Assessment of Platelet Function in the Hemostasis System in Women with Premature Ovarian Insufficiency

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ABSTRACT

Premature ovarian insufficiency (POI) is a polyetiological condition characterized by the cessation of ovarian function before the age of 40, significantly impacting women's quality of life. This study investigates the platelet component of the hemostasis system in 35 women with POI compared to 50 age-matched women with normal ovarian function. Results indicate the presence of consumption thrombocytopathy in women with POI, with a significant reduction in platelet count ($p<0.01$) and decreased aggregation activity, particularly in secondary aggregation ($p<0.01$). Collagen-induced platelet aggregation was also impaired, with a twofold prolongation of the latent phase ($p<0.01$). These changes reflect hyperactive yet dysfunctional platelets, contributing to a pre-thrombotic state in women with POI. The study highlights the need for early interventions to correct endothelial and hemostatic imbalances in patients receiving hormone replacement therapy (HRT) for POI. Timely therapeutic strategies could mitigate the progression to thrombotic complications, improving overall health outcomes and quality of life for these patients.

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Introduction

Premature ovarian insufficiency (POI) is defined as amenorrhea occurring in women of reproductive age (under 40 years) alongside elevated levels of follicle-stimulating hormone (FSH) and decreased ovarian function. According to the European Society of Human Reproduction and Embryology (ESHRE), the diagnosis of POI is established when oligomenorrhea or secondary amenorrhea persists for at least four months, accompanied by FSH levels exceeding 25 IU/L in two separate measurements taken four weeks apart [12]. A large meta-analysis that included data from 31 studies revealed a prevalence of 3.7% for POI and 12.2% for early menopause [2,3,4,9]. The analysis also indicated that POI is more frequently observed in women living in developing countries [5,6,8,10] and shows a strong age-dependent trend. For example, at the age of 20, POI occurs in approximately one in 10,000 women, whereas by the age of 30, the prevalence increases to one in 1,000.

The premature cessation of ovarian function before the onset of natural menopause is a significant challenge for affected women, having widespread negative effects on their overall health, well-being, and the function of various organs and systems. The decline in ovarian estrogen production is strongly linked to the development of cardiovascular diseases in women [1,2,7,11], with the hemostasis system playing a crucial role in this process. Platelets are central to primary hemostasis, where they form the initial "platelet plug" and contribute to thromboplastin-thrombin-fibrin formation, thereby establishing a connection between the platelet-vascular and coagulation pathways of hemostasis. Their role in the hemostasis system is multifaceted, encompassing the maintenance of the normal structure and function of microvascular walls, the formation of a primary platelet plug in damaged vessels through adhesion and aggregation, the induction and maintenance of vasospasm at the site of vascular injury, and active participation in blood coagulation with an inhibitory effect on fibrinolysis. These functions underscore the critical importance of platelets in vascular integrity and injury response, particularly in the context of systemic complications associated with reduced ovarian function.

Materials and Methods

This study assessed the platelet component of the hemostasis system in 35 women diagnosed with premature ovarian insufficiency (POI). A control group of 50 women with normal ovarian function, matched by age, served as the comparator. All participants provided written informed consent prior to inclusion in the study, which was conducted following the principles outlined in the Declaration of Helsinki and approved by the relevant institutional ethics committee.

Clinical and Gynecological Examination

Comprehensive clinical evaluations were performed on all participants, including general physical and gynecological assessments. These examinations aimed to exclude other potential causes of thrombocytopathy and to confirm the diagnosis of POI in the study group. The diagnostic criteria for POI followed the European Society of Human Reproduction and Embryology (ESHRE) guidelines, including persistent oligomenorrhea or amenorrhea for at least four months and elevated FSH levels (>25 IU/L) in two consecutive measurements taken four weeks apart.

Platelet Function Assessment

To analyze the platelet component of the hemostasis system, two main parameters were evaluated:

Platelet Count: Platelet counts were determined from peripheral blood samples collected using standard hematological methods.

Platelet Aggregation Activity: The aggregation capacity of platelets was studied using a photometric aggregometer (single-channel, manufactured by the Experimental Workshops of the Russian Academy of Medical Sciences). The instrument was equipped with a thermostat set at 37°C and a magnetic stirrer to ensure uniform mixing.

Aggregation was induced by stimulating platelets with adenosine diphosphate (ADP) at concentrations of $1x10^{-3}$ M, $1x10^{-5}$ M, and $1x10^{-7}$ M, as well as with collagen. Aggregation curves were recorded, and the maximal aggregation response was analyzed to determine platelet functionality.

Blood Collection and Sample Preparation

Blood samples were drawn aseptically from the cubital vein using sterile needles. Samples were collected into siliconized tubes containing anticoagulant in a ratio of 9 parts blood to 1 part anticoagulant. A 3.8% solution of trisodium citrate was used as the anticoagulant.

To prepare platelet-rich plasma (PRP), the blood samples were centrifuged at 1500 rpm for 7 minutes at room temperature. The supernatant containing PRP was carefully separated for use in aggregation studies. Platelet-poor plasma was obtained by further centrifuging the remaining blood sample at 2500 rpm for 15 minutes and served as a reference.

Statistical Analysis

Data were analyzed using R studio statistical software (version 3.6.2). Descriptive statistics were calculated for all variables, and group comparisons were made using appropriate parametric or non-parametric tests based on data distribution. A p-value <0.05 was considered statistically significant.

Results

The mean age of participants in the main group (women with POI) was 29.1 years, compared to 30.2 years in the control group. Comorbid somatic pathologies were identified in 10 women (28.6%) in the main group and 11 women (22%) in the control group. Hypertension was observed in 3 patients from the main group, obesity in 5 women in the main group and 1 in the control group, and hypothyroidism in 2 patients from the main group (Table 1).

