The Role of Combination Treatment of Aspirin and Prednisone in Women with Idiopathic Recurrent Miscarriage

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Abstract

Objective: To investigate whether the combination treatment of prednisone during the first trimester of pregnancy plus low dose aspirin all through pregnancy is capable of reducing the risk of miscarriage and improving live birth rates in patients with idiopathic recurrent miscarriage.

Material and Methods: 144 Patients were enrolled in the trial, attending outpatient clinics of Kasr El-Aini, Mahmoud Hospital and Misr International Hospital during the period from February 2008 to January 2011. 78 patients gave informed consent and started treatment, 66 patients refused and comprised the control group. Treatment was consisting of prednisone 20mg/d for the first trimester and tapered gradually plus aspirin 81mg for 38 weeks gestation. Treatment started preconceptionally.

Results: The demographic variables of women under trial, did not differ with respect to age, BMI and No. of previous abortions. live birth rates for the treated women and the control were 78.2%, 50.0% respectively. Women who were treated had a 28.2% higher live birth rate than control.

Conclusion: A combination treatment of prednisone and aspirin results in higher live birth rates compared with no treatment in women with idiopathic recurrent miscarriage.

Key Words: Idiopathic recurrent miscarriage – Aspirin – Prednisone.

Introduction

RECURRENT miscarriage (RM), defined as three or more consecutive pregnancy losses prior to 20 weeks. It is a stressful condition for both patients and clinicians alike [1].

The American Society for Reproductive Medicine defines Recurrent pregnancy loss (RPL) as two or more failed pregnancies (documented by ultrasound or histopathological examination) and suggests some assessment after each loss with a thorough evaluation after three or more losses [2,3].

It is one of the most common complications of pregnancy occurring in about 1%-3% of couples [4-7].

Even after a thorough evaluation: A standard diagnostic workup, including hysteroscopy, karyotyping, cervical cultures, comprehensive hormonal status and evaluation of antiphospholipid antibody syndrome, the potential cause remains unexplained in about one third to one half of the cases [8]. Which means that 40%-60% of women are found to have none of these pathologies. i.e idiopathic recurrent miscarriage (IRM). Recurrent miscarriage causes significant psychosocial morbidity, and for many couples the label of ‘unexplained’ is unacceptable.

Various treatment strategies have been tested in women with idiopathic recurrent miscarriage, among them is aspirin, corticosteroids, progesterone, heparin, leucocyte immunization and anti tumour necrosis factor.

Several studies describe live birth rates of up to 75% after a therapy with cortisone with or without aspirin [9-14].

In 1999 Reznikoff-Etievant, et al. [15] conducted a large study, in using a combination treatment of high dose of prednisone (20mg/d) for the first trimester and aspirin (100mg/d) in 277 women with idiopathic recurrent miscarriage and achieved a live birth rate of 90%.

On the other hand many authors found no improvement in live birth rates using low-dose prednisone throughout pregnancy as Laskin, et al. 1997 [16] who compared prednisone (at a dosage of 0.5-0.8mg/kg) and aspirin (100mg/d) with placebo in 202 women who had at least two miscarriage and autoantibodies, there was no difference with respect to live birth rates.
The aim of this study is to determine the effect of a combination treatment of high dose-low duration prednisone plus low dose aspirin in women with idiopathic recurrent miscarriage as a simple, safe and cheap combination and comparing clinical outcomes and side effects in women treated and others refused.

**Material and Methods**

This was a prospective non randomized controlled trial to determine the efficacy of prednisone and aspirin in patients with idiopathic recurrent miscarriage (IRM).

One hundred forty four Patients were enrolled in the study attending outpatient clinics of Kasr El-Aini, Mahmoud Hospital and Misr International Hospital during the period from February 2008 to January 2011. Institutional review board approval was attained before beginning of the trial.

All women underwent a standard diagnostic workup to rule out the presence of antiphospholipid syndrome or anatomic, cytogenic, hormonal, or infectious pathologies.

Diagnostic procedures included hysteroscopy; paternal and maternal karyotype; cervical cultures for Chlamydia, ureaplasma, and mycoplasma; comprehensive hormonal status and evaluation of antiphospholipid antibody syndrome with lupus anticoagulant testing and antiphospholip antibody assessment (IgG and IgM).

**Inclusion criteria:**

Age between 18-40 years old-3 or more consecutive miscarriages with no cause found (idiopathic).

**Exclusion criteria:**

- Known cause for recurrent miscarriage: Antiphospholipid syndrome (positive antiphospholipid antibody or lupus anticoagulant on 2 separate occasion at least 6 weeks apart), thrombophilia (factor V Leiden mutation, APCR resistance, protein C or S deficiency, prothrombin G20210A mutation, antithrombin III deficiency), abnormal thyroid function tests, parental balanced translocation or uterine anomaly.
- Contraindications to steroid or aspirin therapy: Hypertension, diabetes, peptic ulcer or obesity with BMI >35.

