



## RESEARCH ARTICLE

# Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: A population cohort study [version 1; referees: 2 approved with reservations]

Rose McGready <sup>1,2</sup>, Moo Kho Paw<sup>1</sup>, Jacher Wiladphaingern<sup>1</sup>, Aung Myat Min<sup>1</sup>, Verena I. Carrara <sup>1</sup>, Kerry A. Moore<sup>3,4</sup>, Sasithon Pukrittayakamee<sup>5</sup>, François H. Nosten <sup>1,2</sup>

<sup>1</sup>Shoklo Malaria Research Unit, Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Mae Sot, Thailand

<sup>2</sup>Centre for Tropical Medicine and Global health, Nuffield Department of Medicine Research Building, University of Oxford, Oxford, UK

<sup>3</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia

<sup>4</sup>Macfarlane Burnet Institute for Medical Research and Public Health, Melbourne, Australia

<sup>5</sup>Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand

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## Abstract

**Background:** The WHO definition of stillbirth uses 28 weeks' gestation as the cut-point, but also defines extreme preterm birth as 24 to <28 weeks' gestation. This presents a problem with the gestational limit of miscarriage, and hence reporting of stillbirth, preterm birth and neonatal death. The objective of this study is to provide a synopsis of the outcome of a population cohort of pregnancies on the Thailand-Myanmar border between 24 to <28 weeks' gestation.

**Methods:** Records from the Shoklo Malaria Research Unit Antenatal Clinics were reviewed for pregnancy outcomes in the gestational window of 24 to <28 weeks, and each record, including ultrasounds reports, were reviewed to clarify the pregnancy outcome. Pregnancies where there was evidence of fetal demise prior to 24 weeks were classified as miscarriage; those viable at 24 weeks' gestation and born before 28 weeks were coded as births, and further subdivided into live- and stillbirth.

**Results:** Between 1995 and 2015, in a cohort of 49,931 women, 0.6% (318) of outcomes occurred from 24 to <28 weeks' gestation, and 35.8% (114) were miscarriages, with confirmatory ultrasound of fetal demise in 45.4% (49/108). Of pregnancies not ending in miscarriage, 37.7% (77/204) were stillborn and of those born alive, neonatal mortality was 98.3% (115/117). One infant survived past the first year of life. Congenital abnormality rate was 12.0% (23/191). Ultrasound was associated with a greater proportion of pregnancy outcome being coded as birth.

**Conclusion:** In this limited-resource setting, pregnancy outcome from 24 to <28 weeks' gestation included: 0.6% of all outcomes, of which one-third were miscarriages, one-third of births were stillborn and mortality of livebirths

## Open Peer Review

Referee Status: ? ?

Invited Referees		
	1	2
<b>version 2</b> published 19 Jul 2018		
<b>version 1</b> published 23 Dec 2016	 report	 report

1 Halit Pinar, Brown University, USA

2 Shahirose Premji, University of Calgary, Canada

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approached 100%. In the scale-up to preventable newborns deaths, at least initially, greater benefits will be obtained by focusing on the greater number of viable newborns with a gestation of 28 weeks or more.

### Keywords

extreme preterm birth, limited-resource, low-income, marginalized, miscarriage, neonatal death, stillbirth, ultrasound



This article is included in the [Mahidol Oxford Tropical Medicine Research Unit \(MORU\)](#) gateway.

**Corresponding author:** Rose McGready ([rose@shoklo-unit.com](mailto:rose@shoklo-unit.com))

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## Introduction

The lower limit of extreme preterm shifts between and within countries, and tends to be higher in lower resourced settings<sup>1-3</sup>. The World Health Organization (WHO) defines preterm birth (PTB) as any live birth before 37 completed weeks of gestation, which is further subdivided into extreme preterm (<28 weeks), very preterm (28 to <32 weeks) and late preterm (32 to <37 weeks)<sup>4</sup>. Stillbirth also has a WHO definition and refers to a baby born dead from 28 weeks' gestation, but many high income countries (HIC) set the lower limit to 20–24 weeks' gestation<sup>5</sup>. As this lower limit of viability shifts, so does the definition of miscarriage creating a 'grey zone' (Figure 1). These limits of viability are important because they are used to estimate rates of stillbirth and neonatal death<sup>6</sup>.

Most (95%) neonatal deaths occur in low and middle income countries (LMIC), and an estimated 15 million PTB occur each year<sup>4,7</sup>. As the rate of neonatal mortality is on a slower decline than mortality rates for older children, there will continue to be a relative increase in neonatal deaths<sup>8</sup>. Reasons put forth to explain poor progress on reducing neonatal mortality in LMIC include a lack of antenatal care and skilled attendance at birth<sup>9</sup>. It is well known that the day of birth carries the highest risk of dying for mothers and their babies, but the unmet need is stark with two-thirds of approximately 138 million births per year without skilled practitioners<sup>10</sup>. Another factor is the lack of accurate assessment of gestational age, which informs basic obstetric practice in terms of effective preterm labour and stillbirth prevention, including identifying small for gestational age fetuses and appropriate timing of antenatal corticosteroids<sup>11,12</sup>, that make it very difficult to distinguish the important cut-points for definitions related to neonatal death. Without ultrasound, pregnancies with severe congenital abnormality are often carried to viability and these add to the burden of deaths in LMIC that rarely appear now in HIC neonatal mortality rates<sup>13</sup>.

On the Thailand-Myanmar border, *Plasmodium falciparum* malaria was associated with an estimated maternal mortality rate of 1,000 per 100,000 live births, and this has been reduced 6 fold in the past 30 years<sup>14</sup>. Neonatal mortality has fallen more than 4 fold from 49 per 1,000 in 1993–96<sup>15</sup> to 11 per 1,000 in 2011<sup>16</sup>. The definition adhered to for these publications and the work published to date by Shoklo Malaria Research Unit (SMRU) has been the WHO definition of stillbirth with a cut-point for viability set at 28 weeks<sup>5</sup>. The outcomes of pregnancies of 28 weeks or more gestation in this area have been published and are not the focus of this study<sup>12,16,17</sup>. The

aim of this study is to contribute to the sparse body of evidence from limited-resource settings on the outcome of pregnancy at the edge of viability. We describe what a pregnancy outcome in the window of 24 to <28 weeks implies, in terms of viability and mortality at SMRU in a rural and resource poor area.

