Original Article

Corticosteroids for Management of Rh-Isoimmunization : Extended Study in a Tertiary Referral Centre

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ABSTRACT

Background: RhD isoimmunization is a life threatening condition for affected fetuses. It is currently treated only by intrauterine transfusion of packed red blood cells. This procedure required special skill and has potential complications.

Aim : The aim of the present study was to evaluate the role of corticosteroids in prevention of fetal anemia due to RhD isoimmunization.

Material and Methods: The study was conducted on 15 pregnant patients with RH isoimmunization in Shatby Maternity University Hospital, Alexandria, Egypt, during the period from July 30th 2016 to July 30th 2019. Recruited women received 40 mg oral prednisolone starting from 10th week of gestation. Follow up of Anti-Rh antibodies titer and-from 18 weeks gestation- middle cerebral artery peak systolic velocity (MSA-PSV) was done every 2 weeks. Patients were delivered at 34 weeks gestation by elective caesarean section after receiving 4 doses of dexamethasone to enhance fetal lung maturity.

Results: 12 patients continued the trial. Significant reduction was achieved in anti-Rh antibodies titer. Reduction in MSA-PSV was achieved and maintained below 1.5 MOM. Gestational age at delivery ranged from30.3-34 weeks (33.18±1.2 weeks). Fetal eight at delivery ranged from 1550-2270 grams (1978.5±232.5 gm). 9 newborns required NICU admission, only 2 newborns underwent exchange transfusion therapy.

Conclusion: In Rh iso-immunization, oral prednisolone proved to have a good rule in preventing fetal anemia and introducing its use should be considered. More studies with bigger sample size are needed to confirm its efficacy.

Key Words: Corticosteroids; intrauterine transfusion; MSV-PSV; rh-isoimmunisation

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INTRODUCTION

RhD isoimmunization is the most common cause of hemolytic disease of the fetus and newborn HDFN[1]. HDFN is a disorder caused by the binding of transplacentally transmitted maternal immunoglobulin (Ig) G-class antibodies on paternally inherited antigens present on fetal red blood cells (RBCs) (Rh-isoimmunisation, MSV-PSV, corticosteroids, intrauterine transfusion). In developed countries, 1:300 to 1:600 pregnancies are at risk for hemolytic disease of the fetus and newborn[2].

Disruption of the placental barrier normally occurs at birth, miscarriage or other incidences during pregnancy, so that some fetal blood escapes into the mother's circulation stimulating the development of antibodies to RhD positive blood antigens in RhD negative women.[3] When the next pregnancy occurs, maternal IgG-class antibodies bind to fetal RBCs, resulting in hemolysis and / or suppression of erythropoiesis[4].

Prophylaxis from this condition is through administration of anti-Rh antibodies to the mother at 28 weeks gestation, after birth and at other incidences of feto-maternal hemorrhage e.g. miscarriage[1-5].

Intrauterine fetal blood transfusion (IUT) is established as the gold standard in management of fetal anemia in pregnancies complicated by RhD alloimmunization[6-8].

Corticosteroids are established for immune suppression in auto-immune disorders[9]. Their use in cases of Rh isoimmunization is not fully studied.

AIM OF WORK

The aim of the present study was to evaluate the role of corticosteroids in prevention of fetal anemia due to RhD isoimmunization.

PATIENTS AND METHODS

The present study was conducted on sensitized RhD negative pregnant females attending the Fetomaternal Unit, Department of Obstetrics and Gynecology, Shatby Maternity University Hospital, Alexandria, Egypt, during

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the period from July 30th 2016 to July 30th 2019. Shatby hospital is a tertiary referral center for three governorates with total population of 15 million.

Included women were multiparous women with RhD negative blood group and history of miscarriage or successful full term delivery. They were referred to the unit at gestational age of 9-10.7 weeks gestation, with confirmed RhD negative maternal and RhD positive paternal blood groups, indirect Coomb's test positive against anti-RhD antibodies with indirect Coomb's titer of ≥ 1/16. Females with evidence of hydrops fetalis (both immune &non immune) as well as those with first trimester scan abnormalities were excluded from the study.

In this study, 17 patients fulfilling the inclusion criteria presented to the fetomaternal unit. Two patients refused to participate. Other eligible patients, signed an informed consent to participate in the study.

Women at the time of recruitment were subjected to assessment of ABO and Rh blood grouping, measurement of maternal haemoglobin level, postprandial blood glucose level and anti-Rh antibody titre. Ultrasonographic examination was done using Voluson P8 (GE) ® machine. It included: Fetal biometry, anomaly scan and, in fetuses above 18 weeks gestation, peak systolic velocity in middle cerebral artery (PSV-MCA). Detection of fetal anemia was based on normograms of multiple of medians (MoM) of PSV-MCA in different gestational ages[10].

