Maternal Intravenous Immunoglobulin Therapy in the management of severe Rh-immunization : An Analysis of 12 cases.

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Summary: **Management of severe Rh-isoimmunization is a difficult obstetric challenge. Recent reports of non-invasive therapy with maternal Intravenous Immunoglobulin (IVIG) therapy have been encouraging. Intravenous Immunoglobulin blocks Fc mediated antibody transport across the placenta, blocks destruction of fetal red cells and reduces antibody levels. In 12 patients with severe Rh- Immunization, with high maternal antibody titres and previous hydrops and intra-uterine deaths, Intravenous Immunoglobulin was started at 13-18 weeks of gestation and repeated, 3-4 weekly, till delivery or till intra-uterine fetal blood transfusion (IUT) was required. Intensive fetal monitoring was done. Ten pregnancies continued till 32-36 weeks and all 10 babies did well in the neonatal period. There were 2 intrauterine deaths in pregnancies with severe immunization where anaemia developed very early (<22 weeks) and IVIG could not be given according to protocol used. IVIG delayed the onset of fetal anemia by several weeks, deferring and also preventing the need for I.U.T. Thus, Intravenous Immunoglobulin is very useful as primary and adjuvant therapy in the management of Rh-immunization, particularly in non-hydropic fetuses more than 22 weeks gestation.**

Introduction

Rhesus isoimmunization is still prevalent in India, resulting from nil or inadequate anti-D prophylaxis. In the index-pregnancy, the fetus is affected 10 weeks earlier than in the previous pregnancy (Whitfield, 1983). Cord blood sampling and intra-uterine transfusion have revolutionised management, but is associated with a high fetal mortality rate especially in hydropic fetuses (Berkowitz, et al 1986; Harman et al 1990).

High dose Intravenous Immunoglobulin (IVIG) therapy has been found to be very useful in several immune disorders (Newland, 1989). Anecdotal reports of its use in severe Rh isoimmunization has shown great promise (Berlin et.al 1986; Margulies et al 1991), Repeated IVIG therapy was tried in 12 cases of severe Rh (isoimmunization with very had obstetric histories, to study the usefulness of this novel protocol in achieving a favourable prognosis.

Material and Methods

Twelve patients with severe Rh immunization referred to the All India Institute of Medical Sciences, New Delhi were taken up for the study. Informed consent was taken. Indirect Coomb's Test (I.C.T.) was done at booking and repeated weekly after 18 weeks. Serial ultrasound (U/S) was done bi-weekly from 14-16 weeks, for early evidence of fetal anemia - Cardiomegaly, hepatomegaly, placentomegaly, dilatation of hepatic vein and amniotic fluid volume. The appearance of fetal hydrops was considered a late sign of severe fetal anemia. Amniocentesis for spectrophotometric analysis of amniotic fluid bilirubin (A.F.Bil) levels was done at 18-20 weeks of gestation or after that period on increase of ICT titres or when ultrasound features suggested anemia. If amniotic fluid bilirubin was in Liley Zone III, cordocentesis was done. Intrauterine fetal blood transfusion (I.U.T.) was carried out if haematocrit, packed cell volume (PCV) was <30 and the fetus was <32 weeks. Intensive fetal monitoring was done by daily kick counts, biweekly non stress

Table 1
Pregnancy Outcome in Severe Rh-immunization with intravenous immunoglobulin Therapy.

Case No.	Parity Bl. Group	Prev. Hydr. (POG)	IVIG Doses (POG)	ICI	FET ANE (POG)	IUT (POG) Date	Del (POG) Date	Baby (Blood) Group)
A	B	C	D	E	F	G	H	I
1.	G4 PO+3 B-	20	3 (16,20.24)	1:1024	27	(27,29,30)	32 (11-'93)	1 E.T. B+
2.	G3 P1+1+0+1) B-	28	4 (18,22,26,30)	1:256	33+4	-	34+5 (12-'93)	2 E.T. B+
3.	G4 P1+1+1+1 0-	34	4 (18,22,27,31)	1:256	33	-	33 (1-'94)	2 E.T. 0+
4	G4 P1+2+0+1 AB-	26	5 (18,22,25,28,31)	1:256	28	-	33+3 (6-'94)	3 E.T. B+
5	G5 P1+4+1+0 0-	26	4 (13,18,22,28)	1:128	32	-	33 (6-'94)	2 E.T. A+
6	G5 P1+1+2+0 0-	28	4 (18,22,25,28)	1:256	28	29+5	32 (8-'94)	2 E.T. 0+
7	G4 P1+2+0+0 0-	28	4 (17,25,28,30)	1:512	29	(29,31)	31+2 (9-'95)	2 E.T. B+
8	G7 P2+4+0+1 A-	27	4 (19,24,27,30)	1:256	32+5	-	(9-'95)	4 E.T. AB+
9	G5 P2+1+1+1 A-	28	3 (15,18,21)	1:256	22 (IVIG.CORD)	22 (IUD)	24 wks (12-'95)	0+
10.	G3 PO+1+1+0 AB-	32 NND	6 (18,21,24,27, 30,34)	1:32	-	-	38 (3-'96)	2 E.T. B+
11.	G3 P1+1+0+1 0-	27	1 (21)	1:512	20	22	22+3 IUD (6-'96)	A+
12.	G3 P1+1+0+1 A-	26	7 (16,29,22,24 27,30,32)	1:512	32	-	34 (8-'96)	8 E.T. A+

POG - period of gestation (weeks)
IUT - Intrauterine transfusion
DEL - Delivery (weeks)
HYDR - Hydrops
FET ANE - Fetal Anemia
ET- Exchange transfusion

test and weekly bio-physical profile after 28 weeks. Human Intravenous Immunoglobulin (Intra-globin, Bio-Test Pharma., W. Germany), 100 mgm/kg was given at 13-18 weeks of gestation in 11 cases and at 21 weeks in 1 case. IVIG was repeated 3-4 weekly till delivery or Intrauterine transfusison.

