HORMONE THERAPY AND VENOUS THROMBOEMBOLISM RISK DURING SPACE TRAVEL

VARSHA JAIN

ACADEMIC CLINICAL FELLOW

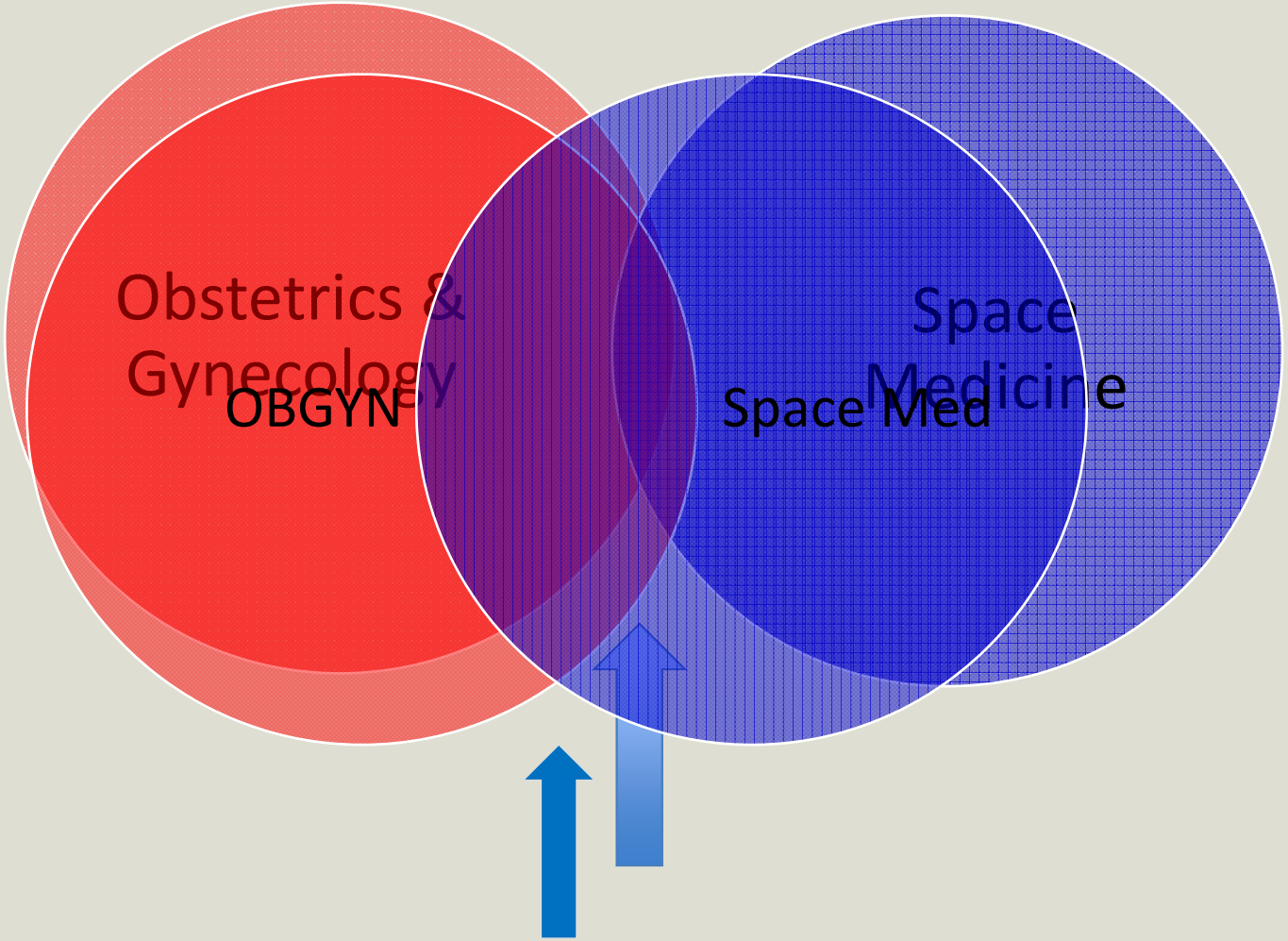
Barts Health NHS
NHS Trust

School of Biomedicine

Centre of Human and Aerospace Physiological Sciences

King's College London
University of London

Introduction



Demographics

Total number of humans in space	534
Total females in space	57
Total US astronauts in space	330
Total US female astronauts in space	48
Age range at US selection	26-47 yrs
Mean age US ASCAN* finalist	**32 yrs**
Mean age US female astronaut at first flight	**38 yrs**
2013 selected female ASCANs*	**50%**

