REPRODUCTIVE ENDOCRINOLOGY

Transgenerational effects of polycystic ovary syndrome identified

> the present study suggests that the daughters of women with PCOS have an increased risk of developing the disease

A new study published in *Nature Medicine* has shown that the daughters of women with polycystic ovary syndrome (PCOS) are five times more likely to be diagnosed with the disorder than daughters born to women without PCOS. The authors also identified genes that might indicate a PCOS phenotype in future generations.

"We have studied the pathophysiology of PCOS in both clinical case–control studies and in experimental animal studies for many years," say co-corresponding authors Elisabet Stener-Victorin and Qiaolin Deng from the Karolinska Institutet, Stockholm, Sweden. "In previous studies we demonstrated that women with PCOS display elevated circulating androgens, irregular cycles and abnormal ovarian morphology, all classical symptoms of PCOS." Further to these data, emerging evidence from the team's clinical studies, as well as from their rodent studies, demonstrates that excess maternal androgen alters the function of placenta and predisposes first generation offspring to PCOS-like symptoms in adulthood. "These studies indicate that an unfavourable intrauterine environment might lead to the epigenetic changes that alter gene expression and increase risk of PCOS in adulthood, but these data do not show how maternal PCOS might affect generations beyond the first generation," adds Stener-Victorin.

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In the present study, Stener-Victorin, Deng and colleagues investigated whether the PCOS-like phenotype observed in the first-generation offspring could be transmitted to the second generation as well as the third generation, who are the first generation to be completely unexposed to the disease. The team started by analysing data within the Swedish medical registers and confirmed that first generation daughters of women with PCOS have an increased risk of developing PCOS in adulthood. "These data, however, did not provide any insight into whether this association reflects a causal association or whether it is due to confounding genetic factors," adds Stener-Victorin. "Furthermore, the daughters in current registers are still too young to access data from second and third generations."

To address these issues, the team used a prenatally androgenized mouse model that had been combined with an obesity model. "We combined these models as women with PCOS often also have obesity," explains Stener-Victorin. The team then performed a transgenerational experiment to investigate whether the PCOS-like phenotype observed in the first-generation offspring could be transmitted to the second and third generations. To identify potential markers of a transgenerational transmission of a PCOS-like phenotype, the team performed single-cell RNA sequencing of metaphase II oocytes for each generation. The team also conducted an analysis of serum RNA taken from the daughters of women with PCOS.

"We found, for the first time, that maternal androgen exposure, but not obesity, is the main cause for the observed transgenerational effects of androgen exposure that are passed on for up to three generations," explains Stener-Victorin. "Importantly, four of the differentially expressed genes across all generations in oocytes were also differentially expressed in serum samples from daughters of women with PCOS."

Taken together, the present study suggests that the daughters of women with PCOS have an increased risk of developing the disease. The risk-associated genes that the team identified could also be used to identify whether future generations could develop a PCOS phenotype.

"Our study indicates that it is intrauterine and/or germ cells that contribute to the development and transmission of PCOS," concludes Stener-Victorin. "At the present time, however, we cannot distinguish between these two factors and our next goal is to disentangle these effects and also investigate epigenetic modifications."

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