Gynecologic Risk Mitigation Considerations for Long-Duration Spaceflight

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INTRODUCTION: As NASA and its international partners, as well as the commercial spaceflight industry, prepare for missions of increasing duration and venturing outside of low-Earth orbit, mitigation of medical risk is of high priority. Gynecologic considerations constitute one facet of medical risk for female astronauts. This manuscript will review the preflight, in-flight, and postflight clinical evaluation, management, and prevention considerations for reducing gynecologic and reproductive risks in female astronauts.

METHODS: Relevant gynecological articles from databases including Ovid, Medline, Web of Science, various medical libraries, and NASA archives were evaluated for this review. In particular, articles addressing preventive measures or management of conditions in resource-limited environments were evaluated for applicability to future long-duration exploration spaceflight.

RESULTS: Topics including abnormal uterine bleeding, anemia, bone mineral density, ovarian cysts, venous thromboembolism, contraception, fertility, and health maintenance were reviewed. Prevention and treatment strategies are discussed with a focus on management options that consider limitations of onboard medical capabilities.

DISCUSSION: Long-duration exploration spaceflight will introduce new challenges for maintenance of gynecological and reproductive health. The impact of the space environment outside of low-Earth orbit on gynecological concerns remains unknown, with factors such as increased particle radiation exposure adding complexity and potential risk. While the most effective means of minimizing the impact of gynecologic or reproductive pathology for female astronauts is screening and prevention, gynecological concerns can arise unpredictably as they do on Earth. Careful consideration of gynecological risks and potential adverse events during spaceflight is a critical component to risk analysis and preventive medicine for future exploration missions.

KEYWORDS: gynecology, reproductive health, long-duration, space, contraception, abnormal uterine bleeding.

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As both NASA and the commercial spaceflight industry plan future long-duration missions outside of low-Earth orbit (LEO), gynecologic and reproductive women's health concerns must be considered. Preflight screening, management, and prevention approaches are the foundation of in-flight medical risk mitigation. While there are numerous pharmacologic and procedural measures to mitigate and treat gynecologic pathology on Earth, the primary arsenal of risk mitigation for female astronauts during flight is pharmacological.[15,30] Historically, this has included estrogen-/progesterone-based hormonal modalities, gonadotropin-releasing hormone (GnRH) agonists, and nonsteroidal anti-inflammatory drugs (NSAIDs).[96]

In women participating in prolonged (≥ 6 mo) missions, the ability to provide individualized medical approaches can direct health care options. Medical decision-making by NASA-affiliated

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gynecologists is often more conservative and personalized than terrestrial recommendations from governing medical bodies. Given the paucity of robust research investigating gynecological concerns in the unique astronaut subpopulation, alterations from terrestrial standards of care largely rely on expert opinion. Here we will review preflight and in-flight clinical evaluation considerations, management, and prevention strategies for reducing spaceflight gynecologic risk.

METHODS

A systematic review was conducted on human and animal studies involving screening, diagnosis, and management of gynecological concerns particularly related to the astronaut population parameters of healthy women aged ~25–55 yr. Literature reviewed included studies, meta-analyses, and clinical practice guidelines regarding common infections, abnormal uterine bleeding (AUB), endometriosis, adnexal masses, fertility, and ovulatory suppression via hormonal supplementation. Additional spaceflight-specific considerations of interest included prevention of thrombosis and minimizing bone loss. Databases included Ovid, Medline, Web of Science, and various medical libraries. NASA archives were searched for additional literature regarding approaches to gynecological care during spaceflight or public records of gynecological concerns within the female astronaut population. Relevant studies matching these criteria and the intent of analysis are presented below.

Benefits and risks of inclusion/exclusion of terrestrial treatment modalities from an exploration medical capability were considered for spaceflight missions outside of LEO without the possibility of rapid evacuation to Earth. Preventive medicine modalities were evaluated for applicability to the astronaut population and the relative risk of such modalities prior to long-duration exploration spaceflight.

RESULTS

Abnormal Uterine Bleeding

Chronic, nongestational AUB has been shown to affect 14–25% of reproductive-aged women in the U.S.[211] and thus represents a relatively common and concerning gynecologic complication that could impact female crewmembers during long-duration spaceflight. The International Federation of Gynecology and Obstetrics (FIGO) characterizes both normal and abnormal bleeding by pattern and etiology.[47,136,137] Etiological definitions of AUB include structural causes such as polyps, adenomyosis, leiomyomas, and malignancy/neoplasia (PALM) as well as nonstructural causes including coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic, and not otherwise classified (COEIN).[47,136,137] Together, these conditions define the "PALM-COEIN" classification system (**Table I** and **Table II**).

It is unknown whether the space environment may be associated with AUB, though limited evidence suggests that simulated microgravity is associated with alterations in estrous cycling in terrestrial animal models.[195] In contrast, early human bedrest studies revealed no changes in the hormonal aspect of the menstrual cycle,[167] and anecdotal reporting has indicated no alteration of cycle length or quantity of menstrual blood flow during spaceflight.

If an astronaut has experienced AUB prior to flight, prior procedural interventions, and their success or failure, should be reviewed.[96] The etiology and pattern of past/current AUB helps guide necessary preflight diagnostic evaluations, their interpretation, and selection of personalized treatment modalities (**Fig. 1**). Terrestrially, clinical suspicion for an anatomical cause of AUB warrants transvaginal ultrasound (TVUS).[25,69,188] At NASA, all female astronaut candidates (ASCANs) undergo screening TVUS regardless of any AUB history.[96] While screening TVUS in asymptomatic patients loses sensitivity/specificity and is not recommended in the general U.S. reproductive-age population,[3,47] benefits of uncovering pathology prior to spaceflight outweigh the risk of false positive findings and subsequent evaluations.

In a screening TVUS, common abnormal findings may include:

1) A thickened/irregular/asymmetric endometrial stripe/mass in the uterine cavity concerning for a polyp, submucosal leiomyoma, or endometrial intraepithelial neoplasia (EIN)/neoplasm;
2) Asymmetric myometrial thickening/heterogeneous myometrium concerning for adenomyosis;
3) Discrete masses within the uterine wall concerning for leiomyomas;
4) An adnexal cyst or mass.[47]

Each of these findings is explored below.

Thickened endometrial stripe and endometrial intraepithelial neoplasia. In the U.S., there are no formal recommendations for escalating evaluation after ultrasound identifies a thickened endometrium in healthy asymptomatic patients of reproductive age because endometrial thickness varies throughout normal menstrual cycling.[37,58,66] In preflight astronauts, timely repeat TVUS is reasonable before further evaluation. If repeat TVUS again reveals an asymptomatic thickened endometrial stripe, or if a thickened endometrial stripe is associated with AUB, benefits of hysteroscopy with direct biopsy may outweigh risks.

The lifetime risk of endometrial cancer is 2.8% among U.S. women. Prevalence is lower in a nonobese, nondiabetic, reproductive-aged population,[145,181] and more likely etiologies of a thickened endometrial stripe in astronauts include physiologic thickening, endometrial polyp, or leiomyoma. Hysteroscopy can be both diagnostic and therapeutic in that polypectomy, submucosal myomectomy, direct biopsy, or dilation and curettage (D&C) can be performed concurrently if indicated. Hysteroscopy with directed biopsy may be more sensitive for diagnosing uterine lesions such as EIN or neoplasm.[24,46,152] However, hysteroscopy is not without risk; complications include bleeding, infection, electrolyte disturbances, gas emboli, adhesions, and uterine perforation, though the overall complication rate in large, retrospective European studies is only

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Table I. Etiological Definitions of Abnormal Uterine Bleeding: Structural Causes. The etiologies described include polyps, adenomyosis, leiomyomas, and malignancy/hyperplasia, which make up the "PALM" classifications.*

