Current Status of Anticoagulant Therapy in Unexplained Recurrent Spontaneous Abortion

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Unexplained recurrent spontaneous abortion (URSA) is a difficult problem in obstetrics which often brings serious psychological and economic burden to patients and families, but there is still no effective prevention and treatment method. Some studies suggest that the occurrence of URSA is related to a prethrombotic state and placental vascular thrombosis. The decrease of placental blood perfusion leads to embryonic dysplasia or abortion. Anticoagulant therapy has always been considered by the obstetrics community, but the research opinions are not consistent. With regard to whether anticoagulant drugs such as low-molecular-weight heparin and aspirin can effectively improve pregnancy outcomes of unexplained recurrent spontaneous abortion, this paper collates the relevant data, summarizes the application status of anticoagulant therapy in patients with unexplained recurrent spontaneous abortion, and provides reference for clinical treatment. (J Reprod Med 2021;66:113–117)

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Unexplained recurrent spontaneous abortion (URSA) refers to 3 or more consecutive spontaneous abortions that have occurred in a woman with the same sex partner and without influences of chromosomal, immune, or endocrine dysfunction and genital tract infections.[1] That is to say, apart from the known etiology of recurrent spontaneous abortion (RSA), there are still about 50% of patients with unknown pathogenic factors, namely URSA.[2] URSA has no specific detection markers at present. Ibrahim et al[3] suggested that the elevated serum amyloid A level in pregnant women could be used as a new biomarker for unexplained recurrent spontaneous abortion. However, there is no effective strategy for the treatment of unexplained recurrent spontaneous abortion. In recent years, continuous clinical studies have shown that the thrombus exists in the placental villus, umbilical blood vessels, and decidua basalis of some URSA patients.[1] Additionally, people with RSA who have antiphospholipid syndrome and thrombophilia tend to have similarities with the URSA population.[4] Because women with prethrombotic state have no obvious clinical manifestations, the diagnosis is difficult.[5] Therefore, some researchers

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advocate empirical anticoagulation therapy for the URSA population.[4] Anticoagulant therapy mainly refers to low-molecular-weight heparin (LWMH) and aspirin to improve blood hypercoagulability.

Low-Molecular-Weight Heparin and Unexplained Recurrent Spontaneous Abortion

LMWH is a chemical or enzymatic depolymerization of unfractionated heparin (UFH), which belongs to antithrombin III–dependent thrombin inhibitor. LMWH fragments are short, the average relative molecular weight is 4,300–5,000 KDa, and UFH molecular weight is 15,000 kDa. The biological activity of LWMH is similar to that of UFH. However, it has a strong anticoagulation factor FXa and weak antithrombin II effect, reduces platelet stimulation, reduces bleeding and thrombocytopenia, reduces risk of osteoporosis during pregnancy, and requires no special monitoring of blood coagulation during medication.[6] In a study of 963 patients with placenta-mediated recurrent pregnancy complications, the incidence of prenatal and postpartum hemorrhage was not significantly different between LMWH and untreated drugs during pregnancy.[7] LMWH has more than 90% bioavailability, so LMWH has more advantages than UFH. After subcutaneous injection of LMWH the peak concentration time is 3–5 hours, the half-life is 3–7 hours, LMWH does not pass through the placenta, and it is not secreted in breast milk. The U.S. Food and Drug Administration has designated it as a Class B drug during pregnancy.[8] However, due to the short half-life of UFH, the LMWH is often converted from LMWH to UFH in the third trimester. After the drug is stopped, labor analgesia, epidural catheterization, or cesarean section can be performed. At present, LMWH commonly used in China includes enoxaparin, dalteparin, and nadroparin.[6] LMWH is routinely administered subcutaneously at 5,000 IU, 1–2 times per day. It is usually started after blood hCG diagnosis of pregnancy or ultrasound to determine intrauterine pregnancy. The first method is relatively early; the latter can exclude ectopic pregnancy and determine the intrauterine development of the embryo, both of which have their own advantages. Although the risk of bleeding caused by LMWH is small, patients should also be observed for epistaxis, bleeding gums, and skin and mucosal bleeding during the medication process, and their coagulation function should be checked every 2–4 weeks. This includes partial thromboplastin time (APTT), prothrombin time, platelet count, platelet aggregation rate, D-dimer, and thromboelastography. Liver and kidney functions should be checked regularly—at least once every 1–2 months.[8]

