Original Article

Transplacental Transfer of Macromolecules: Proving the Efficiency of Placental Transfer of Maternal Measles Antibodies in Mother: Infant Pairs

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Abstract

Background: Smaller substances <600 Daltons (Da) can transit human placenta while larger ones >1000 Da may not. This may not be consistent because maternal measles antibodies (MMA) are large immunoglobulin G molecules with molecular weight of 150,000 Da, could cross the placenta in mother-infant pairs. **Aim:** The objective was to assess the efficiency of placental transfer of MMA in mother-infant pairs at birth. **Subjects and Methods:** Sera collected from mother-infant pairs were analyzed for MMA using enzyme-linked immunosorbent assay. Gestational age (GA) of newborns was determined using the last menstrual period, ultrasound scan, and the Dubowitz criteria, whereas their birth weight (BW) was measured using the bassinet weighing scale. **Results:** Correlation coefficient (r) of MMA of mother-infant pairs at birth was significant ($P = 0.006$) and comparison of mean MMA for term and postterm deliveries were significant ($P = 0.001$) and ($P = 0.007$) respectively. Goodman and Kruskal's Gamma rank correlation of GA and BW was also significant ($P < 0.001$). **Conclusion:** Passage of MMA across placenta was efficient and newborn infants are protected from measles at birth.

Keywords: Macromolecules, Maternal measles antibodies, Mother-infant pairs

Introduction

Macromolecules are large substances that are formed by polymerization of smaller subunits.[1] For example, proteins are macromolecules that are made up of amino acids. Antibodies are immunoglobulins, which makeup about 20% of plasma proteins.[1] The antibody molecule consists of light and heavy polypeptide chains: With the light chains approximately 25,000 Daltons (Da) and heavy chains approximately 50,000 Da molecular weights (MWT).[1] Small molecules <600 Da are known to transit the human placenta to the fetus, while the passage of substances of large MWT >1000 Da, may be restricted from reaching the fetus.[2] Studies in the past have revealed passive processes such as diffusion; internalization and endocytosis to be responsible for tranplacental passage of small MWT substances in mother-infant pairs.[2,3]

Large MWT substance was found to cross the placenta in one study, but differed in another.[2,4] Energy dependent carrier-mediated transfer of large MWT substance could be the reason for its passage across the placenta in mother-infant pairs.[2,5] Maternal antibodies of immunoglobulin G subclass are large MWT substances that offer passive immunity to children especially during infancy. These antibodies are transported across the placenta by active rather than passive movements in mother-infant pairs.[2,5] In order to understand these dynamics in our subjects, the current study used maternal measles antibodies (MMA) to prove placental efficiency in the transfer of macromolecules in mother-infant pairs at birth in the University of Maiduguri Teaching Hospital (UMTH), Maiduguri.

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Subjects and Methods

Study area

The study was carried out at the Department of Pediatrics, Immunology and Obstetrics unit of the (UMTH), Nigeria. The

UMTH is a tertiary center located in North-Eastern Nigeria and a center of excellence for infectious diseases and immunology. It also serves as a referral site for the six North-Eastern States and neighboring countries of Chad, Cameroon and Niger Republics.[6]

Design

The study was a hospital-based comparative cross-sectional study of mother-infant pairs recruited from the labor ward of the UMTH between 15th April and 24st June 2010.

Ethical issues

The study protocol was reviewed and authorized by the Medical Research and Ethics Committee of UMTH, and informed consent from parents was also obtained. Parents had unlimited liberty to deny consent without any consequences and confidentiality was maintained.

Data collection procedure

Mother-infant pairs were enrolled in this study using the systematic random sampling method where the first of every three mother-infant pair was picked at the labor ward. On the enrolment of the mother-infant pairs, study proforma was administered to the mothers to collect information on their bio-data, pregnancy history and antenatal care history. The combination of obstetrics scan and last menstrual period of mothers were used to determine gestational age for booked mothers. Mothers that came unbooked and scan were not available, Dubowitz estimate of physical and neurological indices of the newborn infant's was used to assess the gestational age of newborn infants.[7] Birth weights in kilogram (kg) of newborn infants were also measured using the bassinet weighing scale, which has a sensitivity of 50 g set at zero mark.

