

Clinical Finding Form (CLiFF)

Branch

Baseline

ICL123_Pregnancy

Pregnancy is currently an absolute contraindication for space travel. Not only is there a paucity of animal research evaluating the risks to both the mother and the fetus in the space environment, but a pregnancy in space would have dramatic impacts on the crew dynamics, medical risks, and mission outcomes for the entire crew. While the risk of becoming pregnant can be optimally mitigated with perfect use of contraceptive modalities and emergency contraception, even the best hormonal modalities and human intentions are imperfect. While CLiFF 76 covers the risk of pregnancy following success or failure of emergency contraception, this CLiFF pertains to first trimester pregnancy. Terrestrially, while 98-99% of pregnancies are intrauterine, 1-2% are extrauterine (ectopic) pregnancies. Miscarriage occurs in 8-15% of clinically recognized pregnancies and possibly upwards of ~30% of all pregnancies, however, there is a severe paucity of data on such outcomes during spaceflight as a human pregnancy has never been reported in space. This CLiFF presumes a viable intrauterine pregnancy, a miscarriage, or an ectopic pregnancy in the first trimester. Risks of pregnancy outside of the first trimester are beyond the scope of this CLiFF and may be part of a future effort for long-duration spaceflight.

INCIDENCE DATA INCLUDED IN THE MODEL

The model imports the following incidence information from the MEDPRAT Evidence Library Database: incidence data category, space adaption status, EVA status, incidence data type, incidence and occurrence distribution data and incidence data characteristics. Data category defines the type of data available for incidence calculations (i.e. raw data vs. adjusted data). Space adaptation identifies medical events that where onset occurs in the first 5-7 days of flight and does not reoccur. EVA-related incidence values identify medical events that occur only during an EVA. Incidence values types vary by data category and define the number of medical events per person-year (rates) or medical events per person at-risk (proportion) for each medical condition. Incidence values can be modified by crew characteristics such as gender sex and certain crew medical history characteristics. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crewmember in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the MEDPRAT Technical Description Document.

INCIDENCE DATA

SPACEFLIGHT LITERATURE

There is no spaceflight data evaluating the risk of pregnancy. Review of internal data reveals that of the 126 total flights involving females, that there were 6 post-menopausal female astronauts and 120 reproductive-aged astronauts. All males for long-duration missions are presumed to be of reproductive age. The percentage of male or female astronauts who are infertile, have undergone a sterility procedure, or are using contraceptive options has never been formally assessed.

ANALOG LITERATURE

Some of the closest analogs of spaceflight for this condition might include mixed crews at remote research stations such as in Antarctica or deployed military populations. While we do not have access to Antarctic station data, Grindlay has evaluated unintended pregnancy among active-duty women in the military multiple times. The most representative sample within this analog is the officer population. In Grindlay 2013, the rate of unintended pregnancy among officers was 0.02055 (95% CI: 1.389E-2, 2.923E-2), and in Grindlay 2015 it was 0.02774 (95%CI: 2.048E-2, 3.679E-2). To be clear, this would mean that of female officers in the military during a given 12-month period, 1 in 40 would have an unintended pregnancy. Grindlay also evaluated whether the soldiers were on deployment during the period in which unintended pregnancy occurs which can also be used to adjust our modeling and lowers the incidence substantially as discussed below. While US servicewomen had access and autonomy of using contraception during deployment, there is no mention of whether emergency contraception was available and Grindlay's manuscripts call for access to EC for this population. Lastly, while an incidence rate cannot formally be calculated, Belmont 2010 independently evaluated disease and nonbattle injuries sustained by the US Army Brigade Combat Team during Operation Iraqi Freedom and found that of women who were medically evacuated, that 10.8% (35 out of 325) were evacuated for pregnancy-related concerns, providing further evidence of pregnancy as a concern during deployment. Unfortunately, it is not known what percent of unintended pregnancies were ectopic pregnancies, miscarriages, or viable intrauterine pregnancies in this analog population.

