Feto-maternal outcomes of women with Rhesus iso-immunization in a Nigerian tertiary health care institution.

George Uchenna Eleje[1,2*], Chito Pachella Ilika[1], Chukwuemeka Okwudili Ezeama[1,2], Joseph Chinedu Umeobika[3], Charlotte Blanche Oguejiofor[1]

[1]Department of Obstetrics and Gynaecology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nnewi, Nigeria

[2]Effective Care Research Unit, Department of Obstetrics and Gynecology, Nnamdi Azikiwe University, Nnewi Campus, Nigeria

[3]Department of Obstetrics and Gynaecology, Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Awka, Nigeria

Abstract

Background: Fetomaternal haemorrhage may occur during pregnancy or at delivery and may lead to allo-immunization to the D antigen if the mother is Rhesus (Rh) negative and the baby is Rh-positive.
Objectives: To determine the incidence, socio-demographic characteristics and pregnancy outcomes of Rh negative pregnant women in a Nigeria Tertiary health care institution.
Methods: A review of the clinical records of all Rh-negative pregnant women, managed at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, South-east Nigeria between 1st January 2009 and 31st December 2013 was done. Data were entered into Excel Spread sheet and analysed using computer Epi-Info 2013 version 7.
Results: There were a total of 5561 deliveries and 117 Rh negative pregnancies during the period, given an incidence of 2.1%. Of the 117 Rh negative pregnancies, only 89 (76.1%) case files were available for analysis. Majority, 55.1% of the women were of ABO Blood Group O while ABO blood group discordance occurred in 33.7% of male partners.
Seventy-one (79.8%) of the women have had previous pregnancies and only 33(46.5%) of these received anti-D prophylaxis in the previous pregnancies. Sixty-three (70.8%) of the pregnancies were booked and 48 out of 63 (76.2%) of them booked after 20 weeks of gestation. Indirect Coombs test was done in 61 out of 63 (96.8%) women that were booked but only one (1.6%) woman tested positive. None of the women had a follow-up testing. Only the woman that tested positive for indirect Coombs test had her antibody titre subsequently determined.
Forty-five (50.6%) pregnancies were carried beyond date while 88.5% of the women that had postdate were delivered via caesarean section ($p<0.001$) with the commonest indication being fetal distress (42.9%). Sixty-one (68.5%) babies were tested post-delivery while 49 (80.3%) of 61 babies were rhesus incompatible with the mother. Only 40 (81.6%) of the incompatible mothers had Rh anti-D immunoglobulin administered after delivery. Neonatal jaundice occurred in 21.3% of the babies. There were 14 (15.7%) perinatal deaths.
Conclusions: The incidence of Rhesus negative pregnancies was 2.1% while Rh isoimmunization rate was 1.6% and the uptake of Rhesus Anti-D immunoglobulin is suboptimal. Rh negative primigravida's tend to be unbooked and had significantly higher still births than their multigravid counterparts. Rhesus negative pregnancies carried beyond their dates had a significantly higher caesarean section rates than those delivered at term or before the expected date of delivery. There is need for further studies to clearly explore these trends.

Keywords: Rhesus negative, Pregnancy, Allo-immunization.

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Introduction

Isoimmunization is the process of immunizing an individual with antigen derived from the similar subject, provided that the said antigen was initially absent. The Rhesus (Rh) antigen is found on the surface of human red blood cell (RBC) membrane [1,2]. The ABO system and the Rhesus (Rh) system remain the most clinically significant blood group antigens on the red cell membranes. If the mother is RhD-negative and the fetus RhD-positive, she has the potential to form antibodies if exposed to the fetal antigens, a process known as RhD sensitization [2-5].

The risk of sensitization depends largely upon the following three factors: volume of transplacental haemorrhage, extent of the maternal immune response and concurrent presence of ABO incompatibility [6]. Thus, the incidence of Rh isoimmunization in the Rh-negative mother who is also ABO incompatible is reduced dramatically to 1-2% and is believed to

occur because the mother's serum contains antibodies against the ABO blood group of the fetus [3,6]. During this process, the few fetal red blood cells that are mixed with the maternal circulation are destroyed before Rh sensitization can proceed to a significant extent. Surprisingly about 30% of Rhesus negative individuals never become sensitized when given Rhesus positive blood (non-responders) [6].

