Outcomes of Very Low Birth Weight Infants in Songklanagarind Hospital

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Objective: *To determine the mortality and morbidity rates of very low birth weight (VLBW) infants in Songklanagarind Hospital.*
Material and Method: *A retrospective study of all infants with birth weight < 1,500 g admitted to the neonatal intensive care unit between January 2003 and December 2006.*
Results: *A total of 178 VLBW infants, met the enrollment criteria, with mean (± standard deviation-SD) birth weight and gestational age of 1,123 ± 273 g and 29 ± 3 weeks, respectively. Forty-two (23.6%) were referred from other hospitals. The overall mortality rate was 27.0%. Perinatal risk factors of mortality were birth weight < 1,000 g ($p < 0.01$), congenital anomalies ($p < 0.01$), and Apgar score at 1 minute ≤ 5 ($p < 0.01$). Among the 130 (73.0%) survivors to discharge, 92 (70.8%) survived without major morbidity. The major morbidities were moderate/severe bronchopulmonary dysplasia, retinopathy of prematurity stage 3, necrotizing enterocolitis stage ≥ 2 and intraventricular hemorrhage grade ≥ III in 31 (23.8%), 12 (9.2%), 4 (3.1%) and 2 (1.5%) infants, respectively.*
Conclusion: *The mortality rate of VLBW infants in Songklanagarind Hospital was similar to other developing countries, although greater than in developed countries. Among survivors, the major morbidity rates were acceptable.*

Keywords: *Very low birth weight infant, Outcome, Mortality, Morbidity*

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Very low birth weight (VLBW) infants are defined as newborns who weigh less than 1,500 g and they are predominantly premature, have higher mortality and morbidity than normal newborns and are more likely to suffer some types of long term handicap. Studies have found that the survivals of VLBW infants are directly related to birth weight[1]. These infants demand high technology health care and this care consumes a large amount of resources. Although outcomes of VLBW infants have been reported broadly from neonatal networks of developed countries, less is known about the outcome of such infants in developing countries such as Thailand.

Songklanagarind Hospital, is the major tertiary care unit in southern Thailand, and is also a teaching hospital of the Faculty of Medicine of Prince of Songkla University. The hospital provides maternal and neonatal care and is the referral point for high risk pregnancies and newborns from other hospitals in southern Thailand, especially the lower south. There are 15 beds for neonatal intensive care and 10 beds for intermediate care. Medical staffing consists of 3 neonatologists and specialists in various fields. The objectives of the present study were to determine the mortality and morbidity rates of all VLBW infants cared in Songklanagarind Hospital during the study period, to evaluate the performance of Neonatal Intensive Care Unit (NICU).

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Material and Method

A retrospective study of VLBW infants, who were born in Songklanagarind Hospital or referred from other hospitals within 7 days after birth, and admitted to the NICU between January 1, 2003 and December 31,

2006 was collected. Data obtained from medical records and analyzed included perinatal information, morbidity and mortality rates, and selected major morbidities according to common definitions. The gestational age was estimated by obstetric and physical assessment using the new Ballard maturation score[2]. If the postnatal assessment differed from the obstetric assessment by > 2 weeks, the gestational age was based on the new Ballard Score. If the difference was < 2 weeks, the gestational age was based on obstetric assessment. An infant was defined as small for gestational age (SGA) if the birth weight was less than the 10th percentile for gestational age according to Lubchenco intrauterine growth charts[3]. Respiratory distress syndrome (RDS) was diagnosed by clinical and radiological findings consistent with RDS[4] and requirement of fractional concentration of inspired oxygen (FiO_2) > 0.4. Diagnosis of apnea was cessation of breathing with cyanosis or bradycardia. Hypoglycemia was defined as blood glucose < 40 mg/dL and hypotension was defined as a mean arterial pressure of less than 25 mmHg (birth weight 500-749 g), 30 mmHg (birth weight 750-999 g), 35 mmHg (birth weight 1,000-1,499 g) on two occasions and required cardiovascular support[5]. Congenital heart disease was diagnosed by a pediatric cardiologist through echocardiography. Infants diagnosed with symptomatic patent ductus arteriosus (PDA) met at least 3 of the clinical signs of audible systolic murmur, hyperdynamic precordial impulse, bounding pulse, widening pulse pressure and/or worsening respiratory status[6]. Necrotizing enterocolitis (NEC) was defined according to the criteria of Bell et al[7]. Retinopathy of prematurity (ROP) and intraventricular hemorrhage (IVH) were graded according to the international classification of retinopathy of prematurity[8] and Papile's classification[9], respectively. Bronchopulmonary dysplasia (BPD) was diagnosed according to the consensus workshop of National Institute of Child Health and Human Development/National Heart, Lung and Blood Institute[10].