AUB ETIOLOGY (PALM)	EPIDEMIOLOGY	MANAGEMENT	RECURRENCE & PREVENTION
Polyps			
Overgrowth of cells lining the endometrium leads to the formation of polyps or growths that can extend into the uterine cavity	• Prevalence in 9-33% of women with AUB[42] • Peak incidence 5th decade of life[14]	*Fertility sparing:* • Polypectomy (hysteroscopic if necessary) • Levonorgestrel IUD *Non-fertility sparing:* • Endometrial ablation or endomyometrial resection	Recurrence requiring intervention after polypectomy = 2.5–43%.[150] • Polypectomy + LNG-IUD placement may decrease recurrence rate[40,57] • Endometrial ablation[112,156] — up to 43% amenorrhea rate; 38% require repeat procedure/hysterectomy • Endomyometrial resection[216]—85% amenorrhea rate, up to 10% require repeat procedure/hysterectomy
Adenomyosis			
Endometrial tissue present in myometrium	• Prevalence unclear in women with AUB • Prevalence 7–27% in general population (due to variance in diagnostic criteria)[141,189]	*Fertility sparing*[7]*:* • LNG-IUD • Similar rates of bleeding reduction as patients without adenomyosis but may need replacing more frequently than for contraceptive purposes[157] • Continuous COCs • Fewer studies available than with LNG-IUD but suggest that COCs are effective alternative *Non-fertility sparing:* • Hysterectomy definitive	• Recurrence requiring intervention after focal excision (adenomyoma excision) or adenomyomectomy ~50%. This recurrence risk is decreased to 30% if GnRH agonist added[205] • Hysterectomy definitive with no recurrence risk. However, adenomyosis can be comorbid with endometriosis which can cause continued pelvic pain/bleeding post-hysterectomy
Leiomyoma			
Benign tumor of uterine smooth muscle (myometrium). Can cause swelling or growth into uterine cavity or on uterine exterior	• Prevalence in 12–25% of women with AUB[64] • Prevalence in 70–80% of Caucasian and African American women in general population[19] • Incidence increases with age (3.3 per 1000 women 20–25 yr; 16.0 per 1000 women age 40–44 yr)[123]	*Medical Therapies:* • Hormonal contraceptives: • LNG-IUDs most effective at symptom reduction and avoiding surgery • LNG-IUD 90% blood loss reduction compared to 13% with COCs[7] • GnRH Agonist (Leuprolide) • Short-term preoperatively due to intense side effects (including significant bone loss if used > 6 mo continuously) • Selective Progesterone-Receptor Modulators (SPRMs) • Mifepristone (10–25 mg daily), ulipristal (5–10 mg daily x 12 wk); not available in U.S. • Better tolerated, more effective than leuprolide for fibroid size/symptom reduction[63,139,205] • Ulipristal available as emergency contraceptive (30 mg) in US, used for fibroid size reduction in Europe • Concern that daily progesterone-receptor modulator use may cause endometrial hyperplastic changes *Surgical Therapies*: • Myomectomy • Uterine artery embolization • Hysterectomy—definitive	• Recurrence requiring intervention after myomectomy —20–34% (average time to recurrence—3.5 yr)[80,203] • Recurrence requiring intervention after uterine artery embolization — 15–32%, associated risk of premature ovarian insufficiency • Limited data suggests myomectomy has better fertility rates than uterine artery embolization[78]

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Table I, *Continued.*

AUB ETIOLOGY (PALM)	EPIDEMIOLOGY	MANAGEMENT	RECURRENCE & PREVENTION
Endometrial epithelial neoplasia (EIN) • Abnormal overgrowth of endometrial layer of uterus, most commonly occurs in response to unopposed estrogen (anovulation, hormone use, etc). **Cancer** • Uncontrolled abnormal growth can progress to or coexist with endometrial cancer	• Prevalence of EIN + cancer is 1.31% of women with AUB • Prevalence of cancer only in 0.33% of women with AUB[154] • Age-dependent: o < 40 yr: 0.81% o 40–50 yr: 1.99% o > 50 yr: 14.12% • 10–20% of endometrial cancers occur in premenopausal women	For benign endometrial hyperplasia (low risk of cancer progression): *Fertility Sparing:* • Levonorgestrel IUD • Medroxyprogesterone acetate (10 mg · d^{-1} × 14 days — different from contraceptive dosing) *Non-Fertility Sparing:* • Endometrial resection • Hysterectomy definitive For EIN or in setting of malignancy: • Refer to gynecologist/ oncologist for further work up and management	• Recurrence after LNG-IUD = 0–5%[127,201,204]. However, recurrence increases to 14% if hormonal treatment is discontinued[74] • Once regression achieved, often require maintenance therapy to prevent recurrence: OCPs, progestin-only contraceptives based on patient preference. • Recurrence after endometrial ablation[112,156] = 38%. Up to 43% become amenorrheic[28]. Recurrence of EIN after endomyometrial resection[216] = 10%. Up to 85% become amenorrheic. Hysterectomy generally preferable. This procedure may diagnose previously unsuspected/undetected EIN and adenocarcinoma

* AUB: Abnormal Uterine Bleeding; PALM: polyps, adenomyosis, leiomyoma, malignancy/hyperplasia; NSAID: non-steroidal anti-inflammatory drug; IUD: intrauterine device; LNG-IUD: levonorgestrel intrauterine device; COC: combined oral contraceptive; GnRH: gonadotropin-releasing hormone; POP: progestin-only pill; OCP: oral contraceptive pill.

0.24–0.28%.[135] Less-invasive diagnostic options include sonohysterography and blind endometrial biopsy. Given the risk profile and desire for timely diagnosis/management of intrauterine pathology, hysteroscopy is likely an appropriate evaluation in a preflight astronaut population.[96] Identification of EIN leads to a diagnosis of carcinoma in 40% of patients receiving follow-on hysterectomy for thickened endometrium.[152] While medical management may be considered for EIN, referral to a gynecologic oncologist for definitive surgical management may be appropriate for the astronaut population.

Polyps and adenomyosis. Polyps discovered during screening ultrasound in astronauts are treatable via hysteroscopic polypectomy, with resolution in 70–100% of cases. Polyp recurrence ranges from 12–43%, with polyp-related AUB recurrence between 2.5–3.7%.[8,150,221] In patients who desire future fertility, a levonorgestrel (LNG) intrauterine device (IUD) may reduce recurrence risk.[40,57,156] For women with satisfied parity, endometrial ablation or endomyometrial resection can be considered[129]; however, these procedures may complicate future evaluation of AUB, including the ability to rule out future malignancy.[5,128] Adenomyosis is difficult to manage conservatively. While endometrial ablation, uterine artery embolization, or LNG-IUDs can be considered, the only definitive treatment is hysterectomy.[129,173]

Leiomyomas. Prior review of ASCAN screening TVUS demonstrated uterine leiomyoma incidence of 10%.[96] In terrestrial reports, epidemiologic data regarding either asymptomatic or symptomatic leiomyomas have not been able to accurately predict morbidity, complicating management recommendations.[122,132,206] Pedunculated intracavitary leiomyomas and intramural leiomyomas with endometrial impingement may be at higher risk for AUB; fortunately, these subtypes can be empirically managed hysteroscopically.[42,61,62] Subserosal uterine leiomyomas may require laparoscopic or open surgery.[42,61,62] Surgical decisions require individualized evaluation based on leiomyoma characteristics and the risk/benefit profile of an invasive procedure. The optimal nonsurgical modality to reduce symptoms and prevent morbidity arising from leiomyomas is the LNG-IUD.[7]

Non-anatomical causes. Ovulatory dysfunction may affect the pattern, duration, or volume of bleeding and may be the result of an endocrinopathy such as polycystic ovary syndrome (PCOS), thyroid dysfunction, or prolactinoma. A serum thyroid-stimulating hormone (TSH) with reflex free thyroxine (T4) level can screen for thyroid disease, and a prolactin level may be considered (Fig. 1). Personal or family history of petechiae, easy bruising, or abnormal bleeding should invite consideration of screening for a coagulation defect.[148] Initial laboratory testing of prothrombin time (PT) and partial thromboplastin time (aPTT) is recommended in this setting. A serum von Willebrand factor antigen, von Willebrand-ristocetin cofactor activity, and Factor VIII testing can be considered.[47]

Iron deficiency and anemia. Physiological adaptation to spaceflight may induce a temporary decline in red blood cell mass and a transient decrease in circulating erythropoietin.[4,198] During the U.S. Space Shuttle Program some evidence suggested that this decrease in red blood cell mass can be as much as 10–15% and that, while erythropoietin levels rise within 24 h of return to Earth, red blood cell mass recovery can take as much as 4–8 wk.[98,105,177] More recent studies demonstrate in-flight

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elevation of red blood cell indices, indicating that astronauts do not develop persistent anemia during spaceflight.[103] Even so, it is worth noting that volume status is susceptible to microgravity-induced alterations secondary to redistribution and relative dehydration, particularly early in flight. The potential for anemia secondary to AUB remains a concern both during and after spaceflight.

Evaluation of AUB should include a complete blood count (CBC) and ferritin to evaluate for baseline anemia (hemoglobin $< 12\ g \cdot dL^{-1}$ in women). Anemia with mean corpuscular

Table II. Etiological Definitions of Abnormal Uterine Bleeding: Non-Structural Causes. The etiologies described include coagulopathies, ovulatory dysfunction, endometrial factor, iatrogenic, and not yet classified, which make up the "COEIN" classifications.*

