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Fetal Wastage Syndrome due to Blood Protein/Platelet Defects: Results of Prevalence Studies and Treatment Outcome with Low-Dose Heparin and Low-Dose Aspirin

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Summary: Fetal wastage syndrome is characterized by recurrent spontaneous abortion. Many syndromes are associated with recurrent fetal loss, including anatomical anomalies, endocrine/hormonal abnormalities, and coagulation defects, with coagulation defects accounting for ~30% of cases. Most procoagulant factor defects are due to inadequate fibrin-mediated implantation of the fertilized ovum into the decidua. However, blood protein/platelet defects leading to hypercoagulability and thrombosis are associated with thrombosis of placental vessels, precluding viability of the implanted ovum or later fetus. During the past 2 years, we have seen 46 patients with fetal wastage syndrome due to thrombosis-associated hemostasis defects. In this group, there have been three patients with sticky platelet syndrome, one patient with dysfibrinogenemia, four patients with congenital protein S deficiency, 35 patients with anticardiolipin antibodies, and one patient with a lupus anticoagulant. Patients were started on one low-dose aspirin (ASA), 81 mg per day preconception, at time of diagnosis, and low-dose s.c. porcine heparin at 5,000 units every 12 h was added immediately postconception. The combination of low-dose ASA plus low-dose s.c. porcine heparin was used throughout pregnancy. All patients achieving pregnancy have had uneventful, normal deliveries. It appears that blood protein/platelet defects leading to thrombosis and associated with recurrent fetal loss can be successfully managed with the use of preconception low-dose ASA, followed by immediate postconception addition of fixed low-dose porcine heparin, both used throughout pregnancy. Using this regimen, our success rate has been 100%. Ideal heparin doses, which might be much lower than our empirically chosen and currently used doses, remain to be defined in this particular indication. **Key Words:** Fetal wastage syndrome—Heparin—Aspirin.

Fetal wastage syndrome (FWS) is characterized by recurrent unexplained spontaneous abortion. Many defects and conditions are associated with recurrent fetal loss, including anatomical anomalies, endocrine and hormonal abnormalities, chromosomal disorders and defects, and coagulation abnormalities (1,2). The common coagulation protein defects associated with fetal wastage include factor XIII (3) and factor XII (4) defects, dysfibrinogenemia (5), antiphospholipid syndrome (6), including both anticardiolipin antibodies (ACLA) and lupus anticoagulant (LA), plasminogen defects (7), other fibrinolytic system defects such as elevated plasminogen activator inhibitor, type 1 (PAI-1) or low tissue plasminogen activator (t-PA; 8,9), and congenital protein S defects (herein first reported).

Factor XIII defects and most cases of dysfibrinogenemia are due to inadequate fibrin-induced implantation of the fertilized ovum into the decidua. However, antiphospholipid syndrome, plasminogen defects, fibrinolytic system defects, some cases of dysfibrinogenemia, and other hypercoagulable blood protein/platelet defects are associated with thrombosis of the early placental vessels, precluding viability of the implanted ovum or fetus. It may be postulated, however, that any blood protein or platelet defect associated with hypercoagulability

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and thrombosis could be associated with placental vascular thrombosis and the FWS. The diagnosis of FWS is made by noting one or more unexplained spontaneous abortions, usually in the first trimester, and a high index of suspicion, followed by appropriate clinical and laboratory evaluation. We herein report our experience with 46 women with FWS due to blood protein/platelet defects; prevalence of types of defects found and outcomes with therapy are presented.

MATERIALS AND METHODS

Patient population

All patients were referred for evaluation of blood protein/platelet defects by their obstetricians after having been diagnosed with unexplained FWS and after having other defects potentially accounting for FWS, including diabetes, uterine anatomical abnormalities, hormonal/endocrine abnormalities, and chromosomal abnormalities ruled out. Thus all patients referred for hematological hemostasis evaluation had otherwise unexplained FWS. Because several obstetricians were involved, obstetrical follow-up differed slightly. Generally, however, those patients achieving pregnancy after workup for blood protein/platelet defects were assessed by careful obstetrical follow-up on a monthly basis, including ultrasonography on an average of every trimester. All patients achieving pregnancy were given prenatal vitamin preparations. Hematological evaluation, during pregnancy, consisted of weekly visits for complete blood count (CBC) and platelet count, assay of the hemostasis defect initially found at workup, and plasma heparin levels. After the first trimester, these parameters were assessed monthly, unless dictated otherwise by clinical parameters.