Data were analyzed using R program version 2.8.1. Descriptive statistics (means, standard deviation and proportions) were used to describe the study variables. A logistic regression model was used to identify the independent predictors of mortality. Crude and adjusted odds ratios with its 95% confidence intervals were calculated. Comparisons of survival rate and selected major morbidities of inborn versus referred VLBW infants, used Chi-square test. A p-value of < 0.05 was considered as statistically significant.

Results

From 2003-2006, 178 of VLBW infants were admitted to the NICU of Songklanagarind Hospital. The mean (range) birth weight and gestational age were $1,123 \pm 273$ (500-1,495) g and 29 ± 3 (20-37) weeks, respectively. Forty-two (23.6%) were referrals from other hospitals. The mean birth weight of inborn and referred infants were $1,113 \pm 229$ and $1,115 \pm 254$ g ($p = 0.36$), respectively. They were almost evenly divided between female (51.7%) and male (48.3%). Fifty-five (31%) infants were extremely low birth weight (ELBW) infants weighing less than 1,000 g. The perinatal information is summarized in Table 1. Twenty-six (14.6%) infants were small for gestational age. Eighty-four (47.2%) were delivered by cesarean section. Twenty-nine (16.3%) mothers had no antenatal care and 139 (78.1%) had antenatal problems. The common maternal problems were pregnancy induced hypertension (25.8%), multiple pregnancies (25.8%) and prolonged rupture of membranes (24.2%). Antenatal antibiotics and corticosteroids were given to 18.5% and 48.9%, respectively. Only 40 (22.5%) infants had a full course of corticosteroids. Inborn and referred infants received antenatal corticosteroids at rates of 57.4% (78/136) and 21.4% (9/42), respectively. Apgar scores ≤ 3 at 1 and 5 minutes were recorded in 49 (27.5%) and 15 (8.4%) infants, respectively. One hundred and four (58.4%) infants required positive pressure ventilation at birth.

Table 1. Perinatal information and characteristics of the 178 VLBW infants

Characteristic	Number (%)
Male	86 (48.3)
SGA	26 (14.6)
Cesarean section	84 (47.2)
No antenatal care	29 (16.3)
Maternal problem	139 (78.1)
Pregnancy-induced hypertension	46 (25.8)
Multiple pregnancies	46 (25.8)
Prolonged rupture of membranes	43 (24.2)
Antenatal antibiotics	33 (18.5)
Antenatal corticosteroids	87 (48.9)
Apgar score at 1 minute ≤ 3	49 (27.5)
Apgar score at 5 minute ≤ 3	15 (8.4)
Required PPV at birth	104 (58.4)

* PPV: positive pressure ventilation, SGA: small for gestational age, VLBW: very low birth weight

On initial admission, 147 (82.6%) of VLBW infants had hypothermia (BT ≤ 36.5°C). One hundred and thirty-two (74.2%) required FiO_2 > 0.4, 56 (31.5%) had hypotension, 18 (10.1%) had anemia and 14 (7.9%) had hypoglycemia. There were no statistically significant differences in initial admission problems between inborn and referred infants (Fig. 1).

During admission, the most common morbidity of VLBW infants was RDS (64.0%) followed by sepsis (55.6%), apnea (42.1%), pneumonia (26.4%), isolated symptomatic PDA (25.3%), BPD (24.7%), NEC (15.7%), ROP (14.0%) and IVH (10.7%), as shown in Table 2. Only 21% of RDS received surfactant treatment. Sepsis was proven by blood culture in 16.3% of infants, with causative organisms of *Klebseilla pneumoniae, Escherichia coli, Enterobacter cloacae, Citrobacter freundii, Acinetobacter baumannii, Staphylococcus epidermidis, Staphylococcus aureus* and *Candida albicans.* Most infants of blood-culture proven sepsis (83%) were late onset sepsis (≥ 3 days of life). Sixty-three percent of late onset sepsis infants were caused by Gram negative organisms. The overall stage of NEC were 15.7%, NEC stage ≥ 2 (definite NEC) was encountered in 4 (2.2%) and one infant needed surgical treatment. Ventilatory support was required by 119 (66.9%) VLBW infants, and most (92.4%) required within 24 hours after birth. The mean duration of mechanical ventilation was 14.6 ± 17.8 days. Among VLBW infants, moderate and severe BPD, ROP stage 3 and IVH grade ≥ III were found in 17.3%, 14.0% and 10.7% of infants, respectively.

