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DETERMINATION OF PREGNANCY OUTCOME IN WOMEN WITH THROMBOPHILIA MUTANAT GENES

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ABSTRACT

Background and aim: Thrombophilia mutations in pregnancy is not a very common condition, thrombophilia may cause seriuse problems in pregnancies. Hereditary thrombophilia, such as mutations of factor V Leiden, prothrombin G20210A and MTHFR genes, predisposes mothers to missed pregnancies, preeclampsia and abruption, and neonates to preterm deliveries and IUGR. Despite such untoward consequences, there is still dispute on the usefulness of prophylactic treatments. The present study aims to determine the effect of such treatments on maternal and fetal outcomes in mothers with thrombophilia.

Methods & Materials: A total of 60 pregnant mothers with mutant thrombophilia genes received LMWH (40 mg/d) plus ASA 80 mg/d). Maternal and neonatal outcomes including abortion, preeclampsia, hypertension without preeclampsia, abruption, preterm delivery and IUGR were documented and compared to those occurred in previous pregnancies.

Results: The mean age patients was 30.05±5.49 years (range: 19-43). Mutations of factor V Leiden, prothrombin G20210A and MTHFR genes were documented in 13.3%, 11.7% and 86.7% of cases, respectively. The rate of normal delivery was 85%. Compared to previous pregnancies, the rate of abortion ($p<0.001$), preeclampsia ($p=0.04$) and preterm delivery ($p=0.004$) decreased significantly after treatment. There were no case with new abruption or IUGR. A significant increase in the rate of hypertension without preeclampsia was documented after treatment, as well.

Conclusion: On the basis of our findings, prophylactic treatment with LMWH plus ASA is effective and safe in reducing maternal and neonatal complication in pregnancies with thrombophilia.

KEYWORDS: Thrombophilia, Pregnancy, Treatment.

Introduction

As a hereditary disease, thrombophilia paves the way for venous thromboses (1). The frequency of thrombophilia mutations including Factor V Leiden, prothrombin G20210A, and MTHFR has been reported 6% in general population (2), which may rise up to 9.1% in cases with frequent pregnancy failure (3).

Defects and dysfunction of some coagulation factors increase the risk of thrombosis. On the other hand, physiological changes during pregnancy and increased risk of coagulation in this period and underlying conditions such as thrombophilia, highly increase the possibility of risks and complications. Hereditary thrombophilia is known as a risk factor for frequent failure of pregnancy. Some reasons for this condition include placental vascular blockage, placental abruption, fetal distress syndrome, and pre-eclampsia due to maternal or placental vascular thrombosis (4-6).

In addition to the mentioned complications, IUGR is also considered as a complication of thrombophilia. Genetic mutations, including Factor V Leiden (G1691A), prothrombin factor (G20210A), and deficiency of protein C and S, anti-thrombin, and methyl tetrahydrofolate reductase (MTHFR), as factors of hereditary thrombophilia, have a known role in the occurrence of frequent failure of pregnancy and other disorders of pregnancy (7).

Since there is no definitive treatment for genetic defects, dangerous events during and after pregnancy can be prevented through preventive decisions. Therefore, knowing the effects of genetic factors alone and in association with other factors can be helpful in better controlling the adverse and undesired complications.

Canda et al. attributed the frequent failure of pregnancy to low birth weight, rather than thrombophilia (8). Kazerooni et al. (2013) showed a statistical association of Factor V Leiden with frequent failure of pregnancy in women with polycystic ovaries (9).

Rodger et al. showed the risk of complications in carriers of Factor V Leiden gene and mutation of prothrombin gene in comparison with a control group (10). Nurk et al. demonstrated that mutation in factor V Leiden is associated with increased risk of preeclampsia, preeclampsia before the 37th week of gestation, low birth weight, and fetal death (11).

Khalafallah et al. showed that precise anti-coagulative treatment of thrombophilia in pregnancy is associated with better outcomes of pregnancy (12).

The results of other studies in this regard are heterogeneous and controversial (13-16). Therefore, appropriate treatment of patients with thrombophilia can result in good pregnancy outcomes. However, due to limited number of studies in this regard, the efficacy of anti-coagulative treatment in improvement of pregnancy outcome in hereditary thrombophilia cannot be definitely emphasized. The present study aimed at evaluation of the efficacy of anti-coagulative treatment in improvement of pregnancy outcome in pregnant mothers with known thrombophilia.

