# Comparison of resistance index and peak systolic velocity of fetal middle cerebral artery between normal and fetuses with mutated beta-thalassemia gene

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## Abstract

Background: Beta-thalassemia is the most common inherited single-gene disorder globally. In contrast to alpha-thalassemia, the role of resistance index (RI) and peak systolic velocity (PSV) of the middle cerebral artery (MCA) of the fetuses which are carriers for beta-thalassemia gene is not well understood. The objective of this study was to compare RI and PSV of the MCA in normal fetuses vs. fetuses with mutation of the beta-thalassemia gene.

Methods: In this analytic study, 55 pregnant women with gestational age of 12 weeks and more were included consecutively. The pregnant women had history of giving birth to neonates with major beta-thalassemia or they or their husbands had minor beta-thalassemia. They underwent chorionic villus sampling (CVS). Twenty pregnant women without laboratory indices of beta-thalassemia were included as the control group. They underwent color Doppler ultrasound to measure RI and PSV of the fetal MCA. The data were analyzed using analysis of variance (ANOVA), Kruskal-Wallis test, chi-square test or the Fischer's exact test.

Results: PSV of the MCA was significantly higher in fetuses with beta-thalassemia gene compared to control group ($P< 0.05$). No significant difference existed regarding RI of the MCA between minor, major beta-thalassemia and control groups ($P> 0.05$).

Conclusion: PSV of the MCA of fetuses with major beta-thalassemia was higher than in normal fetuses.

Key words: Major beta-thalassemia, peak systolic velocity, resistance index, middle cerebral artery, Doppler ultrasound

Please cite this article as: Farshchian N. et al. Comparison of resistance index and peak systolic velocity of fetal middle cerebral artery between normal and fetuses with mutated beta-thalassemia gene. World Family Medicine. 2018;16(1):188-192
DOI: 10.5742/MEWFM.2018.93217

## Introduction

Beta-thalassemia is the most common inherited single-gene disorder globally which is inherited in an autosomal recessive fashion. This disorder causes abnormal hemoglobin synthesis. Its homozygote form is called major beta-thalassemia and the affected patients need life-long blood transfusions to survive (1, 2). Beta-thalassemia is relatively common in the Mediterranean area, some areas of northern and western parts of Africa, the Middle East, the Indian subcontinent, and southeast Asia (3-5). The prevalence of beta-thalassemia gene is highest in the northern part of Iran near the Caspian Sea (about 10%), followed by Isfahan province (8%), southern parts of Iran (8-10%), and is about 4-8% in other areas of Iran(6).

When parents have minor beta-thalassemia, the chance of the baby having major beta-thalassemia is 25% at each pregnancy. Currently, more than 20,000 patients with beta-thalassemia live in Iran. Children with major beta-thalassemia need blood transfusion to survive as early as the first year of life. Blood transfusion is associated with several complications. Studies have mentioned that mothers whose fetuses have intermediate beta-thalassemia are willing to terminate their pregnancy (7-9).

Measuring peak systolic velocity (PSV) of the middle cerebral artery (MCA) of the fetus by ultrasound provides more rapid diagnosis of anemia (10). However, it is still not clear whether measuring PSV of the MCA can be useful in prediction of beta-thalassemia (11). In some case reports, it has been shown that PSV of the MCA of fetuses with alpha-thalassemia was higher than normal in the second and third trimesters (12-14). The exact perinatal diagnosis of beta-thalassemia can be done by DNA examination of the sample obtained by chorionic villus sampling (CVS) or amniocentesis (15). Currently, rapid results can be provided by PCR method within 1-2 days (16, 17). The perinatal prediction of beta-thalassemia by CVS or amniocentesis is associated with 1.5-2% risk of spontaneous abortion. Application of non-invasive methods such as measurement of MCA-PSV, CRT (cardiothoracic ratio), and placental thickness by two-dimensional ultrasound has decreased the need for invasive methods in the diagnosis of homozygote alpha-thalassemia (18). As 70% of the blood flow that circulates to the brain enters into the MCA and easy availability of this artery to ultrasound, MCA has become an important target in fetus Doppler ultrasound examination. It seems that increased velocity of blood flow in the MCA when anemia presents is due to increased cardiac output and decreased blood viscosity (19). In addition, as brain tissue is sensitive to oxygen, MCA reacts very rapidly to hypoxia. Therefore, PSV of the MCA can be used as a potential predictor of thalassemia and anemia. Recently, some studies have addressed the role of PSV and resistance index (RI) of the MCA in the diagnosis of thalassemia. It has been shown that MCA-PSV increases in fetuses with thalassemia in comparison to normal fetuses (20-24). Therefore, as the mentioned markers have not been studied in beta-thalassemia, we decided to study these ultrasound indices in beta-thalassemia fetuses. We think that studying these markers will further our knowledge about non-invasive methods in the diagnosis of beta-thalassemia.

