Brief report

First-trimester low-dose prednisolone in refractory antiphospholipid antibody–related pregnancy loss

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The objective of this study was to assess pregnancy outcome in women with a history of refractory antiphospholipid antibody–associated pregnancy loss(es) who were treated with early low-dose prednisolone in addition to aspirin and heparin. Eighteen women with antiphospholipid antibodies who had refractory pregnancy loss(es) were given prednisolone (10 mg) from the time of their positive pregnancy test to 14 weeks' gestation. Before low-dose prednisolone was given as treatment, 4 (4%) of 97 pregnancies had resulted in live births. Among 23 pregnancies supplemented with prednisolone, 9 women had 14 live births (61%), including 8 uncomplicated pregnancies. The remainder were complicated by preterm delivery, preeclampsia, and/or small-for-gestational-age infants. There were 8 first-trimester miscarriages and 1 ectopic pregnancy. There were no fetal deaths after 10 weeks' gestation and no evidence of maternal morbidity. The addition of first-trimester low-dose prednisolone to conventional treatment is worthy of further assessment in the management of refractory antiphospholipid antibody–related pregnancy loss(es), although complications remain elevated. (*Blood*. 2011;117(25):6948-6951)

Introduction

Obstetric antiphospholipid syndrome (APS) includes recurrent first-trimester loss, later fetal loss, and early delivery because of preeclampsia or placental insufficiency.[1,2] Up to 15% of women with recurrent miscarriages have been found to have antiphospholipid antibodies (aPL). In these women, fetal loss may remain high without treatment.[3]

Low-dose aspirin is usually given to pregnant women with aPL, and there is conflicting evidence supporting the additional use of heparin in those with previous pregnancy loss(es).[4,5] However, up to 30% of such women continue to experience recurrent pregnancy loss, and the best approach to treatment of these women is unknown.[6]

Prednisolone in doses of 40-60 mg daily in addition to aspirin has been used successfully in small numbers of women with APS[7] but was largely disregarded as a treatment option after a randomized controlled trial demonstrated that heparin and aspirin were superior to aspirin and prednisolone,[8] and further studies showed that prednisolone in addition to aspirin conferred no benefit.[9,10] Prednisolone was also associated with increased risk of gestational diabetes, elevations in blood pressure during pregnancy, asymptomatic infections, and preterm deliveries.[11]

Evidence from murine models suggests complement-mediated placental damage in APS pregnancies.[12] Theoretically, women with recurrent pregnancy loss refractory to treatment with aspirin and heparin may benefit from immunosuppression to maintain a viable pregnancy.

The purpose of the present study was to assess the outcome of pregnancies in women with aPL and refractory pregnancy loss(es) despite the use of aspirin and heparin, with additional prednisolone given in the first trimester.

Methods

Eighteen women with aPL, seen from August 1999 through September 2008, who repeatedly tested positive for aPL and had at least 1 unsuccessful pregnancy while taking both aspirin and heparin, were offered prednisolone 10 mg daily, in addition to our standard anticoagulation, from the time of their positive pregnancy test to 14 weeks of gestation.[13] Women were informed of the paucity of evidence supporting this practice. Sapporo criteria[1] were used for the definition of APS, because recent guidelines were published in 2006 after the study started.[2]

Women were seen before pregnancy or in early pregnancy and then at booking (8-12 weeks), and their progress was reviewed regularly by a multidisciplinary team. Preeclampsia was diagnosed according to international criteria[14] and managed according to unit protocol. Obstetric definitions were as follows: miscarriage—spontaneous pregnancy loss before 24 weeks; preterm birth—birth 24-36^{+6} weeks; and small for gestational age—< 10th centile according to customized neonatal birth-weight charts (www.gestation.net/birthweight_centiles/centile_online.htm).

Statistical analysis was performed with SPSS Version 17 and included logistic regression analysis and χ^2 and Fisher exact tests with a generalized link function to correct pregnancy outcomes for more than 1 pregnancy in the same woman.

