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Neonatal Outcomes Following Preterm Birth Between 28 and 36 Weeks' Gestation in Vietnam: A Cohort Study

Quynh T. T. Tran[1,2] | Sean K. Seeho[2,3] | Tanya A. Nippita[2,3] | Jonathan M. Morris[2,3] | Thanh Q. Le[1] | Hai N. Tran[1] | Hai T. Pham[1] | Ibinabo Ibiebele[2,3]

[1]Tu Du Hospital, Ho Chi Minh City, Vietnam | [2]Sydney Medical School, The University of Sydney, Sydney, Australia | [3]Reproduction and Perinatal Centre, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Correspondence: Quynh T. T. Tran (quynh.trandr@gmail.com)

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ABSTRACT

Background: Preterm birth leads to adverse neonatal outcomes. Data on neonatal outcomes in middle-income settings like Vietnam are lacking.

Aims: Describe preterm neonatal outcomes in Vietnam.

Materials and Methods: Retrospective cohort study including all live singleton births at 28–36 weeks' gestation in Vietnam from June 2019 to June 2020. Outcomes included neonatal morbidity and mortality and were examined by labour onset and gestational age groups. Logistic regression was used to estimate the odds of neonatal morbidity and mortality following planned birth (labour induction and prelabour caesarean) relative to spontaneous birth.

Results: Among 5374 live singleton preterm births, 663 (12.4%) occurred between 28 and 31 weeks, 824 (15.3%) between 32 and 33 weeks and 3887 (72.3%) between 34 and 36 weeks; 2765 (51.5%) births followed spontaneous labour and 2616 (48.5%) were planned births. Mortality rates decreased with increasing gestational age. More than 90% of neonates born at 28–33 weeks had morbidity, with the rate of morbidity decreasing from 34 weeks. The odds of mortality were no different following labour induction (aOR 1.22, 95% CI, 0.72–2.09) or prelabour caesarean (aOR 1.04, 95% CI, 0.63–1.73) compared with spontaneous labour. The odds of morbidity were higher among pregnancies following labour induction (aOR 1.53, 95% CI, 1.31–1.80) and prelabour caesarean section (aOR 2.14, 95% CI, 1.84–2.50) than spontaneous labour. Among planned preterm births < 35 weeks, antenatal corticosteroids were associated with higher morbidity (90.7% vs. 74.3%, $p < 0.001$) and lower mortality rates (2.5% vs. 5.1%, $p = 0.022$).

Conclusions: Preterm neonates born before 34 weeks are at particularly high likelihood of morbidity and mortality, with planned preterm birth associated with a higher rate of morbidity.

1 | Introduction

Preterm birth (birth before 37 completed weeks of gestation or fewer than 259 days from the first day of a woman's last menstrual period [1]) is a significant global health issue. Global preterm birth rates were estimated at 9.6% in 2005 [2], 11.1% in 2010 [3] and 10.6% in 2014 [4]; with Sub-Saharan Africa and South Asia accounting for the majority of all preterm births [2–4]. Preterm birth is associated with child mortality and short- and long-term morbidity, including respiratory distress, intraventricular haemorrhage and childhood neurological and developmental impairment [5–10].

Preterm birth may occur after planned birth (labour induction and prelabour caesarean section) or spontaneous labour onset. Preterm birth is usually planned when the risk to the mother and/or baby with continuation of pregnancy is deemed greater than the risk of an early delivery [11]. Administration of

antenatal corticosteroids to women at risk of preterm birth less than 35 weeks' gestation has proven benefit, with fewer perinatal deaths, respiratory distress syndrome, intraventricular haemorrhage and developmental delay in childhood [12]. These benefits have been shown in neonates in low-, middle- and high-income countries [13].

There are few studies on preterm neonatal outcomes following planned birth, and these data are derived from high-income country settings [5, 8, 14]. Neonatal outcomes stratified by labour onset and gestational age at birth among a preterm birth population in middle-income countries such as Vietnam are not known. Our study aimed to determine neonatal morbidity and mortality rates after preterm birth and examine the association between labour onset and neonatal morbidity and mortality in a Vietnamese obstetric population. We also aimed to determine the frequency of antenatal corticosteroid administration among planned births at < 35 weeks' gestation and describe mortality and morbidity rates by corticosteroid administration status.

