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IDIOPATHIC RECURRENT MISCARRIAGES;

USE OF ASPIRIN ALONE OR HEPARIN AND ASPIRIN: EMPERICAL OR EVIDENCE BASED MANAGEMENT.

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ABSTRACT… Objectives: The rationale of our study is to investigate whether aspirin alone, or aspirin combined with low molecular weight heparin as compared to placebo (intensive pregnancy surveillance), would improve the live birth rate (primary outcome) among with idiopathic recurrent miscarriages. Secondary outcomes included rate of serious adverse events during pregnancy among pharmacological intervention group and intensive surveillance group: rates of miscarriage, intrauterine fetal death (fetal death after 24 weeks of gestation), small for gestational age, premature delivery, APH and PPH. **Study Design:** A prospective, randomized, single-blinded, placebo- controlled trial was conducted at Tertiary Referral Obstetric Hospital. **Setting:** Fatima Memorial Hospital, Lahore **Period:** 2007 to 2013. **Method:** The participants were 172 women with a diagnosis of idiopathic recurrent miscarriage.12 patients dropped out of the study. Women with 2 or more recurrent fetal losses and after exclusion of all known causes of recurrent miscarriage were randomly allocated to receive aspirin alone (n=54), combination treatment aspirin and heparin (n=56) or placebo (n=50 intensive pregnancy surveillance). The results were analyzed by SPSS (version 17) and they were tested by chi-square test. **Results:** Out of 160 women who underwent randomization, live birth rate did not differ significantly among the three groups. The live birth rate was 70.3% among aspirin only group, 73.2% among aspirin and heparin group and 70% among intensive surveillance group (placebo) with a p value equal to 0.11. No significant differences in secondary outcome were observed among three groups. **Conclusion:** In conclusion, our findings do not support the hypotheses that use of aspirin alone or in combination with enoxapirin improves the live birth rate in women with idiopathic recurrent miscarriages.

Key words: Idiopathic recurrent miscarriage, aspirin, heparin, live birth.

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INTRODUCTION

Recurrent pregnancy loss is commonly defined as 3 or more successive pregnancy losses, affecting 1% to 2% of women of reproductive age group. The scale of problem increases up to 5% if couples with 2 or more successive losses are also included.[1] Although a small proportion is associated with identifiable abnormalities in the mother or the fetus, which include chromosomal abnormalities, uterine structural abnormalities, luteal phase defects, thrombophilias, immunological and endocrinological causes, yet the cause in most cases of recurrent loss remains unknown. About 40 to 60% of these women have idiopathic recurrent miscarriage (IRM).[2,3]

The etiology of idiopathic miscarriage remains uncertain. It is generally accepted that within the idiopathic group there is considerable heterogeneity and it is unlikely that one single pathological mechanism is attributed to the recurrent miscarriages.[4] Currently research is focused at theories on defects in nature's quality control related to implantation, trophoblastic invasion and placentation.[5]

A well-established role of use of low dose aspirin and enoxaparin 40 mg subcutaneously daily in patient with recurrent pregnancy loss due to antiphospholipid syndrome have been seen resulting in high live birth rates of 93% and 80% in studies conducted by Saadia Fawad and Mo D respectively.[6,7] It has been suggested that this treatment may prove beneficial in treatment

of idiopathic recurrent miscarriage too due to presumed similarities in pathogenesis of the two conditions, its prothrombotic phenotype.

Although various interventions have been suggested in cases with idiopathic recurrent miscarriages to improve rates of live birth in such cases, no effective treatment has been identified. Various interventions such as corticosteroids, progestogens, immunotherapy, aspirin, aspirin plus heparin have been tried but treatment largely remains speculative due to uncertain etiology and pathogenesis of this condition, hence posing a challenging situation for treating gynecologist.

Over the past few years, since working in a tertiary care hospital, we have received a number of patients with idiopathic recurrent miscarriages, who had been started with aspirin and heparin by general practitioners without it being the evidence based management. Since the international research shows mixed results we planned to determine the effectiveness in terms of live birth rate of this costly treatment in pregnancy.

