The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies.

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Abstract

BACKGROUND:

Antiphospholipid syndrome is defined by the combination of thrombotic events and/or obstetric morbidity in patients who have tested positive persistently for antiphospholipid antibodies. With good treatment, approximately 70% of pregnant women with antiphospholipid syndrome will deliver a viable live infant. However, current management does not prevent all maternal, fetal, and neonatal complications of antiphospholipidsyndrome.

OBJECTIVES:

This observational, retrospective, single-center cohort study aimed to assess pregnancy outcomein women with antiphospholipid antibodies who were treated with hydroxychloroquine in addition to conventionaltreatment during pregnancy.

STUDY DESIGN:

One-hundred seventy pregnancies in 96 women with persistent antiphospholipid antibodies were analyzed: (1) 51 pregnancies that occurred in 31 women were treated with hydroxychloroquine for at least 6 months before pregnancy, and the therapy continued throughout gestation (group A); (2) 119 pregnancies that occurred in 65 women with antiphospholipid antibodies that were not treated with hydroxychloroquine were included as controls (group B).

RESULTS:

Hydroxychloroquine-treatment was associated with a higher rate of live births (67% group A vs 57% group B; P = .05) and a lower prevalence of antiphospholipid antibodies-related pregnancy morbidity (47% group A vs 63% B; P = .004). The association of hydroxychloroquine with a lower rate of any complication in pregnancywas confirmed after multivariate analysis (odds ratio, 2.2; 95% confidence interval, 1.2-136; P = .04). Fetal losses at >10 weeks of gestation (2% vs 11%; P = .05) and placenta-mediated complications (2% vs 11%; P = .05) were less frequent in group A than group B. Pregnancy duration was longer in group A than group B (27.6 [6-40] vs 21.5 [6-40] weeks; P = .03). There was a higher rate of spontaneous vaginal labor in hydroxychloroquine-treatedwomen compared with group B (37.3% vs 14.3%; P = .01).

CONCLUSIONS:

Despite the heterogeneity in the 2 groups in terms of systemic lupus erythematosus prevalence and previous pregnancy history, our results support the concept that women with antiphospholipid antibodies may benefit from treatment with hydroxychloroquine during pregnancy to improve pregnancy outcome. The addition ofhydroxychloroquine to conventional treatment is worthy of further assessment in a proper designed randomized controlled trial.

Key words

antiphospholipid antibodies; antiphospholipid syndrome; hydroxychloroquine; pregnancy

Antiphospholipid syndrome (APS) is defined by the combination of thrombotic events and/or obstetric morbidity in patients who tested persistently positive for antiphospholipid antibodies (aPL). [1] Laboratory tests to identify aPL include solid-phase enzyme-linked immunosorbent assays

(ELISA) to detect anticardiolipin and anti-β2 glycoprotein 1 antibodies and functional assays for lupus anticoagulants. The presence of aPL must be confirmed at least in 2 occasions >12 weeks apart.[1]

Although initially described in patients with systemic lupus erythematosus (SLE), APS was soon recognized to occur also in patients without underlying autoimmune disease (so called primary APS).[2] Approximately 30% of SLE is positive for aPL[3]; at 20 years of follow-up observation, there is a 50% chance of the development of APS.[4] Obstetric morbidity in APS is characterized by early complications, such as recurrent abortions before week 10 of gestation, and/or later complications, such as fetal death at ≥10 weeks of gestation, and prematurity before 34 weeks of gestation in relation with placental insufficiency.[1] Placental insufficiency can result in intrauterine growth restriction, preeclampsia, eclampsia, placental abruption, and hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome.

The prevention of obstetric complications is based on the use of low-dose aspirin and/or subcutaneous injections of unfractionated heparin or low–molecular-weight heparin.[2, 5 and 6]Women with APS who have had a previous thrombotic event currently are treated with low-dose aspirin and heparin.[2] With good treatment, approximately 70% of pregnant women with APS will deliver a viable live infant.[7] Very recently, Bouvier et al[8] confirmed this observation, reporting a live birth rate of 69.6% in a cohort of women with a purely obstetric APS who were treated with low-dose aspirin and low–molecular-weight heparin. In our unit, overall rates of live birth in women with aPL previously have been reported to be as high as 79%.[7]

However, current treatment does not prevent all maternal, fetal, and neonatal complications of APS, with an overall frequency of failure, despite modern treatment ranges from 20-30%, depending on the therapeutic regime, and the history of thrombosis, and/or pregnancy complications. The best approach to improve the outcome of these pregnancies is still unknown.

