UDC: 618.1/.2+616-005.6

https://doi.org/10.37800/RM.1.2025.420

Optimization of treatment of antiphospholipid syndrome in pregnant women: Clinical research

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ABSTRACT

Relevance: Antiphospholipid syndrome (APS) is a very complex and urgent problem during pregnancy. APS is characterized by venous and arterial thromboses caused by the circulation of antiphospholipid antibodies in the blood. These thromboses lead to various complications and negative consequences of pregnancy, requiring improved therapy.
The study aimed to optimize the management of antiphospholipid syndrome in pregnant women.
Materials and Methods: The study was conducted among 76 pregnant women with APS, divided into 2 groups. The groups were representative regarding age, parity, obstetric, and somatic pathology but differed in treatment methods. The comparison group (traditional therapy) included 28 pregnant women with APS. In this group, all pregnant women received traditional APS therapy, including anticoagulants, antiplatelet agents, and glucocorticoids. The main group included 48 pregnant women with APS. In this group, all pregnant women, in addition to traditional therapy, were given systemic enzyme therapy (SET) and plasmapheresis. The control group included pregnant women with uncomplicated pregnancy, n=30.
Results: After 30 days of treatment, the changes in the traditional therapy group compared to the controls included the increases in Willebrand factor – by 17.7%, platelet aggregation index – by 24.1%, total platelet aggregation index – by 26.2%, soluble fibrin-monomer complexes (SFMC) – by 55.3%, and early fibrin degradation products (EFDP) – by 45.6% ($p<0.05$). The platelet disaggregation index decreased by 18.5% and antithrombin III activity – by 14.3% ($p>0.05$). Multidirectional trends in hemostasis system parameters recorded during traditional therapy generally aggravated the degree of disturbances registered in the initial period of the study.
The treatment provided more significant dynamics toward normalizing the studied parameters in the main group. Reliable differences were revealed with the indicators obtained with traditional therapy: SFMC – by 29.7%, EFDP – by 23.3%, and blood prothrombin time – by 14.0% ($p<0.05$).
Conclusion: Using SET in combination with plasmapheresis and low molecular weight heparin ensures the normalization of hemostasis system parameters in pregnant women with APS.

Keywords: *antiphospholipid syndrome, pregnancy, systemic enzyme therapy (SET), plasmapheresis.*

How to cite: Tanysheva GA, Berikkhanova KE, Kinayatova ShK et al. Optimization of treatment of antiphospholipid syndrome in pregnant women: Clinical research. *Reproductive Medicine (Central Asia).* 2025;1:108-114.
https://doi.org/10.37800/RM.1.2025.420

Оптимизация лечения антифосфолипидного синдрома у беременных: клиническое исследование

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АННОТАЦИЯ

Актуальность: Антифосфолипидный синдром (АФС) при беременности является очень сложной и актуальной проблемой. Характерные для синдрома венозные и артериальные тромбозы, обусловленные циркуляцией антифосфолипидных антител в крови, приводят к различным осложнениям и негативным последствиям беременности, которые требуют улучшения терапии.
Цель исследования – оптимизация лечения антифосфолипидного синдрома у беременных.
Материалы и методы: Исследование проводилось среди 76 беременных с АФС, которые были разделены на 2 группы. Группы были репрезентативны по возрасту, паритету, акушерской и соматической патологии, но отличались по методам лечения. В группу сравнения (традиционного ведения) вошли 28 беременных с АФС. В данной группе все беременные получали традиционную терапию АФС, включающую антикоагулянты, антиагреганты, глюкокортикоиды. В основную группу вошли 48 беременных с АФС. В данной группе всем беременным на фоне традиционной терапии дополнительно применялись системная энзимотерапия и плазмаферез. Отдельно выделена контрольная группа беременных с неосложненным течением беременности, n=30.