MATERIAL AND METHODS

This is a prospective randomized controlled study conducted in Fatima Memorial Hospital, Lahore from 2007 to 2013. Women aged between 18 to 42 years with idiopathic recurrent miscarriages with gestational age of less than 6weeks were included.

Recurrent miscarriages were defined as at least two miscarriages. Miscarriage was defined as pregnancy loss of less than 24weeks, with either urine for pregnancy test positive along with clinical manifestation of miscarriage and or Ultrasonographic evidence of previous pregnancy and or histopathological evidence of products of conception. However biochemical pregnancies were excluded.

Idiopathic recurrent miscarriage was defined when previous miscarriage was not associated with anatomical abnormalities of uterus, normal karyotyping of both partners, endocrine (thyroid dysfunction and diabetes) or immunological causes (absence of antiphospholipid syndrome), thrombophillic disorders (factor V Leiden, prothrombin G20210A mutation and protein C, protein S and anti-thrombin deficiency).

Women with previous history of arterial or venous thrombosis requiring anti-coagulants therapy during pregnancy were excluded from the study. Women allergic to aspirin, platelets count <150x 109/L were also excluded from study.

After the approval of Hospital Ethical Committee and fulfilling the inclusion/exclusion criteria, an informed consent was and their sociodemographic data was recorded. Subjects were randomly assigned to receive aspirin alone, aspirin combined with low molecular weight heparin or placebo starting at less than 6 weeks of gestation. A computer program was used to do the randomization.

We enrolled 172 patients, 12 patients dropped out of the study. There were 54, 56 and 50 patients in aspirin only, combination treatment group (aspirin and heparin group) and placebo.

Aspirin in the form of acetylsalicylic 75 mg daily dose was given. Aspirin and placebo were in similar packs; both were started at 6 weeks of gestation and continued until 36 weeks or stopped at the time of miscarriage or premature delivery.

Low molecular weight heparin in the form of Enoxaparin (clexane) 40mg subcutaneously was started once fetal cardiac activity was confirmed on Ultrasonography, starting at 6 weeks of gestation and continued throughout the pregnancy; women were instructed to stop enoxaparin when labor starts.
Women in placebo group were given tender loving care.

All women were prescribed with folic acid (400micrograms) until 12 weeks, as prophylaxis of neural tube defects. The fetal surveillance to be offered consisting of scans every 2 weeks from the time of diagnosis until 12 weeks and then monthly

scans until 28 weeks. In the combination therapy group (heparin & aspirin) full blood counts will be performed 7 to 10 days after commencement of treatment and thereafter at 28 and 36 weeks of gestation.

Primary outcome measure studied was live birth rate and rate of miscarriage in all the three groups. Secondary outcomes included rate of serious adverse events during pregnancy among pharmacological intervention group and intensive surveillance group: intrauterine fetal death (fetal death after 24 weeks of gestation), small size for gestational age (birth weight below the 10th percentile for gestational age and sex), premature delivery, APH, PPH and low hemoglobin.

The results were analyzed by SPSS (version 17). Chi square test was used to compare efficacy in all three groups. The results were considered as significant at p value <0.05.

RESULTS

We enrolled 172 patients, 12 patients dropped out of the study, 7 patients were lost to follow up, 3 were not adhering to medicine, and 2 declined to be a part of research trail as they wanted to stop celexane after 24 weeks of gestation. Baseline characteristics were similar across the three groups with mean age at randomization was 31 and median range of miscarriage was 3. (Table-I)

There were 54 patients in aspirin alone group, out of which 12 (22.2%) had miscarriages and 2 had termination of pregnancy due to anencephalus and gastroschisis. The ongoing pregnancy was seen in 40 (74.1%) out of which 2 had Intra uterine demise, 1 was small for gestational age and two had premature delivery.

