BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023004
Article Type:	Research
Date Submitted by the Author:	20-Mar-2018
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Keywords:	Preterm Birth, Neonatal Mortality, Neonatal Morbidity, Trend, United States

Temporal trends in neonatal mortality and morbidity following spontaneous and iatrogenic preterm birth: a population-based study

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Word count: Abstract 300; Text 3456.
Funding statement: This work was supported by a Canadian Institutes of Health Research Team grant in severe maternal morbidity (MAH-115445).
Competing interests statement: None declared.
Authors' contribution statement: SL and LR designed the study, LR and SL performed data analysis, and LR and SL wrote the first draft of the manuscript. GM, JT, AS and KL contributed to the interpretation of the results and critically revised the first draft. LR, SL, GM, JT, AS and KL approved the final version of the manuscript.
Ethics approval: All analyses were performed on publicly accessible de-identified data. An exemption from ethics approval was granted by the Department of Social and Health Services, State of Washington.
Data sharing statement: Analyses were based on administrative data collected and maintained by the Department of Health, State of Washington. The availability of the data is restricted. Permission for data access can granted after verification of the research goals by the Department of Social and Health Services, State of Washington.
Acknowledgements: SL is supported by a Michael Smith Foundation for Health Research Scholar Award. JT is supported by the Investigator Grant Award Program from British Columbia Children's Hospital Research Institute. GMM is supported by a Vanier Canada Graduate Scholarship.
Abbreviations: PPROM preterm premature rupture of membranes, AOR adjusted odds ratio, CI confidence interval.
Key words: Preterm Birth, Neonatal Mortality, Neonatal Morbidity, Trend, United States

ABSTRACT

Objective: After a decade of increase, the preterm birth (PTB) rate has declined with the largest decline at late preterm (34-36 weeks). We aimed to describe concomitant changes in gestational age-specific rates of neonatal mortality and morbidity following iatrogenic and spontaneous PTB.

Design, Setting, and Participants: This retrospective population-based study included 754,763 singleton births in Washington State, U.S.A., 2004-2013, using data from birth certificates and hospitalization records. PTB subtypes included iatrogenic delivery (labor induction and cesarean delivery without labor), preterm premature rupture of membranes (PPROM), and spontaneous onset of labor.

Outcome Measures: The composite outcome was defined as death or any severe neonatal morbidity (bronchopulmonary dysplasia, intraventricular hemorrhage, etc.; identified by ICD-9-CM codes). The Cochran-Armitage test was used to assess temporal trends in the outcome at gestational ages (GA) 24-27, 28-31, 32-33, and 34-36 weeks. Logistic regression yielded adjusted odds ratios per 1-year change in outcome (AOR) and 95% confidence intervals (CI).

Results: The rate of PTB following PPROM and spontaneous labor declined, while iatrogenic PTB increased (all $p<0.01$). Overall neonatal mortality remained unchanged (1.3%), though GA-specific iatrogenic PTB mortality varied, with a decline at 32-33 weeks (AOR 0.85, CI 0.74-0.97), and increase at 34-36 weeks (AOR 1.10, CI 1.01-1.20). The overall rate of the composite outcome increased (7.9% to 11.9%). Among late preterm infants, combined mortality or severe morbidity increased following PPROM (AOR 1.13, CI 1.08-1.18), spontaneous labor (AOR 1.09, CI 1.06-1.13), and iatrogenic delivery (AOR 1.10, CI 1.07-1.13). Neonatal sepsis rates increased among all preterm infants (AOR 1.09, CI 1.08-1.11).

Conclusions: The temporal decline in late PTB is a favorable trend with respect to prevention of PTB. However, these changes were associated with increased mortality among iatrogenic late preterm infants and increased combined mortality or severe morbidity among all late preterm infants, mainly due to increased sepsis rates.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large population-based database with detailed demographic and clinical information which allowed adjustment for temporal changes in many known risk factors for preterm birth
- Major clinical preterm birth subtypes were identified and subsequent neonatal outcomes were described by gestational age categories to provide clinically-relevant information
- Data on pregnancy and birth outcomes were collected and coded consistently over the study period
- Clinical details on severity of some neonatal morbidities including necrotizing enterocolitis and retinopathy of prematurity were not available
- Coding for neonatal sepsis did not differentiate between sepsis confirmed by blood or cerebrospinal fluid culture and a clinical diagnosis of sepsis without microbiological confirmation, or between early-onset and late-onset sepsis

INTRODUCTION

Preterm birth, defined as birth before 37 weeks' gestation, is the leading cause of neonatal mortality and morbidity, and a major risk factor for long-term neurological and respiratory morbidity and neurodevelopmental impairment.[1-3] In the United States, the rate of preterm birth increased by 24% between 1990 and 2006, from 10.6 to 13.1 per 100 live births,[4] mainly due to an increase in obstetric intervention at late preterm (34-36 weeks' gestation).[5,6] More recently, preterm birth rates declined to 9.8 per 100 live births in the United States in 2016.[7,8] Nevertheless, the high rate of preterm birth remains a considerable concern.

Preterm birth can result from many possible etiologies.[9] The three major clinical subtypes of preterm birth include: iatrogenic (medically-indicated) preterm birth, preterm birth following preterm premature rupture of membranes (PPROM), and preterm birth following spontaneous labor with intact membranes.[1,9] Iatrogenic preterm birth, including labor induction and cesarean delivery without labor, constitutes about 30-40% of all preterm births, and pre-eclampsia/eclampsia and severe intrauterine growth restriction are the common indications.[9-11] Spontaneous preterm birth can result from multiple causes, including infection or inflammation, incompetent cervix, vascular/placental disorders (other than preeclampsia), and uterine over-distension.[9]

While gestational age at birth is the strongest predictor of adverse neonatal outcomes,[2] the subtype of preterm birth is also important. Preterm infants born to women with spontaneous onset of labor have a better prognosis than infants born following PPROM or iatrogenic intervention.[5,12-16] However, it is unknown whether the temporal decline in preterm birth is associated with changes in neonatal mortality and morbidity among preterm infants, including those born spontaneously and iatrogenically.

Our aim was to describe temporal trends in gestational age-specific rates of neonatal mortality and a composite adverse outcome, defined as neonatal death or any severe morbidity, among preterm infants born following PPROM, spontaneous onset of labor and iatrogenic delivery. We further examined gestational age-specific rates in the specific neonatal morbidity components included in the composite outcome.

METHODS

Study Population

We carried out a population-based study including all singleton hospital births to mothers aged 15 to 60 years in Washington State, U.S.A, between January 1, 2004, and December 31, 2013. We used information from two linked population databases: (1) live birth, fetal and infant death certificates with data on maternal demographic characteristics, obstetric history, and pregnancy and birth factors, from the Birth Events Record Database (BERD); and (2) hospitalization files with information on specific infant morbidities from the Comprehensive Hospital Abstract Reporting System (CHARS). The BERD included information abstracted by trained abstractors using standardized forms about maternal characteristics (e.g., maternal age, pre-pregnancy body mass index [BMI], race, education, marital status, smoking status, chronic hypertension, pre-pregnancy diabetes, and the type of health care insurance provider); obstetric history (e.g., parity, assisted conception); and pregnancy, labor, and birth characteristics (e.g., gestational age at delivery, use of tocolytics, use of steroids at delivery, mode of delivery, prolonged labor, congenital anomalies, neonatal death and birth outcomes). The CHARS database included information on all newborn hospitalizations in Washington State with diagnosis and procedure codes related to each hospitalization episode coded by the International Classification of

Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The completeness and accuracy of these databases was monitored by the Washington State Department of Health with annual assessments and consistency checks.[17-19] Previous validation studies of the linked dataset showed that the positive and negative predictive values for delivery characteristics were above 80% and 98%, respectively.[20,21] Gestational age at delivery was based on ultrasound dating, and last menstrual period dating was used for women with missing ultrasound data. We excluded infants born at less than 24 weeks' and greater than 45 weeks' gestation, and those with missing data on gestational age. We further excluded stillborn infants and those with missing mode of delivery for analyses of neonatal outcomes following preterm birth.

Classification of Preterm Birth

Preterm birth was defined as live birth at 24 to 36 weeks' gestation. Preterm birth subtypes were categorized as follows: (1) spontaneous preterm births following PPROM (>12 hours); (2) medically-indicated iatrogenic preterm births following labor induction or cesarean delivery without labor; and (3) all others as spontaneous preterm births following spontaneous labor onset with intact membranes.