## Methods

### Setting

SMRU is an operational field based research unit uniquely combining humanitarian work with research of direct relevance to the local population. It is a limited-resource setting working with marginalized populations on the western border of Thailand in the Tak Province. In this area, there are an estimated 140,000 refugees and 200,000 migrants from Myanmar. This interim arrangement exists due to decades of neglect of the health system in Myanmar, which the government is currently trying to address, and the difficulties Myanmar people face in obtaining care in well-functioning facilities in Thailand<sup>18,19</sup>.

Place and attendance at birth has shifted from 75% occurring at home with traditional birth attendants with no formal training in 1986, to more than 90% of births occurring in health facilities with skilled attendants in 2015<sup>17</sup>. SMRU is staffed predominantly by locally trained health care workers for antenatal care and ultrasound<sup>20</sup>, child birth<sup>17,21</sup> and emergencies in adults<sup>22</sup> and neonates<sup>16</sup>. Local medics, midwives and nurses do the majority of the clinical work and expatriate doctors provide staff with 24-hour back up. Over 3,000 women register at SMRU antenatal clinics annually. Most women give birth at one of three SMRU facilities situated on the Thai side of the border, including one based in a refugee camp and two in migrant sites.

The seven signal functions for Basic Emergency Obstetric and Newborn Care, including parental administration of an oxytocic, antibiotics and anticonvulsants, removal of retained products of conception, assisted vaginal birth including breech birth, resuscitation of the newborn using a bag and mask and screened blood transfusions, are provided by local staff. A description of the special care baby unit for neonates has been detailed by Turner *et al.*<sup>16</sup>, but there is no capacity for intubation and assisted ventilation and prohibitive costs limit newborn referrals. Aminophylline is used in place of caffeine for apneas, again due to costs. Local protocols guide care and are regularly updated with trainings on their use by local staff. The protocol for preterm labour recommends dexamethasone (beta-methasone is not available) and nifedipine at a gestation of at least

																								Livebirths																			
																								Extreme PTB 24 to <28				Very PTB 28 to <32				Late PTB 32 to <37				Term ≥37							
Miscarriage																								'Grey zone'				Stillbirth – baby born dead from 28 weeks															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40				
Weeks' gestation																																											

**Figure 1. Cut-points for miscarriage, extreme preterm birth and stillbirth (28 weeks' gestation) and the 'grey zone'.** Extreme preterm birth includes livebirths from 24 weeks' gestation, stillbirth includes babies born dead from 28 weeks, leaving the upper limit of miscarriage in the 'grey' zone. PTB, preterm birth.

28 weeks, with exceptions in some cases that are close to 27 completed weeks. Women who need caesarean section or who have complex medical conditions are transferred by car to Thai hospitals (30 to 75 minutes away) at an average cost of XXXX USD per case.

### Pregnancy ultrasound and fetal viability

Ultrasound scans have been performed by local health workers using various scanners, including Toshiba Powervision 7000, Dynamic Imaging (since 2001), Fukuda Denshi UF 4100, and General Electric Voluson-1. Since 2001 all women have been offered two scans: once at booking to determine viability, number of fetus and gestation, regardless of gestational age but preferably between 8 and 14 weeks; and again at 22 (18–24) weeks to reassess viability, measure fetal biometry and major abnormalities and determine placental location<sup>20</sup>. Ultrasound can be repeated at any time as required. For example, if a woman reported absence of fetal movement, or bleeding, or the fundal height did not increase, an ultrasound could be done to determine viability. Measurement of the fetus at each scan was encouraged. Loss of fetal heart beat could also be an incidental finding when the woman attended for her second scan. Loss of viability with ultrasound could be confirmed by presence of a fetus and absent fetal heartbeat. In some cases, ultrasound confirmed pregnancies persisting to 24 weeks' gestation, but a fetus was never observed, e.g. anovulatory gestation or non-classic gestational trophoblastic disease.

For pregnancies managed before the routine availability of ultrasound, loss of fetal viability was confirmed by symphysis fundal height (SFH) measurements, which were increasing and levelled off, or decreased, complaints of loss of fetal movement or never feeling movement, bleeding episodes or expulsion of products. At antenatal care, pregnant women had SFH routinely checked at each visit until the uterine fundus was first palpable and measurable above the symphysis, then SFH was checked monthly up to 32 weeks' and weekly from 36 weeks' gestation. In case of doubt, urine (sometimes serum) pregnancy testing was available.

### Data extraction and data definitions

All birth records at SMRU are computer based and stored at SMRU head office in Mae Sot. All pregnancy records from 1995 until 2015, in the window period from 24 to <28 weeks' gestation were selected and reviewed individually by the study team. The starting point of 1995 was selected, since the first local guidelines for obstetrics was produced at this time. For each record a series of questions were asked to determine classification as follows:

- Was there evidence of fetal demise before 24 weeks, and if there was, could the gestation of loss be estimated?
- Was there evidence of fetal viability from 24 to <28 weeks' gestation and if there was, did the pregnancy outcome result in a live- or stillborn neonate?
- If the outcome was a liveborn neonate, did it survive and for how long?

Pregnancies that were demised before 24 weeks, but were expelled from 24 to <28 weeks, were classified as miscarriage. Pregnancies that appeared viable from 24 to <28 weeks and delivered a live- or

stillborn neonate were classified as births. Congenital abnormalities were coded using the ICD-10 criteria<sup>23</sup>.

