Letter to the Editor / Editöre Mektup

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Sphingosine-1-phosphate in ovarian hyperstimulation syndrome: Biomarker promise and therapeutic peril

Yumurtalık hiperstimülasyon sendromunda sfingozin-1-fosfat: Biyobelirteç vaadi ve tedavi riski

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To the Editor,

Ovarian hyperstimulation syndrome (OHSS) is a serious, potentially life-threatening iatrogenic complication of excessive ovarian response to stimulation during fertility treatments, such as in vitro fertilization, which is part of assisted reproductive technology. It is often triggered by human chorionic gonadotropin (hCG), when used to induce oocyte maturation. Compared with LH, hCG's prolonged luteotropic effect induces vasodilation, increases vascular permeability, and shifts fluid into the third space, leading to ascites, pericardial and pleural effusions, and generalized edema. Severe cases may result in complications such as adult respiratory distress syndrome, thromboembolism, and acute renal failure. Clinically, OHSS presents with enlarged cystic ovaries, abdominal distention, and pain[(1)].

OHSS is a serious complication with unclear pathophysiology. Lipids play important roles in cellular function and various diseases; hence, lipid alterations were investigated by lipidomic analysis of follicular fluid samples obtained from OHSS patients, revealing a significant reduction in some lipid classes, including LPC, dMePE, LdMePE, PI, PE, PC, TG, and sphingomyelin (SM), and an elevation of ChE in the OHSS group. These differential lipids might serve as biomarkers. Notably, sphingosine 1-phosphate (S1P) is a bioactive lipid mediator produced from SM. S1P is found abundantly in blood and regulates vascular permeability, cell recruitment, and clotting during inflammatory processes. This role of S1P is mediated by S1PR1, a member of the family of G protein-coupled receptors, through a signaling pathway. Hence, S1P emerges as a promising biomarker and therapeutic target[(2)]. Future randomized controlled studies should focus on refining the role of S1P as a predictive marker for OHSS.

Studies suggest that women with OHSS have lower S1P levels in their follicular fluid than women without OHSS. This drop in S1P could act as an early warning sign, allowing timely intervention. Identifying such changes may help improve patient safety during fertility treatments[(3)]. In an OHSS rat model, S1P treatment reduced ovarian weight and serum progesterone levels, increased the number of healthy antral follicles, decreased the number of corpora lutea and cystic structures, lowered steroidogenic acute regulatory protein levels, and reduced endothelial swelling. It also restored N-cadherin and VE-cadherin levels while enhancing the expression of claudin-5, occludin, and S1P receptor 1,

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indicating that S1P holds potential as both a diagnostic marker and a therapeutic option for OHSS[4].

S1P shows promise as an early marker for ovarian hyperstimulation syndrome, but its current evidence is derived mainly from in vitro cell studies rather than from studies using human ovarian tissue. While these models offer useful insights, they cannot fully capture the complexity of real patients, making direct clinical application uncertain. To move forward, well-designed human research is essential to confirm its accuracy and usefulness in early detection[5].

The use of S1P to treat OHSS could inadvertently exacerbate or trigger conditions such as endometriosis, adenomyosis, and fibroids. That's because S1P encourages cell growth, angiogenesis, and inflammation, the same processes that promote these disorders. While it may help with OHSS, it carries the risk of exacerbating other hormone-related diseases, thereby limiting its therapeutic potential[6].

The new findings identify S1P as a putative biomarker and therapeutic candidate in OHSS, based on lipidomic data from follicular fluid and animal models in which it inhibits vascular permeability and reduces ovarian size. However, the data presented are limited to in vitro and animal studies because S1P has been reported to worsen disorders such as endometriosis. To translate these findings into clinical practice, most S1P human observational studies must be conducted to validate predictive accuracy; small clinical trials must be performed to ensure localized delivery and reduce systemic risk; and studies of selected modulators of the S1P receptor must be undertaken to develop safer interventions. The endpoint of these activities is to improve risk stratification and therapeutic approaches, thereby improving patient safety in assisted reproductive technologies[1,2,4].

Future research on S1P in OHSS should start with human observational studies to confirm its predictive value and determine safe ranges. Because current evidence derives from animal and lab models, initial human trials should be small and closely monitored, and should preferably use local or targeted delivery to reduce side effects. Safer alternatives may include selective S1P receptor modulators or neutralizing agents, particularly in women with conditions such as endometriosis. Careful patient selection and monitoring will be vital before wider clinical use.

Ethics

Informed Consent: Was obtained.

Footnotes

Authorship Contributions

Concept: S.M.H., M.U., Literature Search: F.K.K., Writing: M.T.

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