## Materials and methods

In this analytic case-control study, the study population consisted of pregnant women (gestational age of greater than 12 weeks) who had history of giving birth to neonates with major beta-thalassemia or they or their husbands had minor beta-thalassemia (thalassemia group, N= 55 subjects). Control group (20 subjects) consisted of pregnant women (gestational age of more than 12 weeks) whose complete blood count did not show anemia and who had no history of beta-thalassemia. They had a singleton pregnancy. Exclusion criteria were presence of systemic diseases such as hypertension, diabetes mellitus, and addiction to drugs, and taking medications.

The documented variables included age, gestational age, parity, gravity, and number of children with thalassemia. Then, color Doppler ultrasound was done using G50 (Siemens) with curve 3.5-MHz probe and RI and PSV of the MCA were measured. The sonographer was blinded to the assignment of the samples in the study groups. The fetuses of the thalassemia group were divided into three groups according to CVS results: major thalassemia, minor thalassemia, and healthy fetuses. The healthy fetuses were added to the control group.

**Statistical analyses**

The difference of RI and PSV were compared between control and thalassemia groups. In order to determine the normal distribution of the data, the Kolmogorov-Smirnov test was applied. Analysis of variance (ANOVA), Mann-Whitney U test, or Kruskal-Wallis tests were used to compare continuous data. The chi-square test or Fisher's exact test was used to compare the categorical variables between the groups. The analyses were done using SPSS software (ver. 22.0).

## Results

Ten fetuses (13.3%) had major beta thalassemia, 20 had minor beta thalassemia, and 45 fetuses did not have beta thalassemia. Mean (±SD) age of the mothers was 28.56 (±6.16) years (range, 17 to 44 years). There were no significant differences among the groups regarding age, parity, and gravidity (Table 1 - next page).

Four mothers (5.3%) had history of giving birth to a child diagnosed by major beta thalassemia, one mother had history of having two children with major beta thalassemia (1.3%), 14 had children with minor beta thalassemia (18.7%), five with two children diagnosed with minor beta thalassemia (6.7%), and six (8%) had children without beta thalassemia. Others including 45 mothers (60%) were primigravida.

There was no significant difference regarding RI of the MCA among the three groups (P= 0.40), however a significant difference existed regarding PSV of the MCA (P< 0.001); Table 2.

**Table 1: Comparison of age, parity, and gravidity among the three studied groups**

| | Study groups | | | P value |
|---|---|---|---|---|
| | Major beta thalassemia | Minor beta thalassemia | Control | |
| Age | 30.2 (±5.59) | 28.33 (±6.47) | 28.25 (±5.86) | 0.54 |
| Gravidity | 1.6 (±0.51) | 1.4(±0.61) | 1.65 (±0.98) | 0.43 |
| Parity | 0.3 (±0.48) | 0.22 (±0.47) | 0.4 (±0.82) | 0.74 |

Data are presented as mean (±standard deviation)

**Table 2: Comparison of resistance index (RI) and peak systolic velocity (PSV) of the middle cerebral artery (MCA) among the three studied groups**

| | Study groups | | | P value |
|---|---|---|---|---|
| | Major beta thalassemia | Minor beta thalassemia | Control | |
| RI | 0.77 (±0.01) | 0.78 (±0.03) | 0.78 (±0.01) | 0.40 |
| PSV, cm/second | 31.16 (±2.37) | 18.8 (±1.4) | 17.99 (±1.79) | < 0.001 |

Data are presented as mean (±standard deviation)

As observed, a significant difference existed regarding PSV between control group and thalassemia group. The PSV was significantly larger in the beta thalassemia group. Also, PSV of major beta thalassemia group was larger than in the minor beta thalassemia group (P< 0.05). However, no significant difference existed between minor beta thalassemia and control groups regarding PSV.