Hemostasis evaluation

To contain costs of evaluation, patients were evaluated in two stages. Stage I consisted of a complete history and physical examination, a routine CBC, and a panel of those blood protein/platelet defects thought to be commonly associated with FWS. If the first panel of blood protein/platelet defect tests was normal, a second panel (stage II), consisting of those blood protein defects thought to be more rarely associated with FWS, was performed.

The blood protein/platelet defect assays performed in panel I consisted of prothrombin time and activated partial thromboplastin time (aPTT) by routine techniques (10) on the ACL 3000, anticardiolipin antibodies [immunoglobulin G (IgG), IgA, and IgM idiotypes] by solid phase enzyme-linked immunosorbent assay (ELISA; 11), lupus anticoagulant (with phospholipid confirmation if positive) by the dilute Russell Viper Venom Time (dRVVT) assay (12–14), functional protein S (15), followed by a protein S panel of immunological (total; 16) and free protein S (17) and C4b-binding protein (18) if the functional protein S level was abnormally low, protein C assay by chromogenic technique (19), factor XIII by immunoassay (20), antithrombin assay by chromogenic technique (21), sticky platelet syndrome assay by the method of Mammen (22), plasminogen assay by chromogenic assay (23), activated protein C resistance (APC-R) by the method of Dahlback (24), and functional fibrinogen assay by the method of Clauss (25). If all of these were negative, the secondary panel consisted of plasminogen activator inhibitor type 1 (PAI-1; 26), tissue plasminogen activator (t-PA; 27), heparin cofactor II (28), tissue factor pathway inhibitor (TFPI; 29), and blood and urine homocysteine levels (30). All abnormal hemostasis results were repeated at least once for confirmation. Plasma heparin levels, for those patients placed on heparin, were done by anti-Xa assay (31).

Treatment program

All patients found to have a blood protein/platelet defect associated with FWS via hypercoagulability and thrombosis (thrombosis/vasculitis) of placental vessels were treated with preconception low-dose ASA at 81 mg/day. The ASA was started immediately on (a) making a diagnosis of FWS (b) associated with a blood protein/platelet defect known to be associated with thrombosis and (c) a desire for pregnancy. Immediately postconception, fixed low-dose s.c. heparin at 5,000 units (anti-Xa) every 12 h was added to the daily ASA regimen. The heparin used was Elkins-Sinn porcine mucosal heparin (20,000 units/ml concentration). Patients were instructed by oncology–hematology nursing staff on the proper methods for self-administration of s.c. heparin. Both drugs were used to term. Patients with hypercoagulability defects were encouraged to continue the use of ASA indefinitely, after delivery.

RESULTS

A total of 48 patients have been referred over the past 24 months; all but two were found to have a blood protein/platelet defect associated with hypercoagulability and thought to account for fetal wastage; the two patients demonstrating no defect were excluded from this analysis. The mean age of patients was 33.7 years (range, 27–49), and the mean number of unexplained miscarriages at time of referral was 2.8 (range, 1–9). Of the 46 patients referred and harboring a blood protein/platelet defect,

32 achieved pregnancy and had uneventful deliveries, eight are currently pregnant, four are attempting pregnancy, and two elected not to pursue pregnancy. No patient has had a fetal loss on the treatment program used in this study (preconception low-dose ASA and immediate postconception addition of low-dose s.c. porcine musocal heparin). Of the 46 women with defects, the following were found: 35 patients had anticardiolipin antibodies (void of lupus anticoagulants), one patient had a lupus anticoagulant (void of ACLAs), four patients had congenital protein S deficiency (three quantitative and one dysfunctional), three had sticky platelet syndrome (two with type I and one with type II), one had dysfibrinogenemia, and one had congenital t-PA deficiency. Two of the protein S–deficient patients were those electing not to pursue pregnancy. Historically, six of the 46 patients (13%) had suffered a prior nonobstetrical thrombotic event. One protein S patient had prior deep vein thrombosis (DVT), the patient with dysfibrinogenemia had prior DVT and pulmonary emboli (PE), three patients with ACLAs had a history of DVT (two accompanied by PE), and one of the ACLA patients had bilateral retinal vascular thrombosis in the past.

