A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: a matched-pair study

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Objective: To compare a combination treatment of prednisone, aspirin, folate, and progesterone with no treatment in women with idiopathic recurrent miscarriage (IRM).

Design: Matched-pair study.

Setting: Academic research institution.

Subject(s): Women with a history of IRM, defined as three or more consecutive miscarriages before 20 weeks’ gestation without associated anatomic, cytogenetic, hormonal, and infectious pathologies or antiphospholipid syndrome.

Intervention(s): Eighty of 210 eligible women consented to participate and were treated with prednisone (20 mg/d) and progesterone (20 mg/d) for the first 12 weeks of gestation, aspirin (100 mg/d) for 38 weeks of gestation, and folate (5 mg every second day) throughout their pregnancies. Fifty of 80 women became pregnant; they were compared with 52 women with IRM (matched for age and number of miscarriages), who became pregnant without treatment during the same observation period.

Main Outcome Measure(s): Live birth rate, complications of pregnancy, such as preeclampsia, premature birth, and intrauterine growth restriction, and therapy-related side effects.

Result(s): The overall live birth rates of the treatment and control groups were 77% (40 of 52) and 35% (18 of 52) (P=.04). The rates of first and second trimester miscarriage among the treatment and control groups were 19% (10 of 52) and 0 (0 of 52), and 63% (33 of 52) and 2% (1 of 52), respectively (P=.09 and P=1.0, respectively). The median gestational age at birth and median birth weight did not differ between the groups. We observed two and three cases of premature birth among the treatment and control groups, respectively (P=.3) and no cases of intrauterine growth restriction and Cushing’s disease. Of 80 women who started treatment, one woman had an ectopic pregnancy and one woman terminated her pregnancy due to fetal chromosome aberration (trisomy 18). Three women stopped treatment due to nausea, depression, and tachycardia.

Conclusion(s): A combination treatment of prednisone, aspirin, folate, and progesterone is associated with a higher live birth rate compared with no treatment in women with IRM. (Fertil Steril® 2006;86:145–8. ©2006 by American Society for Reproductive Medicine.)

Key Words: Idiopathic recurrent miscarriage, treatment, prednisone, aspirin, folate, progesterone

Recurrent miscarriage is defined as three or more consecutive pregnancy losses with the same partner before 20 weeks’ gestation (1). After a standard diagnostic workup, including hysteroscopy, paternal and maternal karyotype, cervical cultures for chlamydia, ureaplasma, and mycoplasma, a comprehensive hormonal status, and evaluation of antiphospholipid syndrome with IgM and IgG anticardiolipin antibody assessment and lupus anticoagulant testing, 40% to 60% of women are found to have none of these pathologies (i.e., idiopathic recurrent miscarriage [IRM]).

Various treatment strategies have been tested in women with IRM, among them corticosteroids, aspirin, heparin, and leucocyte immunization. A series of uncontrolled prospective and retrospective studies describe live birth rates of up to 75% after a therapy with cortisone with or without aspirin (2–6). In a large retrospective study, Réznikoff-Etievant et al. used a combination treatment of high-dose prednisone (20 mg/d) for the first 12 weeks of gestation and aspirin (100 mg/d) in 277 women with IRM and achieved a live birth rate of 90% (7).
Others, however, found no improvement in live birth rates using low-dose corticosteroids throughout pregnancy. For example, Laskin et al. compared prednisone (at a dosage of 0.5–0.8 mg/kg) and aspirin (100 mg/d) with a placebo in 202 women who had at least two miscarriages and antinuclear, anticardiolipin, anti-DNA, or antilymphocyte autoantibodies (8). There was no difference with respect to live birth rates.

Of note, women in the treatment group had a higher rate of premature births, pregnancy-induced hypertension, and gestational diabetes. In addition, a systematic review of five controlled studies on prednisone and aspirin in women with IRM found no decrease in miscarriage rates (9).

Prospective randomized trials have been used to establish the efficacy of aspirin, low-molecular-weight heparin, and a combination of both in women with IRM with or without concomitant antiphospholipid syndrome (10). The results of these trials demonstrate that a combination of low-dose aspirin between 50 mg and 100 mg and low-molecular-weight heparin is superior to either aspirin or low-molecular-weight heparin in women who have a history of IRM with the antiphospholipid syndrome. Whether women with IRM without antiphospholipid syndrome derive benefits from low-dose aspirin therapy has not been evaluated in randomized trials.