Materials and Methods

The effect of anti-coagulative therapy on maternal and fetal outcomes in pregnant women with thrombophilia was investigated in this before/after study. The research was conducted in the perinatology clinic of al-Zahra Hospital of Tabriz for 17 months from October 2014 to February 2015 and the obtained data were analyzed. After a comprehensive explanation of the study and its objectives, an informed consent was obtained from the participants before the inclusion. The study was approved by the ethics committee of Tabriz Medical Sciences University.

Considering an α equal to 0.05, a study power of 80%, and an effect size (the average amount of effect on pregnancy outcome (the maximum rate of abortion)) of 0.4, the sample size was calculated 52 persons. Therefore, to increase the validity of the study, it was decided to include all eligible cases during sampling. Accordingly, 60 patients were included in the study through the convenience sampling method.

Inclusion criteria; women with known thrombophilia homozygous mutations, history of 2 or 3 abortions, at least one unjustified intrauterine death, and severe preeclampsia before 34 weeks.

Exclusion criteria; anatomical defect of uterus and uterine tubes, diabetes, hypothyroidism, polycystic ovaries, progesterone deficiency, TORCH, positive fetal anomaly, presence of anti-phospholipid anti-nuclease, discontinuing the study, and inaccessibility of mothers for any reason.

Among women referred to the perinatology clinic of al-Zahra Hospital, 60 pregnant women with approved mutations of MTHFR, prothrombin G20210A, and Factor V Leiden genes, who were referred once their pregnancy test was positive, were included in the study with informed consent. Pregnancy control and antenatal, intra-partum, and post-partum care were provided in the perinatal center of al-Zahra under supervision of the guide master. With regard to medical ethics, we could not select 60 persons as the control group without treatment; therefore, the previous pregnancy outcomes of these women were considered as control and

then were compared (after-before) with the outcomes of new pregnancy in which the participants received the specified treatment protocol of this research. In the selected group, all pregnant women with gestational age of <6 weeks, one or more mentioned mutant genes already approved through PCR, at least one previous pregnancy with unjustified intrauterine death, severe preeclampsia at 34 weeks, and 2-3 abortions were included in the study. The women were under normal prenatal care and received 40 mg/day subcutaneous LMWH (Clexane) and 80 mg/day ASA (aspirin). The outcome of pregnancy in terms of abortion, placental abruption, intrauterine death, intrauterine growth retard (IUGR), hypertension, preeclampsia, eclampsia, etc. were investigated according to a checklist. After completion of pregnancy, labor was performed through normal delivery or caesarian section and the newborns were examined. After selecting the desired group with at least one pregnancy, the outcomes of mother and neonate were compared with those of previous pregnancies in the same patients in which no anticoagulants and aspirin were used (before-after). Patients previous records were obtained from the archive of medical documents of al-Zahra Hospital or private clinics. Finally, variables of the study were compared before and after treatment.
Statistical analysis: the obtained information is expressed as mean ± standard deviation and frequency (%) and analyzed with McNemar, Mann-Whitney U, chi square or exact Fischer test, and logistic regression model using SPSS-16. P<0.05 was considered statistically significant.

Results

A total of 60 pregnant women with thrombophilia mutant genes were evaluated. Their mean age was 30.05±5.49 years (19-43 years old) and their mean weight was 61.17±8.69 kg (51-100 kg). In terms of education, 32 patients (53.3%) had a diploma or lower degree and 28 patients (46.7%) had a university degree. The mean gravidity and the mean parity of the participants was 3.98±1.23 and 1.19±0.70 (0-4), respectively. Fifty-six patients (93.3%) had a history of abortion. The mean number of previous abortions was 2.1±25.28 (0-8).

The status of thrombophilia-related factors of the patients are summarized in Table 1. In addition, simultaneous defect of MTHFR and Factor V Leiden, MTHFR and prothrombin G20210A, and Factor V Leiden and prothrombin G20210A genes were found in 3 patients (5%), 3 patients (5%), and 3 patients (5%), respectively, and no patient had simultaneous defect of these three genes.

Fifty-one infants (85%) were born healthy, of which 27 (52.9%) were male and 24 (47.1%) were female. Type of delivery was vaginal in 36 cases (70.6%) and caesarean section in 15 cases (29.4%). The mean weight of newborns was 3065.06±473.06 g (1800-3850) and the mean gestational age was 40.27±2.43 weeks (32-41).