Although sensitization is unlikely to affect the current fetus during the first pregnancy, it may result in haemolytic disease of the fetus and newborn (HDFN) during a second RhD-positive pregnancy. In its mildest form, the infant has sensitized RBCs, which are detectable only in laboratory tests. However, HDFN may result in jaundice, anaemia, developmental problems, or intrauterine fetal death [4,5]. Rhesus isoimmunization generally occurs in a rhesus negative mother by one of two mechanisms either from fetomaternal haemorrhage, or from incompatible blood transfusion [6]. Predisposing factors for fetomaternal haemorrhage include delivery, spontaneous or induced abortion, ectopic pregnancy, missed abortion, intrauterine fetal death, abdominal trauma, antepartum haemorrhage, amniocentesis, chorionic villous sampling, fetal blood sampling, embryo reduction, shunt insertion, external cephalic version, manual removal of the placenta and caesarean section [6]. It is important to note that with no apparent predisposing factor, fetal red cells have been detected in maternal blood in 6.7%, 15.9%, and 28.9% of women in the first, 2nd and 3rd trimesters respectively [6].

The incidence of Rh isoimmunization is higher in Caucasians than in blacks [1,6]. The Basque populations in Spain have the highest incidence of Rh negativity (30-35%) [6]. However, a study in Port Harcourt, Nigeria reported 9.5% Rhesus negativity among females of reproductive age [7]. In the survey conducted among the obstetric population in Ibadan, South-western Nigeria, an incidence of 2.6% was reported [5]. This was in keeping with other published data in Enugu, Nigeria which recorded a low incidence of Rh Negativity of 4.5% [4]. In other neighbouring African Countries, 3.9% has been reported in Kenya, 2.4% in Cameroon and 4.06% in Guinea [8-10].

It is part of modern antenatal care to give all RhD-negative pregnant women an anti-RhD immunoglobulin IgG injection at about 28 week's gestations with a booster at 34 weeks gestation [2]. This reduces the effect of the vast majority of sensitizing events which mostly occur after 28 weeks gestation. Anti-RhD immunoglobulin is also given to non-sensitized Rh-negative women immediately within 72 hours after potentially sensitizing events that occur during pregnancy and after delivery [1,2]. All these advances in antenatal management of Rh-negative pregnant women in developed countries are beyond the reach of a vast majority of women in the developing world. Anti-D prophylaxis has significantly reduced the incidence of erythroblastosis fetalis caused by sensitization to the D-antigen and perinatal deaths from alloimmunization have fallen 100-fold in the developed world [2].

There are several possible reasons for continuing cases of Rh isoimmunization among the Rh-negative pregnant population in Sub-Saharan African [1,2]. These include: poor antenatal practices which fail to identify rhesus negative women, cost of procuring anti-D immunoglobulin, absence of a universal access program for all Rh-negative women, failure to recognize potential sensitizing events in pregnancy as such and to treat them appropriately and failure and absence of facilities to assess the extent of fetomaternal haemorrhage. Other factors include failure to offer Rh-negative pregnant women anti-D immunoglobulin following potentially sensitizing event during pregnancy and failure to comply with postpartum prophylaxis guidelines to offer further anti-D immunoglobulin to all Rh-negative women delivered of Rh-positive babies within 72 hours of delivery [1,2].

As a result of the above, antenatal management of Rh-negative pregnant women in sub-Saharan Africa appears suboptimal despite the fact that the prevalence of Rh-negative phenotype is significantly lower among Africans than in Caucasians. Thus, Rh isoimmunization remains a major factor in perinatal morbidity and continues to compromise women's obstetric care in sub-Saharan Africa.

A preliminary study of 67 Rh D-negative women over a 2-year period in Nigeria has shown that isoimmunization due to Rh incompatibility is poorly studied, with many questions unanswered such as the optimal time for delivery of these women and proportion of them that constitute non-responders [11,12]. Though knowledge about immunity in pregnancy is ever increasing daily, continued appraisal is necessary so that local data generated would be useful in counselling, investigating and management of these couples as well as help in proper and adequate health care plan for pregnant women with Rh isoimmunization.

Currently, little is known about the status of Rh Isoimmunization and its outcome in Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria the study hospital. The objective of this study is therefore to determine the incidence, socio-demographic characteristics, trends and pregnancy outcome of Rh negative pregnant women managed in the tertiary health care institution in Nnewi South-east Nigeria.

Materials and Methods

This is a 5-year retrospective study of Rh negative women who were managed at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria from 1st January 2009 to 31st December 2013. Data was obtained from the labour and delivery registers of the hospital as well as the resident doctors's labour ward registers. We included only women whose husbands were Rh D positive. The ABO and Rh D factors are part of the routine investigations during the antenatal booking, labour/delivery management of women who present at the labour and delivery suite of the Hospital.

