

**Title: Analysis on mortality among moderate to late preterm infants born in Lempira province, the Republic of Honduras, from January 2015 to June 2017.**

Type of article: Information

Key words: neonatal mortality, preterm birth, moderate to late preterm infants, hyaline membrane disease, the Republic of Honduras

**Abstract**

**Objective:** Preterm birth is the major cause for neonatal deaths in low and middle income countries. The aim of this report is to evaluate the proportions of deaths of moderate to late preterm infants born at 32 to 36 weeks of gestations as well as the neonates with low birth weights weighing from 1500g to 2499g among the total neonatal deaths and analyze their causes of deaths in Lempira province, the Republic of Honduras. **Study design:** A secondary analysis based on the data sets from the regional office of Ministry of Health. **Methods:** We obtained data sets on infant mortality from January 2015 to June 2017 compiled by a regional office of Ministry of Health in Lempira province. We then calculated proportions of each cause of death in the groups of newborn infants stratified by gestational weeks and birth weights. **Results:** During the study period, a total of 253 neonatal deaths were recorded, comprising 66.9% of the total infant deaths (n=378). The number of the newborn infants who died during early neonatal period was 201 (79.4%). The number of preterm newborn infants who died during neonatal period was 146 (57.7%) and 70 (27.7%) were born at moderate to late preterm periods. 103 (40.7%) were born with their birth-weights below 2500g, and the number of those weighing from 1500g to 2499g were 61 (24.1%) . The leading cause of deaths of moderate to late preterm infants was hyaline membrane disease (n=25/48: 52.1%), as was the case with low birth weight infants weighing from 1500g to 2499g. **Conclusion:** It was shown that approximately one fourths of neonatal deaths occurred in moderate to late preterm infants in Lempira province during the study period. Approximately half of these preterm

infants died of hyaline membrane disease, who could have been saved with simple and low-cost equipment such as bubble continuous positive airway pressure.

## **Introduction**

In 2014, World Health Organization (WHO) launched an initiative “Every Newborn Action Plan” to reduce avoidable and preventable deaths of newborn infants in low and middle income countries (LMICs) <sup>1)</sup>. The initiative proposed measures to tackle three major causes of neonatal deaths, i.e. complications of prematurity, intra partum related causes, and infections<sup>1)</sup>. Among the causes mentioned above, prematurity is the leading cause of the neonatal deaths worldwide<sup>1,2)</sup>. WHO reported that 1.08 million neonatal deaths were attributable to the complications of premature birth, comprising 35% of the total neonatal deaths<sup>1)</sup>.

The Republic of Honduras has been striving to reduce mortality rate of the children under five years of age, resulting in a decline from 58 per 1,000 live births in 1990 to 19.4 in 2015 <sup>3)</sup>. Nevertheless, proportion of neonatal deaths among the total deaths of under-5 children has increased to 55.7% (2,136/3,813) from 38.6% (4,198/10,868) during the same period <sup>3)</sup>. As the significance of preterm births on public health has been increasingly recognized, WHO also outlined cost effective and evidence-based measures to cope with prematurity-related complications <sup>1)</sup>. However, few studies have investigated to what extent these prematurity-related complications affect mortality risk of premature newborn infants stratified by gestational weeks, especially those born at moderate to late preterm periods (32 to 36 weeks of gestations) in LMICs. These moderate to late preterm infants might have been saved in high income countries where the use of antenatal administration of corticosteroid, surfactant and sophisticated modalities of ventilation is widely performed.

The aim of this report is to evaluate the proportions of preterm infant deaths among the total neonatal deaths, especially those born at between 32 and 36 weeks of gestation and low birth weight infants weighing from 1500g to 2499g in Lempira province and to analyze the causes of their deaths.

Lempira province is situated approximately five hour-drive to the west of the capital city of Tegucigalpa with population of 323,500<sup>4,5</sup>). Its provincial hospital is a secondary referral hospital which can offer Emergency Obstetric Care (EmOC) services in the region. Antenatal services are provided free of charge at all the health institutions including primary level facilities such as health posts and maternal and children clinics. Tertiary maternal and neonatal health facilities such as Neonatal Intensive Care Unit (NICU) are only available at Maternal and Children Hospital in the capital city. Ultrasound examinations are seldom performed for most of pregnant women in the province because they are only available at private clinics, thus incurring financial burden and opportunity costs by traveling. Antenatal services are provided by the doctors in “social service”, who are house officers assigned to rural health clinics for one or two years immediately after their graduation from the medical school. Five times antenatal visits and one time post natal visit are recommended by the government. We conducted a survey on the utilization of antenatal services in 2017 and found that more than 89.9% of pregnant women in the province received more than five times antenatal examinations<sup>5</sup>).

We used the data sets in Lempira province because we have been implementing the project called “Proyecto de Fortalecimiento del sistema de Atención Primaria de Salud basado en el Modelo Nacional de Salud (PROAPS)”, or Project for Strengthening Primary Health Care System based on the National Health Model in English, funded by Japan International Cooperation Agency (JICA) in the province since 2013<sup>4</sup>), thus giving us an opportunity to access the data sets on the infant mortality at the provincial level. Another reason for the selection of Lempira province is that almost 100% of the data sets on infant mortality had complete information on death certificates confirmed by the regional office of Ministry of Health (MoH).