2 | Materials and Methods

A retrospective cohort study was conducted in Ho Chi Minh City, Vietnam. Tu Du Hospital is one of the largest referral facilities for obstetrics and gynaecology in Vietnam, with more than 60000 births annually. The study population included all singleton live births between 28 and 36 completed weeks' gestation from June 2019 to June 2020. Stillborn infants, pregnancy terminations and births of unknown gestational age were excluded.

Study data were obtained from maternal and neonatal hospital medical records. Data included maternal demographics, medical and pregnancy conditions and birth outcomes. Eligible births were identified from the electronic database. Handwritten medical records were individually reviewed for eligibility and to extract relevant data. Ethics approval was obtained from the Tu Du Hospital Ethics Committee (approval number 854/QD-BVTD).

Study outcomes were neonatal and infant mortality, and neonatal morbidity. Neonatal mortality was defined as death of a liveborn infant within 28 days of birth during the birth admission. Infant mortality was defined as death of a liveborn infant less than 1 year during the birth admission. Neonatal morbidity was a composite measure comprising admission to the neonatal intensive care unit (NICU), respiratory support (mechanical ventilation, oxygen, continuous positive airway pressure (CPAP) or other methods), surfactant use, transfer to another hospital for a higher level of care and confirmed diagnosis of respiratory distress syndrome, necrotising enterocolitis, sepsis or intraventricular haemorrhage.

Labour onset was categorised as either spontaneous labour or planned birth (labour induction or prelabour caesarean section). Gestational age at birth was calculated from the first day of the last menstrual period or by using the first-trimester ultrasound result (< 14 weeks' gestation). If there was significant difference in the confinement date between the last menstrual period and the first-trimester ultrasound (≥ 7 days), ultrasound calculated date was used.

Maternal and pregnancy characteristics included maternal age, ethnicity, body mass index (BMI), previous preterm birth and pre-existing health conditions. Pre-existing maternal health conditions included chronic hypertension; diabetes mellitus; renal failure and kidney disease; anaemia; human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS); hepatitis B and C; and cardiac, thyroid and chronic respiratory disease. Data on antenatal corticosteroids administration were also collected. Neonatal characteristics included gestational age at birth, gender, Apgar score, resuscitation at birth and hospital transfer.

Differences in characteristics by labour onset and differences in morbidity and mortality by antenatal corticosteroid administration were assessed using Chi-square tests, analysis of variance (ANOVA) and Kruskal–Wallis H tests as appropriate. The associations between labour onset and the study outcomes were assessed using logistic regression. Variables were selected for inclusion in multivariate logistic regression models based on a priori clinical knowledge and statistical significance in univariate models ($p < 0.05$). Crude and adjusted odds ratios are presented with 95% confidence intervals. Analyses were performed using Stata13.1 for Windows (StataCorp LLC, College Station, Texas, USA).

3 | Results

During the study period, 6348 singleton live births between 28 and 36 weeks' gestation were identified. Of these, 974 were excluded due to pregnancy termination ($n = 206$), stillbirth ($n = 44$), twin pregnancy ($n = 1$), unknown gestational age ($n = 710$) and missing records ($n = 13$) (Figure S1). Of the 5374 singleton preterm live births, 663 infants (12.4%) were born at 28–31 weeks, 824 (15.3%) at 32–33 weeks and 3887 (72.3%) at 34–36 weeks' gestation. More than half of the preterm births followed spontaneous onset of labour (2765; 51.5%) and 2616 (48.5%) births were planned. There were 1130 (43.3%) births after labour induction and 1479 (56.7%) after prelabour caesarean section. The study population characteristics are shown in Table 1.

Among 5374 preterm births, the overall neonatal and infant mortality rates were 17.5/1000 and 20.1/1000 livebirths, respectively. Figure 1A shows the mortality rates by gestational age at birth. At 28 weeks' gestation, the neonatal and infant death rates were 184.5 and 252.4/1000 livebirths, respectively. The mortality rate decreased with increasing gestational age at birth to < 10/1000 livebirths after 34 weeks. There was no difference in neonatal mortality rates between planned and spontaneous birth (induced labour aOR 1.22, 95% CI, 0.72–2.09; prelabour caesarean section aOR 1.04, 95% CI, 0.63–1.73) (Table 1).

Neonatal morbidity was observed in 3014 neonates (56.1%) between 28 and 36 weeks' gestation. Regardless of labour onset, the morbidity rate was greater than 90% at less than 33 weeks. Between 34 and 36 weeks' gestation, the rate of

TABLE 1 | Association between onset of labour and study outcomes.

