The Causes and Treatment of Recurrent Pregnancy Loss

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Abstract

Recurrent pregnancy loss is the syndrome that causes repeated miscarriage and/or stillbirth impairing the ability to have a live birth. Recently, the Japan Society of Obstetrics and Gynecology proposed screening tests for recurrent pregnancy loss and reported the frequencies of various causative factors. It has been shown that appropriate treatments after screening tests are effective in achieving a respectable rate of live births. While cases of recurrent pregnancy loss with chromosomal aberrations were previously associated with a high rate of miscarriage and inability to have a live birth, such patients can now expect to have a live baby at a probability of about 60% in the next pregnancy. It has also been shown that patients presenting no abnormality on various tests may achieve a good rate of live births without special treatment.

Many couples with recurrent pregnancy loss are now given the chance of having a live birth through appropriate screening and the best treatment available for the inferred cause.

Key words Miscarriage/Stillbirth, Antiphospholipid antibodies, Coagulation factor disorder, Heparin

Introduction

Miscarriage occurs in approximately 15% of all pregnancies. When miscarriage takes place repeatedly 3 times or more, she is diagnosed with habitual miscarriage. Recurrent pregnancy loss is the syndrome that causes repeated miscarriage, stillbirth, and premature delivery impairing the ability to have a live birth. The probability of habitual abortion is theoretically 0.3–0.4%, but it actually occurs at a rate of 1–2%. This excess over the theoretical probability suggests that there are some pathological factors behind repeated miscarriage.

Ogasawara et al. reported that women who had experienced miscarriage twice, 3 times, and 4 times in the past were likely to lose the next pregnancy with a probability of 43.7%, 44.6%, and 61.9%, respectively.[1] On the other hand, the rate of chromosomal aberrations in lost fetuses decreased with the increasing number of past miscarriages: 59.0%, 55.3%, 38.9%, 38.9%, and 28.6% after 2, 3, 4, 5, and 6 miscarriages, respectively. These clinical facts strongly suggest that an increasing number of past miscarriages is associated with further repetition of miscarriages and stillbirths attributable to factors in the mother or the father rather than the fetus (chromosomal aberrations).

The causes and manifestations of recurrent pregnancy loss are diverse, and the occurrence of this condition is not very high. For these reasons, there is little accurate knowledge about the occurrence in Japan and the risk factors related to recurrent pregnancy loss. In 2005, the Reproductive and Endocrine Committee of the Japan Society of Obstetrics and Gynecology (JSOG) compiled data from 927 couples with recurrent pregnancy loss, and reported their risk factors and the rate of live births after various therapies,[2] indicating methods for screening and treatment of recurrent pregnancy loss for the first time.

This article provides a brief update on the

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Table 1 Frequency of abnormalities in recurrent pregnancy loss in Japan

Types of abnormal test results			%
Chromosomal aberrations	Chromosomal aberrations in a couple		7.7
	Balanced translocations in a couple		3.1
Uterine anomalies			9.0
Endocrine disorder	Hyperthyroidism		2.8
	Hypothyroidism		2.9
	Diabetes mellitus		1.2
Autoimmune disorder	Antiphospholipid antibodies		Approx. 19
	β_2GPI-dependent anti-cardiolipin antibodies		
		Standard level 1.9	1.1
		Standard level 3.5	1.0
	Lupus anticoagulant (LA; dRVVT method)		1.6
	Kininogen-dependent anti-PE antibodies		16.8
Coagulation factor disorder	Factor XII deficiency (<50%)		28.3
Unknown causes (including allogeneic immunity disorder)			Approx. 30

(Cited from Saito S, et al.: Journal of Japan Society of Obstetrics and Gynecology 2005; 57:1057–1059.)

causes (risk factors) and treatment of recurrent pregnancy loss.

Rate of Abnormal Test Results in Patients with Recurrent Pregnancy Loss

The data for 927 couples reported by the Reproductive and Endocrine Committee, JSOG are shown in Table 1.[2] Although these data were collected basically following the screening method of the Committee, it should be noted that not all enrolled couples underwent all tests and the results are not complete. The rate of couples with chromosomal aberrations was 7.7% (4.72% in females, 3.4% in males, and 0.3% in both), and the rate of balanced translocation was 3.1%. Because these are not rare, chromosomal aberration tests are considered an essential element of screening for recurrent pregnancy loss. Other abnormalities detected in the patients were uterine anomalies as diagnosed by hysterosalpingography (HSG) in 9.0% (most notably arcuate uterus in 4.8%) and endocrine abnormalities including hyperthyroidism in 2.8%, hypothyroidism in 2.9%, and diabetes mellitus in 1.2%.