TERRESTRIAL LITERATURE

Finer 2016 evaluated unintended pregnancy rates in the U.S. For those of reproductive age with a college degree, the rate of unintended pregnancy is 0.025 (95%CI: 2.271E-2, 2.746E-2) which is consistent with the rates in the analog population above. While only case reports of ectopic pregnancy in analog populations exist, from terrestrial populations we understand that ectopic pregnancy accounts for ~2% of all recognized pregnancies with an annual incidence of 0.0064 in reproductive-aged women 15-44. In the subset of women 35-44, the incidence is 0.0099 (Marion 2012). Early pregnancy loss occurs in 10% of all clinically recognized pregnancies (ACOG, 2015).

OVERALL INCIDENCE SUMMARY

INCIDENCE

Mean 0.005955 SD 4.08E-4

INCIDENCE SUMMARY

The adjusted Bayesian posterior distribution for the incidence rate of unintended pregnancy given all the relevant data under uninformative priors is Gamma (shape=212.927, rate=35755.97) with mean 0.005955 and SD 4.081E-4 per female person year. The incidence rate of unintended pregnancies is taken from terrestrial women with college degrees and officers in the military, adjusted for deployment status, and further adjusted for the rate of pre-menopausal astronauts who have historically flown. This condition should only be applied in the presence of mixed-sex crews.

TABLE 1. INCIDENCE MODEL

Incidence Details

Incidence Type

General

Segment

All

Env. Exposure

NA

Sex

Female

Crowns

Any

Contacts

Any

Pregnancy

No

Incidence Distribution

Occurrence Dist

Poisson

Incidence Dist.

Gamma

Mean

0.00595501

SD

0.0004081

Gamma

(Shape): 212.927

(Rate): 35756

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Finer, 2016	Terrestrial	2
Grindlay, 2013	Analog	2
Grindlay, 2015	Analog	2
Belmont, 2010	Analog	1
Marion, 2012	Terrestrial	2
ACOG, 2015	Terrestrial	2

Given that all data is taken from terrestrial and analog populations and requires multiple adjustments, our LOC remains neutral.

CREWMEMBER SELECTION/PREVENTION

DISQUALIFYING CONDITIONS

Refer to Medical Evaluation Documents (MED) Volume A, Medical Standards for ISS Crewmembers, International Space Station Program, Rev 3.4 (2016).

PREFLIGHT PREVENTATIVE MEASURES

Astronauts are extensively counseled regarding contraceptive options pre-flight and have the autonomy to choose their form of contraceptive or decide to not use contraception. Furthermore, a pregnancy test is completed within 10 days of flight. This does not completely exclude the possibility of intercourse with a risk for pregnancy occurring during the 10-days before flight. While this risk is not directly factoring into our modeling, the chance of this occurring likely remains consistent with our risk of intercourse modeling already.

BEST CASE SCENARIO DEFINITION

First trimester intrauterine pregnancy inclusive of uncomplicated early pregnancy loss not requiring surgical management.

WORSE CASE SCENARIO DEFINITION

Ectopic pregnancy OR complicated early pregnancy loss requiring surgical management.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None.

BEST CASE/WORST CASE PROBABILITY COMMENTS

While there is no spaceflight data or analog data evaluating the rate of intrauterine vs. ectopic pregnancy, per terrestrial data, the incidence of ectopic pregnancy is 19.7/1000 confirmed pregnancies (Marion, 2012). Furthermore, the rate of emergency curettage for excessive bleeding following medical treatment failure of an intrauterine pregnancy with mifepristone and misoprostol is less than 1% (ACOG 2014). As mifepristone and misoprostol are now a standard of care for maximizing the success of non-surgical management of early pregnancy loss (Schreiber, 2018), an overall BC/WC probability of 98%/2% is reasonable.

