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Temporal Changes in Phenotype and Gut microbiota in PCOS Mouse Model Induced by Prenatal Androgen Exposure.

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PCOS is a complex multigenic disorder with strong epigenetic and environmental influence. Previous reports have suggested that fetal over-exposure to androgens contributes to the development of PCOS after birth. On the other hands, recent studies on both human and rodent models of PCOS have demonstrated the relationship between PCOS and gut microbiome in adulthood. Furthermore, gut microbiome in obese adolescent with PCOS are different from obese adolescent without PCOS. However, the mechanism has not been revealed and it is unclear which events appear first, PCOS phenotypes or gut microbiome. We wondered if prenatal androgen exposure leads gut microbial dysbiosis early in life and is associated with the development of PCOS in later life. To test this hypothesis, we examined the temporal changes in the phenotypes of PCOS and gut microbiome using prenatally androgenized (PNA) model mice, an well-established model of PCOS. PNA model was generated by subcutaneously injecting pregnant dams with dehydroepiandrosterone (DHT) on days 16, 17, and 18 of gestation. Phenotypes and gut microbiome activity were compared between PCOS model mice (n=12/group) and control mice (n=10/group) at each developmental stage of 4 weeks (prepuberty), 6 weeks (puberty), 8 weeks (adolescent), 12 weeks (young adulthood), and 16 weeks (adulthood), respectively. The determinants for PCOS development are onset of puberty, estrous cycle, morphology of ovaries, serum testosterone levels, body weight, the size of parametrial adipocytes, and insulin resistance. For evaluation of gut microbiome, next generation sequencing and bioinformatics analysis of 16S rRNA genes were performed on obtained DNA from mouse fecal samples. PNA groups resulted in delayed puberty onset, disrupted estrous cycle, and increased testosterone levels from 6 weeks. Increased atretic antral follicles were observed in PNA groups at 6, 12, and 16 weeks. Additionally, PNA groups showed increased body weight, hypertrophy of parametrial adipocytes, and insulin resistant from 12 weeks. As for gut microbiome, PNA exhibited altered alpha-diversity from 8 weeks and beta-diversity at 8 weeks. Composition of gut microbiome was already altered from 4 weeks. At phylum level, Firmicutes phylum are significantly increased in PNA groups at 4 and 8, and decreased at 16 weeks. Actinobacteria phylum showed significant decrease at 6 and 8 weeks in PNA groups. At genus level, relative abundance of several bacterial taxa differed significantly between control and PNA groups; Allobaculum, Adlercreutzia which produce equol, Roseburia which produce butyric acid, and Sutterella were significantly decreased in PNA groups at multiple stages of development. In conclusion, our findings suggest that the alteration of gut microbiome appears simultaneously or even earlier than the presence of PCOS phenotypes, and that normalizing microbiome could improve pathologic condition of PCOS. In addition, early intervention of gut microbiome might indicate preventive care for women at high-risk of developing PCOS.

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