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Table 1. Obstetric and thrombotic histories and aPL of women before pregnancy treated with additional prednisolone

		Fetal loss at < 10 weeks: treatment			Fetal loss at > 10 weeks: treatment								
Patient	Previous Thrombo-embolism	None	Aspirin	Aspirin/ heparin	None	Aspirin	Aspirin/ heparin	IUGR	Preeclampsia	Live births; gestation	LA	Ig M ACA < 11MPL U/mL	Ig G ACA < 20.1GPL U/mL
1	0	3	2	2	0	0	0	0	0	0	+	14.6	3.7
2	0	1	0	1	2	0	0	0	0	0	+	16.4	13.3
3	0	7	4	3	0	0	0	0	0	1; 28/40	+	9.8	70
4	1	0	0	2	1	0	0	0	1	1; 38/40	+	74	> 300
5	1	0	0	1	0	0	2; No aspirin*	0	0	0	+	6.5	30.8
6	3	1	0	5	0	0	0	1	1	1; 37/40	+	18	105
7	0	1	0	2	0	0	0	0	0	0	−	14.5	24.2
8	0	0	3	1	0	0	0	0	0	1†	+	26.2	7.2
9	0	6	1	1	0	0	0	0	0	0	+	7.5	11.5
10	0	2	0	2	0	0	0	0	0	0	+	5	18.4
11	1	0	0	0	0	0	1	0	0	0	‡	11.1	93.8
12	2	2	0	1	0	0	0	0	0	0	+	5.7	4.7
13	0	5	0	3	0	0	0	0	0	0	+	9.4	8.1
14	2	0	0	1	0	0	1	0	0	0	+	11.9	140
15	0	3	2	3	1	0	0	0	0	1; 40/40	−	13	9
16	0	2	0	2	0	0	0	0	0	0	−	32.7	79.2
17	0	2	1	2	1	0	0	0	0	0	−	15.5	3.3
18	0	3	0	1; Allergic to LMWH; limited use§	0	0	0	1; Aspirin; allergic to LMWH§	0	1; 40/40	+	1.5	1.1

IUGR indicates intrauterine growth restriction; LA, lupus anticoagulant; ACA, anticardiolipin antibodies (IgM and IgG); and LMWH, low-molecular-weight heparin.
*Intolerant of aspirin; therefore, LMWH alone was given.
†Gestational age at delivery unavailable.
‡Result not available.
§Urticaria at injection sites with LMWH; therefore, LMWH was discontinued.

Table 2. Fetal and neonatal outcomes with the addition of low-dose prednisolone (10 mg)

Patient	Age, y	Fetal loss at < 10 weeks' gestation	Live births	Gestation	Preeclampsia	SGA	Birth weight, kg	Additional treatment
1	35	0	2	38/40	Y	Y	2.35	
	37			40+/40	N	N	3.46	
2	39	0	2	40+/40	N	N	3.46	
	41			38+/40	N	N	3.01	
3	43	0	1	37+/40	N	Y	2.35	
4	36	1	0	5/40				
5	42	1	0	10/40				
6	36	0	0					
7	40	0	0					
8	33	0	0					
9	36	2	1	36+/40	N	N	2.41	
	41			7/40				
	43			8/40				
10	46	0	0					
11	38	0	1	25+/40	Y	Y	0.54	
12	34	Ectopic	1	39+/40	N	N	3.37	
13	41	0	3	31/40	N	N	1.50	
	42			38/40	N	Y	2.50	
	44			39+/40	N	Y	2.68	
14	28	2	0	5/40				
	30			7/40				
15	26	1	0	6/40				
16	33	0	2	40+/40	N	N	3.09	
	35			39/40	N	N	3.32	
17	34	1	0	7/40				
18	31	0	1	40/40	N	N	3.0	No LMWH (allergic)

SGA indicates small for gestational age; Y, yes; and N, no.

Results and discussion

Previous obstetric and thrombotic histories and aPL characteristics and autoantibodies are shown in Table 1. Median age before the pregnancy that was supplemented with prednisolone was 36 years (interquartile range 33-40 years). Before treatment with low-dose prednisolone, there were 93 fetal losses (median 4 [IQR 3-6.8] per woman) and 4 live births (4%).

Twenty-three pregnancies were supplemented with prednisolone; 14 (61%) resulted in live births, of which 8 were uncomplicated pregnancies. There were no congenital abnormalities or late fetal deaths and no evidence of maternal morbidity because of use of low-dose prednisolone. There was no relationship between the number of previous fetal losses before ($P = .18$) or after ($P = .10$) 10 weeks' gestation, previous live births ($P = .29$), age ($P = .45$), lupus anticoagulant ($P = .94$), IgG anticardiolipin antibody ($P = .20$), IgM anticardiolipin antibody ($P = .49$), or antinuclear antibody ($P = .19$) and successful pregnancy outcome. Seven (64%) of 11 women with previous early fetal losses only before 10 weeks' gestation had live births after taking prednisolone, whereas 2 (29%) of 7 women with losses at > 10 weeks' gestation had live births with treatment ($P = .33$).

