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THE INFLUENCE OF GESTATIONAL AGE ON THE LOSS OF MATERNAL MEASLES ANTIBODIES IN NEWBORN INFANTS IN NORTH-EASTERN NIGERIA: A CALL FOR A REVIEW OF MEASLES IMMUNIZATION SCHEDULE

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ABSTRACT

Background: Maternal measles antibodies (MMA) are actively transferred in mother-infant pairs during third trimester of pregnancy. Gestational age (GA) affects the levels of MMA such that longer GA may result in infants starting out with high levels of MMA.

Objective: To determine the influence of GA on the loss of MMA in newborn infants in North-Eastern Nigeria.

Method: A prospective study was conducted on newborn infants at Maiduguri; sera were collected at birth and at six months of age. Enzyme linked immunosorbent assay (ELISA) was used to measure MMA while GA was determined using the last menstrual period, ultrasound scan reports and the Dubowitz criteria.

Results: Seventy eight newborn infants were enrolled. Seventeen (89.5 %) preterm, 43 (95.6 %) term and 14 (100 %) postterm had protective levels of MMA at birth. Two (10.5 %) preterm, nine (20.0%) term and two (14.3 %) postterm had protective MMA at six months of age. Comparison of mean MMA at birth and at six months of age was significant ($p = 0.005$), however, it was independent of GA of the newborn infants.

Conclusion: Significant decline of mean MMA levels was seen in these infants at six months of age, which was independent of their GA. These infants may be prone to measles at an earlier age (less than six months). Therefore, the current recommendation of measles immunization to infants at nine months of age may require reconsideration.

Keywords: maternal measles antibodies, gestational age, measles immunization, newborn infants.

INTRODUCTION

Measles is the most common vaccine preventable cause of death in the world. The World Health Organization (WHO) estimates that 8.703 million disability adjusted life years (DALY) due to measles and 256,000 measles associated deaths still occur yearly (1). Developing countries are worst hit (1). The mainstay of measles control is measles vaccine. Since 1976, the WHO has recommended that measles vaccine be integrated into routine health services and be administered at nine months of age in developing countries (2). This recommendation was based on studies demonstrating seroconversion rates of over 90% in children nine months of age or older in

developing countries (3). In Nigeria, measles vaccine is also being administered at nine months of age. However, 10-15% of measles occur in infants at the age of six-eight months, that is, before they can be immunized against measles (4). Therefore, the question arises whether administration of measles vaccine should be earlier than nine months in order to protect this group of infants. Most infants are protected against measles by MMA but are susceptible to measles when these antibodies fall to unprotective levels (3, 5). As MMA persist in infant, measles vaccine cannot be given because these

antibodies would interfere with its uptake and subsequent seroconversion (5).

Trans-placental MMA transfer occurs mainly in the third trimester of pregnancy and the level of MMA in a neonate is directly proportional to gestational age (6). Study of term infants has demonstrated that MMA are lost to an unprotective levels by seven months of age in developing countries (3, 5). Therefore, measles vaccine administered around that time, theoretically, would be effective in those infants. Keeping in mind that the degree of MMA transfer is related to gestational age, preterm infants are likely to have lower MMA at birth. Thus, preterm infants are likely to become seronegative earlier than term infants. This presumably could be due to early interruption of intrauterine life associated with preterm deliveries. Very few studies have been done to verify this hypothesis (7). If this is so, it stands to reason that, preterm infants would require measles vaccine earlier and also would seroconvert adequately if given measles vaccine at an earlier age like term and postterm infants (8). In view of the above, this study was undertaken to estimate and compare the levels of MMA in preterm, term and postterm infants at birth and six months of age.