The overall mortality rate among VLBW infants in 4 year study period was 48 (27.0%) infants. The mortality rates according to birth weight are shown in Fig. 2. Mortality was directly related to birth weight, and the highest mortality rate (60%) was found in the group of birth weight < 1,000 g. The major cause of mortality was RDS, followed by sepsis and congenital anomalies (Table 3). Eighty-five percent of mortalities occurred within 7 days of birth and nearly half (48%) of those died within the first 24 hours. Multiple logistic regressions indicated that the major statistically significant perinatal risk factors of mortality were birth

Table 2. Morbidities of 178 VLBW infants during admission

	Number (%)
RDS	114 (64.0)
Received surfactant treatment	24 (21.05)
Sepsis 99 (55.6)	
Clinical sepsis	70 (39.3)
Proven by blood culture	29 (16.3)
Early onset sepsis	5 (2.8)
Late onset sepsis	24 (16.3)
Apnea	75 (42.1)
Pneumonia	47 (26.4)
Isolated symptomatic PDA	45 (25.3)
Congenital heart disease (except PDA)	4 (2.2)
Bronchopulmonary dysplasia (BPD)	44 (24.7)
Mild BPD	13 (7.4)
Moderate BPD	28 (15.7)
Severe BPD	3 (1.6)
Necrotizing enterocolitis	28 (15.7)
Stage I	24 (13.5)
Stage II	3 (1.6)
Stage III	1 (0.6)
Retinopathy of prematurity (ROP)	25 (14.0)
Stage 1	4 (2.2)
Stage 2	9 (5.1)
Stage 3	12 (6.7)
Intraventricular hemorrhage (IVH)	19 (10.7)
Grade I-II	17 (9.6)
Grade ≥ III	2 (1.1)

* PDA: patent ductus arteriosus, RDS: respiratory distress syndrome

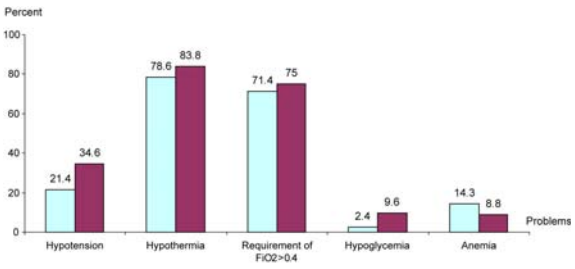

Fig. 1 Initial admission problems of inborn versus referred infants

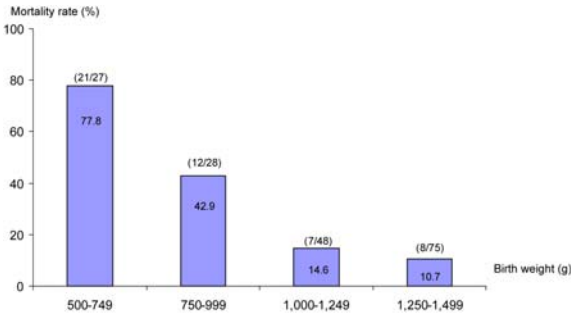

Fig. 2 Mortality rate of VLBW infants according to birth weight

weight < 1,000 g, congenital anomalies and Apgar score ≤ 5 at 1 minute (Table 4).

Overall 130 (73.0%) VLBW infants survived until discharge. Table 5 shows selected major morbidities (presence of moderate/severe BPD, ROP stage ≥ 3, NEC stage ≥ 2 and IVH grade ≥ III) for the survivors. Ninety-two (70.8%) infants had no major morbidity. Of thirty-eight (29.2%) infants with major morbidity, the incidence of moderate and severe BPD were 23.8% (15.4% had moderate/severe BPD alone and 8.5% had combined moderate/severe BPD and ROP stage 3). One-fifth (6/31) of moderate/severe BPD infants still required supplemental oxygen at discharge. There was no more than stage 3 of ROP. ROP stage 3, NEC stage ≥ 2 and IVH grade ≥ III were encountered in 9.2%, 3.1% and 1.5%, respectively. Comparing the survival rates and major morbidities of inborn and referred infants, there were no statistically significant differences between the groups (Table 6). The mean length of hospital stay for the survivors was 49.5 ± 27.3 days.

