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Combined Low Dose Aspirin and Steroids vs Aspirin Only in Management of Unexplained Recurrent Miscarriage

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ABSTRACT

Background: recurrent pregnancy loss (RPL) is defined as at least two or three sequential abortions before the 20th week of gestation. RPL occurs in 1% to 5% of all pregnancies.

Aim of the Work: to assess the efficacy of low dose aspirin and steroids therapy versus Aspirin Study in the management of women with recurrent miscarriage.

Patients and Methods: this randomized clinical trial was conducted in the repeated miscarriage clinics in the Obstetrics and Gynecology Department, in Al-Azhar University Hospital on 100 pregnant women, who fulfilled the inclusion criteria and after taking an informed consent. Group 1: included 50 pregnant females administered with low dose aspirin 75 mg tablet (one tablet twice daily) and prednisolone 5mg two tablets twice daily (20mg). Group 2: included 50 pregnant females administered with low dose aspirin 75 mg tablet (one tablet twice daily). Both groups were followed in Elhussein hospital recurrent miscarriage clinic every two weeks by ultrasonography from the incidence of the pregnancy till delivery.

Results: women treated with prednisolone (PSL) plus LDA had a 32.2% higher live birth rate than group II and according to on-going pregnancy data was in group I 37/50(74%) and in group II 21/50(42%) OR (C.I. 95% 4.128 [2.142-7.952] RR (C.I. 95%1.875 [1.401-2.505] p<0.001, with a significant difference between the two groups. There was a significant difference between the two groups as regards the development of bruising (P<0.05).

Conclusion: combination treatment consisting of prednislone and low dose aspirin might be an effective treatment for women with idiopathic pregnancy loss.

Keywords: Aspirin, Steroids, Unexplained Recurrent Miscarriage.

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as two or three consecutive miscarriages at least before the 20th week of pregnancy. RPL occurs in 1% to 5% of all pregnancies. Although many factors, such as environmental factors, stress factors, chromosomal abnormalities, defects of coagulation protein, anatomic endocrine disorders and the autonomic immune system are involved in about 60% of RPLs, in the remaining 40% of cases, the causes of miscarriage are unknown and classified As a non-justified RPL (URPL) [(1)].

Fifty percent of the RPL is caused by anatomical factors, immunology, genetics, endocrinology, coagulation, and environmental. However, in 50% of cases, the cause of abortion is unknown or idiopathic[(2)]. RPL is a major health problem, affecting 5% of females of childbearing age. Women of childbearing age face significant economic, emotional and social problems due to RPL[(3)]. Established and suggested risk factors for recurrent miscarriage are increasing number of successive previous pregnancy losses [(4)], parental chromosomal anomalies, maternal thrombophilia disorders, and structural uterine anomalies. Finally, increasing maternal age is accepted as the most important risk factor for future miscarriage both in women with recurrent miscarriages and in the general population [(5)].

The proposed and proposed risk factors for recurrent miscarriages are an increase in the number of previous consecutive pregnancies, 4 cases of parental chromosomal abnormalities, maternal thrombosis disorders, and structural defects in the uterus. Finally, the increase in the age of the mother is accepted as the most important risk factor for future abortion in women with recurrent miscarriages and in the general population.

About 50% of recurrent pregnancy loss cases still remain unexplained, or idiopathic. In this group of patients, fetal chromosomal abnormalities have been reported to be the most common cause of recurrent pregnancy loss, accounting for up to 55% of cases, thus leaving a remainder of 24.5% of truly unexplained recurrent pregnancy loss [(6)].

Although progesterone appears to be the main factor initiating decidualization, a number of other factors including cytokines appear to facilitate this event. Failure in either the early blastocyst endometrial dialogue or decidualization may lead to implantation or pregnancy failure, alteration in the expression of a number of factors thought to contribute to the embryo/ endometrial dialogue have been shown at this time in endometrium from women with recurrent miscarriage [(7)].

The concentrations of different endometrial leukocytes have therefore been investigated in a number of studies to find links to the development of miscarriages [(8)]. We performed this study on women who presented with unexplained recurrent to explore

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the efficacy of low dose aspirin and steroids in the management of such cases.