### Statistical analysis

Pregnancies ending from 24 to <28 weeks' gestation were described as the proportion of miscarriage or births. Gestation was not rounded up or down, so that, for example, 24 weeks included women from 24<sup>+0</sup> to 24<sup>+6</sup> weeks, (+6 indicates 6 days). Continuous normally distributed data, such as gestation and birthweight, were described using the mean and standard deviation (SD), and non-parametric data, such as gravidity, were described using median and the interquartile range (IQR). Univariable and multivariable logistic regression was used to assess the association between estimation of gestational age by ultrasound, homebirth and year of birth, and birth outcome (birth rather than miscarriage). Data was analysed using SPSS version 20 (IBM SPSS, Armonk, NY, USA) and Stata version 13 (StatCorp, College Station, TX, USA).

### Ethics statement

Ethical approval for retrospective analysis of pregnancy records was given by the Oxford Tropical Research Ethics Committee (OXTREC 28–09) and after discussion with the local Community Advisory Board (TCAB-4/1/2015)

### Results

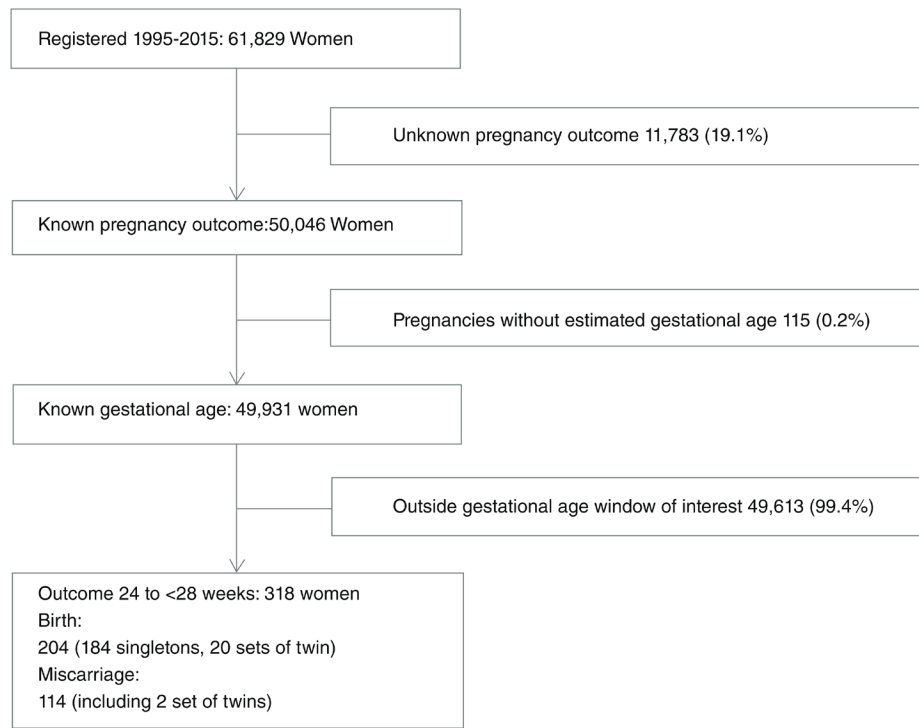
Between 1995 and 2015, the records of 50046 women with a known pregnancy outcome were reviewed by the present study. Only a small proportion, 0.2% (115/50046), of pregnancies could not be assigned a reliable assessment of gestational age (Figure 2). There was also a small proportion, 0.6% (318/49931), of pregnancy outcomes within the gestational window of 24 to <28 weeks (Figure 3), and most of these 67.6% (215/318) were established using obstetric ultrasound dating. The demographic characteristics of these 318 women were summarized (Table 1).

### Miscarriage

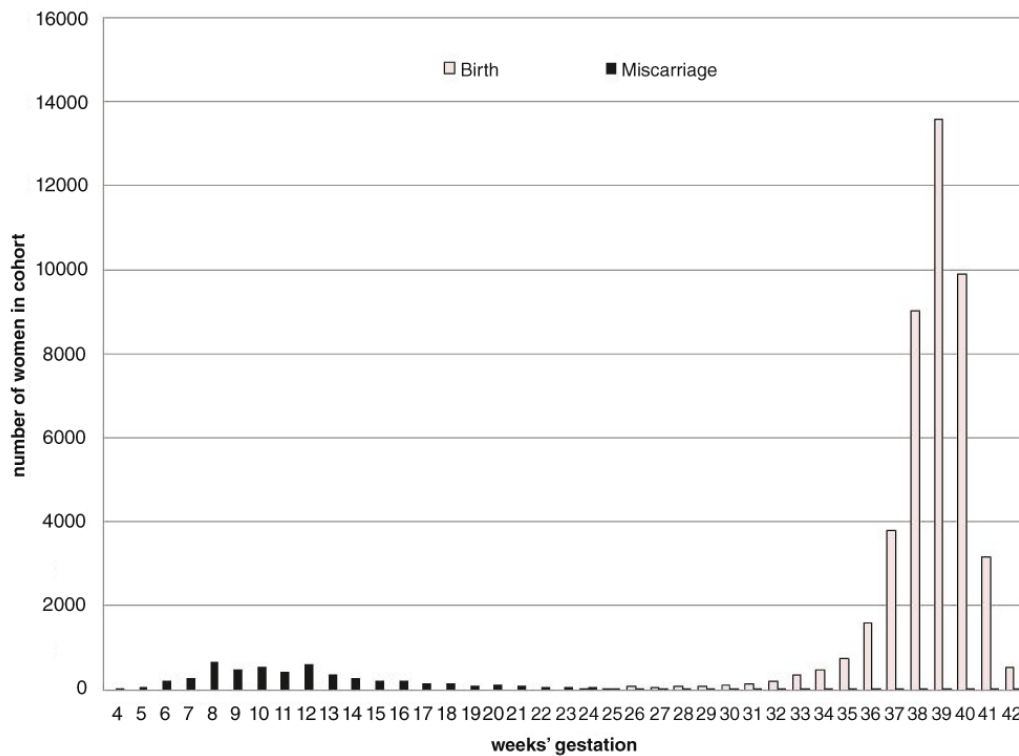
Of the 318 women, 114 (35.8%) women miscarried from 24 to <28 weeks' gestation, two of which were twin pregnancies and three that were molar pregnancies. The proportion of women who miscarried with each gestational age week from 24 through to 27 weeks was highest at 24 weeks: 43.0% (49), 22.8% (26), 15.8% (18), 18.4% (21), respectively. After excluding the molar pregnancies, and three pregnancies where the timing of demise was less than 24 but could not be accurately assigned, fetal demise was confirmed by ultrasound in 45.4% (49/108), and by no increase in the fundal height or complaints about fetal movement in 48.2% (52/108) of miscarriages, with the remaining 6.4% (7) of cases being late outcomes of much earlier pregnancy loss, such as anovulatory pregnancies. The mean±SD (min-max) gestation of ultrasound and non-ultrasound fetal loss was similar: 17<sup>+1</sup>±4<sup>+5</sup> (8<sup>+1</sup> to 23<sup>+6</sup>) and 16<sup>+4</sup>±4<sup>+2</sup> (8<sup>+0</sup> to 23<sup>+6</sup>) in weeks plus days.

