*Letter to the Editor / Editöre Mektup*

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# Vaginal microbiome metabolite shifts as early predictors of premature ovarian insufficiency in adolescents with novel gene variants

## *Yeni gen varyantlarına sahip ergenlerde prematür over yetmezliğinin erken belirleyicisi olarak vajinal mikrobiyom metabolit değişimleri*

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**To the Editor,**

Premature ovarian insufficiency (POI) is a condition in which there is a decline in ovarian function prior to the age of 40 years. Elevated follicle-stimulating hormone (FSH) and estrogen deficiency result in sustained systemic complications, predisposing patients to cardiovascular morbidity, pronounced fertility decline, and diminished longevity. Globally, POI continues to pose a significant health burden, occurring in 3.5% of women. Furthermore, its prevalence increased over the past two centuries, although this trend was not statistically significant ($p>0.05$). For individuals with POI, hormone replacement therapy (HRT), coupled with skeletal preservation and reproductive planning, is advised to reduce chronic complications. Additionally, timely access to expert clinical care is crucial for the optimal management and enhanced outcomes for patients with POI[(1)].

Vaginal microbiome metabolite profiling is an integrated omics-based diagnostic framework that combines metabolic profiling with biochemical-functional remodeling to identify biochemical dysregulations associated with POI. This study leverages non-invasive collection of vaginal samples and advanced high-throughput methods, such as 16S ribosomal ribonucleic acid sequencing and liquid chromatography-mass spectrometry, to quantify metabolic fluxes and pathways. In POI, altered Lactobacillus predominance and specific metabolic derangements have been demonstrated, reflecting condition-specific microbial profiles. These integrated microbial-metabolite signatures enhance diagnostic accuracy beyond taxonomic profiling alone, suggesting strong predictive potential. Overall, this method is an emerging precision medicine strategy that integrates microbial and genetic data to advance early detection and therapeutic management of POI in at-risk youth[(2)].

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Recent studies suggest that vaginal microbiota plays an integral role in women's reproductive health and that alterations in its composition and diversity have been increasingly associated with ovarian dysfunction in POI. A case-control study showed certain microbial alterations, including an increased abundance of *Gardnerella* and *Atopobium* and a reduced abundance of *Bifidobacterium* ($p=0.017$), in women with POI; these alterations were also correlated with reduced anti-Mullerian hormone levels and increased FSH levels ($p<0.001$). These findings suggest that vaginal microbial metabolites may reflect endocrine and follicular impairment[3]. As HRT is a proposed treatment for POI, a cross-sectional study of 40 women with POI who were receiving oral HRT found that 33.4% (n=11) had a vaginal microbiome dominated by *Lactobacillus* species, which is typical of a healthy estrogenized vaginal environment. In contrast, 15.2% (n=5) demonstrated predominance of anaerobic bacteria, suggesting that systemic HRT may partially restore a vaginal microbiome similar to that observed in healthy women[4].

Despite intriguing associations, the routine clinical application of microbiome-based diagnostics in POI faces practical barriers to implementation. Most studies are limited by small sample sizes (<100), cross-sectional or case-control designs, or single-center recruitment, which restrict statistical power and generalizability. Vaginal microbiota sequencing requires specialized laboratories and expertise, which are often unavailable in low-resource settings. Moreover, certain microbiome shifts are not disease-specific, as taxa *Gardnerella* and *Atopobium* are also found in bacterial vaginitis, which further limits diagnostic specificity[5]. These challenges need to be addressed before vaginal microbiome and metabolite-based tools can be integrated alongside hormonal and genomic tests into routine early detection for women with POI.

Considering these points, emerging literature supports incorporating vaginal microbiome-derived metabolite profiling alongside genetic testing into the early diagnosis of POI, especially in women with genetically unexplained POI. This perspective adds to the existing literature by linking the shift in vaginal microbiome metabolites to genetic susceptibility in ovarian dysfunction. However, larger, population-based prospective studies are required to establish standard reference profiles, and specialized tools are needed to enhance diagnostic specificity and enable early risk stratification in adolescent women before irreversible ovarian decline occurs.

### Footnotes

**Conflict of Interest:** No conflict of interest was declared by the authors.

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