Novelty Journals

ISSN 2394-7330

International Journal of Novel Research in Healthcare and Nursing
Vol. 2, Issue 3, pp: (86-90), Month: September-December 2015, Available at: www.noveltyjournals.com

Prenatal Diagnostics to Determine Fetal Anemia in Thalassemia Carrier Parents

Adhi Pribadi

Maternal Fetal Divison Obstetric & Gynecology Department, Medical school of Padjadjaran University, Bandung Indonesia

Abstract: **Prenatal screening is needed in cases of blood disorders that cause hemolysis and eventually lead to anemia and death of the fetus. At this time a constraint for prenatal diagnostic is a fairly expensive for most levels of the Indonesian economy. DNA analysis at this point considered the most accurate and can determine whether the fetus is exposed to major or minor gene abnormality.**

The examination for the actual screening is not feasible because can only be done in a particular city and can not be done in every place. Screening of thalassemia, which had been performed abroad, while in Indonesia currently no program for it although new patient increase. The way a simple laboratory has long been known, especially checking MCV and MCH and blood osmotic fragility test (OTOFT) in the mother, but the main choice is fetal chorionic vilous sampling (CVS) or amniocentesis. Both of these tests require examination of DNA that are quite expensive.

Ultrasonography is a tool that is commonly used today in the field of obstetrics. Technological advances, especially Doppler ultrasound has become commonly used. Detection of fetal anemia on serial ultrasound, either with or without Doppler can be used primarily to detect anemia in fetuses by parents who have thalassemia carrier. Measurement cardiothoracic ratio (without Doppler) and measurement of peak systolic velocity (PSV) in middle cerebral artery (with Doppler), performed serially can detect fetuses with anemia earlier to allow for further examination and treatment in the pregnancy.

Keywords: **Fetal anemia, prenatal diagnostic, thalassemia.**

1. INTRODUCTION

Prenatal diagnostic is a term that means to be equated with the actions or the diagnostic make before the fetal born. At this time growing understanding of prenatal diagnostic including genetic pedigree analysis, population screening, genetic counseling and diagnostic testing on the fetus. Although genetic testing can have broad impact on gene transcription family, but the test is carried out at less than 1% of pregnancies.[1] In thalassemia disease is mainly prenatal diagnostic population screening in pregnant women and their partners as well as the fetus. Thalassemia is a major health public problem in some countries in the world. This is especially true threat in countries including thalassemia belt such as Indonesia, but at the moment does not include priority health problems in Indonesia proven at present there is no specific program for the prevention of this disease.

The condition causes the disease is devoid of news and almost never exist of health promotion in the past. This condition contrast with other countries that have elimination program of this disease since several decades ago. Southeast Asian countries are quite advanced for this program were Thailand and singapore. Thailand doing disease elimination programs with mass screening approach premarital screening, while Singapore with advanced equipment to approach diagnostic prenatal.[2,3]

The discovery of the nature of the case in the general population have been carried out. Lau et al in Honkong get carrier properties (carrier/carrier) of 7.9%.[4] Suhanda get the nature of the medical student population in Bandung,Indonesia.[5] Thomas et al in their study in the UK get a case of the nature of 8.3% the population of pregnant women at the clinic antenatal.[6] Estimates of the carrier in Indonesia between 3-8%, in some areas reached 10% and the estimated birth of new patients is approximately 3000 patients with thalassemia major births per-year by Setianingsih et al study, thalassemia patients reached 32% remaining α, β thalassemia.[7,8]

2. PREMARITAL SCREENING

Screening premarital carried out by Europe countries in the 1960s and 1980s and then continued with a prenatal diagnostic to the method of DNA analysis in the case of the parental carrier especially in certain ethnic. Several countries in Asia are approaching screening mass were India, Saudi Arabia, Iran, and Thailand.[9-11] Mass screening is quite effective, especially in countries which were quite more patient. [12-15]

Initial screening can be done routinely, including antenatal care clinics (ANC) by measuring the absolute value of the erythrocytes as the value Mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Such measurement were conventional way to establish suspected a person as a carrier. The value of the reference person suspected carrier of thalassemia carrier was less than 75 for MCV, and the value of MCH was less than 26 (some literature MCV <80 fl and MCH <27pg). [6,10,14,16-20] Gomber et al recommend MCV less than 70 fl will be more sensitive and specific for screen.[21] Tangvarasittichai et al, get cut-off point MCV <75 fl and MCH <25 pg, with a specificity of 81.5% and 85.0% whereas when combined between MCV and MCH spesivisitasnya value up to 88.5% .[3] This method has been done a long time and proved to be one way that was quite helpful. Counting erythrocytes and hemoglobin requires personal skills when done manually, and highly dependent examiner. This examination was performed with a fairly accurate analysis of blood cells.

