Neurodevelopmental Assessment of Children Born to Mothers with Preeclampsia

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Background:

Preeclampsia is associated with morbidity & mortality in the mother & neonate. It is also known to have long-term adverse effects on neurodevelopment.

Objective:

To document the neurodevelopmental outcome of Filipino babies born to pre-eclamptic mothers who delivered at Region 1 Medical Center from December 2005 – January 2006 and to compare them with established norms for their age.

Methods:

The subjects were prospectively followed up at age 3-4 and their neurodevelopment were assessed. They were then divided into geographic groups for field follow-up and a team of volunteers was organized to conduct the interviews with the mothers using a 10-item researcher-designed validated questionnaire. A total of 350 subjects were identified prospectively followed up in 2009.

Results:

From the sample obtained, 82 % were small for gestation age (SGA) while 6% had intra-uterine growth retardation (IUGR). Only 281 were interviewed: 54 had good neurodevelopment, 175 were below average and 12 had poor neurodevelopment. Significant correlation between low birthweight and developmental delay was noted.

Conclusion:

Children born to pre-eclamptic mothers were below average compared to established norms for Filipino children, reflecting the long term adverse effect of preeclampsia.

Key Words: Pre-eclampsia, neurodevelopmental screening, age of gestation

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Introduction

Chronic hypertensive vascular disease, preeclampsia-eclampsia and gestational hypertension are parts of the hypertensive syndrome which is life-threatening, both for mother & fetus. Apart from being associated with unpredictable onset, it is often incurable, except by terminating the pregnancy. Its incidence is approximately 6 – 10 % of pregnant women.[1] There is no unique definition and classification of the hypertensive syndrome in pregnancy and they differ from one expert group to another.

Preeclampsia is associated with significant morbidity and mortality in both the mother and neonate. Common maternal complications are: placental abruption, intracranial hemorrhage, liver lesions, acute renal disorders and disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), hypovolemia and inhalation of gastric content.[2] Most of the time, delivery is always the appropriate therapy for the mother, but may not be a good solution for the fetus. Standard treatment of preeclampsia include: anticonvulsive therapy, antihypertensive therapy, hydration, and if indicated, management of oliguria, DIC, pulmonary edema and recovery of liver function. Maternal mortality due to pregnancy-induced hypertension is 15-33% out of the total number of maternal deaths. Newborn infants of mothers with preeclampsia present with intrauterine growth restriction (IUGR), prematurity, dysmaturity, and necrotizing enterocolitis.[3]

Silveira, et al [4] reported the growth & neurodevelopment outcome of very low birthweight infants born to severely preeclamptic mothers in two centers in Brazil from December 2003 to May 2005 followed up to 12 and 18 months corrected age (CA). Results showed that catch-up of body weight did not occur in the first 18 months CA in preeclamptic infants. Neurodevelopment outcome was better in infants delivered by preeclamptic mothers than in controls at 18 months CA. Hack, M., et al, [5] have observed that intrauterine and neonatal growth failure of very low birthweight infants may influence adult growth attainment and have long-term implications for adult health. They concluded that VLBW females catch up in growth by 20 years of age whereas VLBW males remain significantly shorter and lighter than controls. Since catch-up growth may be associated with metabolic and cardiovascular risk later in live, these findings may have implications for future adult health of VLBW Survivors.

McCowan and colleagues [6] explored the influence of a range of perinatal variables on neurodevelopment at 18 months in a cohort of small-for-gestational-age (SGA) children born in the mid 1990s. They concluded that few of the perinatal variables previously reported are predictive of early childhood outcome in this cohort of SGA infants.

In the study by Kirsten, et al [7] on “Infants of women with severe early pre-eclampsia: the effect of absent end-diastolic umbilical artery doppler flow velocities on neurodevelopmental outcome",

it was reported that no significant differences were noted in the gross motor development of the babies born to mothers with normal Doppler flow velocimetry and those born to mothers with absent end-diastolic artery Doppler flow. They suggested that reported effects may have been due to socio-economic factors instead. In contrast, in the study by Strauss [8], it was found that adults who were born SGA had significant differences in academic achievements and professional attainment compared with adults who were born AGA. However, there were no long-term social or emotional consequences of being SGA. These adults were as likely to be employed, married and satisfied with life.