An autoimmune disorder called antiphospholipid antibody syndrome is diagnosed when the patient has thrombosis or a past history of miscarriage or stillbirth, in addition to a positive test for β_2GPI-dependent anti-cardiolipin antibodies, anti-cardiolipin antibodies, or lupus anticoagulant (LA). In the data from JSOG, cases meeting these diagnostic criteria were found at an extremely low rate of 2–3% among patients with recurrent pregnancy loss.[2] It is a remarkable fact that 16.8% of patients were positive for kininogen-dependent anti-phosphatidylethanolamine (PE) antibodies, although this parameter is not included in the diagnostic criteria for antiphospholipid antibody syndrome. When these two are combined, 19.0% of patients were positive for antiphospholipid antibodies.

With respect to coagulation factor disorder, coagulation factor XII deficiency was found in 28.3%. The remaining approximately 30% were classified as having unknown causes. However, the decrease in protein S level and the elevation of NK cell activity level measured in limited cases were found to be relatively common risk factors, and a screening incorporating these parameters would further lower the rate of cases of unknown causes. In particular, the Japanese ethnically tend to have protein S deficiency, and the addition of this test to screening for recurrent pregnancy loss is considered appropriate. For this reason, the Japan Society for Immunology of Reproduction (JSIR) is discussing the inclusion of protein S as an essential test parameter in its guidelines entitled "Risk Factors of Recurrent Pregnancy Loss and Its Prognosis in the Japanese." (See the

Table 2 Pregnancy prognosis of recurrent pregnancy loss with chromosomal aberrations

Reported by	Chromosomal aberrations	No. of cases	Live birth rate* (total numbe of pregnancies) %
Stephenson et al. (2006)	Reciprocal translocation	28	62.9
	Robertson translocation	12	69.2
	Inversion	7	100
Sugiura-Ogasawara et al. (2004)	Reciprocal translocation	47	35.8
	Robertson translocation	11	63.6
Goddijn et al. (2004)	Reciprocal/Robertson translocation	25	73.2
Carp et al. (2004)	Reciprocal/Robertson translocation	44	43.2
	Inversion	15	53.3

* Percentage of cases that did not end in miscarriage, stillbirth, or neonatal death

JSIR website at http://jsir.umin.jp/JPN/j_top_frame.html for details.) (in Japanese)

The elevation of NK cell activity is also an indicator of an aspect of immune abnormality in the mother, and JSIR has included it as an elective test parameter. It has been reported that the NK cell activity of 42% or more is associated with the miscarriage rate exceeding 70% in the next pregnancy.[3]

Treatment of Recurrent Pregnancy Loss According to Cause

Chromosomal aberrations

A diagnosis of chromosomal aberration can be extremely trying for a couple with recurrent pregnancy loss. Sufficient explanation should be given before the couple receives tests, and a good deal of time should be used in counseling after the results are given.

Many patients consider chromosomal aberration to be a hopeless condition. However, as shown in Table 2, patients with recurrent pregnancy loss have a good chance of achieving a live birth after a diagnosis of chromosomal aberration. Couples with chromosomal aberrations undergo preimplantation genetic diagnosis (PGD) in Western counties, and this procedure is also offered at some facilities in Japan. However, the live birth rate after PGD does not exceed the rate in natural pregnancy. It is important that couples with recurrent pregnancy loss are given adequate explanation of the live birth rate in natural pregnancy and guided to have hope for success in the next pregnancy.