TABLE 3. BEST/WORST CASE PROBABILITY LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Marion, 2012	Terrestrial	2
ACOG, 2014	Terrestrial	2
Schreiber, 2018	Terrestrial	2

The BC/WC probability is limited by the fact that we do not know rates of ectopic pregnancy amongst spaceflight or analog populations and thus must use terrestrial data (Marion, 2012). Further, if pregnancy were to occur during spaceflight, it is unknown if risks inherent to the space environment may increase the risk of ectopic pregnancy or complicated early pregnancy loss or interfere with medical treatment leading to the need for surgical management.

TABLE 4. CLIFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

Case Scenario	Composite Incidence	Condition Probability %	CP1: Diagnosis		CP2: Treatment			CP3: Condition End State				
			TI%	Duration	TI%	Duration		TI%	RTDC	LOCL		
			Preset	Preset	Preset	Min	Max	Preset	Min%	Max%	Min%	Max%
Treated Best Case (TBC)	mean 0.005955 and SD 4.081E-4	98 - 98	100	1.416	3.25538	24	1344	0	100	100	0	0
Treated Worst Case (TWC)		2 - 2	100	1.916	36.5001	24	336	0	100	100	0	30
Untreated Best Case (UTBC)	N/A	N/A	N/A	1.416	6.85623	24	1344	6.85623	100	100	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1.916	100	24	336	100	100	100	0	60

TABLE 4 KEY

Composite Incidence: The same composite incidence will be used for both TBC and TWC. For EVA conditions: events per EVA (events/EVA). For space adaptation conditions: events per person (events/person). For non-spaceflight conditions: events per person year (events/py).

Condition Probability: The probability that CLIFF condition progresses to a worst case scenario. Best case scenario: 100%-Worst Case.

Clinical Phase General Comments:

- TI% = Task Impairment %. Task Impairment is the % of tasks that the crewmember is incapable of performing without impairment secondary to the medical condition.
- Durations are defined in hours.
- Removal to Definitive Care (RTDC): The probability the entire crew aborts the mission and returns to earth. This is considered as a condition end state result if any of the following criteria are met: 1) the potential for LOCL, 2) potential for significant permanent task impairment, or 3) potential for intractable pain.
- Loss of Crew Life (LOCL): The probability of death of affected crewmember due to medical condition.

Clinical Phase 1: Initial Assessment and Diagnosis:

- Covers only the initial assessment and diagnosis of the affected crewmember to define his or her medical condition. While the affected crewmember is being assessed, he or she is not able to perform any assigned tasks, thus Task Impairment (TI) during this phase is considered 100%. In the untreated case, there is no diagnosis performed, therefore Task Impairment and Duration will always be " not applicable."

Clinical Phase 2: Stabilization, Treatment, and Convalescence:

- The affected crewmember is receiving any appropriate initial or follow-on treatment for his or her medical condition to allow the crewmember to recover as much as he or she is able to recover in the spaceflight environment. Clinical phase 2 also encompasses relapses or recurrences of the same original medical condition in Clinical Phase 1. The duration of Clinical Phase 2 is expressed as minimum and maximum hours.

Clinical Phase 3: Condition End State:

- Reached once the affected crewmember has recovered from the medical condition as much as he or she is able to recover in the spaceflight environment amongst treated and untreated best and worst case scenarios. This may or may not be recovery from the given medical condition to the full extent possible. If this "recovered" state results in Removal to Definitive Care (RTDC) or Loss of Crew Life (LOCL) this will be noted in the condition end state results.

SCENARIO OVERVIEW COMMENTS

Pregnancy in general carries a high rate of morbidity. Ectopic pregnancy is very dangerous and accounts for 4-10% of pregnancy-related deaths terrestrially. Pregnancy in spaceflight may be extremely high risk not only to the individual who is pregnant, but also places the entire success of the mission in jeopardy.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

In a TBC scenario either a viable intrauterine pregnancy is found and managed expectantly without complication, or early pregnancy loss occurs and either resolves without complication spontaneously or is managed with mifepristone/misoprostol and does not lead to excessive bleeding, retained products of conception, intrauterine infection, or other complication that requires surgical management.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

This scenario in fact encompasses two scenarios. Either an intrauterine pregnancy occurs and it is either a miscarriage that requires surgical management, OR it is an ectopic pregnancy. Bleeding from a miscarriage would be managed with available non-surgical techniques such as uterine tamponade with a Foley balloon and tranexamic acid, and an unruptured early ectopic pregnancy would be managed with intramuscular methotrexate.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

As with TBC, either the pregnancy is managed expectantly through the first trimester or ends in a miscarriage that resolves spontaneously.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

In this scenario, a complicated miscarriage with likely heavy bleeding is occurring or an ectopic pregnancy is present. In both of these settings without treatment, there would be catastrophic risks to the patient and mission.