Another simple way and has been widely used is the method of the erythrocyte osmotic fragility test tube or also known as the one tube osmotic fragility test (OTOFT). or naked eye single tube red cell osmotic fragility test (NESTROFT) .[2,9,10,13,15,22-24] Principle of this examination is to test the resistance of erythrocytes in hipotonic environment, if there are abnormalities in the formation of erythrocytes wall (thalassemia) then the cell will be easily broken or lysis compared with cells that do not have abnormal formation of protein (healthy).[22]

At this time in Indonesia, OTOFT method not yet get attention and are not widely used. The experience of countries that have been using this method such as India and Thailand, proved to have a sensitivity and specificity were quite good with a very low cost so it is suitable for mass screening in the country with a large population. Gomber et al get OTOFT 95.59% sensitivity and 84.2% specificity.[21] Tangvarasittichai et al, getting a sensitivity of 91.7% when combined with MCV OTOFT and MCH.[3] Kattamis et al (1981) in Greece has been evaluated with OTOFT screening can detect 96-100% in carriers of thalassemia carrier β.[25] Mass screening policy report in Iran to prevent thalassemia major states ,OTOFT considered more superior than the examination of the absolute value of the erythrocytes which can be done through primary health care.

3. PRENATAL DIAGNOSTIC

Prenatal screening has been widely known to prevent thalassemia major who have severe symptoms, and proved to be 'cheaper' than the treatment of patients who require life-long treatment. Countries that routinely perform specialized prenatal screening thalassemia such as Britain, Canada, Hong Kong, Singapore, and Israel.[14] This was quite a significant role in reducing the number of new patients with thalassemia major. Selection of screening mainly carried out by certain ethnic approach to a population that risk often likely as a carrier of thalassemia carrier. In populations that have more carrier thalassemia highly recommended for pregnant women to do prenatal screening for thalassemia if the status not know.[14,18,24] Universal screening policy greatly depends on each country because of heterogeneity and variants associated with mutations in each ethnic. Thalassemia patients in Indonesia usually have different gene mutation with Europeans, because Indonesia has many tribes and migration and intermarriage or migrant causing mutation variants were quite a lot.

When the population of patients with Thalassemia pretty much, screening can begin by examining MCV, MCH or osmotic fragility resistance test method. This method was quite useful in several studies for the initial screening of the nature of α and βTalasemia especially. Mean corpuscular hemoglobin (MCH) is more useful than the MCV because it is more stabil.[14] Screening MCV / MCH coupled with eletroforesis should be routinely performed on a population with a blood cell disorder such as sickle cell anemia (sickle cell) and Thalassemia carrier.[13]

If the value of MCV and MCH lower, maternal blood should be checked also a partner for screen thalassemia α, β. β thalassemia is suspected when electrophoresis HbA2 increased > 3.5%, while iron deficiency is known with Fe content inspection. Therapy for Fe deficiency for 4 weeks or after the Fe content was normal before do re-examination of the value of MCV and MCH. Nevertheless carrier α thalassemia carrier often have normal MCV, MCH and HbA2.[10,13,14,22,23,26]

In some ethnic like the people of Cyprus, δ or β thalassemia patients suspected when MCV and MCH lower although on electrophoresis HbA2showed normal value. The fetus was suspected thalassemia deletion δ or β and some types of hereditary persistence of fetal hemoglobin (HPFH) when there is an increased level of HbF (5% -30 &) in heterozigot.[14]

Couple with both carriers of thalassemia should consult with a clinician to a possible diagnostic of thalassemia in the fetus. Delivered neonates have possibility 25% to chance becoming a normal child, 50% chance to be a carrier, and 25% is likely to be a Thalassemia mayor.[13]

Invasive procedures commonly performed prenatal by amniocentesis or CVS followed by DNA analysis. At this time the analysis of DNA was the main option, with the PCR method have advantages more simple, fast and relatively "cheap" (not for Indonesia) compared to the method of gene 'mapping'.[2,14]

Diagnosed fetal as thalassemia major, in some countries legal to do abortions and counseling for future pregnancies. Education was important to do before the screening. Counseling includes information about the disease, laboratory testing, inspection procedures and prognosis.[14] There are other ways, namely by cordocentesis which still include invasive procedures but can be done at service centers are not available means for DNA analysis. This procedure do to find signs of fetal anemia by checking directly the profile of blood taken from the umbilical cord, and advanced procedure for Hb electrophoresis and Hb Bart's Portland.[27] This procedure can be continued with transfusions of blood through the umbilical cord after a blood profile showed anemic conditions.