AIM OF THE WORK

The aim of this study is to assess the efficacy of low dose aspirin and steroids therapy vs Aspirin Study in the management of women with recurrent miscarriage.

PATIENTS AND METHODS

This randomized clinical trial was conducted in the repeated miscarriage clinics in the Obstetrics and Gynecology Department, in Elsayed Galal and Elhussein hospitals. Al-Azhar University; Cairo, Egypt from November 2017 till December 2018.

The study was approved by the Ethics Board of Al-Azhar University.

Study groups:

- **Group 1:** This group included 50 pregnant females who administered low dose aspirin 75 mg tab. (One tablet twice daily) and prednisolone 5mg two tablets twice daily (20 mg). The intervention started from the start of the pregnancy till 14 weeks gestation. Low dose aspirin only was continued till 36 week.
- **Group 2:** This group included 50 pregnant females who were administered with low dose aspirin 75 mg tab., one tablet twice daily. The intervention started from the start of the pregnancy.

Both groups were followed in Elhussein hospital recurrent miscarriage clinic every two weeks by ultrasonography from the incidence of the pregnancy till delivery.

Inclusion criteria:

The study included patients with a history of two or more consecutive miscarriages, with ages from 18 years till 35 years with viable current early pregnancy (<8 weeks gestation) and a history of unexplained recurrent miscarriage (which was defined as ≥2 previous miscarriages at <20 weeks, gestation).

Exclusion criteria:

A) Parental chromosomal abnormalities, Anatomical abnormality as uterine anomalies, e.g. uterine septum incompetent internal cervical os, Maternal endocrinological defects e.g. a luteal-phase defect (as determined by a timed endometrial biopsy), which are all known causes of recurrent fetal loss, PCOD (poly cystic ovarian disease), thyroid disease, hyperprolactinemia, Maternal thrombophilia, e.g. Factor V Leidin deficiency protein C deficiency protein S deficiency, antithrombin III deficiency, Maternal anti phospholipid anti body syndrome. Systemic lupus erythematosus that fulfilled four or more of the criteria of the American College of Rheumatology[9] and Diagnosis of pregnancy after 8 weeks gestation.

B) Contraindications of aspirin: confirmed peptic ulcer disease within the past three years and sensitivity to aspirin.

C) Contraindications of steroids:

Diabetes mellitus, previous gestational diabetes mellitus, diastolic blood pressure greater than 90 mm Hg and previously untreated tuberculosis

D) Randomization: was done by using dark, sealed envelopes detailing the intervention, which was selected from a table of numbers either 1 or 2 (1 means the group took low dose aspirin and steroids and 2 means the group took aspirin only); Created by computer generated randomization table program.

E) Allocation:

For each patient, an envelope was selected from the sequentially numbered envelopes on the day of recruitment by a nurse not involved in the study.

Consent:

Informed consents from all participating patients in the study were taken.

History:

A complete history was obtained.

Examination:

- General examination was done for PCOD, thyroid disease galactorrhea, hirsutism, evidence of autoimmune disorder.
- Abdominal examination was done.

Investigation:

Obstetric ultrasonography were conducted to assess the viability of pregnancy and gestational age for all participants and to assess: No. of fetaie, ectopic, fetal viability, congenital fetal malformation, lie, presentation, IUGR, MBPP, and Doppler (if needed). Amniotic fluid amount and turbidity Placental site, grading, morbid adherence, thickness hemorrhage Associated pelvic mass with pregnancy e.g. ovarian cyst, uterine malformations, cervical length, inner to inner diameters Routine laboratory investigations: CBC, urine analysis, random blood sugar, liver and kidney function tests.

