The Prevalence of Thrombophilic Factors in Pregnant Women with Subjectively Oligohydraminos During the Gestational Age of 18- 27 Weeks**

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Abstract

Objectives: To study the prevalence of Factor V Leiden (FVL), prothrombin gene mutation G20210A (F II) and methylenetetrahydrofolate reductase C677T (MTHFR) in pregnant women with subjectively diagnosed oligohydraminos during the gestational age from 18-27 weeks.

Methods: A case-control study was conducted at the Jordan University Hospital and Farah Hospital Amman, Jordan during the period of 2006-2009. 100 pregnant women with oligohydraminos have been compared to 96 normal healthy childbearing age women. All subjects were investigated for the 3 genetically related thrombophilic factors.

Results: Prothrombin gene mutation G20210A (F II) in pregnant women with oligohydraminos was higher 7.0% Vs 0% in the control group with a *P*-value of 0.008. Factor V Leiden (FVL) was also higher among pregnant women with subjectively oligohydraminos, 23.0% Vs 13.5% among the control group, but it did not reach statistical significance, *P*-value was 0.087. Methylenetetrahydrofolate Reductase C677T (MTHFR) was 52% among the pregnant women with subjectively oligohydraminos versus 55.2 % in the control group; *P*-value was 0.653 as shown in Table (2).

Conclusions: As compared to the control group, Factor II G20210A was significantly higher among the pregnant women with subjectively oligohydraminos while FVL was also higher among this group, but it did not reach statistical significance. MTHFR was not higher among this group of pregnant women.

Keywords: Pregnancy, Thrombophilia, Oligohydraminos.

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Introduction

Thrombophilia refers to disorders associated with a persistent hypercoagulable state and a tendency towards thrombosis. They may be inherited, acquired, or complex when both genetic and environmental factors interact. [1] Pregnancy *per se* is an acquired hypercoagulable state. [2]

The recent attention has focused on certain inherited thrombophilic factors that may predispose to arterial and/or venous thromboses and their association with complications during pregnancy. [2] The most common inherited thrombophilic factors are a group of mostly autosomal dominant, inherited gene mutations such as factor V Leiden G1691A (FVL), factor II, or prothrombin G20210A (FII), and Methylene Tetrahydrofolate Reductase C677T mutation (MTHFR). [2]

There is a synergistic amplification of thrombotic risk when an abnormal gene e.g., FVL is associated with an environmental issue e.g., pregnancy. [2] Recent studies have shown that there is an association between thrombophilia and adverse obstetric outcomes such as recurrent miscarriage, intrauterine growth restriction, pre-eclampsia, and placental abruption. [1]

Oligohydraminos is related to adverse perinatal outcomes particularly when associated with fetal growth restriction. [3] Its association with these genetically related thrombophilic factors were studied only in the third trimester not in the second trimester.

Some pregnant women between 18- 27 weeks gestation have subjectively shown oligohydraminos during scanning, this has been described by the obvious lack of fluid, poor fluid-fetal interface, and marked crowding of fetal parts. [4]

Our study is considered as one of the first studies which looks for the association between the most common genetically related thrombophilic factors (FVL, FII and MTHFR) and subjectively diagnosed oligohydraminos in pregnant women during the gestational age from 18-27 weeks.

Patients and Methods

A case-control study was conducted in both a tertiary university hospital and a private obstetric hospital in Jordan during the period 2006-2009. A total of 100 pregnant women were diagnosed as subjectively oligohydraminos. All women were Jordanians; the mean age of the patients was 29.55 years ranging between 19- 42 years. The diagnosis of oligohydraminos was considered during a routine detailed fetal anomaly scan performed between 18-23 weeks gestation for 89 pregnant women; the other eleven pregnant women who were diagnosed to have subjectively oligohydraminos were between 23 and 27 weeks gestation because the detailed anomaly scan was not performed earlier. All these women were scanned by one certified obstetrician sub specialized in fetomaternal medicine using GE voluson expert, GE E-8 or Philips HD-11 as ultrasound machines.

The control group consisted of 96 unrelated healthy childbearing women who have no recent or past history of myocardial infarction, DVT, PE, or stroke. We studied prothrombotic determinants, namely factor V Leiden 1691GA, factor II prothrombin gene mutation 20210GA and MTHFR mutation C677T in all patients and control subjects.

The study protocol was approved by the ethics committee of the hospital.

