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# Impact of Skin Lesions on Morbidity and Mortality in Extremely Premature Infants in One Tertiary Center in Southern Japan

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## Abstract

**Objective:** Skin is an important tissue and influenced by developmental changes in premature newborns. We determined the impact of skin lesions on neonatal mortality and morbidity in extremely premature infants.

**Methods:** From 2004 to 2011, 121 extremely premature infants born at 22 to 25 weeks of gestation were enrolled. Among them, 19 infants were excluded, 47 infants had skin lesion, while the remaining 55 infants served as controls. Univariate and multivariate analysis were used.

**Results:** A multivariate analysis showed the gestational age at delivery to be the only variable that remained significantly associated with skin lesions (OR 2.7) after adjusting for any confounding variables. Temporal changes in the clinical manifestations showed that 90% the infants with skin lesions showed respiratory and circulatory instability first, thus suggesting the skin lesions as a consequence of prematurity. Regarding neonatal mortality, skin lesions and focal intestinal perforation were covariates that remained significant after adjusting for any confounding variables.

**Conclusions:** In extremely premature infants, skin lesions occur as a consequence of prematurity-related circulatory and respiratory instability, which is significantly associated with neonatal mortality. These findings suggest that it is important to manage the respiratory and circulatory condition to prevent the skin lesions in order to improve the survival rate.

**Keywords:** Barrier against infection; Neurological damage; Circulatory instability; Intra ventricular hemorrhage; Periventricular leukomalacia

## Introduction

Recent advances in perinatal medicine have improved the outcome of infants. However, extremely premature infants still have a high mortality and morbidity. These outcomes are influenced by many perinatal factors. For example, antenatal factors include obstetrician's attitude [1], gestational age [2], sex [3], antenatal corticosteroid therapy [3], multi fetal pregnancy [4], growth restriction and so on [5,6], and neonatal factors include circulatory and respiratory instability [7], intracranial hemorrhage, Periventricular leukomalacia [8], intestinal perforation [9], and so on.

Skin is an important tissue that serves not only as a sensor, regulator, and barrier, but also as an indicator of the inside condition of the body. For neonates, for example, the skin works as a barrier against invading microbes and a regulator of both body temperature and fluid control. From a developmental standpoint, the time around 24 weeks of gestation is critical in that a significant keratinization process begins to form a multiple-layer epidermis, similar to adult skin [10-12], these developmental changes in skin may thus have an impact on neonatal mortality and morbidity.

In a previous population–based study on extremely low-birth weight infants, we reported that the perinatal mortality depends on gestational age and centralization, in which the mortality rate was 29% at 22 weeks of gestation, 22% at 23 weeks, 34% at 24 weeks, 7% at 25 weeks, and 6% at 26 weeks [2]. Under these circumstances of perinatal care, we investigated whether the presence or absence of skin lesions may affect neonatal mortality and morbidity in extremely premature infants.

## Methods

This study was performed from 2004 to 2011 at the University of Miyazaki hospital, which is the only tertiary perinatal center in Miyazaki District, having a population of one million and 10,000 deliveries per year. This study was approved by the Ethics Committee, Faculty of Medicine, University of Miyazaki.

During the 8-year study period, we had 121 consecutive extremely premature infants born alive at 22–25 weeks of gestation. After excluding twins (n=15), infants with a major anomaly (n=1), and early neonatal deaths < 24 hours of life (n=3), our study subjects consisted of102 infants. Among them, 12 infants were born at 22 weeks of gestation, 26 infants at 23 weeks, 32 infants at 24 weeks, and 32 infants at 25 weeks. The gestational age was confirmed by 2ultrasonographic measurements during the first trimester.

A skin lesion in this study is defined as one or more of the following lesions; erosion, blisters, ulcer, or pus formation beneath the skin. The head, neck, maxilla, back, groin, and ankles were observed daily for 2 weeks. When skin lesions occurred, which were evaluated and confirmed by dermatologists.