## Discussion

Beta thalassemia includes a group of hereditary hematologic disorders characterized by decreasing or non-synthesis of beta-globin chain and eventually reduction in hemoglobin concentration and number of red blood cells (25). In recent ultrasound studies, fetal MCA-PSV has been referred for a rapid diagnosis of fetal anemia (10). But measuring of this index has remained uncertain in the prediction of beta thalassemia.

According to our results, mean PSV of the MCA in the major beta thalassemia group was significantly higher than that of normal and minor beta thalassemia groups. This finding is compatible with previous studies. It has been shown in previous studies that the level of fetal MCA-PSV increases in line with increase in hemoglobin concentrations (20, 22, 26, 27), and the MCA-PSV is a useful tool for diagnosing fetal anemia. Lam et al., similar to our study, found that MCA-PSV levels in alpha thalassemic fetuses were significantly higher than in the non-alpha thalassemic group (21). Srisupundit and colleagues, in agreement with our results, also found that when MCA-PSV measurements were 1.5 times higher than average values, the number of fetuses detected to have hemoglobin Bart's disease were higher in comparison to the group with MCA-PSV values less than 1.5 times of average MCA-PSV (28).

Another study reported that MCA-PSV levels in fetuses with hemoglobin Bart's disease was higher compared to normal fetuses (29). Leung and colleagues, in agreement with our findings, noted that non-invasive ultrasound parameters such as PSV of the MCA are helpful in the diagnosis and management of fetal anemia in pregnancy (10). Kowalczyk et al., in concordance with the results of our study, reported that MCA-PSV levels in fetuses with severe anemia were higher than those without anemia. However, there was no significant difference between the MCA-PSV of fetuses with moderate, vs. those without, anemia (22).

Another report in compliance with our findings reported that MCA-PSV could predict anemia in a fetus with type 1 homozygote alpha-thalassemia (23). It has been shown that MCA-PSV of fetuses with normal hemoglobin was lower than those with anemia (24). It seems that hemoglobin reduction (anemia) increases the risk of heart conditions, heart rate and peripheral resistance, and decreases blood concentration, leading to an increase in cerebral blood flow to maintain oxygen transfer to the brain (30). On the other hand, reduction of blood hemoglobin is associated with hypoxia and lactate production, which is caused by dilation of blood vessels of the brain and increased blood flow (31). There is also a correlation between hemoglobin concentration and hematocrit and blood flow velocity of cerebral arteries (30). Therefore, when fetal hematocrit concentration increases, blood becomes more concentrated and MCA-PSV decreases (32).

Based on the current results, there was no significant difference between the groups regarding RI of the MCA. In agreement with our results, Mandic et al. reported that PI levels decrease along with the severity of anemia, but there was no difference in the amount of PI between fetuses with and without anemia (33). Although in previous studies, RI has been considered useful in early diagnosis of fetal abnormalities (35), no study has been conducted to compare RI between healthy fetuses and those with thalassemia. This has led to a lack of comparisons of

studies conducted in this regard. Therefore, for further investigation, cross-sectional and prospective studies on comparing RI of the MCA of healthy fetus and beta-thalassemia are recommended.

A limitation of this study was low sample size. It is recommended to conduct future studies of larger sample size. This was a cross-sectional study with no follow-up. Therefore, it is suggested that future studies should be designed with a long follow-up. However, the strength of this study is that so far no study has been done to compare these parameters in fetal beta-thalassemia. Therefore, considering the obtained findings, it can be said that the measurement of the MCA-PSV parameter is a non-invasive and a low cost method in beta-thalassemia fetuses.

## Conclusion

There was a significant difference between healthy and beta-thalassemia fetal PSV of the MCA. This was higher in the beta-thalassemia group. Also, MCA-PSV was higher in major beta thalassemia compared to the minor beta thalassemia group. However, no difference existed regarding PSV of the MCA between minor beta-thalassemia and control groups. It seems that MCA-PSV is a useful index to non-invasively assess fetuses suspected of having thalassemia.

**Acknowledgment**
This article was extracted from the thesis of Dr. Hamidreza Ariafar (No. 93258). We thank all staff who helped us in this study.

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