Antibody screenings are routinely performed at booking on Rh D negative women or on presentation at labour ward for delivery if unbooked. All Rh-negative women are sent for indirect Coombs test at booking visits. If negative, follow-up testing is done at 28 weeks gestation. If positive, the patient is

managed as Rh sensitized. Rh sensitized women with history of no previous fetus affected by Rh isoimmunization are followed up with antibody titers at booking, 20 weeks of gestation and then every 2-4 weeks intervals. Rh sensitized women with history of previous fetus affected by Rh isoimmunization are not followed up with maternal antibody titers because such antibody titers are not helpful since they may be elevated simply as the result of the anamnestic response [13]. Such women are followed up with ultrasound. Umbilical cord blood is taken from all babies born to rhesus negative mothers for estimation of fetal blood group and Rh typing.

The previous obstetric history, transfusion history, and obstetric findings were noted. Other information including age, occupation, and social and family history of the Rh D negative pregnant women, prior intake of Rh anti-D immunoglobulin was obtained from their case files and the labour ward registers. The Rh D blood group system of the husbands of Rh negative women booked for antenatal care is routinely requested by the managing obstetricians. The social class was derived from the Olusanya, Okpere and Ezimokhai protocol of social classification [14]. The study was approved by the Hospital's Ethics committee.

Data were entered after checking for completeness, cleaning and coding into EXCEL Spread sheet and analysed using computer EPI-Info 2013 version 7 (v 7; Epi Info, Centers for Disease Control and Prevention, Atlanta, GA). Data were presented as means, numbers and frequencies (%). The results were analysed further using cross tabulation to explore statistical relationships between variables. Statistical analyses were performed using Student's t-test for continuous variables and the Fisher's exact tests for categorical data. A P-value of <0.05 was considered statistically significant.

Results and Discussion

There was a total of 5561 deliveries and 117 rhesus (Rh) negative pregnancies during the period, given an incidence of 2.1%. Of the 117 rhesus negative pregnancies, only 89 (76.1%) case files were available for analysis. The mean age of the women was 30.4 ± 5.1 years (range=22-40 years). Majority, 52.8% (47/89) have secondary level of education. The socio-demographic characteristic of the respondents' is shown in Table 1. Majority of the women 60.7% (54/89) were from low social class.

Table 1. *Socio-Demographic Characteristics of the Rh-Negative Women.*

Variables	Frequency (N=89)	Percentage
Age (years)		
21-25	11	12.4
26-30	41	46.1
31-35	34	38.2
36-40	3	3.3
Parity		
0	31	34.8
1	34	38.2
2-4	24	27
>5	0	0
Educatonal level		
Primary	3	3.4
Secondary	47	52.8
Tertiary	39	43.8
Social Class		
I	6	6.7
II	29	32.6
III	42	47.2
IV	9	10.1
V	3	3.4

Majority, 49 (55.1%) of the women were of ABO Blood Group O while ABO blood group incompatibility occurred in 33.7% of male partners. This is shown in Table 2. Seventy-one (79.8%) of the women have had previous pregnancies and only 33 (46.5%) of these received anti-D (Rhogam) prophylaxis in the previous pregnancies. Thirty-three (46.5%) of the 71 women who have had previous pregnancies had previous miscarriages. Of the 33 with previous history of miscarriages, only 12 (36.4%) received anti-D (Rhogam) prophylaxis.

Table 2. *The relationship between the mothers and fathers' ABO blood group.*

Mother			Father		
ABO blood group	**Frequency**	**%**	**Frequency %**	**Compatible %**	**Incompatible %**
O	49	55.1	38	77.6	22.4
A	20	22.5	9	45	55
AB	14	15.7	10	71.4	28.6
B	6	6.7	2	33.3	66.7
Total	89	100	59	66.3	33.7

Table 3. *Indications for Caesarean section in the Rh-Negative women.*

Indications	Frequency	%
Fetal Distress	15	42.9
Cephalopelvic disproportion	8	22.9
One previous caesarean section	3	8.6
Fetal macrosomia	3	8.6
Failed induction	3	8.6
Post term	2	5.7
Maternal request	1	2.9
Total	*35	100

Sixty-three (70.8%) of the pregnancies were booked and 48 out of 63 (76.2%) of them booked after 20 weeks of gestation. Antibody screening was done in 61 out of 63 (96.8%) of all the women that were booked but one (1.6%) woman tested positive to the indirect Coombs test. None of the women had a follow-up testing except the one woman who tested positive for indirect Coombs test had her antibody titre subsequently determined.

