RBMO

REVIEW

Reproductive biomedicine in space: implications for gametogenesis, fertility and ethical considerations in the era of commercial spaceflight

BIOGRAPHY

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KEY MESSAGE

Human fertility in space is an urgent concern as commercial spaceflight grows. Space conditions, radiation, microgravity and stress pose risks to reproduction. Limited studies show compromised female and male fertility, and abnormal embryogenesis. A multidisciplinary approach is essential to guide future reproductive research and bioethics in space exploration.

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Declarations: BAM reports grant funding, patents and advisory roles related to reproductive health in space research. BAM also serves as Chair of NASA's Open Science Data Repositary Female Reproduction Analysis Working Group, and is a partner in the SpaceMed programme at Charité Universitätsmedizin Berlin (Germany). No funding from these projects was used in this review. The remaining authors are engaged in space research, including work in astrobiology and/or reproductive health; however, these activities are independent of the present review, and no external funding or institutional support related to them was used in its preparation.

KEY WORDS
Embryology
Radiation
Gravity
Reproductive physiology

ABSTRACT

As the era of commercial and frequent spaceflight advances, the question of human fertility in space is no longer theoretical but urgently practical. Despite over 65 years of human spaceflight activities, little is known of the impact of the space environment on the human reproductive systems during long-duration missions. Extended time in space poses potential hazards to the reproductive function of female and male astronauts, including exposure to cosmic radiation, altered gravity, psychological and physical stress, and disruption to circadian rhythm. This review encapsulates current understanding of the effects of spaceflight on reproductive physiology, incorporating findings from animal studies, a recent experiment on sperm motility, and omics-based insights from astronaut physiology. Female reproductive systems appear to be especially vulnerable, with implications for oogenesis and embryonic development in microgravity. Male reproductive function reveals compromised DNA integrity, even when motility appears to be preserved. This review examines the limited embryogenesis studies in space, which show frequent abnormal cell division and impaired development in rodents. Alongside physiological findings, this review explores ethical issues of space work, particularly with increasing spaceflights involving non-professional astronauts and individuals of all ages. This convergence of space medicine, reproductive biology and bioethics represents a novel and critical intersection that warrants attention. Drawing from multidisciplinary fields, a collaborative framework is proposed for future research, aiming to catalyse cross-disciplinary dialogue and guide the next generation of reproductive biomedical research in space.

INTRODUCTION

> 'The universe is not only stranger than we imagine. It is also stranger than we can imagine.'
>
> J.B.S. Haldane

The latter half of the 20th century witnessed two transformative achievements that reshaped the boundaries of science and society, both in the same year: the first human landing on the Moon in 1969 (*Cortright, 2019*), and publication of the first evidence of human fertilization *in vitro* (*Edwards et al., 1969*) by the very same pioneers who would, only a decade later, announce the birth of the first baby conceived through IVF in 1978 (*Steptoe et al., 1978*). These milestones opened new eras of human endeavour: one pushing the limits of physical space, the other redefining the potential of human reproduction. IVF enabled conception outside the body within tightly controlled laboratory environments, while spaceflight transported the human body into extreme and unearthly conditions. Both challenged what was once considered biologically impossible, and now, they converge in an increasingly urgent and underexplored question: how will human reproduction, natural or assisted, function beyond Earth?

Over the past 50 years, embryology and assisted reproductive technology (ART) have evolved into highly sophisticated and regulated clinical practices incorporating a more diverse demographic. The introduction of automation, artificial intelligence (AI), and non-invasive diagnostics may enhance precision and outcomes, while techniques such as fertility preservation, embryo vitrification, and microfluidics have become routine in IVF laboratories. In parallel, spaceflight has shifted from an elite, male-dominated pursuit of national and military prestige to a rapidly expanding frontier led by commercial ventures and international collaborations. Despite this evolution, fundamental biological questions about reproduction in space remain unanswered (*Jain et al., 2023*). As space missions become longer and more diverse in crew composition, shifting from weeks to months, and eventually years, understanding the risks to fertility and reproduction has become not only relevant but essential.

Humanity is steadily approaching the era of routine space travel, with visions of lunar and Martian settlements shifting from science fiction to commercial ambition (*Denis et al., 2020*). As access to space expands beyond elite astronauts and cosmonauts to include wealthy tourists, civilian crews, and commercial clients, there is an urgent need to reassess existing physiological, medical and bioethical frameworks. National space agencies, such as the National Aeronautics and Space Administration (NASA), European Space Agency (ESA), and the Japan Aerospace Exploration Agency (JAXA), have historically upheld an applied research-driven, safety-first ethos. Conversely, commercial enterprises are motivated by innovation, market competition, and profitability, and private companies plan long-duration missions and future extraterrestrial settlements (*Entrena-Utrilla and Welch, 2017*); as such, it is vital to develop revised ethical guidelines capable of addressing the specific challenges posed by private sector activity in space.

A significantly underexplored domain is the prospect of human reproduction beyond Earth, including conception, gestation and childbirth aboard orbital or planetary platforms. This review examines the ethical dimensions of reproduction in space within the context of commercial spaceflight, where regulatory oversight is inconsistent and motivations may not always prioritize health and safety. It explores the absence of industry-wide standards, gender-specific fertility risks, medical and environmental hazards to gestation and birth, ethical challenges of research on human subjects, and the unique tensions that commercial sponsors may face in a profit-driven model.

The aim is not to promote conception in space, but to reduce the reproductive risks that space travellers may encounter, especially during long-duration missions, and to identify the ethical and scientific gaps that must be addressed. If reproduction is ever to occur beyond Earth, it must do so with a clear commitment to safety, transparency and ethical integrity. This review will use the term 'astronauts', from the Greek words meaning 'star sailor', to mean human beings travelling beyond Earth's atmosphere, regardless of whether they are referred to elsewhere as astronauts, cosmonauts, spationauts, taikonauts, space crew, professionals, commercial flyers, or tourists.

HAZARDS OF SPACE TRAVEL

For human spaceflight, NASA has identified five hazards of space travel: space radiation; isolation and confinement; distance from Earth; gravity

(or lack of gravity); and hostile environments (*Afshinnekoo et al., 2020*). In space, some physiological systems adapt and re-regulate to what has been termed the 'space norm', including cardiovascular, fluid balance, and vestibular systems, while other systems, such as bone density, calcium metabolism, and reproductive function, exhibit incomplete or delayed recovery (*Barratt et al., 2020*; *Nicogossian and Parker, 1982*). Evidence, although limited to date, suggests that key reproductive axes, specifically the hypothalamo–pituitary–gonadal (HPG) and hypothalamo–pituitary–adrenal axes, undergo significant alterations during spaceflight which influence hormonal signalling and gamete quality in ways that may not be corrected fully upon return to Earth (*Mathyk et al., 2024a*).

Radiation is among the most significant hazards in space (*Cucinotta, 2007*), and when combined with the effects of microgravity, it poses serious risks to reproductive health. DNA can be damaged, spermatogenesis and oogenesis can be impaired, and endocrine function can be disrupted (*Gimunová, 2024*).

RADIATION

Radiation exposure, a defining threat in space, is of particular concern for reproductive organs due to their heightened sensitivity to DNA damage (*Ogilvy-Stuart et al., 1993*). In contrast with Earth's surface, where the magnetosphere and atmosphere provide robust shielding, space travellers are exposed to galactic cosmic rays, solar particle events, and geomagnetically trapped radiation around Earth, each varying in dose, energy and biological impact.

In dosimetry, linear energy transfer (LET) refers to the amount of energy an ionizing particle deposits per unit distance as it travels through a material. The biological effects of radiation depend on several factors, including radiation type (high-LET versus low-LET), total dose, exposure duration, and age at which exposure occurs. High-LET radiation, especially heavy ion (HZE) particles from galactic cosmic rays, produces dense ionization tracks that cause direct double-strand DNA breaks, which are significantly more harmful than the single-strand breaks typically induced by low-LET radiation such as earthy X-rays and gamma rays (*Jones et al., 2020*; *Roobol et al., 2020*).

Studies in animal models, such as those documented by *Ronca et al. (2014)*, have shown disrupted ovarian cycles, reduced corpus luteum formation, and altered oestrous cycling following radiation exposure. Human data, however, remain scarce, and much of the current operational shielding and mission planning still relies on decades-old models (*Ruben, 1989*).

Most experiments in space have been conducted within the relatively protected environment of the Van Allen Belts. The Van Allen Belts themselves are located outside low Earth orbit (LEO), and are composed of high concentrations of energetic charged particles, mainly electrons and protons, trapped by Earth's geomagnetic field (*Van Allen, 1959*). The International Space Station (ISS) and research space satellite, for example, orbit within LEO. In 1968, NASA's Apollo 8 mission became the first crewed spaceflight to travel beyond the Van Allen Belts, orbit the Moon, and return safely to Earth. Venturing out further in the future will only increase exposure to radiation.

Radiation protection on Earth is regulated by stringent frameworks designed to protect both workers and the public. This encompasses obligatory dosimetry, engineered controls, training, and safety information, all based on the 'as low as reasonably achievable/practicable' principle. This advocates for restrictions on exposure duration, augmented distance from sources, and the implementation of shielding (*Centers for Disease Control and Prevention, 2025*). Radiation is quantified in sieverts (Sv) or grays (Gy). Gy measure the quantity of radiation energy received by matter, whereas Sv measure its biological effects, hence indicating the potential damage to live tissue (*International Commission on Radiological Protection, 2007*). In situations, temporary increased dose limits may be authorized, such as up to 250 mSv for life-saving interventions in the US (*Radiation Emergency Medical Management, 2025*).

As government space missions and commercial spaceflight expand, space is becoming an increasingly routine workplace. However, current Earth-based radiation frameworks are being tested by the unique hazards of space radiation. Crucially, full understanding of its long-term biological effects, especially concerning fertility and heritable health outcomes, are still lacking. This concern is especially pressing as women now represent nearly half of astronaut candidates, compared with just 15% of all those who have flown previously (*Rose, 2022*). Research suggests sex-specific vulnerabilities; radiation may affect male and female reproductive systems differently (*Mathyk et al., 2024a*), but evidence on outcomes such as radiation-induced menopause or impaired spermatogenesis remains limited and underfunded.

There are transgenerational risks beyond individuals who have ventured into space. Observations of increased childhood cancer rates near nuclear facilities such as Sellafield (*Gardner et al., 1990*), and studies on germ cell radiation effects (*Fukunaga et al., 2022*) point to possible transgenerational impacts. These findings raise both ethical and social challenges that future policy must address. Lessons from terrestrial occupational health warn that, even in well-regulated fields, radiation awareness can be poor. *Xu et al. (2024)* found persistent knowledge gaps among medical professionals. Similar shortcomings in the space sector could expose astronauts to poorly understood and possibly inheritable harms. If human space activity is to continue responsibly, the safeguards used for nuclear workers must be adapted and strengthened for extraterrestrial environments.

The Outer Space Treaty, which was signed in 1967, is an important international agreement that sets rules for how countries might explore and exploit space. The importance of the Treaty rests in setting important rules for space exploration and protecting astronauts. It emphasizes the astronauts' special legal standing, and the need for international labour standards to keep them safe and healthy in space. It is the basis for dealing with the dangers of cosmic radiation, and making sure that astronauts are protected equally in all countries (*United Nations, 1966*).

NASA set radiation exposure limits for astronauts in LEO at 50 mSv/year, with career exposure caps varying by age and gender. Women had stricter limits due to a higher biological risk of cancers such as breast and ovarian cancer (*US Nuclear Regulatory Commission, 2020*). While this aimed to protect health, it raised concerns about potential gender-based discrimination in spaceflight careers (*Mehmeti and Stojchevska, 2020*), and was

later revised in a technical brief (NASA V1 4030) to a total career-effective radiation dose due to spaceflight radiation to be <600 mSv universal for all ages and sexes. (*Yasuda et al., 2022*). However, it is worth mentioning that international space agencies, for example, ESA, JAXA and Russian Federal Space Agency, have a higher limit (1000 mSv), independent of age and gender. JAXA still has radiation exposure career limits based on sex/age dependency using 3% of risk of exposure-induced death at the mean (*National Academies of Sciences, 2021*).

For comparison, the International Commission on Radiological Protection recommends that the general public should receive no more than 1 mSv/year from artificial sources, excluding medical and natural background exposure; for radiation workers, the limit is 20 mSv/year averaged over 5 years, with no single year exceeding 50 mSv (*International Commission on Radiological Protection, 2007*). These limits are far below those encountered in space. A typical person on Earth receives approximately 2.4 mSv/year from natural background radiation (*National Aeronautics and Space Administration, 2023a*; citing United Nations Scientific Committee on the Effects of Atomic Radiation), whereas astronauts aboard the ISS may receive approximately 0.5 mSv/day depending on solar activity (*National Aeronautics and Space Administration, 2023b*). Comprehensive dose limits and comparisons are summarized in **FIGURE 1**.

MICROGRAVITY

While the reproductive risks of ionizing radiation are becoming increasingly well defined, microgravity (weightlessness) adds another layer of complexity, and presents its own distinct physiological challenges. Alterations in gravity remove or change a fundamental mechanical cue, influencing hormonal regulation, gametogenesis and early embryonic development in ways that are still not fully understood (*Santaguida et al., 2023*).

CIRCADIAN DISRUPTION

Clinical analogues, such as those seen in shift workers on Earth, offer clues to the hormonal and metabolic disarray that might occur in space, which include disrupted circadian rhythms, insulin resistance, and menstrual irregularities. Shift work and transmeridian travel disrupt the synchronization between internal circadian rhythms and external environmental cues, often leading to fatigue; sleep disturbances; and heightened risk of mood disorders, cardiovascular disease, and reproductive dysfunction (*Caetano et al., 2021*).

Circadian rhythms, regulated by the suprachiasmatic nucleus and clock genes, are crucial for hormonal balance and the timing of reproductive events such as ovulation. When these rhythms are misaligned, as in the case of shift workers, menstrual irregularities, reduced fertility, spontaneous abortions, and poor pregnancy outcomes have been observed (*Lee et al., 2025*). Sleep deprivation and circadian misalignment can alter levels of key reproductive hormones, such as FSH and oestradiol, potentially increasing the risk of infertility and breast cancer (*Mahoney, 2010*). On a molecular level, 'clock genes', including *CLOCK*, *BMAL1* and the *PER* family, are active in reproductive tissues, and their disruption has been shown to impair oestrous cycles, ovulation and overall fecundity (*Shearman et al., 1997*; *Shigeyoshi et al., 1997*; *Zylka et al., 1998*). Epidemiological studies indicate a greater dependence on reproductive medications among night shift workers, especially women, engaged in social or altered circadian schedules. The precise mechanisms connecting circadian disturbance to infertility are not fully elucidated (*Sciarra et al., 2020*), although a comprehensive study revealed that female night shift workers experienced heightened challenges in having their first child and had increased requirement for ART (*Fernandez et al., 2020*).

ENVIRONMENTAL CONSTRAINTS OF THE SPACECRAFT AND HABITAT

The structural constraints of spacecraft and off-world habitats introduce additional risks. Toxic lunar and Martian dust can pose serious threats to respiratory and overall health, while air and water recycling systems carry the potential for contamination (*Caston, 2018*).

Restricted dietary variety, insufficient caloric intake, and vitamin deficiencies can undermine both fetal development and maternal well-being. Together with the physical challenges is the burden of psychosocial stress. Prolonged isolation, disrupted sleep cycles, and limited social interaction can increase the likelihood of depression and anxiety, which threaten both mental health and mission success (*Mishra and Luderer, 2019*).

Collectively, these multifaceted factors have the potential to have a major influence on reproductive health (**FIGURE 2**).