Recruited patients received oral prednisolone 20 mg tab (Solupred- Sanofi®) twice a day for suppression of maternal anti-Rh antibodies production. Shift towards intrauterine transfusion was planned if fetal anemia still developed during oral prednisolone therapy. For cases whose fetuses survived till 34 weeks gestation, 4 doses of dexamethasone 8mg were given intramuscularly and cases were then delivered by cesarean section. Rationale was to limit duration of maternal exposure to corticosteroids. Further, elective planned cesarean delivery allowed good preparation for probable neonatal intensive care unit (NICU) admission and exchange transfusion therapy for the newborn.

Ultrasonographic examination was repeated every 2 weeks for all patients. The primary outcomes were reduction in anti-Rh antibodies titer below 1/16 as well as reduction in middle cerebral artery peak systolic velocity below 1.5 multiple for means (MOM) for gestational age.

Secondary outcomes included delivery of healthy fetus at 34 weeks gestation, need for neonatal intensive care unit (NICU) admission, need for postnatal blood exchange transfusion and achieving healthy neonatal discharge later.

After delivery, oral prednisolone was gradually withdrawn over a period of 32 days postnatal, with decrease in the dose 5 mg every 4 days.

A written informed consent was obtained from every participant after explaining the objectives and clarifying that they have freedom to refuse participation or cross to the traditional management at any time.

The minimum sample size and therapeutic drug dose required was calculated based on data obtained from a previous preliminary small scale trial conducted 2015 in the same unit[11].

STATISTICAL ANALYSIS

Data was analyzed using IBM SPSS version 21 (Armonk, NY: IBM Corp). Description of baseline characteristics using suitable methods was done. Comparison between patients was done using Chi-square and Fissure-Exact test for qualitative variables and Mann Whitney U test for quantitative variables after testing for normality using Shapiro-Wilk test. Analysis was done at 5% level of significance.

RESULTS

In this study, 17 patients were eligible for the study, 2 of them refused to participate, 15 patients received oral prednisolone therapy. During the course of the study, three patients demanded shifting to intrauterine transfusion and discontinuation of the trial after initiation of therapy.

Table 1 showed distribution of studied groups according to their age, gravidity, parity, number of miscarriage, number of living children and gestational age at recruitment.

Table 2 showed that significant reduction in middle cerebral artery peak systolic velocity below 1.5 multiple of medians (MOM) among fetuses of treated women in follow-up visits.

Table 3 showed follow up of anti-Rh antibodies titer every 2 weeks, showing significant reduction overtime as all patient showed positive test at the first measurement as compared to the 5th visit onward in which all 12 remaining patients showed low positive (titer less than 1/16) to negative test; (P<0.001). Four patients developed preterm labour pains and were delivered before 34 weeks gestation.

The secondary outcome measures are shown in Table 4. The gestational age at delivery ranged from 30.3-34 weeks (33.18 ± 1.2 weeks). The fetal weight at delivery ranged from 1550-2270 grams (1978.5 ± 232.5 gm). 9 newborns required NICU admission, only 2 newborns underwent exchange transfusion therapy.

Table 1: Distribution of studied groups according to their age, gravidity, parity, number of miscarriage, number of children, gestational age at recruitment

Baseline characteristics	Prednisolone therapy (n = 15)	
	No.	%
Maternal age (years)		
Min. – Max.	23.0 – 39.0	
Mean ± SD.	29.27 ± 4.30	
Median	30.0	
Gravidity		
Min. – Max.	3.0 – 8.0	
Median	5.0	
Parity		
Min. – Max.	1.0 – 3.0	
Median	2.0	
No of miscarriages		
Min. – Max.	0.0 – 5.0	
Median	2.0	
No. of living children		
1	9	60.0
2	6	40.0
GA at recruitment (weeks)		
Min. – Max.	9.0 – 10.7	
Mean ± SD.	9.32±0.53	
Median	10	

Table 2: Middle cerebral artery peak systolic velocity multiple of medians (MOM) upon repeated measurements during the follow up visits

MCA - PSV (MOM)	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th# visit	8th# visit
Range	1.25-1.88	1.20-1.75	1.15-1.70	1.00-1.55	1.00-1.31	0.96-1.30	0.85-1.30	0.85-1.22
Mean ± SD.	1.52 ± 0.18	1.42 ± 0.16	1.37±0.18	1.25 ± 0.13	1.18 ± 0.09	1.18 ± 0.08	1.16± 0.11	1.12 ± 0.14
Median	1.52	1.4	1.3	1.25	1.2	1.2	1.12	1.17

