Elucidation of mechanisms underlying female infertility in Abcg5/g8 knockout mice

Y. Yamanashi *[I], T. Komine *[I], Y. Hirota[II], H. Suzuki[I], Y. Osuga[II], T. Takada[I]

[I]Department of Pharmacy, The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan, [II]Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

[Background and Aims] The heterodimer of ATP-binding cassette transporters G5 and G8 (ABCG5/G8) is a sterol exporter in the intestine that excretes dietary sterols from enterocytes. Previous studies have demonstrated that female Abcg5/g8 homozygous knockout (KO) mice are infertile; this infertility is restored by changing the chow diet to a meatball diet. However, underlying mechanisms of the infertility in Abcg5/g8 KO mice were not clear. The aims of this study were to identify the dietary components that induce infertility in Abcg5/g8 KO mice, reveal the mechanisms involved, and assess whether our findings are applicable to humans.

[Methods and Results] Combined studies with serum metabolomics and pregnancy monitoring on dietary modification revealed that phytosterols, especially β-sitosterol and brassicasterol, are potent inducers of infertility in mice. In vitro fertilization (IVF) assays revealed that the phytosterols inhibit ovarian follicle maturation and reduce egg quality. It was also shown that polycomb repressive complex 2 (PRC2)-mediated histone H3 trimethylation at lysine 27 was enhanced in the ovary as a consequence of phytosterol accumulation. In addition, PRC2 inhibitors could rescue the reproductive toxicity of phytosterols. Moreover, analyses of human serum specimens demonstrated that serum phytosterol levels significantly and negatively correlated with the blastocyst development rate of fertilized eggs in women undergoing IVF, suggesting that phytosterols would affect egg quality in both humans and mice.

[Conclusion] Phytosterols, particularly β-sitosterol and brassicasterol, have potent reproductive toxicities by disrupting the epigenomic status in the ovary, causing inadequate maturation of ovarian follicles and reduced egg quality. Thus, avoiding the excessive intake of certain phytosterols would beneficial for female reproductive health.

[Reference] Yamanashi Y., *et al*., *Commun Biol.* 7(1): 1535, 2024.

* The authors marked with an asterisk equally contributed to the work.