Outcome Measures and Covariates

The primary outcomes were neonatal mortality and a composite adverse outcome including death and any severe neonatal morbidity. Neonatal mortality was defined as death of an infant that occurred within the first 28 days after birth, including deaths in the delivery room, in-hospital deaths, and deaths after hospital discharge. Severe neonatal morbidity was identified using ICD-9-CM codes and included (a) bronchopulmonary dysplasia (BPD); (b) intraventricular

hemorrhage grade ≥3 (IVH); (c) periventricular leukomalacia (PVL); (d) retinopathy of prematurity (ROP); (e) necrotizing enterocolitis (NEC), (f) neonatal sepsis; (g) convulsions of newborn; and (h) severe birth trauma (Appendix Table 1).

Temporal changes in maternal characteristics over the study period were examined, including maternal age (<20, 20-29, 30-39, 40+ years); pre-pregnancy BMI (underweight <18.5 kg/m^2, normal BMI 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, and obese ≥30 kg/m^2); race (non-Hispanic White, African American, Native American, Hispanic, and other); maternal education (≤8 years vs. >8 years); smoking during pregnancy (yes/no); marital status (married/common law vs. other); parity (prior live births, yes/no); chronic hypertension (yes/no); pre-pregnancy diabetes (yes/no); assisted conception (yes/no); use of steroids (yes/no); use of tocolytics (yes/no); and type of health insurance coverage (Medicaid, self-pay, private, other). We also examined temporal trends in infant characteristics including gestational ages in completed weeks (within gestational age categories), small-for-gestational age infant (SGA, <10th percentile; yes/no), infant's sex (male/female), congenital anomalies, and stillbirths. Congenital anomalies were identified from BERD and included the following conditions observed within first 24 hours after birth: anencephaly, meningomyelocele or spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction, cleft lip, cleft palate, Down syndrome, chromosomal disorders, and hypospadias. Stillbirth was defined as spontaneous intrauterine death of a fetus. Gestational age-specific rates of stillbirths were calculated using the fetuses-at-risk (FAR) approach.[22] Under this approach, ongoing pregnancies (fetuses in-utero) at each gestation were used as denominators (the appropriate at-risk population) for the calculation of gestational age-specific stillbirth rates.[22,23]

Statistical Analyses

The preterm birth rate was calculated as a proportion of live births at 24 to 36 weeks' gestation among infants born alive at ≥24 weeks. Gestational age-specific temporal trends were described as proportions of extremely preterm births (24-27 weeks), very preterm (28-31 weeks), moderately preterm (32-33 weeks), and late preterm births (34-36 weeks). The Cochran-Armitage test was used to assess the statistical significance of temporal trends over the years. The rates of neonatal mortality and the composite outcome of neonatal death or severe morbidity were also contrasted between years 2004-2006 vs. 2011-13, using rate differences (RD) and 95% confidence intervals (CI).

Logistic regression was used to assess temporal trends in adverse neonatal outcomes adjusted for temporal changes in maternal age, pre-pregnancy BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies. Calendar year was modelled as a continuous variable. Temporal trends in adverse outcomes were expressed as the average annual change in the odds of neonatal mortality and combined neonatal death or severe neonatal morbidity with adjusted odds ratios (AOR) and 95% CI.

Additional analyses

Temporal trends in the individual components of the composite outcome were examined as secondary outcomes using logistic regression models as described above. These analyses were performed including all preterm live born infants, and also for subgroups of infants born at late preterm, at 28-33 weeks, and at 24-27 weeks' gestation.

All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). Missing values for BMI (approximately 10%) were imputed using multiple imputation (PROC MI). Other missing values were <3% of the total, and these records were not included in the multivariable analyses. All analyses were performed on publicly accessible de-identified data. An exemption from ethics approval was granted by the Department of Social and Health Services, State of Washington.

RESULTS

Study Population

Overall, 871 649 singleton births occurred in Washington State from 2004 to 2013. We excluded births at <24 or >45 weeks' gestation, multiple births, births that occurred outside of Washington State and out-of-hospital births, as well as births that could not be matched with hospital records (N=116 886, 13.4%). The study population included 754 763 singleton infants born in hospital at ≥24 weeks; of these, 2 549 infants were stillborn (0.34%). Further, births with missing information on mode of delivery (N=14 503, 1.9%) were excluded for analyses of preterm birth rates by type of delivery (live births included 737 711 infants; Appendix Figure 1).

The rate of stillbirth increased slightly from 3.2 per 1000 fetuses-at-risk (FAR) in 2004-2006 to 3.7 per 1000 FAR in 2011-2013 (p=0.002). Stillbirth rates increased at 24-27 weeks (from 0.7 to 1.0 per 1000 FAR, p=0.003), and at 28-31 weeks' gestation (from 0.4 to 0.7 per 1000 FAR, p=0.002; Table 1).

Maternal characteristics changed over the study period; women who delivered in 2011-2013 were older, more educated, and had higher pre-pregnancy BMI than those who gave birth in 2004-2006 (Table 1). The proportions of births to mothers of Hispanic and African American

origin, unmarried mothers, and nulliparous mothers increased, while the proportions of mothers who smoked during pregnancy decreased over time. More mothers had chronic hypertension or pre-pregnancy diabetes, and more pregnancies occurred from assisted conception in 2011-2013 then in 2004-2006. The use of antenatal steroids for lung maturation at delivery increased over the study period, while the use of tocolytics declined. All temporal changes were statistically significant (p<0.001, Table 1).

Table 1. Changes in maternal and infant characteristics among live born or stillborn singleton infants (≥24 weeks' gestation), Washington State, U.S.A., 2004-2013.

Characteristics	**N (%) by period**			**p-value***
	2004-2006	**2007-2010**	**2011-2013**	
Total births	219 233	310 101	225 429	
Maternal age				
<20 years	18 454 (8.4)	24 985 (8.1)	13 603 (6.0)	**<0.001**
20-29	114 244 (52.1)	161 041 (51.9)	112 427 (49.9)	**<0.001**
30-39	80 300 (36.6)	115 004 (37.1)	92 175 (40.9)	**<0.001**
≥40	6 235 (2.8)	9 071 (2.9)	7 224 (3.2)	**<0.001**
Maternal BMI (kg/m^2)				
Underweight (<18.5)	6 467 (3.0)	8 619 (2.8)	6 477 (2.9)	**<0.001**
Normal (18.5-24.9)	91 968 (42.0)	135 270 (43.6)	97 451 (43.2)	**<0.001**
Overweight (25-29.9)	47 444 (21.6)	74 137 (23.9)	55 439 (24.6)	**<0.001**
Obese (≥30)	41 138 (18.8)	67 336 (21.7)	53 556 (23.8)	**<0.001**
Missing values	21 216 (14.7)	24 739 (8.0)	12 506 (5.6)	**<0.001**
Maternal race				
Non-Hispanic White	143 356 (65.4)	195 980 (63.2)	141 132 (62.6)	**<0.001**
African American	8 964 (4.1)	14 050 (4.5)	11 098 (4.9)	**<0.001**
Native American	4 503 (2.1)	6 194 (2.0)	4 265 (1.9)	**<0.001**
Hispanic	40 603 (18.5)	60 889 (19.6)	42 543 (18.9)	**0.004**
Other	20 558 (9.4)	31 814 (10.3)	25 266 (11.2)	**<0.001**
Maternal education (≤ 8	9 958 (4.5)	11 439 (3.7)	6 334 (2.8)	**<0.001**