### Birth

There were 204 (64.2%) women with a births from 24 to <28 weeks' gestation, of which 90.2% (184/204) were singletons and 9.8% (20/204) were twins. There were 16.2% (33/204), 17.6% (36/204), 35.3% (72/204) and 30.9% (63/204) born at 24, 25, 26,



**Figure 2. Study flow.** Selection of women in the cohort of 24 to < 28 weeks' gestation.



**Figure 3. Histogram of population cohort from 1995–2015 with a known pregnancy outcome (n=49931) across gestation.**

**Table 1. Baseline demographic characteristics of 318 women with pregnancy outcome 24 to <28 weeks' gestation.** Data are mean±SD [range]; median [IQR, range]; or proportion (n). \*Missing data: weight first ANC, weight less than 40 kg at first ANC n=4; BMI and BMI category n=108; anemia at first ANC visit n=18. Abbreviation: ANC, antenatal clinic.

Characteristic	Value
Age, years	27±8 [13–48]
Gravidity, median [IQR, range]	3 [2–5, 1–15]
Parity, median [IQR, range]	2 [0–4, 0–11]
Primigravida, % (n)	24.5 (78)
Grandmultipara (more than 4 births), % (n)	16.7 (53)
Weight first ANC, kg	48±8 [31–81]
Weight less than 40 kg first ANC, n (%)	8.6 (27/314)
BMI, kg/m <sup>2</sup> at first ANC*	21.6±3.3 [13.6–34.2]
Underweight (<18.5), % (n)	13.9 (29)
Normal weight (18.5 to < 23), % (n)	61.0 (127)
Over weight (23 to <27.5), % (n)	19.0 (40)
Obese (≥ 27.5), % (n)	6.2 (13)
Number of ANC consultations, median [IQR, range]	6 [3–12, 1–22]
A total of 4 or more ANC visits, % (n)	59.1 (188)
Anemia at first ANC, % (n)*	13.0 (39/300)
First ANC visit in trimester one (less than 14 weeks), % (n)	50.6 (161)

and 27 weeks, respectively. The gender of the infant was missing for 23.0% (47/204) cases, with the remainder including 58% (91/157) male and 42% (66/157) females.

Amongst the 204 pregnancies, 37.7% (77) were recorded as stillbirths (including first born twin), 57.8% (118) were born alive and in 4.4% (9) this important data was not recorded. Most women birthed vaginally [98.0% (200)] with only 2.0% (4) delivered by caesarean sections. These four cases were in singleton pregnancies, three at 27 weeks and one at 26 weeks, three of whom had placental problems (two placenta praevia and one placental abruption) and one with preterm labour and transverse presentation. These four births all ended in stillbirth with a birth weight reported only in one case (900g).

The birthweight measured in singletons was available for 57.6% (106/184) of neonates. Birth weight was measured on the same day as birth in 104 neonates, and on day 2 and 3 in two neonates born at home. The mean±SD (min-max) birthweight was higher in live-born than stillborn infants: 900±208 (400–1500) and 800±292 (400–1730) g (p=0.140).

Congenital abnormality was not reported for 6.4% (13/204) of newborns. For the remaining cases, 12.0% (23/191) of newborns were reported as congenitally abnormal from ultrasound and

surface examination at birth. Most of these congenital abnormality cases were stillborn [52.2% (12/23)]. The abnormalities by ICD-10 coding are described in [Table 2](#).

Termination of pregnancy involved 7.4% (15/204) of cases in the 24 to <28 weeks' window including: eight for ultrasound confirmed major fetal abnormality; two for life-threatening maternal conditions (both with uncontrollable severe pre-eclampsia); and there were five women that self-induced, including one who was recently widowed.

#### Newborn outcome

Of the 118 livebirths, the fate of one neonate was unknown at one month, 98.3% (115/117) died a neonatal death and 1.7% (2/117) survived the first 28 days. The median [IQR, range] age of neonatal deaths was 1 [1–2, 1–28] day and 80% (92/115) died in the first two days of life, but the majority of neonates died on day one [64.3% (74/115)]. One newborn died at day 33 and the remaining child survived and is still alive at 40 months of age.

The surviving female child was born at 27<sup>+5</sup> weeks, and two ultrasounds, including an early scan at 8 weeks and an agreeable later scan at 18 weeks, assured the gestation. The mother was a 32 year old refugee with a gravidity of two and parity of one, with no history of PTB, who went into spontaneous labour and received



**Table 2. Congenital abnormalities, deformations and chromosomal abnormalities in 23 extreme preterm newborns, according to ICD-10 coding.**<sup>a</sup>multiple abnormalities, enalapril exposure; \*\* also undiagnosed heart murmur.