Study outcomes		Induced OR (95% CI)	Prelabour caesarean section OR (95% CI)	Spontaneous (reference)	Induced adjusted OR[a] (95% CI)	Prelabour caesarean section adjusted OR[a] (95% CI)	Spontaneous (reference)
Neonatal mortality	All preterm births (28–36 weeks)	1.32 (0.79–2.19)	1.22 (0.76–1.97)	1.00	1.22 (0.72–2.09)	1.04 (0.63–1.73)	1.00
	28–31 weeks	1.39 (0.70–2.79)	1.09 (0.57–2.08)	1.00			
	32–33 weeks	0.80 (0.17–3.73)	0.41 (0.09–1.89)	1.00			
	34–36 weeks	1.61 (0.61–4.26)	1.76 (0.71–4.33)	1.00			
Neonatal morbidity	All preterm births (28–36 weeks)	1.24 (1.08–1.44)	1.87 (1.64–2.13)	1.00	1.53 (1.31–1.80)	2.14 (1.84–2.50)	1.00
	28–31 weeks	0.43 (0.08–2.13)	1.97 (0.20–19.1)	1.00			
	32–33 weeks	1.19 (0.56–2.53)	1.95 (0.98–3.88)	1.00			
	34–36 weeks	1.55 (1.31–1.82)	2.12 (1.82–2.47)	1.00			

[a]Adjusted for maternal age, maternal BMI, previous preterm birth, pre-existing health condition, gestational age at birth and infant gender.

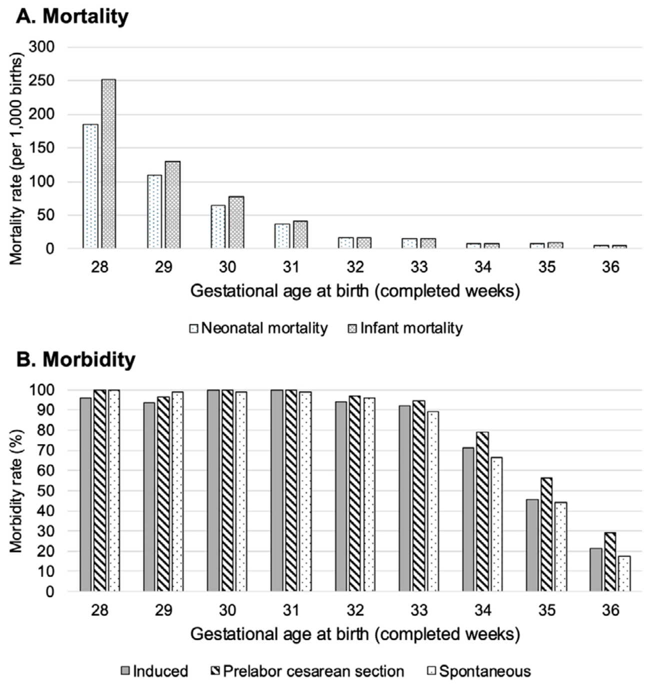

FIGURE 1 | Neonatal mortality and morbidity by gestational age at birth.

morbidity decreased from 71.9% at 34 weeks to 47.7% at 35 weeks and 20.8% at 36 weeks (Figure 1B). Overall neonatal morbidity was higher for planned preterm birth compared with spontaneous labour onset (induced labour aOR 1.53, 95% CI, 1.31–1.80; prelabour caesarean section aOR 2.14, 95% CI, 1.84–2.50) (Table 1). There was no difference in morbidity for planned preterm birth compared with spontaneous labour onset for babies born between 28–31 and 32–33 weeks; however, at 34–36 weeks' gestation planned birth was associated with higher odds of morbidity (induced labour aOR 1.55, 95% CI, 1.31–1.82; prelabour caesarean section aOR 2.12, 95% CI, 1.82–2.47).

From 28 to 32 weeks' gestation, more than 90% of neonates required NICU admission, suffered respiratory distress and needed respiratory support. NICU admission, respiratory distress and respiratory support were the most frequently occurring morbidity categories. The frequency of all neonatal morbidity types declined with increasing gestational age ($p_{trend} < 0.001$) (Table 2).