Up to 20% of women with IRM have been noted to display elevated serum levels of homocysteine (11). In addition, polymorphisms associated with an impaired folate metabolism (e.g., methyltetrahydrofolate reductase C677T) are overrepresented among women with IRM (12). Thus, there is a biologic rationale for therapeutic doses of folate in women with IRM.

Supplementation of progesterone in the first trimester of pregnancy has been used to improve pregnancy outcome in women with IRM. In two meta-analyses of randomized trials, Goldstein et al. and Daya found that progesterone supplementation significantly improved pregnancy outcome in women with recurrent miscarriages (13, 14).

All these data demonstrate that prednisone, aspirin, and progesterone have—at least in some trials—efficacy in treating women with IRM. Combinations of these treatment strategies have not been evaluated in clinical trials. Thus, it is unknown whether combining all these treatments results in a feasible strategy to improve live birth rates of affected women. In addition, it is unknown whether combining different treatments is associated with an unacceptably high rate of side effects.

In a case-control study, we compared clinical outcomes and side effects in women treated with prednisone, aspirin, folate, and progesterone and in women with no treatment. We hypothesized that women with the combination treatment would have a higher live birth rate compared with women with no treatment.

MATERIALS AND METHODS

Patients

A diagnosis of IRM was based on a documented history of at least three spontaneous, consecutive miscarriages before 15 weeks’ gestation with the same partner; this was consistent with the American College of Obstetricians and Gynecologists definition (1). A total of 210 consecutive women who visited our outpatient clinic for recurrent miscarriages between March 2000 and February 2005 were included. All women underwent a standard diagnostic workup to rule out the presence of antiphospholipid syndrome or anatomic, cytogenetic, hormonal, or infectious pathologies.

Diagnostic procedures included hysteroscopy; paternal and maternal karyotype; cervical cultures for chlamydia, ureaplasma, and mycoplasma; a comprehensive hormonal status, and evaluation of antiphospholipid syndrome with IgM and IgG anticardiolipin antibody assessment and lupus anticoagulant testing. Approval from the Institutional Review Board at the Medical University of Vienna was obtained.

Treatment

All women with IRM were asked to participate in a prospective matched-pair study to evaluate a combination treatment consisting of prednisone (20 mg/d) and progesterone (20 mg/d) for the first 12 weeks of gestation, aspirin (100 mg/d) for 38 weeks of gestation, and folate (5 mg) every second day throughout their pregnancies. All treatments were given orally.

Women who consented to participation began the treatment before conception to ensure pharmacologic coverage throughout the pregnancy, independent of the time of diagnosis of pregnancy. A total of 80 women gave informed consent and started the treatment; 52 of these women subsequently became pregnant; 130 women did not participate in the study, 67 of which became pregnant using no other treatment than a folate substitution of 0.4 mg/d for the first 15 weeks of gestation for fetal neuroprotection, as generally recommended for pregnant women in Austria. Of those women, 52 were used as controls after matching for age and number of miscarriages. Controls were matched consecutively starting with the earliest inclusion date. The diagnosis of pregnancy was established by ultrasound. No systematic effort was made to detect biochemical pregnancies.

Statistical Analysis

Variables of interest were described by median and range and mean and standard deviation in case of skewed and normal distributions, respectively. Differences between categorical variables were compared by χ2 test. Differences between paired continuous variables were assessed by paired t test after checking for deviations of normality of distribution according to Shapiro and Wilk.
RESULTS

Patient characteristics are given in Table 1. No significant difference was found in pregnancy rates between women who were treated with the combination treatment and those who were not treated during the study period (52 of 80 [65%] vs. 74 of 130 [57%]; \( P = 1.0 \)). Fifty-two of 80 women (65%) became pregnant using the combination treatment and were assigned to the treatment group. The 52 women who became pregnant without treatment during the same observation period were assigned to the control group after matching for age and number of miscarriages.

Three of 80 women (4%) stopped treatment due to nausea, depression, and tachycardia. The overall live birth rates of the treatment and control groups were 77% (40 of 52) and 35% (18 of 52), respectively (\( P = .04 \)). The rates of first and second trimester miscarriage were 19% (10 of 52) and 0 (0 of 52) among the treatment group and 63% (33 of 52) and 2% (1 of 52) among the control group, respectively (\( P = .09 \) and \( P = 1.0 \), respectively).