System	Description	ICD-10 code	n
Central nervous system	anencephaly	Q00.0	4
	encephalocele <sup>a</sup>	Q01	1
	microcephaly	Q02	1
	hydrocephalus	Q03	2
	brain abnormality, unspecified	Q04.9	1
	spina bifida	Q05	2
Cardiovascular	malformation of cardiac chambers, unspecified	Q20.9	1
Eyes, ears, face, neck	cystic hygroma (lymphangioma)	Q87.8	2
Digestive	oesophageal atresia	Q39.9	2
Urinary system	outflow obstruction	Q64.7	1
Musculoskeletal	phocomelia	Q72.2	2
	talipes (home birth, few details)	Q66.4	1
Other	(suspected) Trisomy-21	Q90	1
	severe amniotic bands**	Q89.9	1
	twin to twin transfusion syndrome	Q89.9	1

a single dose of nifedipine and dexamethasone less than one hour before delivery. Delivery was supervised by skilled birth attendants and after a normal vaginal birth of a 890g baby, the Apgar scores were six and seven, at one and five minutes. The neonate was provided with supportive care (with oxygen delivered by nasal prongs) and discharged home after ten weeks at 1061g. This survivor is still being followed up for neurodevelopment, which is so far within the normal range.

### Trends

The trend in the proportion of pregnancy outcomes reported in the obstetric records as miscarriage and birth changed over time with a greater proportion reported as births in later years. Changes in practice within the timeframe 1995–2015 included introduction of ultrasound (late 2001), and increasing proportion of deliveries with skilled birth attendants. In an analysis including these changes, ultrasound remains the only independent predictor of the outcome being reported as birth rather than miscarriage, after controlling for year of birth (Table 3).

### Discussion

This analysis is based on data collected before and after the introduction of ultrasound, with two-thirds of gestations in the cohort confirmed by ultrasound. The results demonstrate an important bias in data from limited-resource settings that may over-estimate perinatal loss because one-third of pregnancies with an outcome from 24 to <28 weeks' gestation were actually miscarriage. Amongst delivered newborns, 12% had a congenital abnormality, one-third

were stillborn, and 97.5% had a neonatal death, of which two-thirds occurred on day one. Of 118 liveborn infants only one female of 27 weeks gestation survived to one year of age. Not only is the outcome of pregnancies of 24 to <28 weeks' gestation in this setting catastrophic, the proportion of pregnancies that are involved, relative to all pregnancies with a known outcome, is very small at 0.6% (Figure 3). The 97.5% neonatal deaths in the 24 to <28 weeks' gestation contrasts sharply to previously reported very preterm (defined as 28 weeks' or more to <34 weeks' gestation) annual deaths from SMRU in 2008 to 2011 of: 42.3% (11/181), 18.9% (7/215), 30.8% (8/268) and 17.6% (3/259), respectively<sup>16</sup>. This information is important as it emphasizes that the benefits that can be obtained for far greater numbers of more viable newborns, at least initially, in the scale-up to preventable newborns deaths<sup>24</sup>, is in those of 28 weeks or more gestation. This is supported by a recent review from a high income setting that suggests extremely premature infants and extremely low birth weight infants (<1000g) remain at considerable risk, with a mortality of 30–50% and morbidity of 20–50% in survivors, regardless of technological advances and child health expertise<sup>25</sup>. Current resources in HIC offer the possibility of survival for extreme PTB, but this diverges significantly from resources in LMIC<sup>3</sup>. Overall, this data supports the WHO definition of 28 weeks to define stillbirths<sup>5</sup>, and in our setting, also to differentiate between miscarriage and birth.

Just over one-third of pregnancy outcomes between 24 to <28 weeks' gestation had ultrasound confirmation of fetal demise prior to 24 weeks' gestation. Without ultrasound the potential for

**Table 3. Associations of pregnancy outcome (birth rather than miscarriage) from 24 to <28 weeks (n=318) and use of ultrasound for estimation of gestational age, home birth and year of birth.** Numbers are odds ratios (95% confidence interval); p-value. Missing data: homebirth (12). \*The association between year of birth and the log odds of birth was linear (p-value for linearity = 0.1636 [all years] and 0.2531 [ $\geq 2001$ ]). \*\* Ultrasound was not introduced at SMRU until 2001, so we repeated our analyses in the sub-set of births occurring from 2001. Abbreviation: OR, Odds Ratio; EGA, estimated gestational age.

Variable	All years		Years $\geq 2001^{**}$	
	Univariable OR	Multivariable OR	Univariable OR	Multivariable OR
<b>EGA by ultrasound</b>	5.41 (3.26, 9.00); <0.001	4.57 (2.27, 9.17); <0.001	6.85 (3.29, 14.27); <0.001	6.52 (2.95, 14.39); <0.001
<b>Homebirth</b>	0.69 (0.42, 1.12); 0.133	1.12 (0.64, 1.98); 0.682	0.90 (0.51, 1.60); 0.719	1.69 (0.83, 3.40); 0.145
<b>Year of birth*</b>	1.11 (1.07, 1.16); <0.001	1.01 (0.95, 1.07); 0.740	1.11 (1.04, 1.19); 0.002	1.07 (0.99, 1.16); 0.067

misclassification of non-viable miscarriages from births is clearly higher and that is demonstrated in the associations with a pregnancy outcome of birth (Table 3) once routine gestational sonography became available. There are many reasons why these late miscarriages occur in this setting including the following: before ultrasound it took time to diagnose no change in fundal height measurements; women were prepared to wait and see what happens even if a fetal death *in-utero* was diagnosed; delayed care seeking behavior, due to reliance on daily wages or moving place of employment for months at a time; reluctance for referral into the nearest Thai hospital for surgical methods of evacuation; difficulty in securing a supply of cheap induction agents; and hoping for fetus papyraceus, which, surprisingly, is culturally fortunate<sup>26</sup>. Amongst delivered women, five, who we were aware of, self-induced, and unsafe abortion has been reported previously in this setting<sup>27,28</sup>.