AUB ETIOLOGY (COEIN)	INCIDENCE & PREVALENCE	MANAGEMENT
Coagulopathy		
	• Prevalence in 15–20% of women with AUB-HMB o Prevalence of von Willebrand's Disease alone = up to 13% of women with AUB-HMB[7] • Most common cause of AUB in young women and adolescents	• Hematologic workup for inherited disorders (e.g. von Willebrand's Disease) • Hormonal methods may have added beneficial effect on top of hematologic medications (e.g. desmopressin)[7] o LNG-IUD led to amenorrhea in 56% of women with known coagulopathy (not specified by type) o LNG-IUD effective in improving symptomatic bleeding when added to desmopressin or tranexamic acid for previously unresponsive women with von Willebrand's Disease o LNG-IUD had higher continuation rates than POPs for menorrhagia in von Willebrand's Disease o COCs also effective at reducing blood volume and have added benefit of preventing ovulation which reduces risk of hemorrhagic corpus luteum cysts. • NSAIDs contraindicated in most coagulopathies due to anti-platelet effects • Surgical management rarely indicated
Ovulatory Dysfunction		
• Irregular bleeding <21 d or > 35 d cycles • Polycystic ovarian syndrome • Obesity • Hypothyroidism • Hyperprolactinemia • Anorexia/extreme exercise	• Prevalence of polycystic ovarian syndrome = 6–10% of women in general population[34] (but up to 90% in women with oligo- or amenorrhea) • Prevalence of hyperprolactinemia = 0.4% in general population, but 5–17% in women presenting with reproductive disorders including amenorrhea[29] • Prevalence of AUB in women with hypothyroidism is up to 35% • Prevalence of AUB in women with hyperthyroidism is 2–4%[99]	• 1st line: medical correction of endocrine dysfunction • Anovulatory women: increased risk of EIN/malignancy due to unopposed estrogen—important to regulate cycle or add progestin-containing method o COCs regulate cycle and decrease menstrual bleeding volume o Progestin pills, LNG-IUD decrease bleeding volume but do not inhibit ovulation o Hyperthyroidism can cause increase in baseline circulating estrogen levels increasing risk for unopposed estrogen o For polycystic ovarian syndrome: evaluation of co-morbid metabolic syndrome should be performed prior to starting COCs
Endometrial Disorders		
• Conditions interfering with normal endometrial hemostasis and shedding. (Includes drugs that affect prostaglandin receptors, diseases that affect the endometrium (pelvic inflammatory disease, endometritis), or possible congenital structural or functional alterations)	• Unable to report prevalence	• Impractical diagnostic feasibility currently • Combined hormonal contraceptive modalities may provide some benefit through decreased endometrium development • NSAIDS decrease prostaglandin o 25–50% reduction in menstrual volume • Tranexamic acid for adjunctive treatment o 1 g TID for 4–5 d/mo, starting first day of menses o Approximately 50% reduction in bleeding volume per menses[127] • Endometrial ablation
Iatrogenic		
• Contraceptives (systemic hormonal methods, intrauterine devices) • Gonadal steroid-related therapy (selective estrogen receptor modulators, aromatase inhibitors) • Anticoagulants • Agents causing hyperprolactinemia (e.g. Anti-psychotics, metoclopramide)	• Unable to report prevalence	• Combined oral contraceptives: Breakthrough bleeding/spotting decreases with estradiol dose (44% for 20 μg, 27% for 30 μg, 23% for 50 μg)[100] o If continuing to have breakthrough bleeding after 3 mo of COC use can offer ibuprofen (800mg TID x 1–2 wk) or supplemental estrogen for 1–2 wk before increasing dose[172] • Irregular bleeding on progestin-only methods often due to decreased estrogen stabilizing uterine lining, treat with adding back estrogen o Ethinyl estradiol 20μg/day or Estradiol 0.5–1 $mg \cdot d^{-1}$ for 1–2 wk o If no relief, can add low-dose COC for 2–3 mo[172] • Variable evidence of benefit from doxycycline administration[1]

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Table II, *Continued.*

AUB ETIOLOGY (COEIN)	INCIDENCE & PREVALENCE	MANAGEMENT
Not otherwise classified		
	• Unable to report prevalence	Decrease in blood volume by method[127]: • NSAIDS: 25–50% reduction in menstrual flow • Tranexamic acid: 50% reduction • COCs: 50% reduction + regulation of irregular bleeding • Progestin-only methods o POPs: 80% reduction o LNG-IUD: 97% reduction by 12 mo[7] • GnRH agonists: 90% reduction in blood volume but can only use safely for 3–6 mo due to bone density loss

* AUB: Abnormal Uterine Bleeding; COEIN: coagulopathies, ovulatory dysfunction, endometrial factor, iatrogenic, and not yet classified; NSAID: non-steroidal anti-inflammatory drug; IUD: intrauterine device; LNG-IUD: levonorgestrel intrauterine device; COC: combined oral contraceptive; GnRH: gonadotropin-releasing hormone; POP: progestin-only pill; OCP: oral contraceptive pill; AUB-HMB: abnormal uterine bleeding/heavy menstrual bleeding; TID: three times daily.

volume < 80 fL and ferritin < 40 mg $\cdot$ L^{-1} is consistent with iron deficiency.[56,79] Incidence of iron deficiency anemia in non-pregnant U.S. females of reproductive age is 10.4%.[79] Iron deficiency (ferritin levels of < 4 μg $\cdot$ L^{-1}) even in the absence of anemia should be proactively addressed through iron supplementation.[182] Notably, ferritin may be artificially elevated with substantial day-to-day variability in populations undergoing intense exercise[119] and thus may be unreliable during preflight training; similarly, studies have demonstrated alterations of serum iron, serum ferritin, and ferritin saturation following long-duration spaceflight.[179]

Hormonal management. In reproductive-aged women, hormonal management is often the primary prevention and

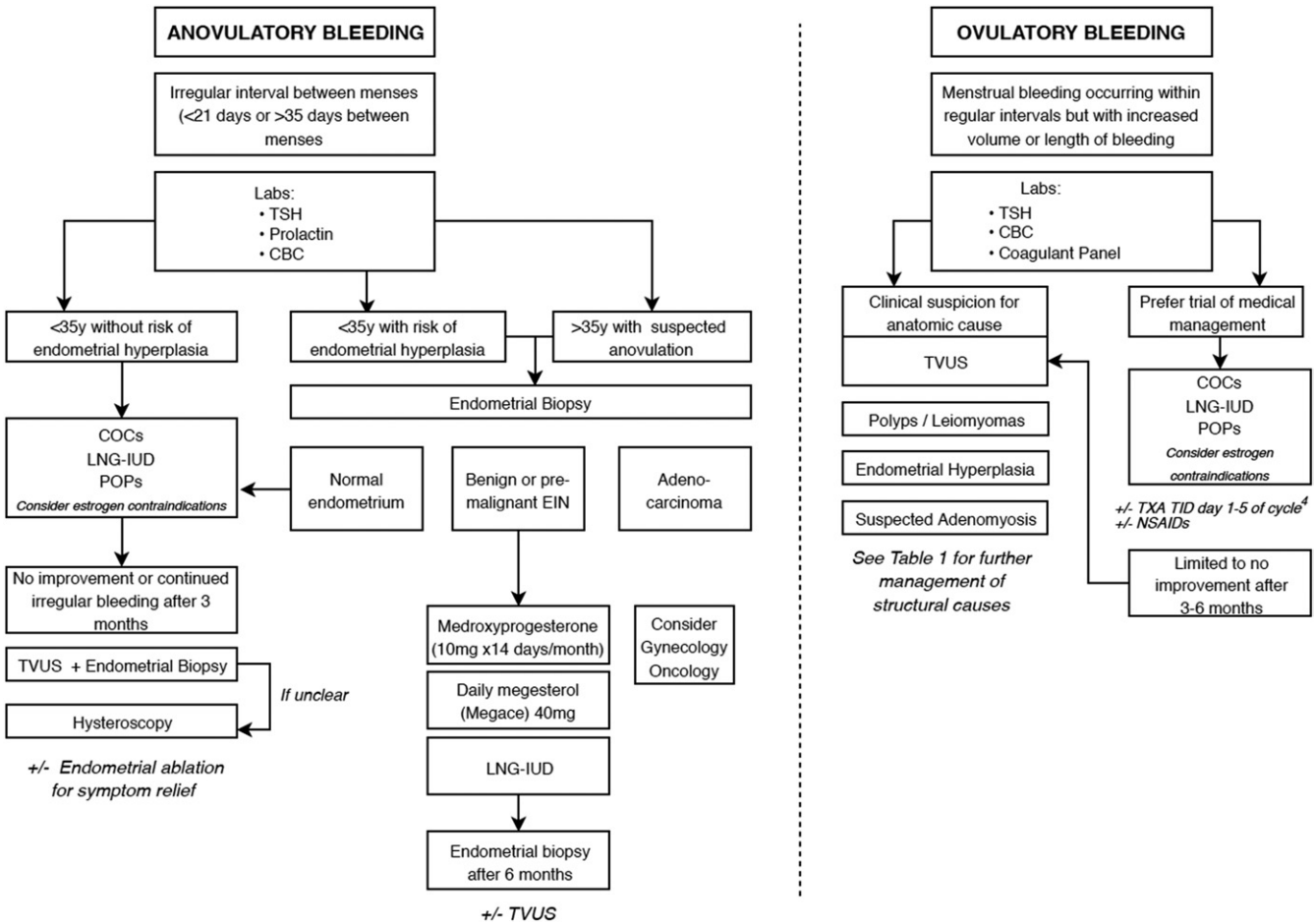

Fig. 1. Diagnostic evaluation, interpretation, and selection of personalized treatment modalities for abnormal uterine bleeding. TSH: thyroid stimulating hormone; CBC: complete blood count; COCs: combined oral contraceptives; LNG-IUD: levonorgestrel intrauterine device; POPs: progestin-only pills; TVUS: transvaginal ultrasound: EIN: endometrial disorders, iatrogenic, and not otherwise classified causes of abnormal uterine bleeding; TXA: tranexamic acid; TID: three times daily; NSAID: nonsteroidal anti-inflammatory drug.

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treatment modality and a common method for reducing recurrence of AUB after procedural interventions (Tables I and II, Fig. 1). Management options include combined hormonal modalities of estrogen and progestin analogs in pill form, vaginal ring, or transdermal patch, and progestin-only modalities in a pill, intramuscular injection, subdermal implant, or IUD. Optimal suppression of menses using these modalities is ideal for mitigating risk of in-flight AUB.[93] Unfortunately there is no perfect hormonal modality for achieving this goal; even the most effective methods achieve average amenorrhea rates of only 60% by 12 mo.[185] Effects of these hormonal agents on menses, contraceptive effectiveness, and risks and side effects are discussed below and in **Table III**. It is worth noting that many astronauts voluntarily choose to suppress menstruation for convenience during flight. The modalities discussed below are capable of suppression for either AUB or voluntary reasons.

