

PREDNISONE AND ASPIRIN IN WOMEN WITH AUTOANTIBODIES AND UNEXPLAINED RECURRENT FETAL LOSS

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ABSTRACT

Background Recurrent fetal loss has been well described in women with antiphospholipid antibodies. Such women also often have other autoantibodies commonly found in patients with systemic lupus erythematosus. Treating them with prednisone and aspirin may reduce the risk of fetal loss.

Methods We screened 773 nonpregnant women who had the unexplained loss of at least two fetuses for antinuclear, anti-DNA, antilymphocyte, and anti-cardiolipin antibodies and for the lupus anticoagulant. Of 385 women with at least one autoantibody, 202 who later became pregnant were randomly assigned in equal numbers to receive either prednisone (0.5 to 0.8 mg per kilogram of body weight per day) and aspirin (100 mg per day) or placebo for the duration of the pregnancy. The women were stratified according to age (18 to 34 years or 35 to 39 years) and the week of gestation at which the previous fetal losses had occurred (≤ 12 or >12 weeks). The primary outcome measure was a successful pregnancy.

Results Live infants were born to 66 women in the treatment group (65 percent) and 57 women in the placebo group (56 percent, $P=0.19$). More infants were born prematurely in the treatment group than in the placebo group (62 percent vs. 12 percent, $P<0.001$). The major side effects of therapy in the mothers were hypertension (treatment group, 13 percent; placebo group, 5 percent; $P=0.05$) and diabetes mellitus (15 percent and 5 percent, $P=0.02$).

Conclusions Treating women who have autoantibodies and recurrent fetal loss with prednisone and aspirin is not effective in promoting live birth, and it increases the risk of prematurity. (N Engl J Med 1997; 337:148-53.)

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THE causes of recurrent fetal loss include anatomical, genetic, and hormonal disorders. However, in approximately 60 percent of women the recurrent fetal loss is unexplained. Recurrent fetal loss is a well-known manifestation of several autoimmune diseases. In the case of systemic lupus erythematosus, there is a strong association with fetal loss that has prompted several investigators to propose an autoimmune pathogenesis for otherwise unexplained recurrent fetal loss.¹⁻⁵ A nonspecific global inhibitor of in vitro coagulation, the lupus anticoagulant, is associated with fetal

wastage in women with systemic lupus erythematosus. This anticoagulant, and numerous other autoantibodies often found in such women, are also found in otherwise normal, healthy women who have recurrent fetal loss.⁶⁻¹³

Treatments for these women have included moderate-to-high doses of prednisone and aspirin,^{6,7,14-16} on the rationale that the women have a subtle autoimmune disorder that is manifested by recurrent fetal loss. None of these studies have definitely shown this potentially toxic therapy to be either effective or ineffective. We studied the efficacy of prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss, with respect to maternal morbidity and fetal survival.

METHODS

We initially evaluated 1080 women from southern Ontario who were referred to our Recurrent Fetal Loss program for this study. We found 773 women who had the unexplained loss of at least two fetuses and thus met the criterion for recurrent fetal loss. Among them, 385 women had at least one repeatedly positive autoantibody test and were deemed eligible for the study when they became pregnant again. Two hundred seventy women agreed to participate in the study. Of these, 202 became pregnant and were randomly assigned to treatment or placebo between February 1988 and November 1994 (Fig. 1). It was established that once pregnant, those eligible for the study would contact the study office immediately.

Selection of Patients

The criteria for inclusion in the study were as follows: an age of 18 to 39 years, at least two consecutive fetal losses before 32 weeks' gestation, and positive results of at least one of the following on at least two of three occasions: activated partial-thromboplastin time test or tests for antinuclear antibodies, anti-DNA antibodies (single- or double-stranded), antilymphocyte IgM, anticardiolipin IgG, or the lupus anticoagulant.

The criteria for exclusion were as follows: a chromosomal or anatomical abnormality or a luteal-phase defect (as determined by

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a timed endometrial biopsy), which are all known causes of recurrent fetal loss; confirmed peptic ulcer disease within the past three years; systemic lupus erythematosus that fulfilled four or more of the criteria of the American College of Rheumatology¹⁷; diabetes mellitus, as evidenced by a repeatedly elevated plasma glucose concentration while fasting, abnormal results of a 100-g oral glucose-tolerance test, or previous gestational diabetes mellitus; sensitivity to aspirin; diastolic blood pressure greater than 90 mm Hg on two or more occasions at least three days apart despite antihypertensive therapy; previously untreated tuberculosis, as determined by an abnormal chest film in the previous year or a positive tuberculin skin test; and previous prednisone therapy.

