TITLE: MATERNAL HISTORY AND PERINATAL OUTCOME IN RHESUS IMMUNIZES PREGNANCIES.

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MATERNAL HISTORY AND PERINATAL OUTCOME IN RHESUS IMMUNIZED PREGNANCIES

Abstract

Objectives: To correlate index pregnancy prognosis and perinatal outcome in Rhesus immunized pregnancies to maternal history. **Methods**: Retrospective review of data prospectively collected from 126 pregnancies. Maternal variables: Previous incompatible blood transfusion (PIBT), lack of anti-D prophylaxis (no anti-D), previous fetal death and/or fetal blood transfusion. Perinatal variables: Gestational age, weight at delivery and fetal death on index pregnancy. **Results**: The most frequent cause of maternal immunization was lack of anti-D use. There were no statistical differences in perinatal outcome and intrauterine treatment between PIBT and no anti-D groups. Gestational age and weight at delivery from mothers with and without PIBT were respectively 35.7 and 37.9 weeks (p=0.03) and 2232 and 2784 g (p=0.04). Previous fetal death had no influence in gestational age and/or weight at delivery. **Conclusion**: Maternal history did not influence prognosis of index pregnancy, except for a reduction in gestational age and weight at delivery from mothers with PIBT.

Key words: Rh immunization, perinatal outcome, fetal therapy, and fetal transfusion

Introduction

Rh immunization is one of the diseases of which the etiology, physiopathology, diagnostic and treatment methods and prophylaxis are known [1]. Although these facts are wide spread in medical knowledge, Rh immunization still occurs due to many reasons, mainly the ones that afflict health systems in third world countries, such as Brazil and other Latin American States [2]. In order to achieve low rates of this disease, as seen in other countries where the frequency has declined tremendously in the past decades, the main problems to be controlled and avoided are failure to administer anti-D prophylaxis and incompatible blood transfusion. Once sensitization occurs, fetal evaluation is the determining factor to obstetrical follow up, which can be performed by amniocentesis as suggested by some [3] or by fetal blood sampling (cordocentesis), considered to be the standard of care by others [3,4]. The selection of the method used to evaluate the fetus relies upon maternal history, anti-D measurements, amniotic fluid delta OD₄₅₀ values and direct fetal hemoglobin cord blood levels. These are all used to predict hemolytic antibody behavior and consequently perinatal outcome [2,3,4]. There are reports from 1950's, as Costa Ferreira, 1956 [5], showing that maternal immunization secondary to incompatible blood transfusion had a worse perinatal prognosis than pregnancy-induced immunization. Walker & Murray, in 1956 [6] also reported a greater risk of fetal death on index pregnancy for woman with previous fetal death. Considering the early dates of these reports and the dramatic changes in treatment approach since their publication, this study examined the correlation between

maternal history and perinatal outcome in women sensitized to Rh blood antigens in a tertiary treatment center.

Methods

A retrospective cohort study was performed with data prospectively collected from women assisted at Fetal Medicine Program, Universidade Estadual de Campinas (UNICAMP), between January 1990 and May 1999. Women were confirmed as Rh sensitized and bearing Rh positive fetuses. Data was collected on a special chart, which contained patient identification, diagnosis, follow up data from pregnancy to postpartum and perinatal outcome. A data bank in EPIINFO 6.0 software was used to store and analyze data. The variables were studied by comparison of means and frequency distribution in relation to maternal history data. A "Chi-square" test was used for this analysis. Continuing variables were analyzed by one-way analysis of variance. Statistical significance was considered of "p" values lower than 0.05.

Maternal variables were: sensitization mode (incompatible blood transfusion or lack of adequate anti-D prophylaxis) and need for intrauterine transfusion. Perinatal variables were: gestational age (Capurro method) and weight at delivery and fetal death on index pregnancy.

Results:

The study evaluated 102 women. There were 24 women without identifiable antecedents for Rh sensitization. Fourteen women were identified with clinical histories of incompatible blood transfusion and only four of these women had this

trace isolated without the occurrence of lack of use of anti-D. The antecedent of lack of use of anti-D was the most frequent fact in maternal history, which corresponded to 88 women in this group. Thirty-two women revealed the occurrence of one previous fetal death and this fact was always associated to other maternal antecedents related to Rh sensitization. Maternal antecedents associated to Rh sensitization are on table 1.

