

2D and 3D Ultrasound Prediction of Homozygous α^0 -Thalassemia

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Abstract

Conventionally, prenatal diagnosis is achieved by an invasive procedure followed by DNA analysis or hematological study. With experienced hand and a good ultrasound machine, a noninvasive approach consisting of serial two-dimensional ultrasound examinations of cardiothoracic ratio and placenta thickness can effectively reduce the need for invasive testing in the majority of unaffected pregnancies. Although middle cerebral artery peak systolic velocity (MCAPSV) is a well-established sonographic marker for predicting fetal anemia due to Rhesus isoimmunization, it is not clear whether MCAPSV is useful in the prediction of affected pregnancies. Preliminary studies have been performed to investigate the use of 3D ultrasound in the prediction of pregnancies affected by homozygous α^0 -thalassemia. It seems that 3D is not superior to 2D ultrasound prediction of affected pregnancies.

Keywords: Homozygous α^0 -thalassemia, prediction, affected pregnancies, 2D, 3D, ultrasound.

BACKGROUND

Homozygous α^0 -thalassemia is the commonest cause of hydrops fetalis in South-East Asia.¹⁻³ The α -thalassemia carrier rates in Guangxi, Guangdong and Hong Kong are 15%, 4% and 4.5% respectively.^{4,5} Couples both being carriers have a 25% risk of having a fetus affected by homozygous α^0 -thalassemia. The affected babies often die towards the end of the pregnancy or soon after birth³ although a few long-term survivors have been reported.⁶ Despite the poor outcome, prenatal diagnosis is necessary because the pregnancies are often complicated by pre-eclampsia and postpartum hemorrhage or occasionally maternal death.³ Conventionally, prenatal diagnosis is achieved by an invasive procedure followed by DNA analysis or hematological study. Noninvasive ultrasound monitoring can be offered as an alternative in prenatal diagnosis of α -thalassemia. Our center has reported the effectiveness of using the prenatal ultrasonic measurements of the fetal cardiothoracic ratio and the placental thickness to exclude homozygous α^0 -thalassemia.⁷⁻⁹ Whether middle cerebral artery peak systolic velocity (MCAPSV) is useful in the prediction of homozygous α^0 -thalassemia is not clear. In general, 3D ultrasound is superior to 2D ultrasound in the precision and accuracy of measurement of volume of irregularly shaped objects. Preliminary studies have been performed to investigate the use of 3D ultrasound in the prediction of pregnancies affected by homozygous

α^0 -thalassemia. The objective of this article is to review the 2D and 3D ultrasound prediction of affected pregnancies.

PRINCIPLE OF ULTRASOUND PREDICTION

The principle of the ultrasound prediction is to detect ultrasonographic features of fetal anemia. Since α -globin dependent hemoglobin F is the major hemoglobin of a fetus from eight weeks' gestation onwards, anemia can occur in an affected fetus after this gestation. Severe anemia and hypoxia result in placentomegaly, fetal cardiomegaly, increased MCAPSV, pericardial effusion, ascites and other hydropic features.

2D ULTRASONOGRAPHIC PARAMETERS

Placental Thickness (PT)

PT was first studied in 1994 by Ghosh et al PT is the measurement of the maximal placental thickness, with the transducer placed perpendicularly to the placenta and measurements taken in the longitudinal and transverse sections.¹⁰ A cut-off point of >18 mm was used to define placentomegaly (Fig. 1) at 12 to 15 weeks' gestation.¹¹ The sensitivity and false positive rate for PT in the prediction of affected pregnancies was 77.1% and 19.0% respectively. There are limitations of assessment of PT. It is difficult to accurately measure PT, when the placenta is adjacent to a focal myometrial contraction or located in the fundus or

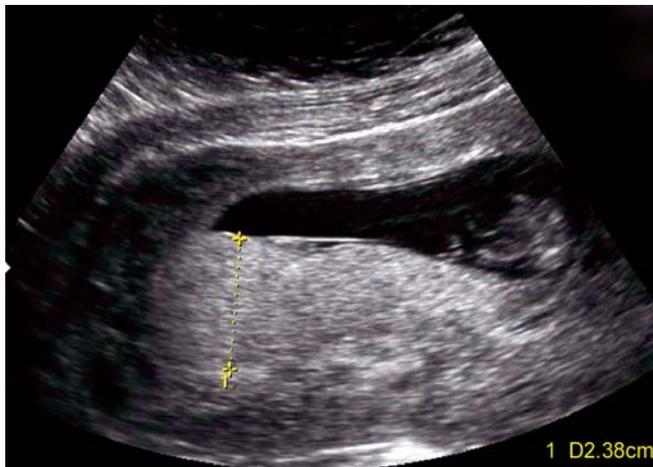


Fig. 1: Increased placenta thickness in a pregnancy affected by homozygous α^0 -thalassemia at 12 weeks' gestation



Fig. 2: Increased cardiothoracic ratio in a pregnancy affected by homozygous α^0 -thalassemia at 12 weeks' gestation

lateral uterine wall.⁷ Besides, the placenta can be large but its thickness can be normal in an affected pregnancy.¹²

Cardiothoracic Ratio (CTR)

The fetal CTR is a ratio of the fetal transverse cardiac diameter taken at the level of the atrioventricular valves between the epicardial surfaces at diastole to the transverse fetal thoracic diameter.¹³ An abdominal 5 or 7 MHz curvilinear transducer or vaginal 5 or 7 MHz vector transducer can be used. At 12 to 14 weeks' gestation, if an optimal view of fetal cardiothoracic ratio (CTR) cannot be obtained through abdominal scan, visualization of the fetal heart may be improved by vaginal ultrasonography. The optimal view is subcostal four-chamber heart view rather than apical view. A cut-off point of ≥ 0.5 , and ≥ 0.52 were used to define cardiomegaly (Fig. 2) at 12 to 13 weeks, 18 to 20 weeks respectively.¹¹ At 12 to 15 weeks' gestation, the sensitivity and false positive rate for CTR in the prediction of affected pregnancies was 97.5% and 9.1% respectively.¹¹ The predictive values for the fetal CTR were better than that for the placental thickness.¹¹

