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Does anticoagulant therapy improve adverse pregnancy outcomes in patients with history of recurrent pregnancy loss?

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ABSTRACT

Objectives: Recurrent pregnancy loss (RPL) is a serious problem in the reproductive age women. We aimed to study the role of anticoagulant therapy on pregnancy complications and perinatal outcomes in pregnant patients with histories of RPL.

Material and methods: One hundred fifty-three pregnants, with RPL history and thrombophilia positivity, were grouped into two as 89 treated with anticoagulant therapy and 64 non-treated. Treated and untreated groups were compared for pregnancy complications, delivery weeks, abortion rates, fetal birth weights, APGAR scores, live birth rates, and newborn intensive care admission rates.

Results: Of the total 153 pregnant patients (63%) 97 developed pregnancy complications; 55 (56.7%) were in the untreated group and 42 (43.3%) were in the treated group, which was statistically significant (p = 0.003). The differences in pregnancy complications were produced by differences in the numbers of IUFDs and anembryonic fetuses among the groups. The average neonatal birth weights of infants whose mothers had taken LMWH + ASA were significantly higher (p=0.011). The prematurely delivered infants were admitted to the neonatal intensive care unit (NICU), and the NICU requirements were not statistically different between the groups (p = 0.446). However, live birth rates were significantly higher in the treated group than in the untreated group (p = 0.001).

Conclusions: Anticoagulant therapy improves pregnancy complications and live birth rates in patients with RPL and hereditary thrombophilia.

Key words: recurrent pregnancy loss, anticoagulant therapy, hereditary thrombophilia

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INTRODUCTION

Recurrent pregnancy loss (RPL), traditionally defined as three or more miscarriages before 20 weeks of gestation, continues to be an important problem among women of reproductive age [1], affecting approximately 1–2% of all pregnancies [1]. The American College of Obstetricians and Gynecologists describes RPL as two or more sequential miscarriages, a definition which increases the incidence rate to 5% [2]. While the causes of approximately half of RPL cases are undetermined, the remaining half are considered to be due to genetic and anatomic abnormalities, endocrine diseases, thrombophilia, and immunologic disorders. The association between inherited thrombophilia and RPL was first reported by Sanson et al., in 1996 [3]. Various thrombophilic polymorphisms have been associated with RPL. The type of thrombophilia and the mode of fetal loss play a role in this relationship [4].

Different authors have confirmed the important role of thrombophilia in RPL [5, 6]. Thrombophilia also causes early intrauterine fetal demise (IUFD), pre-eclampsia, and abruptio placentae. The main cause of obstetric complications is inadequate placental perfusion due to hemostatic imbalance [7]. Factor V Leiden (FVL), prothrombin (PT G202I0A), methylenetetrahydrofolate reductase C677T, and A1298 mutations

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(MTHFR), as well as protein C, protein S, and antithrombin III deficiencies are the most common causes of hereditary thrombophilia. Acquired cases of thrombophilia are due to the presence of antiphospholipid antibodies, such as lupus anticoagulant and anticardiolipin antibody [8].

Successful pregnancy outcomes depend on sufficient utero-placental circulation because hemostatic disorders may cause obstruction in the placental vessels, resulting in pregnancy complications, in particular miscarriage [7]. For this reason, antithrombotic prophylaxis has been used to prevent pregnancy complications. According to one meta-analysis, data on maternal hereditary thrombophilia and early fetal loss are limited [9]. However, thromboprophylaxis is suggested to be helpful in antiphospholipid syndrome cases [10]. Due to considerable variability in research methodology, low number of study patients and placebo group participants, as well as differences in the choices and duration of medication, the results of these studies are not satisfactory. Although, according to the current literature, the effectiveness of anticoagulant prophylaxis is controversial, it has been widely used in pregnant patients with previous poor obstetric history to prevent pregnancy complications and to improve live birth rates.

For the above-stated reasons, the present study focused on the role of anticoagulant therapy in pregnant patients with history of RPL. In addition, we aimed to detect the effect of anticoagulant therapy on pregnancy complications and on perinatal outcomes.

