K. Mammalian mice embryo early development in weightlessness environment on STS 80 space flight. *Israel Aerospace Med Inst Rep* **1998**, 5 (1998).
177. Ma, B. et al. Real-time micrography of mouse preimplantation embryos in an orbit module on SJ-8 satellite. *Microgravity Sci. Technol.* **20**, 127–136 (2008).
178. Wang, Y., An, L., Jiang, Y. & Hang, H. Effects of simulated microgravity on embryonic stem cells. *PLoS ONE* **6**, e29214 (2011).
179. Acharya, A. et al. Modulation of differentiation processes in murine embryonic stem cells exposed to parabolic flight-induced acute hypergravity and microgravity. *Stem Cells Dev.* **27**, 838–847 (2018).
180. Lei, X. et al. Effect of microgravity on proliferation and differentiation of embryonic stem cells in an automated culturing system during the TZ-1 space mission. *Cell Prolif.* **51**, e12466 (2018).
181. Oyama, J. & Platt, W. T. Reproduction and growth of mice and rats under conditions of simulated increased gravity. *Am. J. Physiol.* **212**, 164–166 (1967).
182. Serova LV, D. L., Makeeva, V. F., Chelnaya, N. A. & Pustynnikova, A. M. The effect of microgravity on the prenatal development of mammals. *Physiologist* **27**, 107–110 (1984).
183. Megory, E. & Oyama, J. Hypergravity effects on litter size, nursing activity, prolactin, TSH, T3, and T4 in the rat. *Aviat. Space Environ. Med.* **55**, 1129–1135 (1984).
184. Moore, J. & Duke, J. Effect of chronic centrifugation on mouse breeding pairs and their offspring. *Physiologist* **31**, S120–S121 (1988).
185. Burden, H. W. et al. Effects of space flight on ovarian-hypophyseal function in postpartum rats. *J Reprod. Fertil.* **109**, 193–197 (1997).
186. Wong, A. M. & DeSantis, M. Rat gestation during space flight: outcomes for dams and their offspring born after return to Earth. *Integr. Physiol. Behav. Sci.* **32**, 322–342 (1997).
187. Burden, H. W., Poole, M. C., Zary, J., Jeansonne, B. & Alberts, J. R. The effects of space flight during gestation on rat uterine smooth muscle. *J. Gravit. Physiol.* **5**, 23–29 (1998).
188. Yang, H., Bhat, G. K. & Sridaran, R. Clinostat rotation induces apoptosis in luteal cells of the pregnant rat. *Biol. Reprod.* **66**, 770–777 (2002).
189. Casey, T., Patel, O. V. & Plaut, K. Transcriptomes reveal alterations in gravity impact circadian clocks and activate mechanotransduction pathways with adaptation through epigenetic change. *Physiol. Genomics* **47**, 113–128 (2015).
190. Steller, J. G., Ronca, A., Powell, T. L. & Jansson, T. Effects of near-continuous low-dose neutron irradiation on pregnancy outcomes in mice. *Am. J. Obstetr. Gynecol.* **222**, S570–S571 (2019).

Acknowledgements

BM is supported by the Department of Obstetrics and Gynecology at the University of South Florida. N.S. acknowledges the support of the Osteopathic Heritage Foundation through funding for the Osteopathic Heritage Foundation Ralph S. Licklider, D.O., Research Endowment in the Heritage College of Osteopathic Medicine. We would like to thank our medical illustrator, Ezgi Bozogullarindan, for Figs. 1, 2, 3A. Figure 3B was created with BioRender.com.

Author contributions

Conceptualization: B.M.; original draft: B.M.; review and editing: all authors; figures and visualization: B.M. and E.B.; supervision: B.M., S.T. and A.B.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Begum Mathyk, Savas Tasoglu or Afshin Beheshti.

[1]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of South Florida Morsani College of Medicine, Tampa, FL, USA. [2]Shady Grove Fertility San Diego, San Diego, CA, USA. [3]Department of Obstetrics, Gynecology & Reproductive Sciences, Yale School of Medicine, Yale University, New Haven, CT, USA. [4]Blue Marble Space Institute for Science, Exobiology Branch, NASA Ames Research Center, Moffett Field, CA, USA. [5]Space Research Within Reach, San Francisco, CA, USA. [6]Center for Space Medicine, Baylor College of Medicine, Houston, TX, USA. [7]BioServe Space Technologies, Smead Aerospace Engineering Science Department, University of Colorado Boulder, Boulder, CO, USA. [8]Department of Internal Medicine, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA. [9]Department of Obstetrics and Gynecology, University of South Florida Morsani College of Medicine, Tampa, FL, USA. [10]Space Biosciences Division, NASA Ames Research Center, Moffett Field, CA, USA. [11]Blue Marble Space Institute of Science, Space Biosciences Division, NASA Ames Research Center, Moffett Field, CA, USA. [12]KBR, Moffett Field, CA, USA. [13]Molecular and Cellular Biology, School of Biosciences, University of Sheffield, Sheffield, UK. [14]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Sunnyvale, CA, USA. [15]Ohio Musculoskeletal and Neurological Institute, Heritage College of Osteopathic Medicine, Ohio University, Athens, OH, USA. [16]Department of Physiology and Biophysics, Weill Cornell Medicine, New York, NY, USA. [17]The HRH Prince Alwaleed Bin Talal Bin Abdulaziz Alsaud Institute for Computational Biomedicine, Weill Cornell Medicine, New

York, NY, USA. [18]World Quant Initiative for Quantitative Prediction, Weill Cornell Medicine, New York, NY, USA. [19]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Duke University, Durham, NC, USA. [20]School of Mechanical Engineering, Koç University, Istanbul, Türkiye. [21]Koç University Translational Medicine Research Center (KUTTAM), Koç University, Istanbul, Türkiye. [22]Boğaziçi Institute of Biomedical Engineering, Boğaziçi University, Istanbul, Türkiye. [23]Physical Intelligence Department, Max Planck Institute for Intelligent Systems, Stuttgart, Germany. [24]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA.[25]P.A. is no longer affiliated with Department of Dermatology and Allergy, University Hospital, LMU, Munich, Germany
✉e-mail: abegum@usf.edu; stasoglu@ku.edu.tr; abehesht@broadinstitute.org