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ASPIRIN PLUS HEPARIN VERSUS ASPIRIN AND ORAL PREDNISOLONE IN THE MANAGEMENT OF WOMEN WITH RECURRENT MISCARRIAGE

Israa Adil Dawood Al-Shaboot [1],Hayat Jabir Hamad Al Sutani *[2] and Huda Abdulmunem Shaker[3]

[1]Al-Zahraa teaching hospital. Wassit, Al kut, Iraq
[2] Al Diwaniya Maternity hospital, Al Diwaniya, Iraq
[3] Al Diwaniya Maternity hospital, Al Diwaniya, Iraq
*Corresponding Author hayatjabir68@gmail.com

ABSTRACT

Recurrent pregnancy loss RPL is characterized by at minimum 2 or 3 consecutive losses before the 20th week of gestation. In 1percentage to 5percentage of all pregnancies.

Aim of the Work: assessing the effectiveness of low dosage aspirin and steroid therapy in the management of women with recurrent miscarriage vs. Aspirin and heparin LMWH study.

Patients and Methods: In repeated miscarriage clinics, this randomized clinical experiment was performed in the Obstetrics and Gynecology Department, in Iraqi Hospital on 50 pregnant women, who fulfilled the inclusion criteria and after taking an informed consent. Group 1: included 25 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 25 pregnant females administered with low dose aspirin 75 mg tablet (one tablet twice daily) and heparin. Both groups were followed in hospital recurrent miscarriage clinic every two weeks by ultrasonography from the incidence of the pregnancy till delivery.

Results: Prednisolone (PSL) plus LDA increased the live birth rate by 32.2 percent compared to 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, between the two groups, with a substantial differential. When it came to the development of contusion, there was a substantial variance (P<0.05). among the two groups.

Conclusion: For women with idiopathic pregnancy loss, a combination of prednisone and low-dose aspirin could be a beneficial treatment.

***Keywords*:** Aspirin, Steroids, Unexplained Recurrent Miscarriage, heparin LMWH.

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INTRODUCTION

Spontaneous abortion is a frequent pregnancy consequence described by the spontaneous loss of the embryo before the 20th week of pregnancy and it is classified early spontaneous miscarriage if it occurs before the 12th week of gestation.1 Recurrent spontaneous abortion (RSA) is characterized by loss of three or more pregnancies, while many specialists believe that the loss of two is sufficient for diagnosis. Immunologic, genetic, endocrine, dietary, structural, and infective factors are all common leading causes in RSA.3–5 In over half of all RSA incidents, The fundamental reason, however, is unknown; in this scenario, unexplained RSA is the term used (URSA). unexplained Recurrent

spontaneous abortion therapy is challenging with no commonly acknowledged therapeutic approach, causing both the affected women and their family's distress.

As a result, it's critical to look into effective therapies and raise the rate of successful pregnancies in URSA. As previously stated, there really is no globally approved standard therapy for URSA at the present. It has been reported that the inadequacy of existing diagnostic approaches may skip more obscure causes of URSA, and that various factors, including immunological, coagulation, and dietary factors, may play a role in this condition. As a consequence, treatment options for women with URSA have been recommended, including immunologic intervention, anticoagulant therapy, and micronutrient supplementation. Although folic acid supplementation while perioperative pregnancy may assist to avoid neural tube abnormalities, it has no influence on the rate of miscarriage in women with URSA.

Similarly, Aspirin inhibits aggregation and adherence of the platelet, enhances coagulation activity, helps to prevent microthrombus creation, and inhibits the hypercoagulation in decidua space, although the live birth rate of URSA cannot be improved when taken it alone. Researches combining numerous pharmacological regimens to address various putative reasons of URSA have been conducted since these monotherapies do not appear to enhance pregnancy results. Intravenous immunoglobin plus prednisone, for example, has been proven to improve the surviving birth rate in females with URSA. Furthermore, the medication has showed promise to improve pregnancy outcomes in URSA throughout our actual clinic experience. Results have suggested, it was believed that this triple treatment could help females with URSA lower their chance of spontaneous abortion.