Table 1: Reproductive Function Indicators in Women with Premature Ovarian Insufficiency and the Control Group

Parameter	Main Group (n=35) n(%)	Control Group (n=50) n(%)
Primary infertility	11 (31.4%)	-
Secondary infertility	5 (14.3%)	2 (4%)
Ectopic pregnancy	1 (2.9%)	-
Cesarean delivery	6 (17.1%)	5 (10%)
Live births		
1	12 (34.3%)	14 (28%)
2	3 (8.6%)	26 (52%)
3 or more	-	10 (20%)
Induced abortions		
1	1 (2.9%)	4 (8%)
2–3	-	1 (2%)
More than 3	4 (11.4%)	1 (2%)
Miscarriages		
1	3 (8.6%)	2 (4%)
2–3	3 (8.6%)	-
More than 3	-	1 (2%)
No sexual activity	5 (14.3%)	-

A notable observation was the later onset of menarche in women with POI. The mean age at menarche in the main group was 15.7 years (ranging from 14 to 17 years), compared to 13.2 years in the control group (ranging from 12 to 14 years). Menstrual dysfunction was significantly more prevalent in the main group, affecting over half of the patients (16 women, 45.7%). These dysfunctions included hypomenstrual syndrome (characterized by scant and infrequent menstruations) in 6 women and abnormal uterine bleeding (AUB) in 10 women. Throughout their lives, these patients often required treatment, primarily in the form of hormone replacement therapy. Four women underwent vacuum aspiration procedures due to AUB, and one underwent endometrial polyp removal. In contrast, no menstrual cycle disturbances were identified in the control group.

The duration of menopause among women in the main group ranged from 1 to 6 years, with an average duration of 3.7 years at the time of evaluation.

Table 2. Platelet Component of the Hemostasis System in Examined Women

Indicator	Women Without POI	Women With POI	p-value
Platelet Count ($1x10^9$/L)	280.6 ± 7.2	211.0 ± 15.6	(p<0.01)
Platelet Aggregation (ADP $1x10^{-3}$ M)	40.2 ± 2.5	38.2 ± 1.7	(p>0.05)
Platelet Aggregation (ADP $1x10^{-5}$ M)	32.4 ± 2.1	14.2 ± 1.1	(p<0.01)
Platelet Aggregation (ADP $1x10^{-7}$ M)	18.0 ± 1.1	18.4 ± 1.2	(p>0.05)
Collagen-Induced Aggregation (%)	44.6 ± 1.4	32.4 ± 1.7	(p<0.01)

The findings on the platelet component of the hemostasis system in the examined women are summarized in Table 2. In patients with premature ovarian insufficiency (POI), consumption thrombocytopathy was identified, characterized by a significant reduction in platelet count compared to healthy women (p<0.01). Platelet aggregation intensity upon stimulation with ADP at a concentration of $1x10^{-3}$ M was 16% lower than in the control group of healthy women, though this difference did not reach statistical significance (p>0.05). Secondary aggregation intensity was three times lower in the POI group (p<0.01), with notable signs of impaired release reaction and a marked decrease in the intensity of the second phase of platelet aggregation.

Primary aggregation intensity, when stimulated with ADP at a concentration of $1x10^{-7}$ M, was also reduced compared to healthy women, but the difference was not statistically significant (p>0.05). Platelet aggregation induced by collagen showed a significant decrease in aggregation intensity (p<0.01), along with a twofold prolongation of the latent phase duration, ranging from 40 to 60 seconds.

These results indicate the development of consumption thrombocytopathy in patients with POI. The condition is characterized by a decrease in platelet count and marked dysfunction, including reduced aggregation and secretory activity. These findings highlight significant impairments in platelet function, contributing to the observed hemostatic alterations in this patient population.

Discussion

The conducted studies have revealed significant alterations in the platelet component of the hemostasis system in women with premature ovarian insufficiency (POI). A notable finding was the presence of consumption thrombocytopathy, characterized by a significant reduction in platelet count compared to healthy women (p<0.01). Platelet aggregation intensity upon stimulation with ADP at a concentration of $1x10^{-3}$ M was 16% lower in the POI group than in the control group, though this difference did not reach statistical significance (p>0.05).

Secondary aggregation intensity was markedly reduced, being three times lower in the POI group (p<0.01). Similarly, primary aggregation intensity at an ADP concentration of $1x10^{-7}$ M was slightly lower in the POI group compared to healthy women, though this difference was not statistically significant (p>0.05). These findings indicate impaired platelet functionality, particularly in secondary aggregation processes [2,7,13].

The observed changes strongly suggest the development of consumption thrombocytopathy in women with POI. The condition is characterized by both a quantitative reduction in platelets and significant qualitative dysfunction, including decreased aggregation and secretory activity. These abnormalities highlight the systemic impact of POI on hemostatic mechanisms and emphasize the need for further research to elucidate underlying pathophysiological processes and develop targeted therapeutic strategies.

Conclusions

Thus, premature ovarian insufficiency (POI) is a polyetiological condition that significantly reduces the quality of life for affected women. Patients with POI exhibit hyperactivity of platelets, and changes in platelet functional activity indicate the presence of a pre-thrombotic state. Over time, this condition may progress to the development of thrombotic complications.

Based on the findings of this study, it is possible to implement timely interventions to correct the hemostasis system and endothelial function in women with POI who are receiving hormone replacement therapy. These

measures could help prevent the progression of pre-thrombotic states and reduce the risk of thrombotic events, ultimately improving patient outcomes and quality of life.

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