## Methods

This is a secondary analysis based on the data sets from the regional office of Ministry of Health (MoH). Data sets on infant mortality were obtained from the statistical department of the regional office of MoH in June 2017. The data sets were mainly based on the death certificates and detailed reports from the provincial hospital, which were confirmed by an independent review board consisted of doctors from the provincial hospital and officials from the regional office of MoH. For the cases of infant deaths in rural communities, local physicians stationed at nearest clinics were assigned to investigate the cases of infant deaths by interviewing mothers or other family members. They were required to make a report on each case of infant deaths and submit it to the regional office.

Diagnosis of the causes of deaths in the provincial hospital was made by more than two physicians with additional information based on modalities such as X ray and blood tests. However, for deaths in community, verbal autopsy, which was performed by local physicians at the nearest health facility within a few days, was only the way to determine the causes. In other health institutions such as maternal and child clinics and health posts, diagnoses based on clinical symptoms were made by local physicians stationed at these clinics. There was no algorithm used for diagnosis of the causes of death, which can direct physicians to determine the causes solely based on clinical information and symptoms<sup>6</sup>. Most of the cases had several causes for their deaths, and the categories such as basic, intermediate and direct causes for neonatal deaths were adopted in the data sets by the regional office. In this report, basic causes for death were counted and analyzed. In the data sets, the term, Hyaline Membrane Disease (HMD), was officially used to describe the cases with respiratory distress syndrome (RDS). In this report, we adopted HMD as a cause for death of newborn infants.

Gestational weeks at birth were calculated from their expected date of delivery (EDD) given in their antenatal information cards, which all pregnant women were required to show to physicians when they visited for antenatal examinations. EDD was mostly determined by maternal recall of their last menstrual periods (LMP) or measurements of fundal height at their first visit to the clinics.

Prematurity was defined as gestational ages less than 37 weeks of gestation. We categorized prematurity into three categories, extremely preterm (less than 28 weeks), very preterm (28 to 31 weeks) and moderate to late preterm (32 to 36 weeks). Birth weights under 2500g were also categorized into three groups, those weighing less than 1000g, those weighing from 1000g to 1499g and those weighing from 1500g to 2499g.

Analysis of proportions of preterm infant deaths out of neonatal deaths used all the available gestational data, irrespective of missing data on birth weights. In the analysis of the causes of deaths stratified by gestational weeks and birth weights, we excluded data with missing information on either birth weights or gestational ages. In order to improve reliability of the analysis on the prematurity-related complications among the newborn infants born at moderate to late preterm periods, we excluded the cases whose birth weights were under 2.5th percentile or over 97.5th percentile of corresponding gestational weeks so that the newborn infants whose birth weights seemed to be compatible with gestational ages could be re-evaluated. Data on the birth weights of 2.5th and 97.5th percentiles of corresponding gestational weeks were adopted from the estimates developed by WHO<sup>7)</sup>.

The study design had been approved by the ethical committee of MoH before we collected the data sets. Data collection, analysis and publication of the results on infant and neonatal deaths were ap-

proved by the head of the regional office. Any information leading to the identification of individuals was excluded from the data sets.

## Results

The numbers of neonatal deaths, early neonatal deaths, places of deaths, and numbers of neonatal deaths stratified by gestational weeks and birth weights are given in Table 1. The total number of births in Lempira province from January 2015 to June 2017 was 17,508, out of which 378 (2.2%) infant deaths were recorded during the period.

The total number of neonatal deaths in Lempira province during the period was 253, which was 66.9% of all infant deaths during the period. Out of the total neonatal deaths, the number of early neonatal deaths (from day 0 to day 6 after birth) was 201(79.4%). 221 (87.4%) died in the health institutions including the provincial hospital, Maternal and Children Hospital in the capital city and maternal and children clinics. There was no infant death reported in the health posts.

146 (57.7%) who died in the neonatal period were born premature and 70 (27.6%) were born at moderate to late preterm periods. 103 (40.7%) were born with their birth weights below 2500g, and the number of those weighing from 1500g to 2499g were 61 (24.1%). Birth weights of 76 (30.1%) infants were unknown.

Causes for deaths of the newborn infants stratified by gestational weeks and birth weights are given in Table 2 and Table 3, respectively. We excluded 77 cases from the total number of neonatal deaths since they lacked information on either gestational weeks or birth weights. A total of 176 neonatal deaths were analyzed. The leading cause of the total neonatal deaths in Lempira province during the period was HMD (n=62/176: 35.2%), which was one of the most frequently observed complications caused by prematurity, followed by neonatal infections such as pneumonia and sepsis (n=12/176: 6.8% and n=34/176: 19.3%, respectively). Meconium aspiration syndrome (MAS) is frequently caused by asphyxia, so that the number of deaths related to intra-partum complications was 32

(18.2%). The number of deaths caused by malformations including congenital heart diseases was 24 (13.6%).