PATIENTS AND METHODS

The repeated miscarriage clinics were the setting for this randomized clinical research in the Obstetrics and Gynecology Department, in Iraqi hospitals.

from march 2019 till October 2020.

Study groups:

● **Group 1:** This group included 25 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 25 pregnant females who were administered with 75 mg of low-dose aspirin tab., one tablet twice daily and heparin. low molecular weight heparin (LMWH) enoxaparin (40 mg subcutaneously/day). The intervention started from the start of the pregnancy.

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

Inclusion criteria:

Patients between 18 to 35 years old with a history of 2 or more consecutive losses, a viable current early pregnancy (<eight weeks gestation), and a history of unexplained recurrent miscarriage (defined as ≥2 previous miscarriages at 20 weeks gestation) were enrolled in the research.

Exclusion criteria:

A) Parental chromosomal abnormalities, Anatomical abnormality as uterine anomalies, e.g., uterine septum incompetent internal cervical os, Maternal endocrinological defects for example, a luteal-phase deficiency (as assessed by a timed endometrial biopsy), all of which are common factors of recurrent fetal loss., PCOD (poly cystic ovarian disease), thyroid disease, hyperprolactinemia, Maternal thrombophilia, only a few examples. Factor V Leidin deficit, protein C deficiency, protein S deficiency, antithrombin III deficiency, Maternal anti phospholipid anti body syndrome. Diagnosis of pregnancy after 8 weeks gestation with systemic lupus erythematosus that met 4 or more of the American College of Rheumatology's criteria (9).

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

C) Contraindications of steroids:
Diabetes mellitus, previously untreated TB, prior gestational diabetes mellitus, diastolic blood pressure more than 90 mm Hg

D) Randomization: was accomplished by using black, sealed envelopes with instructions on the intervention, which was chosen from a table of numbers ranging from 1 to 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:
The day of recruiting, a nurse who was not participating in the research chose an envelope for each patient from a stack of sequentially numbered envelopes.

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:
All participants underwent obstetric ultrasonography to evaluate the viability of their pregnancy and gestational 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 lupus, anticardiolipin antibodies, anticoagulant or anti-b2-glycoprotein I antibodies if not previously done. Endocrine screening: prolactin, TSH, and HbA1c if not previously done.

Analysis of the data:
The Statistical Program for Social Science (SPSS) version 20.0 was used to analyze the data. The ± mean standard deviation (SD) were used to express quantitative data. Frequency and percentag were used to represent qualitative data.

RESULTS

Table (1): In terms of age and BMI, Group I and Group II are compared.

	Group I (n=25)	**Group II (n=25)**	**t-test**	**p-value**
Age (years) Mean±SD Range	28.70±4.12 19-35	29.58±4.52 19-35	1.034	0.312
BMI [wt(ht)2] Mean±SD Range	29.50±3.15 24-39	30.08±3.46 23-40	0.769	0.383

There is no statistically substantial difference among groups based on age and BMI in this table.

Table (2): In terms of parity, there is a comparison between Groups I and II.

Parity	**Group I (n=25)**	**Group II (n=25)**	**x2**	**p-value**
Primigravida Multipara	21 (82%) 4 (18%)	17 (76%) 8 (24%)	0.542 0.542	0.461 0.461
Total	25 (100%)	25 (100%)		

There is no statistically substantial variation between groups based on parity in this table.

Table (3): Group I and II were compared based on the number of previous live births.

	Group I (n=25)	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 illustrates that there are no statistically substantial differences among groups based on the number of previous live births and failed pregnancies.

Table (4): In terms of gestational age of miscarriage, Group I and Group II are compared.

Gestational Age at miscarriage	Group I (n=25)	Group II (n=25)	t-test	p-value
Mean±SD	9.77±1.24	9.69±1.07	0.045	0.833 (NS)
Range	8-12	8-13		

According to gestational age at miscarriage, this table demonstrates no statistically substantial differences between groups.

Table (5): In terms of miscarriage, there is a comparison between Groups I and II.

Miscarriage	Group I (n=25)	Group II (n=25)	OR (C.I. 95%	RR (C.I. 95%	x2	p-value
Yes	7 (26%)	14 (58%)	0.267 [0.139-0.515]	0.478 [0.320-0.712]	10.509	**<0.001 (HS)**
NO	18 (74%)	11 (42%)				
Total	25 (100%)	25 (100%)				

This table demonstrates a very statistically substantial difference in miscarriage between groups.

