

# Safety and effectiveness of tinzaparin sodium in the management of recurrent pregnancy loss

S. Dendrinou<sup>1</sup>, M.D.; I. Kalogirou<sup>1</sup>, M.D.; E. Makrakis<sup>1</sup>, M.D.; T. Theodoridis<sup>2</sup>, M.D.;  
E. A. Mahmoud<sup>2</sup>, M.D.; V. Christopoulou-Cokkinou<sup>2</sup>, M.D.; G. Creatsas<sup>1</sup>, M.D.

<sup>1</sup>2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital

<sup>2</sup>Hematology Laboratory, Evangelismos General Hospital, Athens (Greece)

## Summary

**Purpose:** To assess the safety and efficacy of tinzaparin sodium for the management of recurrent pregnancy loss. **Methods:** The study included 62 women with a history of recurrent pregnancy loss and at least one factor of thrombophilic disorder. Of these, 31 received 50 IU/kg of tinzaparin sodium daily (Group A), and 33 received 100 mg of aspirin daily (Group B). **Results:** Group A subjects (receiving tinzaparin sodium) had six new abortions, whereas Group B subjects (receiving aspirin) had 11 (significant difference). Cases of intrauterine growth restriction (none in Group A and 2 in Group B), placental abruption (one in Group A and 4 in Group B), and preeclampsia (one in Group A and 3 in Group B) were comparable between the two groups. Finally coagulation disorders (none in Group A and 6 in Group B) were significantly fewer in Group A. **Conclusion:** A 50 IU/kg daily dose of tinzaparin sodium seems to be effective for the management of recurrent abortion and has high standards of safety.

**Key words:** Recurrent pregnancy loss; Thrombophilia; Low molecular weight heparin; Tinzaparin sodium; Aspirin.

## Introduction

Recurrent pregnancy loss (RPL), which is defined as three consecutive pregnancy losses before 20 weeks of gestation or below a fetal weight of 500 g, affects 1%-3% of women [1]. Implicated causes include various anatomic, autoimmune, endocrinologic and chromosomal abnormalities, but a large proportion of RPL remains grossly unexplained [1, 2].

RPL is a well established complication of the antiphospholipid antibody syndrome; it is thought to involve thrombosis of placenta vessels, although other mechanisms may be implicated [3, 4]. More recently, inherited and acquired thrombophilic disorders have been linked to pregnancy complications. Thrombophilic defects were found in 49%-65% of women with pregnancy complications compared to 18%-22% of women with normal pregnancies, thus suggesting a 3- to 8-fold increase in risk [5-7].

Low molecular weight heparin (LMWH) has been widely used in cases of thrombophilic disorders, and a systematic review of its use in 486 pregnancies revealed a successful outcome in 89% of women with a history of unexplained RPL, although the prevalence of thrombophilia was not determined [5].

The aim of the present study was to assess the safety and effectiveness of tinzaparin sodium in the treatment of RPL.

## Materials and Methods

The study included 62 women who presented at the Recurrent Miscarriage Clinic of the 2<sup>nd</sup> Department of Obstetrics and Gynecology, University of Athens (tertiary referral center), between January 2001 and April 2004, with a history of three to seven previous miscarriages. All the study subjects were investigated according to our protocol, which includes clinical examination, parental karyotyping, anticardiolipin Ab, lupus anticoagulant, thrombophilia testing (antithrombin deficiency, factor V Leiden, APC – activated protein C, protein C and S deficiency, hyperhomocysteinemia, combined thrombophilia), thyroid antibodies and function tests, prolactin assaying, LH and FSH levels on day 3 of the menstrual cycle, progesterone (PRG) and estradiol (E2) on day 21 of the menstrual cycle, transvaginal ultrasound scan and hysteroscopy. Inclusion criteria for entrance in the study were the following: age below 40 years, at least one factor of thrombophilic disorder, absence of obvious anatomic, autoimmune or endocrinologic abnormalities possibly related to RPL, and absence of bleeding diathesis or active bleeding contraindicating anticoagulant therapy.

The study subjects were randomly allocated into two groups. Randomization was performed with the method of blocks (in 5 blocks of 10 and 2 blocks of 6) and the use of random numbers tables. Group A included 31 women who were treated with tinzaparin sodium on a daily dose of 50 IU/kg subcutaneously, and Group B included 31 women who were treated with acetylsalicylic acid on a daily dose of 100 mg orally. Subjects in both groups started treatment with their first positive pregnancy test, which was performed as soon as there was a delay of the expected period. Group A subjects were asked to stop tinzaparin three days before delivery (if applicable), whereas Group B subjects were asked to stop acetylsalicylic acid at 32 weeks of gestation.

Statistical analysis was performed with the use of non-parametric statistical tests (Fisher's exact) and p values < 0.05 were considered as significant.

## Results

Table 1 shows the results of thrombophilia testing in the study population. There were no significant differences in the prevalence of specific thrombophilic disorders between the two study groups.

Table 2 shows pregnancy outcome and complications in the study groups. In Group A 19.4% of women aborted (12.9% had a first trimester abortion and 6.5% a second trimester abortion). In Group B 35.5% of women aborted (29% in the first trimester and 6.5% in the second trimester). In Group A none of the pregnancies were complicated with intrauterine growth restriction (IUGR), but in Group B 6.45% of pregnancies were complicated with IUGR after 28 weeks of gestation. Abruptio of the placenta complicated 3.22% of the pregnancies in Group A, and 12.9% in Group B. Another pregnancy complication was preeclampsia which appeared in 3.22% of Group A pregnancies and in 9.6% of Group B pregnancies. Finally, none of Group A pregnant subjects, but 19.3% of Group B subjects demonstrated coagulation disorders.