The rate of congenital abnormality was high at 12%, and identifying congenital abnormality is one of the recommended measures to reduce stillbirth and neonatal deaths<sup>6,29,18</sup>. The rate of stillbirths in this extreme preterm birth window of 52.2% was very high<sup>29</sup>. Within SMRU, rural clinics can provide routine ultrasound by local health workers and SMRU has trained other organizations locally and in Asia to provide gestational age assessment, but not screening for anomalies. This is in part due to the additional workload and higher level of skill required, but local sonographers still recognize gross abnormalities. These cases are brought to the attention of the doctor and can be discussed during a counseling session with the parents. There is no specialist in this setting, so local doctors frequently network internationally for helpful feedback on diagnosis and management of certain conditions. However, these abnormalities remain unreported when the 28 gestation weeks' cut point is used to define a delivered neonate. In this setting improved preconceptual folate uptake is required.

The median number of six antenatal consultations (Table 1) is high for pregnancies ending before 28 weeks' gestation in a limited-resource setting. Ultrasound was routinely available twice

for women before 28 weeks' gestation if they came early enough (50% attended in first trimester) with ultrasound offered at the first antenatal visit, and again at 18–22 weeks. The WHO has recently, for the first time, recommended one ultrasound scan before 24 weeks of gestation as a standard part of antenatal care<sup>19</sup>. In the same document, the basic ANC model, which included four ANC visits recommended in 2002<sup>30,31</sup>, was finally amended to at least eight 'contacts' to improve a woman's experience of care<sup>19</sup>. SMRU has never used or promoted the ANC basic model of four visits, mostly because only frequent (preferably weekly) contacts were previously shown to reduce maternal death from malaria in an area where chemoprevention failed, due to multidrug resistant *P.falciparum*<sup>14,32</sup> malaria.

A recent review suggests that significant inequality exists not just in the burden of PTB for LMICS compared to HIC but also in the research agenda for progress on preterm birth prevention<sup>33</sup>. There is a recent plethora of publications such as *The Lancet* Every Newborn series (<http://www.thelancet.com/series/everynewborn>) and PLoS collections on Maternal Health (<http://collections.plos.org/s/maternal-health>) directed towards improvements needed in LIC on reporting and reducing stillbirth, PTB and neonatal death. While HIC are racing ahead on issues relating to sophisticated technology for screening and prenatal testing of embryonic and fetal tissue, LIC struggle to provide sufficient human resources and clinical services for basic antenatal services and care in childbirth<sup>10</sup>. Even registration of births is incomplete in many LIC and limited-resource settings<sup>34</sup> and dating pregnancies reliably a particularly challenging issue<sup>35</sup>. On the Thailand-Myanmar border, routine antenatal care has integrated basic ultrasound delivered by local sonographers and this has been highly acceptable to women<sup>36</sup>. Efforts have been directed towards having local staff skilled in routine gestational age scanning<sup>20</sup>, in child birth<sup>17</sup>, and in newborn care<sup>16</sup>. This has permitted us to define outcomes in the gestational window of 24 to <28 weeks as a miscarriage or a birth of a live- or stillborn infant bearing in mind the data is not perfect and some records had limited information available. Improvement of pregnancy outcome



from 24 to <28 weeks is not currently feasible or affordable, and current limited-resources will continue to be directed to use the threshold of 28 weeks or more to define birth. Nevertheless gestation and viability, best confirmed by ultrasound, are important to establish in practice in limited-resource settings to make effective use of affordable interventions, such as corticosteroids and nifedipine, for preterm labour<sup>37</sup>.

In conclusion, the window of gestation from 24 to <28 weeks involves a small proportion of pregnancy outcomes overall and is associated with nearly 100% mortality of newborns in this limited-resource setting. The distinction between miscarriage and delivery could be a source of bias in newborn data from low-income countries from 24 to <28 weeks' gestation. Limited-resource settings are required to make pragmatic decisions; the scale-up to reducing preventable newborn deaths will see greater benefits from directing efforts towards newborns with a gestation of 28 weeks or more.

### Data availability

Data have been de-identified and the dataset is available in SPSS along with syntax file: doi, [10.5287/bodleian:ke7voeBaY38](https://doi.org/10.5287/bodleian:ke7voeBaY38) (<https://ora.ox.ac.uk/objects/uuid:5927da59-bac8-4e8f-aeab-7b21falc7d30>).

### Author contributions

RM, VC and KM conceived the study. RM, VC and KM designed the data extraction. RM, MKP, JW, AMY, VC, KM, SP and FN carried out the research. RM, KM, VC and FN prepared the first draft of the manuscript. MKP, HW and SP contributed to the data design and preparation of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

### Competing interests

No competing interests were disclosed.

### Grant information

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*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

### Acknowledgments

This research would not have been possible without the staff of SMRU and pregnant women who came to the clinics at this difficult gestation, and we take this opportunity to thank them for their participation.

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# Open Peer Review

Current Referee Status: ? ?

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## Version 1

Referee Report 13 March 2017

doi:[10.21956/wellcomeopenres.11154.r20881](https://doi.org/10.21956/wellcomeopenres.11154.r20881)



**Shahirose Premji**

Faculty of Nursing, University of Calgary, Calgary, Canada

Thank you for the opportunity of reviewing this manuscript entitled “Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: a population cohort study.” The work done is impressive and has the potential to provide insight in how we: (a) view and manage the ‘grey zone’ in low resource setting, (b) support mothers and their families who present for care when in this ‘grey zone’, and (c) should allocate the limited resources in reducing neonatal mortality in low resource setting.