Screening for anticardiolipin antibodies, lupus anticoagulant or anti-b2-glycoprotein I antibodies if not previously done. Endocrine screening: prolactin, TSH, and HbA1c if not previously done.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Mann Whitney U test: for two-group comparisons in non-parametric data.
- Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
- Odds ratio: An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.
- Relative risk (risk ratio): The ratio between the risk of the outcome in the first group to the risk of outcome in the second group.
- NNT: Number needed to treat is the number of patients you need to treat to prevent one additional ad outcome.
- Probability (P-value):
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

RESULTS

Table (1): Comparison between Group I and group II according age and BMI

	Group I (n=50)	Group II (n=50)	t-test	p-value
Age (years)				
Mean±SD	28.70±4.12	29.58±4.52	1.034	0.312
Range	19-35	19-35		
BMI [wt(ht)^2]				
Mean±SD	29.50±3.15	30.08±3.46	0.769	0.383
Range	24-39	23-40		

This table shows no statistically significant difference between groups according age and BMI.

Table (2): Comparison between Group I and group II according parity

Parity	Group I (n=50)	Group II (n=50)	x2	p-value
Primigravida	41 (82%)	38 (76%)	0.542	0.461
Multipara	9 (18%)	12 (24%)		
Total	50 (100%)	50 (100%)		

This table shows no statistically significant difference between groups according parity.

Table (3): Comparison between Group I and group II according no. of previous live birth

	Group I (n=50)	Group II (n=50)	z-test	p-value
No. of previous live birth				
Median (IQR)	1 (1)	1 (1)	-0.782	0.434
Range	0-3	0-3		
No. of previous miscarriage				
Median (IQR)	3 (2)	2 (2)	1.046	0.295
Range	2-8	2-7		

This table shows no statistically significant difference between groups according no. of previous live birth and no. of previous misscarrige.

Table (4): Comparison between Group I and group II according miscarriage

Miscarriage	Group I (n=50)	Group II (n=50)	OR (C.I. 95%	RR (C.I. 95%	x2	p-value
Yes	13 (26%)	29 (58%)	0.267 [0.139-0.515]	0.478 [0.320-0.712]	10.509	**<0.001 (HS)**
No	37 (74%)	21 (42%)				
Total	50 (100%)	50 (100%)				

This table shows highly statistically significant difference between groups according miscarriage.

Table (5): Comparison between Group I and group II according gestational age at miscarriage

Gestational Age at miscarriage	Group I (n=13)	Group II (n=29)	t-test	p-value
Mean±SD	9.77±1.24	9.69±1.07	0.045	0.833 (NS)
Range	8-12	8-13		

This table shows no statistically significant difference between groups according gestational age at miscarriage.

Table (6): Comparison between Group I and group II according ongoing pregnancy

On going pregnancy	Group I (n=50)	Group II (n=50)	OR (C.I. 95%	RR (C.I. 95%	Effect size	x2	p-value
Yes	37 (74%)	21 (42%)	4.128 [2.142-7.952]	1.875 [1.401-2.505]	32.2 %	10.509	**<0.001 (HS)**
No	13 (26%)	29 (58%)					
Total	50 (100%)	50 (100%)					

This table shows highly statistically significant difference between groups according on-going pregnancy.

Table (7): Comparison between Group I and group II according bleeding in early pregnancy

Bleeding in Early Pregnancy	Group I (n=50)	Group II (n=50)	OR (C.I. 95%	RR (C.I. 95%	x2	p-value
Yes	20 (40%)	25 (50%)	0.684 [0.366-1.274]	0.818 [0.567-1.178]	1.010	0.315 (NS)
No	30 (60%)	25 (50%)				
Total	50 (100%)	50 (100%)				

This table shows no statistically significant difference between groups according bleeding in early pregnancy.

Table (8): Comparison between Group I and group II according pregnancy complications

Pregnancy Complications	Group I (n=50)	Group II (n=50)	x2	p-value
Pregnancy induced HTN	3 (6.0%)	3 (6.0%)	0.105	0.702
Pre eclamptic toxemia	3 (6.0%)	2 (4.0%)	0.002	0.924
Gestational DM	1 (2.0%)	0 (0.0%)	0.001	0.942
Pre TermLabour PTL	4 (8.0%)	1 (2.0%)	2.310	0.113
Intra Uterine Fetal Death	2 (4.0%)	3 (6.0%)	0.138	0.668
Intra Uterine Growth retardation	5 (10.0%)	3 (6.0%)	0.114	0.692
Thrombocytopenia	2 (4.0%)	0 (0.0%)	2.243	0.118
Epistaxis	5 (10.0%)	2 (4.0%)	1.823	0.158
Bleeding per gum	6 (12.0%)	2 (4.0%)	3.434	0.045*
Heamatourea	7 (14.0%)	3 (6.0%)	2.224	0.120
Brousing	13 (26.0%)	0 (0.0%)	12.873	<0.001**
DVT	2 (4.0%)	1 (2.0%)	0.190	0.948
GIT problem	8 (16.0%)	2 (4.0%)	2.593	0.093
Aprabtioplacente	0 (0.0%)	1 (2.0%)	0.000	0.948