The rate of antenatal corticosteroid administration was high among the 1313 singleton planned births at < 35 weeks, which ranged from 86.5% to 91.9% at 28–33 weeks and 62.3% at 34 weeks' gestation. The combined neonatal morbidity and mortality rate was higher in the antenatal corticosteroid administration group than those who were not administered corticosteroids (90.8% vs. 76.0%, $p < 0.001$). The overall neonatal morbidity rate was higher among planned births < 35 weeks' gestation in which antenatal corticosteroids were administered compared with those in whom antenatal corticosteroids were not administered (90.7% vs. 74.3%, $p < 0.001$) (Table 3). In contrast, the neonatal mortality rate when corticosteroids were administered was lower than in pregnancies without antenatal corticosteroids (2.5% vs. 5.1%, $p = 0.022$) (Table 3).

TABLE 2 | Neonatal morbidity categories by gestational age at birth.

Variable	Gestational age at birth (completed weeks)									
	28 ($N=103$)	29 ($N=147$)	30 ($N=169$)	31 ($N=244$)	32 ($N=305$)	33 ($N=519$)	34 ($N=970$)	35 ($N=1069$)	36 ($N=1848$)	p_{trend}
Admission to NICU	101 (98.0)	141 (95.9)	165 (97.6)	241 (98.8)	286 (93.8)	459 (88.4)	610 (62.9)	404 (37.8)	261 (14.1)	<0.001
Respiratory support[a]	102 (99.0)	141 (95.9)	166 (98.2)	243 (99.6)	289 (94.8)	464 (89.4)	682 (70.3)	488 (45.7)	348 (18.8)	<0.001
Respiratory distress	101 (98.0)	143 (97.3)	164 (97.0)	241 (98.8)	275 (90.2)	392 (75.5)	510 (52.6)	344 (32.2)	226 (12.2)	<0.001
Necrotising enterocolitis	4 (3.9)	4 (2.7)	1 (0.6)	8 (3.3)	4 (1.3)	2 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	<0.001
Sepsis	60 (58.3)	57 (38.8)	61 (36.1)	55 (22.5)	36 (11.8)	36 (6.9)	31 (3.2)	19 (1.7)	12 (0.6)	<0.001
Intraventricular haemorrhage	3 (2.9)	1 (0.7)	4 (2.4)	5 (2.0)	0 (0.0)	1 (0.2)	3 (0.3)	3 (0.3)	1 (0.1)	<0.001
Transfer to another hospital for a higher level of care	25 (24.3)	12 (8.2)	10 (5.9)	13 (5.3)	14 (4.6)	15 (2.9)	22 (2.3)	17 (1.6)	31 (1.7)	<0.001
Surfactant used	41 (39.8)	56 (38.1)	41 (24.3)	37 (15.2)	35 (11.5)	23 (4.4)	26 (2.7)	17 (1.6)	7 (0.4)	<0.001

Note: Columns may add up to more than the column total as neonates could have more than one category of morbidity.
[a]Includes mechanical ventilation, oxygen only, CPAP and other methods.

TABLE 3 | Neonatal mortality and morbidity by gestational age and antenatal corticosteroids administration status for planned births at < 35 weeks' gestation.

Gestational age (completed weeks)	Planned births	Antenatal corticosteroid administration		Mortality			Morbidity		
	n			Yes (%)	No (%)	*p*	Yes (%)	No (%)	*p*
28	56	Yes	*n* = 50	8/50 (16.0)	42/50 (84.0)	0.295	49/50 (98.0)	1/50 (2.0)	1.000
		No	*n* = 6	2/6 (33.3)	4/6 (66.7)		6/6 (100)	0/6 (0.0)	
29	72	Yes	*n* = 66	6/66 (9.1)	60/66 (90.9)	< 0.001	66/66 (100)	0/66 (0.0)	< 0.001
		No	*n* = 6	5/6 (83.3)	1/6 (16.7)		3/6 (50.0)	3/6 (50.0)	
30	89	Yes	*n* = 77	4/77 (5.2)	73/77 (94.8)	0.140	77/77 (100)	0/77 (0.0)	—
		No	*n* = 12	2/12 (16.7)	10/12 (83.3)		12/12 (100)	0/12 (0.0)	
31	128	Yes	*n* = 116	3/116 (2.6)	113/116 (97.4)	0.276	116/116 (100)	0/116 (0.0)	—
		No	*n* = 12	1/12 (8.3)	11/12 (91.7)		12/12 (100)	0/12 (0.0)	
32	149	Yes	*n* = 132	1/132 (0.8)	131/132 (99.2)	0.002	127/132 (96.2)	5/132 (3.8)	0.523
		No	*n* = 17	2/17 (11.8)	15/17 (88.2)		16/17 (94.1)	1/17 (5.9)	
33	222	Yes	*n* = 204	1/204 (0.5)	203/204 (99.5)	0.766	192/204 (94.1)	12/204 (5.9)	0.316
		No	*n* = 18	0/18 (0.0)	18/18 (100.0)		16/18 (88.9)	2/18 (11.1)	
34	597	Yes	*n* = 372	2/372 (0.5)	370/372 (99.5)	0.301	295/372 (79.3)	77/372 (20.7)	0.004
		No	*n* = 225	3/225 (1.3)	222/225 (98.7)		155/225 (68.9)	70/225 (31.1)	
Total	1313	Yes	*n* = 1017	25/1017 (2.5)	992/1017 (97.5)	0.022	922/1017 (90.7)	95/1017 (9.3)	< 0.001
		No	*n* = 296	15/296 (5.1)	281/296 (94.9)		220/296 (74.3)	76/296 (25.7)	

