Comparative Study between Heparin and Prednisone in Women with Repeated Early Pregnancy Loss

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Abstract: Objective: To compare the effect of Heparin versus Prednisone in treatment of women suffering repeated early pregnancy loss. **Design:** Prospective matched pair study. **Setting:** Outpatient clinic of Al-Azhar University. **Subjects:** 100 pregnant women (median age 26) with history of repeated early pregnancy loss (2 or more consecutive miscarriages in the first trimester without anatomic, hormonal and infectious pathology). **Intervention:** 50 women on 5000U of unfractionated heparin subcutaneously 12 hourly. The other 50 women on prednisone (5mg 12 hourly). Two groups matched for age, body mass index and number of previous miscarriages. **Main outcome measures:** fate of pregnancy at the end of first trimester and therapy related side effects. **Results:** In heparin group 84% pass first trimester and 16% had missed abortions while in prednisone group, 80% pass first trimester and 20% had missed abortions. There was no significant difference between two studied groups as regard to fate of pregnancy at the end of first trimester (P- value=0.603). **Conclusion:** There was no significant difference between heparin and prednisone in treatment of women with repeated early pregnancy loss.

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1. Introduction

Repeated early pregnancy loss is by far a common and a major health problem for both the physician and the patient.

It defined as two or more consecutive pregnancy loss in the first trimester and affects 1- 2 % of women in the reproductive stage (1)**,** Whileit is estimated that 5% of women in the reproductive stage have two or more repeated pregnancy loss and around 1% has three or more losses (2).

Etiological factors are varied and often controversial, even more than one factor could be present, the most common causes are genetic, hematological, anatomical, infectious, environmental, endocrinal and immunological factors such as antiphospholilipid antibodies syndrome, altered natural cell activity and increased lympho cytotoxic antibodies (3).

The biological effects mediated by human antiphosphlipid antibodiesinclude reactivity with endothelial structures, which disturb the balance of prostaglandins E2 and thromboxane production, interaction with platelets aggregation, disregulation of complement activation and interaction of anti-phospholipid antibodies with phosphatidylserine exposed during trophoblast syncytium formation which causes the possibilty of more direct effect of these autoantibodies on placental structure (4).

Several drugs were tried in the management of repeated pregnancy loss including aspirin, heparin, low molecular weight heparin (LMWH), folate, progesterone, and prednisolone or combination of the above therapies (5).

A combination of prednisone, aspirin, folate, and progesterone is associated with a higher birth rate compared with no treatment in women with repeated pregnancy loss (6).

An enoxaparin (LMWH) alone may be as effective as a combination treatment of prednisone, progesterone, and aspirin (7).

High numbers of uterine natural killer cells (NK) in preimplantation endometrium of women with RPL can be reduced with administration of prednisone (8).

A recent study has noted the potentiality of glucocorticoids to modulate human leucocyte antigen G (HLA-G) expression which has been implicated in the etiology of repeated pregnancy loss (9).

Till now according to the best of our knowledge, there is no study published to compare between heparin and prednisone treatment in women with repeated early pregnancy loss.

2. Patients and methods

The present study was a prospective matched pair study conducted on one hundredpregnant women with history of repeated early pregnancy loss (2 or more consecutive miscarriages in the first trimester) without associated anatomic, hormonal, and infectious pathology selected from those attending outpatient clinic of AL-Azhar University, new Damietta, Obstetric and Gynecology department at the period from March 2016 to April 2017.

These 100 patients were selected according to the following criteria:

Inclusion criteria:

- Sure of date of first day of last normal menstrual period.
- Two or more spontaneous abortions.
- All are first trimesteric abortions.
- No obvious cause of repeated abortion.

Exclusion criteria:

- Documented cause of recurrent abortion e.g. anti-phospholipid syndrome.
- History of medical disorder like DM or HTN.
- History of chronic disorder like renal cardiac or liver disease.
- History of thromboembolic manifestations.
- Structural anomalies of the uterus.
- Contraindication to use of heparin like sensitivity to heparin, thrombocytopenia and severe renal impairment or prednisone like high blood pressure, diabetes and untreated systemic fungal infection.