The study found that serum tissue plasminogen activity was significantly lower than normal in patients with RSA, while human thrombin and plasminogen activator inhibitors were significantly higher than normal.[9] As a result, the fibrinolytic system activity was weakened, the progress of the prethrombotic state was facilitated, or a thrombus was formed. When the thrombus was formed in the microcirculation of the uterine placenta, multiple microthrombus foci may occur in the small vessels of placenta tissue or local tissue infarction may even occur.[10] Clinical research has shown that the mechanism of action for LMWH may be the following[11]: (1) It promotes thrombolysis and stimulates the endothelial cells to release the endogenous heparin substance to achieve the antithrombus effect and improves the concentration of plasma plasminogen activator. (2) The molecular weight was relatively small and was not neutralized by the platelet factor; thus, LMWH induced the endothelial cells to release the prostacyclin-like substance and increased the plasminogen activator to dissolve the thrombolysis. (3) LMWH activates angiotensin and vasoactive substances, increases blood perfusion, and inhibits vasoconstriction. Characterized by anti-thrombosis and anticoagulant effects, LMWH can protect vascular endothelial cells, reduce blood viscosity, and enhance the microcirculation of the placenta to facilitate embryonic and fetal growth, thereby improving pregnancy outcomes.[12] A randomized prospective study was done to assess the efficacy of early thromboprophylaxis of LMWH in women with URSA. The results showed that there is a significant reduction in the incidence of both early and late miscarriages.[13] Furthermore, treatment with enoxaparin might improve the rate of live births in women with or without evidence of thrombophilia, especially in women with >4 miscarriages.[14] Shaaban et al[13] studied URSA patients with abortion (≥3 times) and no antiphospholipid syndrome, with 150 patients in the LMWH group (Tinzaparin sodium 4,500 IU qd+500 μg folic acid qd started once there was a positive pregnancy test until the 20th week of gestation) and

150 patients in the control group (500 μg folic acid qd alone). The success rate of pregnancy over 20 weeks was compared between the two groups. The LMWH group and the control group were 73.3% vs. 48% (p=0.002), suggesting that the use of LMWH in early pregnancy in URSA pregnant women without antiphospholipid syndrome can improve the success rate of pregnancy.

Pathological examination of the placenta or villus in some URSA patients indicated that inflammation existed in most cases, which indicated that infection and prostaglandin release were one of the causes of induced abortion due to uterine contraction, and these patients did not necessarily have clinical manifestations. Besides anticoagulation, LMWH also has anti-inflammatory and anti-immune effects.

Heparin can also inhibit the adhesion of neutrophils to the vascular endothelium by binding to P-selectin, further inhibiting the inflammatory response.[15]

Patients with unexplained recurrent spontaneous abortion have insufficient trophoblastic proliferation and invasion ability in early pregnancy and are prone to embryonic development abnormalities and miscarriage. LMWH can inhibit the trophoblast apoptosis pathway and promote the proliferation of trophoblast cells, which is beneficial to protect the normal growth of the fetus. At the same time, LMWH also has immunoregulation and immunosuppression, which can reduce the activity of lymphocytes and polynuclear leukocytes and alleviate inflammation. At the same time, LMWH can protect embryos from immune attack and effectively improve the live birth rate.[16]

In recent years, researchers have discovered the classic anticoagulant effect of LMWH and its ability to regulate the function of trophoblast cells during pregnancy and regulate embryo development through various pathways. Luley et al[17] found that LMWH treatment could promote the expression and secretion of IL-10 in the decidua of prethrombotic state mice, increase the level of Tregs in decidua, and achieve anti-inflammatory, anti-apoptotic, and immunomodulatory effects. In 2016 some scholars carried out in vitro studies in which they separated exosomes from peripheral blood of women in an LMWH treatment group, normal early pregnancy group, and normal non-pregnant group, detected their microvesicle proteins, and observed their effects on trophoblast function, endothelial cell migration, angiogenesis, and cell apoptosis in early pregnancy. They found that LMWH treatment could affect the content of microvesicles in maternal peripheral blood, regulate trophoblast proliferation, invasive ability, endothelial cell angiogenesis, and apoptosis, and provide a new method of clinical application using LMWH.[18]

Regardless of age, body mass index, or the number of abortions in women with unexplained recurrent spontaneous abortion, the use of prophylactic doses of calheparin and aspirin could help them safely complete their first trimester.[19] When heparin was used at therapeutic levels, inhibition of trophoblast invasion was demonstrated, and elevated sFlt-1 concentration and impaired VEGF signaling were found in endothelial cells. It was further suggested that a cautious therapeutic dose of LMWH be exposed to placental villi.[20]

Other studies had different evaluations of the efficacy of LMWH in URSA: LMWH or aspirin prevented recurrent abortion or pregnancy loss, with uncertain effects, and increased the side effects of pregnancy.[21] For patients with recurrent spontaneous abortion, prophylactic LMWH did not offer a benefit in subsequent pregnancies even if the mother had an inherited tendency to thrombosis.[22] Schleussner et al[23] conducted a multicenter randomized controlled trial in 2015, and 449 patients with URSA (>2 times) in 14 centers were enrolled in the study. The 24-week pregnancy status was analyzed, and no significant difference was found between the LWMH group and the non-LWMH group (86.8% vs. 87.9%, 95% CI 7.4–5.3, p=0.75). The live-birth rates were analyzed, and again no significant difference was found between the LWMH group and the non-LWMH group (86.0% vs. 86.7%, 95% CI 7.3–5.9, p=0.84), suggesting that the effect of LWMH on URSA patients is not obvious. Pasquier et al[24] conducted a multicenter randomized double-blind placebo-controlled clinical trial of URSA patients for the first time, randomizing 258 patients with URSA into two groups and administering enoxaparin 40 mg/d or placebo, respectively. There was no significant difference in live birth rate (66.6% vs. 72.9%, p=0.34), suggesting that LMWH alone could not improve the live birth rate of RSA patients without thrombophilia.