Our protocol for neonatal intensive care is as follows [7]. On day-1, a total of 60 ml/kg/day fluid was given intravenously. In addition, a10 ml/kg dose of albumin or fresh frozen plasma was administered

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to maintain the blood pressure. Dopamine (> 5 micrograms/kg/min) was routinely infused and dobutamine (> 5 micrograms/kg/min) was added as needed. A prophylactic dose of antibiotics (100 mg/kg of ampicillin and 7.5 mg/kg of amikacin) and antifungal agent were also administered. We also gave probiotics through a nasogastric tube daily before the start of breast milk feeding. Prophylactic corticosteroids were administered for 3 days to infants born at < 24 weeks of gestation. Medical caregivers use disinfected medical gloves to handle the newborns. Electrocardiogram electrodes were attached indirectly on the skin covered with skin-protective patch.

The humidity of the infant incubator is kept at a level of 95% until the core temperature is stabilized at 36.5–37.5 degrees Celsius, and thereafter the humidity is adjusted according to its core temperature.

Cesarean section due to fetal indications was selectively determined based on parental choice at 22 weeks of gestation, and it is offered to all after 22 weeks of gestation.

Perinatal risk factors, which may or may not be associated with skin lesion, include respiratory instability (worsening of the respiratory settings), circulatory instability, culture-based sepsis, clinical sepsis, chorioamnionitis, and intraventricular hemorrhage.

The data were expressed as the mean +SD. Statistical significance ($p < 0.05$) was confirmed by the unpaired Student's t-test, ANOVA, Chi-square test, or Fisher' sex act test. Multiple logistic regressions were used to adjust for the effect of several explanatory variables. Gestational age at delivery was classified into 3 groups; 0 for 25 weeks, 1 for 24 weeks, and 2 for 22 or 23 weeks of gestation. Other variables were dichotomized; 0 for the absence and 1 for the presence of risk factors.

## Results

As shown in (Table 1), the incidence of skin lesions, mortality at hospital discharge, and the incidence of neurological damage among the surviving infants decreased with the increase of gestational age at birth.

Skin lesions: Skin lesions occurred in 47 infants. It occurred more frequently during the first 5 days of life (74%, 35/47). Since the skin structure becomes more mature (4-5 layers) at > 24 weeks of gestation and the number of infants born at 22 or 23 weeks of gestation was too small to carry out a statistical analysis, the infants born at 22 and 23 weeks of gestation were combined for further comparisons.

A univariate analysis showed that skin lesions were significantly associated with gestational age (OR 3.2), respiratory instability (OR 3.2), sepsis based on laboratory data (OR 2.3), intra ventricular hemorrhage (OR 3.2), (Table 2). A multivariate analysis was then performed regarding the relationship between the skin lesions as a dependent variable and the abovementioned 4 risk factors as explanatory variables. Gestational age at delivery was the only variable that remained significantly associated with skin lesions (OR 2.7 95% CI 1.3-5.4).

We also studied temporal changes in the clinical manifestations and found that 87.2% (41/47) of the infants with skin lesions showed respiratory and circulatory instability first, followed by the development of skin lesions later. Only 12.8% (6/47) of the infants had skin lesion without either respiratory or circulatory instability. Those who showed respiratory and circulatory instability first, followed by skin lesions and septic shock, were born extremely prematurely (< 23 weeks of gestation). On the other hand, those who did not show either respiratory or circulatory instability did not have septic shock. It was interesting to note that if respiratory and circulatory conditions are stable, and if septic shock does not occur, then focal intestinal perforation or necrotizing enterocolitistends to be the most frequent cause of neonatal death (5/7).

### Mortality and skin lesions

A univariate analysis was performed between the mortality at hospital discharge and the occurrence of severe neonatal morbidity (Table 3). Six significantly associated factors were identified including gestational age at delivery (OR 3.0), skin lesions (OR 11.2), respiratory instability (OR 4.3), circulatory instability-DOA (OR 4.1), intra ventricular hemorrhage (OR 4.9), and focal intestinal perforation (OR 3.9).A multivariate analysis was performed regarding the relationship between the mortality as a dependent variable and the abovementioned six risk factors as explanatory variables. The skin lesions and focal intestinal perforation were covariates that remained significantly associated with infantile mortality at hospital discharge.

