Combination therapy with anticoagulants, corticosteroids and intravenous immunoglobulin for women with severe obstetric antiphospholipid syndrome

Sirs,

Obstetric antiphospholipid syndrome (APS) is characterised by recurrent early miscarriages, foetal loss in later pregnancy and maternal morbidity by thrombosis (1). Although the first-choice treatment regimen for women with obstetric APS is anticoagulation therapy with a combination of heparin and low dose aspirin (LDA) (2), 20–30% of cases result in pregnancy failure despite appropriate treatment (2, 3). In addition, among such cases are women with a significantly higher risk of developing recurrent severe gestational complications such as maternal thrombosis, preeclampsia and HELLP syndrome (4-5). Combination therapies with standard antithrombotic therapy for severe APS patients have been anticipated. Immunotherapies such as intravenous immunoglobulin (IVIG) and/or corticosteroids may be good candidates for severe obstetric APS patients (6-8). Here, we describe our experiences treating three severe obstetric APS patients with a combination of anticoagulants, corticosteroids and IVIG.

Table I shows background characteristics and pregnancy outcomes of the three patients. All patients were diagnosed based on the revised Sidney criteria (1). We defined women with "severe APS" as those with (1) severe late gestational complications such as preeclampsia or intrauterine foetal death, or (2) any thrombotic event during or soon after pregnancy despite anticoagulation therapy. Based on recommended protocols, continuous unfractionated heparin injections were initiated after a urine pregnancy test (at around 4 gestational weeks) for all three patients (2, 9, 10). LDA administered before pregnancy was continued after conception and warfarin medication was discontinued after initiating heparin injection. The quantity of injected heparin was adjusted to maintain a plasma heparin concentration above 0.2 U/ml, which is associated with a decreased risk of thrombosis during pregnancy (9, 10). Prednisolone (PSL; 10–20 mg/day) was also initiated upon diagnosis of pregnancy. Further to this, a five-day course of IVIG (400 mg/kg body weight) was initiated soon after confirmation of a foetal heartbeat (FHB) (at around 6–7 gestational weeks), as the rate of early natural pregnancy loss decreases after ultrasound confirmation of FHB (10).

Case 1 suffered from severe preeclampsia with thrombocytopenia and splenic infarction during the postpartum period despite antithrombotic therapy with LDA and heparin. Case 2 experienced intrauterine foetal deaths (IUFDs) twice. In addition, she experienced a brain infarction during the postpartum period of the first pregnancy. She took no medications during the first pregnancy, and took LDA and corticosteroids during the second pregnancy. Case 3 experienced a thrombotic event after early pregnancy loss despite heparin injection. All three patients were positive for anti-beta 2 glycoprotein I (β2GPI) antibody, anti-cardiolipin (CL) antibody and lupus anticoagulant (LA). All patients had been taking LDA and warfarin while not pregnant. All three patients achieved live births. Case 2 ended in preterm delivery at 32 gestational weeks; however, this was solely attributed to an obstetric complication (*i.e.* placenta previa with increased genital bleeding). All three patients received anticoagulation therapy with LDA and heparin during the intrapartum period given worries of thrombosis rather than bleeding at delivery. No thrombotic or bleeding complications were observed in any of the patients.

Although results from several studies have not supported the use of immunotherapies such as corticosteroids and IVIG for treating APS (2-3), proper management guidelines for severe obstetric APS patients have yet to be established. Once recent study suggested that low dose corticosteroids given during the first trimester in addition to anticoagulation therapy improved pregnancy outcomes in women with severe obstetric APS (8). However, the live birth rate of the series in that study was 61%. We believe that additional IVIG can improve pregnancy outcomes of severe obstetric APS patients. Further studies will be needed to clarify the effectiveness of additional immunotherapies in treating severe obstetric APS patients.

Table I. Background characteristics and pregnancy outcomes.

Case no.	1	2		3
Age (years)	29	35		31
Height (cm), Body weight (kg)	148, 40	162, 46		162, 52
Gravida, Para	G1P1	G2P2		G1P0
Diagnosis	APS	APS		APS
Age of onset (years)	17	24		19
Disorder	DVT	IUFD		Pulmonary embolism
Past pregnancy history	1st	1st	2nd	1st
Age (years)	27	24	29	27
Medication	LDA (81 mg/day) Heparin (10,000 U/day)	None	LDA (81 mg/day)	Heparin (10,000 U/day)
Complication: Mother	Preeclampsia	Postpartum brain infarction	None	Early pregnancy loss, DVT
Complication: Infant	Intact survival	IUFD	IUFD	–
Gestational age at delivery (wks)	29	24	29	7
Birth weight (grams)	984	222	873	–
Titer of aPL antibodies at non-pregnancy period (normal range)				
anti-CL IgG (0–9 U/ml)	19	69		440
anti-β2GPI IgG (0–3.4 U/ml)	22.9	208		218
LA	Positive	Positive		Positive
Pre-conception clinical symptoms	None	None		None
Pre-conception medications	LDA + warfarin	LDA + warfarin		LDA + warfarin
Method of conception	Natural	Natural		Natural
Gestational age at delivery	37w0d	32w2d		37w3d
Indication of delivery	Previous cesarean section	Total placenta previa (Increased genital bleeding)		Increased genital bleeding
Mode of delivery	Cesarean section	Cesarean section		Transvaginal
Birth weight (SD score)	2692 (-0.1SD)	1484 (-1.4SD)		2052 (-1.7SD)
Thrombotic complication	None	None		None

APS: antiphospholipid syndrome; DVT: deep venous thrombosis; LDA: low-dose aspirin; IUFD: intrauterine foetal death; anti-β2GPI: anti-beta 2 glycoprotein I; anti-CL: anti-cardiolipin; LA: lupus anticoagulant; SD: standard deviation.

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References

1. MIYAKIS S, LOCKSHIN MD, ATSUMI T *et al*.: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295-306.
2. ZIAKAS PD, PAVLOU M, VOULGARELIS M: Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. *Obstet Gynecol* 2010; 115: 1256-62.
3. DE JESUS GR, DOS SANTOS FC, OLIVEIRA CS, MENDES-SILVA W, DE JESUS NR, LEVY RA: Management of obstetric antiphospholipid syndrome. *Curr Rheumatol Rep* 2012; 14: 79-86.
4. FISCHER-BETZ R, SPECKER C, BRINKS R, SCHNEIDER M: Pregnancy outcome in patients with antiphospholipid syndrome after cerebral ischaemic events: an observational study. *Lupus* 2012; 21: 1183-9.
5. LE THI THOUONG D, TIEULIE N, COSTEDOAT N *et al*.: The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. *Ann Rheum Dis* 2005; 64: 273-8.
6. SHERER Y, LEVY Y, SHOENFELD Y: Intravenous immunoglobulin therapy of antiphospholipid syndrome. *Rheumatology* (Oxford) 2000; 39: 421-6.
7. TRIOLO G, FERRANTE A, ACCARDO-PALUMBO A *et al*.: IVIG in APS pregnancy. *Lupus* 2004; 13: 731-5.
8. BRAMHAM K, THOMAS M, NELSON-PIERCY C, KHAMASHTA M, HUNT BJ: First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. *Blood* 2011; 117: 6948-51.
9. BATES SM, GREER IA, PABINGER I, SOFAER S, HIRSH J: Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133 (6 Suppl.): 844S-886S.
10. PAPAIOANNOU GI, SYNGELAKI A, MAIZ N, ROSS JA, NICOLAIDES KH: Ultrasonographic prediction of early miscarriage. *Hum Reprod* 2011; 26: 1685-92.