Women deemed eligible for randomization were asked to provide informed consent and were given a package of written information. The study was approved by the Human Experimentation Committee of the University of Toronto. All the women who gave consent had measurements of serum glucose, electrolytes, immunoglobulins, C3, C4, CH50, creatine kinase, aspartate aminotransferase, and rheumatoid factor; Venereal Disease Research Laboratory tests; tests for lupus erythematosus (LE) cells, anti-DNA antibodies, and antithyroid antibodies; a direct Coombs' test; and chest radiography (or a tuberculin skin test). A collaborating ophthalmologist examined the women for cataracts at base line, mid-way through the pregnancy, and post partum.

Autoantibody Assays

Serum samples were collected on two to three occasions at least 7 to 10 days apart, stored at -20°C, and assayed at the same time in duplicate. If only one of two samples was positive on a given test, a third sample was obtained at least six weeks after the first. Serum levels of anti-DNA single- and double-stranded antibodies (IgG and IgM) and antilymphocyte IgM antibodies were measured with previously described enzyme-linked immunosorbent assays.^{18,19} The results were considered positive if the optical-density readings were more than 2 SD above the mean of serum samples from 504 normal, nonpregnant women randomly selected from the general population. An in-house assay¹⁹ and two commercially available kits (Sanofi-Pasteur and INOVA) were used during the eight-year study period to measure anticardiolipin IgG antibodies. Each method was standardized with serum samples of known anticardiolipin IgG (measured in IgG phospholipid [GPL] values) so that the results of the various assays could be compared. When more than 15 to 22 GPL units were measured, the serum samples were considered positive. Antinuclear antibodies were measured with a HEP-2 cell line; a titer of 1:40 or higher was considered positive.

The lupus anticoagulant was considered present if any of the following were prolonged: the partial-thromboplastin time, the Russell's viper-venom time, the kaolin-cephalin clotting time, or the tissue thromboplastin-inhibition time.

Study Protocol

Women who gave consent were instructed to undergo a pregnancy test as soon as their menstrual periods were delayed or a pregnancy was suspected. Positive tests were confirmed by two quantitative measurements of serum levels of the beta subunit of human chorionic gonadotropin at least 24 hours apart that showed an appropriate increase (a doubling of the value every 48 hours) or by ultrasonography that showed a fetus of appropriate size for its gestational age and with a fetal heartbeat. Before randomization, a second, identical consent form was provided, allowing each woman to reconsider her participation in the study.

The randomization was controlled centrally through the study coordinators' office. The medications were packaged in sealed envelopes, and the randomization code was available only to the persons who packaged them and to the biostatistician, none of whom had any contact with the women in the study. Each woman was assigned the next study number in one of four strata, with a balanced four-block procedure to ensure equal numbers in each group as the study progressed. The women were stratified accord-

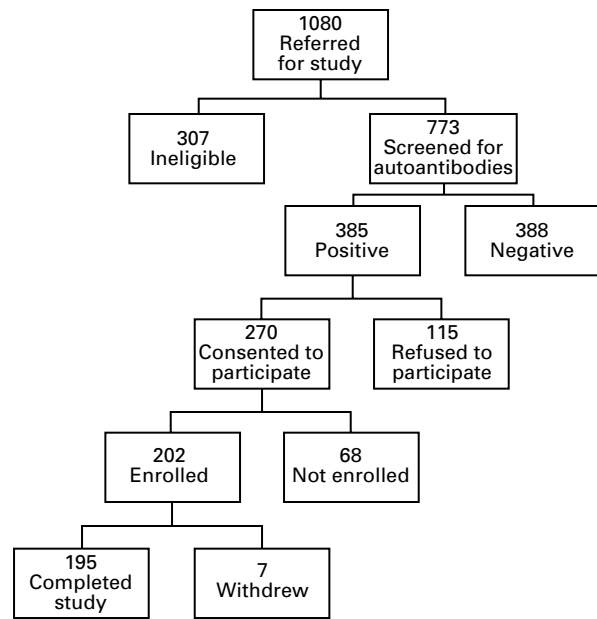


Figure 1. Accrual of Study Subjects with Recurrent Fetal Loss. Women were evaluated and enrolled in the study between 1988 and 1994. The initial screening included 1080 women, 202 of whom were ultimately enrolled.

ing to age (18 to 34 years or 35 to 39 years) and the week of gestation at which their fetal losses had occurred — early (≤12 weeks) or late (13 to 32 weeks). An interim analysis was performed after 80 women had completed 20 weeks' gestation to determine whether the trial should be terminated because of either side effects or a significant difference (P≤0.01) between groups with regard to the primary outcome.