years)				
Smoking during pregnancy	22 073 (10.1)	30 434 (9.8)	20 339 (9.0)	**<0.001**
Unmarried	69 033 (31.5)	106 787 (34.4)	77 143 (34.2)	**<0.001**
No prior live births	88 552 (40.4)	129 513 (41.8)	92 232 (40.9)	**<0.001**
Chronic hypertension	2 650 (1.2)	4 017 (1.3)	3 002 (1.3)	**<0.001**
Pre-pregnancy diabetes	1 367 (0.6)	2 350 (0.8)	1 755 (0.8)	**<0.001**
Assisted conception	1 551 (0.7)	2 849 (0.9)	2 487 (1.1)	**<0.001**
Use of tocolytics	3 754 (1.7)	6 018 (1.9)	2 840 (1.3)	**<0.001**
Steroids use	1 761 (0.8)	3 386 (1.1)	2 541 (1.1)	**<0.001**
24-33 weeks delivery	726/3617 (20.1)	1 517/5331 (28.5)	1 215/4259 (28.5)	**<0.001**
34-36 weeks delivery	546/12808 (4.3)	976/16895 (5.8)	711/12072 (5.9)	**<0.001**
Type of health insurance				
Medicaid	83 608 (38.1)	122 929 (39.6)	91 829 (40.7)	**<0.001**
Self-Pay	2 100 (1.0)	2 708 (0.9)	2 561 (1.1)	**<0.001**
Private	109 452 (49.9)	162 128 (52.3)	115 198 (51.1)	**<0.001**
Other**	13 375 (6.1)	17 112 (5.5)	12 013 (5.3)	**<0.001**
Gestational age				
24-27 weeks	678 (0.3)	997 (0.3)	820 (0.4)	**0.002**
28-31	1 299 (0.6)	1 830 (0.6)	1 520 (0.7)	**0.002**
32-33	1 640 (0.8)	2504 (0.8)	1 919 (0.9)	**<0.001**
34-36	12 808 (5.8)	16 895 (5.4)	12 072 (5.4)	**<0.001**
37+	202 808 (92.5)	287 875 (92.8)	209 098 (92.8)	**<0.001**
SGA infant (<10th percentile)	1 767 (11.5)	2 701 (12.8)	2 122 (13.6)	**<0.001**
Infant sex (male)	112 128 (51.2)	158 291 (51.0)	116 049 (51.5)	**0.026**
Congenital anomalies***	996 (0.5)	1 527 (0.5)	1 133 (0.5)	0.105
Stillbirths [N, per 1000 FAR]				
24-27 weeks	149 (0.7)	224 (0.7)	219 (1.0)	**0.003**
28-31	97 (0.4)	185 (0.6)	152 (0.7)	**0.002**
32-33	77 (0.4)	97 (0.3)	61 (0.3)	0.331
34-36	137 (0.6)	194 (0.6)	160 (0.7)	0.381

≥37	23 (1.1)	323 (1.1)	243 (1.2)	0.659
All (24-45)	691 (3.2)	1023 (3.3)	835 (3.7)	**0.002**
Preterm live births by subtype [N, % by GA category]				
24-27 weeks	489	746	598	**0.002**
PPROM	181 (37.0)	198 (26.5)	130 (21.7)	**<0.001**
Spontaneous labor	135 (27.6)	208 (27.9)	189 (31.6)	0.098
Iatrogenic delivery	173 (35.4)	340 (45.6)	279 (46.7)	**<0.001**
28-31	1 135	1 603	1 357	**0.002**
PPROM	295 (26.0)	350 (21.8)	264 (19.5)	**<0.001**
Spontaneous labor	357 (31.5)	482 (30.1)	416 (30.7)	0.998
Iatrogenic delivery	483 (42.6)	771 (48.1)	677 (49.9)	**<0.001**
32-33	1 469	2 347	1 848	**<0.001**
PPROM	383 (26.1)	495 (21.1)	410 (22.2)	**<0.001**
Spontaneous labor	530 (36.1)	809 (34.5)	649 (35.1)	0.679
Iatrogenic delivery	556 (37.8)	1 043 (44.4)	789 (42.7)	**<0.001**
34-36	12 249	16 352	11 821	**<0.001**
PPROM	1 912 (15.6)	2 224 (13.6)	1 673 (14.2)	**0.018**
Spontaneous labor	5 770 (47.1)	7 673 (46.9)	5 530 (46.8)	0.261
Iatrogenic delivery	4 567 (37.3)	6 455 (39.5)	4 618 (39.1)	**0.004**
All (24-36)	15 342	21 048	15 624	**<0.001**
PPROM	2 771 (18.1)	3 267 (15.5)	2 477 (15.9)	**<0.001**
Spontaneous labor	6 792 (44.3)	9 172 (43.6)	6 784 (43.4)	**<0.001**
Iatrogenic delivery	5 779 (37.7)	8 609 (40.9)	6 363 (40.7)	**0.009**

BMI, pre-pregnancy body mass index; FAR, fetuses-at-risk; GA, gestational age; SGA denotes small-for-gestational-age.

Bolded value indicates statistical significance at $p<0.05$

* p-value for temporal trend over all study years (the Cochran-Armitage test)

** Other medical insurance includes other government insurance, student insurance, Indian Health Care, and other programs.

*** Includes the following conditions observed within first 24 hours after birth: anencephaly, meningomyelocele or spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction, cleft lip, cleft palate, Down syndrome, chromosomal disorders, and hypospadias.

Note: Some percentages do not add up due to missing values; missing values <3% are not shown.

Preterm Birth Rates

There were 737 711 singleton live births between 2004 and 2013; out of these, 52 014 infants were born preterm (7.1%). Among the preterm infants, 16.4% were born following PPROM, 43.7% were born following spontaneous onset of labor, and 39.9% were born following iatrogenic delivery. The overall preterm birth rate declined from 7.3% in 2004-2006 to 7.0% of singleton live births in 2011-2013. This decline was attributed to the decline in spontaneous delivery following PPROM (1.3% to 1.1%), and spontaneous onset of labor (3.2% to 3.0%). In contrast, iatrogenic preterm birth increased slightly from 2.7% to 2.9%. All temporal trends were statistically significant ($p<0.01$, Figure 1).

Gestational age-specific trends in the type of preterm birth varied (Figure 2). There were 1 833 live births at 24-27 weeks (0.2%); of these 27.8% were PPROM, 29.0% were spontaneous onset of labor, and 43.2% were iatrogenic delivery. At 28-31 weeks, there were 4 095 live births (0.6%); 22.3% were PPROM, 30.6% were spontaneous onset of labor, and 47.2% were iatrogenic. At 32-33 weeks, there were 5 664 live births (0.8%); 22.7% were PPROM, 35.1% were spontaneous onset of labor, and 42.2% were iatrogenic. At 34-36 weeks, there were 40,422 live births (5.5%); 14.4% were PPROM, 46.9% were spontaneous onset of labor, and 38.7% were iatrogenic. The overall preterm birth rate increased in all gestational age categories except for late preterm births where the rate declined from 5.8% to 5.3% (all $p<0.01$). In each gestational age category, the iatrogenic preterm birth rate increased, and the PPROM preterm birth rate declined over time (all $p<0.05$).

Neonatal Mortality

Neonatal mortality remained unchanged over time (1.3%, Table 2). Neonatal mortality increased among late preterm infants between 2004-06 and 2011-13 (RD 1.9 per 1000 infants, 95% CI 0.2-3.6 per 1000; average change per year AOR was 1.064, 95% CI 1.003-1.129). Overall, higher neonatal mortality was among infants delivered following PPROM (1.7%) and iatrogenic delivery (1.6%) as compared with spontaneous delivery (0.8%).

A significant decline in mortality was observed among infants born following iatrogenic delivery at 32-33 weeks, from 2.5% in 2004-2006 to 1.0% in 2011-2013 (AOR 0.85, 95% CI 0.74-0.97; Table 3). In contrast, neonatal mortality increased from 0.5% to 0.8% (AOR 1.10, 95% CI 1.01-1.20) among infants following iatrogenic delivery at 34-36 weeks.

Table 2. Gestational age-specific rates of adverse neonatal outcomes among singleton preterm infants, Washington State, U.S.A., 2004-2013.

Outcome and gestational age category	Rates per 100 live births			Adjusted odds ratio per 1-year change† (95% CI)
	N (Rate)		Rate difference (95% CI)	
	2004-2006	2011-2013		
Neonatal death				
24-27 weeks	76 (15.5)	85 (14.2)	-1.33 (-5.59, 2.93)	0.97 (0.92-1.03)
28-31	55 (4.9)	40 (3.0)	-1.90 (-3.44, -0.36)	0.95 (0.89-1.01)
32-33	23 (1.6)	18 (1.0)	-0.59 (-1.37, 0.19)	0.93 (0.84-1.02)
34-36	43 (0.4)	64 (0.5)	**+0.19 (0.02, 0.36)**	**1.06 (1.00-1.13)**
All (24-36)	197 (1.3)	207 (1.3)	+0.04 (-0.21, 0.29)	0.99 (0.95-1.02)
Neonatal death/ severe morbidity				
24-27 weeks	353 (72.2)	429 (71.7)	-0.45 (-5.82, 4.92)	1.00 (0.96-1.04)
28-31	383 (33.7)	496 (36.6)	+2.81 (-0.95, 6.57)	**1.03 (1.00-1.06)**
32-33	166 (11.3)	302 (16.3)	**+5.04 (2.70, 7.38)**	**1.05 (1.02-1.08)**
34-36	307 (2.5)	639 (5.4)	**+2.90 (2.41, 3.39)**	**1.10 (1.08-1.12)**

All (24-36)	1 209 (7.9)	1 866 (11.9)	**+4.06 (3.40, 4.73)**	**1.06 (1.05-1.08)**

CI, confidence interval; severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.
Adjusted odds ratios express the average annual change in the odds of the outcome
Bolded value indicates statistical significance at $p<0.05$
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Table 3. Gestational age-specific rates of neonatal death by subtype of preterm birth, Washington State, U.S.A., 2004-2013.

