Periconceptual prednisolone therapy for the management of recurrent pregnancy loss

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Abstract:

Background: Recurrent miscarriage has been investigated for a long time with different types of therapeutic trials for those with unknown cause. Prednisolone as an immune modulator agent can have beneficial effect in improving pregnancy outcome in those patients. Objective: The aim of this study was to investigate the role prednisolone in preventing miscarriage in patients with recurrent pregnancy loss. Methods: Sixty two patients enrolled in this study, all of them have recurrent miscarriage, after investigations and exclusion of those with antiphospholipid syndrome, medical disease, endocrine disorder and uterine pathology. Patients divided randomly and equally into two groups. Study group give prednisolone therapy 5 mg orally for two months prior to conception & continue during pregnancy till 13 weeks of gestation, while the second group received folic acid 5mg orally before conception and continue till the end of first trimester. Patients were followed up throughout pregnancy till delivery. Results: There was significant association between pregnancy outcome and type of treatment majority (90.3%, n=28) of patients using prednisolone continue treatment, while only (38.7%, n=12) of control group continue their pregnancy. (X²=18.03, P=<0.001). Conclusion: Periconseptual prednisolone therapy can have dramatic improvement in the outcome of pregnancy in those who suffer from recurrent miscarriage

Keywords: Recurrent miscarriage, Prednisolone, Therapy, Pregnancy loss.

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Introduction
Recurrent pregnancy loss, also termed recurrent miscarriage defined as three or more consecutive pregnancy losses before 20th week of pregnancy. One percent of couples are affected and it cause high psychological upset for both couple and their health care provider.\(^1\) The risk of miscarriage increase with increasing number of miscarriages.\(^2\) A lot of studies and researches has been made looking for the underlying causes of this condition and any possible intervention that could help.\(^3\) Although a number of underlying conditions have been recognized as a cause for recurrent miscarriage including antiphospholipid syndrome, antithyroid antibodies, uterine anomalies such as uterine septum and submucous fibroid, still large proportion of these miscarriages remain unexplained.\(^4\) Immunity plays an important role in accepting or rejecting the embryo by the uterine lining, as the embryo has different genes to that of the mother, so immune modulation is a prerequisite for implantation to occur. Natural killer cells which are present in both peripheral blood and the endometrium have a significant role, it is still unclear whether the increase in their number or function that can lead to recurrent miscarriage.\(^4-6\) The immune system of the mother and fetal antigens interact in normal pregnancy, and alloimmune rejection result if this immune adaptation fail resulting in pregnancy loss.\(^7\) For that reason, there is correlating increment in tolerance-promoting action of T regulatory cell (Treg) and a proportional reduction in the pro-inflammatory Th17-cell action. Because of paternal genetic component, trophoblast behave like an allogenic tissue in normal pregnancy thus enhancing an immunomodulatory influence, restrain abortigenic maternal B and T cell reactions resulting in fetal adaptability. Progesterone-induced blocking factor (PIBF) prohibits inflammatory and thrombotic responses towards the fetus. PIBF, a protein produced by activated lymphocytes by the effect of progesterone, enhance the shift toward Th-2 cytokines.\(^8\) Therefore, during normal pregnancy, Th-2 type cytokine reaction mediated blocking antibodies mask fetal trophoblast antigens thus forbidding them from immunological discrimination by maternal Th-1 cell-mediated cytotoxic activity. Other possible ways by which PIBF act to prohibit fetal rejection. It maximizes asymmetric non-cytotoxic blocking antibodies\(^9\) and impede natural killer (NK) cell degranulation.\(^10\) Prednisolone has inhibitory effect on natural killer cells with no cytotoxicity on lymphocytes therefore it has an immune modulatory effect and might have a beneficial effect in modifying the immunity at the level of endometrium thus improve implantation process and pregnancy outcome.\(^11\) Several trials were made to improve pregnancy outcome in women with recurrent miscarriage including the use of prednisolone alone or with other medications in early pregnancy. Since most of the dose of prednisolone taken by the mother will be metabolized in the placenta by the enzyme 11beta-hydroxysteroid dehydrogenase 2 (11beta-HSD2), very small concentration of the drug will reach the fetus and no harmful effect was observed except for the very small increment in the incidence of cleft lip & palate in fetuses exposed to prednisolone in utero from 1/1000 to 2/1000. Hence prednisolone is the safest corticosteroid that can be used in pregnancy. However, prednisolone in high doses can cause maternal complications including impaired glucose tolerance and osteoporosis if used for long period, in addition to increasing the risk of premature rupture of membranes.\(^13\) Therefore, using the minimal effective dose will be the target to avoid its side effects, some researchers used 25 mg daily dose, others use 20 mg daily dose.\(^14\) The aim of this study was to test the effectiveness of using minimal dose of prednisolone (5 mg) in preventing miscarriage in women with recurrent early pregnancy loss.