MALE REPRODUCTIVE BIOLOGY IN SPACE

Space exploration pushes the boundaries of human endurance, yet male reproductive health remains a relatively understudied aspect. However, it is gaining importance as long-duration missions to the Moon, Mars and beyond become a reality (*Gimunová et al., 2024*; *National Aeronautics and Space Administration, 2024*). Understanding the effects of microgravity and radiation on male fertility is vital for astronaut health and the future of space colonization (*Barratt, 2020*).

The testis is particularly sensitive to radiation exposure, as spermatogenesis depends on rapid cellular division, making it highly susceptible to radiation-induced damage (*Georgakopoulos et al., 2024*). Once astronauts move beyond Earth's protective magnetosphere, they are exposed to increased levels of galactic cosmic rays, solar particle events, and trapped radiation belts (*Zeitlin et al., 2013*).

Within their permissible exposure limits for astronauts, NASA also has thresholds specific to the blood-forming organs and testicular tissue (*Dobney et al., 2023*). Doses exceeding approximately 250 mGy can disrupt spermatogenesis, although effects at this threshold may be reversible (*Montesinos et al., 2021*). However, chronic, cumulative radiation exposure during long-duration missions may impair the HPG axis, affecting hormonal signalling, testosterone production, and sperm quality (*Gimunová et al., 2024*). While shielding strategies exist, they are more effective for low-LET radiation; protecting against HZE particles remains a formidable challenge, requiring further technological innovation (*Chowdhury et al., 2023*; *Wang et al., 2025*).

Historical context and mission data

Historical mission data provide valuable insight into human male exposure. The US Apollo missions (1968–1972) were the only

Category	Measurement / Observation	Value / Dose	Biological / Clinical Impact	Reference
Projected Mars Mission	Mission total	0.7–1 Sv (~700–1000 mSv)	At agencies' career limit threshold; fertility risk	Hassler et al. (2014)
JAXA Career Limits	Career limit based on sex- and age-dependent risk model	3 % lifetime Risk of Exposure-Induced Death (REID) at the mean	Cumulative radiation risk below the 3% REID cancer-mortality threshold.	National Academies of Sciences, Engineering, and Medicine. (2021)
ESA, ROSCOSMOS, Career Limits	Consensus with other space agencies	1000 mSv total	Universal across age/sex	National Academies of Sciences, Engineering, and Medicine. (2021)
NASA Career Limit (Revised)	All NASA astronauts	≤600 mSv total	Universal across age/sex	Yasuda et al. (2022)
Apollo 14 Mission	Total dose over 7 days	11.4 mSv	Deep space exposure benchmark	English et al. (1973)
Apollo 8 Mission	Total dose over 4 days	1.6 mSv	Minimal acute risk	English et al. (1973)
ISS Astronaut Exposure	Daily dose	0.5 mSv/day (~110–180 mSv over ~365 days)	Cumulative LEO exposure	Restier-Verlet et al. (2021), NASA (2023b)
NASA Astronauts (LEO)	Annual limit	50 mSv/year	Pre-2020 sex-specific, later universalized	NRC (2020)
LET & DNA Damage	High-LET HZE particles	Dense ionization tracks ⊠ double-strand DNA breaks	Higher mutagenic & carcinogenic potential	Roobol et al. (2020), Jones et al. (2020)
Ovarian Cancer Risk (Rodent)	Charged iron particle exposure	Not quantified	Potential carcinogenesis	Mishra et al. (2018)
High-LET Ovarian Damage (Rodent)	Follicle pool decline	71% (Heavy oxygen ions), 57% (Heavy iron ions)	Severe ovarian tissue impact	Mishra et al. (2016, 2017)
Premature Ovarian Deficiency	Age-dependent risk	97% at 20.3 Gy (birth), 18.4 Gy (10 yrs), 14.3 Gy (30 yrs)	Ovarian reserve loss risk	Wallace et al. (2005)
Female Ovarian Threshold	50% oocyte pool loss	2 Gy	Age-dependent ovarian damage	Wallace et al. (2003)
Testicular Tissue Threshold	Disruption of spermatogenesis	≥250 mGy	Reversible near threshold	Montesinos et al. (2021)
Emergency Limit (US)	Life-saving efforts	Up to 250 mSv	Temporary permissible limit	remm.hhs.gov (2025)
Occupational Radiation Limit	Radiation workers (5-year average)	20 mSv/year (≤50 mSv in a single year)	Occupational safety threshold	ICRP (2005)
Transgenerational Risk	Germ cell mutations	Not quantified	Observed in nuclear worker offspring	Gardner et al. (1990), Fukunaga et al. (2022)
Radiation Workers	Occupational limit (5-year average)	20 mSv/year (≤50 mSv in one year)	Occupational safety limit	ICRP (2005)
Background Earth Radiation	Average annual natural background	2.4 mSv/year	Baseline human exposure	NASA (2023a), UNSCEAR (2008)
General Public Limit	Artificial sources (annual)	1 mSv/year	Standard regulatory exposure limit	ICRP (2005)
Earth Baseline	7-day background exposure	0.046 mSv	Comparison with Apollo missions	Shannoun et al. (2015)

FIGURE 1 Radiation exposure, biological effects, and safety thresholds in spaceflight and on Earth. Sv, sieverts; mSv, millisieverts; JAXA, Japan Aerospace Exploration Agency; REID, risk of exposure-induced death; ESA, European Space Agency; ROSCOSMOS, Russian Federal Space Agency; NASA, National Aeronautics and Space Administration; ISS, International Space Station; LEO, low Earth orbit; NRC, Nuclear Regulatory Commission; LET, linear energy transfer; DNA, deoxyribonucleic acid; HZE, high atomic number and high energy; Gy, grays; Remm.hhs.gov, US Department of Health and Human Services (Radiation Emergency Medical Management); ICRP, International Commission on Radiological Protection; UNSCEAR, United Nations Scientific Committee on the Effects of Atomic Radiation.

human endeavours beyond LEO, exposing astronauts briefly to deep-space radiation (*Delp et al., 2016*). Apollo 8, for example, recorded exposures of approximately 1.6 mSv over 4 days, while Apollo 14 saw 11.4 mSv over 7 days (*English et al.,1973*). In comparison, average background radiation exposure for a human at sea level is 0.046 mSv over 7 days (*Shannoun et al., 2015*). Although these short missions posed minimal reproductive risk, they highlighted the hazards that astronauts would face during extended lunar or Martian exploration (*National Aeronautics and Space Administration, 2023a*). Per publicly available records, at least two Apollo astronauts fathered children following spaceflight, perhaps suggesting that this relatively minimal radiation exposure did not affect their future fertility (*US Congress Senate Committee on Energy and Natural Resources, 1975*; *United Press International, 1985*), but the epigenetic effects on offspring, if any, are unknown.

The Space Shuttle program (1981–2011) and the ongoing ISS missions have provided much richer data on cumulative radiation exposure in LEO (*Cucinotta,*

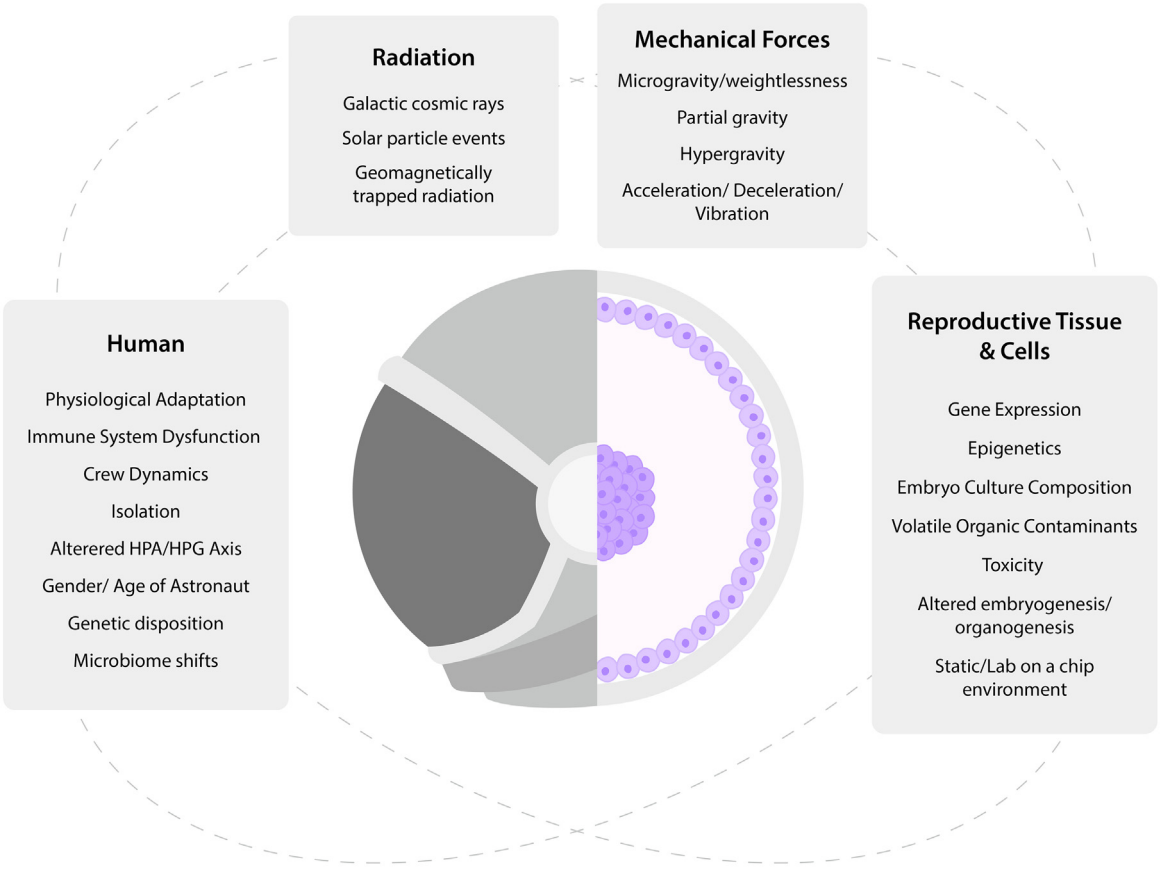

FIGURE 2 Hazards and environmental factors of humans and embryos *in astris*. HPA, hypothalamo–pituitary–adrenal; HPG, hypothalamo–pituitary–gonadal.

2007). Mission durations varied widely, with ISS missions sometimes exceeding 365 days and delivering total estimated doses between approximately 110 and 180 mSv (*Restier-Verlet et al., 2021*). Despite the wealth of physical dosimetry, the authors were unable to find any publicly available, reliable data on reproductive outcomes for male astronauts post-mission. However, as astronauts are getting older, this may also contribute to reduced fertility (*Smith et al., 2020*). Overall, the effect of cumulative radiation exposure on male fertility remains a critical knowledge gap, especially when considering that a mission to Mars would involve exposure to approximately 0.7–1 Sv over its duration, well above levels experienced on the ISS and, if unmitigated, could potentially compromise testicular function, future fertility, and the health of offspring (*Hassler et al., 2014*).

Scientific research in male reproduction in space

To address many of these knowledge gaps, JAXA has employed animal models in its Multiple Artificial-gravity Research System, comparing ground-based controls with mice exposed to artificial gravity and microgravity aboard the ISS. These studies reported no significant differences in genitourinary organ weight, sperm motility, or the capacity to produce healthy offspring, suggesting that short-duration microgravity exposure may not impair male fertility severely (*Matsumura et al., 2019*). However, the model may not be representative of human male reproduction as the male mice used were very young (5–6 weeks old), and this raises concerns about developmental stage and its relevance to extrapolation. In men, the accumulation of spontaneous mutations in the germ line is strongly age-dependent (*Aitken, 2024*). Across decades of spaceflight, the average age of male astronauts at the time of their first mission has been approximately 39–40 years. Replication of these experiments using aged male mice would therefore be more appropriate for testing human reproductive risk. Supporting this concern, a complementary study reported increased DNA damage in cryopreserved sperm retrieved from the ISS, raising additional questions about the long-term genomic stability of male gametes exposed to spaceflight conditions (*Wakayama et al., 2017*).

More recently, researchers have explored the epigenetic impacts of spaceflight. Environmental factors such as diet, air quality, stress and toxins can influence gene expression by altering epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation. These changes can affect how genes work and potentially lead to disease or adaptive responses, such as transgenerational epigenetic inheritance (*Heard and Martienssen, 2014*). Of particular interest, two animal studies have suggested that spaceflight-induced epigenetic changes may have subtle but meaningful effects on sperm function. Mice onboard the ISS for 24 days demonstrated alterations in testes expression of DNA methyltransferase and histone deacetylase compared with ground controls (*Ogneva et al., 2019*); fertility outcomes were not explored. *Yoshida et al. (2021)* found that young

adult mice aboard the ISS for 35 days experienced epigenetic alterations within their male reproductive tract. Spaceflight activated the transcription factor ATF7 in testes tissue, a regulator of heterochromatin formation, which subsequently altered small RNA expression in spermatozoa. These male mice were then bred upon returning to Earth. Interestingly, first-generation offspring demonstrated increased hepatic expression of key DNA replication genes, thus demonstrating an intergenerational effect incurred by short-duration spaceflight.

Although current evidence suggests that short-duration missions do not alter male fertility significantly in the long term, as reviewed above, the possibility of lasting epigenetic changes raises concerns for long-duration missions and intergenerational health. Altered sperm epigenomes could potentially impact not only first-generation offspring but also second-generation descendants, making this an area of profound scientific and ethical importance. At terrestrial level, specific sperm epigenomes are known to be associated with male fertility outcomes (*Jenkins et al., 2017*). For example, specific epigenetic sperm phenotypes can predict the probability of successful intrauterine insemination outcomes (*Miller et al., 2023*). Changes in the human sperm epigenome secondary to spaceflight remain to be published.

Finally, the Micro-11 experiment conducted aboard the ISS demonstrated that sperm capacitation, an essential maturation step involving protein modification and motility changes, was impaired significantly in both human and bovine spermatozoa in space compared with Earth (*Mitra et al., 2020*; *Tash et al., 2020*). Key metrics such as curvilinear velocity, progressive motility, and hyperactivity were blunted in microgravity, and the acrosome reaction rate was diminished. Notably, although sperm motility was not lost entirely during storage or transport in space, the decrease in acrosome activation suggests a fundamental compromise in fertility potential. Finally, significant sperm DNA damage was observed in flight compared with ground controls (*Matsumura et al., 2019*), which may be attributed to the time in frozen storage while upon the ISS. However, during the Micro-11 investigation, it was noted that some DNA damage was observed in the acrosome reaction assays, and this is believed to be due to radiation exposure (*Mitra et al., 2020*).

Protective strategies

Looking ahead, a multifaceted approach will be required to protect male reproductive health during space exploration. Physical countermeasures include optimizing spacecraft shielding to block low-LET radiation, and developing advanced materials or configurations capable of reducing HZE particle exposure. Hydrogen-rich materials, for example, offer promise as effective shields, although the mass and engineering challenges remain considerable (*Thibeault et al., 2012*). As such, NASA decided to add 6.2-cm-thick ultra-high-molecular-weight polyethylene panels on the ceiling and rear walls of the crew quarters onboard the ISS. Overall, the panels reduce crewmember exposures of cosmic radiation by 9% and solar flares by 74% (*Broyan et al., 2008*). New space radiation shielding material approaches are currently in development based on hydrogenous composite and polymer-based materials (*Naito et al., 2020*, *2021*; *Toto et al., 2024*).