Gestational age category and preterm birth subtype	**Neonatal death** [N (per 100 live births)]			**Adjusted odds ratio per 1-year change† (95% CI)**
	2004-2006	**2007-2010**	**2011-2013**	
24-27 weeks				
PPROM	27 (14.9)	30 (15.2)	18 (13.9)	1.05 (0.94-1.17)
Spontaneous labor	21 (15.6)	34 (16.4)	26 (13.8)	0.95 (0.86-1.06)
Iatrogenic delivery	28 (16.2)	47 (13.8)	41 (14.7)	0.94 (0.86-1.03)
28-31 weeks				
PPROM	14 (4.8)	13 (3.7)	5 (1.9)	0.92 (0.78-1.07)
Spontaneous labor	11 (3.1)	15 (3.1)	9 (2.2)	0.91 (0.77-1.06)
Iatrogenic delivery	30 (6.2)	22 (2.9)	26 (3.8)	0.96 (0.88-1.06)
32-33 weeks				
PPROM	2 (0.5)	2 (0.4)	5 (1.2)	1.08 (0.80-1.45)
Spontaneous labor	7 (1.3)	12 (1.5)	5 (0.8)	0.97 (0.83-1.13)
Iatrogenic delivery	14 (2.5)	16 (1.5)	8 (1.0)	**0.85 (0.74-0.97)**
34-36 weeks				
PPROM	14 (0.7)	11 (0.5)	7 (0.4)	0.97 (0.84-1.12)
Spontaneous labor	7 (0.1)	23 (0.3)	22 (0.4)	1.08 (0.96-1.20)
Iatrogenic delivery	22 (0.5)	33 (0.5)	35 (0.8)	**1.10 (1.01-1.20)**
All (24-36 weeks)				
PPROM	57 (2.1)	56 (1.7)	35 (1.4)	1.00 (0.93-1.07)
Spontaneous labor	46 (0.7)	84 (0.9)	62 (0.9)	0.98 (0.92-1.04)

Iatrogenic delivery	94 (1.6)	118 (1.4)	110 (1.7)	0.98 (0.94-1.03)

PPROM, preterm premature rupture of membranes; CI, confidence interval
Adjusted odds ratios express the average annual change in the odds of neonatal death
Bolded value indicates statistical significance at $p<0.05$
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies

Composite outcome: Neonatal Mortality or Severe Morbidity

The rate of combined mortality or severe morbidity increased from 7.9% in 2004-2006 to 11.9% in 2011-2013 (AOR 1.06, 95% CI 1.05-1.08; Table 2). This increase was predominately due to an increase in combined mortality or severe morbidity among infants born at 32-33 weeks and 34-36 weeks' gestation (RD 5.04, 95% CI 2.70-7.38, and RD 2.90, 95% CI 2.41-3.39, respectively, both $p<0.001$); the relative average increase in combined neonatal mortality or severe morbidity was 5% per year among infants born at 32-33 weeks (AOR 1.05, 95% CI 1.02-1.08), and 10% per year among infants born at 34-36 weeks (AOR 1.10, 95% CI 1.08-1.12).

The rate of composite neonatal mortality or severe morbidity increased in each preterm birth subtype (all $p<0.001$, Table 4). The rate was highest among infants born following PPROM (14.8%), and these infants had the largest relative increase (10% per year) in combined mortality or severe morbidity over the study period (AOR 1.10, 95% CI 1.07-1.13). Gestational age-specific analyses of trends in combined neonatal mortality or severe morbidity showed an increase in rates among infants born at 34-36 weeks (in all types of preterm birth), and increases in rates among infants born following PPROM at 32-33 weeks (AOR 1.12, 95% CI 1.06-1.19) and at 28-31 weeks (AOR 1.07, 95% CI 1.02-1.13). In addition, a significant increase in combined neonatal mortality or severe morbidity was observed among infants born following spontaneous onset of labor at 24-27 weeks' gestation. In contrast, iatrogenic delivery at 24-27

weeks was associated with a decline in the rate of composite adverse outcome (AOR 0.93, 95% CI 0.87-0.99).

Table 4. Gestational age-specific rates of neonatal death/severe morbidity by subtype of preterm birth, Washington State, U.S.A., 2004-2013.

Gestational age category and preterm birth subtype	**Neonatal death/severe morbidity** [N (per 100 live births)]			**Adjusted odds ratio per 1-year change† (95% CI)**
	2004-2006	**2007-2010**	**2011-2013**	
24-27 weeks				
PPROM	133 (73.5)	149 (75.4)	98 (75.4)	1.01 (0.94-1.10)
Spontaneous labor	89 (65.9)	149 (71.6)	142 (75.1)	**1.09 (1.01-1.17)**
Iatrogenic delivery	131 (75.7)	242 (71.2)	189 (67.7)	**0.93 (0.87-0.99)**
28-31 weeks				
PPROM	101 (34.2)	120 (34.3)	112 (42.4)	**1.07 (1.02-1.13)**
Spontaneous labor	112 (31.4)	147 (30.5)	144 (34.6)	1.02 (0.98-1.08)
Iatrogenic delivery	170 (35.2)	259 (33.6)	240 (35.5)	1.02 (0.98-1.06)
32-33 weeks				
PPROM	42 (11.0)	79 (16.0)	90 (22.0)	**1.12 (1.06-1.19)**
Spontaneous labor	60 (11.3)	138 (17.1)	87 (13.4)	1.01 (0.96-1.07)
Iatrogenic delivery	64 (11.5)	161 (15.4)	125 (15.8)	1.04 (0.99-1.08)
34-36 weeks				
PPROM	67 (3.5)	140 (6.3)	129 (7.7)	**1.13 (1.08-1.18)**
Spontaneous labor	111 (1.9)	300 (3.9)	245 (4.4)	**1.09 (1.06-1.13)**
Iatrogenic delivery	129 (2.8)	350 (5.4)	265 (5.7)	**1.10 (1.07-1.13)**
All (24-36 weeks)				
PPROM	343 (12.4)	488 (14.9)	429 (17.3)	**1.10 (1.07-1.13)**
Spontaneous labor	372 (5.5)	734 (8.0)	618 (9.1)	**1.06 (1.04-1.09)**
Iatrogenic delivery	494 (8.6)	1012 (11.8)	819 (12.9)	**1.05 (1.03-1.07)**

PPROM, preterm premature rupture of membranes; CI, confidence interval, severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.

Adjusted odds ratios express the average annual change in the odds of neonatal death and/or morbidity

Bolded value indicates statistical significance at p<0.05
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies

Additional analyses

The most prominent temporal trend in the rates of specific severe neonatal morbidities was an increase in the rate of neonatal sepsis, from 4.5% in 2004-06 to 8.5% in 2011-2013 (AOR 1.09, 95% CI 1.08-1.11). The rate of sepsis increased substantially among late preterm infants from 1.7% to 4.5% (AOR 1.12, 95% CI 1.10-1.14), infants born at 28-33 weeks (AOR 1.07, 95% CI 1.05-1.10), and those born at 24-27 weeks (AOR 1.05, 95% CI 1.01-1.09). In contrast, the rate of BPD among preterm infants decreased from 2.0% to 1.7% (AOR 0.95, 95% CI 0.93-0.98; Appendix Table 2), mainly in infants born at 28-33 weeks (AOR 0. 93, 95% CI 0.89-0.97).

DISCUSSION

Our findings show a decline in the preterm birth rate in Washington State between 2004 and 2013 that was predominately due to a decline in spontaneous preterm birth (PPROM and spontaneous preterm labor), while iatrogenic preterm deliveries increased slightly. These changes were associated with increased mortality among late preterm infants born following iatrogenic delivery and increased rates of the composite outcome of neonatal mortality or severe morbidity among all late preterm infants. The rise in neonatal morbidity was driven mainly by the increase in the rate of neonatal sepsis.

After a large increase in the preterm birth rate in the United States in the early 2000s, a decline was observed from 12.8% in 2006 to 9.8% in 2016.[4-8] A recent study by Gyamfi-Bannerman *et al*. showed a decline in both iatrogenic and spontaneous preterm birth rates

between 2005 and 2012.[10] Our study provides more detailed information on preterm birth categories and describes temporal trends in neonatal outcomes adjusted for changes in important risk factors.