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Результаты: В группе традиционной терапии по сравнению с контролем через 30 суток были выявлены превышения по показателям фактора Виллебранда – на 17,7%, индекса агрегации тромбоцитов – на 24,1%, суммарного индекса агрегации тромбоцитов – на 26,2%, растворимых фибрин-мономерных комплексов (РФМК) – на 55,3% и ранних продуктов деградации фибрина (РПДФ) – на 45,6% ($p<0,05$). Отмечается снижение индекса дезагрегации тромбоцитов на 18,5% и активности антитромбина III – на 14,3% ($p>0,05$). При традиционной терапии были зарегистрированы разнонаправленные тенденции показателей системы гемостаза на фоне лечения, которые, однако, в целом приводили к усугублению степени нарушений, имевшейся в исходном периоде исследования.
В основной группе лечение обеспечило более значительную динамику к нормализации исследованных показателей. Были выявлены достоверные различия с показателями, полученными при традиционной терапии: по уровню РФМК – на 29,7%, РПДФ – на 23,3% и по показателю протромбинового времени – на 14,0% ($p<0,05$).
Заключение: Применение системной энзимотерапии в сочетании с плазмаферезом и низкомолекулярным гепарином у беременных с АФС обеспечивает практически полную нормализацию показателей системы гемостаза.

Ключевые слова: *антифосфолипидный синдром (АФС), беременность, системная энзимотерапия (СЭТ), плазмаферез.*

Для цитирования: Танышева Г.А., Берикханова К.Е., Кинаятова Ш.К. и др. Оптимизация лечения антифосфолипидного синдрома у беременных: клиническое исследование. *Репродуктивная медицина (Центральная Азия).* 2025;1:108-114 (на англ.).
https://doi.org/10.37800/RM.1.2025.420

Жүкті әйелдерде антифосфолипидті синдромды емдеуді оңтайландыру: клиникалық сынақ

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АҢДАТПА

Өзектілігі: Жүктілік кезіндегі антифосфолипидті синдром (АФС) – өте күрделі және өзекті мәселе. АФС веноздық және артериялық тромбоздармен сипатталады, олар қандағы антифосфолипидті антиденелердің айналымынан туындайды және әртүрлі асқынулар мен жүктіліктің жағымсыз салдарына әкеледі, терапияны жақсартуды қажет етеді.
Зерттеу мақсаты – жүкті әйелдерде АФС емдеуді оңтайландыру.
Материалдар мен әдістері: Зерттеу АФС бар 76 жүкті әйелдер арасында жүргізілді, олар 2 топқа бөлінген. Топтар жас, паритет, акушерлік және соматикалық патология бойынша репрезентативті болды, бірақ емдеу әдістерінде ерекшеленді.
Салыстыру тобына (дәстүрлі емдеу) АПС бар 28 жүкті әйел кірді. Бұл топтағы барлық жүкті әйелдер дәстүрлі терапияны алды (соның ішінде антикоагулянттар, антиагреганттар және глюкокортикоидтар). Негізгі топқа АПС бар 48 жүкті әйел кірді. Бұл топта барлық жүкті әйелдер дәстүрлі терапия фонында жүйелі ферменттік терапия және плазмаферезбен қосымша емделді. Асқынбаған жүктілігі бар жүкті әйелдердің жеке бақылау тобы бөлінды, n=30.
Нәтижелері: Дәстүрлі терапия тобында бақылаумен салыстырғанда 30 күннен кейін келесілер көрсеткіштердің жоғарылауы анықталды: Виллебранд факторының мөлшерінің 17,7%-ға, тромбоциттер агрегациясының индексінің 24,1%-ға және жалпы ІАТ 26,2%-ға, еритін фибрин-мономер кешендерінің (ЕФМК) және фибриннің ерте ыдырау өнімдерінің (ФЕЫӨ) деңгейі 55,3%-ға және 45,6%-ға сәйкесінше ($p<0,05$). Көрсеткіштердің төмендеуі байқалады: тромбоциттер дезагрегациясының индексі 18,5%-ға, антитромбин ІІІ белсенділігі 14,3%-ға ($p>0,05$). Дәстүрлі терапиямен емдеу кезінде гемостаздық жүйе параметрлерінің көп бағытты тенденциялары тіркелді, алайда бұл жалпы зерттеудің бастапқы кезеңінде болған бұзылулар дәрежесінің нашарлауына әкелді.
Негізгі топта емдеу зерттелетін параметрлерді қалыпқа келтіру бағытында айтарлықтай динамика берді. 30 күннен кейін дәстүрлі терапия тобынан айырмашылығы, бақылау тобының көрсеткіштерімен айтарлықтай айырмашылықтар тіркелмеді. Сонымен қатар, дәстүрлі терапиямен алынған көрсеткіштермен айтарлықтай айырмашылықтар анықталды: ЕФМК деңгейінде – 29,7%-ға, ФЕЫӨ – 23,3%-ға және қандағы протромбин уақытының көрсеткіші бойынша – 14,0%-ға ($p<0,05$).
Қорытынды: Жүйелі ферменттік терапия, плазмаферез және төмен молекулалы гепаринмен бірге қолдану АФС бар жүкті әйелдерде гемостаз жүйесінің көрсеткіштерін қалыпқа келтіруді қамтамасыз етеді.