Forty-five (50.6%) pregnancies were carried beyond date while 26 (29.2%) women were delivered via caesarean section. Twenty-three (88.5%) of the 26 women that had caesarean section were delivered postdate. There is a statistically significant association between the number of babies carried postdate and caesarean delivery ($p<0.001$). The most common indication for caesarean section was fetal distress, 15 (42.9%). This is shown in Table 3. Sixty-one (68.5%) babies were tested post-delivery while 49 (80.3%) of 61 babies were rhesus incompatible with the mother. Only 40 (81.6%) of the incompatible mother had Rhogam administered after delivery.

Table 4 shows the details of the association between women's gravidity and some mothers' obstetrics characteristics. Rh negative primigravida tend not to be booked for antenatal care than their multigravida counterparts, and this association was statistically significant ($p<0.001$). However, mode of delivery and gestational age at delivery do not bear any significant association between the rhesus negative primigravida and multigravida ($p>0.05$).

Table 4. *Association between Women's Gravidity and some Mothers' Obstetrics Characteristics.*

Variable/Outcome	Primigravida (n=18)	%	Multigravida (n=71)	%	p-value
Booking Status					
Booked	5	27.8	58	81.7	*<0.001
Unbooked	13	72.2	13	18.3	
Gestational Age at Delivery (weeks)					
>40	12	66.7	33	46.5	0.1
<40	6	33.3	38	53.5	
Mode of Delivery					
Booked	7	38.9	19	26.8	0.232
Unbooked	11	61.1	52	73.2	

Neonatal jaundice occurred in 21.3% of the babies. There were 14 (15.7%) perinatal death. The relationship between women's gravidity and perinatal outcome is shown in Table 5. Rhesus negative primigravida tend to have less live births than their multigravida counterparts, and this association is statistically significant ($p<0.001$). However, APGAR score at 1 minute, birth weight and neonatal jaundice do not have any significant association between the rhesus negative primigravida and multigravida ($p>0.05$).

Table 5. *Association between Women's Gravidity and Perinatal Outcome.*

Variable/Outcome	Primigravida (n=18)	%	Multigravida (n=71)	%	p-value
Status of babies at birth					
Live births	11	61.1	64	90.1	*0.006
Still birth	7	38.9	7	9.9	
APGAR score (in 1 min)					
>6	7	38.9	19	26.8	0.232
≥ 6	11	61.1	52	73.2	
Birth Weight (kg)					
<4.0	15	83.3	60	84.5	0.574
≥ 4.0	3	16.7	11	15.5	
Neonatal Jaundice					
Yes	4	22.2	15	21.1	0.572
No	14	77.8	56	78.9	

Of the 61 babies that was tested post-delivery, 49 (80.3%) were Rh positive (incompatible with the mother) while 12 (19.7%) were Rh negative (compatible with the mother). Only 40 (81.6%) of the pregnancies incompatible with the mother were given Rhogam after delivery.

This study showed that about 2.1% of the pregnant women managed at NAUTH, Nnewi were rhesus negative which is quite similar to 2.6% by Fawole et al. in Abeokuta [5]. This is far below 4% reported by Keith et al. among black Africans [15]. It is also smaller than 4.5% by Okeke et al. in Enugu, and 14.3% by Belinga et al. in Cameroon but higher than 0.7% by Onwuhafua and Adze in Kaduna, all in Nigeria [12,14,16]. However, the smaller proportion of rhesus negative women in this study may probably be due to the retrospective design of the study since some pregnant women who are rhesus negative may be missed due to inadequate record. This is because only women who carried their pregnancy to the age of viability were captured in our data set.

In this study, the incidence of Rh isoimmunization was 1.6%. This compares favourably with 1.3% reported by Fawole et al. in Abeokuta, Nigeria but higher than 0.7% reported by Okeke et al. in Enugu, Nigeria [4,5]. This was quite lower than 5.5% reported by Adeyemi et al. in Ogbomosho, Nigeria, and 9.1% reported by Onwuhafua and Adze in Kaduna, Nigeria [1,12]. Although none of the women had repeated antibody test in the pregnancy, there have been reports of development of Rh antibodies in the course of the pregnancy. For example, in a study in Enugu, 4.3% of Rh negative women were said to have developed antibodies after the first half of pregnancy even when they earlier tested negative at booking [4].

As revealed in our study, amongst ABO system, blood group O was most common followed by A, AB and B respectively. This is similar to a study by Odokuma et al. in Abraka Nigeria, Egesi et al. in-Niger Delta University, Nigeria and by Okeke et al. in Enugu, Nigeria and that seen among other Africans except that AB blood group was more common than B blood group in our data set [4,17,18].