Maternal antecedents were cross-studied with type of follow up (clinical observation or intrauterine blood transfusion) and perinatal outcome (live born or fetal death, gestational age and weight at birth).

Nine out of twenty-two (28.1%) women with a previous fetal death also had a fetal death in the index pregnancy. Only three of these fetal deaths were of transfused fetuses.

The maternal antecedent of incompatible blood transfusion as sensitization mode, the need for intrauterine transfusion and fetal death on index pregnancy are shown on tables 2 and 3.

The mean gestational age at birth in the group of women with PIBT history was 35.7 ± 3.3 weeks and 37.9 weeks in the group without PIBT (p=0.03). The mean weight at birth in the group of PIBT was $2272\pm713.9g$ and in the group with no PIBT was $2784.2\pm669.4g$ (p=0.04).

The relation between previous fetal death and need of intrauterine transfusion and the number of fetal deaths on index pregnancy are described on tables 4 and 5.

The mean gestational age of babies from women with a previous fetal death was 36.7 ± 3.4 weeks and 37.9 ± 2.6 in the group of women without it (p=0.12). The

mean weight at birth of babies from women with a previous fetal death was $2573.6\pm830.9g$ and $2782.2\pm628.9g$ in the group of women without it (p=0.32).

Discussion

It was observed in this study that there was a partial correlation between the gravity of maternal antecedents and index pregnancy prognosis.

The antecedent of maternal sensitization by incompatible blood transfusion wasn't different than other antecedents to determine a greater number of intrauterine transfusions or fetal deaths on index pregnancy in this group of women.

The relation between the gravity of Rh sensitization to the sensitization mode is not clear in the literature, except for one early publication by Costa Ferreira [5] showing a three times greater risk of fetal death if sensitization occurred by blood transfusion. This study had the hypothesis that the greater antigenic load of this sensitization mode would determine a worse prognosis for the gravity of Rh disease itself. However, this hypothesis was not proved to be true in this study. It was observed that there were differences in gestational age and weight at birth in babies from women with sensitization by incompatible blood transfusion. This study provided no explanation for these events, since there was not a greater number of transfused fetuses in this group, which would tend to shorten the length of pregnancy and thus interfere with these aspects.

Failure to perform adequate Rh sensitization prophylaxis was the most important event in maternal history, even presented associated to the history of incompatible blood transfusion. The observation that only 3.2% of the patients studied had an isolated antecedent of incompatible blood transfusion and that the great majority of cases failed to receive anti-D prophylaxis, raises troubling questions as to why this simple and fairly inexpensive method of avoiding such an extremely dangerous

health problem is yet overlooked by health authorities in this country. This is a situation completely different from the one referred by Portman at al [7], in which they report failure of prophylaxis despite adequate use as the most frequent cause of sensitization. We can consider that 24 out of 126 (19%) patients that had no identified antecedents to sensitization were in fact failed prophylaxis despite its administration. The data presented here regarding mode of sensitization has a potential bias to be detailed on analysis of the influence of incompatible blood transfusion as a determinant of gravity of Rh disease. Unfortunately, the overlapping of both antecedents makes it impossible to have an evaluation absolutely free of errors, since at least one third of the women who received incompatible blood transfusion also failed to receive adequate anti-D prophylaxis. Data from Walker & Murray [6] showed a 70% chance of fetal death for woman with a previous fetal death secondary to Rh sensitization. These data of course have dramatically been changed with treatment of fetuses at risk of death during pregnancy through intravascular intrauterine blood transfusion [1].

By the same method it was observed in this study of the antecedents of blood transfusion or failed prophylaxis, the antecedent of previous fetal death was not associated with a greater number of the needed intrauterine transfusions or with fetal death on index pregnancy. This association of antecedent of previous fetal death and prognosis in index pregnancy is not the same as identified by other authors [1,2,3,5,8]. Although it is known that the curse of sensitization tends to repeat in subsequent pregnancies it must be emphasized that here treatment may have had an influence on the final outcome. When we considered pregnancies with

the antecedent of fetal death, it was observed that none of the variables studied was influenced by it. Again, we know that Rh disease usually tends to either repeat itself or to worsen its course, but this was not the case in this group of women. It may be argued that more aggressive treatment is changing the natural history of the disease. If this was true a greater need for intrauterine transfusions should be observed as well as fetal deaths related to the treatment or to the severity of the disease itself. The only indication that treatment might have influenced perinatal results is the number of fetal deaths on index pregnancy. This, of course, reflects the weight of intrauterine treatment, since overall mortality rate was 17,5%, which is in agreement with data presented recently [9].