All major medical events and the results of the interim analysis were reported to an external safety-monitoring committee composed of consultant specialists.

Drug Administration

The dose of prednisone (Deltasone, Upjohn, Kalamazoo, Mich.) was 0.8 mg per kilogram of body weight per day for four weeks (maximum, 60 mg), followed by 0.5 mg per kilogram per day (maximum, 40 mg) until delivery or fetal loss. At the time of delivery, the attending obstetrician and the woman were informed of the woman's treatment assignment so that glucocorticoid coverage could be begun, all other treatment stopped as appropriate, and the prednisone therapy tapered (decreased by 5 mg every two weeks post partum).

The dose of aspirin (Astrix slow-release, encapsulated aspirin; Faulding Pharmaceuticals, Salisbury, Australia) was 100 mg per day. Aspirin was given until 36 weeks' gestation or shortly before delivery.

Clinical Monitoring

Data on physical symptoms, side effects, and compliance with medication were collected every month throughout the pregnancy. Obstetrical data were collected each trimester.

Laboratory Monitoring

Complete blood counts and tests for all the autoantibodies and the lupus anticoagulant were performed at approximately 8 and 28 weeks' gestation and at delivery. A 50-g glucose-challenge test

TABLE 1. BASE-LINE CHARACTERISTICS OF THE WOMEN IN THE STUDY GROUPS.

CHARACTERISTIC	TREATMENT (N=101)	PLACEBO (N=101)
Mean (\pm SD) age at randomization — yr	33 \pm 3.8	32 \pm 4.1
Mean (\pm SD) no. of previous fetal losses	3.4 \pm 1.3	3.5 \pm 1.4
	no. of women (%)	
Current smoker	12 (12)	11 (11)
\geq 1 First-trimester loss	97 (96)	96 (95)
\geq 1 Loss at 13–20 wk	24 (24)	25 (25)
\geq 1 Loss at >20 wk	10 (10)	12 (12)
No previous live birth	70 (69)	69 (68)
Previous therapeutic abortion	13 (13)	13 (13)
Previous stillbirth	6 (6)	2 (2)
Previous neonatal death	2 (2)	0
Antinuclear antibodies	37 (37)	46 (46)
Anti-DNA antibodies		
Single-stranded	18 (18)	19 (19)
Double-stranded	13 (13)	19 (19)
Antilymphocyte antibodies	38 (38)	26 (26)
Lupus anticoagulant	38 (38)	36 (36)
Anticardiolipin antibodies	6 (6)	14 (14)

TABLE 2. MAJOR OUTCOMES OF PREGNANCY IN THE STUDY GROUPS, WITH A LOGISTIC-REGRESSION ANALYSIS OF THE EFFECT OF TREATMENT AND OTHER VARIABLES ON OUTCOME.

OUTCOME	TREATMENT (N=101)	PLACEBO (N=101)	P VALUE
	no. (%)		
Live birth	66 (65)	57 (56)	0.19
At term*	25 (38)	50 (88)	<0.001
Before term*	41 (62)	7 (12)	
Fetal loss	35 (35)	44 (44)	
VARIABLE IN REGRESSION ANALYSIS†	PARAMETER ESTIMATE	P VALUE	ODDS RATIO (95% CONFIDENCE INTERVAL)
Treatment vs. placebo	0.38	0.19	1.5 (0.8–2.6)
Older vs. younger maternal age	–0.02	0.94	1.0 (0.5–1.8)
Previous fetal losses (late vs. early)	–0.17	0.58	0.8 (0.5–1.6)

*Percentages shown are based on the total number of live births.

†The stratification of maternal age and the week of gestation at which previous fetal losses occurred is described in the Methods section.

was given at 16, 28, and 32 weeks. If the results of that test were elevated, a 100-g oral glucose-tolerance test was given, and if that result was abnormal (value in the fasting state, >105 mg per deciliter [5.8 mmol per liter]; after one hour, >190 mg per deciliter [10.6 mmol per liter]; after two hours, >165 mg per deciliter [9.2 mmol per liter]; after three hours, >145 mg per deciliter [8.1 mmol per liter]), the woman was referred to an endocrinologist for counseling and treatment.