Collection of samples and laboratory assay

A volume of 3 ml of venous and cord blood were taken from mother-infant pairs at birth using sterile disposable 5 mls syringe under aseptic technique. Sera from these blood samples were separated after centrifuging the blood samples at 5000 rpm for 5 min. The sera obtained from the blood samples of mother-infant pairs were stored in a refrigerator at −20°C until the time of MMA assay using enzyme-linked immunosorbent assay (ELISA).[8]

The levels of MMA were measured by ELISA (Demeditec diagnostic Gmbh, Kiel, Germany) in accordance with standardized laboratory procedures.[8] The ELISA well plates were coated with Edmonston MV strain and results were presented in units per milliliter (U/ml). The MMA Levels <8 U/ml were classified as negative, equivocal with levels of 8-12 U/ml and positive when levels are >12 U/ml. On the basis of these recommendations, protective titers for MMA were defined as the levels of MMA >12 U/ml, and unprotective titers as levels of MMA ≤12 U/ml, which is similar to other publications elsewhere.[9-11]

Statistical analysis

Statistical analyses were performed using SPSS statistical software version 16, Chicago, Illinois, USA and a computer program for epidemiologist PEPI version 3.01. Descriptive data were presented in tables. Values were expressed as percentages, mean and standard deviation (SD). Correlation coefficient of MMA was determined and means MMA compared using Student's *t*-test. Goodman and Kruskal's Gamma rank correlation of GA and BW was also determined. $P < 0.05$ was considered to be significant.

Results

A total of 168 mother-infant pairs were enrolled in this study. There were 50.6% (85/168) male and 49.4% (83/168) female newborn infants. The male to female ratio is approximately 1:1. Most newborn infants 76.6% (122/168) were of term gestation as revealed in Table 1, and the range of their gestational age in this study was (30-43) weeks.

Table 2 shows gestational age and birth weight profile of newborn infants, and the majority of them 84.5% (142/168) had birth weight within the normal range. Approximately, 7.1% (12/168) newborn infants had un-protective MMA at birth, out of which 5.4% (9/168), 0.6% (1/168), and 1.2% (2/168) had gestational age of 38, 40 and 36 weeks, respectively. Of the 7.1% (12/168) newborn infants with un-protective MMA, only 3.0% (5/168) of them had their corresponding mothers with un-protective MMA as well. The mean (SD) of birth weight of the newborn infants was 3.05 (0.58) at 95% CI, (2.97-3.14) kg and Goodman and Kruskal's Gamma rank correlation of GA and BW was significant ($P < 0.001$).

The mean (SD) of MMA of mother-infant pairs at birth were 136.04 (93.44) and 181.76 (89.21) respectively, giving a ratio of 1:1.3 [Table 3]. Correlation coefficient (r) of MMA of mother-infant pairs at birth was found to be significant ($P = 0.006$).

Table 4 shows the distribution of mean MMA and gestational age of the newborn infants. Comparison of mean MMA and gestational age of mother-infant pairs at birth were significant for term and post term deliveries.

Discussion

Vast majority of the newborn infants in this study were delivered at term, and their birth weights were observed to

Table 1: GA and sex distribution of the newborn infants

GA (weeks)	Male	Female	Total
Preterm (<37)	11	7	18
Term (≥37 <42)	54	68	122
Postterm (≥42)	20	8	28
Total	85	83	168

GA: Gestational age

Table 2: GA and birth weight profile of newborn infants

GA (weeks)	Birth weights (kg)					Total
	Macrosomia (>3.99)	NBW (2.5–3.99)	LBW (1.5–<2.5)	VLBW (1.0–<1.5)	ELBW (<1.0)	
Preterm (<37)	-	1	14	3	-	18
Term (≥37 <42)	3	116	3	-	-	122
Postterm (≥42)	3	25	0	-	-	28
Total	6	142	17	3	-	168

GA: Gestational age, ELBW: Extremely low birth weight, VLBW: Very low birth weight, LBW: Low birth weight, NBW: Normal birth weight

Table 3: Mean maternal measles antibody of mother-infant pairs at birth

Mother-infant pairs	Maternal measles antibodies (U/ml)	
	Mean (SD)	95% CI
Mothers	136.04 (93.44)	121.81–150.27
Newborn infants	181.76 (89.21)	168.17–195.34

r=0.210, *P*=0.006. SD: Standard deviation, CI: Confidence interval

Table 4: Comparison of mean maternal measles antibodies and GA of 168 mother-infant pairs