**ASCAN – astronaut candidate*

Menstrual Cycle

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

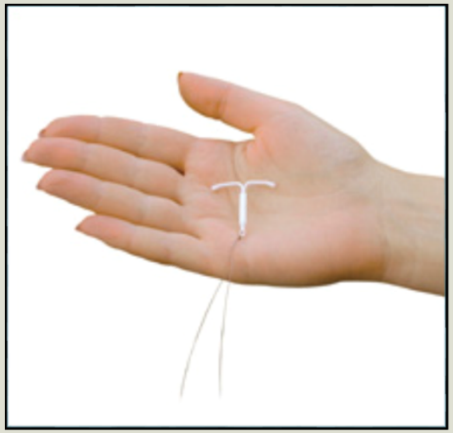
Microgravity environment

Personal choice

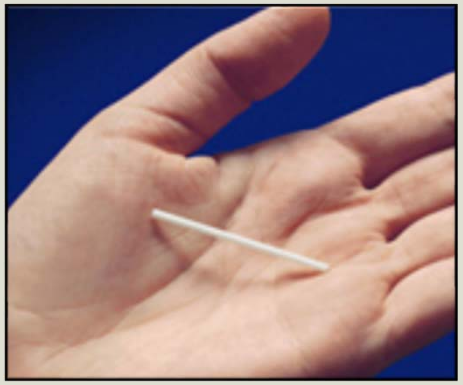
Options for Menstrual Suppression

Oral Contraceptive Pills

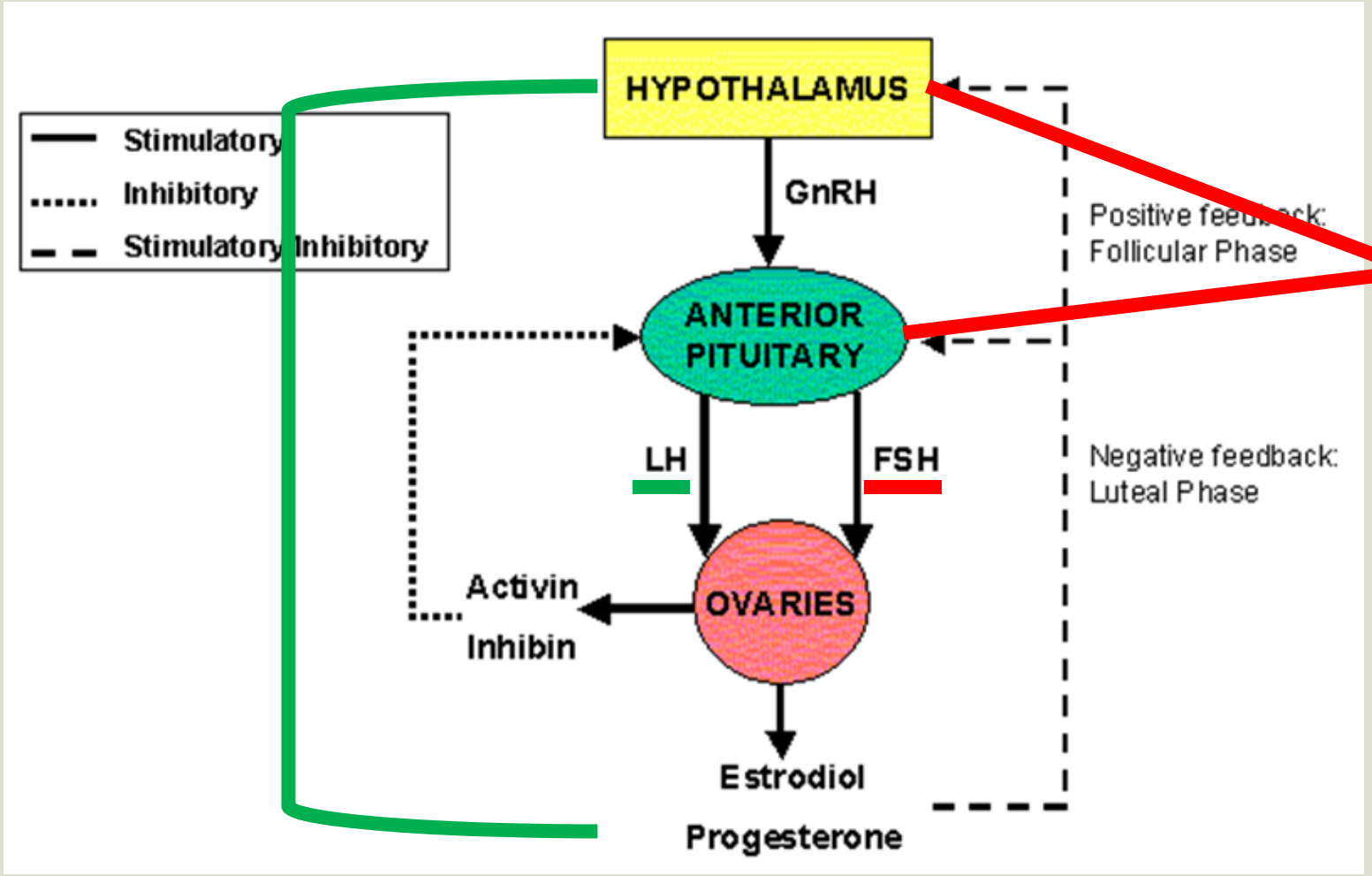
Hormone based intra-uterine systems (IUS) e.g. Mirena or Skyla



Hormone based subdermal implants e.g. Implanon



Hormone Profiles with the OCP



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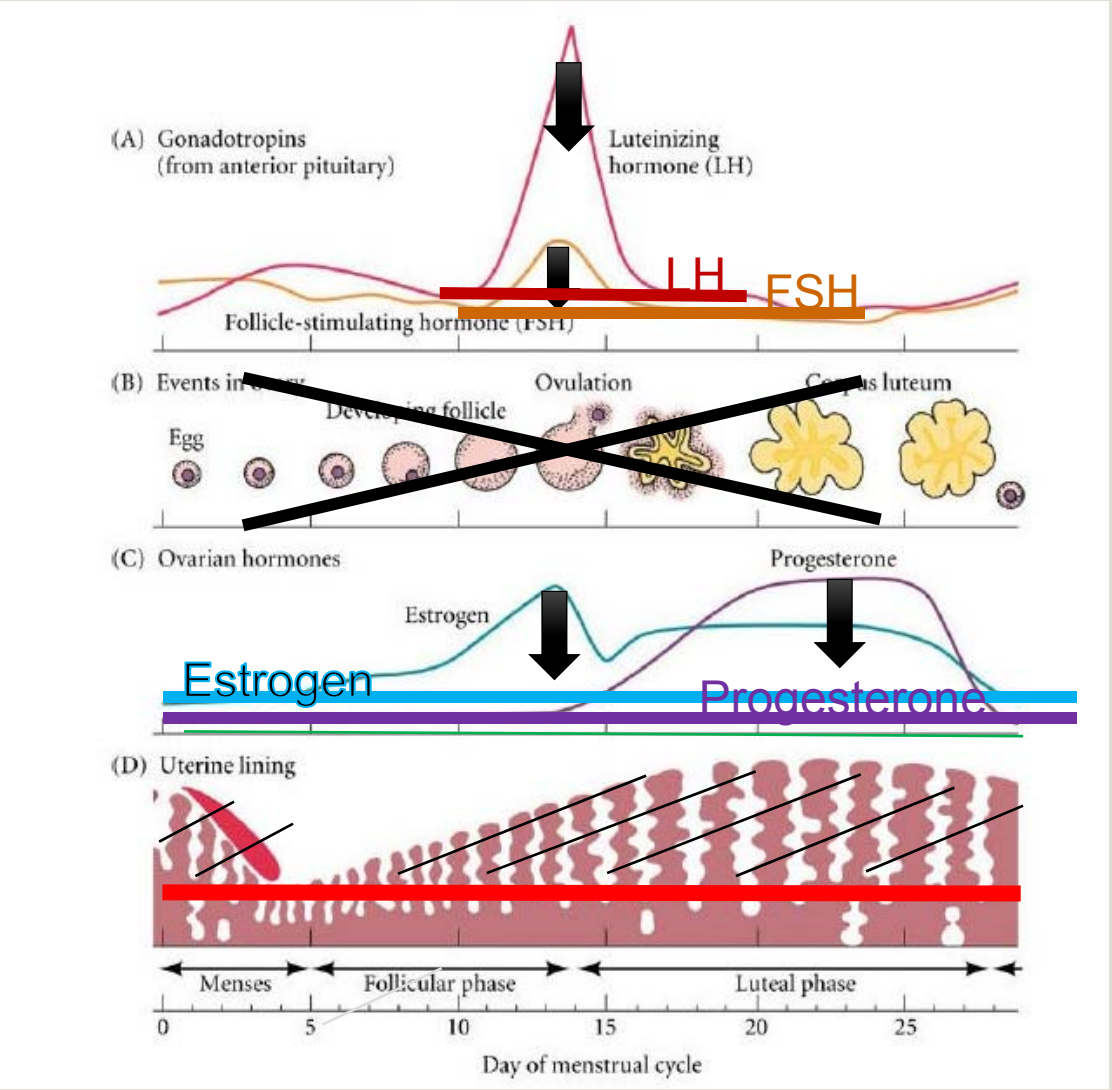
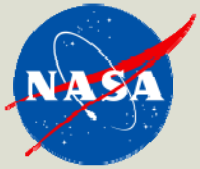


1. Inhibition of FSH
2. Follicle maturation does not occur
3. Estrogen levels do not rise
4. No LH surge
5. No ovulation
6. No corpus luteum
7. No rise in progesterone
8. Endometrium thin and sheds with 7 days of placebo pills

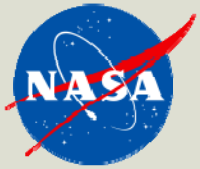


The Contraceptive Pill

- 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

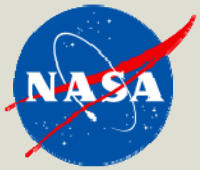


Intra-Uterine Devices (IUDs)