Uterine anomalies

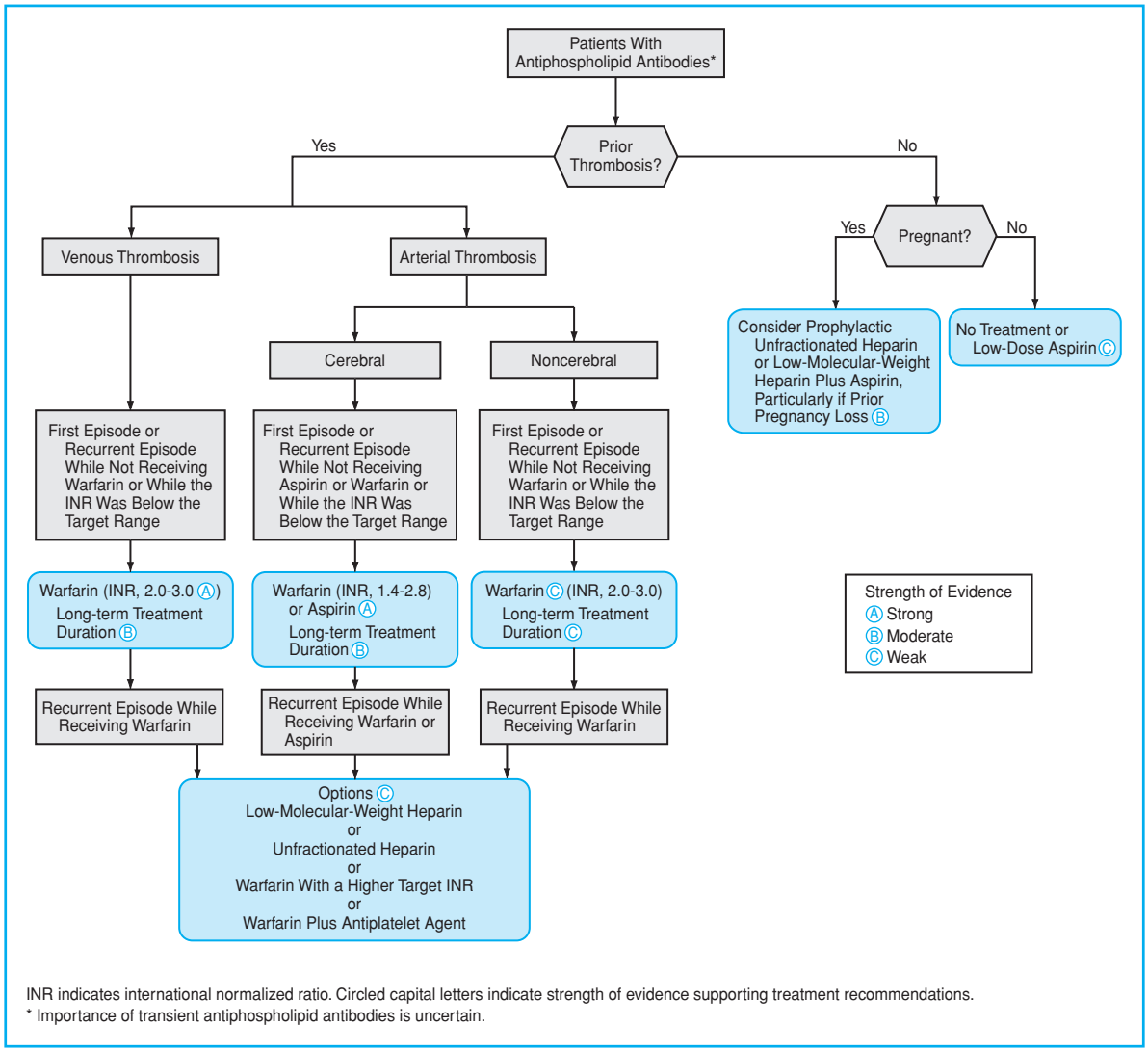
Any anomalies detected by hysterosalpingography are usually confirmed by MRI or other methods. The most frequently observed anomaly is arcuate uterus, followed by septate uterus. Various authors have reported a live birth rate of 70–80% after hysteroplasty, and this has been considered as evidence supporting surgical intervention in cases of recurrent pregnancy loss presenting uterine anomalies. However, it has also been reported that patients with uterine anomalies maintain pregnancy at a rate of 70% without treatment,[4,5] and opinions vary as to whether or not surgery has been established as a treatment method recommended in guidelines.

Endocrine disorders

Patients with thyroid dysfunction or diabetes mellitus are referred to specialist physicians. They are advised to receive detailed examination and expect pregnancy after treatment of the underlying condition. Cooperation with specialist physicians is also recommended in management of the condition during pregnancy.

Antiphospholipid antibody syndrome

A diagnosis of antiphospholipid antibody syndrome is given when the patient has thrombosis or a past history of 3 or more episodes of miscarriage earlier than 10 weeks of gestation, 1 or more episodes of miscarriage or stillbirth after 10 weeks of gestation, or premature delivery earlier than 34 weeks of gestation due to pregnancy-induced hypertension syndrome, eclampsia, or



INR indicates international normalized ratio. Circled capital letters indicate strength of evidence supporting treatment recommendations.
* Importance of transient antiphospholipid antibodies is uncertain.

(Cited from Lim W, et al: JAMA 2006; 295:1050–1057.)

Fig. 1 Algorithm for antithrombotic treatment of patients with antiphospholipid antibodies

placental dysfunction, in addition to a positive test result for β_2GPI-dependent anti-cardiolipin antibodies, anti-cardiolipin antibodies, or LA.

Interestingly, a study on more than 300 cases of recurrent pregnancy loss presenting positive antiphospholipid antibodies identified only 1 case with a past history of thrombosis,[6] indicating that recurrent pregnancy loss with past thrombosis is rare. On the other hand, the 8-year follow-up of the cases of recurrent pregnancy loss presenting positive antiphospholipid antibodies without thrombosis showed that only 2 of the 31 cases receiving aspirin developed thrombosis, compared with the development of thrombosis in 19 of the 34 cases receiving no aspirin.[7] This result suggested a possibility that anticoagulant therapy after childbirth may lower the risk of thrombosis. A prospective study is currently ongoing, and we are looking forward to seeing the results.