### Neurological damage and skin lesions

Neurological damage of the surviving infants included cerebral palsy, mental retardation, and epilepsy. A univariate analysis was also performed regarding the neurological damage of the surviving infants and the occurrence of severe neonatal morbidity (Table 4). Four significantly associated factors were identified including gestational age at delivery (OR 2.4), respiratory instability (OR 4.5), sepsis based on laboratory data (OR 5.3), and intra ventricular hemorrhage (OR 11.0). Since the skin lesions demonstrated borderline significance (p=0.055) according to a univariate analysis, it was therefore added to the multivariate analysis. A multivariate analysis of the relationship between neurological damage as a dependent variable and the abovementioned

| GW (w) | Number | Birth weight (g) | Vaginal delivery | Skin lesion |
|---|---|---|---|---|
| 22 | 12 | 505.3 ± 47.7 | 92% (11/12) | 92%(11/12) |
| 23 | 26 | 582.8 ± 89.9 | 46% (12/26) | 54%(14/26) |
| 24 | 32 | 668.0 ± 87.5 | 38% (12/32) | 40%(13/32) |
| 25 | 32 | 738.8 ± 92.4 | 31% (10/32) | 28%(9/32) |

GW: gestational week
* p<0.05; 22 weeks of gestation compared with other gestational weeks.
** p<0.05; 22, 23 weeks of gestation compared with 25 week.

**Table 1:** Clinical characteristics.

| Univariate | Adjusted odds ratio (95% confidence interval) | P |
|---|---|---|
| Gestational week | 3.2 (1.7-6.3) | 0.0006* |
| Respiratory instability | 3.2 (1.3-7.4) | 0.0088* |
| Circulatory instability : DOA-required | 1.7 (0.68-4.2) | 0.25 |
| Circulatory instability : FFP-required | 1.2 (0.55-2.7) | 0.63 |
| Sepsis; based on culture | 1.2 (0.56-2.7) | 0.61 |
| Sepsis; based on laboratory data | 2.3 (1.1-5.2) | 0.037* |
| IVH grade 3-4 | 3.2 (1.3-8.0) | 0.015* |
| Clinical CAM | 1.2 (0.53-2.5) | 0.73 |
| Histologic CAM | 1.1 (0.49-2.6) | 0.78 |
| FIP | 1.7 (0.54-5.2) | 0.37 |
| Multivariate | Adjusted odds ratio (95% confidence interval) | P |
| Gestational week | 2.7 (1.3-5.4) | 0.0062* |
| Respiratory instability | 1.6 (0.59-4.4) | 0.36 |
| IVH grade3-4 | 1.7 (0.58-5.0) | 0.34 |
| Sepsis; based on laboratory data | 1.6 (0.65-4.1) | 0.29 |

Abbreviations: DOA: dopamine, FFP: fresh frozen plasma, IVH: intraventricular hemorrhage, CAM: Chorioamnionitis, FIP: focal intestinal perforation

**Table 2:** Correlation between the incidence of skin lesions and perinatal factors.

| Univariate | Adjusted odds ratio (95% confidence interval) | P |
|---|---|---|
| Skin lesion | 11.2 (2.4-52.7) | 0.0021* |
| Gestational week | 3.0 (1.4-6.0) | 0.0030* |
| Respiratory instability | 4.3 (1.4-13.2) | 0.0104* |
| Circulatory instability: DOA-required | 4.1 (1.3-12.4) | 0.0138* |
| Circulatory instability: FFP-required | 1.1 (0.37-3.2) | 0.89 |
| Sepsis; based on culture | 1.3 (0.46-3.9) | 0.61 |
| Sepsis; based on laboratory data | 1.8 (0.61-5.2) | 0.29 |
| IVH grade 3-4 | 4.9 (1.6-14.8) | 0.0055* |
| Clinical CAM | 1.2 (0.4-3.3) | 0.8 |
| Histologic CAM | 0.81 (0.27-2.4) | 0.7 |
| FIP | 3.9 (1.1-13.7) | 0.035* |
| Multivariate | Adjusted odds ratio (95% confidence interval) | P |
| Skin lesion | 7.4 (1.3-40.6) | 0.0022* |
| Gestational week | 1.2 (0.48-2.8) | 0.74 |
| Respiratory instability | 2.8 (0.56-14.3) | 0.21 |
| Circulatory instability –DOA | 2.5 (0.62-9.8) | 0.2 |
| IVH grade 3-4 | 2.6 (0.63-10.3) | 0.19 |
| FIP | 7.3 (1.3-39.9) | 0.0223* |
| Abbreviations: DOA: dopamine, FFP: fresh frozen plasma, IVH: intraventricular hemorrhage, CAM: Chorioamnionitis, FIP: focal intestinal perforation | | |