When evaluating the 35 patients with ACLAs, the following was found: 23 patients harbored an IgG, two patients harbored IgA, and 11 patients harbored IgM ACLA idiotypes. Only one patient harbored two idiotypes (IgG plus IgM). No patients with factor XIII, XII, X, VII, V, II, plasminogen, heparin cofactor II, antithrombin or protein C deficiencies, or elevated PAI-1 were found in our series.

The demographics and other characteristics, including defect found, pregnancy status, and prior thrombosis history for all patients is summarized in Table 1. The treatment program is summarized in Table 2.

DISCUSSION

FWS due to blood protein or platelet defects are of two types, those disorders associated with a hemorrhagic tendency or those defects associated with a thrombotic tendency. The hemorrhagic defects associated with FWS presumably lead to inadequate fibrin formation, thus precluding adequate implantation of the fertilized ovum into the uterus. The hemorrhagic defects associated with FWS include factor XIII deficiency (3), factor X deficiency (32), factor VII deficiency (33), factor V deficiency (34), factor II (prothrombin) deficiency (35), and fibrinogen defects, including afibrinogenemia (36) and those dysfibrinogenemias associated with hemorrhage (37). Management of these patients is generally plasma-substitution therapy. The thrombotic defects associated with fetal wastage are thought to occur due to thrombosis of early placental vessels, with peak fetal wastage in the first trimester, but small peaks also occur in the second and third trimesters. The thrombotic hemostasis defects associated with FWS include lupus anticoagulants and ACLAs (these two composing the antiphospholipid syndromes associated with fetal wastage syndrome; 6,38,39), factor XII deficiency (4), dysfibrinogenemias associated with thrombosis (40), protein C deficiency (41), antithrombin deficiency (42), heparin cofactor II deficiency (43), and fibrinolytic defects associated with thrombosis, including plasminogen deficiency (7), t-PA deficiency, and elevated PAI-1 (8). Until this report, congenital protein S deficiency has not yet been reported as a cause of FWS. Our four patients will form the basis of a separate report. Also, although sticky platelet syndrome has been known for more than a decade and leads to a wide variety of thrombotic events, our three cases represent the first reports of sticky platelet syndrome associated with FWS; these three patients will also be reported separately. However, congenital protein S deficiency and sticky platelet syndrome should clearly be added to the list of blood protein/platelet defects associated with hypercoagulability that may also lead to FWS, presumably through thrombosis of placental vessels, similar to the other defects already described.

The antiphospholipid syndrome has clearly been the most common thrombotic defect leading to FWS, and a variety of treatment programs have been advocated. One difficulty in evaluating these has been that some populations have addressed primarily patients with secondary antiphospholipid syndrome and fetal wastage, in particular those with underlying systemic lupus erythematosus or other autoimmune disorders, and only a few investigators have addressed populations with primary antiphospholipid syndrome, with no known underlying disease. Only one patient in our population, the single patient with a lupus anticoagulant, had laboratory [positive antinuclear antibodies (ANA)] and clinical (joint pain, intolerance to sunlight, and unexplained patchy pulmonary infiltrate) suggestions of an autoimmune disorder. All of the patients with ACLAs had negative ANA tests and no clinical stigmata suggestive of underlying autoimmune or other disease, and none was ingesting a drug known to be associated with lupus anticoagulants or ACLAs.