This table shows statistically significant difference between groups according bleeding per gum and brousing.

Table (9): Kaplan-Meier curves between group I and group II regarding pregnancy until delivery

Groups	Median				Log Rank (Mentel-Cox)	
	Estimate	Std. Error	95% Confidence Interval			
			Lower Bound	Upper Bound	x^2	p-value
Group I	32.88	1.94	29.08	36.68	10.385	0.001 (HS)
Group II	22.84	2.19	18.55	27.13		
Overall	27.86	1.55	24.83	30.89		

DISCUSSION

This study assessed the efficacy of low dose aspirin and steroids therapy in the management of women with idiopathic recurrent miscarriage.

The current study showed a statistically significant difference between two groups according on-going pregnancy as in group I 37/50 (74%) and in group II 21/50 (42%) OR (C.I. 95% 4.128 [2.142-7.952] RR (C.I. 95%1.875 [1.401 - 2.505] p<0.001 (HS),the mean age in the group I was (28.70±4.12) and they were in the age group of 19-35 years while the mean BMI was (29.50±3.15). The mean age in the group II was (29.58±4.52) and they were in the age group of 19-35 years while the mean BMI was (30.08±3.46) with no statistically significant difference between the two groups (P>0.05) as regards the age and BMI. As regards other clinic-demographic data of the participants, there was no significant difference between the two groups as regards parity, number of previous live birth, number of previous miscarriages, the duration of previous pregnancies.

Based on current evidence, aspirin (less than 150 mg/d) during the second and third trimesters appears to be safe, while the safety of higher doses of aspirin during the first trimester remains uncertain [(10)].

Although a different design was used, in her study [(11)] evaluated the effect of aspirin (50 mg/day) on live birth rate in 66 pregnant women with preceding RM with or without detectable anticardiolipin antibodies and no other apparent risk factors for their previous miscarriages. RM was defined as three or more consecutive miscarriages (occurring before 22 weeks of gestational age). Aspirin was compared with placebo, and medication was started as soon as a home urinary pregnancy test became positive and continued until delivery. Pooled analysis from 256 patients showed that compared to placebo, aspirin did not increase live birth (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.80 to 1.11) [(11,12)].

Nine studies, including data of 1228 women, were included in the review evaluating the effect of either LMWH (enoxaparin or nadroparin in varying doses) or aspirin or a combination of both, on the chance of live birth in women with recurrent miscarriage, with or without inherited thrombophilia. Studies were heterogeneous with regard to study design and treatment regimen and three studies were considered to be at high risk of bias. Two of these three studies at high risk of bias showed a benefit of one treatment over the other, but in sensitivity analyses (in which studies at high risk of bias were excluded) anticoagulants did not have a beneficial effect on live birth, regardless of which anticoagulant was evaluated (risk ratio (RR) for live birth in women who received aspirin compared to placebo 0.94, (95% confidence interval (CI) 0.80 to 1.11, n = 256), in women who received LMWH compared to aspirin RR 1.08 (95% CI 0.93 to 1.26, n = 239), and in women who received LMWH and aspirin compared to Aspirin only RR 1.01 (95% CI 0.87 to 1.16) n = 322) [(13)].

Also ***Zein et al.*** [(13)] confirmed that, the use of aspirin plus heparin did not significantly increase the live birth rate in women with recurrent unexplained miscarriage.

That agreement with **Kaandorp *et al.*** [(14)] recorded that their findings do not support the hypothesis that either combination therapy with aspirin and nadroparin or aspirin alone improves the chance of a live birth for women with unexplained recurrent miscarriage.