Combined oral contraceptives (COCs) and LNG-IUDs, used continuously, are successful options for menstrual suppression and have been found to be safe in comparison to standard use of COCs (which includes a placebo week during each 28 d cycle).[23,143] Historically, NASA's astronaut population has had autonomy in choosing an individualized management strategy for menstrual suppression, contraception, or other hormonal therapy indications, with most electing for COCs and some choosing the LNG-IUD.[96] Use of alternative combined hormonal modalities like the patch or vaginally-inserted ring have not been documented during spaceflight, nor is there robust terrestrial literature evaluating the efficacy of the patch or ring in inducing amenorrhea. Depot medroxyprogesterone use has been limited in female astronauts given its association with decreased bone mineral density (BMD) with prolonged use,[11] a risk compounded by long-duration spaceflight.

In comparing LNG-IUDs to COCs, LNG-IUDs have some advantages including:

1) LNG-IUDs are a first line agent for treating new-onset AUB and preventing recurrence of AUB;
2) LNG-IUDs do not include estrogen [decreasing side effects or risks such as venous thromboembolism (VTE)];
3) LNG-IUDs can remain efficacious for 5–7 yr, potentially decreasing quantity of medication needed for long-duration missions and the pharmacologic stability of stored medications;[30]
4) LNG-IUD function is not dependent upon strict daily compliance.[10,52,83]

There are no data available regarding compliance with COCs in the astronaut population. In a recent study of U.S. female college students, only 20% of those surveyed met criteria for high adherence to COC administration guidelines.[194] In another small study, incentivized patients reached 83% compliance.[209] In female military aviation personnel using suppressive COCs during missions, $<$ 33% maintained ideal compliance,[158,196] suggesting that compliance with COCs may be challenging in an operational setting. Even so, COCs have been the first-line modality for astronauts seeking suppression as they generally produce higher amenorrhea rates,[84] may be associated with less BMD loss[27] and ovarian cyst formation,[106,134] and use of COCs avoids IUD-associated migratory and expulsion risks.

Another combined hormonal contraceptive (CHC) modality is the vaginal (etonorgestrel/ethinyl estradiol) ring. Like COCs, rings can be used in a continuous fashion with the patient exchanging the intravaginal silicone ring every 28 d. In one year-long study comparing vaginal rings and low-dose COCs, the investigators found no significant difference in amenorrhea rates between the two groups.[208] Another study demonstrated ovarian suppression with both the vaginal ring and COCs, without follicular cyst formation.[134] Further, systemic exposure to ethinyl estradiol is halved with the ring in comparison to a 30-μg ethinyl estradiol-containing COC pill.[166] Thus, the vaginal ring may share similar advantages with COCs while mitigating the risks of daily compliance and potentially decreasing the risk of thrombosis/VTE. However, more data are necessary for full appreciation of the ring's efficacy and safety profile. In addition, vaginal rings must be stored at cooler temperature prior to use; manufacturer recommendations state that the ring should be stored in refrigerated conditions, with allowable storage at room temperature (25°C) for no more than 4 mo.[131]

The transdermal patch is another CHC that can be used continuously. While benefits include weekly compliance rather than daily, there are conflicting data regarding whether the patch may carry higher VTE risk compared to COCs.[191] Further, there are limited data for evaluation of amenorrhea rates.[68,184] Finally, it may be possible to combine CHCs (oral, patch, ring) with an LNG-IUD to maximize the benefits of each, though there are no data regarding safety or efficacy during synergistic use. Unfortunately, no current form of hormonal contraception can maximize all benefits while completely mitigating risks. Investigations into alternative hormonal modalities, such as estetrol (E4) which may provide effective menstrual suppression while decreasing VTE risk,[16] may provide additional options for future astronauts.

When considering use of a hormonal modality, preflight screening for allergies or contraindications and exploring risks associated with each modality is important. Contraindications to estrogen-containing modalities such as COCs, patch, and ring include a history of diabetes, hypertension, cardiac disease, liver disease, thrombosis/VTE, smoking over age 35 yr, migraines over age 35 yr, and migraines with aura at any age.[2,9,39] While these risk factors are rare in the healthy astronaut population, any of these conditions (preexisting or developing) should prompt evaluation of the risks and benefits of hormonal therapy. A recent study demonstrated that, in 700 women who developed VTE while taking COCs, 44.7% subsequently tested positive for an inherited thrombophilia, most commonly Factor V Leiden (30%).[67] Preflight screening for inherited thrombophilias is likely indicated for all astronauts prior to long-duration exploration spaceflight, but particularly for female astronauts on CHCs, to guide treatment options. If an underlying thrombophilia is identified, this should prompt preferential use of a LNG-IUD over CHCs to minimize serum hormonal concentration.

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Table III. Comparative contraceptive modalities, mechanism, efficacy, benefits, risks, and side effects. IUD: intrauterine device; FDA: U.S. Food and Drug Administration.

CONTRACEPTIVE	HORMONE	MECHANISM OF ACTION	CONTRACEPTIVE EFFICACY[197,215]	EFFECT ON MENSES	NON-CONTRACEPTIVE BENEFITS	RISKS, SIDE EFFECTS, OTHER
Hormonal IUD						
• Mirena® • Liletta® • Kyleena® • Skyla®	• 52 mg progestin/ device (20 μg ·d^{-1}) • 52 mg progestin/ device (18.6 μg ·d^{-1}) • 19.5 mg levonorgestrel/ device (17.5 μg ·d^{-1}) • 13.5 mg progestin/ device (14 μg ·d^{-1})	• Thickens cervical mucous, endometrial thinning • 1 IUD q3–7 yr	• Perfect/Typical: >99%[215]	• Amenorrhea by 12 months: 20–50%[22,83] • Amenorrhea by 24 mo: 42–60%[185] • Bleeding may increase or be irregular in first 3–6 mo of use.[22]	• Decreased risk of endometrial cancer	• FDA trials—4.5% expulsion • 8% of users had ovarian cysts (asymptomatic or symptomatic) • Requires provider to insert/ remove • If pregnancy occurs due to IUD failure, higher risk of pregnancy being ectopic or ending in spontaneous abortion with high risk of septic or incomplete abortion. • Not appropriate for patient with pelvic inflammatory disease in last 3 months or signs of cervicitis during insertion. In all other patients, testing for sexually transmitted infection at time of placement, treat if positive.
Copper IUD						
• Paragard®	• None	• Copper = spermicidal • 1 IUD q10–12 yr	• Perfect/Typical: >99%	• Amenorrhea by 12 months: N/A • ~60% of patients experience heavier by regular menses (estimated 50% increase in menstrual volume)[87]	• Most effective emergency (post-coital) contraceptive, effective up to 5 days post-coital. Effective regardless of ovulation status	• Requires provider to insert/ remove • In patients who are anemic/ have history of anemia, can worsen anemia (in healthy patients, does not typically cause anemia) • Not appropriate for patient with pelvic inflammatory disease in last 3 months or signs of cervicitis during insertion. In all other patients, testing for sexually transmitted infection at time of placement, treat if positive.
Implant						
• Nexplanon®	• 68 mg etonogestrel	• Ovulation suppression, cervical mucous thickening, altered endometrium • 1 Implant q3–4 yr	• Perfect/Typical: >99%	• Amenorrhea by 12 months: 20% • 20% have heavier or prolonged bleeding, 40% have irregular, more frequent bleeding[130]		• Requires provider to insert/ remove
3-Month Injection						
• Depo-Provera® (intramuscular or subcutaneous)[155]	• 150 mg medroxyprogesterone (intramuscular) • 104 mg medroxyprogesterone (subcutaneous)	• Ovulation suppression, cervical mucous thickening, altered endometrium	• Perfect: >99% • Typical: 97%	• Amenorrhea by 12 mo: 55% • Amenorrhea by 24 mo: 70% • Amenorrhea by 5y: 80%[9]	• Reduces risk of endometrial and ovarian cancer	• Self-administered subcutaneous formulations well-studied • Transient decrease in bone mineral density (no increased fracture risk) • ~5 lb weight gain/yr • Can worsen mood symptoms in patient with mood disorder

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Table III, *Continued.*

CONTRACEPTIVE	HORMONE	MECHANISM OF ACTION	CONTRACEPTIVE EFFICACY[197,215]	EFFECT ON MENSES	NON-CONTRACEPTIVE BENEFITS	RISKS, SIDE EFFECTS, OTHER
Combined Hormonal Contraceptives (CHCs)				• Amenorrhea by 12 mo: ~70%[84] • Bleeding regular and slightly lighter. • Periods determined by hormonal withdrawal so can be timed under control of patient. • Can have no menses if used continuously without break for placebo/bleeding days. • 60% of continuous users experienced complete amenorrhea[84]	• Reduces risk of new ovarian cyst formation • Reduces risk of endometrial & ovarian cancer • Decreased menorrhagia, dysmenorrhea[9] • Patch had best compliance, ring has least side effects[116]	
1. *CHC: Combined Oral Contraceptives (COCs)*	• 0.15–0.35 mg ethinylestradiol • 0.1–1.0 mg progestin: o etonogestrel o levonorgestrel o northindrone o desogestrel o drospirenone o norgestimate	• Ovulation suppression • 1 pill / d	• Perfect: >99% • Typical: 91–92%			• Common side effects: nausea, headaches, breast tenderness • Estrogen prescribing precautions Different COC formulations may produce different constellation of side effects however in general increased estrogen dose increases menses stabilization but also side effect frequency
2. *CHC: Contraceptive Patch*						
• Xulane® • OrthoEvra®	• 0.35 mg ethinyl estradiol • 1.50 mg norelgestromin	• Ovulation suppression • 1 patch / wk	• Perfect: >99% • Typical: 91–92%			• 60% more estrogen and progestin absorption at steady state than COCs (though COCs have 35% peak concentration)[140] • Decreased efficacy for patients >198 lbs • Estrogen prescribing precautions
3. *CHC: Contraceptive Vaginal Ring*						
• Nuvaring®	• 0.15 mg ethinyl estradiol • 1.20 mg of etonogestrel[8]	• Ovulation suppression	• Perfect: >99% • Typical: 91-92%			• Least issues with hormonal side effects from various combined methods

