Impact of Factor V Leiden, prothrombin and methylenetetrahydrofolate reductase gene mutations on infant birth weight in women with recurrent fetal loss and women with successful pregnancies

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Summary

Purpose: The aim of this study was to verify whether FV Leiden, PT G20210A, MTHFR C667T or MTHFR A1298C mutations influence the risk of recurrent fetal loss in a sample of Turkish women who had experienced recurrent fetal loss and to evaluate whether the aforementioned thrombophilias and recurrent fetal loss may affect the birth weight of subsequent pregnancies. *Methods:* Fifty-eight women with recurrent pregnancy loss and 30 women with successful pregnancies were evaluated. *Results:* The average birth weights for infants of all women in the study group and for infants of thrombophilia-positive women in the study group were markedly lower than the birth weight of infants in the control group ($p < 0.001$ and $p < 0.001$, respectively). *Conclusion:* Successful pregnancies in women with a history of recurrent fetal losses may be associated with lower birth weights compared to controls, irrespective of thrombophilia status. This conclusion warrants further research.

Key words: Inherited thrombophilia; Birth weight; Pregnancy; Turkish population.

Introduction

Thrombophilias have been shown to be associated with fetal loss and adverse pregnancy outcomes [1]. Almost 5% of women experience two or more fetal losses during the reproductive period [2]. Inherited thrombophilias can cause thrombosis, vascular damage and fibrinoid necrosis of decidual vessels, all of which can result in adverse pregnancy outcomes such as miscarriage, preeclampsia, intrauterine growth restriction, placental abruption and stillbirth [3-5]

Thrombophilias usually emanate from single nucleotide polymorphisms. Two common polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene are MTHFR C677T and MTHFR A1298C, which can result in elevated homocysteine levels and vascular thrombotic events [6, 7]. Both of these two mutations have been found in women who experienced spontaneous abortions [8]. Factor V Leiden (FV Leiden) and prothrombin (PT) G20210A SNPs are the two most common causes of inherited thrombophilias [9].

Methods and Patients

Data for 90 women with a history of recurrent fetal loss (defined as three or more consecutive fetal losses) [4] were collected from the obstetric unit data bank. The thrombophilia status of all women had been determined previously. No women were detected to have antithrombin deficiency, protein S deficiency or antiphospholipid syndrome. Two women with protein C deficiency were excluded. The remaining 88 women were investigated about their subsequent pregnancy status. Fifty-eight of these women who conceived naturally and who did not develop adverse pregnancy outcomes (e.g., gestational hypertension, gestational diabetes mellitus) served as the study group. All birth weights are corrected for gestational age. No women were given any anticoagulant therapy because as yet there is no consensus report regarding the use of anticoagulants for recurrent fetal loss with inherited thrombophilia [10]. Additionally, more frequent appointments were applied for patients in the study group. Thirty women with a previous uneventful pregnancy, no history of pregnancy loss, no known history of familial thrombophilia who conceived naturally and gave full-term birth without any adverse pregnancy outcomes were selected as the control group. All patients provided informed consent. The local ethics committee approved the study. Genomic DNA was extracted from EDTA-treated whole blood using the spin-column method (MN Nucleospin Blood). FV Leiden (G1691A), PT G20210A, MTHFR C677T and MTHFR A1298C mutations were identified using the 5' nuclease assay method. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, version 16.0) for Windows; p values < 0.05 were considered statistically significant.

Results

The mean ± SD age was 32.8 ± 4.7 in the study and 29.1 ± 3.6 in the control group ($p < 0.05$). Maternal weight gain was similar in both groups. Birth weight data was available for 58 patients in the study group. All birth weights after correcting for gestational age were found between the 10th and 90th percentiles. There were nine preterm births in the study group and there was only one low birth weight infant among term births in the study group. There were no preterm births and no low birth weight infants in the control group. All comparisons between groups were performed before and after exclud-