While low-dose aspirin (LDA) has been used in the treatment of recurrent pregnancy loss presenting positive antiphospholipid antibodies, the combined use of heparin and LDA has been

shown to achieve higher effectiveness in preventing miscarriage.[8] Although the therapeutic efficacy was similar between the patients treated with steroids and those treated with heparin plus LDA, steroids increased premature delivery and early rupture of membranes.[9] For this reason, heparin-plus-LDA combination therapy is regarded as the standard therapy at the present. Heparin has been assumed to act through suppression of coagulation. However, heparin also has activity to suppress complement activation, and the role of this activity in reducing miscarriage and stillbirth has been demonstrated in a mouse model.[10]

Warfarin, though effective in anticoagulation, lacks activity to suppress complement activation. In addition, it is contraindicated in pregnant women, because it crosses the placenta and has teratogenicity. According to the guidelines for the management of antiphospholipid antibodies, published in the JAMA in 2006, the use of warfarin should be terminated before the 6th week of gestation, and the patient should be switched immediately to management using heparin (Fig. 1).[8]

Anti-PE antibodies are autoantibodies against kininogen bound to phosphatidylethanolamine, and these antibodies suppress the fibrinolysis system.[11] Cases of recurrent pregnancy loss with positive anti-PE antibodies do not satisfy the diagnostic criteria for antiphospholipid antibody syndrome, but the prevalence of positive anti-PE antibodies among Japanese patients with recurrent pregnancy loss is as high as 16.8% (Table 1). There is no established treatment for patients with anti-PE antibodies, and these patients are treated with regimens similar to those for antiphospholipid antibody syndrome. Further verification is needed regarding the efficacy of LDA therapy and heparin therapy in cases of positive anti-PE antibodies.

Coagulation factor disorder

Deficiency or reduced activity (usually a drop to 50% or less is considered pathological) of coagulation factor XII is known to cause pulmonary embolism and other forms of thrombosis, and these are also associated with recurrent pregnancy loss.[12] It has also been reported that anti-factor XII antibodies are detected in LA-positive patients. A survey by JSOG[1] and a NOHA study[13] reported a high prevalence of factor XII deficiency as a risk factor of miscarriage. LDA therapy and LDA-plus-heparin therapy have both shown satisfactory results in cases of recurrent pregnancy loss with coagulation factor XII deficiency.[12,14]

Protein S deficiency is found in approximately 2% of Japanese people, and the prevalence is higher among cases of recurrent pregnancy loss. When cases of recurrent pregnancy loss with protein S deficiency with a past history of miscarriage or stillbirth after 10 weeks of gestation were treated in a study, the rate of live births after LDA therapy was as low as 7%, while the rate of live births after heparin therapy was 79%.[15] Therefore, heparin therapy is considered preferable in these cases.

Other factors

Elevation of NK cell activity is observed in 20–40% of patients with recurrent pregnancy loss, indicating a possibility that enhanced cellular immunity may be attacking the fetus. Aoki et al. measured NK cell activity in the peripheral blood of patients during a non-pregnant period after 2 consecutive miscarriages, and found that 71% of the patients with elevated NK cell activity lost the next pregnancy, while the rate of miscarriage among the patients with normal NK cell activity was 20%.[3]

Immunization with the husband's lymphocytes is known to lower NK cell activity,[16] but there have been no studies examining the efficacy of immunization with the husband's lymphocytes in cases of recurrent pregnancy loss with elevated NK cell activity. At present, the Cochrane Database does not acknowledge the effectiveness of lymphocyte immunization therapy in recurrent pregnancy loss of unknown causes.[17] However, according to data from the Reproductive and Endocrine Committee of JSOG, immunization with the husband's lymphocytes achieved live birth in 80.9% of patients who had no past history of live birth and were negative for all screening tests except for NK cell activity. Therefore, there is a possibility that immunization with the husband's lymphocytes may be effective in selected cases.[2]

Because immunization with the husband's lymphocytes involves a form of blood transfusion, it should be performed after sufficient screening for infections and obtaining written consent to receive blood transfusion. The lym-

phocytes should be treated with irradiation, and appropriate informed consent of patients should be ensured.

Conclusion

Little has been known about the causes and treatment of recurrent pregnancy loss in Japan, but we are now beginning to understand the true nature of this condition. Through systematic screening and the provision of cause-oriented treatment by specialists in recurrent pregnancy loss, we hope that many couples will be able to achieve live births.

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