Interestingly, the risk of sensitization can be highly influenced by concurrent presence of ABO incompatibility [6,12]. This mechanism is noteworthy in this study because, up to 33.7% of husbands in this study were ABO incompatible. Thus, the incidence of Rh isoimmunization in the Rh-negative mother who is also ABO incompatible is reduced drastically. This occurs because the maternal serum contains antibodies which act against the ABO blood group of the fetus. Any available fetal red blood cells that are mixed with the maternal circulation are destroyed before significant Rh sensitization ensues [13].

In this study, Rh negative primigravida tended to have poorer pregnancy outcomes than their multigravid counterparts, and this association was statistically significant ($p<0.001$) with respect to perinatal deaths. The reason for this finding is difficult to explain. This is because sensitization is unlikely to affect the current fetus during the first pregnancy and there was no correlation on the mode of delivery and gestational age at delivery between the primigravida and the multigravida ($p>0.05$). Could it be exposure to maternal antibody in-utero- the so called "grand- mother theory?" [19]. This theory suggests that a Rh-negative woman may have been sensitized from birth by receiving enough Rh-positive cells from her mother during her own delivery to produce an antibody response [19]. The fact that Rh negative primigravida booking status is poorer compared to their multigravid counterparts, as revealed in this study ($p<0.001$) is another possible reason.

In this study, antibody screening was done in almost (97.0%) all the women that were booked but none had a follow-up testing except the woman that tested positive for indirect Coombs test had her antibody titres subsequently determined. Also, none of the women received Rhogam during the antenatal period but following child birth. The overwhelming major challenge to this trend is cost [20,21]. This may explain why only 81.6% of the women who were Rh incompatible with the babies had Rhogam administered after delivery. Similar recent study by Adeyemi et al. in Nigeria revealed that only 60.9% had Rhesus Anti-D immunoglobulin administered to them after delivery or abortion [1]. Thus, if guidelines are followed, a non-sensitized Rh-negative woman should receive 3 vials of anti-D immunoglobulin in an uncomplicated pregnancy (at 28, 34 weeks gestation and postnatally after delivery of a Rhesus positive baby). Repeat doses are given at 6 weekly intervals from 28 weeks because the half-life of immunoglobulin is only 24 days and it persists for only 6 weeks [13]. In addition, fetal-maternal haemorrhage is more likely to occur at delivery [13]. However, this regimen may not be practicable in our environment, such that maternal administration of Rhogam is only recommended within 72 hours post-delivery.

In this study, neonatal jaundice occurred in 21.3% of the babies. There were also 14 (15.7%) perinatal deaths. This could be due to the fact that during the course of Rh incompatibility, the fetus is primarily affected. The binding of maternal Rh antibodies produced after sensitization with fetal Rh-positive erythrocytes results in fetal autoimmune haemolysis. As a consequence, large amounts of bilirubin are produced from the breakdown of fetal haemoglobin.

Generally, in Rh negative pregnant women, delivery should be conducted as for any other normal pregnancy. However, the tendency of pregnancy to overrun the expected date of delivery should not be allowed and should be the goal of management [13,22]. This recommendation is essential, because as shown in this study, 50.6% of the pregnancies were carried beyond date while 88.5% women that had postdate were delivered via caesarean section and the most common indication was fetal distress. There is statistically significant association between the number of babies carried postdate and caesarean delivery ($p<0.001$).

The limitation of this study was that it was retrospective and so out of the 117 recorded cases of rhesus negative pregnancies during the study period; only 89 case files were available for analysis. Therefore, sample size was limited in nature. We could not correlate the relationship between various variables studied in Rh negative pregnant women and Rh positive pregnant women. Also, the proportions of Rh negative women that constitute non-responders (proportion of women with Rh incompatible children that tested negative to Indirect Coombs test even though they did not receive Rh anti-D immunoglobulin in their previous pregnancies) remain unanswered and thus constitute further study.

Conclusion

Rh negative pregnancies constitute a vital facet of our obstetrics population in Nnewi and the incidence is 2.1% while Rh isoimmunization rate is 1.6%. Uptake of rhogam is suboptimal. Rh negative primigravida tend to be unbooked and also had significantly higher still births than their multigravid counterparts. Pregnancies carried beyond their dates had a significantly higher caesarean section rates than those delivered at term or before the expected date of delivery. There is need for further study to clearly explain these trends.

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Conflict of Interest

The authors report no conflict of interest.

Compliance with Ethical Standards

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Author Contribution

The study arose from an original idea from GUE. All authors contributed to the study's design. GUE and CPI wrote the first draft, and COE, JCU and CBO advised on the analysis. All authors contributed to the discussion and conclusion.

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*Correspondence to

George Uchenna Eleje

Department of Obstetrics and Gynaecology

Nnamdi Azikiwe University

Nigeria.

E-mail: georgel21@yahoo.com