### Title

The title is very long and needs to be shortened. Moreover, it needs to better capture the findings of the study.

### Abstract

Introduction: Clearly define WHO and study definitions – this is critical to understanding the study results. Objective: Associations were also examined (page 4) which is not captured here. Methods: a more comprehensive description is required. Results: please share the statistics related to the association found. Conclusion: bold and very relevant!

### Article Content:

#### Introduction

The definition of stillbirth, miscarriage, preterm birth, and neonatal death has been identified as problematic given overlaps in gestational cut-points. Hence, it is imperative that these terms be defined at the outset so that there is conceptual clarity both with respect to variables being examined and the intended purpose of the study. This would also help with interpretation of findings.

There are discrepancies with respect to the definition of miscarriage in the introduction and methodology (e.g., bottom of page 4). Moreover, issues are highlighted about accuracy of gestational assessment, lack of ultrasound diagnosis of congenital abnormality which further impacts definitions of terms particularly with inclusion of data before 2001. It is therefore not clear what the study hopes to accomplish by examining pregnancy outcomes between 24 to < 28 weeks’ gestational age over a 20 year period.

The second paragraph: the information pertaining to preterm births, neonatal deaths, and rationale for the high rates seems misplaced. Explain the relevance of the information shared to the aims of the study. Furthermore, explain the consequence(s) of poor reporting of stillbirth and neonatal deaths.

The third paragraph: relevance of statistics related to mortality secondary to malaria is not clear.

The introduction should more clearly articulate the conceptual approach (i.e., operationalize definitions), explain the rationale of the study, and situate information related to preterm birth, neonatal deaths, maternal mortality within the context of study aims.

## **Methodology**

### **Data extraction and data definition**

Data were reviewed from 1995 to 2015 which is problematic as care patterns have changed significantly in this time frame (details shared in second and third paragraph). For example, the authors explain that there has been a shift from home birth to hospital births and improvement in care during the antenatal period. These changes are likely to reduce fetal mortality, as well as maternal and neonatal mortality. Thus, it is not clear why this time span was used for the purpose of this study. Moreover, ultrasound was introduced in 2001 which means that accurate assessment of gestational age may be an issue prior to this time. Ultrasound has also changed the way in which loss of fetal viability was confirmed (e.g., fundal height measurements). Given the intent to describe viability and mortality in the window of 24 to <28 weeks' gestational age it is important to have consistency in the way definitions are operationalized throughout the course of the study.

Data Quality – birth records are computer based; however is initial data recorded on paper and then transferred to the computer system? Please comment on the accuracy of data and strategies employed in ensuring quality data. Based on the results it appears that there are potential issues with data quality as in 4.4% of the 204 pregnancies between 24 and < 28 weeks' gestational age there was missing data; birth weight data was available for 57.6% of neonates. This is a limitation and your discussion should explain how this impacts interpretation of findings.

Ultrasound assessment – was this done by one person? If multiple assessors please comment on inter-rater reliability of ultrasound dating.

Page 4 – please indicate the actual average of transporting women by car to the Thai hospital. Is this a potential limitation of the study?

### **Statistical analysis**

“Univariable and multivariable logistic regression was used to assess the association between estimation of gestational age by ultrasound, homebirth and year of birth, and birth outcome (birth rather than miscarriage).” A better description needs to be provided about the analytic plan and how it relates to the objectives of the study. The analytic plan should identify how variable were identified to be important to include in the multivariable logistic regression analysis. How were variables entered in the multivariable logistic regression analysis? Explain the rationale for the decision(s). It appears that the outcome of interest is birth however only 57.8% of these were live birth. What outcome was used? Furthermore, only one infant survived. What is the minimal sample size required for your multivariable regression analysis?

## **Results**

Pregnancy outcomes were unknown for 19.1% of the registered women – what was the issue? Only 50.6% of the women had their first antenatal care visit in trimester one which has implications for accuracy of gestational dating using ultrasound (most accurate in the first trimester).

The inclusion of termination of pregnancy is confusing particularly since two were for maternal conditions

at 24 and < 28 weeks' gestation which in high income countries would be managed by inducing labour.

Table 1 – Characteristic age, years – please indicate what the data represents (as you do for other variables).

Figure 2 – study flow diagram can be expanded to more clearly display outcomes including stillbirths, live births, and survival.

Figure 3 – Can be removed as I don't think it provides any additional information.

### Discussion

The results do not demonstrate the bias detailed in the opening paragraph. Is there an opportunity here to compare historical cohorts (before introduction of ultrasound and after introduction of ultrasound)?

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Referee Report 15 February 2017

doi:[10.21956/wellcomeopenres.11154.r20244](https://doi.org/10.21956/wellcomeopenres.11154.r20244)



**Halit Pinar**

Warren Alpert Medical School, Brown University, Providence, RI, USA

The study titled 'Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: a population cohort study' is a well thought out and interesting study and has a lot of potential to be better and more useful to the reader.

The following are some points I am hoping will be useful in the authors' efforts to improve the manuscript.

### Recommendation 1:

The main objectives of the study are not clear. If it is challenging the definition (or lack thereof) of the miscarriages and its overlap with extreme premature deliveries, please say so more clearly. Obviously, this overlap is very confusing and just to demonstrate the conceptual difficulties one faces when trying to analyze a data set like this, is a worthy cause.

Spend more time with these conceptual inconsistencies so the readers who are not familiar with these concepts will have a better understanding of your objectives and results.

### Recommendation 2:

Third paragraph in the Introduction:

The background information given is interesting but very short. In addition, it is not clear what purpose it serves in the general context of the manuscript. Recommendation: It would be ideal to provide more

detailed information that is pertinent to the etiology of maternal diseases, miscarriages, stillbirth etc. in that region to help the reader to better understand the characteristics of the patient population.