Biological and pharmacological countermeasures complement physical defences (*McDonald et al., 2024*; *Vasin et al.,2014*). Radiomodulators, such as dietary antioxidants, work prophylactically to bolster cellular resilience against radiation. Radioprotectors such as amifostine, a thiol compound approved by the US Food and Drug Administration, can be administered shortly before exposure to neutralize reactive oxygen species and protect cellular DNA (*Epperly et al., 2011*). Radiomitigators, including corticosteroids, growth factors, and stem cell therapies, act post-exposure to promote tissue recovery and reduce long-term damage (*Montesinos et al., 2021*). Such agents can be employed in any location where radiation levels could exceed safe human exposure limits, such as nuclear power plants, nuclear powered ships and submarines, and radiation therapy facilities.

While spacecraft design aimed at mitigating radiation damage is one line of defence, more permanent countermeasures should be considered when contemplating permanent or temporary settlement on the Moon or on planets. Caves into solid rock, either natural or artificial, may be a resource (*Carrer et al., 2024*). More experimental ideas involve using magnetic or electrostatic fields to deflect radiation that mimic Earth's protective magnetosphere. These systems are still far from practical deployment (*Tripathi, 2016*).

Interestingly, radiation mitigation through hibernation in mammals has shown potential for reducing radiation damage (*Cerri et al., 2016*; *Musacchia et al., 1968*), aligning with both scientific interest and sci-fi cinematic speculation. Looking further ahead, enhancing DNA repair or selecting individuals with natural resilience may, one day, add a biological layer of defence.

FEMALE REPRODUCTIVE BIOLOGY IN SPACE

Female reproductive health is broadly defined as the physical, mental and social well-being related to the reproductive system across the lifespan. This includes puberty, hormonal regulation, menstruation, oogenesis, fertility, pregnancy, contraception, infections, gynaecological malignancies, preventive screening, and psychological well-being. However, these domains cannot be assumed to function identically in space. They must be re-examined systematically in the context of altered gravity, cosmic radiation, and mission-related stressors. The space environment presents a constellation of physiological challenges, and these extrinsic factors interact with the highly regulated and intricate processes of the HPG axis, steroidogenesis, oocyte maturation, folliculogenesis, implantation, early embryonic development, and hormone signalling (*Jain et al., 2023*; *Mathyk et al., 2024b*).

Pregnancy is contraindicated for current agency-sponsored spaceflights, and contraceptive methods are the choice of each individual. Some astronauts also choose methods to reduce menstrual flow while training and/or on their spaceflight missions. Typical methods include continuous combined oral contraceptive use (i.e. skipping the placebo week) or use of a long-acting reversible contraceptive. The latter can be in the form of a subcutaneous hormone-releasing implant or an intrauterine device. These can function for multiple years and also reduce the mass and volume of medication supplies required for a mission (*Jain and Wotring, 2016*). The authors recommended, in the same paper, that,

for those women not using combined oral contraceptives, cautious use of a very low dose (10 μg/day) of oestrogen can aid the preservation of bone mineral density.

Data available from the 40 female astronauts who flew during the Shuttle era indicate that both pregnancy rates and related complications are comparable with those observed in age-matched women on Earth (*Jennings and Baker, 2000*). However, as longer-duration missions become more common for women, it is crucial to understand the multifaceted effects of spaceflight on reproductive endocrinology, hormones, pregnancy and ART beyond Earth. This endeavour requires not only the adaptation of existing well-woman care and protocols (*Hughes–Fulford et al., 2024*), but also the generation of new evidence to guide diagnostic, preventive and therapeutic strategies in extraterrestrial environments.

It is known that cranial radiotherapy can impair the HPG axis, the central regulator of reproductive endocrinology. Radiation-induced pituitary dysfunction and hypopituitarism may be permanent and progressive, with severity influenced by dose, age, sex and specific cell types affected (*VanKoevering et al., 2020*). Similarly, pelvic radiotherapy has been associated with structural and functional changes in reproductive organs. In colorectal cancer survivors, alterations in cervical length, endometrial thickness, and junctional zone visibility have been documented following pelvic irradiation (*Milgrom et al, 2013*). Nonetheless, rare cases of preserved fertility have been reported, including a recent case of natural conception and full-term delivery following brachytherapy for vaginal cancer at a cumulative dose of 24 Gy (*Gerbasi et al., 2023*).

Similar to other organs, post-radiation ovarian damage is dose- and age-dependent. A dose as low as 2 Gy is sufficient to destroy approximately 50% of the human oocyte pool (*Wallace et al., 2003*), and the risk of premature ovarian insufficiency is increased markedly with higher exposures: 97% at 20.3 Gy at birth, 18.4 Gy at age 10 years, and 14.3 Gy at age 30 years (*Wallace et al., 2005*). Currently, there are surgical procedures such as ovarian tissue cryopreservation and transplantation (*Erden and Oktay, 2025*), and uterine transposition for preserving uterine and gonadal function in patients undergoing pelvic radiotherapy on Earth (*Ribeiro et al., 2023*).

In terms of space radiation, in rodents, heavy oxygen and iron ion exposure resulted in a 71% and 57% decline in the follicular pool, respectively (*Mishra et al., 2016*, *2017*), indicating the severe impact of radiation on ovarian tissue. Another study showed the potential risk of ovarian cancer in mouse ovaries irradiated with charged iron particles (*Mishra et al., 2018*).

Radiation exposure during pregnancy adds further concern; the threshold dose for radiation-induced teratogenesis varies depending on the stage of gestation (*Patel et al., 2007*). During early embryogenesis, exposure tends to produce an 'all-or-none' effect, resulting in either no impact or embryo loss. In contrast, at later stages, the type and severity of fetal effects become more dependent on both the timing of exposure and the radiation dose received (*American College of Obstetricians and Gynecologists, 2017*).

Embryological studies

While fertilization itself may not be inherently gravity-dependent, the post-fertilization events of embryogenesis, gastrulation and implantation appear to be more sensitive to changes in gravitational forces. Simulated microgravity experiments in laboratories on Earth using clinostats and rotating wall vessels have suggested delayed development and abnormal cell differentiation in early embryos, while real microgravity experiments aboard satellites and the ISS have shown that mouse embryos can develop to the blastocyst stage, although with slower development patterns and alterations in DNA methylation and gene expression (*Ruden et al., 2018*, *2024*).

Female reproductive systems may be even more sensitive to these challenges. Oogenesis under simulated microgravity appears disrupted, with decreased follicular survival and oocyte structural abnormalities in mouse models (*Zhang et al., 2017*).

Several studies have reported the unopposed effects of microgravity on mouse oocytes and embryos (*Mathyk et al., 2024a*). Different gravitational forces and duration may result in activation of various signalling pathways. In a recent study, hypergravity was shown to alter markers of the mitochondrial unfolded protein response in human oocytes (*Basar et al., 2024*).

In rodents, microgravity disrupts meiotic spindle formation, induces cytoplasmic blebbing, and can impair the oocyte maturation rate. Fertilization of oocytes is possible under simulated microgravity; however, both morula and subsequent blastocyst formation rates (30% under microgravity versus 57% at 1 *g*), as well as the birth rate (5% under microgravity versus 21% at 1 *g*), were significantly lower compared with control groups (*Kojima et al., 2000*; *Wakayama et al., 2009*).

Similarly, spaceflight studies reported a decline in blastocyst formation (34.3% versus 60.2%) compared with ground control groups. This reduction was linked to compromised blastocyst quality, fewer cells, and elevated levels of DNA damage (*Lei et al., 2020*), the likely consequences of microgravity's known interference with cell cycle regulation and progression (*Ho et al., 2021*).

Supporting this, simulated microgravity has been shown to induce expression of stress-activated protein kinase, and cause cell cycle arrest in mouse embryos (*Wang et al., 2009*).

Some of the mechanisms involved in embryonic development may be altered by microgravity through changes in long non-coding RNA, which influence protein transport pathways and cortical cytoskeletal functions, both of which are critical for pronuclear migration (*Feng et al., 2019*).

Early mouse embryogenesis in space has been studied by different missions. *Lei et al. (2018)*, using an automated culturing system and live imaging techniques aboard a Chinese TZ-1 space vehicle, suggested a detrimental role on three-dimensional growth, proliferation and differentiation of mouse embryo stem cells. The same authors also cultured mouse embryos for 64 h in orbit within a mini-incubator in China's SJ-10 recoverable satellite, where an average dose of radiation of approximately 0.15 mGy/day was recorded. This exposure led to a decreased blastocyst formation rate, and was associated with significant DNA damage and methylation profile abnormalities (*Lei et al., 2018*).

In contrast, *Wakayama et al. (2023)* used a manually operated embryo thawing and

culturing device on the ISS to thaw frozen embryos, and cultured them in microgravity and 1 *g* artificial microgravity conditions. Despite technical hurdles, the study showed that some embryos still progressed to the blastocyst stage under different gravitational forces. While the automated approach of *Lei et al. (2018)* minimized the risk of contamination, it limited in-flight troubleshooting. There are also additional differences between the studies in terms of experimental setting and embryo handling: while the SJ-10 satellite mission launched fresh two-cell stage embryos, the ISS mission used frozen embryos that were thawed in space. Moreover, the total radiation exposure varied between the two missions.

Both male and female reproductive health and embryology in space constitute a complex, multisystem challenge at the intersection of endocrinology, developmental biology, and radiation biology, requiring coordinated interdisciplinary international collaboration informed by advances in ART.

CONTEMPORARY IVF AND ITS EMERGING RELEVANCE TO SPACE EXPLORATION

ART has undergone a remarkable evolution, from treating tubal factor infertility in a small UK hospital 50 years ago, to a global, multifaceted discipline addressing a wide array of reproductive challenges. Today's ART includes male infertility, genetic conditions, fertility preservation, donor gametes, and surrogacy (*Niederberger et al., 2018*), and supports diverse family structures. This evolution parallels transformations in the space industry, where diverse, non-traditional crews, including tourists, are going into space and are increasingly likely to contemplate reproductive repercussions as a core health consideration for future space missions.

Since its origins in basic cell culture techniques, embryology has evolved into a highly regulated discipline characterized by extensive training requirements, rigorous quality control, and close interdisciplinary collaboration (*Campbell et al., 2022*; *Palmer et al., 2019*; *Rienzi et al., 2021*). Emerging technologies have the possibility to redefine embryological practice, potentially offering operator-independent solutions essential for both Earth-based laboratories and space environments.

AI, AUTOMATION, MICROFLUIDICS AND NON-INVASIVE TECHNOLOGIES

AI offers potential in assisted reproduction: advances in AI promise to optimize clinical workflows; alleviate staffing shortages; and enhance decision-making in critical areas such as embryo selection, oocyte assessment and sperm analysis. AI is poised to influence every step of the IVF process (*Cohen et al., 2025*), supporting a more personalized and scalable framework that could be particularly valuable in remote or space-based environments. By enabling decision-assist systems, AI may also reduce dependence on highly specialized personnel, an important consideration for space missions where trained embryologists may not be present. AI-based solutions have been used increasingly in space biology to automate experiment control, analyse omics data, and monitor biological responses to microgravity and radiation. Applications include onboard image analysis, environmental regulation, and post-flight genomic profiling, offering new insights into the physiological and reproductive effects of spaceflight (*Li et al., 2023*; *Sanders et al., 2021*).

In addition to AI, emerging non-invasive technologies, such as non-invasive preimplantation genetic testing (PGT) and metabolomic profiling, are expected to reshape future embryological practices. The integration of these approaches could further personalize IVF, reducing the need for invasive, operator-dependent techniques (*Munné et al., 2025*). This shift away from artisanal procedures towards standardized, automated methods (*Rienzi et al., 2021*) aligns with the operational demands of space-based reproductive research and practice.

While 'lab-on-a-chip' systems have been discussed in IVF settings for years speculating improved embryo culture, gamete handling, and cryopreservation, enhancing physiological relevance (*Palmer, 2013*; *Swain et al., 2013*; *Weng, 2019*), the media-savvy phrase was coined to describe the merger of microfluidics and chip fabrication, capturing the idea of fitting one or multiple laboratory processes on to a single microscale platform. Chip designs are already central to biological experiments on the ISS, in programmes such as Genes in Space and Tissue Chips in Space (*Mu et al., 2022*; *Yang et al., 2020*; *Yau et al., 2023*), highlighting their robustness under microgravity. Their ability to minimize fluid use, automate precise steps, and enable real-time monitoring could make them ideal for reproductive work in space.

Automation is now entering the IVF laboratory: vitrification systems such as Gavi1 (*Dal Canto et al., 2019*) and microfluidic cryopreservation devices (*Zhan et al., 2025*) standardize embryo freezing; cartesian sperm processing robots (*Milan et al., 2024*) eliminate manual variability; and dish preparation platforms are being validated for successful embryo culture (*Lattin et al., 2024*; *Zhu et al., 2023*) using cartesian or rotary robotic platforms. These systems reduce operator dependency, which is a major benefit for space missions staffed by non-specialist crew.

Intracytoplasmic sperm injection (ICSI), the most delicate and skilled manual task, now presents the possibility to be automated. Early efforts by Sun's group (*Liu et al., 2009*, *2010a*, *2010b*; *Lu et al., 2011*) laid the groundwork for robotic ICSI, incorporating force sensing, image-guided navigation, and automated sperm immobilization. A partially automated ICSI rig, operated by engineers, showed proficiency in injecting animal and human oocytes, resulting in the birth of the first babies conceived through automated ICSI (*Costa-Borges et al., 2023*), while *Mendizabal et al. (2025)* used a remote-operated ICSI system to achieve the first live birth through remote micromanipulation, marking a significant milestone in the automation and standardization of fertility laboratories, and with comparable success in terms of conventional oocyte survival, fertilization and blastocyst formation rates. Clinical trials being conducted by Conceivable Life Sciences suggest that these fully automated platforms may be viable alternatives to traditional embryology (NCT06074835).

CRYOSTORAGE IN SPACE

Long-term space exploration may involve transport of Earth-derived gametes and embryos to other worlds with altered gravity that may offer advantages to performing cryopreservation in space.

Current cryopreservation techniques, while highly effective for storing reproductive cells and tissues on Earth, present notable challenges in space environments. Issues related to cryopreservation have been discussed elsewhere (*Chaplia et al., 2024*) but, briefly, liquid nitrogen, typically used to maintain storage at −196°C, is logistically and technically infeasible for long-term space missions due to safety hazards, mass constraints, and the complexity of maintaining cryogenic systems in microgravity. Although space is naturally cold (average temperature −270°C), the absence of an atmosphere results in extreme and rapid thermal fluctuations, from -157°C in Earth's shadow to +121°C in direct sunlight during a 90-min orbit, meaning that passive thermal regulation (purely by the cold space environment alone) is unreliable. Thermal transfer in space occurs via radiation alone, not conduction or convection, complicating precise temperature control without specialized shielding and systems.

While the ISS uses freezers such as the Minus Eighty-Degree Laboratory Freezer and General Laboratory Active Cryogenic ISS Experiment Refrigerator (GLACIER), passive storage in deep space remains elusive (*Ferl et al., 2011*). GLACIER was designed to support experiments that require temperatures between -95°C and +4°C for launch/return and -160°C to +4° C on the ISS.

Ambient temperature alternatives, such as freeze-drying (lyophilization), show promise. Freeze-dried sperm has yielded viable embryos and live births in mice, even after years in orbit (*Alexandrova et al., 2020*; *Wakayama et al., 2021*). Female gamete preservation remains less developed but is advancing, with encouraging data on the in-vitro maturation of porcine oocytes freeze-dried at the germinal vesical stage under terrestrial laboratory conditions (*Dang−Nguyen et al., 2018*).