Aspirin and Unexplained Recurrent Spontaneous Abortion

Low-dose aspirin irreversibly blocked the forma-

tion of thromboxane A2 in platelets, prevented thrombosis of placental vessels, and inhibited platelet aggregation. More recently, novel cytoprotective and antioxidant mechanisms of aspirin have been observed that were independent of cyclooxygenase inhibition. Aspirin acetylated endothelial nitric oxide synthase, leading to nitric oxide release from the vascular endothelium.[25] Two small randomized trials in pregnancy found that evening but not morning administration of aspirin was associated with a reduction in ambulatory blood pressure, and in one of those trials, a reduction in the incidence of preeclampsia and fetal growth restriction was also seen.[26] The circadian rhythm mechanism for preventing fetal growth restriction seems unclear. However, if aspirin is recommended daily, it seems advisable to recommend it at night. At present, it is recommended to take low-dose aspirin (75 mg/d orally) during pregnancy.[5] Coagulation function should be monitored in the course of treatment. Adverse reactions such as ecchymosis, thrombocytopenia, allergic skin rash, and bleeding gums should be noted. However, some studies have shown that low-dose aspirin (81 mg) taken before pregnancy resulted in a higher live birth rate and a lower premature delivery rate for women who had lost a single recent pregnancy. The current research results on the safety of low-dose aspirin were reassuring.[27] The safety of aspirin for the fetus is still at an exploratory stage, but studies have reported that aspirin can cause fetal malformations in rats through the placenta.[28]

Recently, Kaandorp et al[29] studied the live birth rate among 3 groups of pregnant women given aspirin and LMWH, aspirin only, or placebo. The treatment was administered before pregnancy, and the pregnancy was confirmed 6 weeks later. Studies have found that arachidonic acid had a higher response to platelet aggregation. Before pregnancy, platelet was one of the major cytokines involved in coagulation in patients with URSA. URSA was in prethrombotic state before pregnancy. Aspirin alone or in combination with LMWH was recommended. Early initiation may be more effective than LMWH.

Cesarman-Maus et al[30] found that aspirin could prevent thrombosis and improve placental microcirculation. Aspirin alone could not completely inhibit thrombin formation, and patients should also be given LMWH treatment. In fact, D-dimer levels decreased significantly after LMWH injection.[31] Therefore, the combined application improved the live rate. Recent randomized controlled clinical trials conducted by Maged et al[32] found that the combination of aspirin (75 mg/d orally) and LMWH (5,000 IU/d subcutaneously) in URSA patients could significantly increase the clinical pregnancy rate (73.33% vs. 43.33%, p=0.018). The study also showed that the combination of LMWH and aspirin in patients with recurrent loss of pregnancy (before 20 weeks of gestation) increased the live birth rate and birth weight.[33]

At present, opinions on the effect of aspirin in preventing unexplained recurrent spontaneous abortion are not consistent. On the basis of a mouse model, aspirin activated receptor-mediated maternal platelet activation by inhibiting protease. It was assumed that aspirin had a potential role in preventing pregnancy loss.[21] A recent meta-analysis showed that aspirin may have a negative impact on preventing recurrent pregnancy loss, and its inhibition of prostaglandin synthesis may impede the embryo implantation process.[34] The study included 19 trials involving 2,391 recurrent abortion patients with or without thrombosis and 543 with antiphospholipid syndrome. For patients with or without thrombophilia, LMWH therapy was the most likely (61.48%) option. Results of the study did not support the use of combined LMWH and aspirin for RSA and suggested that aspirin may have negative effects for lowering the risk of pregnancy loss.[34]

Conclusion

Might not maternal thrombophilia disrupt this delicate equilibrium, potentiating clotting and potentially fetal loss? Although a hypercoagulable state is often invoked as the cause of recurrent pregnancy loss, this theory is not supported by therapeutic trials of anticoagulation. Excessive thrombosis may be only one of several mechanisms contributing to the overall pathophysiology of adverse pregnancy outcomes.[35]

In summary, although anticoagulant therapy has shown a certain role in the treatment of URSA, the development of a reasonable and effective treatment plan is still a major challenge in clinical work. It is still necessary to further strengthen the research on the pathogenesis of prethrombotic state and clinical experimental indicators, to carry out more large-scale multicenter prospective randomized controlled trials, and to explore more ideal treatment options.

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