In contrast to aspirin lack of efficacy among women with early unexplained recurrent miscarriage, low dose aspirin significantly increased the prospective live birth rate among women with a previous late miscarriage. This support the hypothesis that a number of cases of second trimester miscarriage and later pregnancy complications have a thrombotic aetiology[(15)].

Some are reported the benefit effect of use low dose aspirin as a prophylaxis in treatment of unexplained recurrent miscarriage as ***Ahmed et al.*** [(16)] who reported that The use of prophylactic dose of calheparin and aspirin is associated with increased chance of passing 1st trimester safely regardless the age, body mass index or number of abortion in women with unexplained recurrent spontaneous abortion.

Also ***Rai, et al.*** [(17)] reported that Treatment with aspirin and heparin leads to a significantly higher rate of live births in women with a history of recurrent miscarriage.

Also as regard to use of predinislone alone in treatment of recurrent miscarriage.

Recent study published by ***Tang et al.*** [(18)] about the use of prednisolone in patients with high levels of uterine natural killer (uNK) cells, he conducted his study on 160 eligible women were screened with an endometrial biopsy and those with high uNK cell density were invited to return when pregnant for randomization to prednisolone (20 mg for 6 weeks, 10 mg for 1 week, 5 mg for 1 week) or identical placebo tablets. Randomization was by random number generation and patients, clinicians and outcome assessors were blinded to allocation. Which resulted that, the live birth rate was 12/20 (60%) in the prednisolone group and 8/20 (40%) in the placebo group, and this was not significant (RR1.5, 95% CI 0.8–2.9). There was only one pre-term delivery of 37 weeks in the prednisolone group, and all others delivered at term. The mean birth weight was similar in the two groups, with no pregnancy complications of IUGR or macrosomia.

There were also no reports of gestational hypertension, pre-eclampsia or gestational diabetes in either group. There were no adverse fetal outcomes.

With the same to our regimen, in which 10 mg/d of prednisolone twice daily was administered, it is possible that the steroid had a beneficial effect on pregnancy outcome through the reduction of NK cells. The administration of low-dose aspirin with prednisolone may have reduced uterine vascular resistance by decreasing the local thromboxane A2/ prostacyclin ratio, improving uterine blood perfusion and the implantation rate [19].

Also, ***Gomaa et al.*** [20] confirmed that the addition of prednisolone to heparin and low dose aspirin might be beneficial in patients with unexplained recurrent miscarriage, and this effect might be due to a suppressive effect of steroids on the peripheral CD16 NK cells concentration.as his result was found that in the prednisolone group, 70.3 % of women had successful outcome (defined as an ongoing pregnancy beyond 20 weeks gestation), while 29.7% miscarried before this gestation. On the contrary, among women in the Aspirin only group, 9.2% had successful outcome while 90.8% miscarried before 20 weeks, which was statistically significant. On the other hand, we found that there were no significant paired differences between initial serum levels of the NK cells markers CD16 and CD56 and their levels at 20 weeks gestation in both groups.

This may explained by **Thum *et al.*** [21] who mentioned that the results of this study show that prednisolone is able to suppress the cytolytic activity of the NK cell.

Women who were treated with prednisolone (PSL) plus low dose aspirin (LDA) had a 32.2% higher live birth rate than the control group with a significant difference between the two groups; the results were in accordance with previously reported data by **Etievant *et al.*** [22]. The combination of 20 mg/day of prednisone with aspirin and progesterone allowed 85% of live births in comparison to 48% with placebo ($P < 0.05$). **Fawzy *et al.*** [23] as they conducted a prospective, randomized, single-blinded, controlled trial was conducted at a tertiary referral obstetric hospital. The participants were 170 women with a diagnosis of IRM. Women were recruited after full investigative screening. Women with > or = 3 fetal losses and after exclusion of all known causes of recurrent miscarriage were randomly allocated to receive either enoxaparin alone, combination treatment consisting of prednisone, aspirin, and progesterone or Aspirin only. That resulted of ten patients were dropped out after random assignment. Eighty-one percent of the enoxaparin (46/57) group and 85% of the combination-treated group (45/53) were delivered of live infants compared to 48% (24/50) of the Aspirin only ($P < 0.05$).