TABLE 5. CLINICAL PHASE II DURATION LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
ACOG, 2015		2

Generally, amongst women having menses, a pregnancy test is performed the first week that a period is missed. This week represents the "4 weeks of gestation" but in actuality, it is the 2nd week of the pregnancy. As the CLIFF definition is limited to the first trimester, the max duration would be from Week 4 with an early diagnosis to Week 12 which would represent 8 weeks or 1344 hours. Thus for the BC scenarios, an uncomplicated intrauterine pregnancy or spontaneous miscarriage may be noted within the first 24 hours after a period is missed or the duration may extend through 1344 hours (12 weeks). Moving into the second trimester would be beyond the scope of this CLIFF. If a complicated miscarriage or ectopic pregnancy is noted, the duration can also range from 24 hours through the first trimester, although this would be exceedingly rare as most ectopic pregnancies will rupture by 12 weeks gestation. Given these uncertainties, the LOCL is neutral.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Clinical subject matter expert consensus opinion		4

If pregnancy were to occur in space whether complicated or not, this would necessitate a 100% chance to return to definitive care. This decision by consensus expert clinical opinion is made with high level of confidence.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Marion, 2012	Terrestrial	2
Sagiv, 2012	Terrestrial	
Lawani, 2013	Terrestrial	
Barash, 2014	Terrestrial	
Harylyshyn, 2018	Terrestrial	
Tailor, 2004	Terrestrial	