The effect of treatment on pregnancy outcomes (maternal and neonatal variables) are summarized and statistically analyzed in Table 2. On this basis, and given the results of McNemar test, the rate of abortion, preeclampsia, and preterm delivery was significantly reduced (p<0.001, p<0.04, and *p*<0.004, respectively).

The rate of hypertension without preeclampsia was increased significantly after treatment (p=0.01). No placental abruption and IUGR was occurred after treatment, but due to limited sample size and lack of their occurrence in the treated group, statistical comparison was not possible. Abortion after treatment with respect to the previous live birth and abortion are summarized in Table 3. The effect of treatment on pregnancy outcomes (maternal and neonatal variables) in patients with MTHFR gene mutations is summarized and statistically analyzed in Table 4. On this basis, and given the results of McNemar test, the rate of abortion and preterm delivery was significantly reduced (*p*<0.001 and *p*<0.01, respectively).

The rate of hypertension without preeclampsia was increased significantly after treatment (*p*=0.02). No placental abruption and IUGR was occurred after treatment, but due to limited sample size and lack of their occurrence in the treated group, statistical comparison was not possible. The above comparisons were also done separately in this table in two groups with homozygous and heterozygous mutations of MTHFR gene. In this regard, reduced number of abortion in the homozygous group as well as reduced number of abortion and preterm delivery in the heterozygous group was statistically significant after treatment. The effect of treatment on pregnancy outcomes (maternal and neonatal variables) in patients with Factor V Leiden mutation is summarized and statistically analyzed in Table 5. On this basis, and given the results of McNemar test, the rate of abortion and preterm delivery was insignificantly reduced (*p*<0.50).

In other cases, however, due to limited sample size, statistical comparison was not possible, but the percentage of abortion and preeclampsia decreased and the percentage of hypertension without preeclampsia increased after treatment. However, there was no placental abruption and IUGR before and after treatment. The effect of treatment on pregnancy outcomes (maternal and neonatal variables) in patients with G20210A gene mutations is summarized and statistically analyzed in Table 6. Although statistical comparison was not possible due to limited sample size, the percentage of all cases was reduced after treatment in this group, except for hypertension without preeclampsia.

The variables studied in two groups with and without healthy live births are summarized and compared in Table 7. Accordingly, maternal age and high gravidity (based on Mann-Whitney U test result) were significantly associated with failure in this area.

Based on multivariate analysis (logistic regression), high maternal age was independently associated with the possibility of failure in giving birth of a healthy baby after treatment (*p*=0.04, OR=1.19), while gravidity had no independent role in this field (*p*=0.10, OR=1.66).

Table 1: Status of thrombophilia-related factors in the studied patients.

Factore	Gene Type	frequency (%).
MTHFR		(7/86)52
	homozygous	(1/23)12
	heteroziqot	(9/76)40
Factor 5 Leiden		(3/13)8
	homozygous	(0)0
	heteroziqot	(100)8
Protrombin G20210A		(7/11)7
	homozygous	(6/28)2
	heteroziqot	(4/71)5

The data are shown as frequency (%).

Table 2: Maternal and neonatal outcomes before and after treatment.

Variable	before treatment	after treatment	p-value
Abortion	(3/93)56	(3/13)8	001/0>*
Preeclampsia	(3/18)11	(5)3	04/0*
Blood pressure and pre-eclampsia	(7/1)1	(3/18)11	01/0*
Avulsion pair	(3/3)2	(0)0	-
IUGR#	(7/1)1	(0)0	-
Preterm infants	(3/33)20	(7/11)7	004/0*

The data are shown as frequency (%).

p<0.05 is significant.(*)

#Intrauterine growth restriction (IUGR)

Table 3: Frequency of abortion after treatment according to the status of live births and previous abortion in the current study and previous studies

	The current study			Previous studies
	The number of previous abortions (%)	The number of patients	Current abortion after treatment (%)	The risk of miscarriage (%)
Women who had at least a history of one live birth	0	4	0	12
	1	8	05-Dec	24
	2	26	05-Nov	26
	3	8	25	32
	4	3	Mar-33	26
	5≤	2	0	53
Women who had not at least a history of one live birth	2≤	9	01-Nov	45-40

Table 4: Maternal and neonatal outcomes before and after treatment in patients with MTHFR gene mutation.