**Recommendation 3:**

It appears there is a discrepancy between the definition of miscarriages at the end of the first paragraph of page 4 and the definition given under the header of miscarriage in the second column.

The first definition: When a fetus dies <24 weeks but is delivered between 24-28 weeks.

The second definition is used in the first sentence just under the subtitle of 'miscarriage': 114 women out of 318 women miscarried from 24<28 weeks' gestation and the distribution is given according to the gestational age. In this section it appears that for a fetus to be called he/she does not have to die<24 weeks and be delivered after 28 weeks. In addition, in our experience it not very common for the mother to keep the dead fetus for two or more weeks (in this case up to 4 weeks).

**Recommendation 4:**

Second column on page 6. The correct term for 'surface' examination is 'external' examination.

**Recommendation 5:**

I would recommend exclusion of terminations. That adds more confusion to the calculations and it is considered a very different group.

**Question 1:**

The true consequence of using different GA for the definition of fetal death/stillborn vs miscarriage (except causing confusion) is not clear.

**Question 2:**

Since you have the numbers, what happens if you analyze the data where a pregnancy loss up to 20 weeks gestational age will be classified as a miscarriage and any delivery  $\geq 20$  weeks is classified either as a liveborn or stillborn?

**Competing Interests:** No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 04 Jul 2018

**Rose McGready**, Tropical Medicine Division, Shoklo Malaria Research Unit, Thailand

**Halit Pinar**, Warren Alpert Medical School, Brown University, Providence, RI, USA

**Approved with Reservations**

**The study titled 'Miscarriage, stillbirth and neonatal mortality in the extreme preterm birth window of gestation in a limited-resource setting on the Thailand-Myanmar border: a**



**population cohort study' is a well thought out and interesting study and has a lot of potential to be better and more useful to the reader.**

Agree with potential to be better.

**The following are some points I am hoping will be useful in the authors' efforts to improve the manuscript.**

#### **Recommendation 1:**

**The main objectives of the study are not clear. If it is challenging the definition (or lack thereof) of the miscarriages and its overlap with extreme premature deliveries, please say so more clearly. Obviously, this overlap is very confusing and just to demonstrate the conceptual difficulties one faces when trying to analyze a data set like this, is a worthy cause.**

Thank you for your patience with the manuscript – we are trying to articulate i.e. that this window (22 to <28 weeks) can include miscarriage, a large proportion.

**Spend more time with these conceptual inconsistencies so the readers who are not familiar with these concepts will have a better understanding of your objectives and results.**

We agree that we did not succeed to give clarity on the main objective. We have rephrased the entire manuscript. The aim of this study is to contribute to the sparse body of evidence from limited resource settings that support the use of the 28 weeks' gestational age cut-point for stillbirth. We also argue for the usefulness of <28 weeks' gestational age to define miscarriage.

#### **Recommendation 2:**

**Third paragraph in the Introduction:**

**The background information given is interesting but very short. In addition, it is not clear what purpose it serves in the general context of the manuscript. Recommendation: It would be ideal to provide more detailed information that is pertinent to the etiology of maternal diseases, miscarriages, stillbirth etc. in that region to help the reader to better understand the characteristics of the patient population.**

Thank you for this comment – the introduction has been rewritten to address this point and Recommendation 1.

#### **Recommendation 3:**

**It appears there is a discrepancy between the definition of miscarriages at the end of the first paragraph of page 4 and the definition given under the header of miscarriage in the second column.**

**The first definition: When a fetus dies <24 weeks but is delivered between 24-28 weeks.**

**The second definition is used in the first sentence just under the subtitle of 'miscarriage': 114 women out of 318 women miscarried from 24<28 weeks' gestation and the distribution is given according to the gestational age. In this section it appears that for a fetus to be called he/she does not have to die <24 weeks and be delivered after 28 weeks.**

The definitions have been laid out more clearly. For this analysis the definitions of miscarriage is absence of viability before 22 weeks but delivery in the 22 to <28 week window and extreme preterm birth is presence of viability and delivery at 22 to <28 weeks.

**In addition, in our experience it not very common for the mother to keep the dead fetus for two or more weeks (in this case up to 4 weeks).**

This is a very helpful comment and it is exactly what we want to highlight for an in issue relevant to low resource settings. We have an average of 6 weeks before expulsion.

We suspect this must be a source of confusion in other low resource settings as these types of pregnancy outcomes are hard to document without a reliable method of measuring pregnancy viability e.g. ultrasound or multiple.

We are also trying to highlight that the experience in low resource settings may not match the bulk of published evidence available.

**Recommendation 4:**

**Second column on page 6. The correct term for 'surface' examination is 'external' examination.**

Amended as suggested

**Recommendation 5:**

**I would recommend exclusion of terminations. That adds more confusion to the calculations and it is considered a very different group.**

Amended as suggested

**Question 1:**

**The true consequence of using different GA for the definition of fetal death/stillborn vs miscarriage (except causing confusion) is not clear.**

We have spent more time to explain this in the introduction.

The practice of obstetrics in resource limited settings is not as efficient. Miscarriage can occur at 22-28 weeks (the window of extreme preterm birth) and in the setting described in this manuscript where significant effort has been placed on assessment of gestational age, we present data to prove that point. The WHO definition of 28 week cut-point that defines a stillbirth is attractive and pragmatic for low resource settings.

**Question 2:**

**Since you have the numbers, what happens if you analyze the data where a pregnancy loss up to 20 weeks gestational age will be classified as a miscarriage and any delivery  $\geq 20$  weeks is classified either as a liveborn or stillborn?**

We have gone back to the records to classify outcomes from 22 to  $<28$  weeks gestation as miscarriage, livebirth, stillbirth, neonatal mortality. The records of 20 and 21 weeks start to have too much missing data to contribute reliably to the argument.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above. Competing Interests:** No competing interests were disclosed.  
Close

**Competing Interests:** No competing interests were disclosed.