Table 3. Causes of mortality of 48 VLBW infants

Causes of death	Number (%)
Respiratory distress syndrome	20 (41.7)
Sepsis	13 (27.1)
Culture proven	4 (8.3)
Congenital anomalies	9 (18.8)
Ventriculomegaly	3 (6.3)
Chromosomal abnormalities	2 (4.2)
Lung hypoplasia	2 (4.2)
Severe tetralogy of Fallot	1 (2.1)
Pentalogy of Cantrell*	1 (2.1)
Perinatal asphyxia	5 (10.4)
Pneumothorax	1 (2.1)

* Pentalogy of Cantrell is a rare syndrome that cause defects involving diaphragm, abdominal wall, pericardium, heart, and lower sternum, and has five characteristic findings: omphalocele, anterior diaphragmatic hernia, sternal cleft, ectopia cordis, and intracardiac defect (either ventricular septal defect or a diverticular of the left ventricle

Discussion

The authors present a study on the morbidity and mortality rates and selected major morbidities in the survivors among VLBW infants admitted to a tertiary care center in the south of Thailand during 2003-2006. The majority of infants (76.4%) were inborn, because when problems are suspected, in utero transport was and is preferred to neonatal transport. Most of the VLBW infants had antenatal problems. Multiple pregnancies and prolonged rupture of membranes were common problems leading to preterm birth, which seems to be common according to other reports on VLBW infants from neonatal networks in developed countries such as the United States in 1995-2002[11,12] and Japan in 2003[13]. Pregnancy induced hypertension was higher (25.8%) than reports from the Canadian NICU network during 1996-1997 (13%)[14] and Japan (16-20%)[13] but similar to report from Turkey during 1997-2000 (31%)[15].

In the present study, antenatal corticosteroids were provided in only 48.9% of infants compared to 70-80% in developed countries[11,12,16]. The incidence of RDS was higher (64%) than in developed countries

Table 4. Perinatal risk factors of mortality

	Survivors n = 130	Deaths n = 48	Crude OR (95% CI)	Adjusted OR (95%CI)	p-value
Antenatal corticosteroids	71 (54.6%)	16 (33.3%)	0.4 (0.2- 0.8)	0.5 (0.2-1.8)	0.32
Prolonged rupture of membranes	38 (29.2%)	5 (10.4%)	0.3 (0.1-0.8)	0.4 (0.1-1.7)	0.23
Gestational age ≤ 28 weeks	37 (28.5%)	36 (75.0%)	7.5 (3.5-16.1)	2.5 (0.6-9.3)	0.18
Birth weight < 1,000 g	22 (16.9%)	33 (68.7%)	10.8 (5.0-23.2)	14.3 (3.6-56.8)	<0.01*
Congenital anomaly	7 (5.4%)	8 (16.7%)	3.5 (1.2-10.3)	207.7 (13.6-3177.4)	<0.01*
Apgar score at 1 minute ≤ 5	45 (34.6%)	40 (83.3%)	10.3 (4.3-24.8)	4.8 (1.2-18.9)	0.03*
Apgar score at 5 minute ≤ 5	8 (6.1%)	23 (47.9%)	14.0 (5.6-35.0)	3.1 (0.7-14.1)	0.13
Required positive pressure ventilation at birth	64 (49.2%)	40 (83.3%)	4.9 (2.1-11.3)	1.5 (0.2-8.4)	0.66
Body temperature on initial admission < 36.5°C	104 (80.0%)	43 (89.6%)	5.4 (1.2-23.6)	1.2 (0.1-9.7)	0.83
Hypotension on initial admission	33 (25.4%)	23 (47.9%)	3.1 (1.5-6.2)	1.6 (0.5-6.0)	0.44
Requirement of FiO_2 > 0.4 on initial admission	88 (67.7%)	44 (91.7%)	21.0 (2.8-157.6)	12.7 (0.8-203.7)	0.08

