HORMONE THERAPY AND VENOUS THROMBOEMBOLISM RISK DURING SPACE TRAVEL

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ACADEMIC CLINICAL FELLOW
Introduction
# Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of humans in space</td>
<td>534</td>
</tr>
<tr>
<td>Total females in space</td>
<td>57</td>
</tr>
<tr>
<td>Total US astronauts in space</td>
<td>330</td>
</tr>
<tr>
<td>Total US female astronauts in space</td>
<td>48</td>
</tr>
<tr>
<td>Age range at US selection</td>
<td>26-47 yrs</td>
</tr>
<tr>
<td>Mean age US ASCAN* finalist</td>
<td>32 yrs</td>
</tr>
<tr>
<td>Mean age US female astronaut at first flight</td>
<td>38 yrs</td>
</tr>
<tr>
<td>2013 selected female ASCANs*</td>
<td>50%</td>
</tr>
</tbody>
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*ASCAN – astronaut candidate
Menstrual Cycle

CAUSES OF INFERTILITY

- Female: 30%
- Male: 30%
- Male & Female: 20%
- Unknown: 20%
Benefits of Menstrual Suppression

50 versus 450 menstruations per lifetime

Similar contraceptive efficacy and safety profiles to cyclic use
No difference in compliance or discontinuation due to bleeding
Fewer hormonal side effects
Bleeding patterns improved with continuous use
Edelman et al, Cochrane, 2014

Aids endometriosis, menorrhagia, dysmenorrhea
Menstrual Suppression for Astronauts

- Pregnancy delays selection process
- Pregnancy contraindicated for most training activities
- Contraindicated for spaceflight
- Waste management systems on board station
- Microgravity environment

Personal choice
Options for Menstrual Suppression

Oral Contraceptive Pills

Hormone based intra-uterine systems (IUS) e.g. Mirena or Skyla

Hormone based subdermal implants e.g. Implanon
Hormone Profiles with the OCP

Diagram showing the hypothalamus regulating the anterior pituitary, which controls the ovaries. The diagram highlights the feedback mechanisms involving GnRH, LH, FSH, activin, inhibin, estrogen, and progesterone. OCP (Oral Contraceptive Pill) is indicated as a regulatory point in the diagram.
Hormone Profiles with the OCP

1. Inhibition of FSH
2. Follicle maturation does not occur
3. Estrogen levels do not rise
4. No LH surge
5. No ovulation
6. No corpus luteum
7. No rise in progesterone
8. Endometrium thin and sheds with 7 days of placebo pills
The Contraceptive Pill

• 1950s - 21/7 cycle due to cultural and social pressures

• Combined estrogen and progesterone – multiple preparations

• Inhibits ovulation and changes cervical mucus

• Failure rate – 1%

• Contra-indications: thromboembolic disease, cerebrovascular disease, migraine, diabetes, liver disease, breast cancer, hypertension

• Interactions with other medications due to liver metabolism

• Interference with blood lab tests

• VTE risk doubled
Intra-Uterine Devices (IUDs)

- Intra-uterine camel pebbles
- 1909 – first intra-uterine ring
- 1970s - Dalkon Shield had high rates of pelvic inflammatory disease

- Safe, effective, long acting, reversible

- Non-hormonal IUDs - Copper
- Hormonal IUDs – Levonorgestrel (progestin)
- Mirena - 52mg levonorgestrel; Skyla – 13.5mg levonorgestrel
- Inserted with ultrasound guidance in clinic
Mechanism of Action - Levonorgestrel IUS

- Localized effects
- Down-regulates endometrial estrogen and progesterone
- Endometrium insensitive to circulating estradiol
- Strong anti-proliferative effect

- Mirena (hormonal IUD) can suppress bleeding completely
- Does not affect BMD  
  Wong et al, Aus NZ J Obs Gyn, 2010
- Can be used in conjunction with oral estrogen
- Uterine perforation or expulsion – rare  
  Heineman et al, Am J Obs Gyn, 2014
Hormonal Implant

• Nexplanon or Implanon – etonogesterel (progestin)
• Sub-dermal, single rod contraceptive implant
• Long acting, reversible

• Most effective contraceptive currently available
• Mechanism of action: inhibits ovulation
• Oestradiol levels above threshold for maintaining bone mass  
  Beerthuizen et al, Human Reproduction, 2000

• Only 1 in 10 stop due to irregular bleeding
• 1 in 5 users have amenorrhea within 3 years
Recommendations for menstrual suppression

• Oral contraceptives effective (compliance issues)
• Long acting reversible contraceptive (LARC) possible
• Mirena preferential
• Implanon – potential for irregular bleeding but due to normal BMI of astronauts, may not be a problem

• Start one year prior to flight at minimum
• Add back low dose estrogen (suggest 10 mcg) alongside LARC
• Estrogen effects on bone

• Introduce having a TV US probe on station
Venous Thromboembolism (VTE)