**Table 3:** Correlation between mortality and perinatal factors.

| Univariate | Adjusted odds ratio (95% confidence interval) | P |
|---|---|---|
| Skin lesion | 2.5 (0.98-6.5) | 0.0551 |
| Gestational week | 2.4 (1.2-4.9) | 0.0017* |
| Respiratory instability | 4.5 (1.6-12.2) | 0.0037* |
| Circulatory instability –DOA | 1.3 (0.44-4.1) | 0.61 |
| Circulatory instability -FFP | 0.82 (0.32-2.1) | 0.67 |
| Sepsis; based on culture | 2.4 (0.92-6.0) | 0.074 |
| Sepsis; based on laboratory data | 5.3 (1.9-14.3) | 0.0011* |
| IVH grade 3-4 | 11.0 (3.3-36.4) | <0.0001* |
| Clinical CAM | 1.5 (0.61-3.8) | 0.37 |
| Histologic CAM | 0.88 (0.33-2.3) | 0.79 |
| FIP | 2.0 (0.49-8.2) | 0.33 |
| Multivariate | Adjusted odds ratio (95% confidence interval) | P |
| Skin lesion | 1.7 (0.54-5.6) | 0.36 |
| Gestational week | 2.1 (0.89-5.0) | 0.091 |
| Respiratory instability | 2.4 (0.70-7.9) | 0.16 |
| IVH grade 3-4 | 8.3 (2.2-31.0) | 0.0018* |
| Sepsis; based on laboratory data | 3.6 (1.1-11.5) | 0.0326* |
| Abbreviations: DOA: dopamine, FFP: fresh frozen plasma, IVH: intraventricular hemorrhage, CAM: Chorioamnionitis, FIP: focal intestinal perforation | | |

**Table 4:** Correlation between neurological damage and perinatal factors in the surviving infants.

five risk factors as explanatory variables revealed neurological damage to be significantly associated with intra ventricular hemorrhage and sepsis.

## Discussion

Skin lesions occurred more frequently during the first 5 days of life. Skin lesions area also dependent on gestational age, namely the more premature the infant is, the more frequently skin lesion occurs. This finding is compatible with the generally accepted dermatological point of view. At 12 weeks of gestation, the epidermis begins to differentiate by adding 2 or 3 layers of intermediate cells between the basal cells and periderm. Then, around 24 weeks, 4 or more layers of interstitial cells are present, followed by interfollicular keratinization at 24 to 26 weeks [10-12]. Therefore, the epidermis gradually matures, similar to adult skin at 24 weeks of gestation.

Previously, we investigated the developmental changes in systemic circulation, including the catecholamine requirement, volume load, and corticosteroid usage in premature infants born at 22 to 28 weeks [7], we found that the developmental changes were similar between 22 and 23 weeks of gestation, and such infants needed more supplementation than those born at 24 weeks of gestation or more. Taking these findings and the current results together, we speculated that the circulatory or respiratory condition of those premature infants is likely unstable, and this could be a cofactor that induces skin lesions, particularly at 22-23 weeks of gestation.

The skin surface is physiologically slightly acidic in order to prevent bacterial invasion. The skin pH value ranges from 6.5-7.0 at birth and then decreases to 5 within 4 days, during which time its barrier function may become weaker [13]. Skin also play an important role in stabilizing the body temperature, which is unstable for the first 3 days in infants born < 30 weeks of gestation [14]. These observations support our main finding, namely that skin lesions occur more frequently during the first 5 days of life.

Skin lesions and focal intestinal perforation were significantly and independently associated with infantile mortality (Table 4). Of note, 90% of the infants with skin lesions showed either respiratory or circulatory instability first before the appearance of skin lesions (Figure 1), thus suggesting that the occurrence of skin lesions is one of the manifestations of a prematurity-related general condition. Furthermore, septic shock occurred after the appearance of skin lesions in infants having either circulatory or respiratory instability, thus suggesting that the skin served as a barrier in part against bacterial invasion.