Dehydration-based biobanking, especially with radiation shielding, may offer the best solution to a lightweight, energy-efficient solution for genetic and reproductive material.

In a review of alternative methods of ambient storage, *Comizzoli et al. (2022)* emphasized that further research is essential to refine these technologies, assess species-specific requirements, and ensure both short- and long-term genetic and developmental safety. Ongoing terrestrial research on preservation at ambient temperature continues to lay the groundwork for extraterrestrial applications, including the long-term biobanking of reproductive material for space-based conservation efforts.

Various pieces of apparatus employed in space and used in biological experiments on the ISS are comparable to equipment found in an IVF laboratory on Earth, and are illustrated in Figures 3–6.

GENETIC TESTING AND EDITING

The very success of IVF and the culture of embryos in the laboratory created the possibility of screening and manipulating embryos while they remain in culture. The pioneer Sir Bob Edwards first conceived the idea of PGT in the mid-1960s while working with rabbit embryos, and demonstrated the feasibility of sexing rabbit blastocysts (*Edwards, 1965*; *Gardner and Edwards, 1968*). The authors explicitly noted the potential clinical applications of such work, including identifying autosomal-inherited diseases. It would take several more decades before technology advanced sufficiently to bring their visionary concept of PGT into clinical practice (*Gardner and Johnson, 2011*).

Since the first successful application of PGT through embryo biopsy in 1990 (*Handyside et al., 1990*), genetic testing in

FIGURE 3 National Aeronautics and Space Administration (NASA) astronaut and Expedition 73 Flight Engineer Jonny Kim conducts research operations inside the Destiny laboratory module's Microgravity Life Science Glovebox aboard the International Space Station (ISS). View also showing the Minus Eighty Laboratory Freezer for ISS apparatus. Courtesy of NASA, 2025.

FIGURE 4 View of Expedition 15 astronaut, Sunita Williams, inserting biological samples into the Minus Eighty Laboratory Freezer for the International Space Station during spaceflight. Courtesy of National Aeronautics and Space Administration, 2007.

IVF has advanced significantly in parallel with developments in clinical embryology. These improvements have been driven by the introduction of high-resolution techniques such as next-generation sequencing and single nucleotide polymorphism arrays (ESHRE PGT *Consortium Steering Committee, 2020*). Today, PGT for aneuploidy is considered the most objective and reliable method for assessing embryo ploidy and detecting chromosomal abnormalities, with almost one-third of IVF/ICSI cycles now incorporating PGT (*Bacal et al., 2025*; *Theobald et al., 2020*). However, the

FIGURE 5 National Aeronautics and Space Administration (NASA) astronauts Tracy Caldwell Dyson (right) and Shannon Walker prepare to insert biological samples in a dewar tray in the Minus Eighty Laboratory Freezer in the Kibo Laboratory of the International Space Station. Courtesy of NASA, 2010.

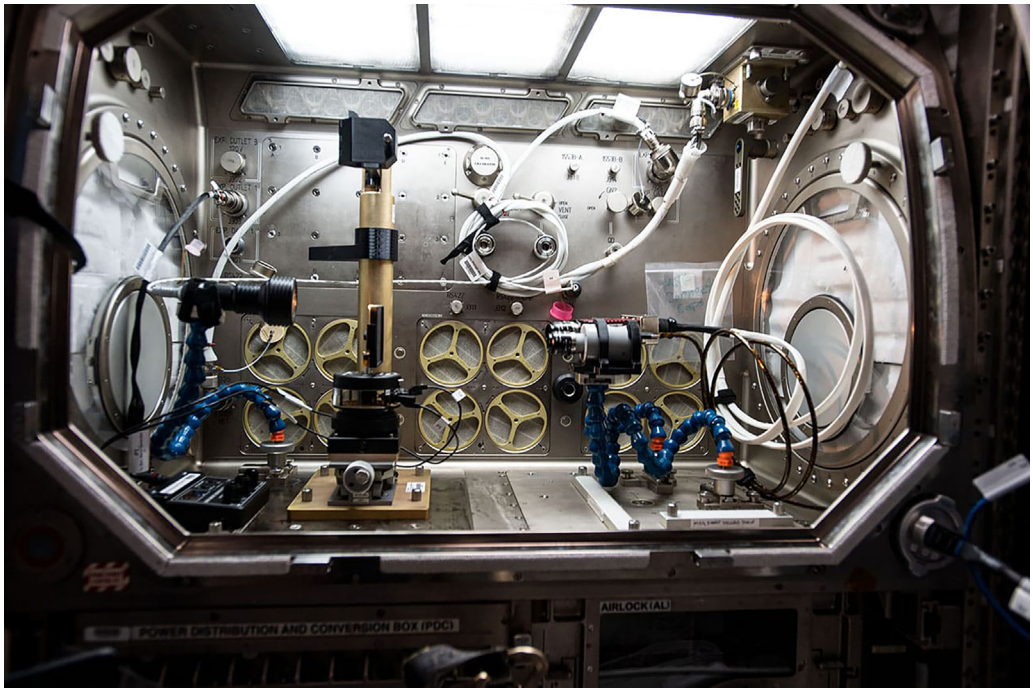

FIGURE 6 Microgravity Experiment Research Locker/Incubator in its open position. This provides a thermally controlled environment for scientific experiments, and is capable of providing temperatures between -20°C and +48.5°C. Courtesy of National Aeronautics and Space Administration, 2017.

invasive nature, high cost, and persistent concerns about biopsy-related risks and mosaicism have driven growing interest in non-invasive, AI-assisted alternatives (*Chavez-Badiola et al., 2020*; *Munné et al., 2025*). These emerging techniques are particularly well suited to the constraints of spaceflight, where laboratory capabilities and personnel are limited.

Importantly, genetic screening in IVF is part of a broader trajectory in reproductive genetics. The same technologies are paving the way for more advanced interventions, including gene editing.

Clustered regularly interspaced short palindromic repeats (CRISPR) stands out as one of the most transformative examples. While screening enables the selection of embryos free of specific mutations, CRISPR offers the ability to modify genetic material directly, shifting the paradigm from selection to correction. While that opens enormous possibilities, it also raises major ethical concerns, especially when it comes to editing embryos. The IVF community remembers the global backlash that followed the claim of the first gene-edited babies by Dr. Jiankui He in China (*Marchione, 2018*; *Regalado, 2018*). That moment sparked a wave of concern and a renewed call for clear regulatory frameworks and safety standards (*O'Neill et al., 2019*).

However, in other high-risk contexts, such as cancer treatment and space exploration, CRISPR is pushing boundaries in ways that are more widely accepted. It is already revolutionizing therapies such as chimeric antigen receptor T-cell treatment in oncology (*Tao et al., 2024*). Now, some scientists are asking: could gene editing make astronauts more resilient to the dangers of space? Radiation, muscle loss, and bone degeneration are serious challenges in long-duration spaceflight. As certain genes may make some people more susceptible than others, there is growing interest in the idea of switching specific genes on or off to enhance human endurance beyond Earth (*Mason, 2023*; *Rutter et al., 2024a*, *2024b*).

Recent advances in CRISPR and catalytically inactive Cas9 (dCas9) technologies, including a personalized in-vivo gene-editing therapy for a rare metabolic disease (*Musunuru et al., 2025*), a near-infra-red light-activatable split (d) Cas9 system (*Zhang et al., 2025*), and a comprehensive review of dCas9-based regulatory capabilities (*Cai et al., 2023*), suggest compelling opportunities for deep-space missions.

These systems could enable compact, 'hardware-light' gene regulation in spacecraft, allowing rapid, customizable responses to molecular damage such as radiation-induced mutations, while the non-cutting, programmable nature of dCas9 also suits the caution required in space medicine. A future spacecraft medical bay might thus contain a minimal gene-regulation toolkit for preventive and emergency genomic or epigenomic interventions. However, challenges in delivery, off-target safety, and radiation or microgravity effects on editing fidelity remain. Such prospects are promising but raise ethical concerns about heritable modification, long debated in space medicine and bioethics (*Szocik, 2020*).

ETHICAL CONSIDERATIONS

As space activities expand and commercial spaceflight increases, there is a need to create clear standards and establish ethical guidelines (*Rahimzadeh et al., 2023*). An advantage of national space agencies is that they are centralized and collaborative, so it is both imperative and relatively easy to establish a shared set of behavioural and medical standards (*Grigoriev et al., 2009*). In commercial space travel, clear policies are still emerging; there are no widely accepted guidelines regarding matters such as human reproduction in space. National space agencies have established bioethical review boards, oversight bodies, and international collaboration through treaties (*Soroka and Kurkova, 2019*).

Commercial entities remain largely self-regulated, and the competitive nature of the commercial space industry incentivizes rapid advancement over cautious deliberation. Without binding international or interindustry ethical standards for either research on reproduction or human reproductive activity, the health of a gestating parent and their fetus may be put at risk (*Seylani et al., 2024*).

The industry must confront several general questions with ethical implications. Should they monitor pregnancy status in employees? In commercial travellers and tourists? Should they require full medical reports, including any comorbidities? Should informed consent forms include estimations of altered long-term risks for reproductive success, and for possible damage to a fetus? Is there a role for partner consent? Should potential space travellers undergo genetic screening, and how can equity of access be ensured, especially if talking about reproductive activity in space?

Incentives to advance space exploration quickly may lead to companies carrying out reproductive research or allowing space-based conception and gestation without sufficient medical, ethical or legal preparation, compromising ethical principles such as informed consent, safety prioritization, and transparency. In the absence of regulation, critical concerns such as consent under constrained conditions, the rights of future children born in space, and protection from coercion or exploitation remain undeveloped.

Unlike governmental agencies, commercial space companies are beholden to investors, market forces, and branding pressures — conditions that give rise to a distinct set of ethical challenges (*Langston, 2017*). The drive for profit may, at times, conflict with safety; for example, the need to demonstrate innovation or stand out in the market could incentivize premature attempts at in-space reproduction to gain media attention or attract funding, even when safety data remain incomplete. Safeguards may also be weaker: commercial companies may be less inclined to regulate the actions of paying customers, or to monitor their medical conditions and personal data consistently.

Transparency poses another challenge. As private companies often treat reproductive and medical data as proprietary information, they may keep it confidential to protect intellectual property, potentially hindering collaborative efforts to establish best practices and ensure safety. Legal complexities further compound the issue, as companies can choose to operate under flags of convenience or in jurisdictions with limited bioethical oversight, making regulatory enforcement difficult.

However, commercial entities are also more vulnerable to lawsuits and other legal repercussions than national space agencies. This liability creates an incentive to comply with established ethical and safety standards. A single damaging lawsuit could have a chilling effect on the entire commercial space sector. It is therefore essential to harness this tension between risk and accountability to encourage the development and enforcement of robust industry standards that serve both public interest and the long-term viability of commercial space endeavours.

Human spaceflight is undergoing a major transition as commercial companies and private individuals participate increasingly in missions previously led solely by governments. Within the USA, the Federal Aviation Administration (FAA) is responsible for protecting public safety on the ground and within the National Airspace System by licensing commercial space launches and re-entries, verifying the proper operation of human-carrying vehicles, overseeing crew qualifications and training, and conducting safety inspections. However, Congress currently restricts the FAA from regulating the safety of individuals onboard spacecraft — a 'moratorium' in place since 2004 and extended several times. This restriction will expire on 1 January 2028. To prepare for potential future safety regulations, the FAA created the Space Flight Aerospace Rulemaking Committee (SpARC) in April 2023 to work with industry partners. SpARC delivered its final safety-focused report to the FAA on 4 April 2025, and the FAA plans to release it publicly soon (*FAA, 2025*; *Lindbergh, 2025*).

DURATION-SPECIFIC ETHICAL CONCERNS

The nature of ethical challenges varies substantially depending on the duration and type of space travel. In short-duration spaceflights (e.g. suborbital tourist and commercial spaceflight), direct reproductive activity is unlikely. However, incidental conception prior to spaceflight, or shortly thereafter, may pose unanticipated risks if the gestational parent is unaware of the pregnancy during the spaceflight. Ethical concerns here involve disclosure, screening protocols, and the rights of participants to make informed decisions about fertility and health risks in these ventures.

In the context of long-duration spaceflights (including months-long orbital missions or 6-month Mars transits), space radiation, microgravity, isolation and constrained medical support introduce significant risk. The environment is not optimized for the complex physiological processes of conception or gestation. Ethical questions multiply: should conception be regulated pre- or during spaceflight? What protections must be in place? Should long-term commercial spaceflights encourage pre-spaceflight banking of gametes or embryos? Who bears responsibility for adverse outcomes? If medical abortion or emergency delivery is needed, are these even possible on a spacecraft?

The temptation to pursue reproduction in semi-permanent settlements (e.g. the Moon or Mars) for colonization may be stronger, but planetary conditions, extreme radiation, altered gravity, toxic dust, and limited medical facilities create substantial health risks (*Szocik, 2018*). Proper facilities to care for medically fragile neonates is also a concern. Ethical issues include the long-term rights of children born off-Earth, the autonomy of settlers under contractual obligations, whether and when it is morally permissible to attempt such experimental births, and the implications of rearing offspring in an environment that might make their bodies ill-suited to ever return to Earth's gravity.

Much of the discussion on space reproduction focuses on gestation, but male fertility also warrants ethical scrutiny. This raises two primary ethical issues. Firstly, should men be allowed or encouraged to bank spermatozoa before spaceflight? Should conception be attempted with potentially damaged spermatozoa in space, risking genetic abnormalities in offspring? Secondly, current research on male fertility in space is reported to lag behind that of female astronauts (*Ahrari et al., 2022*), raising gender bias and equality concerns. This

disparity not only weakens understanding of reproduction, but introduces gender bias into policy development. Ethical reproductive planning requires investment in understanding the reproductive health of all genders equally.

Perhaps the most daunting ethical territory involves gestation and birth in space. As noted earlier, numerous terrestrial studies and animal models suggest that microgravity may disturb placentation (e.g. *Ronca and Alberts, 2000*), and that space radiation damages embryonic and fetal DNA (e.g. *Moreno-Villanueva et al., 2017*). Birth in low gravity may be physically complicated or unmanageable without surgical facilities, and may result in developmental abnormalities in newborns due to altered gravitational loading on bones, muscles and organ systems (*Meigal, 2012*). Labour and pain management during labour and delivery are other considerations. Another life-treating complication pertaining to pregnancy is antepartum and postpartum haemorrhage that may require blood transfusion, and medical and surgical intervention (*American College of Obstetricians and Gynecologists, 2019*).

These risks raise profound ethical questions: should we allow gestation or childbirth in space at all? If so, under what safeguards? How much research, and what levels of knowledge, are sufficient to allow reproduction in space? Who is responsible when there are complications or need for unavailable special equipment or services? What rights and protections exist for the unborn or newborn child?

These limitations mean that, for the foreseeable future, reproductive attempts in space would lack the fundamental environmental conditions required for ethical pregnancy and parenting support. Proceeding without mitigation would violate core medical ethics principles safeguarding the safety and well-being of patients and their offspring, reminding us 'primum non nocere'.

ETHICAL CONSIDERATIONS IN HUMAN SUBJECTS AND EMBRYO RESEARCH

On Earth, nearly five decades of IVF have not been without controversy. Consent in IVF, especially regarding embryo donation for research, has prompted ongoing ethical scrutiny. Key safeguards aim to ensure that consent is informed, voluntary and free from coercion. Crucially, safeguards stress the ethical separation between the decision to donate and the research itself, reducing the risk of undue influence (*Pennings, 2007*).

