International Journal of Gynecology and Obstetrics (2008) **101**, 281–284

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CLINICAL ARTICLE

Increasing the noninvasive management of rhesus isoimmunization

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Received 8 October 2007; received in revised form 23 November 2007; accepted 23 November 2007

KEYWORDS
Doppler assessment;
Fetal anemia;
Middle cerebral artery;
Peak systolic velocity;
Red cell alloimmunization

Abstract

Objective: To determine the clinical outcome of isoimmunized pregnancies managed by middle cerebral artery peak systolic velocity (MCA-PSV) in an intention-to-treat study. *Method:* Rhesus isoimmunized pregnancies were managed with serial ultrasound and Doppler studies at 7-day intervals up to 34 weeks of gestation, between 2001 and 2005. Invasive diagnostic and therapeutic procedures were carried out when MCA-PSV was indicative of moderate or severe anemia. *Results:* The overall sensitivity in detecting moderate to severe fetal anemia at less than 34 weeks was 100% (95% confidence interval, 54.1–100.0 L). Twenty-two cases were managed with MCA-PSV. Twelve cases needed fetal blood sampling and 6 cases needed intrauterine transfusion. Cordocentesis revealed a hematocrit of more than 26% in 6 fetuses. *Conclusion:* Management by MCA-PSV Doppler at weekly intervals is a highly sensitive method for detecting fetal anemia. It reduces the number of fetal blood samples needed and significantly lowers interventional procedures.

1. Introduction

Rhesus alloimmunization has been known since 1609, but it was not until 1932 that Diamond et al. demonstrated that hydrops fetalis and neonatal jaundice were part of the same in-utero disease process. The hemolytic disease was named erythroblastosis fetalis because of the presence of erythroblasts in fetal and neonatal blood [1].

Since 1968, rhesus immunoglobulin has been available for rhesus negative pregnant women, which has reduced the incidence of hemolytic disease from 13% to 0.8% per 1000 liveborn infants. Nevertheless, the problem still remains owing to the existence of more than 400 antigens capable of producing hemolytic disease, and the inability to investigate all of them during pregnancy [1].

Up until 6 years ago, pregnancies complicated by rhesus isoimmunization in our unit were monitored by ultrasound, indirect Coombs maternal titers, and invasive diagnostic procedures. It has now been shown that in pregnancies at risk for maternal red cell alloimmunization, moderate and severe

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0020-7292/$ - see front matter
doi:10.1016/j.ijgo.2007.11.021

Table 1 Sensitivity, specificity, and positive and negative predictive values (%) for the serial ultrasound method

	Percent (%)	95% confidence interval
Sensitivity	100.0	54.1–100.0
Specificity	78.6	59.1–91.7
Positive predictive value	50.0	21.1–78.9
Negative predictive value	100.0	84.6–100.0

anemia can be detected noninvasively using Doppler ultrasound based on an increase in the peak velocity of systolic blood flow in the middle cerebral artery (MCA-PSV) [2]. This technique has proven superior to maternal titers or serial ultrasound.

Since MCA-PSV Doppler proved to have a better predictive accuracy for detecting fetal anemia, thereby reducing the need for fetal blood sampling, we replaced the conventional management of these high-risk pregnancies in our unit according to the guidelines proposed by Mari et al. [2]. Invasive procedures are used only in cases where MCA-PSV is indicative of moderate to severe anemia.

The aim of this intention-to-treat study was to assess the outcome of rhesus isoimmunized pregnancies managed with MCA-PSV as the initial diagnostic approach. In 1991, we reported the results of 41 pregnancies complicated by isoimmunization [3]. The comparison of these two strategies for managing rhesus isoimmunized pregnancies has enabled us to draw useful and clinically important conclusions.