MATERIAL AND METHODS

A retrospective review of the medical records of pregnant patients, who were admitted to the Bulent Ecevit University Antenatal Care outpatient clinic between 2012 and 2014, was conducted. Local Ethics Committee approved of the study. Pregnant patients with history of two or more early pregnancy losses were studied. Women with chronic diseases, autoimmune disorders, infectious diseases, abnormal fetal or parental karyotypes, uterine anomalies, endocrine disorders, positive antiphospholipid antibodies, or having a known cause of RPL other than hereditary thrombophilia were excluded from the study. Of the 153 patients who met the inclusion criteria, the most commonly screened inherited thrombophilia mutations (FVL, PT G202I0A, and MTHFR C677T/A1298 mutations) were noted. Our study group included patients with history of RPL, at least one type of mutation of the most commonly screened thrombophilia, and no history of anticoagulant therapy during their previous pregnancies. The selection of the study group is illustrated in Table 1.

Patient records were reviewed for age, gravidity, parity, previous abortions, and live births. Inherited thrombophilia patterns were recorded. Patients were then divided into two groups according to whether they had or had not received anticoagulant therapy during their last pregnancy. Patients who had received anticoagulant therapy took low-molecular-weight heparin (LMWH, 100 IU/kg) + acetylsalicylic acid (ASA), 80 mg/day.

Treated and untreated groups were compared for pregnancy complications (IUFD, anembryonic pregnancy, gestational diabetes, intrauterine growth retardation [IUGR], pre-eclampsia, placental abruption, and placenta previa), gestational age at delivery (weeks), and modes of delivery with respect to the last pregnancy, cesarean indications, abortion rates, fetal birth weights, APGAR scores, live birth rates, and newborn intensive care admission rates.

Hereditary thrombophilia genetic tests for Factor V Leiden, PT G20210A, and MTHFR C677T/A1298C gene polymorphisms were analyzed by polymerase chain reaction. Patients with more than one mutation were categorized as combined thrombophilia in determining thrombophilia patterns.

Statistical analysis

Statistical analyses were performed with SPSS 19.0 software (SPSS Inc., Chicago, IL). Distribution of data was determined by the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), and categorical variables as frequency and percent. Continuous variables were compared with the independent sample t-test or Mann-Whitney U test, and categorical variables were compared using Pearson's chi-square test or the Fisher exact chi-square test. The p-value of < 0.05 was considered as statistically significant for all tests.

RESULTS

One hundred and fifty-three patients with at least one type of hereditary thrombophilia and history of two or more early pregnancy losses were included in the study. Of the 153 patients, 96 (62.7%) had no living children, 50 (32.7%) had 1 living child, and 7 (4.6%) had 2 living children. Sixty-four patients had not received any anticoagulant treatment, whereas eighty-nine had received LMWH + ASA during their last pregnancy. Median age of the treated and the untreated groups was 31 (20–41) and 31 (20–40) years, respectively, and the difference was not statistically significant ($p = 0.603$). Gravidity, parity, abortion, and previous live birth rates were not statistically different between the groups (Table 1).

In the untreated group, 48 women (75%) had MTHFR mutations (14 homozygous and 34 heterozygous); 4 (6.3%) had PT G202I0A mutations (1 homozygous and 3 heterozygous); and only 1 patient had an FVL heterozygous mutation.

Table 1. Demographic properties of the patients

	LMWH + ASA treated group (n = 89)	Untreated group (n = 64)	P value
Age	31 (20–41)	31 (20–40)	0.603
Gravida	4 (2–9)	3 (2–6)	0.036
Parity	2 (0–3)	2 (0–3)	0.441
Abortions	2 (2–8)	2 (2–4)	0.055
Live births	0 (0–2)	0 (0–2)	0.370

The datas were given as median (min–max). $p < 0.05$ was accepted as significant

Table 2. Mutation status of the groups

Mutation	LMWH + ASA treated N (%)	Untreated N (%)
MTHFR		
Homozygous	18 (20.2%)	14 (21.9%)
Heterozygous	34 (22.2%)	34 (53.1%)
PT		
Homozygous	0 (0%)	0 (1.6%)
Heterozygous	4 (4.5%)	3 (4.7%)
FVL		
Homozygous	0 (1.1%)	0 (0%)
Heterozygous	2 (2.2%)	1 (1.6%)
Combined mutation	30 (33.7%)	11 (33.7%)
Total	89 (100%)	64 (100%)

Results are given as number (%). Percentiles are given within the group. Combined mutation is accepted as one or more type of hereditary thrombophilia positivity