* Significant level at p < 0.05

Table 5. Selected major morbidity of the 130 survivors to discharge

	Number (%)
Survived without major morbidity	92 (70.8)
Survived with major morbidity	38 (29.2)
Moderate/severe BPD alone	20 (15.4)
Moderate/severe BPD + ROP stage 3	11 (8.5)
ROP stage 3	1 (0.8)
NEC stage $\geq$ 2	4 (3.1)
IVH grade $\geq$ III	2 (1.5)

ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, IVH: intraventricular hemorrhage

Table 6. Survival rates and major morbidities of inborn versus referred VLBW infants

	Inborn n = 136 (%)	Referred n = 42 (%)	p-value
Survivals	97 (71.3)	33 (78.6)	0.35
Moderate/severe BPD	24 (17.6)	7 (16.7)	0.88
ROP stage 3	10 (7.3)	2 (4.8)	0.60
NEC stage $\geq$ 2	3 (2.2)	1 (2.4)	0.82
IVH grade $\geq$ III	1 (0.7)	1 (2.4)	0.43

ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, IVH: intraventricular hemorrhage

(44-50%)[11,12]. In 2006, Systematic review by Cochrane Collaboration concluded that corticosteroids given prior to preterm birth (as a result of either preterm labor or elective preterm delivery) are effective in preventing RDS and neonatal mortality[17]. In the study period the mothers who did not receive corticosteroids, did not receive them because of having the problems of prolonged rupture of membranes, clinical signs of chorioamnionitis, hypertension and delivery almost immediately upon arriving at the hospital. The inborn VLBW infants were more likely to receive antenatal corticosteroids than the referred infants (57% versus 21%). Systematic review by Cochrane Collaboration noted evidence to suggest benefit from corticosteroid use in the subgroups of women with premature rupture of membranes without an increased risk of maternal or neonatal sepsis and those with hypertension syndrome and recommend that a single course of antenatal corticosteroid should be considered routine for preterm delivery and provided immediately to mother on hospital admission[18].

Among VLBW infants, more than half (58%) needed positive pressure ventilation at birth due to having perinatal asphyxia and immature lungs. On initial admission, hypothermia of all VLBW infants was very high (84%). There was no statistically significant difference between inborn versus referred infants (Fig.1). It is known that hypothermia in neonates increases mortality and morbidity: for example, Laptook et al[19] reported that mortality increased 28% and late onset sepsis increased 11% per 1°C of admission temperature decreased. In VLBW infants, conventional interventions for hypothermia, including drying and radiant heating to reduce core temperature fall, are not very effective. Some special interventions are required such as wrapping the infants with plastic wrap immediately upon birth and placing them on a transwarmer mattress, which have been reported to be effective in keeping preterm infants warmer, leading to higher temperature on admission to the neonatal unit and less hypothermia[20]. The other important problem on initial admission noted in the present study was requirement for $FiO_2 > 0.4$ resulting from some types of post-delivery problem such as perinatal asphyxia, hypotension or respiratory immaturity, and needing supplemental oxygen.

Of all VLBW infants, RDS was the most common morbidity and the leading cause of mortality. Only 21% of infants with RDS received postnatal surfactant treatment and none of them received it for prophylaxis. This seems to be the norm in other NICUs in Thailand because of limited budgets[21,22]. The second most common morbidity and cause of death was sepsis. Over half of the VLBW infants were diagnosed sepsis by clinical conditions and provided antibiotic treatment, only 16.3% had blood-culture-proven infection (Table 2). This indicated that the rational use of antibiotics should be promoted. Most of blood cultures indicated sepsis were late onset sepsis, 63.3% of those were caused by Gram negative organisms. This was different from the report of the National Institute of Child Health and Development (NICHD) Neonatal Research Network in 2002, which found that the majority of late onset sepsis in VLBW infants (70%) were caused by Gram-positive organisms, with coagulase-negative staphylococci accounting for 48% of infections. The infants who were infected were significantly more likely to die than those who were uninfected, especially if they were infected with Gram negative organisms[23].

The overall mortality rate of VLBW infants was 27.0%. It was higher than the reports from developed countries such as Canada, Japan and the United States (4-15%)[12-14] but comparable to the reports from Taiwan, South America and others from Thailand (19-30%)[21,22,24,25]. All reports indicate that advances in perinatal care, medical resource and the number of ELBW infants influence the survival rates. The mortality rate in the ELBW group was also greater than is found in developed countries (60% versus 14-22%)[26,27]. The birth weight < 1,000 g and congenital anomalies were the significant perinatal risk factors of mortality liked the other report in Thailand[21]. The other major perinatal risk factor of mortality was an Apgar score ≤ 5 at 1 minute, which was a different finding from other reports from Thailand which have found that an Apgar score at 5 minutes ≤ 5 was a predictor[21,22].