Conclusion:

Maternal antecedent of the mode of sensitization for Rh disease does not identify fetuses at greater risk on index pregnancy. In the same way, maternal antecedent of previous fetal death does not identify fetuses at risk for intrauterine transfusion or the occurrence of fetal death on index pregnancy, although there might be an effect of intrauterine treatment on modifying the natural course of the disease.

Table 1. Maternal antecedents in pregnant women with Rh disease.

Antecedents	Number	Grouped by association
	(n)	
No antecedent identified	24	24
Previous incompatible blood Transfusion	2	
(PIBT)		
PIBT + previous fetal death	2	14
PIBT + no Anti-D prophylaxis	6	
PIBT + no Anti-D + previous fetal death	4	
no Anti-D prophylaxis	62	
no Anti-D prophylaxis + previous fetal death	26	88
Total	126	126

Table 2: Maternal sensitization antecedents and intrauterine transfusion on index pregnancy.

	Intrauterine transfusion		Total
Maternal Antecedent	Not performed	Performed	
No antecedent identified	18	6	24
With PIBT	9	5	14
No anti-D prophylaxis	61	27	88
Total	88	38	126
p=0.43			

Table 3: Maternal sensitization antecedents and fetal death on index pregnancy.

Maternal Antecedent	Fetal death on index pregnancy		Total
	Absent	Present	
No antecedent identified	20	4	24
With PIBT	10	4	14
No anti-D prophylaxis	74	14	88
Total	104	22	126
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Table 4: Previous fetal death and the need for intrauterine transfusion.

Previous fetal death	Intrauterine transfusion		Total
	Not performed	Performed	-
No antecedent identified	18	6	24
With previous fetal death	21	11	32
Without previous fetal death	49	21	70
Total	88	38	126
p=0.79			

Table 5: Previous fetal death and occurrence of fetal death on index pregnancy.

Previous fetal death	Fetal death or	Total	
	Absent	Present	
No antecedent identified	20	4	24
With previous fetal death	23	9	32
Without previous fetal death	61	9	70
Total	104	22	126
p=0.2			

References

- Bowmam JM: Hemolytic disease. *In* Maternal-Fetal Medicine Ed. Robert Creasy & Robert Resnik (eds). 4th edition W.B.Saunders, USA, 1999, pg. 736-66.
- Howard HL, Martkew VJ, McFadyen IR & Clarke CA: Preventing Rhesus D haemolytic disease of the newborn by giving anti-D immunoglobulin: are the guidelines being adequately followed? Br J Obstet Gynecol 1997; 104:37-41.
- Parer JT: Severe Rh isoimmunization current methods of in utero diagnosis and treatment. Am J Obstet Gyncol 1998; 158:1323-1329.
- 4. Nicolaides KH, Rodeck CH, Mibashan RS, Kemp JR: Have Liley charts outlived their usefulness? Am. J. Obstet. Gynecol. 1986; 15:90-94.
- Costa-Ferreria H: Importância das transfusões de sangue como agentes sensibilizantes da doença hemolítica do recém-nascido [The importance of blood transfusion as sensitizing agents on perinatal haemolitic disease of newborn] Rev. Clin. São Paulo 1956:32-35
- 6. Walker W. & Murray S: Haemolytic disease of the newborn as a family problem. B. M. J. 1956; i:681, 187-193.
- Portman C, Ludlow J, Joyce A, and Chan FY: Antecedents to and Outcomes of RH(D) Isoimunization. Aust. N Z J. Obstet. Gynaecol. 1997; 37:(1), 12-16.
- Weiner CP, Williamson RA, Wenstrom KD, Sipes SL, Grant SS, Widness JA: Management of fetal hemolytic disease by cordocentesis. I. Prediction of fetal anemia. Am J Obstet Gynecol 1991;165(3):546-53
- Cheong YC, Goodbrick J, Kyle PM and Soothil P: Management of anti-D-Rhesus antibody in pregnancy: a review from 1994 to 1998. Fetal Diagn Ther 2001;16:294-298.

Acknowledgments: this study was sponsored by FAPESP process 98/14737-3.