genetic mutation	Variable	before treatment	after treatment	p-value
Total (52 items)	Abortion	(3/92)48	(5/13)7	001/0>*
	Preeclampsia	(2/19)10	(8/5)3	07/0
	Hypertension without preeclampsia	(9/1)1	(3/17)9	02/0*
	Placenta Detachment	(9/1)1	(0)0	-
	IUGR	(9/1)1	(0)0	-
	Preterm infants	(6/34)18	(5/13)7	01/0*

Homozygous (12)	Abortion	(7/91)11	(25)3	01/0*
	Preeclampsia	(3/8)1	(3/8)1	99/0
	Hypertension without preeclampsia	(0)0	(3/33)4	-
	Placenta Detachment	(0)0	(0)0	-
	IUGR	(0)0	(0)0	-
	Preterm infants	(25)3	(7/16)2	99/0
Heterozygous (40)	Abortion	(5/92)37	(10)4	001/0>*
	Preeclampsia	(5/22)9	(5)2	07/0
	Hypertension without preeclampsia	(5/2)1	(5/12)5	22/0
	Placenta Detachment	(5/2)1	(0)0	-
	IUGR	(5/2)1	(0)0	-
	Preterm infants	(5/37)15	(5/12)5	01/0*

The data are shown as frequency (%).

p<0.05 is significant (*).

Table 5: Maternal and neonatal outcomes before and after treatment in patients with Factor V Leiden gene mutation.

Variable	before treatment	after treatment	p-value
Abortion	(100)8	(5/12)1	-
Preeclampsia	(5/12)1	(0)0	-
High Blood pressure and pre-eclampsia	(0)0	(25)2	-
Placenta Detachment	(0)0	(0)0	-
IUGR	(0)0	(0)0	-
Preterm infants	(5/37)3	(5/12)1	50/0

The data are shown as frequency (%).

Table 6: Maternal and neonatal outcomes before and after treatment in patients with prothrombin G20210A gene mutation.

Variable	before treatment	after treatment
Abortion	(100)7	(6/28)2
Preeclampsia	(3/14)1	(0)0
High Blood pressure and pre-eclampsia	(0)0	(3/14)1
Placenta Detachment	(3/14)1	(0)0
IUGR	(3/14)1	(0)0
Preterm infants	(9/42)3	(0)0

The data are shown as frequency (%).

Table 7: Comparison of the studied variables in two groups with and without healthy live birth after treatment.

Variable		Successful (51 items)	Unsuccessful (9 cases)	p-value
Maternal age (years)		29	34	01/0*
Weight (kg)		May-67	70	21/0
Gravity		4	5	02/0*
Parity		1	1	96/0
Level of Education	Diploma or less	(9/54)28	(4/44)4	72/0
	Academic	(1/45)23	(6/55)5	
History of abortion		(2/92)47	(100)9	51/0
The number of previous abortion		2	2	24/0
A history of preeclampsia		(2/92)10	(1/11)1	48/0
Hypertension without preeclampsia		(0)0	(1/11)1	15/0
Placenta Detachment		(9/3)2	(0)0	72/0
History of IUGR		(2)1	(0)0	85/0
A history of preterm birth		(3/35)18	(2/22)2	70/0
MTHFR gene disorders		(3/86)44	(9/88)8	66/0
Factor 5 Leiden gene disorders		(7/13)7	(1/11)1	66/0
Prothrombin gene disorder G20210A		(8/9)5	(2/22)2	28/0

The data are shown as frequency (%) or median.

p<0.05 is significant (*).

Discussion

In the current study, the effect of treatment with LMWH and ASA was investigated in pregnant women with thrombophilia. Accordingly, this treatment resulted in a significant reduction in abortion, preeclampsia, and preterm birth. However, there was no new cases of placental abruption and IUGR and hence statistical comparison was impossible.

Deligiannidis et al. also studied the effect of anticoagulant therapy in improvement of pregnancy outcomes in women with thrombophilia. Twenty-nine patients received LMWH and low-dose aspirin. In this study, 23 similar pregnant women were used as a control group. Finally, in line with our findings, the pregnancy outcomes including successful birth rate in the intervention group was significantly better (17).

In a review article by Grandone et al., it was concluded that despite controversies in the use of prophylactic treatments in pregnant women with hereditary and acquired thrombophilia, most studies have recommended the use of prophylactic treatments in this regard (18).