**Methods**

**Study design and patients**
This case control study included sixty two patients who complaining of recurrent first trimester miscarriage that is of unknown etiology (idiopathic), exclusion criteria involve patients with chronic disease, acquired or inherited thrombophilia, antithyroid peroxidase positive, and patients with genital tract pathology congenital or acquired. Patients were divided into two groups, thirty one patients received prednisolone therapy (study group) and the other thirty one patients received folic acid only (control group). The study was explained to the participants and their consent was obtained, all investigations needed to exclude underlying pathology were performed and after obtaining the negative results, prednisolone was administered to study group in a dose of 5 mg daily for two months prior to conception then allow the patients for unprotected intercourse to get pregnancy while on prednisolone. Two of those patients have difficulty to conceive and no pregnancy achieved for four months, ovulation induction was given to them to avoid keeping them for long period on steroid therapy to avoid its complications. After achieving pregnancy, patients continued on prednisolone therapy for the whole first trimester (until 13 weeks of pregnancy) then prednisolone was stopped and continue patient follow up for the whole period of pregnancy. Control group received folic acid in the first trimester and followed up.

Data Analysis

Analysis of data was performed using SPSS version 21 (SPSS, IBM Company, Chicago, USA). Frequencies and percentages used for expressing categorical variables. Means ± SD used for expressing Continuous variables. The difference in means between two groups was analysed using Independent samples t-test. Categorical variables were analysed using Fisher’s-exact test & Pearson chi-square. P value of ≤ 0.05 regarded as significant.

Results

Table 1 shows mean differences of age (years) according to type of treatment including (prednisolone and placebo). Differences between means of age between the two groups were not found to be significant.

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Group</th>
<th>N</th>
<th>Mean ± SD</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Study</td>
<td>31</td>
<td>29.16 ± 6.48</td>
<td>0.404</td>
<td>0.688</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>31</td>
<td>28.51 ± 6.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 shows difference in parity & number of miscarriages of women in study & control groups. There was no significant difference of these variables between the two groups.
Table 2 on between type of treatment and study variables

<table>
<thead>
<tr>
<th>Study variables</th>
<th>Type of treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisolone</td>
<td>Control group</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P0</td>
<td>9 (29.0)</td>
<td>9 (29.0)</td>
</tr>
<tr>
<td>P1</td>
<td>6 (19.4)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>P2</td>
<td>11 (35.5)</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td>P3 or more</td>
<td>5 (16.1)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (100.0)</td>
<td>31 (100.0)</td>
</tr>
<tr>
<td>History of miscarriage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice</td>
<td>11 (35.5)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Three times</td>
<td>11 (35.5)</td>
<td>15 (48.4)</td>
</tr>
<tr>
<td>Four times</td>
<td>5 (16.1)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Fifth times or more</td>
<td>4 (12.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (100.0)</td>
<td>31 (100.0)</td>
</tr>
</tbody>
</table>

*P value ≤ 0.05 was significant. Fisher-exact test.