Түйінді сөздер: *антифосфолипидті синдром, жүктілік, жүйелі ферменттік терапия, плазмаферез.*

Introduction: Antiphospholipid syndrome (APS) is a clinical and laboratory diagnosis characterized by both persistent laboratory signs of antiphospholipid antibodies (aPL) and associated complications, which may include venous thrombosis, arterial thrombosis, and adverse pregnancy outcomes [1-3]. APS is based on a specific vasculopathy associated with thrombotic occlusive vascular disease in the absence of inflammatory or degenerative changes in the vascular wall [4-6].

The appearance of auto-antiphospholipid antibodies disrupts thrombus formation. As their action increases, the activation of the endogenous physiological inhibitor of protein C, which limits the action of plasma factors V and VIII, is disrupted, leading to venous and arterial thrombosis [7, 8].

Pregnancy complications in APS include preeclampsia, intrauterine growth retardation syndrome, premature birth, and spontaneous miscarriages. Critical conditions include complications such as premature detachment of a normally located placenta, hemolytic uremic syndrome, and HELLP syndrome [9-12].

The pathological conditions described above during pregnancy require timely diagnosis of APS and improved treatment.

The study aimed to optimize the management of antiphospholipid syndrome in pregnant women.

Materials and methods: Assuming the potentiation of the effects of systemic enzyme therapy (SET), plasmapheresis, and low molecular weight heparins (LMWH), a complex therapy of APS was developed with the simultaneous use of the above-mentioned treatment methods in combination.

For achieving the objectives, pregnant women with APS (n=76) were divided into 2 groups. The main group (n=48) included pregnant women with APS who, in addition to traditional therapy, received SET and plasmapheresis [13]. The comparison group (traditional therapy) (n=28) included pregnant women with APS who received traditional APS therapy, including anticoagulants, antiplatelet agents, and glucocorticoids [14-18]. The groups were representative regarding age, parity, obstetric, and somatic pathology but differed in treatment methods.

A separate control group (n=30) of pregnant women with uncomplicated pregnancy was identified.

Results: SET is a therapeutic method based on combined enzyme preparations. The basis of these preparations is highly purified proteinases [19].

Indications for plasmapheresis were pronounced activity of the autoimmune process, manifestations of chronic DIC syndrome, allergic reactions to antiplatelet agents and anticoagulants, activation of bacterial and viral infections, exacerbation of gastric ulcer and duodenal ulcer, in which the use of prednisolone is impossible [20].

Plasmapheresis has detoxifying, rheo-, coagulo-, and immunocorrective effects. Its inclusion in the complex therapy of patients with APS is pathogenetically justified and potentiates the positive effect of drugs [20, 21]. The use of heparins in women with thrombosis and thrombotic readiness is determined by the need to prevent thrombosis of placental vessels [22]. When obstetric pathology was detected in pregnant women in both groups (miscarriage, preeclampsia, placental insufficiency, etc.), experimental obstetric pathology was treated against the background of APS treatment. In traditional care of pregnant women with APS, antiplatelet agents, anticoagulants, and glucocorticoids were used against the obstetric pathology treatment without SET plasmapheresis. The main group received traditional APS treatment plus additional SET with plasmapheresis in several intermittent modes every two weeks under hemostasis control.