GA (weeks)	Mean maternal measles antibodies (SD) U/ml		*P*
	Mothers	Newborn infants	
Preterm (<37)	132.81 (92.58)	175.84 (93.02)	0.173
Term (≥37<42)	143.83 (105.43)	184.72 (89.22)	0.001*
Postterm (≥42)	145.11 (91.73)	205.64 (68.45)	0.007*

*P<0.05 (significant). GA: Gestational age, SD: Standard deviation

be within normal range of values. Of the newborn infants with un-protective levels of MMA in this study, two-third of them had mothers with protective MMA, and minute fraction of them was born preterm at 36 weeks gestation. A possible explanation for this could be the negative influence of hypergammaglobulinemia, which reduces placental transfer of MMA from mothers to their fetuses.[12-14] As a result of this, newborn infants would start out with rather low MMA relative to that of their mothers. The previous studies have demonstrated that the impairing effect of hypergammaglobulinemia on placental transfer of MMA is much more in African mothers, compared to mothers in industrialized countries.[9,15] Africa is one region of the world in which infective diseases are endemic. [12] this could have been responsible for the negative effect of hypergammaglobulinemia that was reported. Despite that 30 week gestation was the lowest observed in this study; none of our subjects at this gestational age had un-protective MMA. This agrees to the observation that the majority of MMA transfer across the placenta takes place during the third trimester of gestation and are receptor mediated.[2,5,10]

Regarding those infants that had their corresponding mothers with un-protective MMA in the current study, this is expected because MMA in mother-infant pairs are more often than not similar. These concurred findings of other researchers.[9-12] Overall the mother-infant pairs in the present study had high protective mean MMA at birth, but newborn infants were having higher levels than their corresponding mothers. Similar observation was made in past studies conducted in Nigeria and abroad.[9,10] This indicates a more efficient placental transfer of MMA in mother-infant pairs, possibly from active placental transfer.[10-12,14] In contrast, other workers have reported lower MMA in newborn infants compared to their respective mothers.[11,12] One reason advanced for this is that the malaria and human immunodeficiency virus could directly damage the placenta and impair the transfer of MMA to the fetus.[12,13,16]

In this study, the mean MMA of mother-infant pairs was directly proportional to their gestational age. Preterm delivery was associated with lower but protective levels of MMA and postterm deliveries with higher levels of MMA than term deliveries. However, this relationship in preterm newborns was not significant. This corroborates previous studies that compared the influence of gestational age on MMA in different countries.[12,16] Most likely explanation would be hemodilution which could lower MMA in preterm, the result of which would be unequalled transfer of MMA.[14,16] Accordingly, preterm newborn infants are endowed with relatively lower levels of MMA due to deficiencies of placental MMA receptors.[12,14,16] These receptors are needed in order to bind and enable efficient transport of MMA in mother-infant pairs. More so, MMA transport across the placenta in mother-infant pairs may be demonstrating specific transport mechanisms in relation to the size (macromolecule) and gestational age.[5] By implication, preterm newborns would have lower levels of passive measles immunity than term and post term deliveries as observed in this study. Simultaneously, these preterm newborn infants may also have lower levels of other important macromolecules needed for growth and development, such as erythropoietin.[5]

Since the levels of MMA in the fetal circulation increases until the time of birth,[10,12,14,16] it seems reasonable to assume that this levels of MMA will be reduced as gestational age decreases. In the light of this, some authors observed that MMA transport from mother to fetus begins at about 16 weeks gestation and increases as gestation proceeds, but the bulk of these are actively transported through the placenta from 30 to 32 weeks gestation and onwards.[10,12,14,16] Such that term and post term newborns infant have higher MMA than that of preterm as evident in the current study.

Conclusion

There were efficient transplacental transfers of MMA in mother-infant pairs such that term and post term newborns had higher levels than preterm. Newborn infants were also

having higher MMA than their mothers, which indicates that human placenta may be having specific transport mechanism for example active transport for macromolecules in relation to gestational age.

Acknowledgment

We are grateful for the support given by Mr. Bukbuk D and Dawurung JS and by the staff of Obstetrics and Gynaecology, as well as, Paediatric departments of the UMTH.

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How to cite this article: ????

Source of Support: Nil. **Conflict of Interest:** None declared.