Non-invasive procedure can be performed serial ultrasound examination with Doppler or without Doppler, can be done regularly, especially to look for cases of severe anemia as in homozygous α thalassemia, which if not to be hydrops fetalis (Hb Bart). Theoretically diagnostic can be established as early as possible so that the condition of severe anemia in the fetus can be addressed to prevent the condition gets worse and cause hydrops.[14]

Experience and good machine ultrasound needed to monitor the possibility of severe anemia in the fetus, especially both parents thalassaemias carrier. The easiest way was without Doppler by measuring the cardiothoracic ratio serially. Checks can be started at gestation week 12 to 15, followed by the age of 18 to 20 and the last at the age of 30 weeks. Measurements are performed each cardiothoracic ratio ≥ 0:50 at the age of 12 weeks, at 18 weeks ≥ 0.52 ≥ 0.59 and at 30 weeks. Anomaly placental signs such as plasentomegali (placental thickness > 18 mm at 12 weeks of gestation). If no abnormalities sign recommended to be done CVS or amniocentesis for DNA analysis as confirmation of α-thalassemia mayor.[14]

This approach can be applied to single or multiple fetuses and can be used also for screening congenital abnormalities. At 12 weeks gestation can be done simultaneously measuring Nuchal Translucency (NT). When the measurement of cardiothoracic at the age of 12 weeks is less than optimal can be repeated 2-3 weeks later, especially if the mother did not want to do an invasive procedure. Screening couple with eletroforesis should be do in addition to routine monitoring of serial ultrasonography, except that thalassemia status was already established.[14]

Serial examination by Doppler ultrasound to measure serial peak systolic velocity blood flow in the middle cerebral artery (MCA). These checks had the principle of blood flow velocity will increase due to an increase cardiac output and a decrease in viscosity when the fetus suffers anemia.[28] Mari et. al studied the relationship of anemia with the peak systolic flow MCA, examination value should converted first into terms of multiples of the median (MoM) depend on

gestational age. Reason needs to be converted first based on gestational age because peak systolic will change and different mean accordingly gestational age.[29] Doppler MCA better than amniocentesis to diagnose fetal anemia, with a sensitivity of 88% and a specificity of 82%.[28]

DNA analysis despite having high accuracy, but there are some flaws that can cause the error checking, such as contamination of specimens from the mother, or problem analysis technique itself. Contamination can be avoided by separating the maternal decidua with fetal trophoblast as well and as accurately as possible. Non-invasive way can be do by find fetal DNA in maternal blood flow derived from fetal blood cells contaminating the mother's blood. This method requires special equipment that is very advanced technologi. Fetal blood cells contained mutations derived from the father, that made differentiation between fetal and maternal cells blood.[14]

Premarital screening to determine the status of carrier both parents should have been done prior to prenatal diagnostic. When if carrier couples marriage, prenatal diagnostic should be done depends on the type of thalassemia. Mass screening can be taken as prevention of the disease and cut the generation from suffer. Simple method such as OTOFT or erythrocytes profile screening merely preliminary and need further investigation including DNA analysis.Serial ultrasound monitoring for signs of fetal anemia, followed by CVS or amniocentesis for DNA analysis is highly recommended for couples who both as thalassemias carrier.

REFERENCES

[1] Jenkins TM, Wagner RJ. Prenatal diagnostic of congenital disorders. In: Creasy RK, Resnik R, editors. Maternal-Fetal medicine. 1 ed. Philadelphia: Saunders; 2004. p. 235-80.

[2] Sanchaisuriya K, Fucharoen S, Fucharoen G, Ratanasiri T, Sanchaisuriya P, Changtrakul Y, et al. A reliable screening protocol for thalassemia and hemoglobinopathies in pregnancy. Am J Clin Pathol. 2005;123:113-8.

[3] Tangvarasittichai O, Jeenapongsa R, Sitthiworanan C, Sanguansermsri T. Diagnostic value of combined parameters for α-thalassemia-1 screening in pregnant women. Naresuan university journal. 2004;12(2):19-24.

[4] Lau Y, Chan L, Chan Y, Ha S, Yeung C, Waye J, et al. Prevalence and genotypes of α and β thalassemia carriers in Hong Kong-implications for population screening. NEJM. 1997:1298-301.

[5] Suhanda I. The prevalence of thalassemia carrier carrier based screening with a tube osmotic fragility examination at Padjadjaran university medical school student. Bandung (thesis): Universitas Padjadjaran; 2007.

[6] Thomas P, Oni L, Alli M, Hilaire J, Smith A, Leavey C, et al. Antenatal screening for haemoglobinopathies in primary care: a whole system participatory action research project. B J Gen Pract. 2005;55:424-8.