56 patients were enrolled in combination therapy group (aspirin and heparin), 13 (23.2%) had miscarriages, and one had termination of pregnancy due to fetal renal agenesis. 42 (75%) had ongoing pregnancy, 2 were small for gestational age and 3 had premature delivery. Antepartum hemorrhage was observed in 4 patients.

11 of the 50 patients receiving placebo had miscarriages. 3 intrauterine demise, 1 small for gestational age and 2 premature deliveries were observed among 39 (78%) who had ongoing pregnancy.

The primary outcome studied was of Live birth rate that did not differ significantly across the three groups. Live birth rate was 70.3%, 73.2% and 70% among aspirin, combination group (aspirin and heparin group) and placebo. Absolute difference in live birth rate: combination therapy Vs placebo, 1.21 percentage points; 95% CI, -15.36 to 18.05; aspirin Vs placebo,-1.63 percentage points; 95% CI, -18.51 to 15.60. (Table-II)

Variable	Aspirin only (n= 54)	Aspirin + Heparin (n = 56)	Placebo (n= 50)
Age	32± 5	29 ± 4.6	31 ± 5
≥ 36 years – n (%)	9 (16.7%)	7 (12.5%)	8 (16%)
Gravidity (median)	6	7	5
Miscarriages			
Median (range)	3 (2-6)	3 (2-9)	3 (2-7)
≥ 3 miscarriages - n (%)	38 (70.4%)	41 (73.2%)	37 (74.0%)
≥ 1 miscarriages - n (%)	16 (29.6)	15 (26.8%)	13 (26%)
Number of primary aborters	32 (59.3%)	35 (62.5%)	31 (62%)
Number of secondary aborters	22 (40.7%)	21 (37.5%)	19 (38%)
Gestational age at entry	42	42	36
(Ump- median & range)	(33-44)	(32-45)	(33-47)

Table-I. Characteristics of patients participating in the study

Variable	Aspirin only (n= 54)	Aspirin + Hepain (n = 56)	Placebo (n= 50)	p-value	Aspirin only vs. Placebo		Aspirin + Hepain vs. Placebo	
					Relative Risk (95% C.I)	Absolute Risk Difference (95% C.I)	Relative Risk (95% C.I)	Absolute Risk Difference (95% C.I)
Live birth rate	38 (70.4%)	41 (73.2%)	36 (72%)	0.11	1.023 (0.801 – 1.307)	-1.63 (-18.51-–15.60)	0.983 (0.778 – 1.243)	1.21 (-15.36 –18.05)

Table-II. Primary outcomes

No significant difference in secondary outcome was seen among three groups. Though there was an increased tendency to bruise, injection site pain and itch in combination treatment group. (Table-III)

Complications of early pregnancy	Aspirin only (n= 54)	Aspirin + Hepain (n = 56)	Placebo (n= 50)	p-value	Absolute Risk Difference (95% C.I)	
					Aspirin only vs. Placebo	Aspirin + Hepain vs. Placebo
Number of miscarriage	13 (22.2%)	13 (23.3%)	11 (22%)		0.22 (-15.80–15.94)	1.21 (-14.86 – 16.81)
Termination of Pregnancy	2 (13.70%)	1 (1.85%)	-	NA	NA	NA
Gestational age at miscarriage	9.0 ± 2.8	8.7 ± 2.2	9.0 ± 2.9	0.790	-	-
On-going pregnancy outcome	40 (74%)	42 (75%)	39 (78%)	0.889	-3.93 (-19.88–12.55)	-3.00 (-18.70 – 13.29)
IUD	2 (5%)	1 (2.38%)	3 (7.69%)	0.546	-2.69 (-15.83 – 9.87)	-5.31 (-18.09 – 5.83)
SGA	1 (2.5%)	2 (4.76%)	1 (2.56%)	0.808	-0.06 (-10.88 –10.53)	2.20 (-8.96 – 13.43)
Premature delivery	2 (5%)	3 (7.14%)	2 (5.12%)	0.779	-0.13 (-12.43 –11.96)	2.01 (-10.64 -14.45)
APH	1 (2.5%)	4 (9.52%)	-			
Less adverse outcomes						
Injection site bruising	0	17	0			
Nose bleed	1	6	0			
Anemia	1	3	1			
Injection site pain	0	1	0			
Injection site itch	0	3	0			
Gastric upset	0	2	0			
Thrommbocytopenia	0	1	1			