The use of this approach demands an accurate measurement of the fetal cardiothoracic ratio. Adequate training and subsequent quality control are essential. We have demonstrated that this noninvasive approach can be applicable in another center after adequate training and quality control.¹¹

The predictive values of the fetal CTR vary with gestational age.³ In advanced gestation, hydropic signs including ascites or pleural effusion are more apparent than cardiomegaly in affected pregnancies.¹¹ At 10 to 11 weeks' gestation, an optimal fetal cardiothoracic ratio could be obtained in only half of women even though vaginal scan

was performed (unpublished data). Besides, there were no significant differences in the ultrasonographic measurements obtained at these gestations between the affected and unaffected pregnancies.

MCAPSV

Although, middle cerebral artery peak systolic velocity (MCAPSV) is a well-established sonographic marker for predicting fetal anemia due to rhesus isoimmunization,¹⁴ whether MCAPSV is useful in the prediction of homozygous α^0 -thalassemia is not clear. Several case reports have shown that MCAPSV in affected pregnancies was greater than normal in second or third trimester.¹⁵⁻¹⁷ In a prospective study of 80 at risk pregnancies of which 19 were affected the median MCAPSV at 12 to 13 weeks' gestation in the affected pregnancies (19 cm/s) was significantly higher than the unaffected pregnancies (14 cm/s).¹⁸ However, there was a lot of overlap in MCAPSV between the affected and unaffected pregnancies and no good cut-off point for the prediction could be found.¹⁸ On the other hand, our preliminary analysis showed that MCAPSV at 16 to 20 weeks' gestation was associated with a low false positive rate.¹⁹ Whether, the combination of CTR and MCAPSV is superior to CTR alone need further study.

Other 2D Ultrasound Parameters

Limb reduction defects,²⁰ echogenic bowel,²¹ increased nuchal translucency,²² increased cardiac flow,²³ or abnormal ductus venosus Doppler²⁴ were found in some of the affected fetuses. However, none of these ultrasound parameters are sensitive enough for the prediction of affected fetuses.

3D Ultrasound Parameters

A preliminary study showed that the mean placental volume/crown rump length in affected pregnancies (1.37 cm³/cm) was larger than in unaffected pregnancies (1.13 cm³/cm), but the difference was not significant.²⁵ It seems that three-dimensional assessment of placenta is not superior to two-dimensional ultrasound in the first trimester prediction of affected pregnancies.²⁵ Although, placental volume/crown-rump length ratio in affected pregnancies was larger than that in unaffected pregnancies, the difference was not significant.²⁵

Cost-effectiveness of Ultrasound Prediction

With experienced hand and a good ultrasound machine, a noninvasive approach consisting of serial two-dimensional ultrasound examinations of CTR and PT can effectively reduce the need for invasive testing by about 75%.^{11,26,27} In other words, about eight lives could be saved in 1000 at-risk pregnancies, if 1% risk of miscarriage after CVS or amniocentesis is assumed. The cost saving was relatively small, in comparison to the cost of the whole prenatal screening program for thalassemia.²⁸

Clinical Practice

The noninvasive approach can be offered as an alternative to avoid invasive procedures in couples both being carrier of α^0 -thalassemia trait and having a history of an affected pregnancy. This approach is applicable in singleton, as well as twin pregnancies,²⁹ and can be used to confirm normality in pregnancies conceived after preimplantation genetic diagnosis.³⁰ If a woman is a carrier of α^0 -thalassemia trait while her husband is not available for blood testing, this noninvasive approach can be used with limitations.

12 Weeks' Gestation

An ultrasound examination can be performed as early as 12 weeks' gestation to exclude affected pregnancies in at-risk women. If there is fetal cardiomegaly, and/or placentalomegaly, chorionic villus sampling will be offered.¹⁰ With the use of quantitative polymerase chain reaction, a rapid report can be available within one to two days after the procedure.³¹ On the other hand, if the sonographic findings are normal, an invasive procedure will be omitted and an ultrasound examination will be repeated at 18 week's gestation to confirm an unaffected pregnancy and to exclude gross fetal abnormalities. If the CTR and /or PT are near

the upper limit of normal or the image quality of the fetal heart is suboptimal, two options including (a) rescan in 2 to 3 weeks time, or (b) an invasive testing will be offered.¹¹ The risk of delaying the diagnosis of an affected pregnancy till second trimester and the disadvantages of second trimester termination should be balanced against the risk of an invasive testing.

18 Weeks' Gestation

CTR is the main parameter for assessment. If cardiomegaly is found, amniocentesis will be offered. If CTR is normal, rescan at 30 weeks' gestation is recommended to confirm normality and assess fetal growth.

30 Weeks' Gestation

At 30 weeks' gestation, sonographic findings of an affected pregnancy is usually obvious, and may include gross cardiomegaly, pericardial effusion, ascites, subcutaneous edema, polyhydramnios, intrauterine growth restriction, and increased MCAPSV. If sonographic findings are normal, hemoglobin analysis of the cord blood after delivery is required to confirm an unaffected pregnancy.

CONCLUSION

With experienced hand and a good ultrasound machine, a noninvasive approach consisting of serial two-dimensional ultrasound examinations of CTR and PT can effectively reduce the need for an invasive testing in the majority of unaffected pregnancies. Further study is required to determine the role of MCAPSV. It seems that 3D is not superior to 2D ultrasound prediction.

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