Obstetric interventions, changes in practice patterns, and implementation of specific evidence-based guidelines for high-risk women may be reasons behind the decline in preterm birth following spontaneous onset of labor. The use of 17 α-hydroxyprogesterone caproate (17P) and cerclage for women with previous spontaneous preterm births, and the use of vaginal progesterone for select women with short cervical length and without prior preterm birth progressively increased between 2006 and 2013 and may have led to a decline in spontaneous preterm births.[6,24-28] More aggressive pursuit of expectant management in PPROM, preeclampsia and intrauterine growth restriction may have led to a delivery at later gestation in high-risk mothers.[29-31] Other changes including declines in births to teenage mothers and multiple births may have contributed to an overall decline in the preterm birth rate, while increases in maternal age, obesity, and assisted conception have likely contributed to an increase in iatrogenic delivery in general.[32-35]

In 1999 and 2009, the American College of Obstetrics and Gynecologists (ACOG) advocated against elective deliveries under 39 weeks of gestation in an effort to prevent non-medically-indicated preterm births and the potentially avoidable morbidity associated with these deliveries.[36,37] Previous studies have shown that timely medically-indicated iatrogenic delivery can prevent stillbirth and reduce neonatal mortality.[23,38,39] A population-based study of all births in the United States showed that the 68% increase in iatrogenic preterm births between 1995 and 2005 was not associated with increased rates of neonatal mortality/morbidity.[5] In our study, the small increase in iatrogenic interventions was associated with reduced mortality at 32-33 weeks

and reduced mortality/severe morbidity at 24-27 weeks. However, at late preterm, declines in spontaneous and PPROM birth and increases in iatrogenic delivery were associated with increased mortality/severe morbidity.

The increase in neonatal sepsis was observed in all subtypes of late preterm birth, which points to possible common causes relatively independent of delivery type. The unfavorable trends in adverse neonatal outcomes in our study warrant further investigation, as past trends in the rate of clinical sepsis (defined broadly as 'other infection specific to neonatal period') in the first 3 months after birth showed a small decline between 1988 and 2006 among preterm infants in the U.S.A.[40] The reasons behind the increased rates of sepsis in our study may include temporal changes in the proportion of vulnerable infants, increased use of antenatal steroids, or changes in antibiotic use and antibiotic resistance.[40,41] Currently, there is lack of clinical diagnostic criteria or ideal laboratory marker for neonatal sepsis with excellent sensitivity for daily clinical operations, rendering the assessment of variation in the incidence rates of neonatal sepsis difficult.[41-43] Antibiotics are essential in the treatment of bacterial sepsis, and are the most commonly used medications in neonatal intensive units; however, overly liberal antimicrobial use has been associated with increased adverse neonatal outcomes.[44] A large population study in California showed substantial variations in antibiotic use that was not related to proven infection, NEC, surgical case volume, or Neonatal Intensive Care Unit (NICU) mortality, especially among community and intermediate NICUs.[44]

The strengths of our study include a large population-based database with detailed information on demographic and clinical risk factors (e.g., BMI, assisted conception) and obstetric history (e.g., parity, prior adverse outcomes). We were, therefore, able to adjust for temporal changes in a large spectrum of known risk factors for preterm birth. Data on pregnancy

and birth outcomes were collected consistently over the study period, and neonatal morbidity was also coded consistently using exclusively ICD-9-CM during the entire study period. The ICD-9-CM code for neonatal sepsis did not change over the study period, and there was no indication of any major changes in clinical diagnostic criteria.

This study has a few limitations. First, clinical details on severity of some neonatal morbidity were not available, for example, the NEC Stage I or ROP Grade I, both of which can be treated conservatively. This led to the inclusion of infants with less severe NEC and ROP or other components of the composite outcome. Second, the ICD-9-CM code for neonatal sepsis did not differentiate between sepsis confirmed by blood or cerebrospinal fluid culture and a clinical diagnosis of sepsis without microbiological confirmation, or between early-onset and late-onset sepsis. This could lead to over-diagnosis of neonatal infection. Third, information on iatrogenic termination of pregnancy was not available, thus we could not account for these temporal changes. However, the vast majority of iatrogenic pregnancy terminations would be included as stillbirths in this study. Fourth, potential errors and omissions are inevitable in large databases; these may have led to non-differential misclassification, which may have resulted in the underestimation of temporal trends. Fifth, the data sources had detailed information on mode of delivery that allowed accurate categorization of preterm birth subtypes; however, this categorization may have overestimated the proportion of deliveries following PPROM.[45] Lastly, a relatively large number of temporal trends were assessed, possibly rendering some trends statistically significant due to chance.

CONCLUSION

Our objectives were to assess temporal trends in gestational age-specific rates of neonatal mortality and a composite outcome of neonatal mortality/severe morbidity among preterm infants. The small decline in the preterm birth rate in Washington State from 2004 to 2013 was predominantly due to a decline in the rates of spontaneous onset of labor and PPROM at late preterm. This was associated with increased neonatal mortality among late preterm infants born iatrogenically, and increased composite outcome including neonatal death or severe morbidity among all late preterm infants. The increase in adverse neonatal outcomes among late preterm infants and increase in sepsis rates among all preterm infants warrant further investigation. Our findings serve as hypothesis generating for further research and are important for identifying areas for improvement in obstetric and neonatal health care.

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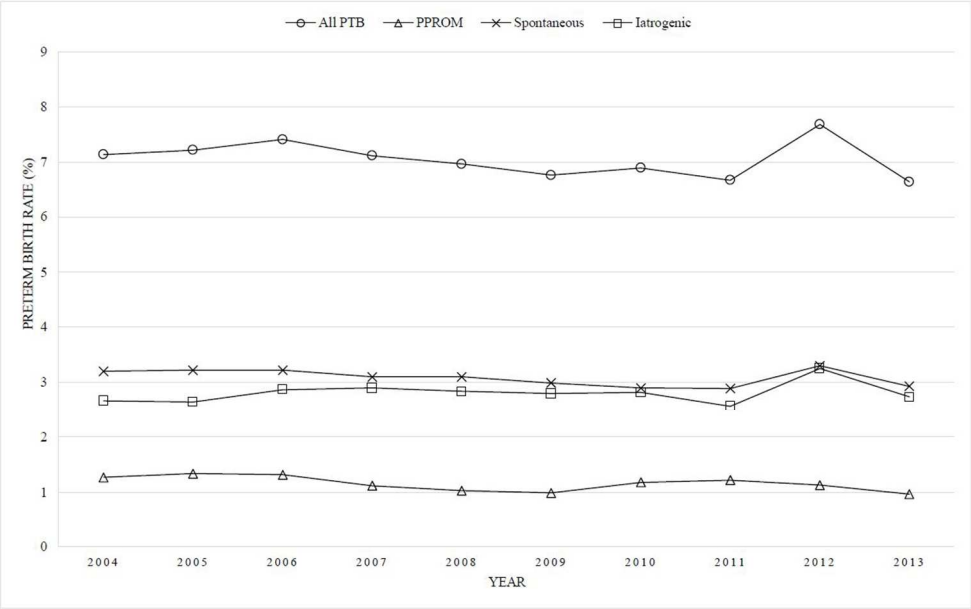


Figure 1. Temporal trends in the rates of singleton preterm birth following PPROM, spontaneous labor and iatrogenic delivery, Washington State, U.S.A., 2004-2013.

225x143mm (144 x 144 DPI)