Because fetal wastage associated with hemorrhagic disorders is thought to come about because

TABLE 1. *Patient characteristics*

Patient	Age	No. Abs	Defect	Idiotype ACLA IgG	IgA	IgM	Other defects	Status
1	27	2	ACLA	P	N	N		D
2	33	2	ACLA	N	N	P		P
3	33	2	ACLA	P	N	N		P
4	29	2	ACLA	N	N	P		P
5	35	3	ACLA	N	N	P		D
6	34	1	ACLA	P	N	N	HELLP	D
7	30	1	ACLA	P	N	N		D
8	32	1	ACLA	P	N	N		D
9	35	1	ACLA	P	N	P	DVT/PE	D
10	30	2	ACLA	N	N	P		D
11	39	2	ACLA	P	N	N		D
12	27	2	ACLA	P	N	N		D
13	33	2	ACLA	P	N	N		D
14	49	2	ACLA	P	N	N	DVT/PE	D
15	35	3	ACLA	P	N	N	DVT	D
16	32	3	ACLA	P	N	N		D
17	37	3	ACLA	N	N	P		D
18	35	3	ACLA	P	N	N		D
19	35	3	ACLA	P	N	N		D
20	30	3	ACLA	P	N	N		D
21	37	3	ACLA	P	N	N		D
22	38	3	ACLA	P	N	N		D
23	37	4	ACLA	P	N	N	Retinal thromb.	D
24	31	4	ACLA	P	N	N		D
25	28	4	ACLA	P	N	N		D
26	33	5	ACLA	N	N	P		D
27	39	6	ACLA	P	N	N		D
28	39	9	ACLA	N	P	N		D
29	37	1	ACLA	P	N	N		D
30	29	1	ACLA	P	N	N		D
31	33	3	ACOA	N	N	P		W
32	34	1	ACLA	N	N	P		D
33	32	1	ACLA	N	P	N		W
34	41	3	ACLA	N	N	P		D
35	36	2	ACLA	N	N	P		P
36	33	3	ACLA	P	N	N		W
37	30	1	Protein S deficiency					NO
38	30	4	Protein S deficiency					D
39	29	3	Protein S deficiency				DVT	NO
40	34	7	Protein S deficiency					D
41	27	3	SPS type I					W
42	40	2	SPS type I					W
43	37	2	SPS type II					P
44	35	3	Dysfibrinogenemia				DVT/PE	D
45	28	3	t-PA deficiency					P
46	33	3	Lupus anticoagulant					P
Mean	33.4	2.76						

D, delivered; P, pregnant; W, awaiting pregnancy; NO, elected no pregnancy; ACLA, anticardiolipin antibody; P, positive; N, negative; SPS, sticky platelet syndrome; t-PA, tissue plasminogen activator; HELLP, HELLP syndrome; DVT, deep venous thrombosis; PE, pulmonary embolism; Ab, antibody.

what is the incidence in the general pop. of 33.4 yr. Pts & who have the blood defect?

of interference with adequate fibrin formation for implantation of the fertilized ovum into the uterine lining, we chose to not use vigorous preconception antithrombotic therapy and decided on low-dose ASA at 81 mg/day; this may be of theoretical concern only, in view of the recent report of Sher, who used preconception low-dose heparin with a high success rate for in vitro fertilization techniques (44). However, we remain concerned and continue to advocate low-dose ASA as the preconception antithrombotic therapy. The regimen of postconception addition of fixed low-dose porcine mucosal heparin at 5,000 units every 12 h was empirical, as higher doses seem to be associated with bleeding and a lower success rate. However, it may be that even lower doses might suffice. We do not advocate using corticosteroid therapy in this population, based on the negative experience of others in FWS, and our own preliminary experience of using steroids, in conjunction with antithrombotics, in pa-

TABLE 2. *Recommended treatment for fetal wastage syndrome associated with hypercoagulability*

1. Demonstration of unexplained spontaneous fetal loss
2. Demonstration of a blood protein/platelet defect associated with hypercoagulability and thrombosis
3. Desire to become pregnant
4. Start low-dose aspirin (ASA; 81 mg/day) preconception
5. Add low-dose subcutaneous porcine heparin at 5,000 units every 12 h immediately postconception
6. Use both agents to term
7. Depending on defect and clinical course, continue on ASA, or if warranted, other antithrombotic therapy after delivery

tients with antiphospholipid syndrome and other types of thrombosis, wherein the corticosteroid use could be shown to decrease antiphospholipid antibody titers but failed to abort thrombotic events (38,39,45,46).