Statistical analysis revealed that subjects treated with tinzaparin had significantly fewer new miscarriages ( $p = 0.04$ ) and demonstrated significantly fewer coagulation disorders ( $p = 0.01$ ). The incidence of IUGR, placenta abruptio and preeclampsia was comparable between the two groups.

Table 1. — Results of thrombophilia testing in the study population.

Thrombophilic disorder	Number of subjects		Prevalence in the study population
	Group A	Group B	
Antithrombin deficiency	—	—	—
Protein C deficiency	2	0	3.22%
Protein S deficiency	2	0	3.22%
Factor V Leiden (heterozygous)	6	8	22.6%
Factor V Leiden (homozygous)	1	1	3.22%
Prothrombin gene mutation	—	—	—
Hyperhomocysteinemia	5	7	19.35%
Homozygous MTHFR C677T	3	5	12.9%
Antiphospholipid antibodies	7	5	17.7%
Acquired APC resistance	7	9	25.8%

Table 2. — Pregnancy outcome and complications in the study population.

	Group A	Group B	p values
Patients (n)	31	31	
Patients with new abortion (n)	6	11	0.04
Pregnancies with IUGR (n)	0	2	0.24
Pregnancies with placenta abruptio (n)	1	4	0.17
Pregnancies with preeclampsia (n)	1	3	0.3
Patients with coagulation disorders (n)	0	6	0.01

## Discussion

Thrombophilic disorders have been reported in 49%-65% of women with pregnancy complications compared with 18%-22% of women with normal uncomplicated pregnancies, suggesting a 3- to 8-fold increase in complication risk [6, 7]. A genetic disorder characterized by

an impaired anticoagulant response to APC is Factor V Leiden (FVL) [5]. A heterozygous mutation, found in 5%-8% of the population, is associated with a 4- to 8-fold increase in risk for complications. Homozygous FVL occurs in one of 1,600 individuals and confers an 80-fold increased risk. A large number of case studies found a high prevalence of FVL in women with unexplained pregnancy loss (up to 30%) compared with 1%-10% of control subjects [6, 8, 9]. In addition, three retrospective studies found that FVL carriers have a 2-fold increased risk for fetal loss [5, 10, 11]. Acquired APC resistance has been found in 9%-38% of women with unexplained RPL, compared with 0%-3% in controls [12, 13]. The prothrombin gene mutation was found in 4%-9% of women with RPL compared with 1%-2% of those with uncomplicated pregnancies and in a meta-analysis including 2,087 women, the mutation was associated with a 2- to 3-fold increased risk for RPL [14].

Anticoagulant protein deficiencies increased the risk of fetal loss in most [15, 16, 18] but not all of the limited number of studies [17]. Hyperhomocysteinemia is an independent risk factor for both first and recurrent thromboembolism [19]; it has been found in 17%-27% of women with first or recurrent fetal loss compared with 5%-16% of control women, whereas a meta-analysis reported a 3- to 4-fold increased risk of early RPL [20]. A specific point mutation (C677T) in the methylenetetrahydrofolate reductase (MTHFR) gene results in a variant thermolabile enzyme with reduced activity for the remethylation of homocysteine. A few studies have suggested that an homozygosity mutation increases the risk of recurrent pregnancy loss, but the majority of them reported no significant association, whereas a meta-analysis including 1,818 women found no association with recurrent fetal loss [14]. Finally women with multiple thrombophilic defects had a 14-fold increased risk of late pregnancy loss compared with a 4-fold higher risk in those with only a single defect [18].

Regarding specific pregnancy complications in women with thrombophilic disorders, data on the risk of fetal growth restriction are limited and conflicting. Thrombophilic defects were found by some investigators in 60%-70% of women with a history of IUGR compared to 13%-18% of those with normal pregnancies, suggesting a 4-5 fold increase in risk [6]. In contrast, a larger case-control study failed to reveal any significant association between maternal thrombophilia and fetal growth restriction [21]. Concerning placenta abruptio, some studies have suggested no association with thrombophilia [22, 23], whereas others suggested a higher prevalence of FVL [6, 24]. Finally, the association of thrombophilic disorders and preeclampsia was investigated in nine control studies and a significantly higher prevalence of FVL was reported [6, 25].

LMWH has been shown to be a safe and effective anticoagulant for the prevention and treatment of venous thromboembolism in a variety of clinical settings [26]. Pregnancy outcome can be significantly improved with the use of LMWH and aspirin [27-29]. Tinzaparin has an

average molecular weight of 6.5 kD, an anti-Xa activity of 86 U/mg and an anti-factor IIa activity of 46 U/mg with reference to the first international standard for LMWH. For tinzaparin the recommended daily dose for prophylaxis in moderate-risk non-pregnant patients is 50 IU/kg but Norris *et al.* suggested that pregnant patients start on a dose of 75 IU/kg to prevent thrombosis although larger studies are required to determine whether this increased dose would be more effective in preventing thrombosis during pregnancy than the lower dose of 50 IU/kg [28]. Finally, not only in our study, aspirin therapy seems to be ineffective for preventing recurrent miscarriage in women who do not have any autoimmune explanation for previous pregnancy losses [30].

## Conclusion

In our study we have found that in women with recurrent pregnancy loss, a starting dose of 50 IU/kg tinzaparin sodium IV gives good results, is safe and has a better outcome with fewer complications compared to acetylsalicylic acid alone. Larger studies are needed to further assess the effectiveness of tinzaparin sodium in women with recurrent pregnancy loss.

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Address reprint requests to:  
I. KALOGIROU, M.D.  
4 D. Eginitou Str.  
11528 Athens (Greece)