The most common cause of death in the moderate to late preterm infants was also HMD, comprising 52.1% (25/48) of the total deaths in this group. Neonatal infections were the second most common cause (n=13/48:27.1%), followed by malformation (n=6/48:12.5%). There was no case of asphyxia-related death in this group.

There were five cases whose weights were greater than 97.5th percentile and eleven cases whose weights were under 2.5th percentile of the estimated weights of the newborn infants born between 32 and 36 weeks of gestation. After excluding these cases, a total of 32 cases were analyzed. The number of those who died of HMD was 18 of 32 infants (56.3%), which was still the leading cause of death of the moderate to late preterm infants. The number of deaths caused by both neonatal sepsis and pneumonia was 8 (21.9%), which was the second most common cause for the death of this group of preterm infants.

In order to approximate the number of those who were delivered at moderate to late preterm periods, death causes of those weighing from 1500g to 2499g were examined. It was found that 40.0% (24/60) of this group of infants died of HMD, followed by neonatal infections (19/60: 31.7%).

However, in this group, there were 26 (43.3%) infants whose estimated gestational age was > 37 weeks. Thus, newborn infants with fetal growth restriction could have been included in this group.

## Discussion

It was found that more than half of the neonatal deaths occurred in those born preterm in Lempira province, as was the case with the national data in 2009 and 2010<sup>8)</sup>. As has been reported previously<sup>9, 10)</sup>, analysis of the data in Lempira province suggested that approximately one fourth of the total neonatal deaths occurred at 32 to 36 weeks of gestation, reaching almost half of the deaths of the preterm infants born in the province. National data do not provide the number of deaths of the infants born at the same gestational weeks but it gives the number of deaths of preterm infants born at 28 to 36 weeks of gestation, amounting to 40% of the total preterm deaths in 2009 and 2010<sup>8)</sup>. Our data in Lempira province showed that proportion of preterm infant deaths born at 28 to 36 weeks of gestation was 46.6% (118/253).

Among prematurity-related diseases, several studies reported high morality rates of HMD in the newborn infants admitted to Neonatal Intensive Care Unit (NICU) in LMICs<sup>11-14)</sup>. We found that nearly 35% of the total neonatal deaths in Lempira province were caused by HMD, roughly corresponding to the results of the national data (32% in 2009 and 40% in 2010)<sup>8)</sup>. Our analysis in the moderate to late preterm infants whose birth weights seemed to be compatible with gestational weeks revealed that approximately half of this group of neonates died of HMD. High incidence of HMD in this group of infants could be attributed to prematurity of their lung functions and the fact that they might have died before being referred to well-equipped NICU available only in the capital city.

Considering the large volume of moderate to late preterm infant deaths, measures to reduce deaths caused by HMD would be considered to be most effective to reduce the neonatal mortality rate in the province. Recently, low-cost equipment such as bubble continuous positive airway pressure (bCPAP) has been tested extensively in resource limited settings<sup>15,16)</sup>. Based on the historical re-

view on the effects of the introduction of the treatment modalities in the United States of America, Kamath et al. estimated that CPAP plus oxygen administration would salvage 70% of the premature infants born at >1500g who died of HMD<sup>17)</sup>. Our analysis estimated 25 deaths in this group of premature infants who died of HMD so that 18 infants could be saved with the equipment.

At the provincial hospital of Lempira province, oxygen administration is the only treatment currently available for the newborn patients with respiratory failure. bCPAP does not require specially designed parts to be assembled and most of them can be procured in local markets with low costs.

However, it needs a flow generator, which requires constant electric power supply. Unstable electric power supply in the province should be overcome to promote its installation in the hospital.

Several limitations should be mentioned. Firstly, when analyzing causes of deaths of preterm infants, a large number of data were excluded due to lack of information on either birth weights or gestational ages. Secondly, estimation of gestational weeks of the fetus entailed uncertainty due to inaccurate maternal recall of last menstrual period. There was no means to confirm methods of determination of EDD in the data sets. In order to improve reliability of the data, we omitted the data with birth weight below 2.5th percentile and beyond 97.5th percentile developed by WHO for the analysis of moderate to late preterm infants, but it further reduced the number of cases to be analyzed. In addition, it should be reminded that the cases with birth weight under 2.5th percentile might have included the cases with fetal growth restriction. Thirdly, limited availability of modalities could inevitably lead to unreliable diagnosis on the causes of death of the newborn infants, especially when they occurred in the communities. Investigations of the causes of the deaths were not based on predefined algorithms, so that criteria on diagnosis could have varied between the physicians.

## **Conclusion**

It was estimated that more than half of the neonatal deaths occurred in preterm period and approximately 50% of these preterm deaths were those born at moderate to late preterm periods in Lempira province, the Republic of Honduras. Approximately half of this group of preterm infants died of HMD. Targeting those preterm infants could be effective to improve the neonatal mortality rate with an introduction of low-cost interventions such as bCPAP for HMD.

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