4 | Discussion

To our knowledge, this is the first study describing neonatal morbidity and mortality rates by gestational age and labour onset in a Vietnamese obstetric population. We found that neonatal mortality rates decreased with increasing gestational age, with no difference in the odds of mortality by labour onset. In contrast, there was increased likelihood of neonatal morbidity following labour induction and prelabour caesarean compared to spontaneous labour, possibly due to the underlying aetiology resulting in the planned birth. Antenatal corticosteroid administration < 35 weeks gestation was associated with reduced rates of neonatal mortality but surprisingly greater rates of morbidity when compared to no antenatal corticosteroids.

Our neonatal mortality rate at 28–36 weeks' gestation was 1.8%, which was higher than the 1.4% in a study from the United States [10], but lower than 3.2% among births from 28 to 36 weeks in a Chinese study [15]. Our neonatal mortality rate was approximately 35-fold greater at 28 weeks than at 36 weeks (18.5% at 28 weeks, 1.5% at 33 weeks and 0.5% at 36 completed weeks' gestation). This rate is much higher than the 2% at 28 weeks, 0.2% at 33 weeks and zero deaths from 34 to 36 weeks' gestation reported in a cohort study conducted in 25 hospitals in the United States, although both studies show a steady decline in mortality with each advancing week of gestation [10]. A study in China (upper-middle-income country) demonstrated higher neonatal mortality rates than found in our study, with 15.8% versus 8.3%, 3.7% versus 1.5%, 1.5% versus 0.6% at 28–31 weeks, 32–33 weeks and 34–36 weeks, respectively [15].

Our neonatal mortality rates of 1.95% after planned birth and 1.56% following spontaneous labour onset are similar to a study from the United States that reported the mortality rate of preterm neonates being 1.9% for planned births and 1.2% for spontaneous labour onset [14]. We were unable to identify any studies that described mortality rates following planned birth compared to spontaneous labour onset in middle-income countries, especially in Asia.

We found that there was no difference in the neonatal mortality rate with induction of labour and prelabour caesarean section compared with spontaneous birth. Our findings differ from a Latin American study by Barros and colleagues spanning 1985–2003 which reported that infants born following planned preterm birth had higher mortality rates (adjusted odds ratios ranging 1.23–1.91) than those who were born after spontaneous labour. The reason for these differences is unclear. In contrast, among singleton preterm births in Scotland between 1980 and 2004, Norman et al. described lower neonatal mortality following planned birth compared with spontaneous labour onset at 24–36 weeks' gestation. These findings were described in the context of increasing planned births, decreasing perinatal mortality and an increase in prolonged neonatal hospital stay among preterm births over time [16].

Our overall neonatal morbidity rate was 56.1% at 28–36 weeks, with rates > 90% between 28 and 33 weeks' gestation. From