“Venous Thromboembolism is a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE)”

i.e. blood clots in the venous system of the legs or lungs

Sudden Death

Underdiagnosed

Lethal

Preventable

Common

Dangerous

Serious

Treatable

Economic burden

Silent killer

Public health problem
Risk Factors for VTE

- Smoking
- Age
- Demographic Status
- Family History
- Hormone Replacement Therapy
- Contraceptive Pill
- Rheumatoid Arthritis
- Congestive Cardiac Failure
- Asthma
- Cancer
- Obesity
- Immobility
- Hospitalization
- Hyperhomocysteinaemia
- Varicose Veins
- Hip Fracture/Surgery
- Pregnancy
- Thrombophilia
- Contraceptive Pill
VTE and spaceflight

• No episodes pre-, during or post-flight documented
• Oral contraception doubles risk of VTE terrestrially
• Terrestrial risk calculators do not consider astronaut selection, pre-flight training or space flight environment
• Pre-flight Training:
  – Long haul travel
  – Diving
  – Injury risk
  – Immobility – Soyuz training
Potential In flight Risk Factors

- **Hemoglobin**: <1st centile $\rightarrow$ OR of VTE is 3.4
- **Mean Corpuscular Volume (MCV)**: <1st centile $\rightarrow$ OR for VTE is 1.95 (hematinics); >99th centile $\rightarrow$ OR for VTE is 2.65
- **Hematocrit**: upper 20% of normal range $\rightarrow$ 1.5 times $\uparrow$ VTE risk
- **Reticulocyte count**: indication of blood turnover
- **Platelet count**: acute phase protein, high levels increase coagulability of blood
- **Prothrombin time**: <11 secs $\rightarrow$ increased coagulability of blood
- **Homocysteine**: >15mcmol/L $\rightarrow$ RR of VTE is 1.5-2 (increases due to Vit B12, folate deficiency)
Methods

• LSAH database – medical and research data
• Post 2000, female short and long duration flights, not on HRT
• Repeat fliers counted as separate episodes

• Last pre-flight value and first post-flight value used to calculate:
  1. Comparing post-flight data of dependent variables to normative high risk data from the literature.
  2. Characterizing descriptively the changes between pre vs post-flight data of each dependent variable and determining if significant changes by using repeated measures t-test.

HYPOTHESIS: Predict spaceflight does not increase risk of VTE compared to terrestrial population
First pass analysis of data from short duration suggests no obvious trend towards abnormality or increased risk of VTE, thus supporting hypothesis.
Haemaglobin

• Hemoglobin: <1st centile → OR of VTE is 3.4
• **Mean Corpuscular Volume (MCV):**
  - <1st centile → OR for VTE is 1.95 (hematinics);
  - >99th centile → OR for VTE is 2.65
Iron Preflight

Iron Postflight

Green bars indicate increases post-flight relative to pre
Purple bars indicate decreases post-flight relative to pre
Total Iron Binding Capacity

No OCP Use in flight

Used OCP in flight

Total Iron Binding Capacity Preflight

Green bars indicate increases post-flight relative to pre
Purple bars indicate decreases post-flight relative to pre

Total Iron Binding Capacity Postflight
Ferritin

No OCP Use in flight

Used OCP in flight

Person-Flight

- Ferritin ng/ml Preflight
- Ferritin ng/ml Postflight

Green bars indicate increases post-flight relative to pre
Purple bars indicate decreases post-flight relative to pre
Transferrin

<table>
<thead>
<tr>
<th>Person-Flight</th>
<th>No OCP Use in flight</th>
<th>Used OCP in flight</th>
</tr>
</thead>
</table>

- Green bars indicate increases post-flight relative to pre
- Purple bars indicate decreases post-flight relative to pre

Transferrin (%) Saturation Preflight

Transferrin (%) Saturation Postflight
Reticulocyte count

Green bars indicate increases post-flight relative to pre
Purple bars indicate decreases post-flight relative to pre

• *Reticulocyte count*: indication of blood turnover
**Haematocrit**

- **No OCP Use in flight**
- **Used OCP in flight**

Green bars indicate increases post-flight relative to pre.
Purple bars indicate decreases post-flight relative to pre.

- **Hematocrit**: upper 20% of normal range → 1.5 times ↑ VTE risk
**Platelet Count**

- **Platelet count**: acute phase protein, high levels increase coagulability of blood.

Green bars indicate increases post-flight relative to pre.
Purple bars indicate decreases post-flight relative to pre.
Prothrombin Time

- **Prothrombin time**: <11 secs → increased coagulability of blood

Green bars indicate increases post-flight relative to pre
Purple bars indicate decreases post-flight relative to pre
• Current menstrual suppression regimes could be adapted to LARC use +/- estrogen add-back
• Additional risk factors for astronaut population could include:
  – Lack of lower limb activity
  – Levels of dehydration and red cell lysis
  – Stress as an immunosuppressant
  – Radiation impacts
• Exercise mitigation strategies
• Compression stockings post-flight
• Longer duration missions and their impact
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