[7] Wahidiyat PAW. Problems and management of Thalassemia in Jakarta. Thalassemia material course; 2007; Jakarta. Eijkman Institute; 2007.

[8] Setianingsih I, Harahap A, Nainggolan IM. Alpha talasemia in Indonesia: phenotypes and molecular defects. In: Marzuki, Verhoef, Snippe, editors. Tropical diseases. New York: Kluwer academic/Plenum; 2003. p. 47-56.

[9] Maccioni L, Cao A. Osmotic fragility test in heterozygotes for alpha and beta thalassemia. J Med Genet. 1985 Oct;22(5):374-6.

[10] Gajra B, Chakraborti S, Sengupta B. Prenatal diagnostic of thalassemias. Int J Hum Genet. 2002;2(3):173-8.

[11] Al-Suliman A. Prevalence of β-thalassemia carrier in premarital screening in Al-Hassa Saudi Arabia. Ann Saudi Med. 2000;26 (1):14-6.

[12] Bain B. Screening of antenatal patients in a multiethnic community for β thalassemia carrier. J Clin Pathol. 1988;41:481-5.

[13] Cunningham F, Leveno, Gant N, Gilstrap L, Hauth J, Wenstrom. Williams Obstetrics. 21 ed. New York: McGraw Hill.

[14] Leung K, Cheong K, Tang M, Chan V. Prenatal diagnostic of thalassemia. JPOG. 2008 Jan/Feb;34 (1):37-42.

[15] Manglani M, Lokeshwar M, Vani V, Bhatia N, Mhaskar V. 'NESTROFT'-an effective screening test for beta thalassemia carrier. Indian pediatrics. Aug 1997;34:702-7.

[16] Permono B, Ugrasena I. Talasemia. In: Permono B, Sutaryo, Ugrasena I, Windiastuti E, Abdulsalam M, editors. Buku ajar Hematologi-Onkologi anak. Jakarta: badan penerbit IDAI; 2005. p. 64-84.

[17] Randolph M. Thalassemia. In: McKenzie S, editor. Clinical laboratory hematology. New Jersey: Pearson prentice hall; 2004. p. 239-62.

[18] Rogers M, Phelan L, Bain B. Screening criteria for βhalassemia carrier in pregnant women. J Clin Pathol. 1995;48:1054-6.

[19] Tatu T, Prakunwist D, Sayajak S, Chiampanichayakul S, Kasinrek W. RBC count and its differentiation potential among alpha thalassemia (SEA type), beta thalassemia and Hb E heterozygotes. CMU JNatSci. 2007;6(1):57-64.

[20] Chan L, Ma S, Chan A, Ha S, Waye J, Lau Y, et al. Should we screen for globin gene mutations in blood samples with mean corpuscular volume (MCV) greater than 80 fl in areas with a high prevalence of thalassemia? J Clin Pathol. 2001;54:317-20.

[21] Gomber S, Sanjeev, Madan N. Validity of Nestroft in screening and diagnostic of beta-thalassemia carrier. J Trop Pediatr. 1997 Dec;43(6):363-6.

[22] Cohen A, Galanelo R, Pennel D, Cunningham M, Vichinsky E. Hematology. 2004;1:14-22.

[23] Forget B, Cohen A. Thalassemia syndrome. In: Hoffman R, Benz E, Shattil S, Furie B, Cohen H, McGlave P, editors. Hematology basic principles and practice. 4 ed. Philadelphia: Elsevier; 2005. p. 557-89.

[24] Maheshwari M, Arora S, Kabra M, Menon P. Carrier screening and prenatal diagnostic of β-Thalassemia. Indian pediatrics. 1999;36:1119-25.

[25] Kattamis C, Efremov G, Pootrakul S. Effectiveness of one tube osmotic fragility screening in detecting beta-Thalassemia carrier. J med Genet. Aug 1981;18(4):266-70.

[26] Huch R, Christian B. Anaemia in pregnancy and the puerperium. Bremen: UNI-MED; 2005.

[27] Vanderdijs F, VandenBerg G, Schermer J, Muskiet F, Landman H, Muskiet F. Screening cord blood for hemoglobinopathies and thalassemia by HPLC. Clin Chem. 1992;38(9):1864-9.

[28] Moise KJ. Ultrasound evaluation of Hydrops Fetalis. In: Callen PW, editor. Ultrasonography in Obstetrics and Gynecology. 5 ed. Philadelphia: Saunders Elsevier; 2008. p. 676-97.

[29] Mari G, Deter R, Carpenter R. Noninvasive diagnostic by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. N Eng J. 2000:342-9.