Comparison of the effectiveness of various methods of pregnancy loss prevention in women with antiphospholipid syndrome

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For citation: Orlova E. S., Chepanov S. V., Kornyushina E. A., Ryzhov Y. R., Zainulina M. S., Selkov S. A. Comparison of the effectiveness of various methods of pregnancy loss prevention in women with antiphospholipid syndrome. *Vestnik of Saint Petersburg University. Medicine*, 2019, vol. 14, issue 4, pp. 371–373. https://doi.org/10.21638/spbu11.2019.430

Around 10–15% women with recurrent pregnancy loss are diagnosed with antiphospholipid syndrome. In 20–30% women conventional therapy approaches do not lead to desirable outcomes. A possible approach to improve pregnancy outcomes in women with antiphospholipid syndrome is combined use of plasmapheresis and intravenous immunoglobulin in addition to a conventional therapy, which was assessed in this study in comparison with conventional therapy+plasmapheresis only; with conventional therapy+intravenous immunoglobulin only and with conventional therapy only. According to the results, combined use of plasmapheresis with immunomodulating intravenous immunoglobulin and conventional therpapy leads to the most significant antiphospholipid antibodies titer lowering, reduces prevalence of pregnancy complications, such as threatened abortion, mild preeclampsia, placental insufficiency, intrauterine growth restriction and increases prevalence of favourable pregnancy outcomes. It can be assumed that this approach can be considered as the most effective for the treatment of pregnant women with antiphospholipid syndrome for prevention gestational complications and pregnancy loss.

Keywords: antiphospholipid syndrome, antiphospholipid antibodies, recurrent pregnancy loss, intravenous immunoglobulins, plasmapheresis.

Background

Pregnancy loss rate accounts for up to 15% of all the pregnancies and is an important medical and social problem, which influences key demographic indicators, women's emotional and psychological status and reproductive state. Around 10–15% women with recurrent pregnancy loss are diagnosed with antiphospholipid syndrome (APS) [1]. Antiphospholipid antibodies are found in 11–29% of pregnant women with preeclampsia [2]. According to present international recommendations, the optimal prevention of recurrent pregnancy loss in women with APS is the use of low molecular weight heparins (LWMHs) and low-dose aspirin during pregnancy. Nevertheless, with such a therapy adverse pregnancy outcomes persist in 20–30%. Using of intravenous immunoglobulins (IVIg) as immunomodulator in APS is off-label therapy and considered only as recommendation. At the same time opportunities of IVIg therapy are widely discussed. Taking into account that in

20–30 % women conventional therapy approaches do not lead to desirable outcomes and do not prevent pregnancy pathology, in recent studies efferent therapy and immunomodulating agents are considered as second-line treatment [3].The promising methods for this challenging condition include efferent procedures, such as plasmapheresis or immunoadsorption. Pathogenetic therapy of APS is focused on antiphospholipid antibody titer lowering (mechanical elimination). However efferent therapy does not influence on antiphospholipid antibody production and consequently has time-limited effect, what eventually leads to contrary opinions regarding its effectivity. A possible approach to improve pregnancy outcomes in women with APS is combined use of plasmapheresis and IVIg.

Objective

To develop a clinical and immunological rationale for the combined use of plasmapheresis and IVIg in pregnant women with APS.

Materials and methods

The study included 89 women of reproductive age, surveyed and treated at Federal State Research Institute of obstetrics, gynecology and reproductology named after D. O. Ott (St. Petersburg, Russia). All women signed their informed consent to participate in the study. The following exclusion criteria were applied: (1) age under 18 and over 42 years; (2) multiple pregnancies; (3) concominant diseases (diabetes mellitus type-1 and type-2 taking insulin, chronic glomerulonephritis, bronchial asthma, chronic kidney disease, liver failure, viral hepatitis). APS was diagnosed according to International criteria (Sydney Consensus Workshop, Sydney, 2006).

All eligible patients with APS were treated with conventional therapy (LMWHs and low-dose aspirin according to their weight and coagulation state) and assigned to one of the following groups.

1. Pregnant women with APS, treated with conventional therapy and IVIg only (n = 31).
2. Pregnant women with APS, treated with conventional therapy and plasmapheresis only (n = 15).
3. Pregnant women with APS, treated with conventional therapy, IVIg and plasmapheresis (n = 29).
4. Pregnant women with APS, treated only conventionally with LMWHs and low-dose aspirin (n = 14).

Plasmapheresis was carried out using Haemonetics MCS (USA) and Gemma (Russia) devices in amount of 3–4 procedures per course of treatment.

Immunomodulating therapy was carried out with human polyclonal donor's IgG [IVIG] for intravenous administration (Microgen, Russia) at a course dose of 300 ml (15 g) by 3 intravenous infusions of 100 ml (5 g) each with an intervals of 1 week.

Results and discussion

Significant differences in lowering of antiphospholipid antibodies titer were observed between group 3 and group 1 ($p < 0.001$) and between group 3 and group 4 ($p < 0.0001$). And also significant differences in lowering of antiphospholipid antibody titer were observed between group 3 and group 2 ($p < 0.0001$).

The study showed that the lowest rate of threatening miscarriage (68.9 %) and mild preeclampsia (3.4 %) was in group 3. However, in this group we observed 1 case of severe preeclampsia that required preterm delivery by cesarean section at 33/34 weeks of gestation. The state of newborn was relatively stable and it had favourable prognosis. It should be noted that this patient had extremely unfavourable obstetrical medical history (1 missed abortion, 1 intrauterine fetal death of morphologically normal fetus, 1 extremely premature delivery associated with severe preeclampsia and early neonatal death). During the pregnancy she had multiple hospital admissions, underwent 3 plasmapheresis and 3 IVIg treatment courses and had multiple pregnancy complications — threatening abortion, placental insufficiency, intrauterine growth restriction.

Group 3 was also characterised by the lowest prevalence of placental insufficiency (6.9 %), intrauterine growth restriction (6.9 %) and the highest prevalence of favourable pregnancy outcomes (term delivery) — 79.3 %. Preterm delivery and missed abortion rate were 10.3 %. To be noticed is that 2 of 3 cases of missed abortion were associated with fetal chromosomal abnormalities.

The rationale for abovementioned therapeutic approach is based on putting together of 3 components: antithrombotic effect of LMWHs minimize antiphospholipid antibodies induced thrombotic complications; plasmapheresis, when used according to the schedule, nonselectively eliminates large amounts of antibodies from maternal circulation; IVIg further increase antiphospholipid antibodies clearance.

Conclusion

Thus, combined use of plasmapheresis with immunomodulating IVIg leads to the most significant antiphospholipid antibodies titer lowering, reduces prevalence of pregnancy complications, such as threatened abortion, mild preeclampsia, placental insufficiency, intrauterine growth restriction and increases prevalence of favourable pregnancy outcomes. It can be assumed that this approach can be considered as the most effective for the treatment of pregnant women with APS for prevention gestational complications and pregnancy loss.

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Received: February 12, 2020
Accepted: June 3, 2020

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