There is not spaceflight or analog data to evaluate LOCL from first trimester pregnancy. Amongst the terrestrial population, there is also not robust data from resource-limited (no surgical capability) environments. The risk of mortality from ectopic pregnancies with the availability of surgical management has decreased to a rate of 0.5 per 100,000. Unfortunately, per Tailor, only 40% of all tubal ectopic pregnancies were safely managed with expectant management (60% failure). In other studies, the rate of treatment failure with methotrexate can still be as high as 40%. With no surgical options available to treat an ectopic pregnancy that has failed expectant and medical management, the chance of LOCL could theoretically be as high as 60% in the worst case if the ectopic pregnancy ruptured and led to uncontrollable intra-abdominal hemorrhage. As treatment can work, this risk was halved for the TBC scenario. This LOC is very limited given the lack of any modern evidence for outcomes without surgical intervention of ectopic pregnancy.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Overview This Cliff assumes that pregnancy has already occurred. The pregnancy can be intrauterine or extrauterine. If intrauterine, there is a high risk of miscarriage, and thus management options include expectant management, pharmacologic management of an inevitable, complete, incomplete, or missed abortion. This condition can also consider pharmacologic management of medical abortion. If extrauterine, given the dangers associated with a pregnancy occurring in a location that is not compatible with life nor can contain a growing pregnancy, the recommendations would be for pharmacologic management of the ectopic pregnancy. CNES: None Diagnostic Scope and Resourcing As the best-case scenario may predominantly be characterized by an uncomplicated intrauterine pregnancy, it can also include an uncomplicated miscarriage. This is deemed uncomplicated because it does not require surgical management to reach resolution. The diagnostic resourcing for the best case scenario would involve taking an HPI, checking vital signs, performing an abdominal/pelvic physical exam, checking a pregnancy test, and performing an ultrasound. Transvaginal ultrasound would be primary 1 if available, and transabdominal ultrasound would be a secondary option. For the worst-case scenario which would include complicated intrauterine pregnancies or ectopic pregnancies that may require surgery, additional CP1 resourcing includes placement of an IV and collection of a CBC and serum bHCG. Clinical Phase 1 Duration and Rationale This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows: CP1 BC (Treated or Untreated): 1.41 CP1 WC (Treated or Untreated): 1.91 The duration involves obtaining a history, standard set up time and analysis of the pregnancy test. It is the same for both BC and WC. Treatment Scope and Resourcing For the best-case scenario, an uncomplicated intrauterine pregnancy for which expectant management is desired may only require a prenatal vitamin. However, if a miscarriage occurs or the pregnancy is desired to be interrupted, mifepristone and misoprostol can be used. In the worst-case scenario, retained products of conception leading to severe can occur, however, surgical options such as dilation and curettage will be unavailable. Thus, management strategies can include TXA, uterine tamponade with a foley catheter, oral and IV hydration, blood transfusion, and a blood transfusion reaction bundle. If the pregnancy is an ectopic, the standard of care is intramuscular methotrexate and checking repeat bHCG levels on day 4 and day 7 after. Surgical management for ectopic pregnancy will not be available. Support Needs Ground-support can assist with worst-case diagnosis, however, is not needed for best-case diagnosis. They can also assist with treatment recommendations in the worst-case scenario. References The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstet Gynecol. 2015 May;125(5):1258-1267. doi: 10.1097/01.AOG.0000465191.27155.25. PMID: 25932865. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy. Obstet Gynecol. 2018 Mar;131(3):e91-e103. doi: 10.1097/AOG.0000000000002560. Erratum in: Obstet Gynecol. 2019 May;133(5):1059. PMID: 29470343. Practice bulletin no. 143: medical management of first-trimester abortion. Obstet Gynecol. 2014 Mar;123(3):676-692. doi: 10.1097/01.AOG.0000444454.67279.7d. PMID: 24553166. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. N Engl J Med. 2018 Jun 7;378(23):2161-2170. doi: 10.1056/NEJMoa1715726. PMID: 29874535; PMCID: PMC6437668. Song T, Kim MK, Kim ML, Jung YW, Yun BS, Seong SJ. Single-dose versus two-dose administration of methotrexate for the treatment of ectopic pregnancy: a randomized controlled trial. Hum Reprod. 2016 Feb;31(2):332-8. doi: 10.1093/humrep/dev312. Epub 2015 Dec 23. PMID: 26701971.

IMM CLIFF RECONCILIATION COMMENTS

No previous IMM.

LIMITATIONS SUMMARY

The data driving this CLIFF is very limited given mammalian pregnancy has never occurred in spaceflight to date. However, if a pregnancy does occur, this will be very dangerous to the astronaut and the crew. The predominant limitation occurs with the incidence in that spaceflight data for this condition do not exist. Further limitations include combining multiple pathologic outcomes such as miscarriage and ectopic pregnancy into one definition despite their clinical differences. Duration is limited by the definition, a proper RTDC decision is assumed by expert clinical opinion, and the LOCL is extremely limited given we do not even have robust terrestrial data on mortality rates for ectopic pregnancy in the absence of a surgical option. Thus, LOCL rates are based off of treatment failure rates, though treatment failure does not necessarily equal LOCL.

TABLE 8. TASK IMPAIRMENT CALCULATION BASED ON AFFECTED HUMAN SYSTEMS TASK CATEGORIES (HSTC)

Clinical Phase 2: Treatment												
	Affected HSTCs											
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)												
Untreated Best Case (UTBC)									13			
Treated Worst Case (TWC)	223	664		89			145		13	6		
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6		
	Affected HSTCs (Continued)								TI Calculation		TI Score	
	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)							34	211	245	3763	0.0651076	6.51076
Untreated Best Case (UTBC)							34	211	258	3763	0.0685623	6.85623
Treated Worst Case (TWC)	132	564	414	22	196	34	34	211	2747	3763	0.730003	73.0003
Untreated Worst Case (UTWC)	132	564	414	22	196	34	34	211	3763	3763	1	100
Clinical Phase 3: Condition End State												
	Affected HSTCs											
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)												
Untreated Best Case (UTBC)									13			
Treated Worst Case (TWC)												
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6		
	Affected HSTCs (Continued)								TI Calculation		TI Score	