- 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

Lethal

Underdiagnosed

Preventable

Common

Dangerous

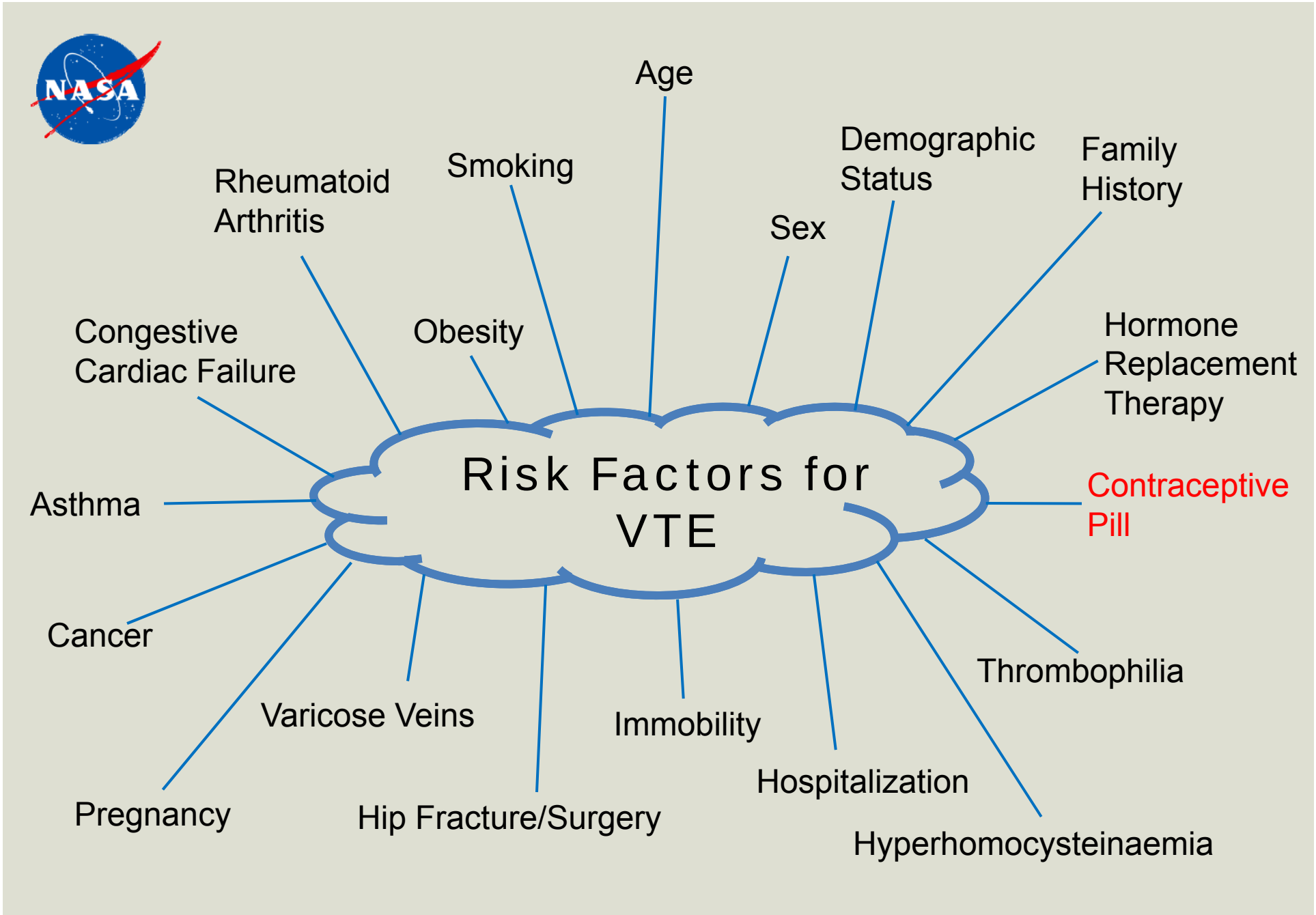
Serious

Treatable

Economic burden

Public health problem

Silent killer


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

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 → 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
- **Hematocrit**: upper 20% of normal range → 1.5 times ↑ VTE risk
- **Reticulocyte count:** indication of blood turnover
- **Platelet count:** acute phase protein, high levels increase coagulability of blood
- **Prothrombin time:** <11 secs → increased coagulability of blood
- **Homocysteine:** >15mcmol/L → 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:

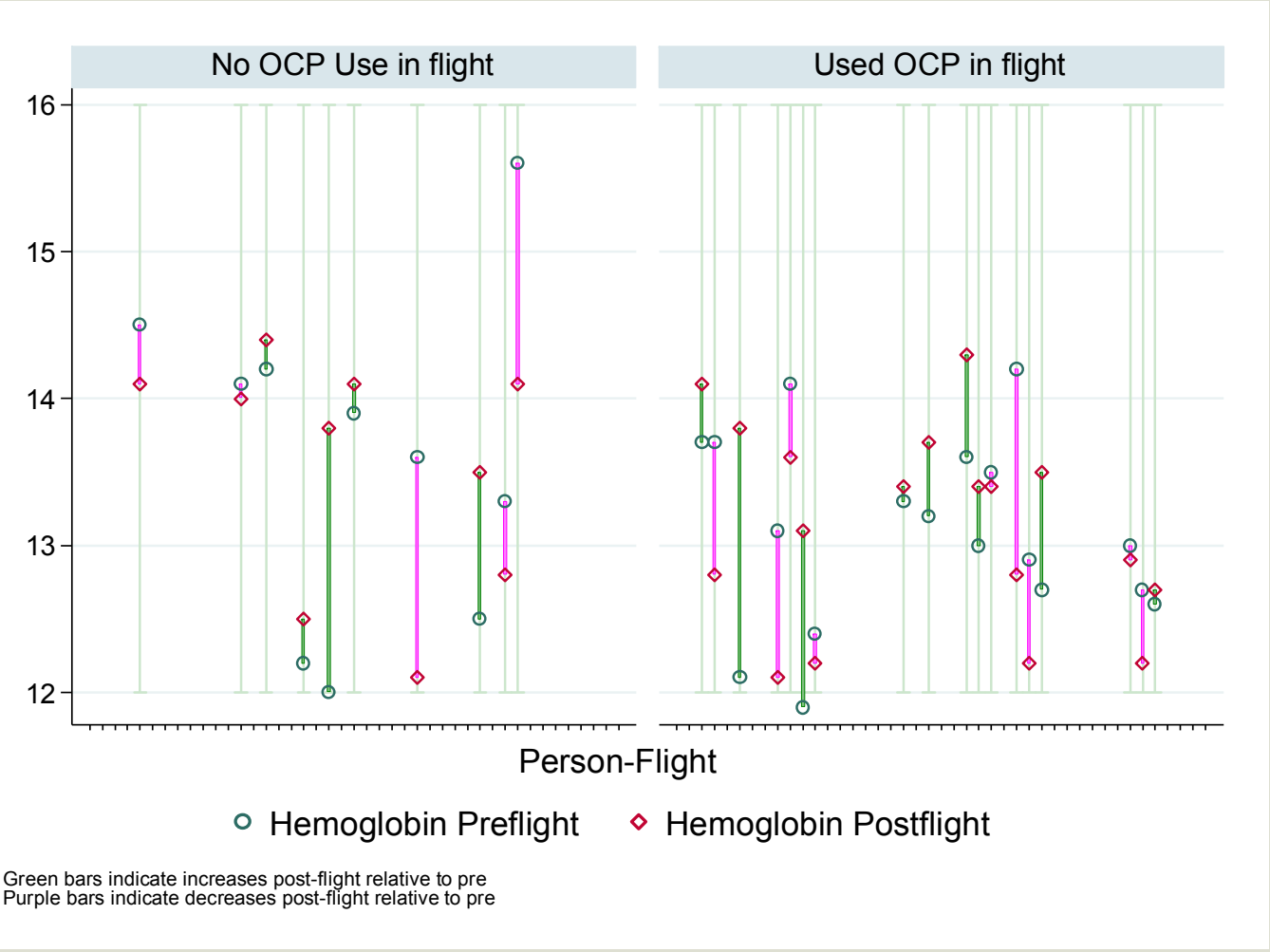
1. Comparing post-flight data of dependent variables to normative high risk data from the literature.
2. Characterizing descriptively the changes between pre vs post-flight data of each dependent variable and determining if significant changes by using repeated measures t-test.