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Table III, *Continued.*

CONTRACEPTIVE	HORMONE	MECHANISM OF ACTION	CONTRACEPTIVE EFFICACY[197,215]	EFFECT ON MENSES	NON-CONTRACEPTIVE BENEFITS	RISKS, SIDE EFFECTS, OTHER
Progestin-only pills	• 3.50 mg norethindrone	• Thickens cervical mucous, sometimes suppresses ovulation • 1 pill/d	• Perfect: 99% • Typical: 95%	• Frequently causes alterations in menses which range from amenorrhea to prolonged bleeding. Similar to Implant: frequent, irregular bleeding most common alteration.	• Reduces risk of endometrial cancer	• Requires more rigid timing (administration same time each day ± 3 h for efficacy) • Due to incomplete inhibition of ovulation, follicular atresia may be delayed and follicles may enlarge abnormally. Typically self-resolving, asymptomatic
Diaphragm & Cervical Cap +Spermicidal gel	• None	• Acts as barrier, preventing sperm entry	• Perfect: 94% • Typical: 84–88%	• No effect	• Moderate prevention of sexually transmitted infections	• Should not be left in place for > 12 h or used during menses due to risk of toxic shock syndrome
Male Condoms	• None	• Acts as barrier, preventing sperm entry	• Perfect: 98% • Typical: 82–85%	• No effect	• Transmission prevention for sexually transmitted infections	
Female Condoms	• None	• Acts as barrier, preventing sperm entry	• Perfect: 90% • Typical: 75–79%	• No effect	• Transmission prevention for sexually transmitted infections	

In-flight assessment/management. Prevention of AUB is a necessary part of any spaceflight medical capability given that AUB, if it occurs, could rapidly deplete medical and pharmacological supplies while complicating spacecraft waste disposal systems. As there are no perfect modalities of inducing amenorrhea or preventing AUB during missions, an in-flight management plan is imperative. With advanced surgical options likely unavailable during long-duration spaceflight, pharmacological intervention will likely be the mainstay of treatment.[15]

Ideally, all crew medical officers (CMOs) should have some preflight training in pelvic examination for gynecological complaints during exploration spaceflight. For acute AUB occurring during spaceflight, a pelvic exam performed by the CMO may identify anatomical causes for AUB such as uterine leiomyomas, cervical/vaginal polyp, or possible prolapsing endometrial polyp/leiomyoma. At present, vaginal specula are not available onboard the International Space Station (ISS) and it may not be feasible to create an appropriate device using point-of-care additive manufacturing; inclusion of a speculum in future flights may improve physical evaluation capabilities. Feasible diagnostic laboratory tests may include point-of-care CBC and pregnancy test. Ultrasound imaging may provide further diagnostic insight. Currently, ultrasound capabilities in LEO include transabdominal but not intracavitary evaluation, precluding the possibility of TVUS. While intracavitary probes may be included in future onboard capabilities, the pelvis can be evaluated transabdominally using a phased-array transducer. In one study, the sensitivity for transabdominal and transvaginal ultrasound to detect uterine fibroids was 89% compared to 95%, and identification of a uterine mass was 84% vs. 96%, respectively.[60]

If the patient has an IUD, there should be an attempt to locate this device via physical exam or sonography. On ultrasound, a LNG-IUD appears as two hyperechoic signals, representing the proximal and distal ends of the vertical arm of the device, with acoustic shadowing[76] (**Fig. 2**). Displacement of the IUD into the cervix or vagina can cause AUB and, if identified in either location, the device should be removed (**Fig. 3**). The rate of IUD expulsion during the first year after placement can be 2–10%[81,94,118]; expulsion rates decline in subsequent years[118] and risk may be lower with preflight sonographic confirmation of placement.

Another procedural therapy that might be performed during spaceflight is a cervical polypectomy, or removal of prolapsing endometrial polyp/leiomyoma. However, given a paucity of safety data available and potential complexity of this procedure, it should only be attempted if the polyp causes significant bleeding and concern for morbidity. This intervention would require

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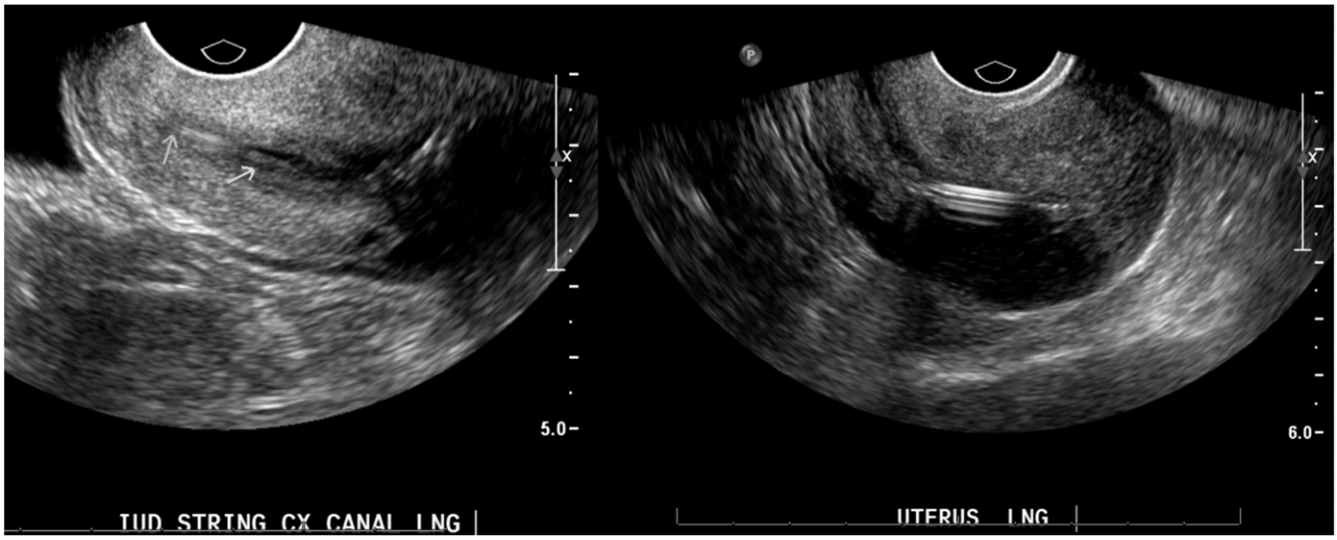

Fig. 2. Identification of intrauterine device by intracavitary ultrasound. A hyperechoic linear levonorgestrel intrauterine device can be visualized in the uterine fundus with a light hyperechoic linear signal, representing the intrauterine device strings, passing through the uterine cervix.

preflight training and experience for the CMO; just-in-time training may not prepare CMOs for potential complications and management of complex outcomes.

For all other causes of AUB, including AUB of unknown origin, pharmacologic management will likely be the only available management strategy. Under the assumption that all female astronauts will be using a LNG-IUD or CHCs, if new-onset AUB occurs, current contraceptives should be continued and a hormone burst-taper can be temporarily added. While the addition of ethinyl estradiol alone would be more beneficial than progesterone in the case of atrophic endometrium, onboard options may be limited to combined hormonal modalities; in this case, combined tapers can still be beneficial. Tapers function by preventing follicle stimulating hormone (FSH) secretion and promoting endometrial stability with estrogen, while progestin prevents the luteinizing hormone (LH) surge required for ovulation and promotes an atrophic endometrial lining.[73]