	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	T1 Decimal	T1 %
Treated Best Case (TBC)									0	3763	0	0
Untreated Best Case (UTBC)							34	211	258	3763	0.0685623	6.85623
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)	132	564	414	22	196	34	34	211	3763	3763	1	100

TABLE 8 KEY

Human System Task Category (HSTC) Definitions: Cognitive-Simple: Tasks requiring simple cognitive involvement (low levels of attention, following simple checklists, and not requiring extensive decision making) in conjunction with inputs from other systems. Cognitive-Complex: Tasks requiring complex cognitive involvement (requiring constant attention, frequent interpretation of outside stimuli to inform real-time situations) in conjunction with inputs from other systems. Communication: Tasks requiring primarily communication, via hearing and speaking. Interpersonal Skills: Tasks requiring interpersonal, social interaction between crew including complex technical tasks that require extended crew interaction. Vision: Tasks in which visual information is required. Hearing: Tasks in which primarily auditory information is required, excluding communication, e.g. hearing alarms, medical auscultation, OOHAs. Cardiopulmonary: Tasks requiring greater-than-baseline cardiopulmonary effort, e.g. physically strenuous activities. Dentition: Tasks requiring use of teeth for mastication. GI (Gastrointestinal): Tasks requiring use of the alimentary system, e.g. solids/liquids consumption and solids excretion. GU (Genitourinary): Tasks requiring use of the male/female genitourinary systems. Hand (Dominant): Tasks performed using primarily the hand, requiring use of the dominant hand (piloting, medical procedures, dental procedures). Hand (Any): Tasks performed using primarily the hand(s), with no preference for dominance, with equivalent bilateral effectiveness. Upper Extremity: Tasks requiring specific use of the upper extremities, excluding hands. Lower Extremity: Tasks requiring specific use of the lower extremities (excluding ambulation and standing in the presence of gravity), e.g. using exercise equipment. Ambulation and Standing (g): Tasks requiring use of both lower extremities to accomplish ambulation or standing in the presence of gravity. Translation and Stabilization (microgravity): Tasks requiring use of either the upper or lower extremities to accomplish translational movement and stabilization (securing oneself to remain stationary) in the setting of microgravity. Don/Doff Equipment: Tasks requiring the donning of personal equipment (including pressure suit, exercise harness, EVA equipment, etc). Pressure Ops: EVA/contingency tasks performed while pressurized in a suit.

Criteria for Assignment of Conditions to HSTCs (any of the following):

- 1) Is affected crew member physically incapable of performing the human system task category, without impairment, with the condition?
- 2) Would the treatment (e.g. medications) impair the crewmember's ability to perform the human system task category? (Does not apply to UTx)
- 3) Does the condition have a high likelihood of causing a significant aeromedical contraindication with an associated human system task category?
- 4) Would performing tasks in an associated task category worsen the condition? (If so, it is affected).
- 5) Does pain associated with the condition impair any further human system categories?

TASK IMPAIRMENT COMMENTS

No comments.

EVIDENCE COLLECTION PROCESS

Mesh terms that most closely resembled the best-case and worst-case scenarios, and associated Conditions Included but Not Explicitly Stated (CNES), were utilized to build incidence, duration, RTDC, and LOCL searches by best- and worst-case.

Incidence:

Databases searched for spaceflight and analog incidence data included: PubMed, Google Scholar, NASA Technical Reports Server (NTRS) public search, Defense Technical Information Center (DTIC), and Barratt MR, Baker E, Pool SL. Principles of Clinical Medicine for Space Flight. New York, NY: Springer; 2019. 2nd Edition. Databases searched for terrestrial incidence included: DynaMed, PubMed, and Google Scholar.