Then patients are put into two groups:

- **Group 1 (50):** This group will take Heparin (calheparin 5000IU) subcutaneous twice daily from time of positive pregnancy test.
- **Group 2 (50):** This group will take prednisone (Hostacortin ®) 5mg twice daily from time positive pregnancy test.
- All cases were on low dose Aspirin (Jusprin 81mg) once daily from time of positive pregnancy test.

History taking:

Stressed on age, the number of previous abortions, gestational age at which abortions occur, history of medical disorder like DM or HTN, history of chronic disease like renal cardiac or liver disease, history of Thromboembolic diseases like cerebrovascular or cardiovascular stroke or DVT, history of regular drug intake, history of operations in the uterus, family history of diseases, ask about consanguinity.

Examination:

- **General examination:** weight, height, blood pressure, pulse.
- **Pelvic examination**: trying to find any pathology of uterus or cervix.
- **Investigations:**
  - **Routine labs;** ABO+RH, Complete blood picture, random blood sugar.
  - **Trans vaginal ultrasound:** every three weeks from 5th week gestation till the end of the first trimester using Medison 8000SA live (Korea), ultrasound machine, equipped with a 7-9MHZ trans-vaginal probe.

Data was collected and studied in relation to:

- Occurrence of complications in the first trimester like abortion, missed abortion and its relation to the use of heparin and prednisone and the relation to the time of administration of the drug, age of patient, weight, number of previous abortions.
- Occurrence of complications of drug intake like bleeding from body orifices or thrombocytopenia due to heparin and nervousness, sleeping troubles and infections due to use of prednisone.
- SPSS computer program (version 21 windows) was used for data analysis.

3. Results

Follow chart

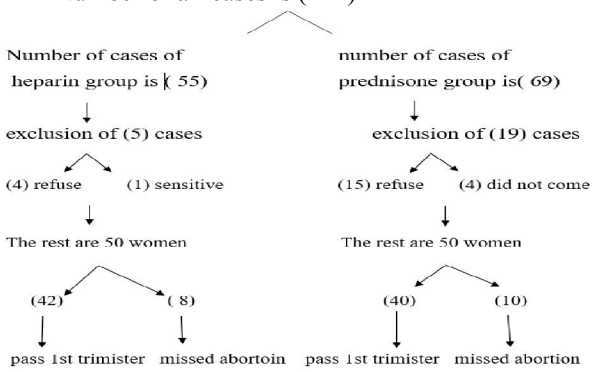

Table 1: Demographic data in the two studied groups:

	Heparin (n = 50)	**Prednisone (n = 50)**	**T**	**P**
Age	**26.22± 4.89**	**27.26± 4.98**	1.054	0.295
BMI	**25.51± 2.47**	**25.40± 1.54**	0.268	0.790
Gravidity	**4.42**	**4.2**	2.109	0.716
Parity	**.92**	**1.1**	2.686	0.443
No. of Previous abortions	**2.5**	**2.36**	1.218	0.544
Cx. Length	**3.49±.34**	**3.38 ±.46**	1.468	0.145

As shown in table the two groups are matched as regard to Age, BMI, Gravidity, Parity, No. of previous abortions and cervical length.

Table 2: Comparison between the two studied groups as regard to GS, Fetal pole and Fetal pulse in 1st visit (5-6weeks gestation):

	On Heparin (n = 50)		**On Prednisone (n = 50)**		**χ^2**	**P**
	No	%	**No**	**%**		
GS	47	94%	50	100%	3.093	0.079
Fetal pole	39	78%	45	90%	2.679	0.102
Fetal pulse	11	22%	19	38%	3.048	0.081

The table showed, on heparin group, 94% of cases have visible GS,78% with visible fetal pole and 22% with visible fetal pulse. On prednisone group, All cases have visible GS, 90% with fetal pole and 38% with visible fetal pulse. So the two groups are matched as regard to GS, fetal pole and fetal pulse.

Table 3: Comparison between the two studied groups as regard to GS, Fetal pole and Fetal pulse in the 2nd visit (8 weeks gestation):

	Heparin (n = 50)		**Prednisone (n = 50)**		**χ^2**	**P**
	No	%	**No**	**%**		
GS	49	98%	50	100%	1.010	0.315
Fetal pole	47	94%	45	90%	0.543	0.461
Fetal pulse	43	86%	41	82%	0.543	0.461

As shown in the table, in the 2nd visit, in heparin group, 94% of cases have fetal pole and 86% with visible pulse, in prednisone group, 90% have fetal pole and 82% with visible pulse. So, there is no significant difference between the two studied groups regarding GS, Fetal pole and Fetal pulse at 8weeks gestation.