Our group showed that the addition of first-trimester low-dose prednisolone to conventional treatment improved the rate of live births in refractory aPL-related first trimester pregnancy loss. After treatment with low-dose prednisolone, nearly two-thirds of pregnancies (61%) resulted in live births, of which 8 (57%) were uncomplicated term pregnancies. However, the frequency of some complications remained elevated, mainly preterm delivery (21%).[9] Other treatments, including intravenous immunoglobulin, have failed to confer benefit.[10]

Hydroxychloroquine, traditionally an antimalarial drug, has been used widely in the treatment of patients with autoimmune conditions, mainly SLE where has been associated with a prevention of flares and better survival through its immunomodulatory effects, including antiinflammatory, antiaggregant, and immune-regulatory properties.[11, 12, 13 and 14]

Original studies of fetal morbidity and death in APS suggested that the pathogenesis was thrombotic for second- and third-trimester complications and possibly through trophoblast inhibition in first-trimester loss.[15]

However, recent animal models and in vitro studies have suggested that the cause of adverse pregnancy events in aPL may be caused by inflammatory processes, including increased cytokine production, complement deposition, and immune cell activation.[16]Recently, hydroxychloroquine has been shown to reverse the aPL-inhibition of trophoblast interleukin-6 secretion and aPL-inhibition of cell migration.[17] Also, it has been reported that hydroxychloroquine restores trophoblast fusion that is affected by aPL.[18] These studies suggest that hydroxychloroquine may improve pregnancy outcome in women with aPL, especially in those with recurrent pregnancy loss refractory to conventional treatment.[19]

Several studies have assessed the effect of hydroxychloroquine on pregnancies in women with SLE and demonstrated that hydroxychloroquine is safe in pregnancy. In case series published in the 1980s and 1990s, Parke[20 and 21] suggested that hydroxychloroquine was safe to use in pregnant patients with SLE. Buchanan et al[22] reported that exposure to hydroxychloroquine during pregnancy did not have any teratogenic effects. Data regarding 257 pregnancies from the Hopkins cohort showed no fetal abnormalities that were attributable directly to hydroxychloroquine; this study also

reported that the stopping of hydroxychloroquine therapy during or just before pregnancy resulted in increased disease activity.[23] The European League Against Rheumatism recommendations for the management of SLE support the safety and efficacy of hydroxychloroquine during pregnancy.[24] Very recently, data from a European multicenter retrospective study that included 30 patients with APS with 35 pregnancies showed a better outcome of pregnancies that were treated by the addition of hydroxychloroquine when compared with previous pregnancies under the conventional treatment.[25]
The purpose of the present cohort study was to assess the outcome of pregnancies in a large cohort of women with aPL who were exposed to hydroxychloroquine during pregnancy when compared with women with aPL who did not receive hydroxychloroquine therapy.

Methods

This was an observational, retrospective, single center cohort study. All the records of women who attended the Lupus & Antiphospholipid Pregnancy clinic from January 2008 to July 2014 were searched. All the pregnancies in women with persisting aPL were identified.

aPL positivity was defined according to the current classification criteria and confirmed at least 12 weeks apart [1] in all the included women before the index pregnancy. Women with equivocal or unconfirmed aPL positivity were excluded from our analysis. Our final cohort included 170 pregnancies, which occurred in 96 women with aPL.
Anticardiolipin antibodies (isotypes immunoglobulin G and M) were quantified by indirect ELISA with the use of AEUSKULISA Cardiolipin-GM reagents (Grifols UK, Cambridge, UK). Anti β2-glycoprotein I antibodies (isotypes immunoglobulin G and M) were quantified by indirect ELISA with the use of QUANTA Lite reagents (INOVA Diagnostics Inc, San Diego, CA). Lupus anticoagulant detection that was in compliance with published guidelines[26] was determined by dilute Russell's viper venom time and dilute activated partial thromboplastin time, accompanied by appropriate confirmatory tests. Patients on oral anticoagulation therapy additionally received screening with Taipan snake venom time with the use of Diagen Taipan venom (Diagnostic Reagents, Thames, UK) with an Ecarin time confirmatory test using *Echis carinatus* venom (Diagnostic Reagents).
Patients were divided in 2 groups: Group A included aPL patients who received hydroxychloroquine treatment during pregnancy. Group B included patients without hydroxychloroquine treatment.