Table (6): In terms of early pregnancy bleeding, there is a comparison between Groups I and II.

Bleeding in Early Pregnancy	Group I (n=50)	Group II (n=50)	OR (C.I. 95%	RR (C.I. 95%	x2	p-value
Yes	10 (40%)	12 (51%)	0.684 [0.366-1.274]	0.818 [0.567-1.178]	1.01	0.315 (NS)
No	15 (60%)	13 (49%)				
Total	25 (100%)	25 (100%)				

This table illustrates that there is no statistically substantial difference among groups when it comes to early pregnancy bleeding.

Table (7): In terms of pregnancy complications, Group I and Group II are compared.

Pregnancy Complications	Group I (n=25)	Group II	x2	p-value
Pregnancy induced HTN	1 (6.0%)	2 (6.0%)	0.105	0.702
Pre eclamptic toxemia	1 (6.0%)	1 (4.0%)	0.002	0.924
Aprabtioplacente	0 (0.0%)	1 (2.0%)	0	0.948
GIT problem	4 (16.0%)	1 (4.0%)	2.593	0.093
DVT	1 (4.0%)	1 (2.0%)	0.19	0.948
Gestational DM	1 (2.0%)	0 (0.0%)	0.001	0.942
Pre TermLabour PTL	2 (8.0%)	1 (2.0%)	2.31	0.113
Intra Uterine Fetal Death	1 (4.0%)	2 (6.0%)	0.138	0.668
Intra Uterine Growth retardation	2 (10.0%)	2 (6.0%)	0.114	0.692
Epistaxis	2 (10.0%)	1 (4.0%)	1.823	0.158
Thrombocytopenia	2 (4.0%)	0 (0.0%)	2.243	0.118
Bleeding per gum	2 (12.0%)	1 (4.0%)	3.434	0.045*
Heamatourea	1 (14.0%)	2 (6.0%)	2.224	0.12
Brousing	5 (26.0%)	0 (0.0%)	12.873	<0.001**

According to bleeding per gum and brousing, this table indicates statistically substantial differences among groups.

Table (8): In terms of ongoing pregnancy, Group I and Group II are compared.

On going pregnancy	Group I (n=25)	Group II (n=25)	OR (C.I. 95%	RR (C.I. 95%	Effect size	x2	p-value
Yes	18 (74%)	11 (42%)	4.128 [2.142-7.952]	1.875 [1.401-2.505]	32.20%	10.509	**<0.001 (HS)**
No	7 (26%)	14 (58%)					
Total	25 (100%)	25 (100%)					

This table illustrates a statistically substantial difference among groups based on the number of weeks pregnant.

DISCUSSION

The recent research discovered that 47.2 percent of females with early RSA (unexplained recurrent spontaneous abortion), which enhanced the rate of effective therapy in these females. Multivariate logistic regression analysis was performed to confirm the relation among therapy and successful treatment. Nearly 10%–15percent of females lose their pregnancies spontaneously at some time, with 80% of these miscarriages occurring before the 12th week of pregnancy (early spontaneous abortion). For the majority of these women, spontaneous abortion is a one-time occurrence; nevertheless, there are circumstances when spontaneous abortion occurs on a regular basis. In accordance with a previous report, the loss of two or more pregnancies was classified as RSA in this study. According to the research, about half of all RSA instances have an unidentified cause. In line with this, 47.2 percent of

women with early RSA also had URSA, according to the existing research. According to a recent research RSA could account for 20%–33% of all spontaneous abortions. The frequency of RSA (recurrent spontaneous abortion;) was 32.3 percent within all spontaneous abortions in the recurring research, which is at the high end of the range. This increased rate could be due to the fact that females with a complicated medical history, such as RSA, are commonly referred to the research facility (an experienced center well known for treatment of RSA).