HYPOTHESIS: Predict spaceflight does not increase risk of VTE compared to terrestrial population

Results

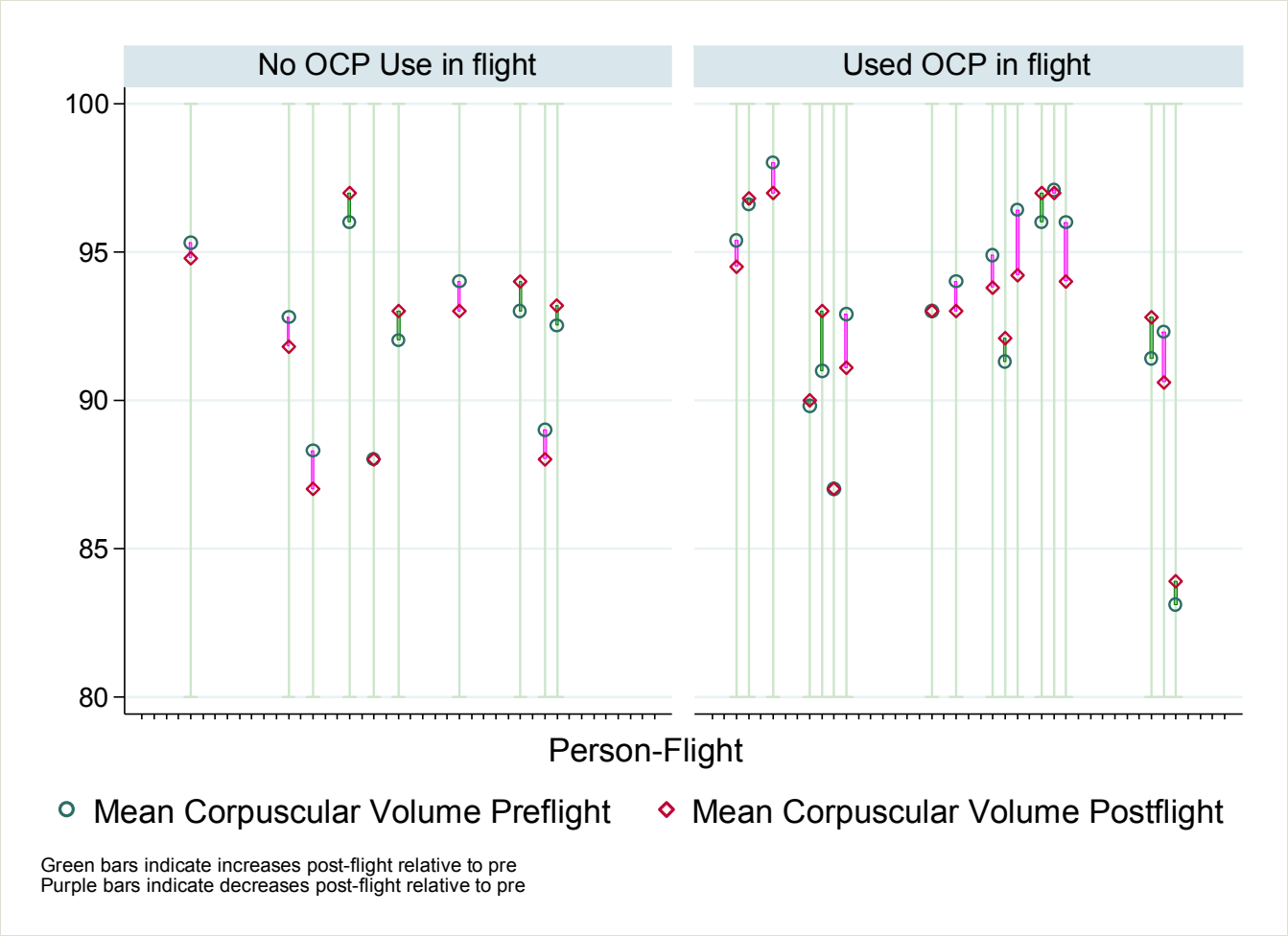
First pass analysis of data from short duration suggests no obvious trend towards abnormality or increased risk of VTE, thus supporting hypothesis.