The following baseline data were registered and compared between the 2 groups: frequency of aPL only, primary APS, aPL with SLE and APS with SLE, mean disease duration, history of pregnancy morbidity and/or thrombosis, conventional risk factors for cardiovascular events (hypertension,[27] body mass index ≥30 kg/m^2, hyperlipemia,[28]diabetes mellitus,[29] smoking>5 cigarettes/daily), aPL profile, and the presence of other autoantibodies (antinuclear antibodies, anti–double stranded DNA, anti-extractable nuclear antigens antibodies).
For each pregnancy, the following data were collected: treatment, pregnancy outcome and maternal/fetal/neonatal complications.

Neonatal outcomes that were recorded included survival, gestational age at delivery, neonatal weight, and occurrence of intrauterine growth restriction.

Pregnancy morbidity was defined according to the current classification criteria for APS. [1]
Therapy other than hydroxychloroquine varied according to the clinical manifestations and can be summarized in the following manner: women without previous pregnancy morbidity or thrombosis received low-dose aspirin. Low–molecular-weight heparin (LMWH) at thromboprophylactic doses was associated only if previous failure of low-dose aspirin alone. Women with previous fetal death or previous early delivery because of severe preeclampsia or placental insufficiency received low-

dose aspirin plus LMWH at thromboprophylactic doses. Patients with thrombotic APS who undergo long-term anticoagulation were treated with low-dose aspirin and LMWH at therapeutic doses.

Statistical analysis was performed with SPSS software (version 17; SPSS Inc, Chicago, IL) and included logistic regression analysis and χ^2 and Fisher exact tests with a generalized link function to correct pregnancy outcomes for >1 pregnancy in the same woman.
A stepwise forward conditional procedure that included biologic relevant and significant risk factors that were obtained from the univariate analysis was then used for the logistic regression analysis to identify significant independent risk factors. Computed variables included age, aPL profile, presence of SLE, history of pregnancy morbidity and/or thrombosis, presence of other autoantibodies (antinuclear antibodies, anti–double stranded DNA, anti-extractable nuclear antigens antibodies, treatment during pregnancy (low-dose aspirin, LMWH, steroids, and/or immunosuppressant use).

Patients

Previous obstetric and thrombotic events, concomitant autoimmune conditions, and autoantibodies are shown in Table 1.

Hydroxychloroquine group (group A)

Between January 2008 and July 2014, 51 pregnancies occurred in 31 women who had been treated with hydroxychloroquine for at least 6 months before pregnancy (mean time treatment before pregnancy, 41.7 ± 9.2 months) and continued throughout gestation (only 1 patient started hydroxychloroquine at the time of a positive pregnancy test). Indications for hydroxychloroquine treatment were SLE as defined by the American College of Rheumatology criteria30 (n = 20; 64.5% of group A). One patient did not meet 4 American College of Rheumatology classification criteria for SLE but had arthralgias and was positive for anti-SSA/Ro antibodies (n = 1; 3.2%). In patients with primary APS, the indication was lupus-like syndrome (ie, severe fatigue and arthralgia without serologic positivity for SLE (n = 10; 32.3%). At study entry, 7 women (22%) were primigravid, and 24 were multiparous. Six pregnancies occurred after in vitro fertilization treatment. The median age of patients at the time of delivery was 32 years (range, 21–42 years).In 26 pregnancies, the women received hydroxychloroquine 200 mg twice daily; in 25 pregnancies, the women received hydroxychloroquine 200 mg once daily. When low-dose aspirin or heparins was excluded, hydroxychloroquine was used in 30 pregnancies as sole immunomodulation treatment. Other treatments are reported in Table 2.

Group not exposed to hydroxychloroquine (group B)

Between January 2008 and July 2014, 119 pregnancies occurred in 65 women who had not been treated with hydroxychloroquine during pregnancy. Five patients with SLE (7.7%) who refused hydroxychloroquine treatment (they had concerns about potential side-effects), 45 women (69.2%) had primary antiphospholipid syndrome, and 15 patients were aPL positive without previous events (23.1%) who did not have clinical indication to receive hydroxychloroquine.

