

Supplemental Material

Supplemental Table 1: Sample characteristics.

Timing of the progesterone add-back phase	Immediately following the gonadal suppression phase (N=27)	Together with estradiol (N=3)	After 5 weeks of estradiol, 0.1 mg per day, followed by 2 week washout (N=10)
Progesterone after gonadal suppression (ng/mL), median (range)	0.4 (0.1-1)	0.4 (0.2-0.6)	0.4 (0.1-1.4)
Progesterone after progesterone add-back (ng/mL), median (range)	11.75 (0.4-47.7)	10.7 (7.3-20.8)	11 (2-30)
Scores at the rating scale for premenstrual tension syndrome after gonadal suppression	2 (0-11)	3(0-3)	2(0-16)
Scores at the rating scale for premenstrual tension syndrome after progesterone add-back	3.5 (0-26)	13 (12-19)	4.5 (0-30)

Supplemental Table 2. Summary of the literature on effects of sex steroids on amino acid metabolism. Abbreviations and symbols: OC: oral contraceptives; ↔ no significant changes; ↑increased concentration; ↓decreased concentration; reference category underscored; * q<0.1.

GROUPS	<u>GONADAL SUPPRESSION v PROGESTERONE (current study)</u>	FOLLICULAR v LUTEAL		<u>OC-FREE v OC</u>
		OC-FREE	OC	
Alanine	↓(controls)	↓(Moller, Moller, Olesen, & Fjalland, 1996; Nagata et al., 2014; Soupart, 1960)	↓(Moller et al., 1996)	↔(Moller et al., 1996; Ruoppolo et al., 2014)
Isoleucine	↔	↔(Moller et al., 1996; Nagata et al., 2014)	↔(Moller et al., 1996)	↔(Moller et al., 1996); ↑(Ruoppolo et al., 2014)
Leucine	↔	↔(Moller et al., 1996), ↓pre-ovulation(Nagata et al., 2014)	↔(Moller et al., 1996)	↔ ¹⁹
Valine	↔	↔(Moller et al., 1996; Nagata et al., 2014)	↔(Moller et al., 1996)	↔(Moller et al., 1996; Ruoppolo et al., 2014)
Amino Acids with Hydrophobic Side Chain – Aromatic				
Phenylalanine	↔	↔(Nagata et al., 2014), ↓(Moller et al., 1996)	↓(Moller et al., 1996)	↔(Moller et al., 1996; Ruoppolo et al., 2014)
Tryptophane	↔	↔(Moller et al., 1996; Nagata et al., 2014)	↔(Moller et al., 1996)	↔(Moller et al., 1996; Ruoppolo et al., 2014)
Tyrosine	↓(controls)*	↓(Moller et al., 1996; Nagata et al., 2014)	↓(Moller et al., 1996)	↓(Moller et al., 1996; Ruoppolo et al., 2014)
Amino Acids with Polar Neutral Side Chains				
Asparagine		↓(Moller et al., 1996; Nagata et al., 2014)	↓(Moller et al., 1996)	↔(Moller et al., 1996; Ruoppolo et al., 2014)
Cysteine				↔(Ruoppolo et al., 2014)
Glutamine	↓	↓(Nagata et al., 2014)		↔(Ruoppolo et al., 2014)
Methionine	↓(controls)*	↓(Moller et al., 1996; Nagata et al., 2014)	↓(Moller et al., 1996)	↔(Moller et al., 1996; Ruoppolo et al., 2014)
Serine	↔	↓(Craft & Wise, 1969; Moller et al., 1996; Nagata et al., 2014; Soupart, 1960)	↓(Moller et al., 1996)	↔ ¹⁹
Threonine	↓*	↓(Moller et al., 1996; Nagata et al., 2014; Soupart, 1960)	↔(Moller et al., 1996)	↑(Moller et al., 1996)
Amino Acids with Electrically Charged Side Chains – Acidic				
Aspartic acid	↓			↔(Ruoppolo et al., 2014)
Glutamic acid	↔	↓(Zlotnik et al., 2011)		↔(Ruoppolo et al., 2014)
Amino Acids with Electrically Charged Side Chains – Basic				
Arginine	↓*	↓(Moller et al., 1996)		↔(Ruoppolo et al., 2014)
Histidine	↓(controls)			↑(Ruoppolo et al., 2014)
Lysine	↓*	↓(Moller et al., 1996)		↓(Ruoppolo et al., 2014)
Glycine		↓(Moller et al., 1996; Nagata et al., 2014)	↓ Mid(Moller et al., 1996)	↓(Moller et al., 1996; Ruoppolo et al., 2014)
Proline	↓	↓(Moller et al., 1996)		↓(Ruoppolo et al., 2014)

Supplemental bibliography

- Craft, I. L., & Wise, I. J. (1969). Changes in amino acid metabolism during the menstrual cycle. *The Journal of Obstetrics and Gynaecology of the British Commonwealth*, 76(10), 928–933.
- Moller, S. E., Moller, B. M., Olesen, M., & Fjalland, B. (1996). Effects of oral contraceptives on plasma neutral amino acids and cholesterol during a menstrual cycle. *European Journal of Clinical Pharmacology*, 50(3), 179–184.
- Nagata, C., Wada, K., Tsuji, M., Hayashi, M., Takeda, N., & Yasuda, K. (2014). Plasma amino acid profiles are associated with biomarkers of breast cancer risk in premenopausal Japanese women. *Cancer Causes & Control: CCC*, 25(2), 143–149.
<https://doi.org/10.1007/s10552-013-0316-8>
- Ruoppolo, M., Campesi, I., Scolamiero, E., Pecce, R., Caterino, M., Cherchi, S., ... Franconi, F. (2014). Serum metabolomic profiles suggest influence of sex and oral contraceptive use. *American Journal of Translational Research*, 6(5), 614–624.
- Soupart, P. (1960). [Aminoacidemia and aminoaciduria during the menstrual cycle in the normal woman]. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, 5, 235–249.
- Steiner, M., Haskett, R. F., & Carroll, B. J. (1980). Premenstrual tension syndrome: the development of research diagnostic criteria and new rating scales. *Acta Psychiatrica Scandinavica*, 62(2), 177–190.
- Zlotnik, A., Gruenbaum, B. F., Mohar, B., Kuts, R., Gruenbaum, S. E., Ohayon, S., ... Teichberg, V. I. (2011). The effects of estrogen and progesterone on blood glutamate levels: evidence from changes of blood glutamate levels during the menstrual cycle in women. *Biology of Reproduction*, 84(3), 581–586.
<https://doi.org/10.1095/biolreprod.110.088120>