Of VLBW infants who survived until discharge, 70.8% had no major morbidity, which is very similar to reports from developed countries (69-72%)[12,14]. Of the infants who survived with major morbidity, the incidence of moderate/severe BPD were 23.8%, a similar result to the NICHD Neonatal Research Network during 1996-2002 and a large multicenter neonatal research network of Japan in 2003 (22% and 28%, respectively)[12,13]. The rest major morbidities were ROP stage 3 (9.2%), definite NEC (3.1%) and severe IVH (1.5%). The favorable incidence was due to the smaller number of survived ELBW infants in the present study (22/130). Comparison the mortality or morbidity in the VLBW infants of any NICU, needs to specify each birth weight group.

In conclusion, the present study assessed the outcomes of VLBW infant care in the NICU of Songklanagarind Hospital during 2003-2006, and the findings indicate that there is room for improvement. The study provides baseline information for beginning a more comprehensive database for prospective evaluation and intervention.

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ผลการดูแลรักษาทารกแรกเกิดน้ำหนักน้อยมากของโรงพยาบาลสงขลานครินทร์

ประสิน จันทร์วิทัน, กนกพรรณ เรืองนภา, วาริชา เจนจินดามัย, สุภาภรณ์ ดิสนีเวทย์

วัตถุประสงค์: เพื่อศึกษาอัตราการตาย และการเจ็บป่วยในทารกแรกเกิดน้ำหนักน้อยมากของโรงพยาบาลสงขลานครินทร์

วัสดุและวิธีการ: ศึกษาแบบย้อนหลังในทารกแรกเกิดน้ำหนัก < 1,500 กรัม ทุกราย ที่ได้รับไว้ในหออภิบาลทารกแรกเกิดระหว่างเดือนมกราคม พ.ศ. 2546 ถึง ธันวาคม พ.ศ. 2549

ผลการศึกษา: ทารกแรกเกิดน้ำหนักน้อยมากรวมทั้งสิ้น 178 ราย น้ำหนักแรกเกิดเฉลี่ย 1,123 $\pm$ 273 กรัม และอายุครรภ์เฉลี่ย 29 $\pm$ 3 สัปดาห์ ทารกจำนวน 42 ราย (ร้อยละ 23.6) ส่งตัวมาจากโรงพยาบาลอื่น อัตราการตายโดยรวมเท่ากับร้อยละ 27.0 ปัจจัยเสี่ยงช่วงปริกำเนิดของการตายได้แก่ น้ำหนักแรกเกิดน้อยกว่า 1,000 กรัม ($p < 0.01$) ภาวะพิการแต่กำเนิด ($p < 0.01$) และคะแนน Apgar ที่ 1 นาที ≤ 5 ($p < 0.01$)) ทารกที่รอดชีวิตจนถึงวันจำหน่ายออกจากโรงพยาบาล 130 ราย (ร้อยละ 73.0) พบว่า 92 ราย (ร้อยละ 70.8) ไม่มีภาวะแทรกซ้อนที่สำคัญ ภาวะแทรกซ้อนที่สำคัญพบภาวะ bronchopulmonary dysplasia ระดับปานกลาง และรุนแรง, retinopathy of prematurity stage 3, necrotizing enterocolitis stage ≥ 2 และ intraventricular hemorrhage grade $\geq$ III เท่ากับ 31 (ร้อยละ 23.8), 12 (ร้อยละ 9.2), 4 (ร้อยละ 3.1) และ 2 (ร้อยละ 1.5) ราย ตามลำดับ

สรุป: อัตราการตายของทารกแรกเกิดน้ำหนักน้อยมากของโรงพยาบาลสงขลานครินทร์ใกล้เคียงกับ การศึกษาอื่น ๆ ในกลุ่มประเทศกำลังพัฒนา แม้ว่าอัตราการตายสูงกว่าประเทศที่พัฒนาแล้ว ในส่วนของทารกที่รอดชีวิตพบว่าภาวะแทรกซ้อนที่สำคัญอยู่ในเกณฑ์ที่ยอมรับได้