At study entry, 14 women were primigravid, and 51 women were multiparous. Twenty-two pregnancies occurred after in vitro fertilization treatment. The median age at the time of delivery was 35.6 years (range, 18–42 years).

Results

Treatment with hydroxychloroquine was well tolerated, and no side-effect was reported. No patients suspended treatment with hydroxychloroquine during the follow-up period.

As indicated in Table 1, women who were treated with hydroxychloroquine had a significant higher prevalence of SLE (64.5% in group A vs 7.7% in group B; $P < .001$), which is consistent with the higher frequency of antinuclear antibodies and extractable nuclear antigens antibodies that were

observed in group A ($P < .001$). Disease duration (either APS and/or SLE) was longer in group A when compared with group B (5.3 ± 4.1 vs 2.7 ± 2.4 years).

Group B had a higher prevalence of primary antiphospholipid syndrome (16.1% in group A vs 69.2% in group B; $P < .001$) and of previous pregnancy morbidity (22.6% in group A vs 53.8% in group B; $P = .004$), which failed to reach statistically significance when we analyzed spontaneous abortion at <10 week of gestation, fetal loss beyond week 10 of gestation, or placenta-mediated complications separately.

No statistical differences were seen between the 2 groups in age at the start of pregnancy, ethnicity, primigravidity, conventional cardiovascular risk factors, and previous thrombotic events.

Table 2 shows the pregnancy outcome in the 2 groups. Hydroxychloroquine treatment was associated with a higher rate of live births (66.7% in group A vs 57.1% in group B; $P = .05$) and a lower prevalence of overall pregnancy morbidity (47.1% in group A vs 63.0% in group B; $P = .004$).

The beneficial effect of hydroxychloroquine in the reduction of aPL-related complication in pregnancy was confirmed after multivariate analysis (odds ratio, 2.2; 95% confidence interval, 1.2–136; $P = .04$).

Previous pregnancy morbidity (odds ratio, 12.1; 95% confidence interval, 1.4–134; $P = .03$) and triple aPL positivity (odds ratio, 2.6; 95% confidence interval, 1.9–22; $P = .04$) were confirmed as independent factors that were related with poor pregnancy outcome after multivariate analysis.

In details, fetal losses at >10 weeks of gestation were less frequent in group A than group B (2% vs 10.9%; $P = .05$). Placenta-mediated complications (preeclampsia, abruption placenta, and intrauterine growth restriction were less prevalent in women who were treated with hydroxychloroquine than in control subjects (2% vs 10.9%; $P = .05$); however, when we stratified for each manifestation, they did not reach a statistical significance.

No significant difference was observed when we compared the rate of spontaneous abortions before week 10 of gestation.

We observed a significant higher prevalence of spontaneous vaginal labor in women who were treated with hydroxychloroquine compared with group B (37.3% vs 14.3%; $P = .01$). Overall pregnancy duration was longer in group A than group B (27.6 [range, 6-40] vs 21.5 [range, 6-40] weeks; $P = .03$). When calculated for patients who were reaching viability, pregnancy duration was confirmed to be longer in group A than group B (39 [range, 34-41] vs 37.5 [range, 31-40]; $P = .049$).

The rate of preterm live births before week 37 of gestation was lower in group A than group B (3.9% vs 13.4%), although it failed to reach a statistical significance.

No thrombotic event was observed during the follow-up period.

The included patients with SLE were stably in remission/with low disease activity at the time of pregnancy. Only 2 minor flares that consisted in exacerbation of arthralgia were recorded in group A; the flares were treated with minimal adjustment of oral steroids dose (up to 7.5 mg/d). When we stratified for SLE clinical manifestations, which included lupus nephritis, no further association with any pregnancy morbidity was observed.

Comment

To the best of our knowledge, this study is the first to provide clinical evidence from a large cohort that supports a beneficial effect of hydroxychloroquine on pregnancy outcome in women with aPL.

In our study, hydroxychloroquine was well tolerated, and no serious side-effects were observed.