Ariel and associates[9] examined neurological and intellectual outcome of growth restricted newborns of pregnancies complicated with preeclampsia and without preeclampsia. After adjustment for gestational age, there was no significant difference in the neurological exam score between groups, but the IQ was 85.5 in the preeclamptic group and 96.9 in the no preeclamptic group ($p < 0.03$). They concluded that newborns born growth restricted after pregnancies complicated by preeclampsia have lower IQ at the age of 3 years compared to growth restricted babies without preeclampsia. In a review by Grantham-McGregor, et al, [10] the cognitive development and behavior in the first six years of life of small for gestational age babies born at term in 3 different studies were reviewed. In all 3 studies of SGA children tested at age 3 years, SGA children had lower scores than did normal birthweight controls. SGA children tested between ages 4 & 7 years had generally lower scores than NBW children, but differences were not always statistically significant.

Locally, however, few data are available on the long term effects of the disease on the growing Filipino infant.

Objectives

General: To examine neurodevelopmental outcome of Filipino babies born to pregnancies complicated with preeclampsia.

Specific:

1. To document the neurodevelopmental outcome of babies born to preeclamptic mothers who delivered at Tertiary Center from December 2005 – January 2006.
2. To compare the development of the subjects with established norms on developmental milestones for their age at the time of the conduct of the study.

Methods:

A prospective cohort research was done. The Admission Registry of the Department of Obstetrics & Gynecology of Region 1 Medical Center was reviewed and all cases of term, singleton, cephalic pregnancies complicated with preeclampsia and terminated vaginally from December 2005 to January 2006 were taken as subjects. These subjects were previously studied by the same author assessing their birth weights and APGAR scores to

demonstrate the adverse effects of preeclampsia on the newborn. All of these subjects were prospectively followed in 2009, when they were about 3-4 year old to assess their neurodevelopment.

The subjects were then demographically divided based on their given addresses into 7 geopolitical groups (Dagupan City, Urdaneta City, Sn Carlos City, Eastern Pangasinan, Western Pangasinan, Central Pangasinan and Outside of Pangasinan). A team of volunteers consisting of midwives, NGOs and relatives who were brainstormed to help conduct the interviews to maximize time and resources was assembled.

Instrument:

A 10 point questionnaire was formulated patterned after the Screening Behavior Inventory used as a standard for assessing developmental milestones in a child by the Philippine Pediatric Society, (Fe Del Mundo, 5th ed.) Ideally, the assessment of the child's neurodevelopment should be done by a pediatrician or child psychologist. However, due to the limited time and resources the questionnaire was devised to facilitate the assessment. The questions cover the motor, language and social components of a child's development. Interview of the mothers through the questionnaire forms were conducted by the team who were trained initially and further mentored by the main researcher. The subject's development was compared with the established norms.

Statisical Package:

Data collected was analyzed using the Windows SPSS version 17 and encoding was done using Windows Excel 2007.

Results

The Admissions Registry of the Department of Obstetrics & Gynecology of Region 1 Medical Center from January 2005 to December 2006 was reviewed and a total of 350 subjects were obtained. All were term, cephalic, singleton pregnancies of preeclamptic mothers, delivered vaginally, either spontaneously or by assisted vaginal delivery (outlet forceps or vacuum extraction). The birthweight and classification of the mothers of the subjects into the preeclampsia clinical subgroups were also noted.

Table 1. Cases of Degree of Preeclampsia with various fetal conditions

Pre-eclampsia Condition	N= Cases	Percentage
Mild		
IUGR	9	
SGA	12	
AGA	34	
LGA	6	
Sub-Total	61	17.4 %
Severe		
IUGR	12	
SGA	274	
AGA	3	
Sub-Total	289	82.6 %
TOTAL	N = 350	100 %

Of the 350 subjects, 61 were under the preeclampsia mild subgroup and 289 were under the preeclampsia severe group. The rest of the subgroups can be gleaned from the table.

Of the 289 subjects under the preeclampsia severe subgroup,12 pregnancies had babies diagnosed to have IUGR, 274 had small for gestational age infants and only 3 had appropriate for gestational age infants. These were noted for correlation with present neurodevelopmental status of the subject. The questionnaires were then collated, tallied and descriptively evaluated. Table 2 shows the demographic profile of the subjects.