ART remains deeply influenced by cultural, religious and ethical debates. These tensions have led to considerable legal variation worldwide, resulting in a patchwork of fertility regulations. Many patients pursue cross-border reproductive care to access treatments permitted in more permissive jurisdictions, highlighting how national borders often fail to contain reproductive decision-making (*Van Hoof and Pennings, 2013*). So how can we expect to regulate these issues in the vast, unregulated expanse of space?

In the USA, renewed debates over the personhood and legal status of preimplantation embryos reflect the continuing divisiveness of reproductive ethics which varies by state (*Ginod et al., 2024*). As human efforts turn towards long-term space habitation and reproduction beyond Earth, these unresolved issues are likely to grow more complex in off-world settings.

In the UK, the concept of the 'welfare of the child' adds another layer of ethical and legal responsibility. Set out in the *Human Fertilisation and Embryology Act (1990)*, this principle requires clinics to assess the prospective child's future well-being, including the emotional and social capacity of parents to provide a stable environment. It stands as a unique form of anticipatory protection within reproductive medicine.

What legal, ethical or cultural framework will govern conception beyond Earth? Will planetary borders echo the fragmented policies of Earth, or will entirely new standards emerge? As we venture into space, the unresolved tensions of terrestrial reproduction are unlikely to stay behind.

Research on human reproduction in space necessarily involves living human subjects, many of whom will be in vulnerable positions due to isolation, contractual employment, or corporate oversight. Some ethical standards differ in the responsibilities of investigators to subjects and clinicians to patients, and those roles can be confused in space travel.

Ensuring true informed consent becomes deeply problematic in environments where psychological stress is high and individuals may feel obligated to meet contractors' expectations, making voluntary and fully informed decision-making uncertain. Within such contexts, reproduction might not be entirely free from coercion; companies invested in long-term colonization goals could subtly or overtly incentivize reproduction, placing participants under implicit pressure to comply.

When conception in space is treated primarily as a research opportunity rather than a form of medical care, it opens the door to non-therapeutic experimentation, raising serious ethical concerns about exposing gestational parents and potential offspring to unknown risks for the sake of scientific advancement. Compounding these issues are the rights of future children conceived or born in space, who cannot provide consent and may live with lasting health effects or identity challenges shaped by the conditions of their birth and the intentions behind it.

Research ethics guidelines require that studies involving human reproduction in extreme environments be designed with the utmost care, undergo rigorous review, and provide the strongest possible protections to participants. However, few mechanisms currently exist to ensure this in the private space sector (*Rahimzadeh et al., 2023*).

LUNAR AND EXTRAPLANETARY RESEARCH: PARTIAL GRAVITY EXPERIMENTS AND FUTURE DIRECTIONS

Reproduction studies on the Moon remain a future goal rather than an active field. Most current lunar and Martian biological research focuses on plants and microbial life as stepping stones to understanding life's limits and adaptability (*De Micco et al., 2023*). However, as infrastructure grows through programmes such as Artemis (*Creech et al., 2022*) and the *Commercial Lunar Payload Services (2025)*, it is expected that a more robust research programme will take place that also includes reproduction and developmental biology as recommended by the *National Academies of Sciences, Engineering and Medicine (2023)*.

The path to the US-led Artemis initiative has been long and not without setbacks (*Vidal, 2025*), highlighted by domestic US

political and budgetary instability that threatens progress, and in competition with rival lunar development programmes such as the China–Russia International Lunar Research Station (*Freeman, 2025*).

The Moon remains the most immediate and practical testing ground for understanding how life functions in reduced gravity. It could act as a natural springboard for controlled, ethical and carefully designed reproductive studies that could, one day, make sustained life on Mars possible (*Garshrek, 1994*).

Partial gravity environments such as those on the Moon (0.16 *g*) and Mars (0.38 *g*) introduce biological stresses that differ fundamentally from microgravity aboard spacecraft or stations. These environments challenge how cells grow, differentiate and reproduce factors essential for any sustained human or biological presence beyond Earth. Presently, very few data are available regarding physiology in partial or hypergravity environments. Therefore, studies based on gravity as a continuum (GAAC) should be leveraged by: utilizing model organisms to focus on the gravitational effects on physiological systems, needed by exploration-class missions to the Moon, Mars and beyond; pursuing dose responses and mechanisms of adaptation to altered gravity; considering artificial gravity as a cross-cutting countermeasure; and continuing to partner with international entities to realize GAAC studies (*Alwood et al., 2021*).

As humanity prepares again to go beyond LEO, the NASA Space Biology programme is advancing its research priorities towards work that will enable organisms to thrive in deep space. The Space Biology programme has selected 11 space biology projects under its ROSES-2022 'Space Biology Research Studies', aimed explicitly at understanding biological responses relevant for future lunar exploration and, in particular, how exposure to lunar dust/regolith impact both plant and animal systems (*Cockell et al., 2024*; *NASA Science Editorial Team, 2023*). JAXA has already designed small-animal habitat systems that could support these types of biological investigations in orbit and on lunar bases (*NASA Space Biology Science Plan, 2025*).

ESA's Strategy for Science at the Moon similarly outlines opportunities for life science payloads and biological experiments that would support human presence and sustainability on the lunar surface (*European Space Agency, 2019*, *2025*).

Although no embryo or gamete data exist to date under lunar or Martian gravity, methods to simulate these conditions are advancing. Centrifuges, random positioning machines, and combined environment simulators are being used to model how partial gravity affects early cellular and developmental processes (*Manzano et al., 2018*; *Okamura et al., 2024*).

As research in this area is still at such an early stage, it is essential first to establish the fundamentals understanding basic cell behaviour, fertilization dynamics, and developmental viability under partial gravity before considering more speculative or technologically extreme possibilities.

Ectogenesis, such as artificial wombs, shows promise in addressing the medical challenges of preterm birth (*Bird, 2017*; *Ikeda et al., 2024*), and ex-utero culture systems (*Aguilera-Castrejon, 2021*) advance understanding of implantation and early embryogenesis in human and stem-cell-based systems; however, this topic lies outside the scope of the present review.

Likewise, the concept of seed ships or generation ships (vessels carrying frozen gametes and embryos) — first proposed by rocket engineer Robert H. Goddard, one of the forefathers of modern rocketry and the namesake of NASA's Goddard Space Flight Center — remains pure speculation. In his 1918 essay 'The Ultimate Migration,' (*Goddard et al., 1966*), Goddard envisioned an interstellar ark departing the solar system in the distant future, long after the Sun had reached the end of its life cycle. While such concepts highlight the far-reaching possibilities of human expansion beyond Earth, they extend beyond the scope of this review, which focuses on current understanding and near-term research initiatives.

The present focus should remain on achievable, ethically sound, and scientifically grounded steps mentioned in this review that deepen understanding of how life begins and develops beyond Earth.

CONCLUSION AND RECOMMENDATIONS

Space is toxic to terrestrial life. It is an inherently hostile environment for terrestrial biology to thrive. The microgravity, cosmic radiation, circadian disruption, pressure differentials, and extreme temperatures found in orbit or beyond present unique and multifactorial stressors to the human body. Often overshadowed by sensationalized or speculative portrayals, the topic of reproduction in space nonetheless demands serious attention. Beneath the intrigue lie pressing concerns related to sexual activity in space, including its implications for behavioural health, crew dynamics, and the risks associated with pregnancy and embryogenesis — areas marked by significant unknowns and potential complications (*Bacal, 2009*). However, there is potential for protection, and countermeasures should be studied implicitly.

ART is evolving rapidly into a highly technological field, integrating AI, automation and microengineering. These innovations not only address terrestrial challenges, but also align IVF with the environmental constraints of spaceflight. As we move towards long-duration missions and off-Earth colonization, reproductive autonomy and continuity become vital. IVF, once a purely manual task, is now poised to play a critical role in the future of human space exploration.

ART has evolved into a highly sophisticated technology, now encompassing a broad and expanding range of applications in family-building, reaching more people than ever before. Similarly, space exploration has transformed from a field once dominated by elite military test pilots to one characterized by growing diversity, private enterprise, and extended mission durations. These parallel advancements now converge at a critical frontier: understanding human fertility and reproduction in space.

Both IVF and early spaceflight were marked by considerable technical uncertainty. The parallels between the tightly controlled environments required for successful IVF and the extreme constraints imposed by space environments are particularly striking. As missions extend in duration and humanity moves towards establishing permanent off-world habitats, such as lunar bases or Mars expeditions, concerns about fertility and reproductive health are no longer hypothetical but pressing.

The ethical implications of using space-conceived or space-exposed gametes warrant scrutiny. Research aimed at protecting astronaut fertility also holds promise for Earth-based applications; advances in radioprotective agents could benefit radiation workers, military personnel, cancer patients, and populations exposed to environmental hazards.

Although short-term missions appear to have minimal impact on fertility, the long-term effects of radiation, microgravity, hormonal disruption, and epigenetic change remain unclear. To protect reproductive health, space agencies should implement advanced shielding, pharmacological countermeasures, and pre-flight fertility options, and discuss gamete cryopreservation.

Pre-mission, male astronauts should be screened for oligozoospermia, asthenozoospermia, teratozoospermia, varicoceles and hormonal imbalances (*World Health Organization, 2021*) to provide both a fertility baseline and early intervention opportunities.

Technological advances in IVF, particularly AI, offer promising tools for assessing sperm quality at the single-cell level (*Goss et al., 2024*; *Mendizabal-Ruiz et al., 2022*). AI-driven analysis, already in use in ART laboratories (*Mendizabal-Ruiz et al., 2024*), may detect subtle indicators of DNA damage, oxidative stress, or epigenetic changes, enabling precise monitoring of reproductive health before and after spaceflight.

The increasing participation of commercial actors in human spaceflight introduces new challenges. Unlike

Recommendations:

To responsibly confront these ethical challenges and prepare for the reality of human reproduction in space, the following recommendations should be adopted:

Establish an International Framework

Create a binding international treaty or governance body that regulates reproductive research and activity in space, with mandatory ethical protocols for all spacefaring entities, including commercial space companies.

Implement Precautionary Policies

Apply the precautionary principle: prohibit conception, gestation, or childbirth in space until evidence of safety is established through ground-based and non-human studies, and then through carefully designed and ethically scrutinized space-based research.

Conduct Extensive Ground-Based Research Prior to Space-Based

Validate every stage of the reproductive process—fertility, conception, implantation, gestation, birth, and early development—in analog earth environments before attempting it in space.

Prioritize Transparent, Collaborative, Ethical Research

Require companies to register all research protocols involving human reproduction, share anonymized findings in public databases, and collaborate with international ethics bodies.

Prioritize Safety of Gestational Parent and Child Over Commercial Interests

Enshrine in law the principle that individual well-being supersedes corporate or mission objectives. Protect against pressure or incentivization to reproduce in space.

Establish a Collective Industry Ethics Review Board

Form a joint ethics board across the space industry to evaluate all reproductive-related research, composed of independent bioethicists, physicians, former astronauts, and child rights advocates.

FIGURE 7 Recommendations for the future of reproductive biomedicine in space.

traditional astronaut programmes, which impose stringent selection and medical oversight, the inclusion of non-professional astronauts currently lacks standardized reproductive health guidelines. There is no unified framework addressing fertility preservation, hormonal regulation, or the management of unintended or incidental pregnancy in space.

This review has focused specifically on the hazards that spaceflight poses to fertility, rather than the broader and still largely speculative question of human reproduction in extraterrestrial environments.

As we enter a new era of space exploration, defined by longer missions, broader participation, and eventual human settlement beyond Earth, the question is not simply whether reproduction can occur in space, but whether human fertility can be preserved, protected and comprehensively understood in an environment fundamentally different from that in which our species evolved.

In conclusion, IVF and human spaceflight have charted distinct but increasingly intersecting paths. IVF is now a standard component of clinical practice, and has become increasingly commercial with large networks of clinics taking control. Likewise, spaceflight has moved from national programmes to a new era of commercial exploration. However, both remain reliant on tightly controlled environments: IVF within the laboratory, and human biology within the life-support systems required for space. Where these domains converge, particularly around fertility and reproduction in space, a critical gap in knowledge becomes evident.

Terrestrial reproductive technologies continue to advance into a data-intensive, semi-automated field, with tools such as microfluidics, non-invasive diagnostics, and AI-guided decision-making practices. These innovations may eventually be adaptable to space-based reproduction, although major technical, physiological and ethical challenges remain. The traditional role of the embryologist may ultimately shift towards automated, closed-loop systems capable of functioning in extraterrestrial environments.

Despite mounting evidence, reproductive health considerations remain largely absent from formal spaceflight policy. While NASA's REACH framework (*Maks et al., 2002*) has acknowledged the general risks, detailed reproductive planning, especially for long-duration and commercial missions, is lacking. As non-professional and untrained individuals are accessing space increasingly, opportunities to collect essential biological data risk being overlooked.

To confront these ethical challenges responsibly and prepare for the reality of human reproduction in space, there is a need to establish guidelines to form an International Framework and Collective Industry Ethics Review Board (**FIGURE 7**). To accelerate progress, responsible dedication into evaluating all reproduction-related research is needed to ensure comprehensive oversight.

At the same time, valuable lessons can be drawn from Earth-based contexts, such as radiation exposure following the Chernobyl disaster or in cancer patients undergoing radiotherapy, which may inform protective strategies for astronauts. Advancing this work requires close cross-disciplinary collaboration among experts in space medicine, oncology, reproductive biology, and radiobiology to develop and implement effective countermeasures. The question of whether humanity should reproduce beyond Earth is no longer hypothetical — it is a pressing ethical frontier. In the context of commercial spaceflight, where ambition often outpaces caution, the stakes are higher than ever. Without robust frameworks, rigorous research, and a deeply human commitment to ethical principles, there is a risk of exporting not just life but injustice, exploitation and harm into the cosmos. To be worthy of the stars, we must earn our place, not only through technological prowess, but through ethical wisdom.

ACKNOWLEDGEMENTS

The authors wish to thank Daniela Wild BSc, MSc for designing and adapting the tables and figures.

DECLARATION OF GENERATIVE AI IN WRITING PROCESS

During the preparation of this manuscript, some paragraphs were remodelled using ChatGPT-4o for improved clarity. Additionally, ChatGPT-4o was used to assist with reducing the word count. After using this tool, the authors reviewed and edited the content repeatedly as needed, and take full responsibility for the content of the publication.

REFERENCES

Afshinnekoo, E., Scott, R.T., MacKay, M.J., Pariset, E., Cekanaviciute, E., Barker, R., Gilroy, S., Hassane, D., Smith, S.M., Zwart, S.R., Nelman-Gonzalez, M., 2020. Fundamental biological features of spaceflight: advancing the field to enable deep-space exploration. Cell 183, 1162–1184.

Aguilera-Castrejon, A., Oldak, B., Shani, T., Ghanem, N., Itzkovich, C., Slomovich, S., Tarazi, S., Bayerl, J., Chugaeva, V., Ayyash, M., Ashouokhi, S., 2021. Ex utero mouse embryogenesis from pre-gastrulation to late organogenesis. Nature 593 (7857), 119–124.

Ahrari, K., Omolaoye, T.S., Goswami, N., Alsuwaidi, H., du Plessis, S.S., 2022. Effects of space flight on sperm function and integrity: a systematic review. Front Physiol 13, 904375.

Aitken, R.J., 2024. Paternal age, de novo mutations, and offspring health? New directions for an ageing problem. Hum Reprod 39, 2645–2654.

Alexandrova, S., Arav, A., Hood, K., Natan, Y., Zhang, J.J., Pasquale, P., 2020. Successful production of normal euploid human blastocysts derived from sperm after partial freeze drying, rehydration and ICSI: towards developing a novel method for safe storage of biological samples. Fertil Steril 114, e37–e38.

