

Dysregulation of steroid metabolome in follicular fluid links phthalate exposure to diminished ovarian reserve of childbearing-age women

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Widely used phthalates (PAEs) have attracted increasing attention due to their endocrine disruption and reproductive toxicity, while steroid metabolome was essential for follicular development. However, the mechanism by which PAEs exposure affects follicle growth and development through steroid metabolome is unclear. Cross-sectionally, this study recruited 264 childbearing-age women in Tianjin (China) from April 2019 to August 2020. Target steroid metabolome in follicular fluid (FF) was performed for diminished ovarian reserve (DOR) against normal ovarian reserve (NOR) women by analyzing eighteen steroids. Eleven PAE metabolites (mPAEs) in FF were further analyzed and three DOR-related reproductive outcomes were associated, including (normal) fertilization rate and high-quality cleavage embryos rate. Differential steroids were identified using Mann-Whitney U test. Multiple linear regression and quantile g-computation (qgcomp) models were used to associate individual mPAEs and mPAE mixture with the DOR-related differential steroids in FF. The network between mPAEs, DOR-related differential steroids, and reproductive outcomes was also observed by xMWAS. Androstenedione (A4), corticosterone (CORT), cortisol (COR), aldosterone (ALDO), and cortisone were significantly down-regulated in FF from women with DOR. Eight mPAEs with detection frequencies > 60% and median concentrations of 0.02-4.86 ng/mL were incorporated into statistical models. Negative associations with COR and CORT were found for mono-ethyl phthalate (mEP), mono-(2-ethyl-5-oxohexyl) phthalate (mEOHP), and mono-2-ethylhexyl phthalate (mEHP). Positive associations with cortisone and ALDO were found for mEOHP, mEHP, monobutyl phthalate (mBP), and mono (2-isobutyl) phthalate (miBP). The mPAE mixture also showed negative associations with COR and CORT and positive with cortisone and ALDO, in which mEP and mEHP contributed the most. Through xMWAS, mEP, mEOHP and mEHP were negatively associated with (normal) fertilization rate through COR or CORT. In conclusion, A4, CORT, COR, ALDO, and cortisone were DOR-related steroids and PAE exposure may promote DOR and DOR-related adverse reproductive outcomes by downregulating COR and CORT.