Due to a lacking of detectable aberrant hospital indices and a defined treatment plan, clinical management of URSA remains a challenge. Multiple factors, including autoimmune, coagulation, and nutritional factors, have lately been suggested as potential contributors to URSA .8 Nevertheless, such reasons are hard to discover by conventional hospital examination indices. The immune activity to autoantigens or auto sensitized lymphocytes is referred to as autoimmunity. When autoantibodies and lymphocytes attack cells, it can develop to autoimmune disease, producing pathologic changes in the tissues and organ malfunction (e.g., systemic lupus erythematosus and rheumatoid arthritis). In the case of RSA autoimmunity, data suggests that autoantibodies disrupt cell signaling and thereby interfere with zygote formation, implantation, and embryo progression. These also raise the danger of placental embolism and hypercoagulability, which can lead to spontaneous miscarriage. Another key pathologic factor in RSA is coagulation. During an assessment of hereditary and acquired indications of thrombosis, 78 percent of women with URSA exhibited hemostatic problems, according to a former research. Furthermore, nutrition during the peri-conceptional phase has been recognized as important, and a lack of numerous microelements raises the risk of RSA. Folic acid has been commonly used to avoid neural tube abnormalities during pregnancy, and researches have indicated that supplementing with folic acid lessens the risk of early RSA through modulating homocysteine levels, a known risk factor for spontaneous abortion. The above-mentioned factors are thought to be probable causes of URSA, even though the pathogenic mechanisms are unknown. Routine hospital tests, however, are insufficient to characterize in depth the aberrant indices that underpin these probable reasons, making it challenging to establish the root causes of URSA. Therefore, when treating females with URSA, it is critical to look into treatments that address numerous potential causes. Antiplatelet agglutination therapy with aspirin is routinely used in clinics, and its usage in URSA was first documented in the 1980s. Nevertheless, researches have indicated that aspirin alone, or aspirin combined with heparin, has no impact on URSA in considerations of live birth rate. Prednisone is an immunosuppressive glucocorticoid that is used to protect the zygote from being rejected by the mother's immune system during embryo implantation. It has been found to be harmless and efficient in the treatment of immunological disorders associated with pregnancy. Due to limitation efficacy of these single treatments in decreasing the chance of spontaneous abortion, multivitamins containing folic acid minimize birth defects, including deformation of the fetal neural tube, to enhance the live birth rate in females with URSA, combined treatments have been developed and verified. Furthermore, earlier clinical experience revealed that a combination of aspirin, prednisone, and a multivitamin could lower the risk of miscarriage and enhance pregnancy results in females with URSA. Prednisone, aspirin, folate, and progesterone, in combination, improved birth results in females with idiopathic recurrent miscarriage, according to a related research. Moreover, whether or not progesterone supplementation must be administered to females with URSA is still debatable. In additional, immunological factors, dietary variables, and coagulation disorders are more likely to be the causes of URSA. The triple therapy of aspirin, prednisone, and multivitamins was found to enhance the rate of successful treatment when compared to the control therapy, despite the fact that the rate of successful pregnancy was identical in both groups. It is possible that Aspirin's anti-coagulant activity may have lowered the chance of thrombosis, while prednisone controlled the maternal autoimmune response to the zygote and promoted effective implantation, as well as reducing the danger of fetal deformity, thereby boosting the rate of successful therapy. It's also probable that URSA has a variety of reasons and complications; As a result, the study's treatment failed to address

the underlying pathophysiology of URSA or was inadequate to provide a higher rate of successful pregnancy.

CONCLUSION

For females with idiopathic pregnancy loss, a combination of prednisolone and low-dose aspirin could be a beneficial treatment. Females with recurrent abortion who get a combination of treatments have a strong live birth rate. In the early stages of pregnancy and following effective placenta, this combination may encourage successful embryonic implantations, and protect against uteroplacental thrombosis. The methodology utilized in this experiment should be refined to evaluate the advantages of pre-conceptional administration and whether it may be stopped after 13 week without adversely impacting the rate of live births. Successful pregnancies, on the other hand, have a significant risk of problems during all three trimesters. These pregnancies should be closely monitored during pregnancy and delivered in a unit with specialized obstetric and neonatal critical care capabilities. Due to the low number of participants, non-randomization of groups, and discrepancy in number among groups, reliable findings from this study are limited, and a larger research is required.

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