Association of Immune Status in Preterm Babies and Occurrence of Sepsis

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ABSTRACT: This is the first study aiming to compare the immunological parameters in the cord blood between preterm babies with sepsis and those without sepsis. Cord blood was taken from 36 preterm babies and the following parameters were determined: immunoglobulin G, A and M, complement 3 and 4, NBT and lymphocyte subsets. All babies were then prospectively followed up for two weeks for the development of neonatal sepsis. Eleven percent of the subjects developed clinical septicaemia. Overall, these preterm babies had significantly reduced cord blood levels of IgG, IgA, IgM, C3, C4 and NBT, but only IgA levels and NBT were significantly lower in babies with septicaemia than those without septicaemia (0.19 vs 0.21 g/l; p value: 0.007 and 3.50% vs 8.00%; p value: 0.017 respectively). Even though most immunological parameters were reduced in the cord blood of preterm babies, only IgA levels and NBT were significantly associated with the occurrence of clinical septicaemia.

Keywords: preterm babies, immunoglobulin, complement, NBT, neonatal sepsis

Introduction

Preterm delivery was the most important risk factor for both mortality and morbidity due to infections (Ishani, 2002). It is generally believed that the high incidence of neonatal sepsis is closely related to the state of immunodeficiency that is present in these preterm babies (Moore, and Persaud, 1993). Several studies have shown that different parts of the immune system tend to be less well developed in preterm babies than in term babies (Moore and Persaud, 1993; Avroy *et al*., 1992; Colten and Goldberger, 1979; Adinolfi *et al.*, 1967). Very few studies have also correlated the finding of these parameters to the neonatal incidence of sepsis (Ballow *et al*.,1986) Most studies have measured and compared the immunological parameters in preterm and term babies date from decades back under the range of preterm babies and the limits of viability were very different then from now (Mc Cracken and Eicherwald, 1971; Park *et al*., 1970; Sawyer *et al.*, 1985; Thomas and Linch, 1983). Furthermore, no local data or reference values for these immunological parameters are available for the Malaysian babies.

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Published 12 Jan 2010

This study was undertaken to correlate immunological parameters in preterm newborns with the presence of neonatal sepsis. This study is an initial evaluation to identify trends and to determine the direction of a future study with a similar aim.

Materials and Method

This is a cross sectional study, which was conducted in Universiti Sains Malayisia Hospital, from April 2003 till June 2004 using convenient sampling method. After written informed consent was obtained from the parents, cord blood was taken from 36 preterm babies. The babies born at 22 to 37 weeks of gestation were eligible for the study. The gestational age of babies is determined by assessment from the mother's menstrual history or ultrasound. The babies were excluded in the study if they had presumed infection or any congenital abnormalities and if the mother had any medical illness.

Neutrophil function was tested by using the nitroblue tetrazolium test (NBT) from Sigma Aldrich (USA). Determination of complement and immunoglobulin levels was performed through immunoturbidometry technique (Orion Diagnostica, Finland) using turbox analyzer. All babies were prospectively followed up for the first two weeks after birth for the development of neonatal sepsis.

Results were compared using Mann-Whitney U test.

Results

Cord blood samples from 36 preterm babies were analyzed. They were 20 boys and 16 girls. The mean period of amenorrhoea among mothers of preterm babies (**FIG. 1**) was 34.47 weeks of gestation (range from 29 weeks to 36 weeks).

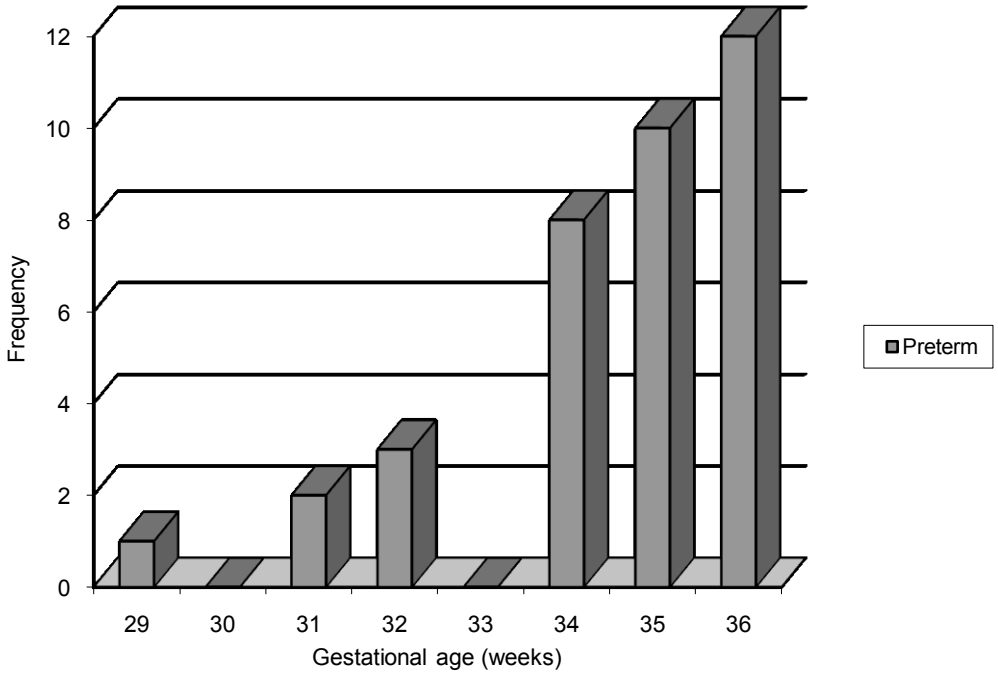

FIG. 1- Gestational age of preterm babies

Follow-up of the babies for 2 weeks after birth showed that sepsis occurred in 11.1% of preterm babies (4 out of 36) as shown in **FIG. 2**. In all of them, the infection affects predominantly the respiratory system. All of the preterm babies who had been diagnosed as sepsis were culture negative sepsis but they were diagnosed clinically based on signs and symptoms of sepsis. There was no case of urinary infection, meningitis or serious systemic infection. These babies were treated with IV (intravenous) antibiotics and showed a good response to this therapy. No other explanation could be found for their signs and symptoms.