34 weeks' gestation, the rate decreased, with approximately one in five neonates experiencing morbidity at 36 weeks. Manuck and colleagues reported that 17.7%–95.4% of neonates born at 28–36 weeks' gestation in the United States suffered some morbidity compared with 71.7%–97.1% of neonates in our study [10]. The difference in morbidity rates is likely to be due, in part, to differences in how morbidity status is defined in studies. For example, Manuck and colleagues considered persistent pulmonary hypertension, hyperbilirubinemia and hypotension requiring treatment as forms of neonatal morbidity. In contrast, our study defined morbidity as respiratory distress syndrome, necrotising enterocolitis, sepsis, intraventricular haemorrhage, admission to NICU, respiratory support, surfactant use and transfer to another hospital for a higher level of care. Our findings are consistent with findings from Australia, the United States and Israel demonstrating that the overall neonatal morbidity rate decreases with advancing gestational age from 33 weeks' gestation [5, 10, 17]. Another important finding is the association between planned preterm birth and a higher rate of neonatal morbidity when compared to spontaneous labour onset, which is similar to a Latin American study [8]. The reasons for this association are not entirely clear; however, it is well-established that prelabour caesarean section is associated with higher rates of respiratory distress [18]. Although we performed multivariate analyses to adjust for some variables such as pre-existing health conditions, it was not possible to account for all variables. It is likely that women who had chorioamnionitis or fetal growth restriction, conditions associated with increased neonatal morbidity, were more likely to have planned births. Another reason for the increase in morbidity associated with planned birth may be because in the hospital, women with preterm prelabour rupture of membranes (PPROM) are recommended planned birth after they reach 34 weeks' gestation, as recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynecologists (ACOG) [19, 20]. The PPROMT study found that among pregnancies with PPROM between 34 and 36 completed weeks' gestation, immediate delivery increased the length of time in the NICU (median, four vs. 2 days; $p < 0.001$) and the risk of preterm morbidities, such as neonatal respiratory distress (RR 1.6; 95% CI, 1.1–2.3) [21].

Comparison of neonatal morbidity between studies is challenging due to differences in definitions. Our data showed a higher rate of respiratory distress and lower rate of intraventricular haemorrhage than demonstrated in a systematic review by Teune and colleagues [22]. In contrast, an Australian study reported higher rates of intraventricular haemorrhage among neonates at 28–31 weeks than found in our study [23]. The higher intraventricular haemorrhage rate in the Australian study is likely the result of ascertainment bias from routine ultrasonographic screening among early preterm babies in Australia, whereas screening in this hospital only occurs when symptoms or signs of intraventricular haemorrhage are present. Our study and another study in this hospital during 2017–2018 [24] also found lower rates of surfactant treatment for preterm neonates < 32 weeks' gestation when compared with the Australian study [23]. The lower surfactant use in Vietnam almost certainly reflects its high cost and more restrictive usage.

Our rate of antenatal corticosteroid administration was high, ranging from 86.5% to 91.9% for babies born at 28–33 weeks, and 62.3% at 34 weeks' gestation. Manuck et al. reported a similar pattern of antenatal corticosteroids administration: 77.5%–93.4% at 28–33 weeks and 39.7% at 34 weeks' gestation [10]. Antenatal corticosteroid administration reduces preterm neonatal morbidity, including respiratory distress syndrome and its administration to women at risk of preterm birth has become routine clinical practice worldwide, including in Vietnam [12]. Consistent with a Cochrane review in 2020, we found antenatal corticosteroid administration was associated with reduced neonatal mortality [12]. The Cochrane review found that using antenatal corticosteroids among women at risk of preterm birth in low-, medium- and high-income settings reduces perinatal and neonatal mortality. Surprisingly, our study found higher rates of neonatal morbidity among mothers who received corticosteroids before 35 weeks' gestation compared with mothers who did not receive corticosteroids. The reason for this is not clear. However, the higher morbidity rate in women administered corticosteroids in our study may reflect a bias by clinicians to administer corticosteroids more frequently to those women they considered to be at greater risk of neonatal morbidity and mortality, with women thought to be a lower risk not given corticosteroids.

The strengths of this study are the large cohort of preterm births and the validity of the data with clearly defined outcome measures. This hospital is one of the largest maternity hospitals in Vietnam and our findings are anticipated to reflect outcomes in similarly sized and resourced maternity hospitals in Vietnam. A limitation of this study is missing information on variables which are not captured in the hospital records. Furthermore, neonatal outcomes in our study were limited to the time of hospital discharge, and morbidities that occurred after neonates were transferred could not be determined.

Our study is the first to determine preterm neonatal mortality and morbidity rates in a Vietnamese population stratified by gestational age and labour onset. Morbidity and mortality rates are high in the early third trimester but are much lower by 36 weeks' gestation. Our study provides obstetric care providers and women at risk of preterm birth in Vietnam with data on the risks associated with early birth, and may guide changes in clinical practice to safely prolong pregnancy when possible.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.