SUBJECTS AND METHODS

The study was conducted on 19 preterm, 45 term and 14 postterm infants delivered at the University of Maiduguri Teaching Hospital (UMTH), Borno State. After clearance from the Medical Research and Ethics Committee of UMTH, informed consent from parent was obtained. Gestational age at birth was assessed from the last menstrual period and ultrasound scan reports where available and correlated with the Dubowitz criteria (9). Each infant was allotted a serial number at birth. Three millilitres of cord blood was collected in a sterile bottle and serum separated by centrifugation at 5000 rpm for five minutes. Serum samples collected were stored in a refrigerator at -20°C until the time of MMA assay. Each infant was thereafter followed up periodically at the well baby clinic. At sixth month of postnatal life, another blood sample was collected by venepuncture from each infant aseptically and stored in a similar manner as above.

On completion of collection, the samples were assayed for MMA using ELISA (Demeditec diagnostic GmbH Kiel Germany) in accordance with the manufacturer's instructions.¹⁰ Optical densities (OD) of reactions in the well plates were read in an automated analyzer at 450 nanometre (nm) wavelength, MMA titres were obtained by plotting

graphs of OD against measles IgG concentrations. On the basis of manufacturer's recommendations, protective titres for MMA were defined as the levels of MMA >12 U/ml, and unprotective titres as levels of MMA ≤ 12 U/ml (10).

Data analysis. Appropriate statistical method was used to analyze the data obtained from this study using SPSS statistical software version 16, Illinois, Chicago USA. A p value < 0.05 was considered significant. Tables were used appropriately for illustrations.

RESULTS

The study group consisted of 78 newborn infants, out of which 40 (51.3 %) were males and 38 (48.7 %) were females. The male to female ratio was 1.05: 1. Of these newborn infants, 19 (24.4 %) were preterm, 45 (57.7 %) term and 14 (17.9 %) postterm infants respectively (Table 1). Table 2 indicates that 17 (89.5 %) preterm, 43 (95.6 %) term and 14 (100 %) postterm newborn infants at birth had protective MMA. Whereas, two (10.5 %) preterm, nine (20.0%) term and two (14.3 %) postterm were having protective MMA at six months of age. Table 3 shows that the overall comparison of mean MMA at birth and at six months of age was significant (p = 0.005). However, the comparison of mean MMA at birth and at six months of age was independent of GA of the infants at birth (p = 0.158) and at six months of age (p = 0.83).

DISCUSSION

Majority of the preterm, term and all postterm newborn infants in this study were found with protective levels of MMA at birth. With Preterm having lower but protective levels and postterm having higher protective MMA than term deliveries. This was the observation made in previously conducted studies that compared the influence of gestational age on MMA in different countries (5-7). This may be related to decreased MMA from haemodilution, and unequalled transfer of measles IgG subclass mostly seen in the first and second trimester of pregnancy (11). Since MMA in foetal circulation increases until the time of birth (5, 11), it seems reasonable to assume that these MMA will be reduced as gestational age decreases. Also, the placenta of infants born before 37 weeks of GA may have fewer mature receptors for MMA than those of full-term infants (5). All these could lead to lower levels of MMA being transported across the placental barrier to the foetus. In view of this, some authors suggested that GA was the single most important factor in transplacental transfer of MMA between mother and child (7).

TABLE 1: GESTATIONAL AGE AND SEX DISTRIBUTION OF THE 78 INFANTS

GA (Weeks)	Male	Female	Total
Preterm (< 37)	12	7	19
Term (≥37 < 42)	20	25	45
Post term (≥ 42)	10	4	14
Total	40	38	78

GA= Gestational age

TABLE 2. DISTRIBUTION OF MATERNAL MEASLES ANTIBODIES ACCORDING TO GESTATIONAL AGE OF THE NEWBORN INFANTS

MMA (U/ml)	Preterm infants (n= 19)		Term infants (n=45)		Postterm infants (n= 14)	
	Birth n (%)	6 months n (%)	Birth n (%)	6 months n (%)	Birth n (%)	6 months n (%)
Protective levels	17 (89.5 %)	2 (10.5 %)	43 (95.6 %)	9 (20.0%)	14 (100 %)	2 (14.3 %)
Unprotective levels	2 (10.5 %)	17 (89.5 %)	2 (4.4 %)	36 (80.0 %)	0 (0 %)	12 (85.7 %)