Among the treatment and control groups, two and three women, respectively, gave birth prematurely (2 of 52; 4% vs. 3 of 52; 6%; \( P = 0.3 \)). Among the treatment group, premature birth occurred in the 27th and 24th weeks of gestation due to severe preeclampsia and cervical insufficiency, respectively. Among the treatment group, Cushing’s disease and intrauterine growth restriction were not observed. Among the treatment group, the median gestational age at birth was 38 weeks (range 24–41 weeks), and the median birth weight was 3,110 g (range 625–4,120 g). This was not significantly different from the control group, with a median gestational age at birth of 37 weeks (range 29–40 weeks) and a median birth weight of 2,955 g (range 1250–4260 g). One woman in the treatment group had an ectopic pregnancy, and for one woman in the treatment group, pregnancy was terminated due to fetal chromosome aberration (i.e., trisomy 18).

DISCUSSION

This study demonstrates that a combination treatment consisting of prednisone, aspirin, progesterone, and folate results in a higher live birth rate than no treatment in women with IRM. Women who were treated with this combination had a 42% higher live birth rate than controls. In addition, we did not note a higher rate of preterm birth or intrauterine growth restriction among the treatment group. Our results are in accordance with previously reported data by Réznikoff-Etievant et al. (7) and others suggesting that prednisone treatment limited to the first trimester may be effective in the treatment of IRM, while not being associated with an increased rate of side effects, such as preterm birth or intrauterine growth restriction.

Others have reported no effect of corticosteroid treatment in women with recurrent miscarriages and IRM (8, 9). The difference between these studies and the data obtained by Réznikoff-Etievant et al. and our group might be due to both the dosage and the duration of corticosteroid use. Studies that were not able to assess a positive effect of corticosteroid treatment used low-dose treatment during the whole duration of pregnancy.

In contrast, a high-dose treatment covering the first trimester might deliver antiinflammatory protection during the most sensitive period. In addition, the treatment scheme used in our study aimed at covering the full length of early pregnancy by starting the treatment before pregnancy, whereas others started treatment after establishing a diagnosis of pregnancy (8, 9). Similar to folate neuroprotection, this strategy might severely limit the protective effect of corticosteroids.

The results of our study must be interpreted with caution. First, the number of women included in the study is low and does not allow for ruling out small differences in unwanted side effects. Thus, although a positive effect of this combination therapy has been demonstrated within this particular patient sample, the safety of this treatment cannot be estab-

### Table 1

Characteristics of women with IRM undergoing combination treatment (treatment group) and no treatment (control group).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment group</th>
<th>Control group</th>
<th>( P ) value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>30.1 (28–35)</td>
<td>31.5 (23–41)</td>
<td>.3</td>
</tr>
<tr>
<td>No. of miscarriages</td>
<td>3.1 (3–5)</td>
<td>3.8 (3–6)</td>
<td>.4</td>
</tr>
<tr>
<td>No. of livebirths</td>
<td>0.5 (0–2)</td>
<td>0.3 (0–3)</td>
<td>.9</td>
</tr>
<tr>
<td>Primary aborters</td>
<td>64%</td>
<td>70%</td>
<td>.5</td>
</tr>
<tr>
<td>Secondary aborters</td>
<td>36%</td>
<td>30%</td>
<td>.5</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,110 (625–4120)</td>
<td>2,955 (1250–4260)</td>
<td>.2</td>
</tr>
<tr>
<td>Weeks of gestation</td>
<td>38 (24–41)</td>
<td>37 (29–40)</td>
<td>.6</td>
</tr>
</tbody>
</table>

Note: Values are median (range).
<sup>a</sup> Mann-Whitney \( U \) test; \( \chi^2 \) test (primary vs. secondary aborters).
lished by this small study. The safety of a high-dose, low-duration prednisone treatment, such as the one tested in this study, has to be established in a larger series.

It is a further limitation of this study that women were compared in a matched-pair design. Possible selection bias in separating treatment- and control-group patients might have been caused by this open study design. We tried to minimize any bias by using matched pairs of women with IRM. However, women who agreed to use the treatment might still be significantly different from those who refused to take the medication. In addition, we have not karyotyped the aborted pregnancy tissue and, therefore, are not able to differentiate between euploid and aneuploid miscarriages. It could be speculated that the efficacy of the treatment investigated in this study would be greater if women with aneuploid miscarriages are excluded from analysis.

Our data indicate that a combination treatment consisting of high-dose, low-duration prednisone and aspirin, progesterone, and folate might be an effective treatment for women with IRM. The data presented constitute level II evidence, and prospective-randomized trials are encouraged to establish this treatment scheme.

REFERENCES