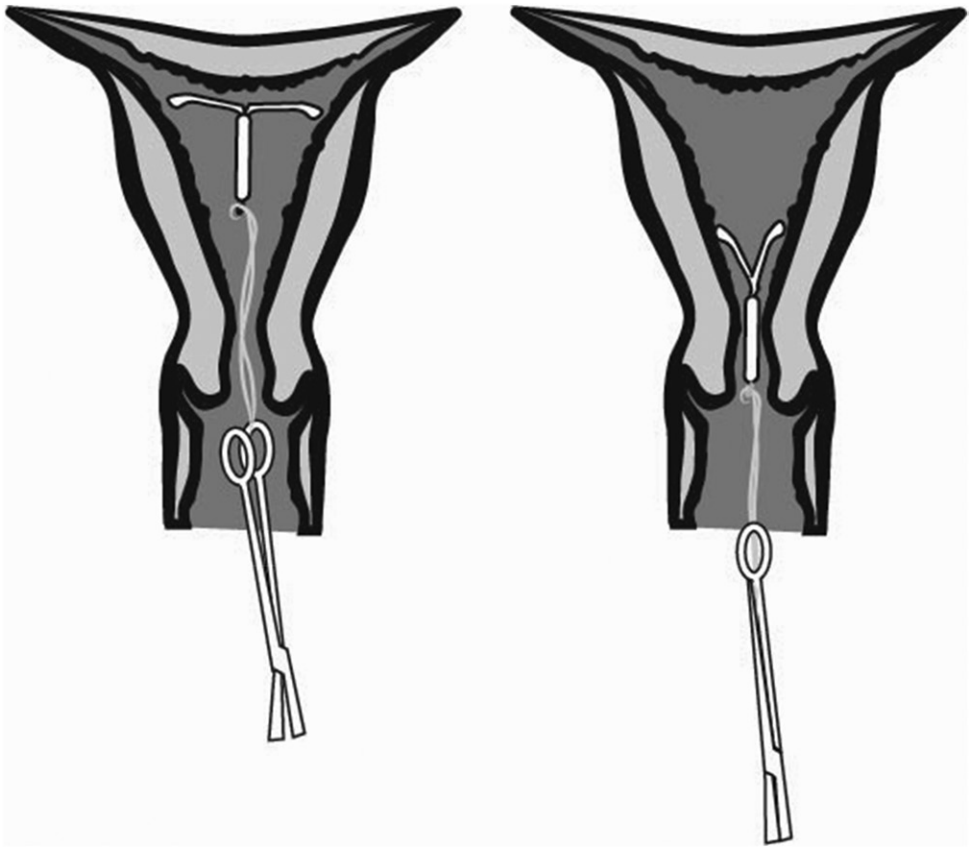

Fig. 3. Removal of intrauterine device. An intrauterine device is graphically depicted in the correct position in the uterine fundus with device strings passing through the uterine cervix. These strings may be grasped by forceps and gently pulled to remove the device, with the flexible device arms collapsing together.

Though COC tapers are commonly used to manage acute AUB in emergency settings,[10,36,88] there are few published or standardized regimens.[138,174] One common protocol involves increasing the dose from one COC pill-per-day to three pills-per-day for 7 d before returning to baseline dosing; this regimen successfully stopped bleeding in 88% of subjects.[138] During spaceflight, the most feasible options would likely include typical daily COCs and a burst-taper of a second or

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third COC pill-per-day, or adding a daily COC pill to a LNG-IUD.[32,43] Increased hormone doses may lead to side effects including nausea, vomiting, and potential mood changes; in addition, taking a higher dose of estrogen/progesterone may temporarily increase the risk of thrombosis/VTE, though the benefits in this scenario, including limiting anemic sequelae, may outweigh the risks. Availability of additional COCs onboard any long-duration spaceflight would provide management options in the event of AUB, assuming such medications could be effectively stored and stability ensured.

If severe AUB persists despite a burst-taper, options become increasingly limited. In one historical case, a gonadotropin-releasing hormone (GnRH) agonist was used in-flight for undisclosed medical reasons.[96] GnRH agonists work by suppressing pituitary gonadotropin secretion, leading to suppression of ovarian steroidogenesis and inducing temporary functional menopause.[72,113] An alternative approach could be to use a GnRH antagonist with estrogen add-back (to avoid bone loss as with GnRH agonists),[113,180] or a high-dose progesterone analog such as medroxyprogesterone, megestrol, or norethindrone,[48] if available.

Additional nonhormonal pharmaceuticals that may be included in an onboard formulary and could augment primary hormonal management include nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid (TXA). For patients experiencing AUB-HMB, 600-1200 mg of ibuprofen daily has been shown to decrease the duration and volume of menses.[111] TXA administered every 6-8 h can be used to decrease the volume of bleeding during severe AUB, without increasing thrombosis/VTE risk, by preventing plasmin formation, fibrin degradation, and clot degradation.[117] In addition, doxycycline has been shown to reduce bleeding in women using some forms of progestins through inhibition of protease activity.[1,207] Given that doxycycline is currently in the ISS formulary[144] and may be carried forward for exploration spaceflight, it is not unreasonable to consider adjunctive administration in a case of AUB.

In severe cases complicated by hemodynamic instability, management would likely include intravenous fluid resuscitation or attempted uterovaginal tamponade with transcervical insertion of a balloon catheter[96] in addition to the pharmaceutical modalities above. The potential for crewmember donation of non-cross-matched whole blood has been discussed for management of emergent hemorrhagic conditions during spaceflight[101,102]; such extreme interventions could be considered in the case of severe AUB. An onboard CMO should have a basic gynecologic fund of knowledge to assess and manage AUB. Telemetry and communication capabilities should be able to support consultation with a flight surgeon or gynecologist on Earth[15]; however, communication delays during exploration spaceflight may limit timely guidance in the case of an acute or life-threatening complication.

As pharmacologic measures remain the predominant in-flight treatment strategy, there has been interest regarding whether the space environment, namely radiation, may impact the stability of medications.[31] If the space environment does expedite degradation of an onboard formulary, this could lead to inadequate efficacy or even toxic effects that could compromise astronaut safety.[30,54,217] While evidence is limited, studies have identified pharmacological degradation of flown medications exceeding expected instability.[30,65,218] Missions with lengths that exceed pharmacological shelf life may compound this concern.[30] Further investigation is warranted to identify the clinical impact of such concerns.

Bone Mineral Density

Given the known effects of gravitational unloading on bone health, careful analysis of how hormonal modalities affect BMD is important. Terrestrially, 0.30-0.35 mg of ethinyl estradiol in COCs have not been associated with decreased BMD[27]; hence, such doses have traditionally been the mainstay of hormonal treatment for astronauts in flight. In animal models subjected to hind-limb unloading as a microgravity analog, oral estradiol protects against cortical and cancellous BMD loss after 6 wk.[121] Preliminary results of studies investigating long-acting progesterone modalities and BMD in simulated microgravity suggest that etonorgestrel may preserve BMD in diaphyseal bone with minimal impact on metaphyseal bone.[6] Terrestrial studies have demonstrated dramatic BMD reduction after 2 yr of depot medroxyprogesterone acetate use,[27] though studies involving low-dose progesterone modalities, such as the LNG-IUD, have not found a negative impact on BMD.[18,222] One study from Hong Kong associated LNG-IUD use with higher BMD.[214]

For women aged 19–50 yr, daily intake of calcium and vitamin D is terrestrially recommended at doses of 1,200 mg and 600 IU, respectively.[164] Due to concerns for nephrolithiasis secondary to increased bone resorption leading to high circulating calcium during spaceflight,[212,213] astronauts receive daily vitamin D supplementation but do not ingest additional calcium outside of food sources.[178] Resistive exercise is essential for mitigating BMD loss in all astronauts,[115] and there is growing evidence in support of initiating bisphosphonates three weeks prior to spaceflight and continuing for the entire mission duration,[77,110] though use of bisphosphonates for long-duration spaceflight $>$ 6 mo has not been evaluated.

Ovarian Cysts

COCs have been considered superior to alternative suppressive modalities in astronauts given the role estrogen may play in ovarian cyst suppression and reduction in the incidence of corpora hemorrhagicum and spontaneous bleeding following ovulation. Combined hormonal modalities have a higher serum hormone concentration than LNG-IUDs, providing negative feedback to the pituitary and suppressing ovulation.[146] Specifically, follicles will not grow or mature with ovulatory suppression, and thus the risk that a follicle may become a functional ovarian cyst is mitigated. With a LNG-IUD, the amount of hormone that reaches the serum varies, but generally stabilizes within the first few weeks following insertion[22] at much lower serum concentrations than induced by COCs. While "localized" LNG-IUD action has many benefits for the patient, it is less likely that a LNG-IUD may cause pituitary suppression,

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and thus these devices have been correlated with a higher rate of ovarian cyst development than COCs. Studies evaluating this concern demonstrate that functional cysts associated with LNG-IUDs are typically < 5 cm and resolve spontaneously.[83,89] In a multicenter international study evaluating lower-dose LNG-IUDs, ovarian cysts were present in 1.6% of women before placement and 1.1–2.4% at each subsequent visit during the 3-yr study period.[142] Of these cysts, 88% were in the 3–5 cm range and, while 13% of the cysts remained > 3–6 mo, none persisted > 9 mo.[142]

Scandinavian studies demonstrated baseline incidence of ovarian cysts as high as 5–7% in a reproductive-age population.[33,41,89] A previously published report found ovarian cysts in 5.7% of female ASCANs that received a preflight screening ultrasound.[96] Ovarian cysts ranging from 5–12 cm are at highest risk of ovarian torsion, a twisting of the ovarian pedicle causing vascular occlusion and, potentially, ischemia. Terrestrially, this is a surgical emergency and accounts for 2.7% of emergency surgeries in the U.S.[82] There are not adequate epidemiologic data regarding incidence/prevalence to stratify which population of patients with cysts may experience torsion or when this may occur. Ovarian torsion has not been reported before or during spaceflight in the astronaut population.

In the general reproductive-age population, observation of ovarian cysts is recommended when the sonographic ovarian mass morphology suggests benign disease.[13] Follow-up ultrasound is recommended whenever there is uncertainty of a diagnosis or when a benign or cancerous neoplasm is in the differential diagnosis.[13] In a preflight astronaut population, benefits may outweigh the risks of laparoscopically managing any ovarian mass not presumed to be a follicular cyst.