During the treatment, pregnant women with APS were monitored for indicators of various links of the hemostasis system.

In the blood of pregnant women in the traditional therapy group, the content of von Willebrand factor in the initial period was increased relative to the control group by 17.2%. In the dynamics of traditional treatment, this indicator decreased, and after 10 days, its value exceeded the control indicator by 11.4%. However, after 30 days, an opposite trend towards its growth was observed, and the degree of excess was 17.7%.

The dynamics of the platelet aggregation index (PAI) was initially aimed at decreasing relative to the initial level, but after 30 days, its increase was observed again, and the excess over the control group level was 24.1% ($p<0.05$).

At the same time, platelet aggregation rate (PAR) was significantly higher than the control group indicator at the initial examination, and after 10 days ($p<0.05$), and after 30 days, it decreased.

The total PAI level changed similarly to PAI. Initially, there was a decrease in this indicator from a 17.5% excess over the control group to the equality with its level. However, after 30 days, this indicator reliably increased compared with the control (by 26.2%, $p<0.05$).

During the observation period, a decrease in the platelet disaggregation index was revealed in the traditional therapy group. The differences with the control group reached the level of reliability only after 30 days from the initial examination (18.5%, $p<0.05$), indicating a deterioration of the hemostasis system parameters in pregnancy complications [23].

The level of soluble fibrin-monomer complexes (SFMC) and early fibrin degradation products (EFDP) had a reliable excess in the initial period and a tendency to increase when analyzing the differences between the initial indicator and the state after 30 days. In the latter case, the excess over the controls amounted to 55.3% and 45.6%, respectively, $p<0.05$.

The prothrombin time in the blood increased. It had no significant differences with the control after 10 days and practically normalized after 1 month from the start of correction in the main group.

Similar dynamics characterized the international normalized ratio, which in the comparison group tended to decrease (hypercoagulation), and in the main group, it was completely normalized upon completion of the course of treatment.

Antithrombin III activity decreased compared with the control group at the outcome (by 12.6%, $p>0.05$) and after 30 days (by 14.3%, $p>0.05$).

Table 1 shows the dynamics of hemostasis parameters in pregnant women with antiphospholipid syndrome using complex treatment (SET, plasmapheresis, and anticoagulants).

Table 1 – The effect of complex treatment using SET, plasmapheresis, and low molecular weight heparins on hemostasis system parameters in pregnant women with antiphospholipid syndrome

Indicators	Pregnant women with uncomplicated pregnancy (n = 30)	Traditional therapy (n=28)			SET with plasmapheresis (n = 48)		
		Before treatment	After 10 days of treatment	After 30 days of treatment	Before treatment	After 10 days of treatment	After 30 days of treatment
Ejection fraction, %	88.5±6.2	103.7±7.7	98.6±4.9	104.2±5.1	108.2±6.0*	95.7±5.5	96.1±5.7
ADP-dependent aggregation							
PAI, %	37.8±2.3	45.2±3.5	41.8±2.9	46.9±3.3*	47.3±2.9*	42.2±3.0	40.5±2.5
TPA, extra units/ min	0.025±0.002	0.033±0.002*	0.031±0.002*	0.030±0.002	0.034±0.002*	0.032±0.002*	0.029±0.001
TPAI, %	49.2±3.0	57.8±4.4	50.5±3.7	62.1±4.5*	58.5±3.7	51.3±3.3	52.0±4.1
PDT, %	20.5±1.3	18.4±1.1	17.9±1.2	16.7±1.0*	17.4±0.9	19.2±1.2	19.6±1.1
Plasma coagulation component							
Fibrinogen, g/L	3.61±0.25	3.95±0.18	3.88±0.14	4.15±0.21	4.12±0.17	3.72±0.12	3.84±0.15
SFMC, mg/mL	6.60±0.45	8.69±0.63*	8.34±0.58*	10.25±0.60**	10.24±0.49**	7.65±0.31	7.21±0.30#
EFDP, mg/mL	11.83±0.90	14.70±1.05*	12.95±0.76	17.22±1.09*	16.08±1.05*	11.45±0.87	13.20±0.72#
Prothrombin time, s	24.2±1.1	19.1±1.5*	18.5±1.4*	17.9±1.4*	18.5±1.1*	20.7±1.3	23.1±1.3
INR	1.24±0.08	0.97±0.06*	0.94±0.07*	0.89±0.05*	0.99±0.08*	1.15±0.07	1.22±0.10
Antithrombin III, %	87.2±5.4	76.2±3.9	79.7±4.1	74.7±4.2	71.5±3.9*	77.2±4.1	75.8±3.7
XIIa-dependent fibrinolysis, min	5.3±0.4	6.4±0.4	5.0±0.3	5.9±0.4	7.0±0.3*	5.1±0.2	5.3±0.2