The main serious effects that are associated with hydroxychloroquine exposure are very rare and involve cardiac and retinal toxicities.31 Cardiac toxicity remains controversial; in the largest prospective study, the rate of heart conduction disorders during the 12-month follow-up period was similar to what is expected in the general population.32 With regard to retinal toxicity, a follow-up study that included 2043 adult patients showed 0.1% of hydroxychloroquine-related retinopathy that was associated with a median duration of hydroxychloroquine treatment of >10 years.12 With regard to the fetal outcome in pregnancies that were treated with hydroxychloroquine, several studies have shown no significant risk of congenital malformations, retinopathy, or ototoxicity.33 and 34 Taken all together, the risk of hydroxychloroquine-related side-effects seems negligible when exposure is <12 months, making hydroxychloroquine a suitably low-risk drug to trial in pregnancy. Its use during pregnancy is now recommended in the European League Against Rheumatism guidelines for SLE management.24

Previous studies supported the use of aspirin and LMWH as standard treatment for aPL-related pregnancy morbidity.6, 8 and 14 However, in a recent observational study, aspirin and LMWH treatment failed to reduce the incidence of placenta-mediated adverse pregnancy outcome.8 An excess of placenta-mediated complications of 7.8% was observed when we compared women with APS with control subjects. These results suggest that current treatments are of limited efficacy in the prevention of late pregnancy complication; our data suggest a role for hydroxychloroquine in this setting.

In our cohort, the use of hydroxychloroquine was associated with a higher rate of live births and a lower frequency of overall aPL-related pregnancy complication. In detail, the use of hydroxychloroquine was associated with both a lower incidence of fetal loss and placenta-mediated complications ($P = .05$). Hydroxychloroquine showed beneficial effect on the overall duration of the gestation ($P = .034$), with a marginally statistical benefit on reduction of the rate of preterm births ($P = .06$).

In our study, there were no differences in the rate of abortions before week 10 of gestation in the 2 groups. Previously, no difference in the rate of spontaneous abortion recurrences has been observed in women with APS who were treated with LMWH and low-dose aspirin when compared with control subjects.8 This finding may reflect different underlying mechanisms for early and late pregnancy complications. Because of its preliminary nature, this study was not powered to analyze this aspect specifically.

Recent in vitro studies have shown that the immunomodulatory properties of hydroxychloroquine may confer beneficial effects on pregnancy outcome in patients with aPL, potentially the ability of aPLs to target both the fetal side (invading trophoblast)18 and 35directly and the maternal side (decidua and endometrial endothelial cells)36 of the human placenta and to induce a negative effect on placentation.

We acknowledge some major limitations in this study. First, this was a retrospective study, and these findings should be confirmed in a prospective fashion. Second, the prevalence of SLE is different between group A and B. Furthermore, we observed a higher frequency of previous pregnancy morbidity in the patients who were not treated with hydroxychloroquine, which potentially reflects the higher percentage of primary antiphospholipid syndrome in group B compared with Group A. We are a tertiary referral center for APS, and we treat women with some of the worst obstetric histories. We acknowledge that this might represent a bias when data are analyzed and that caution should be applied in interpreting our preliminary observations. However, the association of a better pregnancy outcome with hydroxychloroquine treatment was confirmed after multivariate analysis, which supports the strength of our findings. Third, in this study we could not assess the effect of other therapies (including steroids and azathioprine) rather than hydroxychloroquine use because treatment was not controlled, but varied according to the clinical manifestations.

In conclusion, the use of hydroxychloroquine during pregnancy seems to be safe and to have a beneficial impact on pregnancy outcome in women with aPL when associated with the conventional treatment.

We are currently planning a prospective randomized controlled trial to confirm or refute these observations (HYdroxychoroquine vs placebo during Pregnancy in women with AnTIphospholipid Antibodies [HYPATIA trial]).

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Table 1.

Clinical characteristics of pregnant women with antiphospholipid antibodies who were treated with or without hydroxychloroquine