MMA=Maternal measles antibodies

TABLE 3. COMPARISON OF GESTATIONAL AGE AND MEAN MATERNAL MEASLES ANTIBODIES AT BIRTH AND SIX MONTHS OF AGE

GA (Weeks)	Mean maternal measles antibodies ± SD (U/ml)		
	Birth	Six months	p- value
Preterm (<37)	188.16 ± 87.99	7.21 ± 5.93	0.000
Term (≥37 <42)	207.27 ± 77.44	7.44 ± 8.07	0.000
Post term (≥42)	239.00 ± 29.90	8.79 ± 10.01	0.000
p- value	0.158	0.830	

t = 14.194, p= 0.005 GA= Gestational age

In the present study, no significant difference was noted in the levels of MMA transferred in preterm, term and postterm neonates at birth. This is consistent with the finding of a study conducted in India (7). Therefore; it can be derived that though important, GA may not be the only factor affecting transplacental MMA transfer in mother-infant pairs. It is postulated that the levels of measles antibody present in a mother at the time of delivery besides maternal age and nutrition, also depends on measles virus exposure and measles vaccine induced immunity (5).

In this study, it was found that at six months of age, 89.5%, 80.0% and 85.7% of preterm, term and postterm infants were having unprotective MMA. This observation corroborated that of other workers (7) where the loss of MMA was linked to its normal catabolism with the passage of time. The present study also found that there is a significant decline of mean levels of MMA from birth to six months of age in preterm, term and postterm infants, which was independent of their GA. This is similar to the observation made in Congo where GA of neonates did not contribute significantly to the loss of MMA in

infancy (12). On the contrary, some authors have shown that MMA in neonates at term onward may persist throughout the first year of life, only to decline to unprotective levels after the first birthday (5). This difference may be explained by the fact that the latter study was undertaken in developed country, while the present study was carried out in a developing country, where the loss of MMA have been postulated to occur at a faster rate (3, 5, 12).

Some of the reasons advanced for the early decay of MMA in developing countries were sickness and repeated blood sampling for diagnostic tests in neonates. This results to the removal of measles antibody containing plasma and replacement by packed red blood cells does not replace the measles antibody lost (5). Additionally, the higher incidence of infections leads to hyper catabolic state causing faster catabolism of MMA in these infants (5). Cases of respiratory tract infections and diarrhoeal diseases were reported in some of the infants in this study. This could have contributed to the rapid decline of MMA in our study population.

Regarding the optimal age of measles immunization of infants in the current study, 89.5%, 80.0% and 85.7% of preterm, term and postterm infants are likely to seroconvert at six months of age. The measles vaccination failure rate thus would be 10.5%, 20.0% and 14.3% for preterm, term and postterms infants respectively. Presently, the vaccination failure rate at nine months in developing countries is about 5-10% (13). For successful uptake of measles vaccine, two conditions should be fulfilled. Firstly, MMA should be absent and/or should not interfere with uptake. Secondly, the immune system of the patient must be capable of mounting an adequate immune response.

The present study revealed that most of the infants lose their MMA by six months of age, with preterm

infants having the highest percentage. As far as the second factor is concerned, Pabst *et al* (14) have pointed out that the capacity to produce antibodies to a variety of antigens increases as a function of age. Thus, it is possible that an immature immune system would cause diminished antibody response to measles vaccine in preterm infants. However, a study conducted on the response of preterm infants to Varicella vaccine have demonstrated that by four months of age, the response of preterms was comparable to term and postterm infants (15). This comparable immune response can be explained by the fact that by virtue of their early exposure to extrauterine life, the immune system of a preterm neonate matures rapidly and may be capable of mounting immunological response required for satisfactory uptake of vaccine (8). Therefore, it is quite possible that the measles antibody response to measles vaccine given at six months of age would be adequate.

Conclusion

A significant decline in transplacentally transmitted mean MMA levels was seen in preterm, term and postterm infants over a period of six months after birth, which was independent of their GA. These infants irrespective of their GA are thus prone to measles at an earlier age (less than six months). Therefore, the current recommendation of immunizing infants at nine months of age may require reconsideration.

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