The current time course study also showed that focal intestinal perforation was another limiting cofactor to survive, when these infants

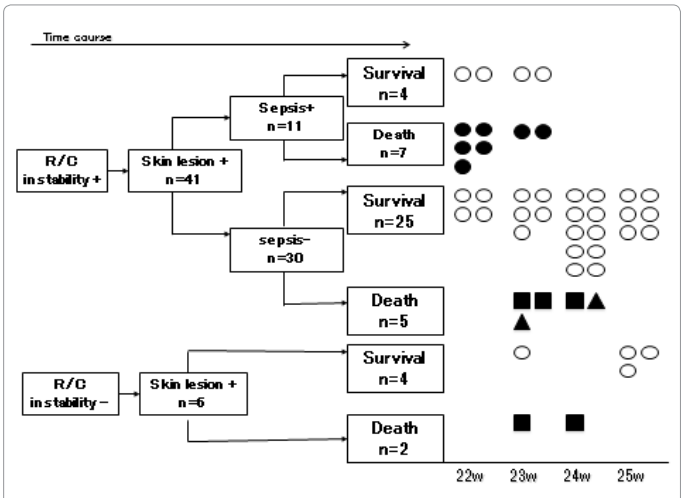


**Figure 1:** Temporal changes in the clinical manifestations of infants with skin lesions. Most infants with skin lesions (87%, 41/47) had either respiratory or circulatory instability (R/C instability) first, followed by the onset of skin lesions. Then sepsis ensued in one quarter of them, thus resulting in a poor prognosis. Only 10% of the premature infants had skin lesions without either preceding respiratory or circulatory instability. Open circles; survivors, closed circles; deaths by septic shock, closed rectangles; deaths by intestinal perforation, and closed triangles; remote deaths.

had skin lesions, but did not have septic shock. This finding implies the existence of a close association between the neonatal skin and the intestine, probably through similar developmental changes which lead to the onset of skin and intestinal lesions. The pathogenesis of focal intestinal perforation is still not clearly understood, but prematurity is associated with circulatory and respiratory instability, temperature instability, infection, and poor oral feeding, which are factors that may attributed to focal intestinal perforation. We previously reported that intrapartum; repetitive severe variable decelerations on fetal heart rate monitoring are associated with focal intestinal perforation in infants born at 22-28 weeks of gestation [9]. We speculated that those variable decelerations are more likely associated with mild circulatory instability, which might therefore influence the incidence of intestinal perforation.

From a developmental viewpoint, gastric emptying occurs more regularly after 24 weeks of gestation, thus indicating that the fetus swallows amniotic fluids containing epidermal growth factors which possibly allow the gastrointestinal tract to mature [15,16]. Therefore, infants born < 25 weeks are vulnerable to focal intestinal perforation, which is compatible with our findings (Figure 1).

In the surviving infants, skin lesions were no longer associated with neurological damage. This result was probably due to the fact that the infants with skin lesions had already died.

This study is associated with some limitations. One was due to its retrospective nature, and thus there was risk of underestimating the skin lesions. Another limitation was the small number of subjects, although some differences reached statistical significance. Furthermore, we could not perform a thorough pathological examination on the skin in all premature newborns.

In spite of these limitations, the findings of this study are still considered to have merit. Most importantly, we described that the occurrence of the skin lesions in premature infants is an important clinical manifestation which is significantly associated with perinatal adverse outcomes. In addition, this study was performed at a tertiary center of a certain district where the perinatal mortality is one of the lowest in the world (<4/1,000 delivery), and therefore the poor outcome observed in this study is considered to be more directly linked to the underlying pathogenesis, rather than due to the occurrence of accidental events.

We therefore concluded that, in extremely premature infants, most of the observed skin lesions occur as a consequence of prematurity-related circulatory and respiratory instability, which is significantly associated with neonatal mortality, but not with neurological damage. We therefore speculate that it is important to manage the respiratory and circulatory condition to prevent the occurrence of skin lesions and thereby improve the survival rate of premature infants.

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