Duration, RTDC, LOCL:

Databases searched for duration, RTDC, and LOCL included: Dynamed, Cochrane, PubMed, and Google Scholar. Note, that if duration, RTDC, or LOCL data was found in a DynaMed search, the other search engines were not included. Relevant articles were selected and reviewed. If applicable, the article was included in the CLIFF.

LEVEL OF CONFIDENCE (LOC) SCORING

Articles obtained to update the evidence behind this CLIFF were scored by ExMC editors, based on their applicability to the Exploration Spaceflight environment using the following grading scale:

- 4 – Confident
- 3 – Somewhat confident
- 2 – Neutral
- 1 – Somewhat unconfident
- 0 – Not confident

The following considerations factor into the grading scale above:

- How closely does the paper describe the medical condition as defined by the IMPACT 1.0 Condition List (relevance)?
- How closely does the population included resemble the astronaut population?
- Quality of the paper (number of subjects, methods, etc.)
- How much does the editor trust the source of the evidence?
- How closely does the editor think that the data represents the exploration spaceflight environment?
- Other considerations, at the discretion of the editor, supported in the comments for LOE scoring.

REFERENCES

Reference

The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. *Obstet Gynecol.* 2015 May;125(5):1258-1267. doi: 10.1097/01.AOG.0000465191.27155.25. PMID: 25932865.

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy. *Obstet Gynecol.* 2018 Mar;131(3):e91-e103. doi: 10.1097/AOG.0000000000002560. Erratum in: *Obstet Gynecol.* 2019 May;133(5):1059. PMID: 29470343.

Practice bulletin no. 143: medical management of first-trimester abortion. *Obstet Gynecol.* 2014 Mar;123(3):676-692. doi: 10.1097/01.AOG.0000444454.67279.7d. PMID: 24553166.

Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med.* 2016; 374(9):843–852.

Grindlay K, Grossman D. Unintended pregnancy among active-duty women in the United States military, 2011. *Contraception.* 2015 Dec;92(6):589-95. doi: 10.1016/j.contraception.2015.07.015. Epub 2015 Sep 4. PMID: 26345183.

Holt K, Grindlay K, Taskier M, Grossman D. Unintended pregnancy and contraceptive use among women in the U.S. military: a systematic literature review. *Mil Med.* 2011 Sep;176(9):1056-64. doi: 10.7205/milmed-d-11-00012. PMID: 21987966.

Goyal V, Borrero S, Schwarz EB. Unintended pregnancy and contraception among active-duty servicewomen and veterans. *Am J Obstet Gynecol.* 2012;206(6):463-469. doi:10.1016/j.ajog.2011.11.018

Grindlay K, Grossman D. Contraception access and use among U.S. servicewomen during deployment. *Contraception.* 2013 Feb;87(2):162-9. doi: 10.1016/j.contraception.2012.09.019. Epub 2012 Oct 31. PMID: 23121821.

Auñón-Chancellor SM, Pattarini JM, Moll S, Sargsyan A. Venous Thrombosis during Spaceflight. *N Engl J Med.* 2020 Jan 2;382(1):89-90. doi: 10.1056/NEJMc1905875. PMID: 31893522.

Westhoff CL, Torgal AT, Mayeda ER, Shimon N, Stanczyk FZ, Pike MC. Predictors of noncompliance in an oral contraceptive clinical trial. *Contraception.* 2012 May;85(5):465-9. doi: 10.1016/j.contraception.2011.09.019. Epub 2011 Nov 12. PMID: 22079603.

Powell-Dunford NC, Cuda AS, Moore JL, Crago MS, Kelly AM, Deuster PA. Menstrual suppression for combat operations: advantages of oral contraceptive pills. *Womens Health Issues.* 2011 Jan-Feb;21(1):86-91. doi: 10.1016/j.whi.2010.08.006. PMID: 21185993.

Trego LL, Jordan PJ. Military women's attitudes toward menstruation and menstrual suppression in relation to the deployed environment: development and testing of the MWATMS-9 (short form). *Womens Health Issues.* 2010 Jul-Aug;20(4):287-93. doi: 10.1016/j.whi.2010.03.002. PMID: 20627773.

Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. *Clin Obstet Gynecol.* 2012 Jun;55(2):376-86. doi: 10.1097/GRF.0b013e3182516d7b. PMID: 22510618.

Steller JG, Blue RS, Burns R, Bayuse TM, Antonsen EL, Jain V, Blackwell MM, Jennings RT. Gynecologic Risk Mitigation Considerations for Long-Duration Spaceflight. *Aerosp Med Hum Perform.* 2020 Jul 1;91(7):543-564. doi: 10.3357/AMHP.5538.2020. PMID: 32591031.

Sagiv R, Debby A, Feit H, Cohen-Sacher B, Keidar R, Golan A. The optimal cutoff serum level of human chorionic gonadotropin for efficacy of methotrexate treatment in women with extrauterine pregnancy. *Int J Gynaecol Obstet.* 2012;116(2):101–104.

Barash JH, Buchanan EM, Hillson C. Diagnosis and management of ectopic pregnancy. *Am Fam Physician.* 2014 Jul 1;90(1):34-40. PMID: 25077500.

Lawani OL, Anozie OB, Ezeonu PO. Ectopic pregnancy: a life-threatening gynecological emergency. *Int J Womens Health.* 2013 Aug 19;5:515-21. doi: 10.2147/IJWH.S49672. PMID: 23983494; PMCID: PMC3751381.

ACRONYMS

ACRONYM	PHRASE
AAOMS	American Association of Oral and Maxillofacial Surgeons
AMA	American Medical Association
ARCL	All Remaining Conditions List
ARS	Acute Radiation Sickness
BHP	Behavioral Health and Performance
CAC	Coronary Artery Calcium

CHS	Crew Health and Safety
CL	Condition List
ClIFF	Clinical Finding Form
CMO	Crew Medical Officer
COMFORT	Clinical Outcome Metrics for Optimization of Robust Training
CP1	Clinical Phase 1
CP2	Clinical Phase 2
CP3	Clinical Phase 3
CRL	Clinical Resource Level
CRT	Capability Resource Table
CST	Clinical Science Team
DCS	Decompression Syndrome
DRM	Design Reference Mission
ED	Emergency Medicine Doctor
EL	Evidence Library
EMCL	Exploration Medical Condition List
EMT	Emergency Medical Technician
EVA	Extravehicular Activity
EXMC	Exploration Medical Capability
HRP	Human Research Program
ICD	International Classification of Disease
ICL 1.0	IMPACT 1.0 Medical Conditions List
ICU	Intensive Care Unit
IMCL	iMED Condition List
IMED	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT-MD	Impact Medical Database
IP	Incidence Proportion
IR	Incidence Rate
ISS	International Space Station
IV	Intravenous
JSC	Johnson Space Center
LEO	Low-Earth orbit
LEVA	Lunar Extravehicular Activity
LOCL	Loss of Crew Life
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSO	Lunar Surface Operations
MCL	Master Condition List
MEVA	Medical Extravehicular Activity
NASA	National Aeronautics and Space Administration
N/A	Not Applicable
NP	Nurse Practitioner

OBGYN	Obstetrics and Gynecology
OR	Occurrence Rate
PA	Physician Assistant
PDQ	Pain Disability Questionnaire
PFCL	Proposed Future Conditions List
PPE	Personal Protective Equipment
PTRS	Project Technical Requirements Specification
PRL	Pharmaceutical Resource Level
QTL	Quality Time Lost
RCL	Removed Conditions List
REP	Rochester Epidemiology Study
RTDC	Removal to Definitive Care
SANS	Spaceflight-Associated Neuro-ocular Syndrome
SAS	Space Adaptation Syndrome
SEVA	Spaceflight Extravehicular Activity
SME	Subject Matter Expert
SoP	Standard Operating Procedure
SPE	Solar Particle Event
TBD	To Be Determined
TI	Task Impairment