Haemaglobin



•**Hemoglobin**: <1st centile → OR of VTE is 3.4

Mean Corpuscular Volume



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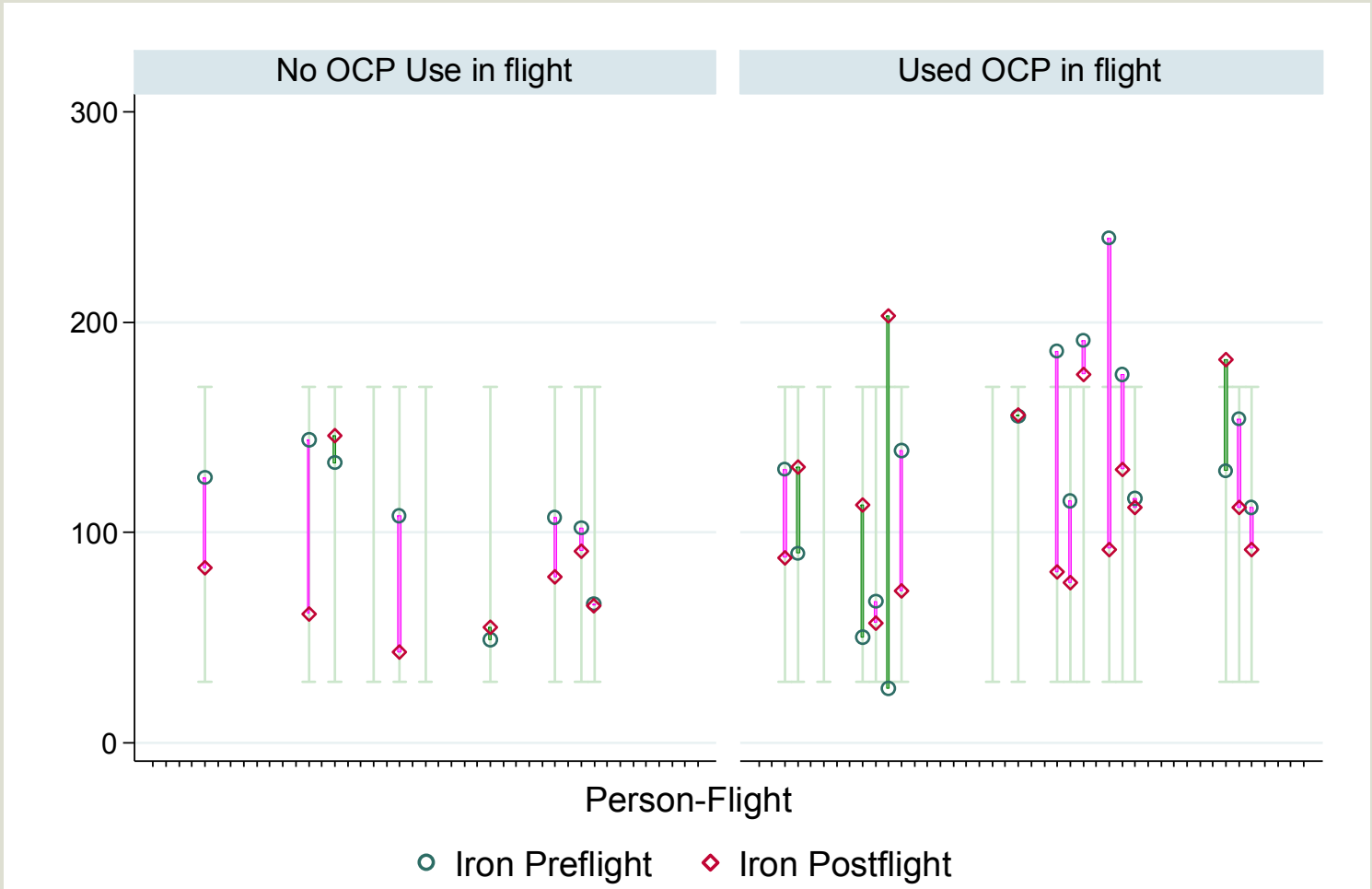
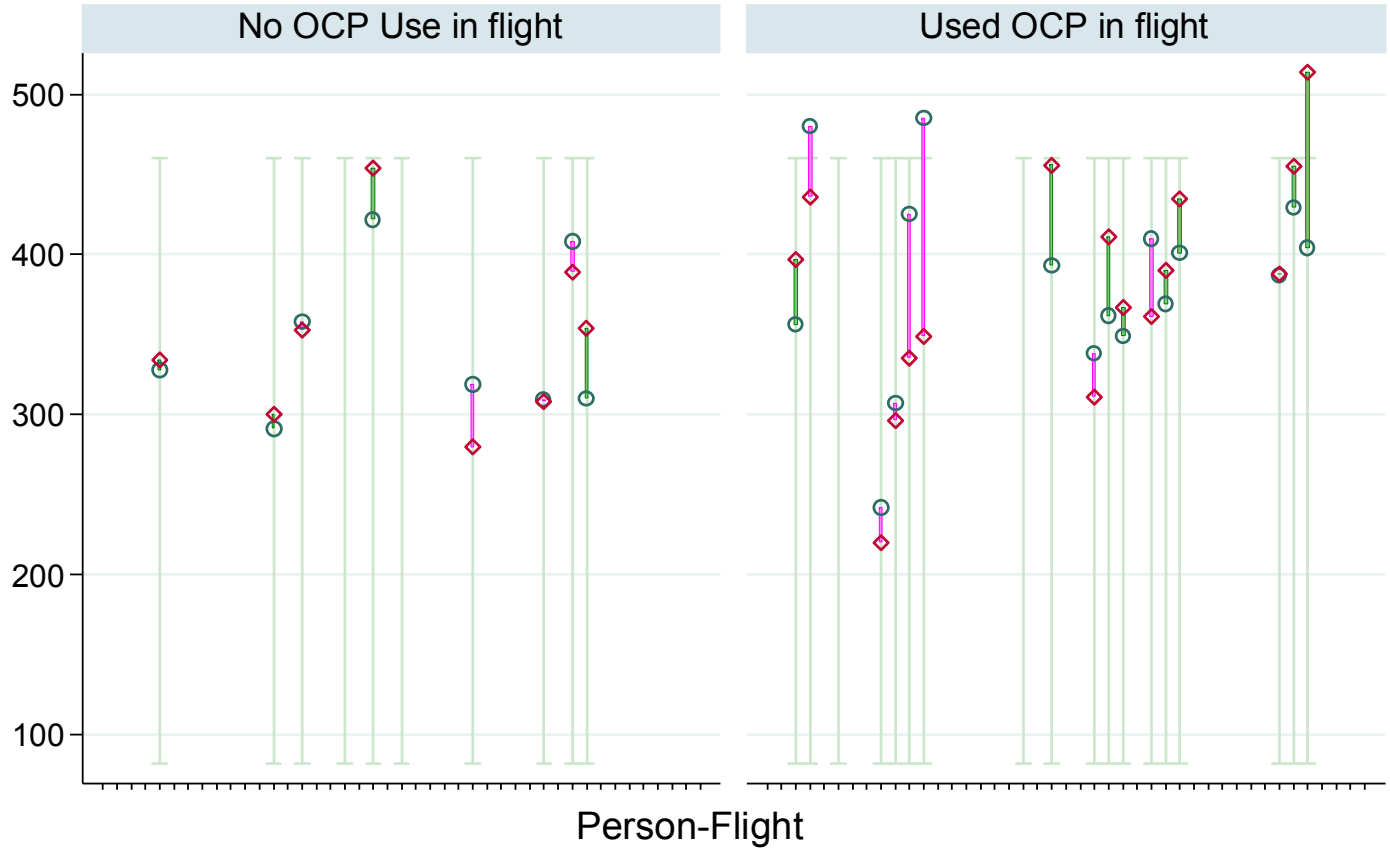
Iron