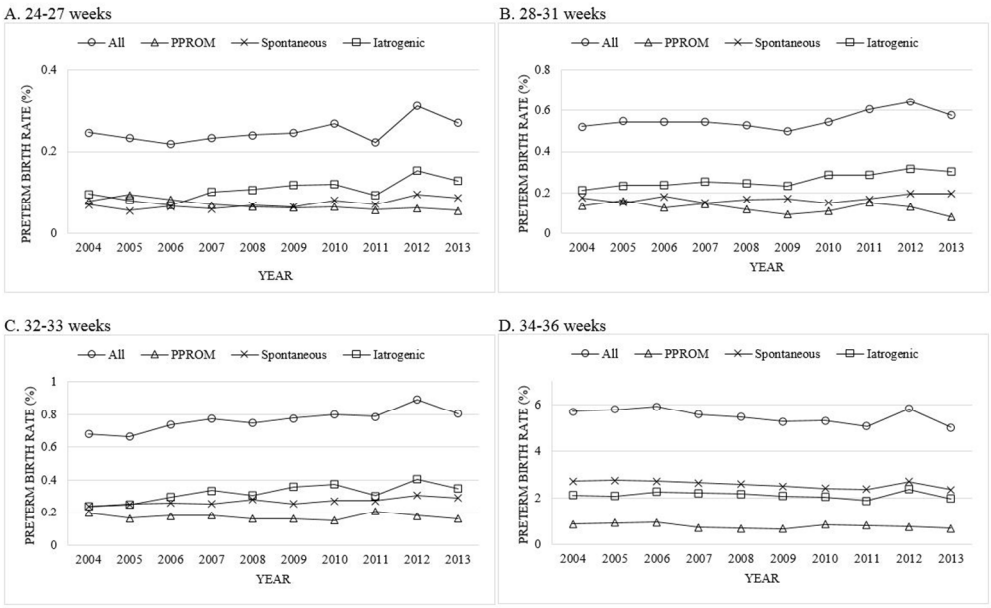


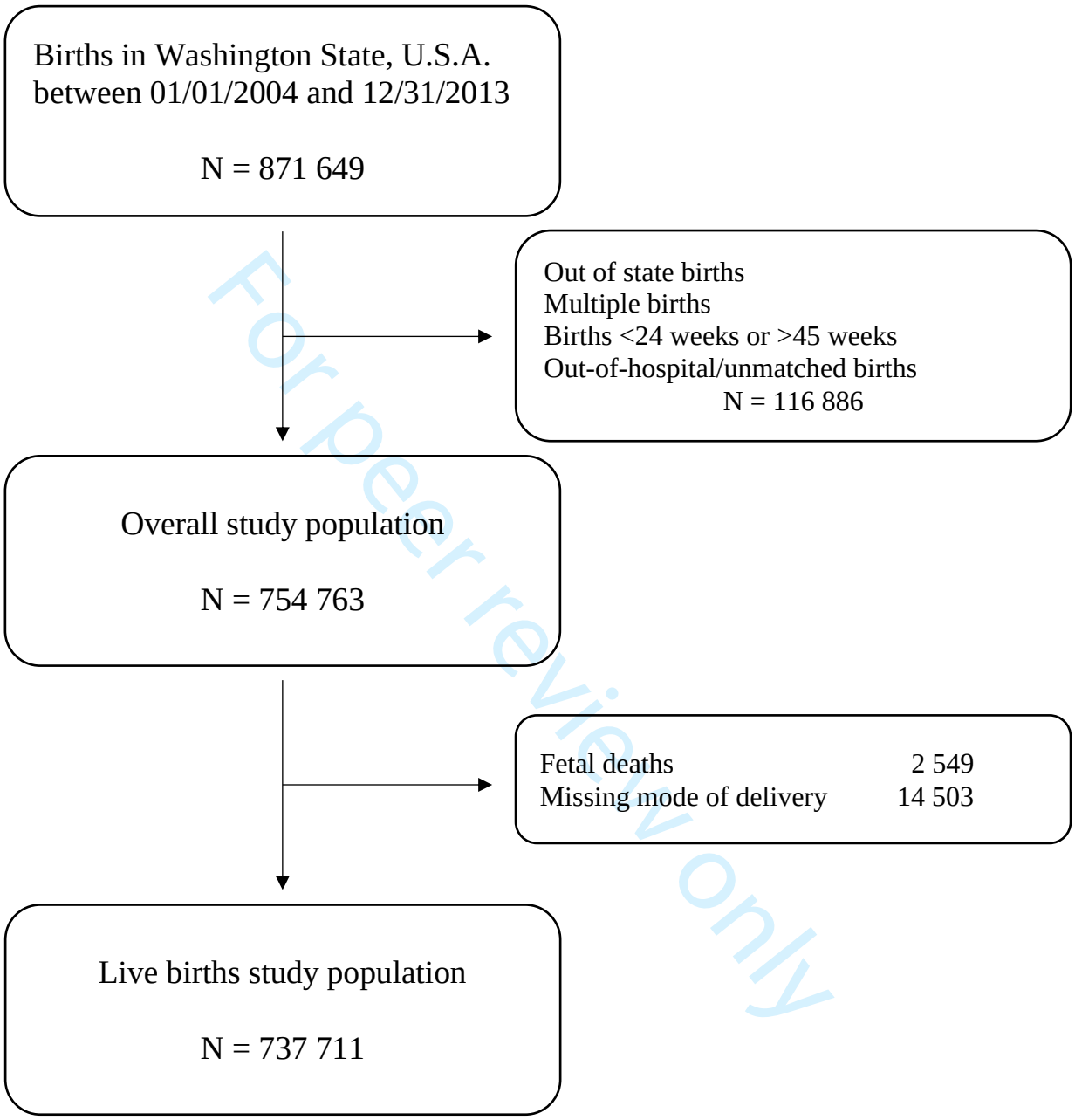
Figure 2. Temporal trends in gestational-age specific preterm birth rates following PPROM, spontaneous labor and iatrogenic delivery, Washington State, U.S.A., 2004-2013.

207x128mm (144 x 144 DPI)

Appendix Table 1. Severe neonatal morbidity components and ICD-9-CM codes.

Neonatal morbidity	ICD-9-CM code
Bronchopulmonary dysplasia	770.7
Intraventricular hemorrhage	
Grade III – bleeding with enlargement of ventricle	772.13
Grade IV – bleeding into cerebral cortex	772.14
Periventricular leukomalacia	779.7
Retinopathy of prematurity	362.2
Necrotizing enterocolitis	777.5
Sepsis	
Septicemia of newborn	771.81
Convulsions	
Fits in newborn; seizures in newborn	779.0
Severe birth trauma	
Subdural and cerebral hemorrhage (whether described as due to birth trauma or to intrapartum anoxia or hypoxia; subdural hematoma (localized); tentorial tear	767.0
Epicranial subaponeurotic hemorrhage (massive); subgaleal hemorrhage	767.11
Injury to spine and spinal cord including:	767.4
Dislocation of spine or spinal cord due to birth trauma	
Fracture of spine or spinal cord due to birth trauma	
Laceration of spine or spinal cord due to birth trauma	
Rupture of spine or spinal cord due to birth trauma	

Appendix Figure 1. Study population flow chart, Washington State, U.S.A., 2004-2013.



Appendix Table 2. Temporal trends in gestational-specific rates of severe neonatal morbidity components, Washington State, U.S.A., 2004-2013.

Neonatal Morbidity	Rates of Outcome by Period [N (per 100 live births)]		Adjusted Odds Ratio† (95% CI)
	2004-2006	2011-2013	
All PTB (24-36 weeks)			
BPD	306 (2.0)	269 (1.7)	**0.95 (0.93-0.98)**
IVH (grade ≥3)	72 (0.5)	61 (0.4)	**0.95 (0.90-1.00)**
PVL	13 (0.1)	27 (0.2)	1.10 (1.00-1.22)
ROP	60 (0.4)	86 (0.6)	1.02 (0.98-1.07)
NEC	129 (0.8)	173 (1.1)	1.02 (0.99-1.06)
Sepsis	686 (4.5)	1 331 (8.5)	**1.09 (1.08-1.11)**
Convulsions	53 (0.4)	62 (0.4)	1.00 (0.94-1.04)
Severe birth trauma	29 (0.2)	26 (0.2)	0.96 (0.89-1.04)
Late PTB (34-36 weeks)			
BPD	6 (0.1)	4 (0.0)	0.96 (0.81-1.12)
IVH (grade ≥3)	3 (0.0)	3 (0.0)	0.97 (0.78-1.21)
PVL	0 (0.0)	0 (0.0)	1.05 (0.64-1.72)
ROP	0 (0.0)	2 (0.0)	1.56 (0.85-2.87)
NEC	16 (0.1)	21 (0.2)	1.04 (0.95-1.14)
Sepsis	211 (1.7)	530 (4.5)	**1.12 (1.10-1.14)**
Convulsions	26 (0.2)	28 (0.2)	1.01 (0.93-1.09)
Severe birth trauma	16 (0.1)	14 (0.1)	0.97 (0.87-1.08)
PTB at 28-33 weeks			
BPD	121 (4.7)	95 (3.0)	**0.93 (0.89-0.97)**
IVH (grade ≥3)	24 (0.9)	19 (0.6)	0.92 (0.84-1.01)
PVL	8 (0.3)	15 (0.5)	1.06 (0.93-1.21)
ROP	35 (1.3)	63 (2.0)	1.05 (0.99-1.11)
NEC	76 (2.9)	89 (2.8)	1.00 (0.95-1.05)
Sepsis	306 (11.8)	554 (17.3)	**1.07 (1.05-1.10)**
Convulsions	19 (0.7)	20 (0.6)	0.96 (0.87-1.05)
Severe birth trauma	9 (0.4)	9 (0.3)	0.95 (0.82-1.11)
PTB at 24-27 weeks			