2. Methods

"Alexandra" Maternity Hospital is the tertiary referral centre for rhesus sensitized pregnancies in Athens, Greece. We studied 36 singleton rhesus isoimmunized pregnancies during a five-year period from January 2001 through December 2005. All gestations were complicated by maternal alloimmunization and were referred for specialist prenatal care in our fetal medicine unit. Inclusion criteria were an obstetric history of isoimmunization and increased indirect Coombs maternal titers. Fetal blood sampling was performed only when MCA-PSV values were indicative of moderate or severe anemia. During the study period, a titer of $\geq$1:32 was considered significant and monitoring was conducted at 7-day intervals; in women with titers of 1:16 we followed maternal values at monthly intervals [3]. If the mother was already sensitized (history of an anemic fetus in a previous pregnancy), titer control was not routinely performed. Monitoring in this case was initiated 10 weeks prior to the appearance of the disease during the last pregnancy.

Maternal medical records were available to confirm the presence of a clinically significant antibody, titer level, and ultrasonographic evidence. Neonatal records were retrieved and reviewed for antigen status, initial hemoglobin level, bilirubin level, neonatal course and outcome. Gestational age was calculated according to the first day of the last menstrual period and was confirmed by first trimester ultrasound.

The serial ultrasound examinations for MCA-PSV measurements were performed at 7-day intervals by transabdominal ultrasound examination (Ultramark 9; Advanced Technology Laboratories, Bothell, USA). This ultrasound equipment is approved for obstetric use, with spatial peak temporal average intensity of less than 100 mW/cm^2. An axial section of the brain including the thalami, cavum septum pellucidum, and circle of Willis was obtained. The MCA was measured 2 mm from the internal carotid artery as previously described [4]. Doppler images were recorded at a time when there was an absence of marked fetal body and respiratory movements.

The optimal threshold values for PSV in the MCA for 100% detection of severe, moderate, and mild anemia were 1.55, 1.50, and 1.29 multiples of the median (MoM) for gestational age [2]. The expected median value for peak systolic velocity was calculated by the formula MCA-PSV = $e^{(2.31+0.046\ GA)}$, where GA is gestational age [2]. The study protocol was approved by the institutional Ethics Committee and patients provided written informed consent. We did not perform reproducibility studies because only two experienced fetal medicine specialists (NP, GD) performed the ultrasound examinations. Furthermore, previous studies have shown that Doppler measurements of MCA-PSV are highly reproducible [4].

Statistical analysis was performed and continuous variables are expressed as mean ± standard deviation, while categorical variables are expressed with absolute and relative frequencies.

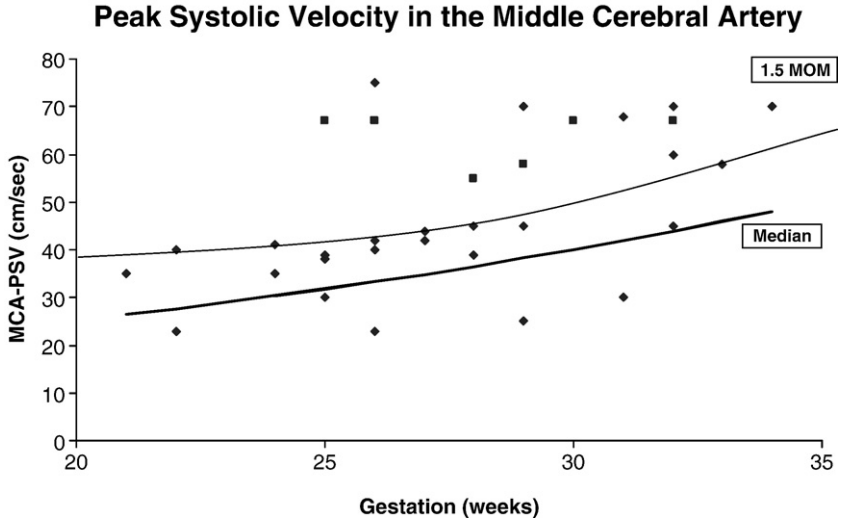

Figure 1 Peak systolic velocity in the middle cerebral artery in 34 fetuses. Key: ■ = anemic fetuses requiring intrauterine transfusion.