Note: * – differences with the baseline are significant, p <0.05, ** – p <0.01 # – differences with the traditional therapy group are significant, p <0.05 ADP – adenosine diphosphate, PAI – platelet aggregation index, PDI – platelet disaggregation index, SFMC – soluble fibrin-monomer complexes, EFDP – early fibrin degradation products, TPA - total platelet aggregation, TPAI – total platelet aggregation index

Discussion: Previously, studies were conducted among women of fertile age with APS to develop a method of pregravid preparation for a planned pregnancy and assess its clinical results. This study provides a comparative analysis of the effectiveness of complex therapy for APS during pregnancy. With traditional therapy, multidirectional trends in hemostasis system parameters were recorded during treatment, which generally led to an aggravation of the disorders present in the initial period of the study. At the same time, with complex therapy (SET, plasmapheresis, anticoagulants), reliable differences with the control group were recorded in the initial examination period [23].

The course of treatment provided more significant dynamics toward the normalization of the studied parameters. If reliable differences with the group of pregnant women without complications in the initial period were revealed in the parameters of von Willebrand factor, PAI, PAR, PV, SFMC, RPDF, antithrombin III and XIIa-dependent fibrinolysis, then after 10 days – only by PAR and protrombine time – by 28.0% and 15.7%, respectively (p<0.05).

After 30 days, there were no significant differences between the parameters of the main group and the traditional therapy group. At the same time, significant differences with the parameters obtained with traditional therapy were revealed: in the level of RFMC - by 29.7%, RPDF - by 23.3%, and PV - by 14.0% (p<0.05).

Conclusion: According to the hemostasis system parameter analysis, SET in combination with plasmapheresis and LMWH ensures almost complete normalization of condition in pregnant women with APS. This complex treatment is of great practical significance for pregnant women; it improves the course and outcomes of pregnancy.

Получено/Received/Жіберілді: 18.11.2024
Одобрено/Approved/Мақұлданған: 25.01.2025
Опубликовано на сайте/Published online/Сайтта жарияланған: 31.03.2025

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Вклад авторов:

Разработка концепции, Административное руководство исследовательским проектом, Написание рукописи – рецензирование и редактирование – Танышева Г.А., Берикханова К.Е.

Проведение исследования – Танышева Г.А., Кинаятова Ш.К., Егежанова Г.М.

Валидация результатов – Танышева Г.А., Берикханова К.Е.

Написание черновика рукописи – Ерланкызы Е., Советова С.Д.

Финансирование: Авторы заявляют об отсутствии финансирования исследования.

Конфликт интересов: Авторы заявляют об отсутствии конфликта интересов.

Прозрачность исследования: Авторы несут полную ответственность за содержание данной статьи.

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Funding: Authors declare no funding of the study.

Conflict of interest: Authors declare no conflict of interest.

Transparency of the study: All authors take full responsibility for the content of this manuscript.