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

Total Iron Binding Capacity



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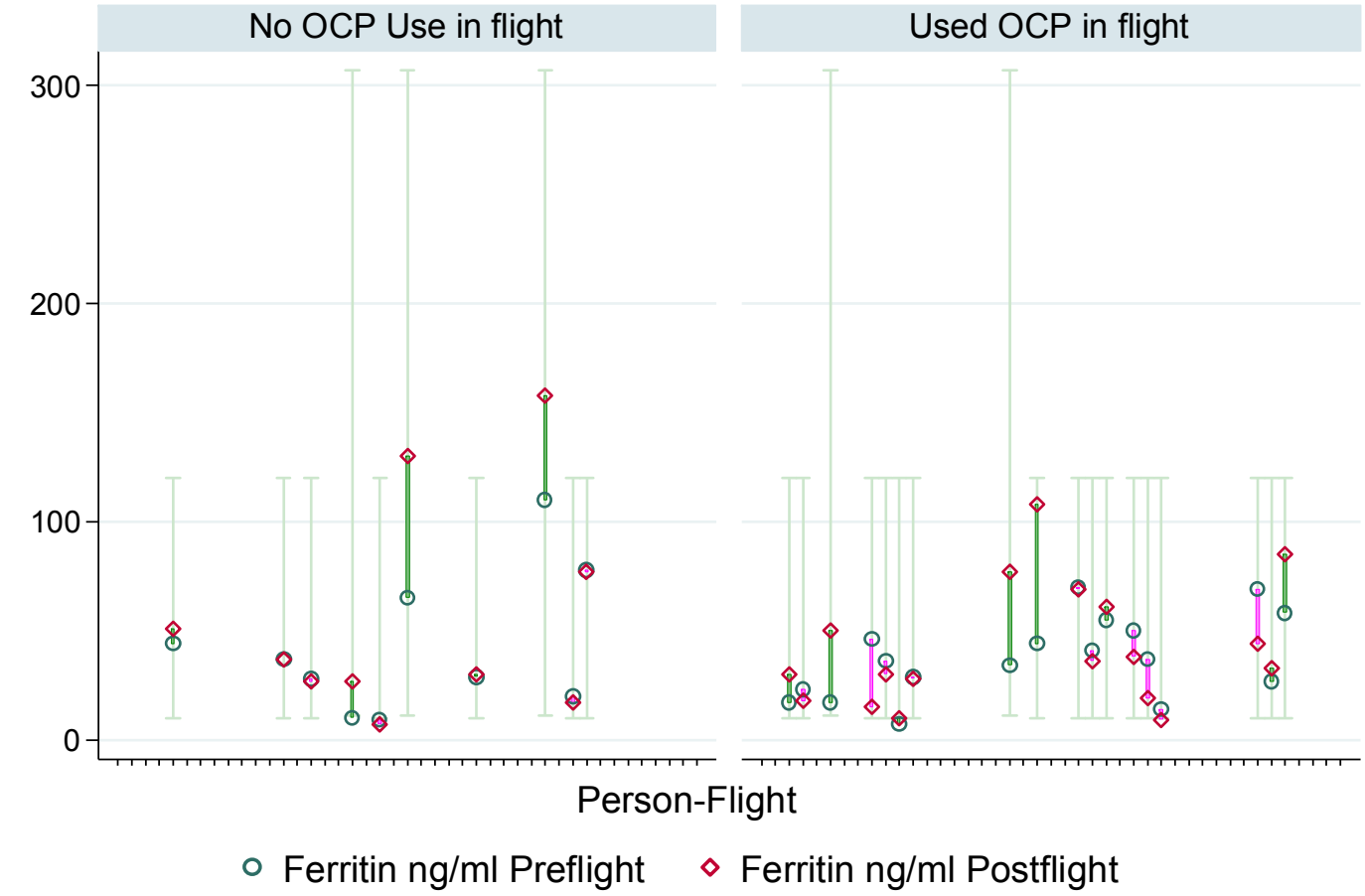
Ferritin



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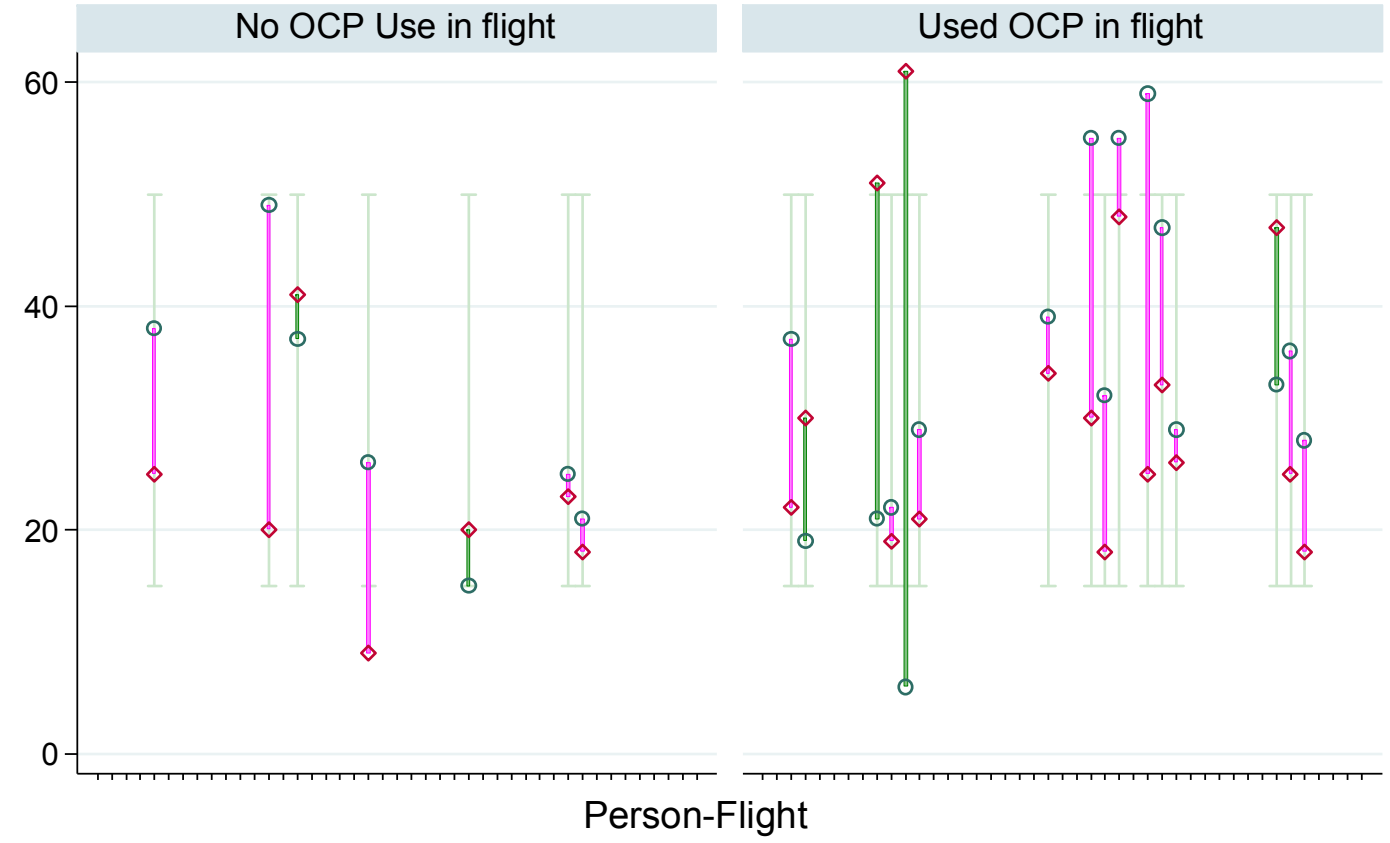
Transferrin