The association between immunological parameters and sepsis in preterm babies are shown in **TABLE 1**. The NBT reduction and IgA level were found to be significantly different between the groups of preterm babies with sepsis and preterm babies without sepsis.

For NBT reduction, the median for preterm babies with sepsis was significantly lower than for those without sepsis (3.50% versus 8.00% with p value = 0.017). The median level of IgA level was significantly lower in preterm babies with sepsis than in preterm babies without sepsis (0.190 versus 0.210 g/l, p value = 0.007) whereas IgG, IgM, C3 and C4 levels were not significantly different between the 2 groups.

In summary, using univariate analysis, NBT reduction and IgA level were significantly lower in preterm babies with sepsis than those without sepsis whereas C3 level, C4 level, IgG level, IgM level, CD3%, CD4%, CD8%, CD19 (B cell)% and CD16/56 (NK cell)% were not significantly different between the two groups.

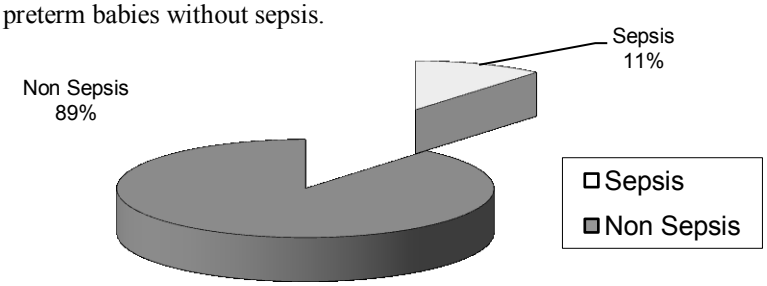

FIG. 2- Distribution of sepsis in preterm babies

TABLE 1- Association of sepsis with immunological parameters in preterm babies

Variables	Sepsis Median (IQR) (n=4)	Not sepsis Median (IQR) (n=32)	Z stat a	p value
NBT (%)	3.50 (1.75)	8.00 (4.00)	-2.33	0.017
C3 (g/l)	0.44 (0.24)	0.51 (0.13)	-0.93	0.366
C4 (g/l)	0.05 (0.04)	0.08 (0.03)	-1.70	0.092
IgG (g/l)	7.25 (6.20)	9.89 (3.35)	-1.13	0.269
IgA (g/l)	0.19 (0.02)	0.21(0.02)	-2.64	0.007
IgM (g/l)	0.14 (0.11)	0.11 (0.02)	-0.41	0.716

a = Mann -Whitney Test
$p < 0.05$ significant at 95% CI

Discussion

The frequency of infection in the group of preterm babies in this study was very low (11.1%) compared to previous studies done in HUSM (Halder *et al*., 1999). These differences are most likely due to the difference in gestational age. In this study, most of the babies were 34 – 36 weeks. In all the preterm babies, the infection was thought to affect predominantly the respiratory system. The higher frequency of infections in the lower respiratory airways of preterm babies has been demonstrated by previous study (Ballow *et al*., 1986).

Using univariate analysis, we found that only neutrophil function (NBT reduction) and IgA level were associated with occurrence of sepsis in preterm babies. IgG, IgM and complement levels were not associated with occurrence of sepsis. However, these data may be affected by the limited number of babies with sepsis.

In literature, only association of IgG level and sepsis has been reported but not the other parameters. There was no previous study done to compare our findings on IgA, IgM and complement levels.

If in a larger follow-up study, with these results of a lower NBT reduction in the cord blood of babies developing sepsis, preventive intervention could be considered for those preterm babies with very low NBT. Few studies have reported attempts to transfuse polymorph nuclear cells (PMN) to babies with established sepsis. Three of five groups of researchers found that patients' survival had increased after transfusion of PMNs (Cairo *et al*., 1988; Laurent *et al*., 1981; Christensen *et al*., 1982). Two other groups showed no change of patient survival (Baley *et al*., 1987; Wheeler *et al*., 1987). No study has been described about the role of PMNs transfusion in preventing neonatal sepsis. However, abnormalities in PMNs at birth may indicate a potential role of buffy coat PMNs transfusion as a prophylaxis for neonatal sepsis.

For IgG level, only few researchers tried to determine the definite association of IgG level and sepsis. Our study was consistent with a study (10) who found that there was no definite association between IgG concentration and the incidence of presumed or proven infection.

Few researchers believed that the low concentration of IgG level was responsible for increased risk of infection. The administration of intravenous IgG (IVIG) to preterm babies has been studied extensively. Work in this area to date has produced conflicting results. A study (Lacy and Ohlsson, 1995) concluded that routine administration of IVIG to preterm babies to prevent infection was not recommended. The result of a Canadian multidisciplinary consensus-building initiative (Consensus, 1997) has showed that the use of IVIG for prophylaxis of neonatal infection was inappropriate. Another study (Ohlsson and Lacy, 2003) concluded that IVIG administration results in a 3% reduction in sepsis and 4% reduction in any serious infection.

In summary, neutrophil function (NBT reduction) and IgA level were associated with occurrence of sepsis in preterm babies. However, this may be due to limited numbers of babies with sepsis.

Acknowledgements

We thanked the Universiti Sains Malaysia for providing the short term grant for this project and also staff of Immunology department and Labour Room, Hospital Universiti Sains Malaysia for their support

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