A variety of treatment programs have been used for women with antiphospholipid (ACLAs or lupus anticoagulants) and FWS; however, many of these studies have studied only very small populations or fail to distinguish between primary or secondary antiphospholipid syndrome in the information provided. Brown (47) reported a 90% failure rate (miscarriage) among untreated women; Perino (48) reported a 93% failure rate in untreated women; and Many et al. (49) reported a 93% failure rate in untreated patients. Lubbe and Liggins (50), in a small group of women noted a successful term pregnancy rate of 80% with use of prednisone and ASA, and a similar success rate with this regimen was noted by Lin (51). Cowchuck et al. (52) noted a 75% success rate with prednisone alone or ASA alone but also noted more undesirable effects in the prednisone-treated population. Landy et al. (53), in a small population, reported a success rate of 90% with either ASA alone or prednisone alone. However, Many et al. (49) noted only a 43% successful term-pregnancy rate with ASA and prednisone, and Semprini et al. (54) noted only a 14% success rate with prednisone alone. Several studies have assessed the role of postconception addition of heparin; however, most have used higher doses than used in our population. Rosove et al. (55) reported a 93% success rate with dose-adjusted s.c. heparin, the mean heparin doses being ~25,000 units/day. Kuttah (56), in a population of 25 patients treated with ASA plus dose-adjusted s.c. heparin, noted a success rate of 76%; the mean heparin dose was 26,000 units/day. In the study of Many's et al. (49), patients treated with prednisone plus ASA plus heparin at 5,000 units twice a day had a better outcome (69%) than did those treated with ASA plus prednisone (43%) or prednisone alone (7%). Based on our results, it appears that fixed low-dose porcine heparin is more effective than the high-dose, dose-adjusted regimens, with 100% of our population with antiphospholipid FWS having a normal term delivery. It may be that higher doses of heparin somehow contribute to adverse outcomes, such as small periplacental hemorrhages. Parke (57) reported on the combination of low-dose heparin used in conjunction with intravenous immunoglobulin (IVIG); her success rate, however, was only 27%, suggesting that IVIG has little role in antiphospholipid FWS.

CONCLUSION

In summary, we report a 100% success rate in patients with recurrent FWS due to blood protein/platelet defects leading to hypercoagulability and thrombosis treated with preconception low-dose ASA and immediate addition of fixed low-dose porcine heparin at 5,000 units every 12 h, with both agents being used to term. Although the great majority of our patients had antiphospholipid FWS, several had other defects, including congenital protein S deficiency, dysfibrinogenemia, and t-PA deficiency; these other hypercoagulable disorders appear to respond to our ASA plus low-dose porcine heparin regimen. In our series, we have not noted factor XIII, XII, X, VII, V, II, plasminogen, antithrombin, protein C, or heparin cofactor II deficiency, nor have we noted APC resistance, afibrinogenemia, PAI-1 elevation, or homocysteinemia to be associated with the FWS. In interests of cost containment, we chose to develop two panels (I and

TABLE 3. *Hemostasis assessment of patients with fetal wastage syndrome*

Panel I
Anticardiolipin antibodies
Lupus anticoagulant
Sticky platelet syndrome
Protein S deficiency
Antithrombin deficiency
Protein C deficiency
Factor XIII deficiency
Functional fibrinogen
Panel II
Factor XII deficiency[a]
Factor X deficiency[a]
Factor VII deficiency[a]
Factor V deficiency[a]
Factor II deficiency[a]
Plasminogen deficiency
t-PA deficiency
PAI-1 elevation
Heparin cofactor II deficiency
Tissue factor pathway inhibitor
Homocysteinuria ?

[a] Should be suggested by prolongation of routine prothrombin time or activated partial thromboplastin time.

II) of assays, going from the most likely to least likely hemostasis defects to be associated with FWS; these are presented in Table 3. Finally, even though only selected hypercoagulable syndromes have been reported to cause the recurrent FWS, as discussed previously, it might be anticipated that any blood protein/platelet defect may give rise to FWS via thrombosis of placental vessels.

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