Table 2. Demographic Profile of the Patients followed up

AREA	MALES	FEMALES	LOCATED		NOT LOCATED	TOTAL
			alive	died		
Dagupan City	43	36	73	0	3	76
San Carlos City	1	0	1	0	0	1
Urdaneta City	3	1	4	0	0	4
Western Pangasinan	44	44	75	11	2	88
Eastern Pangasinan	43	23	35	4	27	66
Central Pangasinan	59	51	93	9	11	113
Outside Pangasinan	1	1	0	0	2	2
Total	194	156	281	24	45	350

The Neurodevelopment of the subjects were then assessed based on the scores from the questionnaires. A score of 7-10 means good neurodevelopment and the subject was at par with established norms. A score of 4-6 mean below average neurodevelopment and a score of 3 or lower means poor neurodevelopment.[11] Table 2 shows the neurodevelopmental assessment scores of the subjects.

Table 3. Neurodevelopmental Assessment Scores of the Subjects

Neurodevelopmental Assessment Scores	No. of Subjects	Percentage
Good (7 – 10)	54	15.43
Below Average (4 – 6)	175	50
Poor (3 & below)	52	14.86
Not assessed	69	19.71
total	350	100

The birth weights and the neurodevelopmental scores were then correlated using the univariate analysis of variance.

Table 4 shows the computed statistical correlation.

Table 4. Correlation between Birthweight & Neurodevelopmental Status of Subjects					
Source	Type III Sum of Squares	df	Mean Square	F	P value
Corrected Model	150.773[a]	41	3.677	1.418	.057
Intercept	1837.864	1	1837.864	708.891	.000
WEIGHT	150.773	41	3.677	1.418	.057
Error	627.407	242	2.593		
Total	7513.000	284			
Corrected Total	778.180	283			
a. R Squared = .194 (Adjusted R Squared = .057)					

It was found that a direct relation exist between the birthweight, intrauterine growth restriction & neurodevelopment of a child. IUGR & SGA babies were found to be below average or have poor neurodevelopment as compared to what is expected of normal birthweight children at their age.

Table 5. Weight Classification of Subjects at birth

Weight Classification	Subjects	Percentage
IUGR	21	6
SGA	286	81.72
AGA	37	10.57
LGA	6	1.71
Total	350	100

G6PD deficiency is a recessive sex-linked trait thus males are predominantly affected. Males have only one copy of the G6PD gene, but females have two copies. Recessive genes are masked in the presence of a gene that encodes normal G6PD. Accordingly, females with one copy of the gene for G6PD deficiency are usually normal, while males with one copy have the trait. Being an X-linked disorder, the disease would generally be thought to affect only males. However, some carrier females have been reported to show symptoms due to lyonization which is a random inactivation of an X-chromosome in certain cells creating a population of G6PD deficient erythrocytes coexisting with normal cells.[16] A study by Iranpour et al revealed a 3.2% incidence of the disease in Iranian newborns, with a male: female ratio of 5.5:1. [17] The male:female ratio in Pangasinan is 2.4:1 showing a higher prevalence among Pangasinense female infants in contrast to Iranian female newborns.

The mean enzyme levels of both male and female cases are classified as severe enzyme deficiency levels (<2.92 U/gHb).[18] However, the enzyme levels gathered in this study are from the newborn screening. The results of confirmatory tests are not included in the study, which may differ from the enzyme levels reported here. However, it can be conferred that the severe enzyme deficiency levels by newborn screening increases the possibility of a G6PD deficient patient by confirmatory test. A preliminary study done by Reclos et al. showed a high percentage of partially deficient females that are missed during neonatal screening. [19] The screening test done in the said study used a cut-off of 2.1 units/gm Hb. The newborn screening test of the National Institutes of Health employs a cut off of 8.4 units/g Hb, well above the value recommended by the study which is 6.4 units/g Hb.

Conclusion

Pangasinan has a prevalence rate of G6PD deficiency that is comparable with the worldwide prevalence of the disease. G6PD screening is recommended in the newborn period to diagnose the disease and if positive, screening of all members of the family should be done. Males are more affected than females but the male:female ratio in the province shows that Pangasinense females have a greater tendency to have the disease than females. It is recommended to look into the next prevalence rate studies based on 2009 – 2013 data.

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