Table 3: Anti-Rh antibodies titer level throughout the follow up visits

COOMB's titre (Every 2 weeks) 1(n=15)		Number of visit													
		2 (n=15)	3 (n=15)	4 (n=12)	5 (n=12)	6 (n=12)	7 (n=12)	8 (n=12)	9 (n=12)	10 (n=12)	11 (n=8)	12 (n=8)			
High positive (≥ 1/16 - < /512)	no.	15	11	7	4	1	0	0	0	0	0	0	0	Fr_c^2 25.65	P# 0.0013*
	%	100.0	73.3	46.7	26.7	6.7	0	0	0	0	0	0	0		
Low positive to Negative (< 1/16)	no.	0	4	8	8	11	12	12	12	12	12	8	8		
	%	0.0	26.7	53.3	73.3	93.2	100	100	100	100	100	100	100		

P value for Friedman test for repeated measurement of an ordinal variable

(n) in each measurement is affected by the timing of delivery and the number of women attending follow up visits

*: Statistically significant at $p \leq 0.05$

Table 4: Display of gestational age at delivery, live birth number, fetal weight at delivery, NICU admission and the need for postnatal exchange transfusion in cases that continued prednisolone therapy

	Continued Prednisolone therapy (n = 12)
Gestational age at delivery (weeks)	
Min. – Max.	30.3 – 34.0
Mean ± SD.	33.18 ± 1.29
Median	34.0
Live birth	12
Fetal weight at delivery (grams)	
Min. – Max.	1550-2270
Mean ± SD.	1978.5±232.5
Median	2000
NICU Admission	
No	6
Yes	9
Need for exchange transfusion	
No	10
Yes	2

DISCUSSION

RhD iso-immunization is the most common causes of hemolytic disease of the fetus and newborn. Maternal immunization to fetal red blood cell antigens causes fetal anemia. In untreated cases, this mostly leads to hydrops fetalis and increased perinatal mortality[1].

Treatment of these fetuses is currently through repeated intrauterine transfusion, several possible complications exist including preterm labour or fetal death[12-13].

Pharmaceutical treatment is currently of limited use. The current study proposed the use of relatively high doses of corticosteroids for immune suppression. The underlying principle is suppression of maternal Anti-Rh antibodies which cross the placenta and cause fetal haemolysis[11]. The use of oral prednisolone is of no documented teratogenic effects in human fetuses[12].

Use of oral prednisolone is safe in pregnancy[14]. Early use of this mode of treatment was successful to suppress the formation of antibodies, allowing the fetal bone marrow and reticulo-endothelial system to maintain adequate hemoglobin levels and thus normal cardiovascular function. Hepatosplenomegaly was not documented in any case and there was no evidence of ascites in studied cases.

Treatment with 40 mg oral prednisolone helped save twelve fetuses of isoimmunised mothers without the need for the invasive procedure of intrauterine transfusion. It could be used alone or in conjunction with other modes of treatment. Delivery at 34 weeks gestation was decided to minimize duration of maternal exposure to prednisolone therapy.

Birth weights ranged from 1550-2270 grams, which is normal for this duration of pregnancy, and rules out growth restriction secondary to maternal exposure to corticosteroids.

Nine newborns required admission to neonatal intensive care unit, mainly for phototherapy. This may be due to improved lung maturity by antenatal administration of Dexamethasone. Only two of the newborns required exchange transfusion, probably this is secondary to the low titer of Anti-Rh antibodies in maternal serum under prednisolone therapy, preventing severe neonatal hemolysis after delivery. All cases had good outcome.

Other studies reported other methods for immunological therapy for Rh isoimmunization. Mayer *et al*[2] reported three cases successfully treated by weekly administration of intravenousimmunoglobulins (IVIG) starting before 20 weeks of gestation, but remarked on the high cost of the treatment.

Odendaal *et al*[15] reported the successful use of plasmapheresis with Azathioprine and 20-30 mg prednisolone in management of fetal anaemia due to RhD isoimmunisation. He recruited 9 cases; one had intrauterine fetal death due to placenta abruption. Plasmapheresis however remains a more expensive approach than oral prednisolone, and azathioprine could be associated with fetal growth restriction.

Isojima *et al*[16] reported the successful use of plasmapheresis and high doses of gamma globulins for dilution and neutralization of anti- Rh antibodies, but only in one case. Houston *et al*[17] reported another case managed with the same combination, none of them added corticosteroids. Again, immunoglobulins remain a more expensive mode of treatment compared to oral prednisolone.

Success rate of oral prednisolone therapy in this study was better than our previous pilot study in 2015[10], most probably due to earlier start of therapy.

CONCLUSIONS

In cases with Rh iso-immunization, oral prednisolone proved to have a great role in preventing fetal anemia and introducing its use should be considered. More studies with bigger sample size are needed to confirm its efficacy.

CONFLICT OF INTERESTS

There are no conflict of interests.

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