Table-III. Secondary outcomes

DISCUSSION

From the results of our study we concluded that neither aspirin alone or in combination with enoxaparin improves the chances of live birth rate in women with idiopathic recurrent pregnancy loss.

Different treatment modalities have been tested for treatment of idiopathic recurrent pregnancy loss. Based on the hypothesis of thrombosis in decidual vessels most of the studies have tested the role of aspirin alone or in combination with enoxaparin. Others have also studied the role of intra venous immunoglobulin in treatment of IRM.[8] Use of prednisone in combination with heparin and aspirin has also been tested.

Based on hypothesis of thrombosis in decidual vessels, role of aspirin alone or in combination with heparin has been tested the most. It has been stated that not only the thrombosis but also the activated coagulation factors induce cell death and inhibit the growth of trophoblast cells.[9] More over considering IRM as a prothrobotic phenotype and beneficial effect of aspirin and heparin seen in pregnancy outcomes with antiphospholipid syndrome has lead to empirical use of aspirin and heparin in IRM.

Literature review over years many studies have been conducted. Kaandrop et al[10], did a large randomized trial, the anticoagulant for living fetus (ALIFE) in recent years. The trial was done on 364 patients with 2 or more miscarriages at 6 or more weeks with IRM and also included patients with IRM trying to conceive. Women were randomly allocated to three groups, aspirin alone, aspirin and heparin and placebo. Live birth rate was 50.8%, 54% and 57% in three groups respectively. This study did not prove the beneficial effect of aspirin or heparin over placebo. This study also highlights the fact that not all the miscarriages are attributed to thrombosis and neither heparin nor aspirin can reverse the defective trophoblastic differentiation or embryonic growth defect.

Another large study conducted by Peter Clark, SPIN (Scottish Pregnancy Interval)[11] was a multicenter randomized controlled trail of LMWH and low dose heparin in women with IRM. It concluded that pragmatic use of heparin has no measurable benefit in preventing future loss as compared with intensive fetal surveillance.

Muhammad Faway[12] did a prospective randomized, single blind, placebo controlled trial including 170 women with IRM. He randomly allocated women to receive enoxaparin alone, combination group (predinsone, aspirin, progesterone) and placebo. He found significantly lower miscarriage rate in enoxaparin and combination treatment group ($P<0.05$) as compared with placebo. Live birth rate was 81%, 85% in enoxaparin and combination group as compared to 48% in placebo group.

Similar results were obtained by Clemen et al[13] in his research trial comparing a combination treatment of prednisone, aspirin, folate, progestogen with placebo. He found that combination treatment group is associated with higher live birth rate as compared to no treatment in women with IRM.

The limitation to our study is using a broad definition of recurrent miscarriages (2 or more), in accordance with ACOG[14] as compared to 3 or more miscarriages, according to RCOG[15], which might have diluted the results of our study. We also support the provision of tender loving care and emotional support in patients with IRM. The effect of tender loving care has been previously evaluated by Stray Pederson[16] in 1983 and showed a success rate of 80%. A more recent study by Liddell et al[17] in 1991 reported a success rate of 86% with tender loving care as compared to 33% in the absence of emotional care.

We conclude our study by giving reference of RCOG guideline on recurrent miscarriages emphasizing on data suggesting that the use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted. These women with IRM can be reassured that the prognosis for a successful future pregnancy with supportive care alone is in the region of 75%.[18]

We believe we should strictly adhere to the RCOG guidelines till some large RCT proves it vice versa, especially when it comes to such a costly treatment in a country like Pakistan where patient pays for their health facilities.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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