**Treatment:**

All women were asked to participate in the prospective study to evaluate a combination treatment consisting of prednisone (hostacortin, Hoechst) 20mg/d for the first trimester and tapered gradually and (aspirin, Bayer) 81mg for 38 weeks gestation. Treatment started preconceptionally at day 21 from the cycle to ensure pharmacological coverage, independent of the time of diagnosis of pregnancy.

Women were counseled on the use of prednisone and aspirin during pregnancy and the risks involved.

Seventy eight patients gave informed consent and started treatment. 66 patients comprised the control group who discontinued treatment at the time of conception or during pregnancy, it was mainly due to gastrointestinal distress or fear of its teratogenicity.

Women 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 beta subunit of human chorionic gonadotropin or by ultrasonography that showed a fetus of appropriate size for its gestational age and with a fetal heartbeat.

All women were advised to take folic acid (400 µg daily), starting before conception and continuing until 12 weeks of gestation, as prophylaxis for neural-tube defects.

Women received standard care provided by their own obstetrician throughout pregnancy.

**Statistical analysis:**

Data were statistically described in terms of mean ± standard deviation (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

Seventy eight women continued on the treatment as scheduled while 66 women refused or discontinued treatment. (control group).
Table (1) describes the demographic variables of women under trial, which did not differ with respect to age, BMI and no. of previous abortions.

Table (2) showed among 78 women received treatment 78.2% (61) had live birth rate while in control group among 66 women 50% (33) only had live birth rate, \( p \) value: <0.001.

There were no maternal complications except one patient in the treatment group had mild vaginal bleeding at 25 weeks due to partial abruption, bleeding subsided despite continuation of treatment. No major complications at delivery. Gestational age at delivery did not differ from the treatment and control groups which was 37.98±0.8, 38.04±0.8 weeks respectively, birth weight at delivery was larger in the treatment group than control group which was 3.22±1.2 versus 2.79±0.19Kg, \( p \) value was 0.005.

As regards neonatal congenital anomalies only one case in the treatment group which was neck hemangioma.

**Table (1): Demographic details of the patients.**

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=78)</th>
<th>Control group (n=66)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>23.84±3.11</td>
<td>22.84±3.28</td>
<td>0.063</td>
</tr>
<tr>
<td>BMI (Kg/m(^2))</td>
<td>25.3±3.2</td>
<td>26.2±2.7</td>
<td>0.073</td>
</tr>
<tr>
<td>No. of previous miscarriage</td>
<td>3.4±0.56</td>
<td>3.58±0.66</td>
<td>0.079</td>
</tr>
</tbody>
</table>

**Table (2): Comparison of aspirin plus prednisone versus no treatment.**

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=78)</th>
<th>Control group (n=66)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of live births</td>
<td>61 (78.2%)</td>
<td>33 (50.0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gestational age (weeks) at delivery</td>
<td>37.98±0.8</td>
<td>38.04±0.8</td>
<td>0.655</td>
</tr>
<tr>
<td>Mean birth weight (Kg)</td>
<td>3.22±1.2</td>
<td>2.79±0.19</td>
<td>0.005*</td>
</tr>
<tr>
<td>Major complications at delivery</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies at birth</td>
<td>Neck hemangioma</td>
<td>None</td>
<td></td>
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</tbody>
</table>

*: \( p \) value significant.

**Discussion**

Recurrent miscarriage is a significant psycho-social frustrating problem, for both the patient and the clinician.

After thorough evaluation, 40%-60% of women are found to have no pathology, for many couples the label of ‘unexplained’ is unacceptable.

This study demonstrates that combination treatment of prednisone and aspirin result in higher live birth rates than no treatment in women with idiopathic recurrent miscarriage. Women who were treated had a 28.2% higher live birth rate than the control group, the results were in accordance with previously reported data by Reznikoff-Etievant, et al. (1999) [15].

Others reported no effect of corticosteroid treatment in women with recurrent miscarriage [16].

Empson M., 2002 [17] did a systematic review of five controlled studies on prednisone and aspirin in women with idiopathic recurrent miscarriage found no decrease in miscarriage rate.

The combination treatment of aspirin and prednisone was chosen because it has an anti-inflammatory effect during the most sensitive period of pregnancy and also has been recommended in the literature for prevention of abortion [18,19]. In addition the treatment scheme used aimed at covering the full length of early pregnancy by starting the treatment before pregnancy, whereas others started treatment after establishing the diagnosis of pregnancy or even after, when fetal heart beat is positive [16,17].

The results of the study should be interpreted with caution as the number of women in the trial is low and does not allow ruling out the safety of this combination treatment, especially the safety of the high dose-low duration prednisone treatment.

Further more I tried to limit any bias in choosing patients who will receive the treatment, however women who agreed to use the treatment might be different from those who refused to take the treatment.

The data of the study indicate that combination treatment of low dose aspirin and high dose low-
duration prednisone might be an effective, simple and cheap treatment with least side effects for women with idiopathic recurrent miscarriage.

Prospective randomized controlled trials in large number of patients are encouraged to establish the efficiency of this combination treatment.

References