Evaluation of Efficacy

The primary end point was the survival of the infant for more than one week. The secondary end points included maternal side effects during pregnancy, such as gestational diabetes mellitus, cataracts, epistaxis, hypertension, rash, facial swelling, headaches, hospitalization, and premature birth. For the infants, the end points included the birth weight, Apgar score, and whether there was a need for admission to the neonatal intensive care unit.

Data Collection and Management

At delivery, a form was completed on which information about the labor, delivery, and health of the infant was recorded. Placental disease was evaluated whenever possible. Cranial ultrasonography of the neonates was performed whenever possible, to screen for intraventricular hemorrhage. The laboratory values were measured again six months after fetal loss or delivery.

Statistical Analysis

Two-sample t-tests (two-tailed) were used to test for the equality of the means of continuous variables, and chi-square or Fisher's exact tests were used to test for the equality of proportions in the case of categorical variables. Logistic-regression analysis was used to assess the effect of treatment on the probability of a successful pregnancy, with control for age (35 to 39 years vs. 18 to 34 years) and the week of gestation at which the previous fetal loss had occurred (early or late). The study groups were compared with respect to secondary outcome variables by two-sample t-tests in the case of continuous variables and chi-square or Fisher's exact tests in the case of categorical variables. To assess the safety of treatment with prednisone and aspirin, the number of women who withdrew from the study and the frequency and duration of important adverse events were compared between groups by Fisher's exact test or the chi-square test, depending on the frequency of the events. All the data were entered in a data base (Oracle, Belmont, Calif.) and analyzed with SAS software (SAS Institute, Cary, N.C.).

RESULTS

We enrolled 202 women in the study and subsequently began treating them; there were 101 in each group. Each woman was followed throughout her pregnancy and for at least two years post partum, regardless of the outcome of the pregnancy. Seven women withdrew from the study before delivery (Fig. 1), one because of side effects and the remaining six because they decided not to participate in the study and chose only to continue the follow-up.

The characteristics of the treatment and placebo groups were similar at the time of randomization (Table 1). Forty-four of the 202 women (22 percent) had two fetal losses, and 158 (78 percent) had three or more. Fifty percent of the women originally screened (385 of 773) had at least one autoantibody test that was repeatedly positive (Fig. 1), and 111 of those women (29 percent) had repeatedly positive tests for more than one autoantibody or were posi-

tive for the lupus anticoagulant. The lupus anticoagulant was found in 38 women in the treatment group and 36 in the placebo group; 6 and 14 women, respectively, were positive for anticardiolipin IgG.

Fetal Survival and Other Outcomes of Pregnancy

There were 66 live births (65 percent) in the treatment group and 57 (56 percent) in the placebo group ($P=0.19$) (Table 2). Treatment had no effect after adjustment for maternal age and the week of gestation at which the previous fetal losses occurred (early or late) ($P=0.19$) (Table 2).

Among the women who tested positive for anticardiolipin antibodies or the lupus anticoagulant, 60 percent of those in the treatment group had live births (25 infants were born to 42 mothers), as compared with 52 percent of those in the placebo group (24 infants were born to 46 mothers). Adding an interaction term to the regression analysis (Table 2), in order to relate the presence of anticardiolipin antibody or the lupus anticoagulant to treatment, revealed no significant difference between treatment and placebo in this subgroup ($P=0.81$), indicating that the effect of treatment in the subgroup was not different from that in the group as a whole.

Preterm delivery, premature labor, and premature rupture of the membranes were all significantly more frequent in the treatment group than in the placebo

group ($P<0.001$) (Table 2). The women in the treatment group delivered their babies earlier, with most of the births occurring between 32 and 38 weeks of gestation (Fig. 2). All the deliveries after 30 weeks in both groups were of live infants who survived for more than 1 month. All the spontaneous abortions, stillbirths, and neonatal deaths occurred before 23 weeks of gestation. Despite the higher frequency of prematurity in the treatment group, the birth weight of all the neonates in either group was appropriate for their gestational ages — that is, between the 10th and 90th percentiles in almost all cases (Fig. 3). Birth weight below 2500 g was no more frequent in the treatment group than in the placebo group ($P=0.20$). More infants in the treatment group were admitted to the neonatal intensive care unit ($P<0.001$). There was no significant difference between the groups with respect to the incidence of infections or congenital anomalies (Table 3).