The present study suggests that women with refractory aPL-related pregnancy losses may have improved pregnancy outcomes with low-dose prednisolone taken until 14 weeks' gestation. In our unit, rates of fetal loss have fallen from 30% to 9%[15,16] after use of a protocol that includes aspirin and heparin; however, there remains a small group of women in whom this treatment is unsuccessful. In the present study, before use of corticosteroids, the median number of fetal losses per woman was 4, and nearly half of the women had experienced losses after 10 weeks' gestation, with a 4% live birth rate. After treatment with prednisolone, nearly two-thirds (61%) of pregnancies resulted in live births, of which 8 (57%) were uncomplicated term pregnancies.

There was considerable early enthusiasm for steroids and aspirin in the management of obstetric APS. Live birth rates in women with recurrent fetal loss on such treatment were reported to be as high as 76%.[17] In addition, others found a reduction in fetal growth restriction in those treated with prednisolone compared with untreated women with obstetric APS.[7] High-dose steroid (40 mg) was used to suppress aPL titers and then tapered as antibody levels fell, but continued through pregnancy.[7]

However, a randomized controlled trial that compared outcomes after treatment with aspirin plus prednisolone (40 mg) or a prophylactic dose of heparin demonstrated no difference in live birth rate but an increased frequency of preterm delivery because of premature rupture of membranes or preeclampsia in the group treated with prednisolone.[8] Another randomized controlled trial in women with 2 or more first-trimester losses found no benefit in rates of fetal loss but increased preterm delivery in women treated with prednisolone (20 mg) plus aspirin compared with aspirin alone.[10] Another report suggested that fetal losses were actually higher in women treated with prednisolone (10-60 mg).[9]

A more recent study in women with autoantibodies showed no increase in live birth rate but an increased risk of prematurity and significant side effects, including gestational diabetes, infection, and hypertension, in women treated with prednisolone (0.2-0.8 mg/kg) plus aspirin compared with placebo.[11] Hence, the use of high-dose prednisolone for treatment of obstetric APS was largely discontinued, and current guidelines support use of aspirin or aspirin and heparin,[18] because other treatments, including intravenous immunoglobulin, have failed to confer benefit.

Despite the use of aspirin and heparin treatment for women with obstetric APS, birth rates remain suboptimal.[18] The present study suggests that low-dose prednisolone in addition to aspirin and heparin may be of benefit in women with APS refractory to standard treatment. Studies demonstrating adverse effects of prednisolone have used doses up to 60 mg. Prednisolone is metabolized by the placenta to a relatively inactive metabolite, only 10% of which crosses into the fetal circulation at doses < 20 mg,[19] and therefore, it might be anticipated that low doses may have fewer side effects. Preterm delivery was high in the present study (21%), and preeclampsia occurred in 2 women, although this rate was not higher than anticipated in women with refractory APS.[13]

The pathophysiology of obstetric APS is poorly understood, but there is increasing evidence for underlying inflammatory mechanisms. In murine models of APS, anticoagulation alone is insufficient to protect pregnancies, but heparin inhibits activation of complement on trophoblasts in vitro and in vivo and prevents pregnancy loss.[20] Complement-induced tissue injury is also found in placentas of humans with aPL.[21] Prednisolone is recognized to impair complement activation,[22] which may allow adequate trophoblast invasion and placentation to be established in women with refractory APS

Endometrial natural killer cells have been shown to be associated with recurrent miscarriage.[23] Case reports suggest a benefit of prednisolone in women with recurrent miscarriage,[24] but effects on pregnancy outcome are under investigation. Women with aPL in the present study may have had increased numbers of preconception endometrial natural killer cells contributing to recurrent pregnancy loss, moderated by prednisolone. Placental bed biopsy samples from women with APS have higher concentrations of inflammatory cells, which may also be affected by prednisolone use.[25]

Limitations of the present study include the small number studied and the potential for bias with the use of historical self-controls. However, the results appear encouraging in a very refractory patient population and warrant further investigation.

Authorship

Contribution: K.B. and M.T. collected data, and all authors contributed to manuscript preparation.

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