Variable	Hydroxychloroquine	%	Without hydroxychloroquine	%	Significance
Patient, n	31		65		
Pregnancies, n	51		119		
Pregnancies per woman, n (range)	1.65 (1-5)		1.83 (1-7)		
Ethnicity, n (%)					
White	17 (54.8)		39 (60)		
Black	6 (19.4)		10 (15.4)		
Other	8 (25.8)		16 (24.6)		
Mean age, y ± SD (range)	32.5 ± 4.6 (21-42)		35.6 ± 5.2 (18-42)		NS
Antiphospholipid antibodies only, n	6	19.4	15	23.1	NS
Primary antiphospholipid syndrome, n	5	16.1	45	69.2	P <.001
Systemic lupus erythematosus + antiphospholipid antibodies, n	11	35.5	0	0.0	P <.001
Systemic lupus erythematosus and antiphospholipid syndrome, n	9	29.0	5	7.7	P =.006
Mean disease duration, y ± SD	5.3 ± 4.1	—	2.7 ± 2.4	—	P = .042
Previous thrombosis, n	10	32.3	19	29.2	NS
Venous	5	16.1	13	20.0	NS
Arterial	5	16.1	7	10.8	NS
Previous pregnancy morbidity, n					
Any	7	22.6	35	53.8	P = .004
Spontaneous abortions before week 10	4	12.9	18	27.7	NS
Fetal Loss beyond week 10	0	0.0	4	6.2	NS
Placenta-mediated complicationa	3	9.7	11	16.9	NS
Antinuclear antibodies, n	23	74.2	13	20.0	P < .001
Anti-extractable nuclear antigens antibodies (anti-Ro/anti– lupus anticoagulant), n	15	48.4	6	9.2	P < .001
Lupus anticoagulant positivity, n	21	67.7	49	75.4	NS
Anticardiolipin antibodies positivity, n	14	45.2	35	53.8	NS
Immunoglobulin G/immunoglobulin M (GPL/MPL)					
Mean ± SDb	68.8 ± 22.1/49.2 ± 8.7		61.3 ± 20.7/47.9 ± 9.1		NS
Median (range)b	72.6 (41-110)/48.9 (40-		69.7 (40-107)/49.1 (40-77)		NS

Variable	Hydroxychloroquine	%	Without hydroxychloroquine	%	Significance
	75)				
Antibeta2-glycoprotein I positivity (GPL/MPL), n	6	19.4	6	9.2	NS
Immunoglobulin G/immunoglobulin M					
Mean ± SDb	35.3 ± 20.7/30.8 ± 18.6		36.3 ± 18.7/29.4 ± 12.6		NS
Median (range)b	22 (15-75)/20 (14-70)		20.5 (15-65)/18 (14-59)		NS
Cardiovascular risk factors, n					
Smoking >5 cigarettes	3	9.7	1	1.5	NS
Diabetes mellitus26	0	0.0	4 (Gestational)	6.2	NS
Hyperlipidemia25	0	0.0	0	0.0	NS
Hypertension24	2	6.5	10	15.4	NS

GPL, IgG **antiphospholipid** units/mL; *MPL*, IgM **antiphospholipid** units/mL; *NS*, not significant.

a Placenta-mediated complication; preeclampsia, abruption placentae, intrauterine growth restriction

b Evaluated in positive tests only.

Table 2.

Pregnancy outcomes of pregnant women with antiphospholipid antibodies who were treated with or without hydroxychloroquine

Variable	Hydroxychloroquine	%	Without hydroxychloroquine	%	Significance
Pregnancies, n	51		119		
Live births, n	34	66.7	60	57.1	*P* = .05
Antiphospholipid antibody–related pregnancy morbidity, n	20	47.1	75	63.0	*P* = .004
Preterm live births <37 weeks, n	2	3.9	16	13.4	*P* = .06
Spontaneous abortions before the week 10, n	16	31.4	46	38.7	NS
Fetal loss beyond the week 10, n	1	2.0	13	10.9	*P* = .05
Placenta mediated complication, n	1	2.0	13	10.9	*P* = .05
Preeclampsia	1	2.0	8	6.7	NS
Abruption placentae	0	0	3	2.5	NS
Intrauterine growth restriction	0	0	2	1.7	NS
Mode of delivery, n					
Vaginal					
Spontaneous	19	37.3	17	14.3	*P* = .011
Induced	3	5.9	9	7.6	NS
Cesarean	10	19.6	23	19.3	NS
Median gestation duration, wk (range)	27.6 (6-40)	—	21.51 (6-40)		*P* = .034
Birthweight, kg (range)[a]	3 (1.3-5)	—	2.3 (1.4-4.1)	—	*P* = .04
Prednisolone,	21	41.2	13	11.0	*P* < .001
mean mg/d	5		5		NS
Azathioprine, n	15	29.4	5	4.2	*P* < .001
Mean mg/d	100		150		NS
Low-dose aspirin, n	100	100	100	100	NS
Low–molecular-weight heparin, n	37	72.5	94	79.0	NS

NS, not significant.

a For viable live infants.