While most ovarian cysts are classified as simple (one round fluid-filled sac), "complex" characteristics include multilocularity, solid areas, or papillary excrescences.[90] Complex characteristics, bilateral ovarian masses, or the presence of ascites raise clinical concern. Tumor markers including elevated beta-human chorionic gonadotropin (β-hCG), L-lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), and inhibin levels may be included in a workup for malignancy given their association with germ cell and granulosa cell tumors in reproductive-aged women.[13] Complex ovarian masses are additionally associated with increased risk of ovarian torsion due to asymmetric weight and a lower likelihood of spontaneous resolution.[13] Thus, preflight surgical management of all complex ovarian cysts or adnexal masses may be appropriate, irrespective of biomarker results.

If a female astronaut develops acute abdomino-pelvic pain in flight, a pregnancy test would be necessary to rule out pregnancy-related pathology. An abdominal exam should be performed to evaluate for peritoneal signs, a pelvic exam could evaluate for an adnexal mass, and transabdominal (or transvaginal, if available) ultrasound could be used to evaluate for ovarian torsion or alternative intraabdominal pathology. Given a relative lack of sensitivity and specificity of sonographic evaluation,[125] ovarian torsion can become a surgical diagnosis. Current and predicted future in-flight capabilities do not include surgical management of torsion; thus, conservative measures including pain control and management of sequelae would be appropriate. Complications after nonsurgical torsion management include ischemia and ovarian necrosis, infection, loss of ovarian function with an effect on future fertility, and, less likely, death.[86,168] In the case of ovarian loss with otherwise successful expectant management, data suggest that the nonaffected ovary may compensate for the lack of hormone production from the necrosed ovary[107] and long-term risks of osteoporosis or infertility are low.

Venous Thromboembolism

Astronauts may be at greater risk for thrombosis or VTE during spaceflight due to a number of factors, such as relative lower limb immobility in microgravity, altered hydration status and fluid distribution, elevated stress levels, and immunosuppression.[91,92] The lack of gravity may increase the incidence of upper extremity and cerebral thrombosis. The use of exogenous hormonal modalities may compound this risk.[91,92] Indeed, two recent articles have highlighted a finding of an upper extremity thrombus in an astronaut.[17,124] The authors of these articles discuss risk factors including microgravity-induced blood flow stasis and use of COCs in the development of VTE during spaceflight.[17,124]

In U.S. reproductive-age women, the annual terrestrial VTE risk while using CHCs is 0.7–1.2%, a four- to six-fold increase compared to nonusers[149] or LNG-IUD users.[192] This meta-analysis did not evaluate VTE risk in subgroups using continuous COCs, nor did it address any added risk from the space environment; the actual risk during long-duration spaceflight is unclear. Further, a recent Cochrane review found that third generation COCs are associated with a slightly higher risk for VTE compared to other COCs, and that ethinyl estradiol has a positive dose-response relationship with DVT risk.[21] Continued data collection from astronauts taking CHCs will improve understanding of VTE risk in long-duration spaceflight.

While a detailed discussion of in-flight management of VTE is beyond the scope of this manuscript, if a thromboembolic event were to occur in an astronaut, the risks of continued exogenous exposure to estrogen would likely exceed the risks of normal/abnormal menstrual bleeding from discontinuation of COCs, and discontinuation would be appropriate.

Endometriosis

Endometriosis in itself is not a disqualification for spaceflight unless associated with serious dysmenorrhea, endometriomas, or pelvic adhesive disease.[96] There is no reported increase in incidence or complication of endometriosis during spaceflight.[96] Approximately 10% of terrestrial women of reproductive age suffer from endometriosis. Laparoscopy is the gold standard diagnostic modality; there are no available noninvasive screening modalities to accurately diagnose endometriosis prior to spaceflight.[147] As with other invasive abdominal procedures, laparoscopic investigation for endometriosis has the potential to cause peritoneal adhesions, leading to risks of bowel obstruction (reported as high as 1.5–2.8%) or strangulation and

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ischemia.[55,114] Decisions regarding surgical investigation or treatment of endometriosis should be made on an individual basis. In patients with long-standing endometriosis, continuous CHCs, high-dose progestins, or even GnRH agonists or GnRH antagonists with add back estrogen may be used.[190]

Health Maintenance

As in-flight screening is unlikely to identify pathology that can be managed during a mission, thorough preflight screening should be a mainstay of astronaut health. Additional routine preflight considerations include screening for common sexually transmitted infections including chlamydia, gonorrhea, trichomonas, syphilis, herpes simplex virus (HSV), human immunodeficiency virus (HIV), and human papilloma virus (HPV). For women aged 30–65 yr, a high-risk HPV assay (hrHPV) and cytologic "cotesting" should be performed every 3–5 yr rather than cytology alone.[49,169,171] These guidelines are likely appropriate for the astronaut population, with the additional recommendation of repeating additional cotesting within the 12 mo preceding long-duration spaceflight to identify and manage abnormal findings before flight. The U.S. Food and Drug Administration has approved administration of the HPV vaccine to all men and women aged 9–45 yr.[199,220] Vaccination of all astronauts should be encouraged.

It was previously reported that 23% of ASCANs had a history of treated or current cervical dysplasia.[96] Abnormal HPV or cytologic findings should be managed with the caveat that recommended follow up care will not be available during long-duration missions. Thus, early colposcopy for abnormal cervical dysplasia screening results may be beneficial regardless of age or cytologic abnormality, including a low threshold for cervical biopsy and endocervical curettage.

Other strains of HPV are known to cause genital warts, with a reported prevalence of 7.2% in U.S. reproductive-age populations.[59] While any acute risk of genital warts is exceedingly low during a mission, lesions may cause itching and discomfort, and thus preflight management with imiquimod, laser therapy, or electrocautery may be indicated.[151] Like HPV, HSV can also cause chronic infection, intermittent symptoms, and the potential for operational impact. HSV prevalence is ~16% of the U.S reproductive-age population[200] and, among patients who have had a symptomatic first outbreak, 70–90% will have at least one recurrent outbreak within the first year and an average of two recurrences per year between years 1 and 5.[26] There is increasing evidence of immunosuppression and subsequent reactivation of other viral infections, such as varicella zoster, during spaceflight[44]; it is possible that such risk may translate to an increased risk of HSV reactivation during spaceflight. In the general public, suppressive antiviral therapy is beneficial for patients experiencing four or more recurrences per year[108]; given the low risk of prophylactic medication, future astronauts with a known history of HSV may benefit from daily antiviral suppression for the duration of the mission.[163]

To complete a thorough health maintenance evaluation, screening for perimenopausal symptoms (hot flashes, vaginal dryness, or mood changes), urogynecologic symptoms (urinary/fecal urgency, incontinence, or vaginal bulge symptoms), and vulvar/vaginal dermatoses would be appropriate. Family history of breast, ovarian, uterine, colon, or pancreatic cancer should be documented, and surgical history should be reviewed, including history of cesarean section or hysteroscopic, laparoscopic, or open surgeries of the appendix, uterus, fallopian tubes, ovaries, or cervix.

Family carcinogenesis history would be particularly important in considering the risk of a gynecologic hereditary cancer syndrome including BRCA, hereditary nonpolyposis colorectal cancer (HNPCC), or Cowden's Syndrome. Use of family history and genetic screening for astronaut selection or mission assignment is restricted by the 2008 Genetic Information and Nondiscrimination Act.[159,165] However, such information could help inform astronauts of personalized risk and aid ongoing screening efforts for prevention and early-intervention of disease.[159] Excluding these cancer syndromes, the lifetime risk of breast cancer in U.S. women is around 12%.[50] Some evidence suggests increased risk of breast cancer after exposure to ionizing radiation for therapeutic purposes[50]; however, current reports of astronauts exposed to the space radiation environment have not revealed an increased breast cancer risk. Risk of breast cancer in the astronaut population may yet be increased by prolonged exposure to interplanetary radiation as well as other factors[20] including the common practice of delaying parity and breastfeeding in female astronauts[35,38,104] and, potentially, the use of CHCs or the LNG-IUD.[12,133] Simultaneously, risk may be somewhat reduced by low astronaut incidence of obesity.[160]

Breast cancer has been diagnosed in previously flown astronauts and has resulted in at least one death.[153] In accordance with ACOG and ACR guidelines, clinical breast exams are routinely performed in all female astronauts on an annual basis and annual diagnostic mammograms, with additional ultrasound for dense breast tissue, are routinely performed starting at age 35 yr[96] (as opposed to the terrestrially recommended 40 yr[50]). Though this may lead to a higher discovery rate of benign findings, such as breast cysts, prompting biopsy or excision, the benefits of heightened screening to detect possible early breast cancers outweigh the risks in this subpopulation. Magnetic resonance imaging (MRI) can be used for adjunctive breast tissue evaluation, though specificity is low and MRI may be associated with increased false positive findings.[20,176] However, high sensitivity for abnormal findings may warrant early MRI evaluation, particularly for astronauts assigned to long-duration missions where diagnostic and treatment options are limited.