Table 4: Comparison between the two studied groups as regard to Fetal pole and Fetal pulse in the3rd visit (11 weeks gestation):

	Heparin (n = 50)		**Prednisone (n = 50)**		**χ^2**	**P**
	No	%	**No**	**%**		
Fetal pole	47	94%	45	90%	.543	0.461
Fetal pulse	42	84%	4o	8o%	0.271	0.603

The table and figure show that, in the 3rd visit, in heparin group, 94% of cases have fetal pole and 84% have fetal pulse. While in prednisone group, 90% have fetal pole and 80% with visible fetal pulse. So, there is no significant difference between the two studied groups.

Table 5: Comparison between the two studied groups as regard to Fetal pole and Fetal pulse in the 4th visit (13-14 weeks gestation):

	Heparin (n = 50)		**Prednisone (n = 50)**		**χ^2**	**P**
	No	%	**No**	**%**		
Fetal pole	47	94%	45	90%	.543	0.461
Fetal pulse	42	84%	4o	8o%	0.271	0.603

The table, in the 4th visit, in heparin group, 94% of cases have fetal pole and 84% have fetal pulse. While in prednisone group, 90% have fetal pole and 80% with visible fetal pulse. So, there is no significant difference between the two studied groups.

Table 6: Fate in the two studied groups:

	Heparin (n= 50)	**Prednisone (n= 50)**	***p*-value**
Pass 1st trimester	42 (84%)	40 (80%)	0.603*
Missed abortion	8 (16%)	10 (20%)	

As shown in the table and figure, it is a comparison between heparin and prednisone groups as regard to fate of pregnancy at the end of first trimester. In heparin group, 84% of women pass the first trimester but 16% have missed abortion. While in prednisone group, 80% of women pass the first trimester and 20% have missed abortion. So, there is

no significant difference between the two studied groups regarding fate of pregnancy in the1st trimester.

94% of patients on heparin had no complication, but 4% complain nasal and gum bleeding and 2% had thrombocytopenia. While in prednisone group, 96% had no complication, 2% had infections and 2% had nervousness and sleeping troubles.

4. Discussion

In the Heparin group, 42 from 50 patients pass 1st trimester with incidence 84% on the other hand 8 patients fail to pass 1st trimester with incidence 16%. While, in the Prednisone group, 40 from 50 patients pass 1st trimester with incidence 80% while 10 patients fail to pass 1st trimester with incidence 20%. There was no significant difference in the fate between the two studied groups (*p*-value=0.603).

Our results are in accordance with the study held by **Zolghadri et al**. (10), Among group taking prophylactic dose of LMWH and aspocid 41 from 50 patients with incidence 83.7% end in live birth and 9 patients end in abortion with incidence 16.3%. While in the group in no treatment27 patients with incidence 54% end with live birth and 23 patients with incidence 46% end with abortion (*p* value=0.001).

In a study held by **Tempfer et al**. (6), demonstrate that a combination treatment consisting of prednisone (20mg/d), aspirin (100mg/d), progesterone (20mg/d) and folate (5mg/d) result in a higher live birth rate than no treatment. The rate of 1st trimester miscarriage was 19% (10 of 52) in the treatment group, while it was 63% (33 of 52) in the no treatment group.

In contrast, some investigators have reported no effect of corticosteroid treatment in women with recurrent miscarriage (11, 12)**.** However, in the present study, we found an improvement in outcome of first trimister.

The difference between reported studies and our data might be attributable to both the dosage and the duration of heparin and prednisone use.

Conclusion

Daily subcutaneous injection of heparin to women with history of repeated early pregnancy loss result in 84% success rate to pass 1st trimester. Only 6% had complications of heparin in the form of gum and nasal bleeding and transient thrombocytopenia.

Daily intake of prednisone (Hostacortin ® 5mg twice daily) result in 80% success rate to pass 1st trimester. Only 4% had complications of prednisone in the form of infections and sleeping troubles.

At the end of this study, there is no significance difference between heparin and prednisone in treatment of repeated early pregnancy loss.

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