Alwood, J., Ronca, A., Iyer, J., Mhatre, S., Shirazi, Y., Fuller, C., 2021. Gravity as a Continuum. NASA Ames Research Center. Space Biosciences Division. https://science.nasa.gov/wpcontent/uploads/2023/05/20_e8f918e24d9db80a62e766e84e31ab06_GravityAsAContinuum_20211031___v5.pdf [Assessed 15/11/2025].

American College of Obstetricians and Gynaecologists, 2017. Guidelines for diagnostic imaging during pregnancy and lactation. ACOG, Washington, DC. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/10/guidelines-for-diagnostic-imaging-during-pregnancy-and-lactation. [Accessed 25 June 2025].

American College of Obstetricians and Gynecologists, 2019. ACOG practice bulletin no. 209: obstetric analgesia and anesthesia. Obstet Gynecol 133 (3), e208–e225 Mar.

Bacal, K., 2009. Complicating factors: issues relating to romance and reproduction during space missions. Medscape Intern Med. https://www.medscape.com/viewarticle/585644_4?form=fpf.

Bacal, V., Li, A., Shapiro, H., Rana, U., Zwingerman, R., Avery, L., Palermo, A., Philipoppolous, E., Chan, C., 2025. A systematic review and meta-analysis of the diagnostic accuracy after preimplantation genetic testing for aneuploidy. PLoS One 20, e0321859.

Basar, M., Mathyk, B., Arici, A., Halicigil, C., 2024. Hypergravity affects mitochondrial unfolded protein response in human oocytes. Presented at the American Society for Gravitational and Space Research (ASGSR), December 2024, Puerto Rico.

Barratt, M.R., 2020. Physical and bioenvironmental aspects of human space flight. In: Barratt, M.R., Pool, S.L. (Eds.), Principles of Clinical Medicine for Space Flight. Springer, New York, NY, pp. 3–37.

Barratt, M.R., Baker, E.S., Pool, S.L., 2020. Principles of Clinical Medicine for Space Flight. Springer, New York. https://doi.org/10.1007/978-1-4939-9889-0.

Bird, SD., 2017 Jan 1. Artificial placenta: Analysis of recent progress. European Journal of Obstetrics & Gynecology and Reproductive Biology 208, 61–70.

Broyan JL Jr, Borrego MA, Bahr JF (2008) International Space Station USOS crew quarters development. https://ntrs.nasa.gov/api/citations/20080013462/downloads/20080013462.pdf [Accessed 30/07/2025].

Caetano, G., Bozinovic, I., Dupont, C., Léger, D., Lévy, R., Sermondade, N., 2021. Impact of sleep on female and male reproductive functions: a systematic review. Fertil Steril 115, 715–731.

Cai, R., Lv, R., Shi, X.E., Yang, G., Jin, J., 2023. CRISPR/dCas9 tools: epigenetic mechanism and application in gene transcriptional regulation. International Journal of Molecular Sciences 24, 14865.

Campbell, A., Cohen, J., Ivani, K., Morbeck, D., Palmer, G., Mortimer, S., 2022. The in vitro fertilization laboratory: teamwork and teaming. Fertil Steril 117, 27–32.

Carrer, L., Pozzobon, R., Sauro, F., Castelletti, D., Patterson, G.W., Bruzzone, L., 2024. Radar evidence of an accessible cave conduit on the Moon below the Mare Tranquillitatis pit. Nat Astron 8, 1119–1126.

Caston, R., Luc, K., Hendrix, D., Hurowitz, J.A., Demple, B., 2018. Assessing toxicity and nuclear and mitochondrial DNA damage caused by exposure of mammalian cells to lunar regolith simulants. GeoHealth 2, 139–148.

Centers for Disease Control and Prevention, 2025. Radiation safety and ALARA. CDC, Atlanta, GA. https://www.cdc.gov/radiation-health/safety/alara.html. [Accessed 27 June 2025].

Cerri, M., Tinganelli, W., Negrini, M., Helm, A., Scifoni, E., Tommasino, F., Sioli, M., Zoccoli, A., Durante, M., 2016. Hibernation for space travel: impact on radioprotection. Life Sci Space Res 11, 1–9.

Chaplia, O., Mathyk, B.A., Nichols-Burns, S., Basar, M., Halicigil, C., 2024 Oct 11. Beyond Earth's bounds: navigating the frontiers of Assisted Reproductive Technologies (ART) in space. Reprod Biol Endocrinol 22 (1), 123.

Chavez-Badiola, A., Flores-Saiffe-Farías, A., Mendizabal-Ruiz, G., Drakeley, A.J., Cohen, J., 2020. Embryo Ranking Intelligent Classification Algorithm (ERICA): artificial intelligence clinical assistant predicting embryo ploidy and implantation. Reprod Biomed Online 41, 585–593.

Chowdhury, R.P., Stegeman, L.A., Lund, M.L., Fry, D., Madzunkov, S., Bahadori, A.A., 2023. Hybrid methods of radiation shielding against deep-space radiation. Life Sci Space Res 38, 67–78.

Cockell, C.S., Green, D.A., Caplin, N., et al., 2024. BioMoon: a concept for a mission to advance space life sciences and astrobiology on the Moon. Discov Sp 128, 5.

Cohen, J., Silvestri, G., Paredes, O., Martin-Alcala, H.E., Chavez-Badiola, A., Alikani, M., Palmer, G.A., 2025. Artificial intelligence in assisted reproductive technology: separating the dream from reality. Reprod Biomed Online 50, 104855.

Comizzoli, P., He, X., Lee, P.C., 2022. Long-term preservation of germ cells and gonadal tissues at ambient temperatures. Reprod Fertil 3, R42–R50.

Commercial Lunar Payload Services, 2025. https://www.nasa.gov/commercial-lunar-payload-services/(Accessed: 31 October 2025).

Cortright, E.M., 2019. Apollo Expeditions to the Moon: The NASA History 50th Anniversary Edition. Courier Dover Publications.

Costa-Borges, N., Munne, S., Albo, E., Mas, S., Castello, C., Giralt, G., Lu, Z., Chau, C., Acacio, M., Mestres, E., Matia, Q., 2023. First babies conceived with automated intracytoplasmic sperm injection. Reprod Biomed Online 47 (3), 103237.

Creech, S., Guidi, J., Elburn, D., 2022 Mar 5. Artemis: an overview of NASA's activities to return humans to the Moon. 2022 IEEE aerospace conference (AERO). IEEE, New York, pp. 1–7. [Accessed 31/10/2025].

Cucinotta, F.A., 2007. Space radiation organ doses for astronauts on past and future missions. https://ntrs.nasa.gov/citations/20070010704. [Accessed 27 June 2025].

Dal Canto, M., Moutier, C., Brambillasca, F., Guglielmo, M.C., Bartolacci, A., Fadini, R., Renzini, M.M., Buratini, J., 2019. The first report of pregnancies following blastocyst automated vitrification in Europe. J Gynecol Obstet Hum Reprod 48, 537–540.

Dang-Nguyen, T.Q., Nguyen, H.T., Nguyen, M.T., Somfai, T., Noguchi, J., Kaneko, H., Kikuchi, K., 2018. Maturation ability after transfer of freeze-dried germinal vesicles from porcine oocytes. Anim Sci J 89, 1253–1260.

Delp, M.D., Charvat, J.M., Limoli, C.L., Globus, R.K., Ghosh, P., 2016. Apollo lunar astronauts show higher cardiovascular disease mortality: possible deep space radiation effects on the vascular endothelium. Sci Rep 6, 29901.

De Micco, V., Leys, N., Zabel, P., et al., 2023. Plant and microbial science and technology as key elements of space life-support systems for long-duration missions to the Moon and Mars. NPJ Microgravity 9, 3.

Denis, G., Alary, D., Pasco, X., Pisot, N., Texier, D., Toulza, S., 2020. From new space to big space: how the commercial space dream is becoming a reality. Acta Astronaut 166, 431–443.

Dobney, W., Mols, L., Mistry, D., Tabury, K., Baselet, B., Baatout, S., 2023. Evaluation of deep space exploration risks and mitigations against radiation and microgravity. Front Nucl Med 3, 1225034.

Edwards, R.G., Bavister, B.D., Steptoe, P.C., 1969. Did fertilization occur? Nature 221, 981–982.

Edwards, R.G., 1965. Maturation in vitro of human ovarian oocytes. Lancet 286, 926–929.

English RA, Benson RE, Bailey JV, Barnes CM (1973) Apollo experience report: protection against radiation. *NASA Tech Note* NASA-TN-D-7080. https://ntrs.nasa.gov/api/citations/19730010172/downloads/19730010172.pdf [Accessed 24 June 2025]

Entrena Utrilla, C.M., Welch, C., 2017. Development roadmap and business case for a private Mars settlement. New Space 5, 170–185.

Epperly, M.W., Wang, H., Jones, J.A., Dixon, T., Montesinos, C.A., Greenberger, J.S., 2011. Antioxidant-chemoprevention diet ameliorates late effects of total-body irradiation and supplements radioprotection by MnSOD-plasmid liposome administration. Radiat Res 175, 759–765.

Erden, M., Oktay, KH., 2025 Jul 1. Pharmacologic and surgical strategies to improve cryopreserved ovarian tissue transplantation longevity and outcomes. Fertil Steril 124 (1), 170–171.

Consortium Steering Committee, ESHRE PGT, 2020. ESHRE PGT Consortium good practice

recommendations for the organisation of PGT. Hum Reprod Open 2020 (3), hoaa021.
European Space Agency, 2025. ESA Strategy 2040. European Space Agency, Paris. https://www.esa.int/About_Us/ESA_Strategy_2040. [Accessed 15/11/2025].
European Space Agency, 2019. ESA strategy for science at the Moon. ESA, Paris. https://sci.esa.int/documents/34161/35992/1567260389633-ESA_Strategy_for_Science_at_the_Moon.pdf.
Federal Aviation Administration, 2025. Human Space Flight. Office of Commercial Space Transportation, Washington, DC. https://www.faa.gov/space/human_spaceflight. [Accessed 15/11/2025].
Feng, M., Dang, N., Bai, Y., Wei, H., Meng, L., Wang, K., Zhao, Z., Chen, Y., Gao, F., Chen, Z., Li, L., 2019. 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.
Ferl, R.J., Zupanska, A., Spinale, A., Reed, D., Manning-Roach, S., Guerra, G., Cox, D.R., Paul, A.L., 2011. The performance of KSC Fixation Tubes with RNALater for orbital experiments: a case study in ISS operations for molecular biology. Adv Space Res 48, 199–206.
Fernandez, R.C., Moore, V.M., Marino, J.L., Whitrow, M.J., Davies, M.J., 2020. Night shift among women: is it associated with difficulty conceiving a first birth? Front Public Health 8, 595943.
Fukunaga, H., Yokoya, A., Prise, K.M., 2022. A brief overview of radiation-induced effects on spermatogenesis and oncofertility. Cancers 14, 805.
Freeman, CP., 2025 Oct 20. The Impact of US-China Strategic Competition on the Idea of Space as a 'Global Commons. Frontiers in Space Technologies 6, 1664300.
Gardner, M.J., Snee, M.P., Hall, A.J., Powell, C.A., Downes, S., Terrell, J.D., 1990. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Br Med J 300, 423–429.
Gardner, R.L., Johnson, M.H., 2011. Bob Edwards and the first decade of Reproductive BioMedicine Online. Reprod Biomed Online 22, 106–124.
Gardner, R.L., Edwards, R.G., 1968. Control of the sex ratio at full term in the rabbit by transferring sexed blastocysts. Nature 218, 346–348.
Garshnek, V., 1994 Jun 1. The moon as a 'real-time' life sciences laboratory. Advances in Space Research 14 (6), 265–269.
Georgakopoulos, I., Kouloulias, V., Ntoumas, G.N., Desse, D., Koukourakis, I., Kougioumtzopoulou, A., Kanakis, G., Zygogianni, A., 2024. Radiotherapy and testicular function: a comprehensive review of the radiation-induced effects with an emphasis on spermatogenesis. Biomedicines 12, 1492.
Gerbasi, G.J., Deckers, P., Kanaguchi, G., Pastore, C.B., Cintra, G.F., Maia, M.A., Lopes, A., 2023. Pregnancy after surgery and brachytherapy for vaginal cancer. Gynecol Oncol Rep 48, 101208.
Gimunová, M., Paludo, A.C., Bernaciková, M., Bienertova-Vasku, J., 2024. The effect of space travel on human reproductive health: a systematic review. npj Microgravity 10, 10.
Ginod, P., Dahan, M.H., 2024. Embryos as unborn children: the Alabama Supreme Court's ruling and its possible impact for legal rulings in other states. F&S Rep 5, 130.
Goddard, R.H., Goddard, E.C., Pendray, G.E., 1966. The Papers of Robert H. Goddard, Volume I: 1898—1924 [1927 and 1933: Material for an Autobiography]. Clark University, Worcester, MA. https://commons.clarku.edu/papersgoddard/1. (Accessed: 11 November 2025).
Goss, D.M., Vasilescu, S.A., Vasilescu, P.A., Cooke, S., Kim, S.H., Sacks, G.P., Gardner, D.K., Warkiani, M.E., 2024. Evaluation of an artificial intelligence-facilitated sperm detection tool in azoospermic samples for use in ICSI. Reprod Biomed Online 49, 103910.
Grigoriev, A.I., Williams, R.S., Comtois, J.M., Damann, V., Tachibana, S., Nicogossian, A.E., Bogomolov, V.V., Pool, S.L., Sargsyan, A.E., Knowingkov, O.L., Doarn, C.R., 2009. Space medicine policy development for the International Space Station. Acta Astronaut 65, 603–612.
Handyside, A.H., Kontogianni, E.H., Hardy, K., Winston, R.M., 1990. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature 344, 768–770.
Hassler, D.M., Zeitlin, C., Wimmer-Schweingruber, R.F., Ehresmann, B., Rafkin, S., Eigenbrode, J.L., Brinza, D.E., Weigle, G., Böttcher, S., Böhm, E., Burmeister, S., 2014. Mars' surface radiation environment measured with the Mars Science Laboratory's Curiosity rover. Science 343, 1244797.
Heard, E., Martienssen, R.A., 2014. Transgenerational epigenetic inheritance: myths and mechanisms. Cell 157, 95–109.
Hughes-Fulford, M., Carroll, D.J., Allaway, H.C., Dunbar, B.J., Sawyer, A.J., 2024. Women in space: a review of known physiological adaptations and health perspectives. Exp Physiol. https://doi.org/10.1113/EP091527.
Human Fertilisation and Embryology Act, 1990. https://www.legislation.gov.uk/ukpga/2008/22/contents. [Accessed 5 July 2025].
Ho, C.N., Tran, M.T., Doan, C.C., Hoang, S.N., Tran, D.H., Le, L.T., 2021. Simulated microgravity inhibits the proliferation of Chang liver cells by attenuation of the major cell cycle regulators and cytoskeletal proteins. Int J Mol Sci 22, 4550.
Ikeda, H., Watanabe, S., Sato, S., Fee, E.L., Carter, S.W., Kumagai, Y., Takahashi, T., Kawamura, S., Hanita, T., Illanes, S.E., Choolani, MA., 2024 Jan 2. Upregulation of hepatic nuclear receptors in extremely preterm ovine fetuses undergoing artificial placenta therapy. The journal of maternal-fetal & neonatal medicine 37 (1), 2301651.
International Commission on Radiological Protection, 2007. The 2007 recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP 37 (2—4), 1–332.
Jain, V., Chuva de Sousa Lopes, S.M., Benotmane, M.A., Verratti, V., Mitchell, R.T., Stukenborg, J.B., 2023. Human development and reproduction in space—a European perspective. npj Microgravity 9, 24.
Jain, V., Wotring, V.E., 2016. Medically induced amenorrhea in female astronauts. npj Microgravity 2, 1–6.
Jenkins, T.G., Aston, K.I., James, E.R., Carrell, D.T., 2017. Sperm epigenetics in the study of male fertility, offspring health, and potential clinical applications. Syst Biol Reprod Med 63, 69–76.
Jennings, R.T., Baker, E.S., 2000. Gynecological and reproductive issues for women in space: a review. Obstet Gynecol Surv 55, 109.
Jones, J.A., Karouia, F., Pinsky, L., Cristea, O., 2020. Radiation and radiation disorders. In: Barratt, M., Baker, E., Pool, S. (Eds.), Principles of Clinical Medicine for Space Flight. 2nd edn Springer, New York, NY, pp. 39–108. https://doi.org/10.1007/978-1-4939-9889-0_2.
Kojima, Y., Sasaki, S., Kubota, Y., Ikeuchi, T., Hayashi, Y., Kohri, K., 2000. Effects of simulated microgravity on mammalian fertilization and preimplantation embryonic development in vitro. Fertil Steril 74, 1142–1147.
Langston, S.M., 2017. Commercial space travel: understanding the legal, ethical and medical implications for commercial spaceflight participants and crew. *2017 8th International Conference on Recent Advances in Space Technologies (RAST)*, 19—21 June 2017. IEEE, pp. 489–494.
Lattin, M.T., Djandji, A.S., Kronfeld, M.T., Samsel, T., Ling, R., Ciskanik, M., Sadowy, S., Forman, E.J., Williams, Z., 2024. Development and validation of an automated robotic system for preparation of embryo culture dishes. Fertil Steril 122, 297–303.
Lee, C.Y., Moawad, K., Pien, G.W., 2025. Impact of night shift work on women's fertility, pregnancy and menopause. Front Sleep 4, 1545258.
Lei, X., Cao, Y., Zhang, Y., Qian, J., Zhao, Q., Liu, F., Zhang, T., Zhou, J., Gu, Y., Xia, G., Duan, E., 2018. 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.
Lei, X., Cao, Y., Ma, B., Zhang, Y., Ning, L., Qian, J., Zhang, L., Qu, Y., Zhang, T., Li, D., Chen, Q., 2020. Development of mouse preimplantation embryos in space. Natl Sci Rev 7, 1437–1446.
Li, K., Desai, R., Scott, R.T., Steele, J.R., Machado, M., Demharter, S., Hoarfrost, A., Braun, J.L., Fajardo, V.A., Sanders, L.M., Costes, S.V., 2023. Explainable machine learning identifies multi-omics signatures of muscle response to spaceflight in mice. npj Microgravity 9, 90.
Lindbergh, R., 2025. Commercial Human Spaceflight Safety Regulations. Focus Report IF12508. Congressional Research Service, Washington, DC. Available at: https://www.congress.gov/crs-product/IF12508.
Liu, X., Kim, K., Zhang, Y., Sun, Y., 2009. Nanonewton force sensing and control in microrobotic cell manipulation. Int J Robot Res 8, 1065–1076.
Liu, X., Lu, Z., Sun, Y., 2010a. Orientation control of biological cells under inverted microscopy. IEEE/ASME Trans Mechatron 99, 1–7.
Liu, X., Fernandes, R., Jurisicova, A., Casper, R.F., Sun, Y., 2010b. In situ mechanical characterization of mouse oocytes using a cell holding device. Lab Chip 10, 2154–2161.
Lu, Z., Zhang, X., Leung, C., Esfandiari, N., Casper, R.F., Sun, Y., 2011. Robotic ICSI (intracytoplasmic sperm injection). IEEE Trans Biomed Eng 58, 2102–2108.
Maks, L., Coleman, J., Hennessy, J.F., 2002. REACH: real-time data awareness in multi-spacecraft missions. SpaceOps 2002. https://ntrs.nasa.gov/citations/20020081271. [Accessed 27 June 2025].
Marchione, M., 2018. Chinese researcher claims first gene-edited babies. AP News. https://apnews.com/article/ap-top-news-international-news-ca-state-wire-genetic-frontiers-health-4997bb7aa36c45449b488e19ac83e86d. [Accessed 5 July 2025].