Mitić et al. studied the effect of prophylactic treatment with LMWH in pregnant women with hereditary thrombophilia and with a history of previous missing pregnancies (38 patients). In this study, LMWH was used in doses of 35-75 units per kilogram of body weight. The rate of successful pregnancy in this group was 76% and accordingly, it was concluded that the use of LMWH in this group of pregnant women was successful in maintaining pregnancy outcome and hence recommended (19).

In a recent review article by Areia et al., the outcomes of pregnancy in women with hereditary thrombophilia who were treated with LMWH and aspirin or aspirin alone were studied.

In this study, the results of four clinical trials in this field was summarized, and the used treatments were effective in terms of increased possibility of live births (OR=1.7), reduced abortion (p=0.69), and reduced premature/preterm birth (OR=0.99), although the risk of preeclampsia was increased (OR=1.49) (20).

As can be seen, in the recent study, unlike ours, the risk of preeclampsia was increased after treatment. In our study, there was the risk of hypertension without preeclampsia which was in fact the only drawback of the prophylactic treatment. The main reason for this increased risk is not clear, but requires more studies to reach firm conclusions.

It was already shown that hereditary thrombophilia can significantly increase the risk of abortion. The largest and most common abnormal conditions in this field include mutations related to Factor V Leiden, MTHFR, and prothrombin G20210A genes (21).

Despite these findings, there are still controversies about screening for this class of problems and even in the field of preventive treatment in women with hereditary thrombophilia (22-27).

In a review article, Gebhardt and Hall discussed about the necessity of preventive treatment with heparin in pregnant women with inherited or acquired thrombophilia. The study also concluded that a definitive decision cannot be made in this regard due to absence of proper clinical trials with sufficient sample size (28).

In a review study, Wouters et al. (2003) provided a similar conclusion in this regard (29).

The idea of LMWH use in combination with ASA in women with hereditary thrombophilia is derived after observation of the beneficial effects of this treatment in women with antiphospholipid syndrome which is a risk factor for thrombosis (30, 31).

LMWH is able to facilitate both embryo implantation and placenta formation, therefore, it has anti-inflammatory effects and immune regulatory functions and is safe for both mother and fetus (32-34).

However, studies on the usefulness of LMWH as a prophylactic treatment in pregnant women with thrombophilia are limited and have technical problems, therefore, no decision is made in line with obstetricians and gynecologists (35, 36).

Accordingly, in a comprehensive review which has collected the results of randomized clinical and quasi-randomized trials, it was concluded that treatment of women with hereditary thrombophilia using LMWH and ASA is still empirical, because evidence regarding the treatment efficacy is limited (37).

However, in some other studies such as those conducted by Bujold et al., it was concluded that simultaneous treatment with LMWH and ASA in pregnant women with inherited thrombophilia is effective and recommended (38).

This conclusion is also confirmed in our study.

Repeated abortion may arise from coagulation disorders of mother. In a successful pregnancy, invasion of trophoblasts to the uterine artery and establishment of placental-uterine blood circulation are considered as main components. It has been shown that in the presence of thrombophilia, these mechanisms are not properly established and result in undesirable consequences such as abortion, intrauterine growth retardation, preeclampsia, preterm labor, and fetal death (39).

Several studies emphasized the association of hereditary and acquired thrombophilia with abortion (40-49). In addition, there are also studies which have shown desirable impact of anti-thrombotic therapy in the prevention of abortion in pregnant women with hereditary thrombophilia (50, 51).

Some recent studies have shown that the major cause of abortion in these circumstances is the presence of pre-coagulative microparticles in 50% of patients. Accordingly, it seems that excited coagulation status, regardless of inherited or acquired mechanism, can lead to poor pregnancy outcomes in this group of women. This justifies the desired effects of heparin in thrombophilic conditions (52).

However, studies conducted by Rodger et al. and Hoffmann et al. have shown that thrombophilia may significantly increase the risk of problems associated with the placenta such placental abruption (22, 53).

As mentioned above, although no new case of placental abruption was observed in our study, a definitive decision cannot be made based on statistical tests.

Extensive vascular damage in thrombophilia leads to endothelial dysfunction and occurrence of preeclampsia and organ damage including the uterus and placenta. This can result in intrauterine growth retardation that is an adverse fetal outcome in these patients (54).

In our study, there were no new cases of intrauterine growth retardation after treatment, however, same as placental abruption, definitive determination of the optimal effect of treatment in this regard needs further studies with larger sample sizes (see the suggestions).

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