Adverse Effects in the Mothers

Hypertension was more common among the women in the treatment group (13 percent, as compared with 5 percent in the placebo group; $P=0.05$), as was gestational diabetes mellitus (15 percent vs. 5 percent, $P=0.02$). One woman in the treatment group withdrew from the study because of gestational diabetes mellitus. Cataracts developed in two

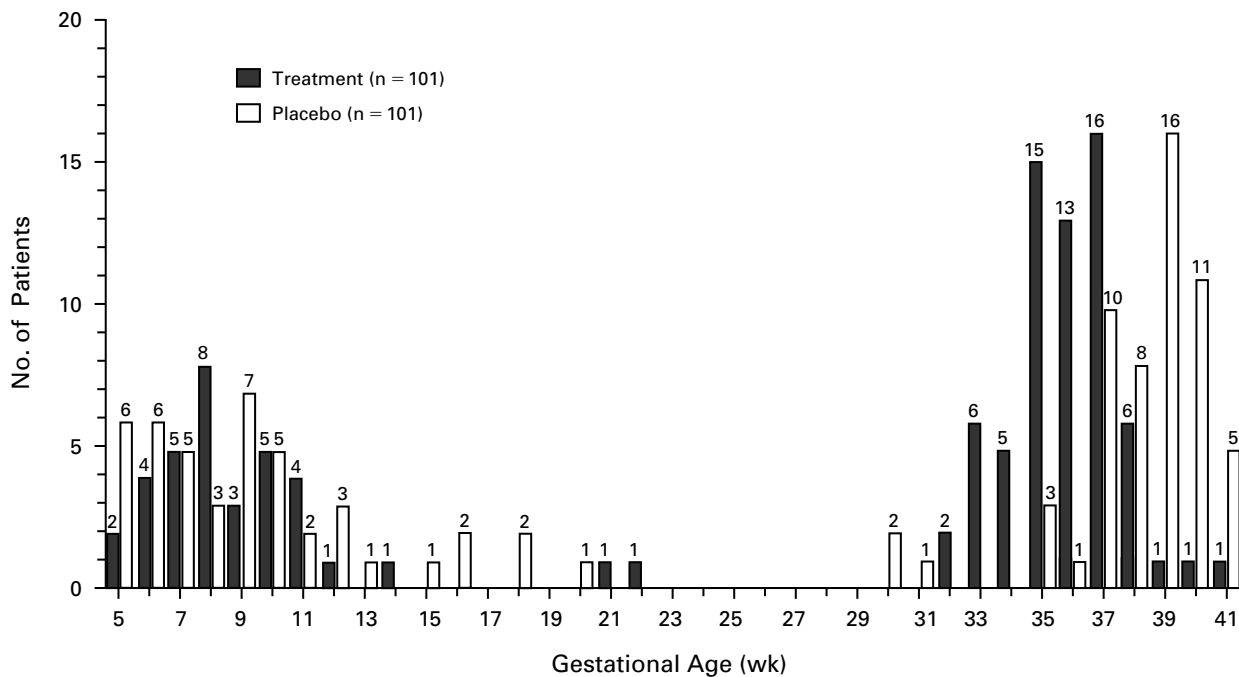


Figure 2. Deliveries in the Treatment and Placebo Groups, According to the Week of Gestation. Early birth was significantly more common in the treatment group than in the placebo group. All infants born at 30 weeks' gestation or later were born alive. The majority of births in the treatment group occurred between 32 and 38 weeks of gestation, whereas in the placebo group the majority of infants were born between 37 and 41 weeks.

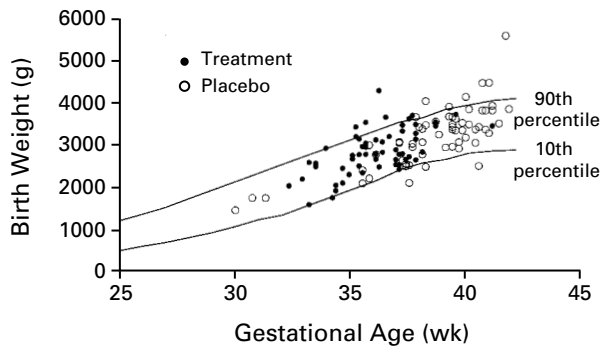


Figure 3. Birth Weights of Infants in the Treatment and Placebo Groups, According to Gestational Age.