Mahoney, M.M., 2010. Shift work, jet lag, and female reproduction. Int J Endocrinol 2010, 813764.
Mason, C.E., 2023. To Mars and beyond: engineering life as a moral duty. GEN Biotechnol 2, 103–105.
Mathyk, B., Imudia, A.N., Quaas, A.M., Halicigil, C., Karouia, F., Avci, P., Nelson, N.G., Guzeloglu-Kayisli, O., Denbo, M., Sanders, L.M., Scott, R.T., 2024a. Understanding how space travel affects the female reproductive system: to the Moon and beyond. npj Womens Health 2, 20.
Mathyk, B.A., Tabetah, M., Karim, R., Zaksas, V., Kim, J., Anu, R.I., Muratani, M., Tasoula, A., Singh, R.S., Chen, Y.K., Overbey, E., 2024b. Spaceflight induces changes in gene expression profiles linked to insulin and estrogen. Commun Biol 7, 692.
Matsumura, T., Noda, T., Muratani, M., Okada, R., Yamane, M., Isotani, A., Kudo, T., Takahashi, S., Ikawa, M., 2019. Male mice, caged in the International Space Station for 35 days, sire healthy offspring. Sci Rep 9, 13733.
Manzano, A., Herranz, R., den Toom, L.A., Te Slaa, S., Borst, G., Visser, M., Medina, F.J., van Loon, J.J., 2018 Apr 4. Novel, Moon and Mars, partial gravity simulation paradigms and their effects on the balance between cell growth and cell proliferation during early plant development. npj Microgravity 4 (1), 9.
McDonald, J.T., Kim, J., Farmerie, L., Johnson, M.L., Trovao, N.S., Arif, S., Siew, K., Tsoy, S., Bram, Y., Park, J., Overbey, E., 2024. Space radiation damage rescued by inhibition of key spaceflight associated miRNAs. Nat Commun 15, 4825.
Mehmeti, S.S., Stojchevska, M.S., 2020. A legal perspective on career limitations upon female astronauts due to cosmic radiation exposure. ILIRIA Int Rev 10 (1).
Meigal, A., 2012. Interplanetary space flight compared with fetal/neonatal motor strategy: theoretical and practical implications. Pathophysiology 19, 269–276.
Mendizabal-Ruiz, G., Chavez-Badiola, A., Hernández-Morales, E., Valencia-Murillo, R., Ocegueda-Hernández, V., Costa-Borges, N., Mestres, E., Acacio, M., Matia-Algué, Q., Farías, A.F., Carreon, D.S., 2025. A digitally controlled, remotely operated ICSI system: case report of the first live birth. Reprod Biomed Online 50, 104943.
Mendizabal-Ruiz, G., Chavez-Badiola, A., Figueroa, I.A., Nuño, V.M., Farias, A.F., Valencia-Murillo, R., Drakeley, A., Garcia-Sandoval, J.P., Cohen, J., 2022. Computer software (SiD) assisted real-time single sperm selection associated with fertilization and blastocyst formation. Reprod Biomed Online 45, 703–711.
Mendizabal-Ruiz, G., Paredes, O., Álvarez, Á, Acosta-Gómez, F., Hernández-Morales, E., González-Sandoval, J., Mendez-Zavala, C., Borrayo, E., Chavez-Badiola, A., 2024. Artificial intelligence in human reproduction. Arch Med Res 55, 103131.
Milgrom, S.A., Alberto Vargas, H., Sala, E., Frankel Kelvin, J., Hricak, H., Goodman, K.A., 2013. Acute effects of pelvic irradiation on the adult uterus revealed by dynamic contrast-enhanced MRI. Br J Radiol 86, 20130334.
Millan, C., Parra, A.A., Mendizabal, G., Medina, V., Farías, A.F., Barragan, C.P., Carreon, D.S., Valadez, A., Aleriano, K., Silvestri, G., Lopez, M., 2024. Development and preliminary testing of a fully automated semen preparation robot. Fertil Steril 122, e122.
Miller, R.H., DeVilbiss, E.A., Brogaard, K.R., Norton, C.R., Pollard, C.A., Emery, B.R., Aston, K.I., Hotaling, J.M., Jenkins, T.G., 2023. Epigenetic determinants of reproductive potential augment the predictive ability of the semen analysis. F&S Sci 4, 279–285.
Mishra, B., Ripperdan, R., Ortiz, L., Luderer, U., 2017. Very low doses of heavy oxygen ion radiation induce premature ovarian failure. Reproduction 154, 123–133.
Mishra, B., Ortiz, L., Luderer, U., 2016. Charged iron particles, components of space radiation, destroy ovarian follicles. Hum Reprod 31, 1816–1826.
Mishra, B., Lawson, G.W., Ripperdan, R., Ortiz, L., Luderer, U., 2018. Charged-iron particles found in galactic cosmic rays are potent inducers of epithelial ovarian tumors. Radiat Res 190, 142–150.
Mishra, B., Luderer, U., 2019. Reproductive hazards of space travel in women and men. Nat Rev Endocrinol 15, 713–730.
Mitra A, Chancellor J, Feustel AJ, Aunon-Chancellor S, Yarns E, Piper SS, et al. (2020) Impact of space flight radiation and microgravity on DNA integrity and fertility risk of human & bovine sperm on the ISS. *Proceedings from the American Society of Gravitational and Space Research (ASGSR)*.
Moreno-Villanueva, M., Wong, M., Lu, T., Zhang, Y., Wu, H., 2017. Interplay of space radiation and microgravity in DNA damage and DNA damage response. npj Microgravity 3, 14.
Montesinos, C.A., Khalid, R., Cristea, O., Greenberger, J.S., Epperly, M.W., Lemon, J.A., Boreham, D.R., Popov, D., Gorthi, G., Ramkumar, N., Jones, J.A., 2021. Space radiation protection countermeasures in microgravity and planetary exploration. Life 11, 829.
Mu, X., He, W., Rivera, V.A., De Alba, R.A., Newman, D.J., Zhang, Y.S., 2022. Small tissue chips with big opportunities for space medicine. Life Sci Space Res 35, 150–157.
Munné, S., Almansa, J.A., Seth-Smith, M.L., Perugini, M., Griffin, D.K., 2025. Non-invasive selection for euploid embryos: prospects and pitfalls of the three most promising approaches. Reprod Biomed Online 51, 105077.
Musacchia, X.J., Barr, R.E., 1968. Survival of whole-body-irradiated hibernating and active ground squirrels; Citellus tridecemlineatus. Radiat Res 33, 348–356.
Musunuru, K., Grandinette, S.A., Wang, X., Hudson, T.R., Briseno, K., Berry, A.M., Hacker, J.L., Hsu, A., Silverstein, R.A., Hille, L.T., Ogul, AN., 2025. Patient-specific in vivo gene editing to treat a rare genetic disease. New England Journal of Medicine 392, 2235–2243.
Naito, M., Kodaira, S., Ogawara, R., Tobita, K., Someya, Y., Kusumoto, T., Kusano, H., Kitamura, H., Koike, M., Uchihori, Y., Yamanaka, M., 2020. Investigation of shielding material properties for effective space radiation protection. Life Sci Space Res 26, 69–76.
Naito, M., Kitamura, H., Koike, M., Kusano, H., Kusumoto, T., Uchihori, Y., Endo, T., Hagiwara, Y., Kiyono, N., Kodama, H., Matsuo, S., 2021. Applicability of composite materials for space radiation shielding of spacecraft. Life Sci Space Res 31, 71–79.
National Academies of Sciences, Engineering, and Medicine, 2021. Space Radiation and Astronaut Health: Managing and Communicating Cancer Risks. The National Academies Press, Washington, DC. https://doi.org/10.17226/26155. [Accessed 26 July 2025].
National Academies of Sciences, Engineering & Medicine, 2023. Thriving in Space: Ensuring the Future of Biological and Physical Sciences Research: A Decadal Survey for 2023-2032. National Academies Press, Washington, DC.
National Aeronautics and Space Administration Science Editorial Team, 2023. NASA selects 11 space biology research projects to inform biological research during future lunar exploration missions. NASA, Washington, DC. https://science.nasa.gov/science-research/biological-physical-sciences/nasa-selects-11-space-biology-research-projects/. [Accessed 15/11/2025].
National Aeronautics and Space Administration, 2025. Space Biology Science Plan 2016—2025. NASA, Washington, DC. https://science.nasa.gov/wp-content/uploads/2023/05/NASA_Space_Biology_Science_Plan_2016_2025_TAGGED.pdf. [Accessed 15/01/2025].
National Aeronautics and Space Administration, 2023a. LSAH Newsletter — Vol. 28, Issue 2. NASA, Washington, DC.. https://www.nasa.gov/wp-content/uploads/2023/10/lsah-newsletter-2023-vol28-issue2.pdf. [Accessed 13 July 2025].
National Aeronautics and Space Administration, 2023b. NASA-STD-3001 Volume 1 Revision C: NASA Space Flight Human-System Standard. NASA, Washington, DC.. https://www.nasa.gov/wp-content/uploads/2023/11/nasa-std-3001-vol-1-rev-c-with-signature.pdf. [Accessed 13 July 2025].
National Aeronautics and Space Administration, 2024c. NASA outlines latest Moon to Mars plans in 2024 architecture update. NASA, Washington, DC.. https://www.nasa.gov/news-release/nasa-outlines-latest-moon-to-mars-plans-in-2024-architecture-update/. [Accessed 15 June 2025].
Nicogossian AE, Parker JF (1982) Space physiology and medicine. Vol. 447. National Aeronautics and Space Administration Scientific and Technical Information Branch, Chapter 7, pp. 127—140.
Niederberger, C., Pellicer, A., Cohen, J., Gardner, D.K., Palermo, G.D., O'Neill, C.L., Chow, S., Rosenwaks, Z., Cobo, A., Swain, J.E., Schoolcraft, W.B., 2018. Forty years of IVF. Fertil Steril 110, 185–324.
Ogilvy-Stuart, A.L., Shalet, S.M., 1993. Effect of radiation on the human reproductive system. Environ Health Perspect 101 (Suppl 2), 109–116.
Ogneva, I.V., Usik, M.A., Loktev, S.S., Zhdankina, Y.S., Biryukov, N.S., Orlov, O.I., Sychev, V.N., 2019. Testes and duct deferens of mice during space flight: cytoskeleton structure, sperm-specific proteins and epigenetic events. Sci Rep 9, 9730.
Okamura, Y., Gochi, K., Ishikawa, T., Hayashi, T., Fuseya, S., Suzuki, R., Kanai, M., Inoue, Y., Murakami, Y., Sadaki, S., Jeon, H., 2024 Nov 20. Impact of microgravity and lunar gravity on murine skeletal and immune systems during space travel. Scientific Reports 14 (1), 28774.
O'Neill, H.C., Cohen, J., 2019. Live births following genome editing in human embryos: a call for clarity, self-control and regulation. Reprod Biomed Online 38, 131–132.
Palmer, G.A., 2013. Future developments. In: Varghese, A.C., Sjoblom, P., Jayaprakasan, K. (Eds.), *A Practical Guide to Setting Up an IVF Lab, Embryo Culture Systems and Running the Unit*, Chapter 19. JP Medical Ltd, London.
Palmer, G.A., Kratka, C., Szvetecz, S., Fiser, G., Fiser, S., Sanders, C., Tomkin, G., Szvetecz, M.A., Cohen, J., 2019. Comparison of 36 assisted