Statistical Analysis

We used a case-control design to allow quantitative comparison between groups. All statistical tests were independent t-test and Pearson Chi square which were used to test for association in the distribution of categorical variables (Thrombophilia genetic factors (FVL, FII, MTHFR). P-values less than α level of 0.05 were considered statistically significant. Because of the small number in some of the cells (FII in control subjects was not detected), Fisher's exact test was used to assess the statistical significance of the association. The analyses were performed by using the SPSS package version 16.0.

Results

Clinical Characteristics

During the period of 2006- 2009, 113 pregnant women diagnosed with oligohydraminos were enrolled. 13 of them were excluded because the results of genetically related thrombophilia were not available in their files. The patients' characteristics are shown in Table (1). The mean age of the patients was 29.55 ± 4.57 years ranging from 19-42 years. The mean gravidity was 2.66 gestations ranging from 1 to 12 gestations. The mean parity was 1.15 ranging from zero to six deliveries. The mean gestational age at the time of scanning was 21.36 weeks ranging from 18 to 27 weeks. The mean number of miscarriage was 0.52, ranging from zero to six miscarriages, whereas the control group had a total of 96 women with a mean age of 29.55 ± 7.93 years with a range of 17- 49 years as shown in Table (1).

Factor V Leiden

Among all pregnant women with subjectively oligohydraminos, 23(23.0%) had factor V Leiden, 21(21.0%) were heterozygous and 2(2.0%) were homozygous mutation which didn't reach any statistically significant difference from the frequency of factor V Leiden in the control group 13(13.50%) with difference of 9.5%, and a *P*-value of 0.087 (Table 2).

Factor II G20210A

The frequency of Factor II G20210A in pregnant women with oligohydraminos was 7.0%, while in the control group the frequency of Factor II G20210A was 0% with difference of 7.0, which is statistically significant difference, *P*-value 0.008 (Table 2).

MTHFR C677T

The frequency of MTHFR, C677T variant was 52 (52.0%) as compared to 53 (55.2%) for the control group, which shows no statistically significant difference between the case and the control groups as the *P*-value is 0.653 as shown in Table (2).

Table (1): Baselines and Clinical Characteristics of Cases and Control Subjects.

	Pregnant women with Oligohydramnious N = 100	***Childbearing age healthy women N=96***
Age and pregnancy distribution		
Age in years {mean ±SD}	*29.55 ± 4.57*	*29.55 ± 7.93*
Age range in years	*19-42*	*17-49*
Race	***100%** Jordanians*	***100%** Jordanians*
Gravida{mean ±SD}	*2.66 ± 1.86*	
Gravida range	*1-12 gestation*	
Parity {mean ±SD}	*1.15 ± 1.31*	
Parity range	*0 – 6 deliveries*	
***Gestational age** {mean ±SD}*	*21.36 ± 1.81*	
***Miscarriage** {mean ±SD}*	*0.52 ± 1.0 miscarriage*	
Miscarriage range	*0 – 6*	

Table (2): The Frequency of Genetically Related Thrombophilic Factors in all Pregnant Women with Oligohydramnious and Control Group.

	Cases No =100	***Control No= 96***	***P-value***
Factor V Leiden Mutation	*23(23%)*	*13(13.5%)*	*0.087*
Factor II G20210A	*7(7%)*	*0(0%)*	*0.008*
MTHFRC677T	*52 (52%)*	*53(55.2%)*	*0.653*

Discussion

Our study is considered the first which subjectively evaluates oligohydraminos in the second trimester and its association with genetically related thrombophilia while all previous studies evaluated the presence of these factors in women with oligohydraminos during the third trimester. In our study, it has been found that the frequency of Factor II G20210A in pregnant women with oligohydraminos was higher than that in the control group 7.0%, Vs 0% with a *P*-value of 0.008. Also, it has been found that FVL is higher in the patients group as compared to the control group, but it didn't reach any statistical significance 23% Vs 13.5% with a *P*-value of 0.087. The frequency of MTHFR, C677T variant in our patient group is not higher than that in the control group 52% Vs 55.2% with a *P*-value of 0.653.

Magriples et al. (2006) in their retrospective study of a cohort of patients who were referred for pregnancy complications and who were found to have genetic thrombophilia. [5] Ultrasounds were reviewed in treated and untreated pregnancies for the presence of growth restriction, oligohydramnios, or abnormal Doppler results. [5] Their conclusion was that treatment markedly improves ultrasound parameters of growth, fluid and feto-placental blood flow in patients with thrombophilia.