Only one infant in the treatment group had a birth weight below the 10th percentile, as compared with three infants in the placebo group. In contrast, eight infants in the treatment group and seven in the placebo group had birth weights above the 90th percentile.

TABLE 3. CHARACTERISTICS AND OUTCOMES OF INFANTS BORN TO MOTHERS IN THE STUDY GROUPS.

VARIABLE*	TREATMENT†	PLACEBO‡	P VALUE
	no./no. studied (%)		
Birth weight <2500 g	17/61 (28)	11/61 (18)	0.20
Male sex	40/64 (62)	28/61 (46)	0.06
Admission to NICU	18/52 (35)	2/54 (4)	<0.001
Days in NICU§	4.4±3.2	6.0±1.4	0.41
Sepsis	1/53 (2)	0/49	1.00
Congenital anomaly	0/56	2/56 (4)	0.50

*NICU denotes neonatal intensive care unit.

†Two pairs of twins are included in this group.

‡Six pairs of twins are included in this group.

§Values shown are means ±SD. Data are based on 18 infants in the treatment group and 2 infants in the placebo group.

women in the treatment group, as compared with none in the placebo group.

DISCUSSION

The presence of circulating autoantibodies and lupus anticoagulant in women with recurrent fetal loss has been well documented.²⁰⁻²⁴ Fifty percent of the women screened for this trial had repeatedly positive tests for at least one of the autoantibodies we studied, but none met the American College of Rheumatology criteria for systemic lupus erythematosus¹⁷ or other connective-tissue diseases. We have continued to follow these women by either clinical evaluation or questionnaires. At this writing, rheumatoid arthritis has developed in one and systemic lupus erythematosus in another.

Among the women with recurrent fetal loss who had autoantibodies, prednisone and aspirin were no more effective than placebo in preventing fetal loss during a subsequent pregnancy. Gestational diabetes mellitus and hypertension were important maternal side effects of the therapy, although neither was as frequent as in previous studies.^{25,26} In addition to these expected side effects, two women in the treatment group acquired cataracts, which have not progressed on follow-up evaluation. These effects of prednisone and aspirin on the mothers would not have been sufficiently severe to warrant withholding the treatment had it proved effective in preventing fetal loss.

There was a significantly higher incidence of preterm delivery (delivery before 37 weeks' gestation) in the treatment group, in accordance with the findings of previous uncontrolled studies.²⁷ Although the frequency of prematurity was high, few infants were born before 34 weeks' gestation, and all the neonates treated in the neonatal intensive care unit were discharged without needing readmission. More important, weight was appropriate for gestational age in every infant. Because no increased rate of prematurity was found in two large, randomized trials of low-dose aspirin for the prevention of preeclampsia, it is unlikely that aspirin was responsible for the preterm deliveries.^{28,29}

Our study would have been strengthened by the inclusion of a group treated with aspirin alone, but that would have required a considerably larger study. Also, if aspirin alone were an effective treatment, the prednisone would have had to have a blunting effect, a possibility we consider unlikely.

Our determination of the effect of treatment on women with high levels of anticardiolipin antibodies, late fetal loss, and other manifestations of the antiphospholipid-antibody syndrome was limited by the size of our sample. Interaction analysis did not show a greater response to treatment in this subgroup. Few women with these characteristics were identified among the 1080 women initially screened for this study.

We conclude that prednisone and aspirin are not effective in preventing fetal loss in women with serum autoantibodies and a history of recurrent fetal loss.

Supported by a grant from the Medical Research Council of Canada.

We are indebted to Faulding Pharmaceuticals, Inc., Salisbury, Australia, and the Upjohn Co., Kalamazoo, Mich., for continued support and for providing medication and placebo; to the members of our safety-monitoring committee, Drs. Adel Fam, Raymond Osborne, and Andrew Willan; to our study ophthalmologist, Dr. Michael Easterbrook, and the study pathologists, Drs. Brendan Mullen, Toby Rose, and Meredith Silver; to the late Dr. Michael Glynn and his staff for performing the coagulation testing; to our independent specialist consultants, Drs. Irving Gottesman, Denise Feig, JoAnne Friefeld, and Douglas Ryan; to Ms. Janet Raboud for designing the data base; and to our many referring physicians for their continued support.

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