reproduction laboratories monitoring environmental conditions and instrument parameters using the same quality-control application. Reprod Biomed Online 39, 63–74.
Patel, S.J., Reede, D.L., Katz, D.S., Subramaniam, R., Amorosa, J.K., 2007. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 27, 1705–1722.
Pennings, G., 2007. The ethics of using embryos in research. Reprod Biomed Online 14, 92–97.
Radiation Emergency Medical Management, 2025. REMM . https://remm.hhs.gov/. [Accessed 9 July 2025].
Rahimzadeh, V., Fogarty, J., Caulfield, T., Auñón-Chancellor, S., Borry, P., Candia, J., et al., 2023. Ethically cleared to launch? Science 381, 1408–1411.
Regalado, A., 2018. Chinese scientists are creating CRISPR babies. MIT Technol Rev. https://www.technologyreview.com/2018/11/25/138962/exclusive-chinese-scientists-are-creating-crispr-babies/. [Accessed 5 July 2025].
Restier-Verlet, J., El-Nachef, L., Ferlazzo, M.L., Al-Choboq, J., Granzotto, A., Bouchet, A., Foray, N., 2021. Radiation on Earth or in space: what does it change? Int J Mol Sci 22, 3739.
Ribeiro, R., Baiocchi, G., Moretti-Marques, R., Linhares, J.C., Costa, C.N., Pareja, R., 2023 Dec 1. Uterine transposition for fertility and ovarian function preservation after radiotherapy. Int J Gynecol Cancer 33 (12), 1837–1842.
Rienzi, L., Fauser, B., 2021. Future challenges for clinical embryologists. Reprod Biomed Online 43, 973–975.
Ronca, A.E., Baker, E.S., Bavendam, T.G., Beck, K.D., Miller, V.M., Tash, J.S., Jenkins, M., 2014. Effects of sex and gender on adaptations to space: reproductive health. J Womens Health 23, 967–974.
Ronca, A.E., Alberts, J.R., 2000. Physiology of a microgravity environment: selected contribution—effects of spaceflight during pregnancy on labor and birth at 1G. J Appl Physiol 89, 849–854.
Roobol, S.J., Van Den Bent, I., Van Cappellen, W.A., Abraham, T.E., Paul, M.W., Kanaar, R., Houtsmuller, A.B., van Gent, D.C., Essers, J., 2020. Comparison of high- and low-LET radiation-induced DNA double-strand break processing in living cells. Int J Mol Sci 21, 6602.
Rose, B.I., 2022. Female astronauts: impact of space radiation on menopause. Eur J Obstet Gynecol Reprod Biol 271, 210–213.
Rubin, P., 1989. Law and order of radiation sensitivity, absolute versus relative, radiation tolerance of normal tissues. Front Radiat Ther Oncol 23, 7–40.
Ruden, D.M., Bolnick, A., Awonuga, A., Abdulhasan, M., Perez, G., Puscheck, E.E., Rappolee, D.A., 2018. Effects of gravity, microgravity or microgravity simulation on early mammalian development. Stem Cells Dev 27, 1230–1236.
Ruden, D.M., Rappolee, D.A., 2024. Effects of gravity, microgravity or microgravity simulation on early mouse embryogenesis: a review of the first two space embryo studies. Mechanobiol Med 2, 100081.
Rutter, L.A., Cope, H., MacKay, M.J., Herranz, R., Das, S., Ponomarev, S.A., Costes, S.V., Paul, A.M., Barker, R., Taylor, D.M., Bezdan, D., Szewczyk, N.J., Muratani, M., Mason, C.E., Giacomello, S., 2024. Astronaut omics and the impact of space on the human body at scale. Nat Commun 15, 4952.
Rutter, L.A., MacKay, M.J., Cope, H., Szewczyk, N.J., Kim, J., Overbey, E., Tierney, B.T., Muratani, M., Lamm, B., Bezdan, D., Paul, A.M., Schmidt, M.A., Church, G.M., Giacomello, S., Mason, C.E., 2024. Protective alleles and precision healthcare in crewed spaceflight. Nat Commun 15, 6158.
Sanders LM, Yang JH, Scott RT, Qutub AA, Martin HG, Berrios DC, Hastings JJ, Rask J, Mackintosh G, Hoarfrost AL, Chalk S (2021) Beyond low Earth orbit: biological research, artificial intelligence, and self-driving labs. *arXiv* preprint arXiv:2112.12582.
Santaguida, M., Dubé, S., 2023. Sexual health in space: a 5-year scoping review. Curr Sex Health Rep 15 (3), 148–179.
Sciarra, F., Franceschini, E., Campolo, F., Gianfrilli, D., Pallotti, F., Paoli, D., Isidori, A.M., Venneri, M.A., 2020. Disruption of circadian rhythms: a crucial factor in the etiology of infertility. Int J Mol Sci 21, 3943.
Shearman, L.P., Zylka, M.J., Weaver, D.R., Kolakowski, L.F., Reppert, S.M., 1997. Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. Neuron 19, 1261–1269.
Shigeyoshi, Y., Taguchi, K., Yamamoto, S., Takekida, S., Yan, L., Tei, H., Moriya, T., Shibata, S., Loros, J.J., Dunlap, J.C., Okamura, H., 1997. Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. Cell 91, 1043–1053.
Seylani, A., Galsinh, A.S., Tasoula, A., AR, I., Camera, A., Calleja-Agius, J., Borg, J., Goel, C., Kim, J., Clark, K.B., Das, S., 2024. Ethical considerations for the age of non-governmental space exploration. Nat Commun 15, 4774.
Shannoun, F., 2015. Medical exposure assessment: the global approach of the United Nations Scientific Committee on the Effects of Atomic Radiation. Radiat Prot Dosimetry 165, 125–128.
Smith, M.G., Kelley, M., Basner, M., 2020. A brief history of spaceflight from 1961 to 2020: an analysis of missions and astronaut demographics. Acta Astronaut 175, 290–299.
Soroka, L., Kurkova, K., 2019. Artificial intelligence and space technologies: legal, ethical and technological issues. Adv Space Law 3, 131–139.
Steptoe, P.C., Edwards, R.G., 1978. Birth after the reimplantation of a human embryo. The Lancet 312, 366.
Swain, J.E., Lai, D., Takayama, S., Smith, G.D., 2013. Thinking big by thinking small: application of microfluidic technology to improve ART. Lab Chip 13, 1213–1224.
Szocik, K., Marques, R.E., Abood, S., Kędzior, A., Lysenko-Ryba, K., Minich, D., 2018. Biological and social challenges of human reproduction in a long-term Mars base. Futures 100, 56–62.
Szocik, K., 2020. Is human enhancement in space a moral duty? Missions to Mars, advanced AI and genome editing in space. Camb Q Healthc Ethics 29, 122–130.
Tash, J.S., Mitra, A., Feustel, A.J., AunonChancellor, S., Yarns, E., Piper, S.S., et al., 2020. Fertilization—critical motility & acrosome reaction of human & bovine sperm are negatively impacted by space flight on the ISS. In: Proceedings from the American Society of Gravitational and Space Research (ASGSR). Nov. 2020.
Tao, R., Han, X., Bai, X., Yu, J., Ma, Y., Chen, W., Zhang, D., Li, Z., 2024. Revolutionizing cancer treatment: enhancing CAR-T cell therapy with CRISPR/Cas9 gene editing technology. Front Immunol 15, 1354825.
Theobald, R., SenGupta, S., Harper, J., 2020. The status of preimplantation genetic testing in the UK and USA. Hum Reprod 35, 986–998.
Thibeault, S.A., Fay, C.C., Lowther, S.E., Earle, K.D., Sauti, G., Kang, J.H., Park, C., McMullen, A.M., 2012. Radiation shielding materials containing hydrogen, boron, and nitrogen: systematic computational and experimental study. https://ntrs.nasa.gov/citations/20160010096. [Accessed 30 July 2025].
Toto, E., Lambertini, L., Laurenzi, S., Santonicola, M.G., 2024. Recent advances and challenges in polymer-based materials for space radiation shielding. Polymers 16, 382.
Tripathi, R.K., 2016. Meeting the grand challenge of protecting astronauts' health: electrostatic active space radiation shielding for deep space missions. NASA, Washington, DC. https://www.nasa.gov/wpcontent/uploads/2017/07/niac_2011_phasei_tripathi_electrostaticactivespace_tagged.pdf. [Accessed 20 July 2025].
United Nations, 1966. Treaty on principles governing the activities of states in the exploration and use of outer space, including the Moon and other celestial bodies. United Nations General Assembly Resolution 2222 (XXI), adopted 19 December 1966. https://www.unoosa.org/oosa/oosadoc/data/resolutions/1966/general_assembly_21st_session/res_2222_xxi.html [Accessed 15 Jan 2026]
United Press International, 1985. Apollo XIV astronaut Edgar Mitchell, the sixth man to walk on the moon. https://www.upi.com/Archives/1985/11/01/Apollo-XIV-astronaut-Edgar-Mitchell-the-sixth-man-to/8642499669200/. [Accessed 24 June 2025].
US Congress Senate Committee on Energy and Natural Resources, 1975. Nominees to the Nuclear Regulatory Commission: Hearings Before the Joint Committee on Atomic Energy, Congress of the United States, Ninety-Third Congress, Second Session, December 10 and 18, 1974. US Government Printing Office; Washington, D.C.
US Nuclear Regulatory Commission, 2020. Radiation exposure and cancer risk. USNRC, Bethesda, MD. https://www.nrc.gov/about-nrc/radiation/health-effects/rad-exposure-cancer.html. [Accessed 5 July 2025].
Van Allen, J.A., 1959. Radiation belts around the Earth. Sci Am 200, 39–47.
Van Hoof, W., Pennings, G., 2013. Cross-border reproductive care around the world: recent controversies. In: Botterill, D., Pennings, G., Mainil, T. (Eds.), Medical Tourism and Transnational Health Care. Palgrave Macmillan, London. https://doi.org/10.1057/9781137338495_7.
VanKoevering, K.K., Sabetsarvestani, K., Sullivan, S.E., Barkan, A., Mierzwa, M., McKean, E.L., 2020. Pituitary dysfunction after radiation for anterior skull base malignancies: incidence and screening. J Neurol Surg B Skull Base 81, 75–81.
Vasin, M.V., 2014. Comments on the mechanisms of action of radiation protective agents: basis components and their polyvalence. SpringerPlus 3, 1–6.
Vidal, F., 2025 Oct 17. NASA's Artemis Lunar Program: Hybrid Venture, Complex

Infrastructure Regime and Governance Crisis. Astropolitics 1–26.
Wang, Y., Xie, Y., Wygle, D., Shen, H.H., Puscheck, E.E., Rappolee, DA., 2009 Oct. A major effect of simulated microgravity on several stages of preimplantation mouse development is lethality associated with elevated phosphorylated SAPK/JNK. Reproductive sciences 16 (10), 947–959.
Wakayama, S., Kamada, Y., Yamanaka, K., Kohda, T., Suzuki, H., Shimazu, T., Tada, M.N., Osada, I., Nagamatsu, A., Kamimura, S., Nagatomo, H., 2017. Healthy offspring from freeze-dried mouse spermatozoa held on the International Space Station for 9 months. Proc Natl Acad Sci USA 114, 5988–5993.
Wakayama, S., Ito, D., Kamada, Y., Shimazu, T., Suzuki, T., Nagamatsu, A., Araki, R., Ishikawa, T., Kamimura, S., Hirose, N., Kazama, K., 2021. Evaluating the long-term effect of space radiation on the reproductive normality of mammalian sperm preserved on the. International Space Station. Sci Adv 7, eabg5554.
Wakayama, S., Kikuchi, Y., Soejima, M., Hayashi, E., Ushigome, N., Yamazaki, C., Suzuki, T., Shimazu, T., Yamamori, T., Osada, I., Sano, H., 2023. Effect of microgravity on mammalian embryo development evaluated at the International Space Station. iScience 26 (11), 107682.
Wakayama, S., Kawahara, Y., Li, C., Yamagata, K., Yuge, L., Wakayama, T., 2009. Detrimental effects of microgravity on mouse preimplantation development in vitro. PLoS One 4, e6753.
Wallace, W.H., Thomson, A.B., Kelsey, T.W., 2003. The radiosensitivity of the human oocyte. Hum Reprod 18, 117–121.
Wallace, W.H., Thomson, A.B., Saran, F., Kelsey, T.W., 2005. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 62, 738–744.
Wang, M., Wang, Q., Xiao, Y., Wang, M., Wang, J., Wang, H., Chen, Z., 2025. Review of passive shielding materials for high-energy charged particles in Earth's orbit. Materials 18, 2558.
Weng, L., 2019. IVF-on-a-chip: recent advances in microfluidics technology for in vitro fertilization. SLAS Technol 24, 373–385.
World Health Organization, 2021. WHO Laboratory Manual for the Examination and Processing of Human Semen, 6th ed. WHO, Geneva. https://www.who.int/publications/i/item/9789240030787. [Accessed 10 July 2025].
Xu, X., Xie, Y., Li, H., Wang, X., Shi, S., Yang, Z., Lan, Y., Han, J., Liu, Y., 2024. Awareness and preparedness level of medical workers for radiation and nuclear emergency response. Front Public Health 12, 1410722.
Yang, C., Deng, Y., Ren, H., Wang, R., Li, X., 2020. A multi-channel polymerase chain reaction lab-on-a-chip and its application in spaceflight experiment for the study of gene mutation. Acta Astronaut 166, 590–598.
Yasuda, H., Sihver, L., 2022. Broadening the selection criteria for astronauts undertaking long-term space travel. Front Nucl Med 2, 997718.
Yoshida, K., Fujita, S.I., Isotani, A., Kudo, T., Takahashi, S., Ikawa, M., Shiba, D., Shirakawa, M., Muratani, M., Ishii, S., 2021. Intergenerational effect of short-term spaceflight in mice. iScience 24 (7), 102755.
Yau, A., Wang, Z., Ponthempilly, N., Zhang, Y., Wang, X., Chen, Y., 2023. Biosensor integrated tissue chips and their applications on Earth and in space. Biosens Bioelectron 222, 114820.
Zeitlin, C., Hassler, D.M., Cucinotta, F.A., Ehresmann, B., Wimmer-Schweingruber, R.F., Brinza, D.E., Kang, S., Weigle, G., Böttcher, S., Böhm, E., Burmeister, S., 2013. Measurements of energetic particle radiation in transit to Mars on the Mars Science Laboratory. Science 340, 1080–1084.
Zhan, L., Hinnen, H., Gopinathan, K.A., Toner, M., 2025. Autonomous cryoprotectant loading of the oocyte using microfluidic transistors. Device (published online 27 Feb 2025).
Zhang, S., Wu, Y., Weng, Y., Xu, Z., Chen, W., Zheng, D., Lin, W., Liu, J., Zhou, Y., 2017. In vitro growth of mouse preantral follicles under simulated microgravity. J Vis Exp 130, 55641.
Zhang, L., Zhang, X., Qiu, L., Mao, S., Sheng, J., Chen, L., Khan, U., Upputuri, P.K., Zakharov, Y.N., Coughlan, M.F., Perelman, LT., 2025. Near-infrared light activatable chemically induced CRISPR system. Light: Science & Applications 14, 229.
Zhu, Y., Feng, H.L., Jiang, M.X., 2023. Evaluation of an automated dish preparation system for IVF and embryo culture using a mouse model. Sci Rep 13, 16490.
Zylka, M.J., Shearman, L.P., Weaver, D.R., Reppert, S.M., 1998. Three period homologs in mammals: differential light responses in the suprachiasmatic circadian clock and oscillating transcripts outside of brain. Neuron 20, 1103–1110.

Received 13 April 2025; received in revised form 19 November 2025; accepted 8 December 2025.