BPD	179 (36.6)	170 (28.4)	0.97 (0.94-1.01)
IVH (grade ≥3)	45 (9.2)	39 (6.5)	0.95 (0.88-1.01)
PVL	5 (1.0)	12 (2.0)	1.13 (0.96-1.32)
ROP	25 (5.1)	21 (3.5)	0.95 (0.87-1.02)
NEC	37 (7.6)	63 (10.5)	1.04 (0.98-1.10)
Sepsis	169 (34.6)	247 (41.3)	**1.05 (1.01-1.09)**
Convulsions	8 (1.6)	14 (2.3)	1.02 (0.91-1.14)
Severe birth trauma	4 (0.8)	3 (0.5)	0.94 (0.76-1.15)

CI, confidence interval; PTB, preterm birth; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.
Adjusted odds ratios express the average annual change in the odds for each morbidity.
Bolded value indicates statistical significance at $p<0.05$
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies. NOTE: some covariates were excluded from the regression models due to collinearity.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract **a population-based study; title page**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **This was done; abstract, page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **This was done, page 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **This was done, page 5**
Methods		
Study design	4	Present key elements of study design early in the paper **This was done, page 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **This was done, page 5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **This was done, page 5-6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **This was done, page 6-7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **This was done, page 5-6**
Bias	9	Describe any efforts to address potential sources of bias **This was done, page 6-7 (inclusion/exclusion criteria, consistent use of case ascertainment by ICD-9-CM codes from administrative data to avoid recall bias or diagnostic bias)**
Study size	10	Explain how the study size was arrived at **This was done, page 5 (population-based)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

		This was done, page 6-8
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding **This was done, page 8**
		(b) Describe any methods used to examine subgroups and interactions **This was done, page 8**
		(*c*) Explain how missing data were addressed **page 9**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **n/a**
		(*e*) Describe any sensitivity analyses **not included**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **This was done, page 9**
		(b) Give reasons for non-participation at each stage **This was done, page 9**
		(c) Consider use of a flow diagram **This was done, Appendix Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **This was done, Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **This was done, Table 1**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **This was done, page 10-12, Table 1, Table 2, Table 3, Table 4, Figure 1, Figure 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **This was done, Table 2, Table 3, Table 4**
		(*b*) Report category boundaries when continuous variables were categorized **This was done**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **This was done**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **This was done, page 12, Appendix Table 2**
Discussion		
Key results	18	Summarise key results with reference to study objectives **This was done, page 13**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **This was done, page 15-16**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **This was done, page 16**
Generalisability	21	Discuss the generalisability (external validity) of the study results **This was done, page 13-14**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **This was done, page 1**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Temporal trends in neonatal mortality and morbidity following spontaneous and clinician-initiated preterm birth in Washington State, U.S.A.: a population-based study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023004.R1
Article Type:	Research
Date Submitted by the Author:	12-Sep-2018
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology, Paediatrics
Keywords:	Preterm Birth, Neonatal Mortality, Neonatal Morbidity, Trend, United States

Temporal trends in neonatal mortality and morbidity following spontaneous and clinician-initiated preterm birth in Washington State, U.S.A.: a population-based study

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Word count: Abstract 300; Text 4178.
Funding statement: This work was supported by a Canadian Institutes of Health Research Team grant in severe maternal morbidity (MAH-115445).
Competing interests statement: None declared.
Authors' contribution statement: SL and LR designed the study, LR and SL performed data analysis, and LR and SL wrote the first draft of the manuscript. GM, JT, AS and KL contributed to the interpretation of the results and critically revised the first draft. LR, SL, GM, JT, AS and KL approved the final version of the manuscript.
Ethics approval: All analyses were performed on publicly accessible de-identified data. An exemption from ethics approval was granted by the Department of Social and Health Services, State of Washington.
Data sharing statement: Analyses were based on administrative data collected and maintained by the Department of Health, State of Washington. The availability of the data is restricted. Permission for data access can granted after verification of the research goals by the Department of Social and Health Services, State of Washington.
Acknowledgements: SL is supported by a Michael Smith Foundation for Health Research Scholar Award. JT is supported by the Investigator Grant Award Program from British Columbia Children's Hospital Research Institute. GMM is supported by a Vanier Canada Graduate Scholarship.
Abbreviations: PPROM preterm premature rupture of membranes, AOR adjusted odds ratio, CI confidence interval.
Key words: Preterm Birth, Neonatal Mortality, Neonatal Morbidity, Trend, United States

ABSTRACT

Objective: After a decade of increase, the preterm birth (PTB) rate has declined in the United States since 2006, with the largest decline at late preterm (34-36 weeks). We described concomitant changes in gestational age-specific rates of neonatal mortality and morbidity following spontaneous and clinician-initiated PTB among singleton infants.

Design, Setting, and Participants: This retrospective population-based study included 754,763 singleton births in Washington State, U.S.A., 2004-2013, using data from birth certificates and hospitalization records. PTB subtypes included preterm premature rupture of membranes (PPROM), spontaneous onset of labor, and clinician-initiated delivery.

Outcome Measures: The primary outcomes were neonatal mortality and a composite outcome including death or severe neonatal morbidity. Temporal trends in the outcomes and individual morbidities were assessed by PTB subtype. Logistic regression yielded adjusted odds ratios (AOR) per 1-year change in outcome and 95% confidence intervals (CI).

Results: The rate of PTB following PPROM and spontaneous labor declined, while clinician-initiated PTB increased (all p-values<0.01). Overall neonatal mortality remained unchanged (1.3%; AOR 0.99, CI 0.95-1.02), though gestational age-specific mortality following clinician-initiated PTB declined at 32-33 weeks (AOR 0.85, CI 0.74-0.97), and increased at 34-36 weeks (AOR 1.10, CI 1.01-1.20). The overall rate of the composite outcome increased (from 7.9% to 11.9%; AOR 1.06, CI 1.05-1.08). Among late preterm infants, combined mortality or severe morbidity increased following PPROM (AOR 1.13, CI 1.08-1.18), spontaneous labor (AOR 1.09, CI 1.06-1.13), and clinician-initiated delivery (AOR 1.10, CI 1.07-1.13). Neonatal sepsis rates increased among all preterm infants (AOR 1.09, CI 1.08-1.11).

Conclusions: Timing of obstetric interventions is associated with infant health outcomes at preterm. The temporal decline in late PTB among singleton infants was associated with increased mortality among late preterm infants born following clinician-initiated delivery and increased combined mortality or severe morbidity among all late preterm infants, mainly due to increased rate of sepsis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large population-based database with detailed demographic and clinical information which allowed adjustment for temporal changes in many known risk factors for preterm birth
- Major clinical preterm birth subtypes were identified and subsequent neonatal outcomes were described by gestational age categories to provide clinically-relevant information
- Data on pregnancy and birth outcomes were collected and coded consistently over the study period
- Clinical details on severity of some neonatal morbidities including necrotizing enterocolitis and retinopathy of prematurity were not available
- Coding for neonatal sepsis did not differentiate between sepsis confirmed by blood or cerebrospinal fluid culture and a clinical diagnosis of sepsis without microbiological confirmation, or between early-onset and late-onset sepsis

INTRODUCTION

Preterm birth, defined as birth before 37 weeks' gestation, is the leading cause of neonatal mortality and morbidity, and a major risk factor for long-term neurological and respiratory morbidity and neurodevelopmental impairment.(1–3) In the United States, the rate of preterm birth increased by 24% between 1990 and 2006, from 10.6 to 13.1 per 100 live births, mainly due to an increase in obstetric intervention at late preterm (34-36 weeks' gestation).(4–6) More recently, preterm birth rates declined to 9.8 per 100 live births in the United States in 2015.(7,8) Nevertheless, the high rate of preterm birth remains a considerable concern.

Preterm birth can result from many possible etiologies.(9) The three major clinical subtypes of preterm birth include: clinician-initiated preterm birth, preterm birth following preterm premature rupture of membranes (PPROM), and preterm birth following spontaneous labor with intact membranes.(1,9) Clinician-initiated preterm birth, including labor induction and cesarean delivery without labor, constitutes about 30-40% of all preterm births, and pre-eclampsia/eclampsia and severe intrauterine growth restriction are the common indications.(9–11) Spontaneous preterm birth can result from multiple causes, including infection or inflammation, incompetent cervix, vascular/placental disorders (other than preeclampsia), and uterine over-distension.(9)

While gestational age at birth is the strongest predictor of adverse neonatal outcomes, the subtype of preterm birth is also important. Preterm infants born to women with spontaneous onset of labor have a better prognosis than infants born following clinician-initiated delivery.(5,12–15) However, it is unknown whether the temporal decline in preterm birth is associated with changes in neonatal mortality and morbidity among preterm infants.