Results

Individual data of the twelve cases, showing pregnancy outcome with Intravenous Immunoglobulin therapy regarding earliest appearance and detection of fetal anemia, need for intra-uterine transfusion, and fetal outcome, compared to previous obstetric historic controls are shown in Table I.

All cases had previous history of hydrops fetalis or neonatal deaths attributable to Rh-incompatibility. The I.C.T. titres were above critical levels in all the cases at booking.

Thus, in 7/11 cases intravenous immunoglobulin alone was used. Three other cases (1,5,7) required I.U.T. and all 10 babies did well in the neonatal period. The two intrauterine deaths were in cases (9,11) who could not receive I.V.I.G. according to the protocol used for the other cases and required intra-uterine transfusions very early (<22 weeks).

Discussion

The incidence of severe Rhesus-iso-immunization worldwide has been drastically reduced by the prophylactic use of Anti-D. But a very large number of cases are still referred to the All India Institute of Medical Sciences, who have received nil or inadequate prophylactic Anti-D, had unrecognised abortions or received Rh-incompatible blood transfusion.

Indirect coomb's test on maternal blood, amniocentesis and amniotic fluid bilirubin levels on Liley's chart along with intensive fetal monitoring, to time premature delivery and post-natal blood transfusion is the traditional method of management.

Serial ultrasound evaluation of the fetus for evidence of anemia - Cardiomegaly, hepatomegaly, dilatation of umbilical vein, ascitis, placentomegaly (Reece, et al 1989), Cord blood sampling for direct estimation of fetal Hb, PCV, and Intra-uterine fetal blood transfusion (Berkowittz et al 1986) have revolutionised management. Cordocentesis and Intra-uterine blood transfusion are however, invasive procedures with their attendant risks. (Harman, et al 1990; Pielet, et al 1988).

Anecdotal reports suggest that non-invasive therapy with Intravenous Immunoglobulin may be extremely useful in the management of severe Rh immunization.

I.V.I.G therapy was first described by Berlin et al (1985) in a case of severe Rh-isoimmunization managed with plasmapheresis, but with problem of inadequate venous access after 10 titres exchange. At 25 weeks I.V.I.G. (0.4g/kg/day) was given to the mother, after which no therapy was required. At 35 weeks Caesarean Section was done after A.F. Spectrophotometry was in Liley's Zone III. The baby required 2 exchange transfusions. Subsequently, several cases citing the successful use of maternal high dose I.V.I.G. therapy along with plasmapheresis or Intrauterine fetal blood transfusion were reported (Sacher, 1986; Scott, 1988).

Intravenous Immunoglobulin as sole therapy for Rh immunization was reported in 2 cases referred for IUT (Camera, 1990) in a series of 24 cases (Margulies, 1991) and 6 cases (Gottvall, 1995).

"In-Vitro" studies by Sacher et al (1986), showed that IVIG blocked the uptake of opsonised Rh +ve cells by macrophages. It also probably blocks Reticulo-Endothelial Fc receptors in mother and fetus and blocks Fc mediated antibody transfer across the placenta (Newland, 1989; Sheth, et al 1993).

Analysis of our 12 cases with previous hydrops prenatal deaths showed that IVIG could significantly delay the exacerbation of Rh-disease. In 7 cases Intravenous Immunoglobulin was the sole treatment used. Adjuvant fetal blood transfusion was required in 3 cases (Cases 1,6,7), several weeks later than the period of gestation at which hydropic stillbirth occurred in the preceeding pregnancies. All these 10 babies required limited number of exchange transfusions in the neonatal period and are doing well.

In only 2 cases (Cases 9,11) anemia appeared early (20-22 weeks). Case 9 had reaction to IVIG in the form of itching and rashes, so the last 2 doses could not be completely given, after which fetal anemia soon appeared. Case II received IVIG late (21 ultrasound, as she could not afford it earlier. Intrauterine death occurred as a consequence of very early, severe fetal anemia, with the hazards of intrauterine transfusion at this period of gestation, compared to the risks of IUT done at later gestations (>27 weeks). Gottvall et al (1995) claims that IVIG treatment can successfully be used to prevent anemia if started only before severe fetal anemia or hydrops developed, and perhaps only after 22 weeks.

The pharmacology of Intravenous Immunoglobulin is complex, a dose of 100 mgm/kg results in an average increase of 200 mgm/dl above baseline and reaches preinfusion levels by day 21 to 28 (Buckley, 1982). The Indian women, being lighter did very well with the dose of Intravenous Immunoglobulin used, primarily as they could not afford the very high cost of the dosage prescribed by some earlier workers. Clinical responses also vary between individuals and the disease process (Newland, 1989).

This study therefore is in agreement with our initial observations citing the extreme usefulness of Intravenous Immunoglobulin in the management of severe Rh immunization (Deka, 1996). High cost of therapy limits its application, but this novel therapy holds promise as the primary or adjuvant therapy for these very high risk pregnancies before severe anemia or hydrops develops.

Thus, repeated maternal high dose IVIG therapy can prevent hydrops fetalis and intrauterine death, delay or prevent the need for intra-uterine fetal blood transfusion. I.V.I.G. however, does not seem to be effective in hydropic fetuses or in very early gestation <22 weeks.

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