Pregnancy and Fertility

Intermittent pregnancy testing may be considered during routine medical care for female astronauts, and a final preflight pregnancy test is routinely performed ~10 d prior to launch.[95] Female astronauts should be encouraged to discuss fertility desires and timing before mission assignment. Some female astronauts prefer to delay pregnancy until after spaceflight, and the average maternal age at time of first pregnancy for female

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astronauts is ~35 yr.[96,162] Risks associated with advanced maternal age rise > 35 yr,[75,170] thus, female astronauts should receive individualized counseling regarding age-related risks for reduced ovarian reserve, infertility, miscarriage rates, and aneuploidy (**Table IV**). Historically, fertility outcomes following space travel have been relatively poor[96]; however, current data do not suggest that spaceflight worsens these outcomes compared to age-based norms. Though there is inherent risk from the space environment itself such as the risk of ovarian irradiation, maternal age is likely the driving factor. Female astronauts may desire information and counseling regarding the assessment of ovarian reserve, oocyte or embryo banking, and the utility of prenatal genetic screening.

Currently, pregnancy is an absolute contraindication for space travel. There is a paucity of animal research evaluating the risks to both the mother and fetus in the setting of space radiation or altered gravitational force; it is conservative to assume that risks would be high until more robust data is available.[161,183] While the risk of becoming pregnant can be optimally mitigated during long-duration spaceflight with use of continuous COCs or LNG-IUDs, hormonal modalities are not without the possibility of error. Up to 49% of conceptions in the U.S. reproductive-aged population are unintended, and 48% of those occur while using some form of contraception.[202] Hormonal contraceptive failure rates are declining among U.S. reproductive-aged women, decreasing from 14.9% in 1995 to 10.3% in 2006-2010 based on the National Survey of Family Growth, with failure most likely in the first 3 mo of use.[186] Failure rates vary across contraceptive methods due to discrepancies between ideal use and "typical" use, where effectiveness is limited by patient actions (e.g., variability of dosage timing). Methods that require no participation by the patient, such as IUDs and subdermal implants, have typical uses equal to ideal use (> 99% efficacy). For other methods, typical use is often lower than ideal use. In a given year, COCs are 99% successful at preventing pregnancy with ideal use versus 92% with typical use; similar discrepancies are seen with progestin-only pills (99% vs. 90–97%) and male condoms (98% vs. 85%).[215] Illustrated differently, long-acting methods like the LNG-IUDs will result in 5 pregnancies per year in 10,000 women, while COCs will result in 900 pregnancies per 10,000.[197] These risks compound over a multiyear period.

Patient demographics can also affect unintended pregnancy rates. In the U.S. reproductive-aged population, nulliparous women are less likely to have method failure than parous women (5% vs. 14%).[70] While higher education and socioeconomic status decrease the rate of unintended pregnancy, rates remain elevated, with one study reporting an unintended pregnancy rate of 25/1000 female college graduates and 18/1000 high-income women.[70] In the general population, contraceptive effectiveness can be improved with patient-centered care that allows patients to choose their methods, switch methods as needed, follow up to address issues, and have adequate access to emergency contraception.

Lastly, it is difficult to accurately characterize human sexual behavior in general and not feasible to characterize this in the astronaut population, particularly during future long-duration missions for isolated mixed crews. It is sufficient to state that the risk of pregnancy, including potentially devastating complications of unexpected, ectopic, or abnormal pregnancy, is not zero. The risk of pregnancy would never be ignored in a similar terrestrial circumstance; similarly, these risks should be built into preflight counseling for long-duration spaceflight and should be considered when weighing the risks and benefits of exploration medical capabilities. While all contraceptive modalities have associated risks, the risk of unintended pregnancy during spaceflight likely outweighs all other contraceptive-associated risks.

Table IV. Maternal Age-Related Risks of Various Fetal Chromosomal Abnormalities.

AGED-BASED RISK OF CHROMOSOMAL ABNORMALITIES			
MATERNAL AGE	**T:21***	**T:18***	**ANY CHROMOSOMAL ABNORMALITY**
30 yr	1:700	1:2727	Unknown
35 yr	1:296	1:1152	1:134
40 yr	1:86	1:336	1:49
45 yr	1:22	1:184	1:11

*T:21 = Trisomy 21; T:18 = Trisomy 18.[71]

Additional Postflight Considerations

In addition to typical postflight medical issues, postflight considerations relevant to women's health include long-term decreased BMD and cancer risk. While advancing age is associated with both of these risks, protracted exposure to the space environment may exacerbate or accelerate these processes.

Osteoporosis has fivefold greater prevalence in women and is estimated to affect approximately 30% of women > 50 yr and 77% of women > 80 yr in the U.S.[219] The rate of bone loss in astronauts during spaceflight > 5 mo could be 10 times higher than terrestrial postmenopausal women.[187] While U.S guidelines recommend initiating bone densitometry evaluation via dual-energy X-ray absorptiometry (DXA) in women > 65 yr,[53] standard of care for astronauts includes pre/postflight DXA, triennial DXA thereafter, and consideration of quantitative computed tomography and bone geometry of the hips.[175]

Multiple pharmacologic modalities are available to treat terrestrial loss of BMD. The Institute of Medicine suggests that women aged 51–70 yr consume 1,200 mg · d^{-1} of calcium and 600 IU/day of vitamin D to prevent bone loss.[164] Vitamin D dose should be increased to 800 IU/day for women > 71 yr.[164] Bisphosphonates are generally considered first-line for treatment of known osteoporosis and have been demonstrated to be a useful supplement in the astronaut population during and after flight.[109] Selective estrogen receptor modulators, such as raloxifene, are also antiresorptive and add the benefit of decreasing risk of invasive breast cancer for high-risk patients, though these medications can increase VTE risk.[53,126] Such treatment options could be considered for long-duration astronauts, particularly given a potential for increased risk of cancer secondary to space radiation exposure. Recently published follow-up analyses following the Women's Health Initiative found that

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all-cause mortality (including heart disease and cancer) for all age groups receiving hormonal therapy was unchanged,[120] and that, if instituted before age 60 yr (or within 10 yr of menopause), the benefits of hormonal therapy for bone health may outweigh the risks.[193] Finally, vigilant follow-up with a bone endocrinology specialist would be recommended for all postflight female astronauts for individualized screening and pharmacologic management.

The life-time risk of a cancer diagnosis and cancer-related mortality for U.S. women is approximately 27% and 18%, respectively.[85] Based on current analysis of released data on U.S. astronauts, breast or gynecological cancer incidence has not been found to be increased in female astronauts. Further, use of CHCs is known to reduce the incidence of ovarian and endometrial cancers.[97] New evidence suggests that LNG-IUDs similarly reduce these risks.[210] Even so, prolonged exposure to the interplanetary space radiation environment may alter lifetime risk of cancer. Standard screening recommendations for gynecological cancers in high-risk women in the U.S aged 21–39 yr include pelvic exam if symptomatic, breast self-awareness, self-breast exam monthly on day 7–10 of the cycle, clinical breast exam with a physician every 1–3 yr, and Papanicolaou and HPV screening per ASCCP guidelines.[45,49,51] For women aged 40–64 yr, recommendations include annual clinical breast exam (depending on specialty guidance as clinical utility is uncertain), annual mammogram, consideration of breast MRI, and colonoscopy at 50 yr (and every 10 yr thereafter).[45,49,51] For the postflight female astronaut population, deviations from the above recommendations to be considered include annual clinical breast exam, earlier and more frequent screening for colon cancer (starting at 40 yr and every 5 yr thereafter), annual eye exam, and annual skin exam with a dermatologist.[95,96]

DISCUSSION

In-flight management of gynecological concerns requires a detailed understanding of the complexities and challenges of female reproductive health. Long-duration exploration spaceflight will introduce new challenges for maintenance of gynecological and reproductive health. The impact of the space environment outside of LEO on gynecological concerns remains unknown, with factors such as increased radiation exposure adding complexity and potential risk. Expanding the boundaries of human spaceflight to the Moon, Mars, or other interplanetary destinations adds the challenges of increasing distance from definitive terrestrial health care interventions and limited to no evacuation opportunities. Onboard medical capabilities will be limited by necessity, given constraints of mass, power, and vehicle design, as well as limited skillsets of onboard medical officers. These factors and others may impose greater risk of gynecological complications for female crewmembers in future spaceflight missions.

There is a need for increased data collection and analysis, particularly regarding gynecological risk as well as diagnostic and therapeutic modalities that could be employed in the space environment to address gynecological complications of spaceflight. Prevention of gynecological disease or complication is certainly preferable to onboard treatment options, and thus efforts should be made to focus on expanding preventive medicine efforts that specifically address long-duration spaceflight in remote settings with limited resources. In particular, stability of onboard medications such as contraceptives, hormonal suppression modalities, and acute therapeutic interventions is key as many management options involve the use of pharmaceuticals.[15,30,31] Similarly, any alteration of pharmacokinetics or pharmacodynamics during spaceflight could alter the effectiveness of pharmaceutical-based interventions described above.[30] Finally, age may be a consideration for long-duration mission assignment; while advanced age does decrease the risk of some gynecological concerns (for example, pregnancy), increased age is also associated with higher incidence of other disease (such as neoplasm), comorbidities, pharmaceutical adverse events or interactions, and other considerations.

While thorough screening remains the most effective means of minimizing morbidity and mortality from gynecologic or reproductive pathology, gynecologic concerns in spaceflight can arise unpredictably as they do on Earth. Careful consideration of gynecologic risks and potential adverse events during spaceflight is a critical component to risk analysis and preventive medicine for future exploration missions.

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