Table 3. Pregnancy outcomes of the groups with RPL and thrombophilia

Obstetric complications	LMWH + ASA treated N (%)	Untreated N (%)
Intrauterine fetal demise (IUFD)	14 (33.3%)	31 (56.4%)
Anembryonic pregnancy	6 (14.3%)	17 (30.9%)
Gestational diabetes (GDM)	9 (21.4%)	2 (3.6%)
Intrauterine growth retardation (IUGR)	3 (7.1%)	2 (3.6%)
Preeclampsia	7 (16.7%)	2 (3.6%)
Abruptio placenta	1 (2.4%)	0 (0%)
Placenta previa	2 (4.8%)	1 (1.8%)
Total	42 (100%)	55 (100%)

Results are given as number (%). Percentiles are given within the group. The total number of complication was statistically higher in untreated group ($p = 0.003$). The difference in pregnancy complications was produced by the differences in the numbers of IUFDs and anembryonic fetuses among groups

A total of 11 subjects (17.2%) were combined thrombophilia carriers (Table 1). In the treated group, 52 (58.4%) had MTHFR mutations (18 homozygous and 34 heterozygous), 4 (4.5%) had heterozygous PT G202I0A mutations, and 3 (3.3%) patients had FVL mutations (1 homozygous and 2 heterozygous). A total of 30 (17.2%) treated patients were combined thrombophilia carriers (Table 2).

Patient records were reviewed for maternal complications during the latest pregnancy (Table 3). Of the total 153 pregnant patients, 97 (63%) developed pregnancy complications: 55 (56.7%) in the untreated and 42 (43.3%) in the treated group. Statistically significant differences between the two groups were observed ($p = 0.003$). Differences in pregnancy complication rates resulted from the differences in the numbers of IUFDs and anembryonic fetuses among the groups. Intrauterine exitus was observed in 31 (56.4%) of the untreated patients, whereas 14 (33.3%) of the treated patients had IUFDs. Also, 17 (30.9%) pregnancies from the

Table 4. Perinatal outcomes and modes of delivery of groups

	LMWH + ASA treated N (%)	Untreated N (%)
Delivery week	37 (27–40)	36 (31–40)
Cesarean section	60 (67.4%)	14 (21.9%)
Vaginal delivery	(19.1%)	14 (21.9%)
Abortions/currettage	12 (13.5%)	36 (56.3%)
Apgar 1 min	7 (0–9)	8 (0–8)
Apgar 5 min	10 (0–10)	10 (0–10)
Live birth*	68 (80%)	17 (20%)
Neonatal intensive care requirement Yes No	 10 (13.9%) 62 (86.1%)	 1 (5.6%) 17 (94.4%)

*The ratios are within total number of live birth babies (n = 85). The p value for live birth ratio was significant (p = 0.001)

Table 5. Cesarean indications of the groups

Cesarean indications	LMWH + ASA treated N (%)	Untreated N (%)
Previous cesarean history	18 (30.5%)	4 (28.6%)
Acute fetal distress	12 (20.3%)	7 (50.0%)
Cefalopelvic disproportion	17 (28.8%)	2 (14.3%)
Abruptio plasenta	2 (3.4%)	0 (0%)
Preeclampsia	4 (6.8)	0 (0%)
Macrosomic fetus	5 (8.5%)	0 (0%)
Placenta previa	1 (1.7%)	1 (7.1%)
Total	59 (100%)	14 (100%)

Results are given as number (%). Percentiles are given within the group

Table 6. Regression model for potentional factors contributing live birth

		Odds ratio	95,0% CI for EXP(B)		P value
		Upper	Lower	Lower	Upper
Step 1	Age	0.974	0.487	0.905	1.049
	Abortion history	1.471	0.159	0.859	2.520
	Combined mutation	1.766	0.137	0.834	3.741
	Constant	1.278	0.850		

untreated group were terminated due to anembryonic pregnancies. Moreover, 6 (14.3%) pregnancies from the treated group were terminated for the same reason. When we omitted IUFDs and anembryonic pregnancies, no statistically significant differences were noted between the groups with regard to other pregnancy complications.

Approximately one-third of pregnancies from the untreated group and two-thirds of pregnancies from the treated group resulted in live births through cesarean section (21.9% and 67.4%, respectively); whereas for vaginal delivery the rates were 21.9% and 19.1%, respectively. A total of 48 (31.4%) patients had therapeutic curettages due to IUFDs or to anembryonic pregnancies, including 36 (56.3%) in the untreated and 12 (13.5%) in the treated group. The number of patients who underwent therapeutic curettage was significantly higher in the untreated group (Table 4). Indications for cesarean sections were all due to obstetric causes, which are presented in Table 5.