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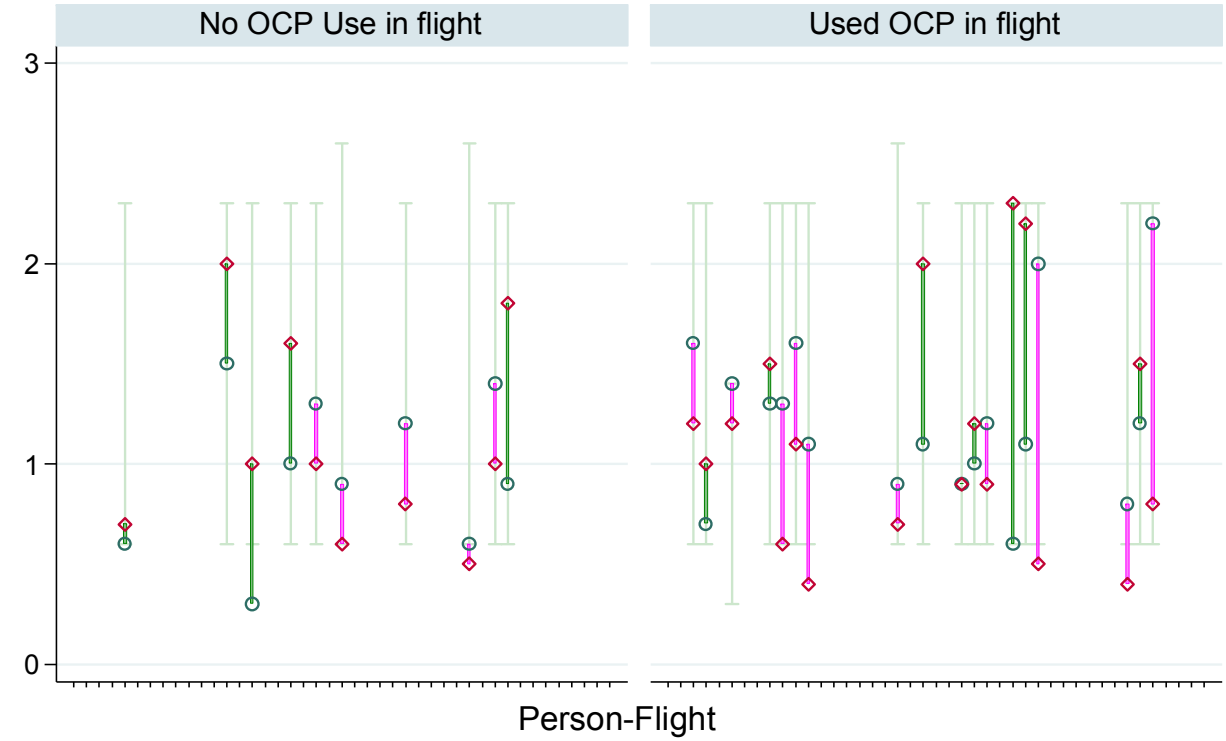
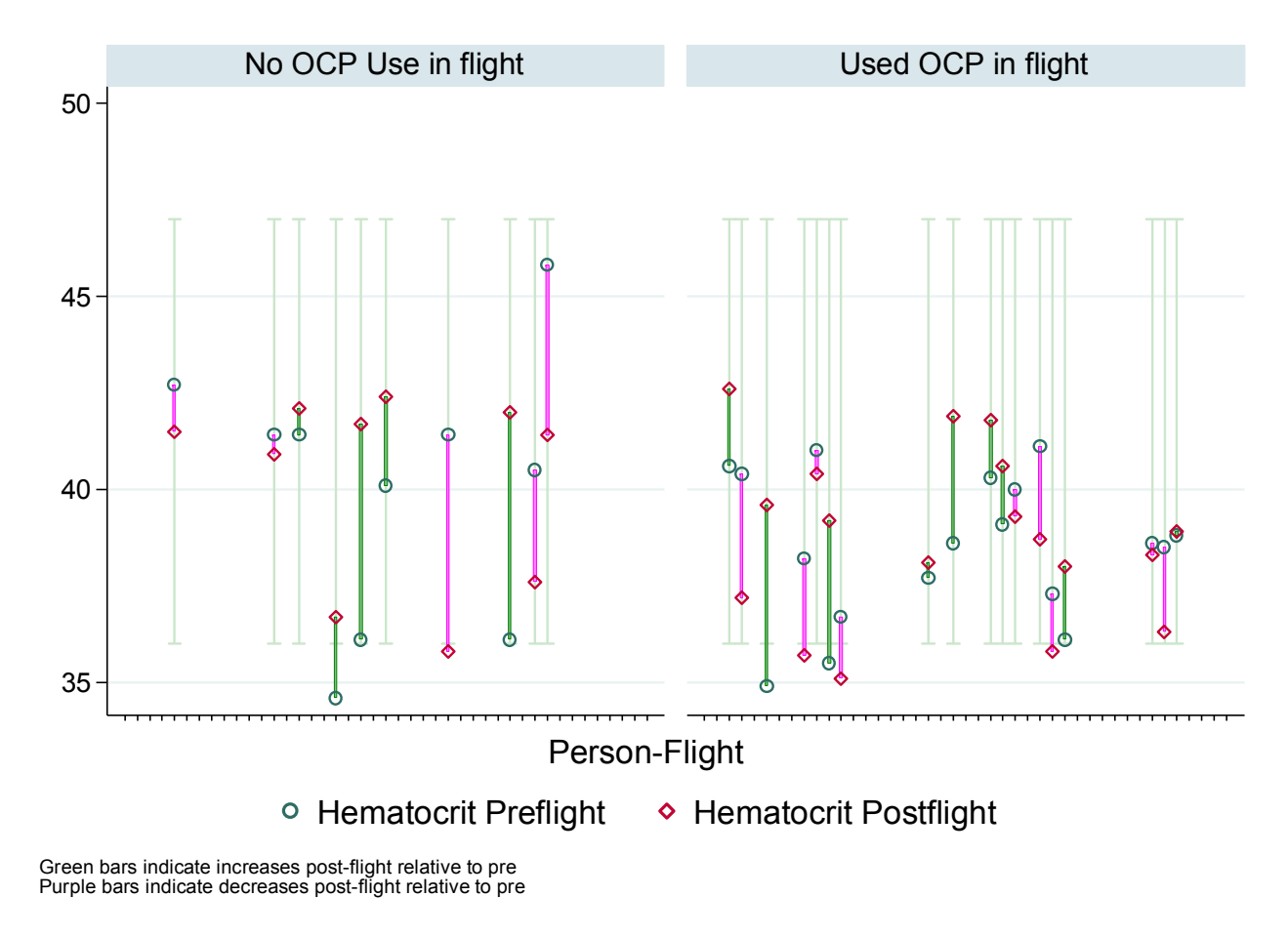
Reticulocyte count