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ing preterm births. Birth weight in the study group was significantly lower than that in controls before and after excluding preterm births ($p < 0.001$ and p = 0.001, respectively). When thrombophilia-positive women in the study group were compared before and after excluding preterm births, mean birth weights were 3039 ± 436 g and 3166 ± 342 g, respectively, also significantly lower than that for the controls ($p < 0.001$ and $p < 0.05$, respectively). Moreover, women with one or two thrombophilias tended to have lower weight infants in the study group than the controls. Maternal weight gain significantly but weakly correlated with birth weight in the study and control groups (r = 0.206, $p < 0.05$ and r = 0.135, $p < 0.05$, respectively). The distribution of the mean ± SD birth weight in the study and control groups is summarized in detail in Table 1. Additionally, no difference between the number of thrombophilias (n = 48) among women who gave birth in the study group and the control group (n = 27) was found.

Table 1. — *Mean ± SD birth weight distribution in the study and control groups.*

Thrombophilia Status	Study group* n; mean ± SD BW (g)	Controls n; mean ± SD BW (g)	*p*
MTHFR C677T	18; 3043 ± 454	12; 3425 ± 303	0.01
MTHFR A1298C	15; 3054 ± 527	11; 3328 ± 200	ns
MTHFR C677T + MTHFR A1298C	33; 3048 ± 481	23; 3379 ± 258	0.002
PT G20210A	5; 2936 ± 456	1; 3500	ns
FV Leiden	10; 3062 ± 270	3; 3320 ± 329	ns
PT G20210A + FV Leiden	15; 3020 ± 331	4; 3365 ± 283	ns
Thrombophilia positives	48; 3039 ± 436	27; 3377 ± 256	< 0.001
Thrombophilia negatives	10; 2803 ± 293	3; 3136 ± 23	ns
All	58; 2998 ± 422	30; 3353 ± 253	< 0.001

BW: birth weight, MTHFR: methylenetetrahydrofolate reductase; PT: prothrombin; FV Leiden: Factor V Leiden; ns: non significant. * The total number of given birth weights for the study group was 58.

Discussion

There have been conflicting reports about recurrent fetal loss and inherited thrombophilia in the literature [11-13]. Among 68.9% of women with a history of three or more in-vitro fertilizations and embryo transfer failures at least one thrombophilia was detected, of which MTHFR C677T was the most common [14]. This mutation was also the most prevalent type of thrombophilia observed in our study. Nonetheless, recommendations for thrombophilia screening [15] do not include MTHFR C677T and MTHFR A1298C mutations. In this study, we include these two mutations to determine the frequency in our region.

Previous research by Nath *et al*. [16] reports that thrombophilia status is not the only cause of low birth weight infants, and that preterm births are the predominant factor. On the contrary, a cohort study reported that MTHFR C677T can be used as a marker to recognize pregnant women who are at risk for having fetuses that are small-for-gestational-age [17]. A recent meta-analysis found a notable association only between FV Leiden mutation and intrauterine growth restriction [18].

In our study, we found that the birth weights of infants born to women in the study group were significantly lower than the birth weight of the infants born to women in the control group. However, we could not link this difference either to preterm births or thrombophilias. Thus, it can be proposed that women with recurrent fetal loss tend to have lower weight infants in their subsequent pregnancy. Additionally, in our study, the mean age of the study patients was higher than that of controls. It is thought that age is an important factor influencing birth weight, but this hypothesis is controversial [19, 20]. It is also possible that the lower infant weight observed in infants born to women in our study group may be associated with paternal thrombophilia status [21], but this is beyond the scope of our study.

One of the limitations of our study is the relatively small population of the study group but our data is solid. Additionally, due to the limited number of patients in the study group it is not possible to make a strict conclusion. However, a substantially larger trial is needed to make a clear decision.

Although, it has been suggested previously that inherited thrombophilias may play an important role in recurrent pregnancy loss, inherited thrombophilias have not been accepted as the sole or adjunct cause of recurrent pregnancy loss or low birth weight infants. In this retrospective case-control study, we demonstrated that irrespective of a woman's thrombophilia status, past history of recurrent pregnancy loss may be associated with lower birth weight infants in subsequent successful pregnancies. This conclusion warrants further research with prospective randomized trials.

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