The groups were compared with respect to gestational age at delivery, birth weight, APGAR scores at 1 and

5 min, live births, and neonatal intensive care requirement rates. Mean neonatal birth weight of infants whose mothers had taken LMWH + ASA was significantly higher than those whose mothers had not received anticoagulant therapy ($p = 0.011$). Differences between APGAR scores at 1 and 5 min. were statistically insignificant between the groups ($p = 0.077$ and $p = 0.111$, respectively). Prematurely delivered infants were admitted to the neonatal intensive care unit (NICU), and the NICU requirements were not statistically different between the groups ($p = 0.446$). However, live birth rates were significantly higher in the treated group as compared to the untreated group ($p = 0.001$; Table 4).

Regression analyses of live births were performed using maternal age, the number of previous abortions, and the combined thrombophilia status. Unfortunately, none of the investigated risk factors were found to be predictive for risk ratio of live births (Table 6).

DISCUSSION

Various authors have reported that poor pregnancy outcomes and neonatal risk are increased in pregnant patients with hereditary thrombophilia [11–13]. For the most part, poor obstetric outcomes result from hemostatic disturbances, which cause obstruction in the placental vessels [14]. In recent studies, placenta-associated complications (IUFD, IUGR, RPL, pre-eclampsia, and placental abruption) have been confirmed as the leading causes of maternal/fetal morbidity and mortality [15, 16].

It has been demonstrated that a history of RPL also constitutes a risk factor for the current pregnancy. Paidas et al., stated that the recurrence rate of obstetric complications without thrombophilia is approximately 23%, with the presence of thrombophilia further increasing the risk [17]. In another study, pregnant women with poor obstetric history were shown to have a 52% risk for pre-eclampsia, while the risk for IUGR and IUFD was 56% and 48%, respectively [18]. In our study, RPL was found in 56 patients (36% in the untreated and 13.5% in the treated group).

In accordance with the definition of the American College of Obstetricians and Gynecologists [2], the present study included pregnant patients whose previous pregnancies resulted in two or more miscarriages. Thus, the traditional definition of RPL (three or more miscarriages) was not considered in this study.

Numerous studies have been conducted in pregnant patients with thrombophilia and history of RPL to improve maternal and fetal complications and perinatal outcomes. In animal models, the improvement of trophoblast invasion has been studied with the aid of LMWH in patients with history of RPL [19]. Clinical studies have also supported this finding. De Carolis et al., demonstrated that the use of LMWH in patients with hereditary thrombophilia and poor obstetric history resulted in a higher number of live births, increased birth weight, and decreased rate of perinatal complications [20]. Brenner et al., also found that LMWH improved live birth rates [21]. Alguel et al., who detected a higher risk in women with history of thromboembolism, suggest that LMWH improved the number of favorable pregnancy outcomes [22].

With respect to its effectiveness in improving maternal and fetal complications, ASA has also been compared with LMWH. Giancotti et al., reported that LMWH or LMWH + ASA combination therapy is significantly more protective against fetal losses than ASA-only treatment [23]. They also recommend thromboprophylaxis for women with history of RPL, without considering the positivity of thrombophilia markers. In another study, anticoagulant therapy with LMWH + ASA was suggested to provide better obstetric outcomes in women with thrombophilia and poor obstetric history [24]. Our study also showed that the use of LMWH + ASA increased live birth rates and birth weight. Our results were similar to the study of Mak, in which a combination of heparin and aspirin was found to be superior to aspirin alone in enhancing the number of live births in patients with RPL and anti-phospholipid antibodies positivity [25].

Our study was not without limitations. First, due to its retrospective and not prospective nature, we were able to evaluate only one type of anticoagulant treatment modality used in our clinic. Since performing randomized placebo-controlled trials in pregnant patients has been a big challenge due to ethical issues, retrospective studies generally have been reported. To the best of our knowledge, only two placebo-controlled studies, i.e. the Anticoagulant Fetus and the Scottish Pregnancy Intervention, have been performed to date [26, 27]. Anticoagulant use in patients with RPL independent from thrombophilia positivity was examined in these studies, which were unable to demonstrate a significant difference in live birth rates between the study- and control-group patients, since there was a contradiction with respect to the design and results of the studies.

The other limitation of our study was a relatively small sample size. Thus, regression analysis of the potential factors (age, number of previous abortions, combined mutation status) could not predict the relative risk of live birth.

We reported better perinatal outcomes in patients with previous RPL and hereditary thrombophilia in pregnant patients treated with anticoagulant therapy. However, randomized controlled trials are needed in order to recommend routine administration of anticoagulant therapy to pregnant patients with history of RPL.

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