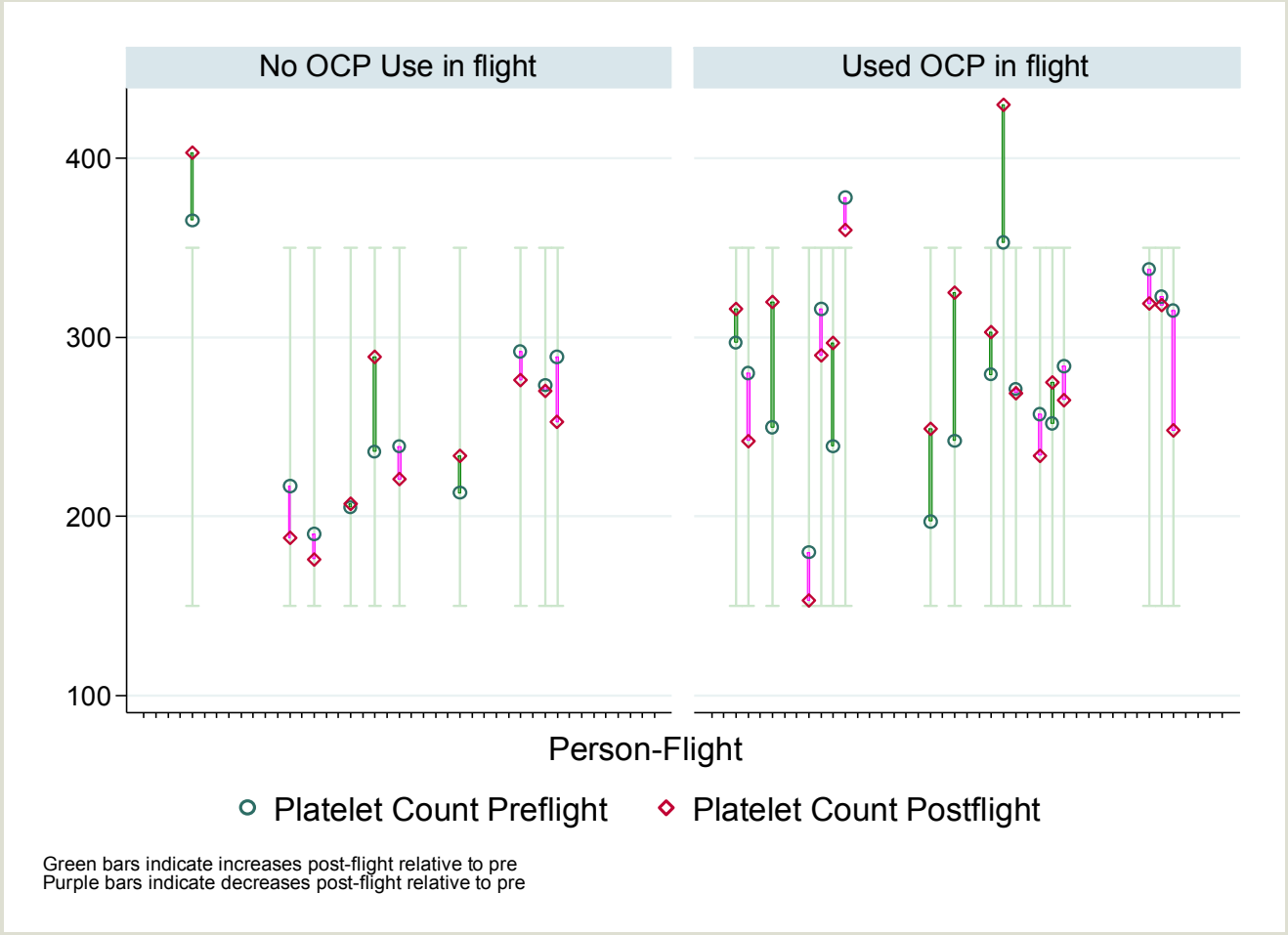
- **Reticulocyte count:** indication of blood turnover

Haematocrit



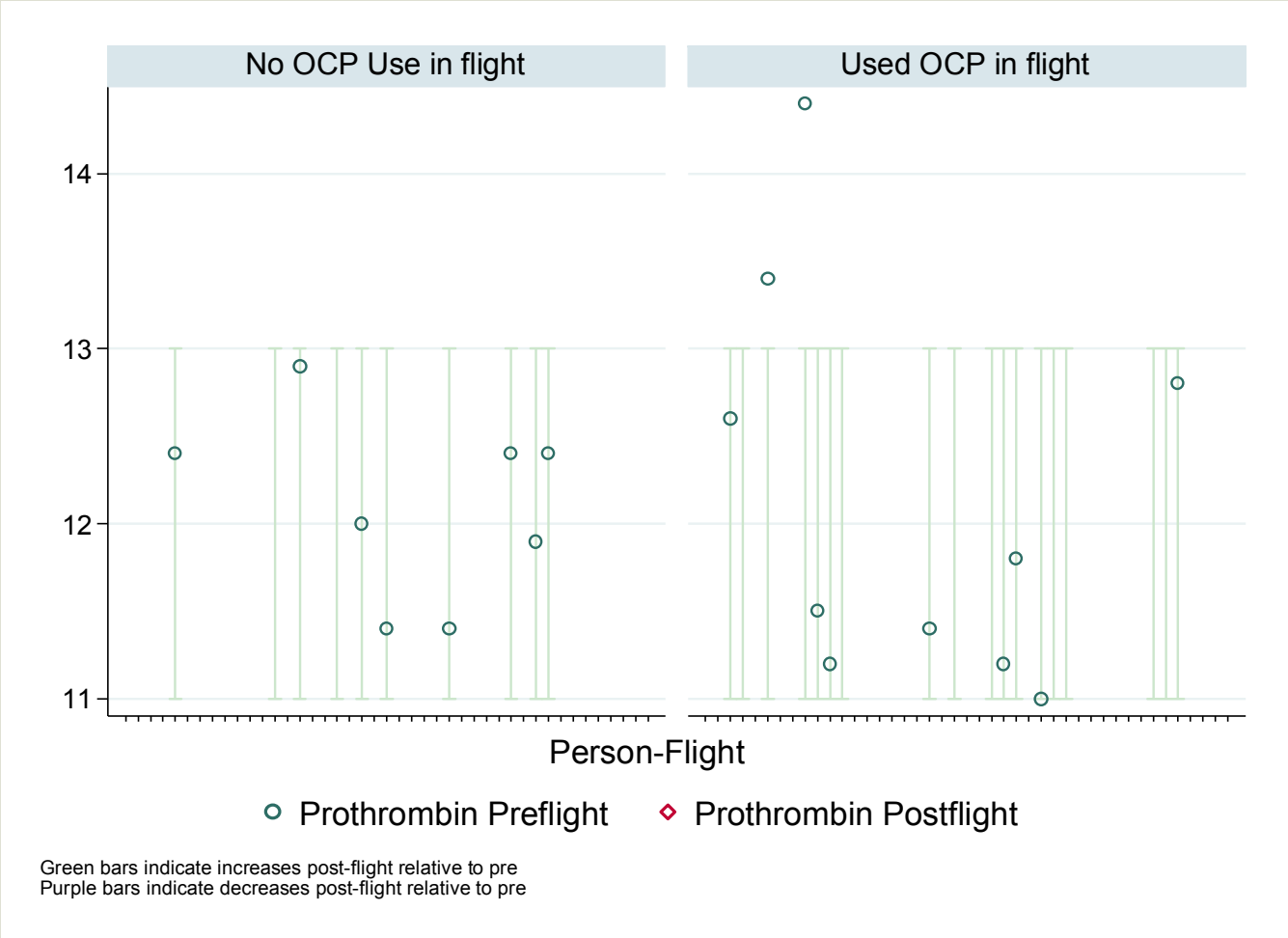
•**Hematocrit**: upper 20% of normal range → 1.5 times ↑ VTE risk

Platelet Count



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

Prothrombin Time



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

Food for thought

- 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

Acknowledgements

This project would not have been possible without:

- Virginia Wotring
- Rob Ploutz-Snyder
- Richard Jennings
- Ellen Baker
- Michele Blackwell
- Serena Aunon
- Mike Barratt
- Pam Baskin
- Jackie Charvat and LSAH team
- Janine Bolton
- Team at USRA

CONTACT DETAILS

DR VARSHA JAIN

ACADEMIC CLINICAL FELLOW (OB/GYN) – BART' S H LTH NHS TRUST

HONORARY RESEARCH ASSOCIATE – KING' S COLL ONDON

EMAIL: VARSHA.JAIN@KCL.AC UK

Barts Health NHS
NHS Trust

KING'S College LONDON
University of London

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