The Association between Pregnancy Outcome and Type of Treatment

Figure 1 shows the association between pregnancy outcome including (miscarriage or continue pregnancy) and Type of Treatment including (prednisolone and placebo). There was significant association between pregnancy outcome and type of treatment majority (90.3%, n=28) of patients using prednisolone continue treatment, while only (38.7%, n=12) of control group continue their pregnancy. (X²=18.03, P<0.001*).
Discussion

Recurrent miscarriage can be caused by many etiological factors. However, no identifiable cause could be found in about 40–50% of patients with recurrent miscarriage. Maternal immune response need to shift from (proinflammatory) Th1 to (anti-inflammatory) Th2 phenotypes is required for a pregnancy to continue as shown by several studies. Unexplained recurrent miscarriage may be due to immunologic factors. In the last few years, comprehensive studied highlighted the participation of the many proteins and immune cells which are necessary in every phase of natural pregnancy. A variety of immune remedies have been tried with inconstant clinical evidence in women with recurrent miscarriage with different efficacy. However, these types of therapy need further evaluation regarding their mode of action, any possible adverse effect and indications for their use. Controlled studies using placebo drugs are required to test different types of medications in treating patients with idiopathic recurrent pregnancy loss (15). Patients were randomly selected for the study group taking prednisolone periconceptually or control group who were given folic acid only and followed up. No statistically significant difference was found between the two groups in terms of age, parity and number of previous miscarriages. Both groups were followed up for the end of pregnancy and as figure 1 showed 90.3% of patients taking prednisolone achieved successful pregnancy and only 9.3% miscarried, on the other hand 38.7% of patients who were given folic acid with follow up had successful pregnancy while 61.3% of the had miscarriage. The difference between the two groups was statistically significant which mean that prednisolone therapy in preiconceptual period can improve pregnancy outcome which is thought to be due to its anti-inflammatory action that enhance endometrial receptivity to the implanting embryo and thus improve placentation and subsequent development of the fetal maternal interaction that has its effect throughout pregnancy to its end at term. A study done by Tempfer CB et al who used combination of prednisolone, aspirin & folic acid at the first trimester for patients with idiopathic recurrent miscarriage found statistically increased live birth rate when compared with the control group who were patients conceived at the same period with no treatment (14). Prednisolone may have a role in reducing raised NK cells within the endometrium in patients with recurrent pregnancy loss (16). However, Laskin et al. demonstrated in a placebo-controlled randomized study that giving steroids to reduce autoantibody titers will not promote the live birth rate. Moreover, it may increase the incidence of preterm delivery (17). In a study by Reznikoff-Etievant et al. (18), low-dose aspirin and prednisolone were significantly beneficial in 214 women complaining of recurrent miscarriage compared with 63 patients receiving aspirin only. This may be explained by reduced T regulatory cell activity and increased prothrombotic mechanisms were ameliorated in the prednisone and aspirin group, whereas only the prothrombotic hyperactivity was decreased in the aspirin only group. A Cochrane review concluded that administering of prednisolone with aspirin to patients with recurrent pregnancy loss due to antiphospholipid antibody syndrome (APS) associated with significant complications of gestational diabetes & prematurity, and without improving pregnancy outcome (19). It has been proposed that early and preconception steroid treatment that is limited to first trimester in patients with non-APS autoimmunity might be effective in improving the outcome. However, still we have to be cautious about complications of glucocorticoids during pregnancy that include increased incidence of premature labour secondary to membranes rupture and the emergence of gestational diabetes and preeclampsia (17). The role of prednisolone treatment in women with recurrent pregnancy loss may be explained by altered angiogenic growth factor expression within the endometrium and impaired maturation of blood vessels (20).
Conclusion

The use of prednisolone therapy can be effective in reducing the incidence of miscarriage in women with unexplained recurrent pregnancy loss. Double blind studies with larger sample size of patients with RM are needed for enforcing the results of this study.

Conflicts of interest: None of the authors have any conflicts of interest relevant to this research subject.

Ethical clearance: The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki. The study protocol and subject information were reviewed and approved by a local Ethics Committee.

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References