Women who were treated with combination therapy had a 4.2% higher live birth rate than enoxaparin group. This difference was not significant. Miscarriage rates were significantly lower in the treated groups compared with Aspirin only ($P<0.05$). There were no significant differences in late obstetric complications or neonatal mortality between groups.

Also in study of **Tempfer *et al.*** [24]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. Their study resulted: The overall live birth rates of the treatment and control groups were 77% (40 of 52) and 35% (18 of 52) (P 0.04). 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 0.09 and P1.0, respectively). The median gestational age at birth and median birth weight did not differ between the groups. They observed two and three cases of premature birth among the treatment and control groups, respectively (P0.3) 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.

In our study, as regarding the occurrence of complications in both groups, there was no statistically significant difference between the two groups as regards bleeding in early pregnancy, pregnancy induced HTN, pre eclamptic toxemia, gestational DM, preterm labour, intrauterine fetal death, intrauterine growth retardation, thrombocytopenia, epistaxis, bleeding per gum, hematuria, DVT, GIT problem, Abruptio placentae ($P> 0.05$). There was a significant difference between the two groups as regards the development of bruising ($P < 0.05$).

Which match agreement of ***Ahmed et al.*** study which recorded, the outcome regarding completion of first trimester was not related to age, BMI or number of previous abortions in both the study groups. Complications of the use of aspirin calheparin occurred in 60% of the patients. The most common complication was bruising at injection site occurring in 60% of the patients followed by bleeding gums (14.4%), gastrointestinal troubles (12.2%), epistaxis (10%) and transient thrombocytopenia in only 2.22% of the patients. thus we preferred predinisolone association with low dose aspirin in treatment of unexplained recurrent miscarriage due to its low side effect than heparin as Cecilia documented that, Corticosteroids are known to be associated with

significant side effects, especially at a high dose; these include preterm delivery, preeclampsia, gestational diabetes, and hypertension. Despite this, it was demonstrated that women taking low doses of prednisone until 14 weeks of gestation plus standard therapy can experience favorable pregnancy outcome, with a higher live birth rate [25].

Explaining by other studies demonstrating adverse effects of prednisolone have used doses up to 60 mg. Prednisolone is metabolized by the placenta to a relatively inactive metabolite, only 10% of which crosses into the fetal circulation at doses < 20 mg, and therefore, it might be anticipated that low doses may have fewer side effects [19].

On the other hand, **Xiao *et al.*** [26] said that Long-term usage of prednisone during pregnancy may provoke obstetric complications.

Steroids are widely used during pregnancy in patients with various inflammatory or auto-immune diseases. Among possible adverse effects, high amounts of steroids could result in arterial hypertension, diabetes, prematurity, and low birth weight, but pregnancy adverse effects are uncommon with low prednisone amounts (<10 mg/day). Several studies assessed the risk of fetal malformation in women taking steroids in first trimester and mainly showed no increased risk.

The only controversial data are on concern the risk of oral cleft. Several retrospective and prospective case– controls studies showed no increase of the risk of oral cleft in women exposed to steroids [27].

However, a randomized controlled trial that compared outcomes after treatment with aspirin plus prednisolone (40 mg) or a prophylactic dose of heparin demonstrated no difference in live birth rate but an increased frequency of preterm delivery because of premature rupture of membranes or preeclampsia in the group treated with prednisolone. Another randomized controlled trial in women with 2 or more first-trimester losses found no benefit in rates of fetal loss but increased preterm delivery in women treated with prednisolone (20 mg) plus aspirin compared with aspirin alone. Another report suggested that fetal losses were actually higher in women treated with prednisolone (10-60 mg) [19].

These results are in agreement with **Cowchock *et al.*** [28] who reported low incidence of preeclampsia and DVT in the treated patients with steroids plus low dose aspirin.

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

CONCLUSION

Our data indicate that a combination treatment consisting of prednislone and low dose aspirin, might be an effective treatment for women with idiopathic pregnancy loss. The data presented constitute sufficient evidence, and prospective-randomized trials are encouraged to establish this treatment scheme.

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