Alfirevic et al. (2002) in their systematic review of studies including women with adverse obstetric complications, investigated for one or more acquired and inherited thrombophilias. [6] Their main objectives were to determine the prevalence of thrombophilia in women with severe pre-eclampsia/eclampsia, severe placental abruption, intrauterine growth restriction or unexplained stillbirth. [6] They conclude that women with adverse pregnancy outcome are more likely to have a positive thrombophilia screen. However, these studies are too small to adequately assess the true size of this association. [6]

Ogunyemi et al. (2002) study evaluated in their study the association between obstetrical complications in pregnancy and thrombophilic factors in 75 pregnant women with obstetrical complications and 66 controls with live births without obstetrical complications which were tested for thrombophilia. All subjects were negative for thromboembolic disease. The obstetrical complications in the study group were unexplained oligohydraminos in 16 (21%), intrauterine growth retardation in 17 (23%), preeclampsia <32 weeks in 15 (20%), recurrent abortions in 42 (56%), fetal demise in 14 (19%), abruption in 8 (11%). They found that comparing women with obstetrical complications versus controls, factor V Leiden mutation was present in 7 (10%) versus 1 (2%). *P*-value was 0.064, Odds Ratio (OR) was 7, 95%, CI = 0.8-58.5. Their conclusion was that an association is suggested between non-thromboembolic pregnancy complications and hypercoagulable disorders including unexplained oligohydraminos, and prophylactic anticoagulant therapy may be associated with improved pregnancy outcome. [7] Also, it has been found that there is no association with these adverse pregnancy complications and methylenetetrahydrofolate reductase gene mutation. The results of their study are in agreement with the results of our study regarding the prevalence of FVL and MTHFR.

Conclusion

From this study, it has been concluded that Factor II G20210A is associated with oligohydraminos which is diagnosed early during the gestational age between 18 and 27 weeks and to a less extent FVL, but MTHFR is not associated with this adverse pregnancy complication. Depending on these findings, the early prophylactic anticoagulant therapy may be indicated in patients with oligohydraminos detected early during the gestational age between 23-27 weeks. However, further investigations are needed to find if this early prophylactic anticoagulant therapy will improve the pregnancy outcome in these patients. [7]

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تكرار التغيرات الوراثية في قابلية تخثر الدم لدى النساء الحوامل مع قلة الصاء الذاتي خلال العمر الحملي (للجنين) 18–27 اسبوع

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الملخص

الأهداف: دراسة تكرار تغيرات العوامل الوراثية لتخثر الدم وهي عامل ليدن الخامس FVL والعامل الثاني (FII) G20210A وعامل مختزلة الميثيلين تترا هيدروفولات (MTHFR) C677T لدى النساء الحوامل مع قلة الصاء الذاتي خلال العمر الحملي (للجنين) 18–27 اسبوع .

الطريقة: أجريت الدراسة استباقيا لحالات وشواهد في مستشفى الجامعة الأردنية، ومستشفى فرح بين الأعوام 2006–2009 على 100 امرأة حامل مع قلة الصاء مقارنة مع 96 شواهد نساء في سن الأنجاب وتم إجراء فحص عوامل تخثرالدم الوراثي لجميع الحالات والشواهد.

النتائج: أن تكرار التغيرات الوراثية للعامل الثاني (FII) G20210A لدى النساء الحوامل مع قلة الصاء هي اعلى 7% مقارنة مع الشواهد 0% وبدلالة إحصائية P=0.008 . اما عامل ليدن الخامس FVL فكان أعلى عند النساء الحوامل مع قلة الصاء 23 % مقارنة مع الشواهد13.5 % ولم يكن الاختلاف فيها ذو دلالة احصائيا P=0.087 ولعامل مختزلة الميثيلين تترا هيدروفولاتMTHFR كان 52 % لدى النساء الحوامل مع قلة الصاء مقارنة مع الشواهد 55.2% وذو دلالة احصائية P=0.653.

خاتمة: أن تكرار التغيرات الوراثية لدى النساء الحوامل مع قلة الصاء هي اعلى للعامل الثاني مقارنة مع الشواهد بينما عامل ليدن الخامس كان أكثر لدى النساء الحوامل مع قلة الصاء منه لدى الشواهد و تكرار هذه التغيرات لم تكن بدلالة إحصائية أكثر لدى الشواهد النساء في سن الأنجاب و اما عامل مختزلة الميثيلين تترا هيدروفولات كان أكثر لدى النساء الحوامل الشواهد من النساء الحوامل مع قلة الصاء.

الكلمات الدالة: الحمل، تخثر الدم الوراثي، قلة الصاء الذاتي.