Our aim was to describe temporal trends in gestational age-specific rates of neonatal mortality and a composite adverse outcome, defined as neonatal death or any severe morbidity, among preterm infants born following PPROM, spontaneous onset of labor and clinician-initiated delivery. We further examined gestational age-specific rates in the specific neonatal morbidity components included in the composite outcome.

METHODS

Study Population

We carried out a population-based study including all singleton hospital births to mothers aged 15 to 60 years in Washington State, U.S.A., between January 1, 2004, and December 31, 2013. We used information from two linked population databases: (1) live birth, fetal and infant death certificates with data on maternal demographic characteristics, obstetric history, and pregnancy and birth factors, from the Birth Events Record Database (BERD); and (2) hospitalization files with information on specific infant morbidities from the Comprehensive Hospital Abstract Reporting System (CHARS). The BERD included information abstracted by trained abstractors using standardized forms about maternal characteristics (e.g., maternal age, pre-pregnancy body mass index [BMI], race, education, marital status, smoking status, chronic hypertension, pre-pregnancy diabetes, and the type of health care insurance provider); obstetric history (e.g., parity, assisted conception); and pregnancy, labor, and birth characteristics (e.g., gestational age at delivery, use of tocolytics, use of steroids at delivery, mode of delivery, prolonged labor, congenital anomalies, neonatal death and birth outcomes). The CHARS database included information on all newborn hospitalizations in Washington State with diagnosis and procedure codes related to each hospitalization episode coded by the International Classification of

Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The completeness and accuracy of these databases was monitored by the Washington State Department of Health with annual assessments and consistency checks.(16–18) Records flagged with inconsistent or out-of-range entries were addressed systematically through hospital review and correction. The frequency of diagnostic and procedure codes was monitored in annual reports.(18) Previous validation studies of the linked dataset showed that the positive and negative predictive values (PPV and NPV) for delivery characteristics were above 80% and 98%, respectively; (19,20) for example, labor induction had PPV 89.0% and NPV 94.5%.(20) Gestational age at delivery was based on ultrasound dating, and last menstrual period dating was used for women with missing ultrasound data. We excluded infants born at less than 24 weeks' and greater than 45 weeks' gestation, and those with missing data on gestational age from the overall study population. After analysis of temporal trends in stillbirth, we excluded stillborn infants and those with missing mode of delivery to limit the analyses of neonatal outcomes following various types of preterm birth to live births only.

Classification of Preterm Birth

Preterm birth was defined as live birth at 24 to 36 weeks' gestation. Preterm birth subtypes were categorized using the following algorithm: (1) first, spontaneous preterm births following PPROM (>12 hours); (2) second, clinician-initiated preterm births following labor induction or cesarean delivery without labor; and (3) third, all other births were classified as spontaneous preterm births following spontaneous labor onset with intact membranes (Supplementary File 1, items no 62, 64, 65).

Outcome Measures and Covariates

The primary outcomes were neonatal mortality and a composite adverse outcome including death or severe neonatal morbidity. Neonatal mortality was defined as death of an infant that occurred within the first 28 days after birth, including deaths in the delivery room, in-hospital deaths, and deaths after hospital discharge. Severe neonatal morbidity was identified using ICD-9-CM codes and included (a) bronchopulmonary dysplasia (BPD); (b) intraventricular hemorrhage grade ≥3 (IVH); (c) periventricular leukomalacia (PVL); (d) retinopathy of prematurity (ROP); (e) necrotizing enterocolitis (NEC), (f) neonatal sepsis; (g) convulsions of newborn; and (h) severe birth trauma (Appendix Table 1).

Temporal changes in maternal characteristics over the study period were examined, including maternal age (<20, 20-29, 30-39, 40+ years); pre-pregnancy BMI (underweight <18.5 kg/m^2, normal BMI 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, and obese ≥30 kg/m^2); race (non-Hispanic White, African American, Native American, Hispanic, and other); maternal education (≤8 years vs. >8 years); smoking during pregnancy (yes/no); marital status (married/common law vs. other); parity (prior live births, yes/no); chronic hypertension (yes/no); pre-pregnancy diabetes (yes/no); assisted conception (yes/no); use of steroids (yes/no); use of tocolytics (yes/no); and type of health insurance coverage (Medicaid, self-pay, private, other). We also examined temporal trends in infant characteristics including gestational ages in completed weeks (within gestational age categories), small-for-gestational age infant (SGA, <10th percentile (21); yes/no), infant's sex (male/female), congenital anomalies, and stillbirths. Congenital anomalies were identified from BERD and included the following conditions observed within first 24 hours after birth: anencephaly, meningomyelocele or spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis,

limb reduction, cleft lip, cleft palate, Down syndrome, chromosomal disorders, and hypospadias. Stillbirth was defined as spontaneous intrauterine death of a fetus. Gestational age-specific rates of stillbirths were calculated using the fetuses-at-risk (FAR) approach.(22) Under this approach, ongoing pregnancies (fetuses in-utero) at each gestation were used as denominators (the appropriate at-risk population) for the calculation of gestational age-specific stillbirth rates.(22,23)

Statistical Analyses

The preterm birth rate was calculated as a proportion of live births at 24 to 36 weeks' gestation among infants born alive at ≥24 weeks. Gestational age-specific temporal trends were described as proportions of extremely preterm births (24-27 weeks), very preterm (28-31 weeks), moderately preterm (32-33 weeks), and late preterm births (34-36 weeks). The Cochran-Armitage test was used to assess the statistical significance of temporal trends over the years. The rates of neonatal mortality and the composite outcome of neonatal death or severe morbidity were also contrasted between years 2004-2006 vs. 2011-13, using rate ratio (RR) and rate difference (RD) and 95% confidence intervals (CI).

Logistic regression was used to assess temporal trends in adverse neonatal outcomes adjusted for temporal changes in risk factors that may have changed over the study period: maternal age, pre-pregnancy BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies. Calendar year was modelled as a continuous variable. Temporal trends in adverse outcomes were expressed as the average annual change in

the odds of neonatal mortality and combined neonatal death or severe neonatal morbidity with adjusted odds ratios (AOR) and 95% CI.

Additional Analyses

Temporal trends in the individual components of the composite outcome were examined as secondary outcomes using logistic regression models as described above. These analyses were performed including all preterm live born infants, and also for subgroups of infants born at late preterm, at 28-33 weeks, and at 24-27 weeks' gestation.

All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). Missing values for BMI (approximately 10%) were imputed using multiple imputation (PROC MI). Other missing values were <3.0% of the total, and the complete case multivariable analysis excluded 7.0% of preterm births. All p-values are reported as recommended by the American Statistical Association.(24) All analyses were performed on publicly accessible de-identified data. An exemption from ethics approval was granted by the Department of Social and Health Services, State of Washington.

Patient and Public Involvement

No patients or public were directly involved in this study.

RESULTS

Study Population

Overall, 871 649 singleton births occurred in Washington State from 2004 to 2013. We excluded births at <24 or >45 weeks' gestation, multiple births, births that occurred outside of Washington State and out-of-hospital births, as well as births that could not be matched with hospital records (N=116 886, 13.4%). The study population included 754 763 singleton infants born in hospital at ≥24 weeks; of these, 2 549 infants were stillborn (0.34%). Further, births with missing information on mode of delivery (N=14 503, 1.9%) were excluded for analyses of preterm birth rates by type of delivery (live births included 737 711 infants; Appendix Figure 1).

The rate of stillbirth increased slightly from 3.2 per 1000 total births in 2004-2006 to 3.7 in 2011-2013 (p=0.002). Stillbirth rates increased at 24-27 weeks (from 0.7 to 1.0 per 1000 fetuses-at-risk (FAR), p=0.003), and at 28-31 weeks' gestation (from 0.4 to 0.7 per 1000 FAR, p=0.002; Appendix Figure 2).

Maternal characteristics changed over the study period; women who delivered in 2011-2013 were older, more educated, and had higher pre-pregnancy BMI than those who gave birth in 2004-2006 (Table 1). The proportions of births to mothers of Hispanic and African American origin, unmarried mothers, and nulliparous mothers increased, while the proportions of mothers who smoked during pregnancy decreased over time. More mothers had chronic hypertension or pre-pregnancy diabetes, and more pregnancies occurred from assisted conception in 2011-2013 then in 2004-2006. The use of antenatal steroids for lung maturation at delivery increased over the study period, while the use of tocolytics declined. All temporal changes were statistically significant (p<0.001, Table 1).

Table 1. Maternal and infant characteristics among all singleton infants born at ≥24 weeks' gestation), Washington State, U.S.A., 2004-2013.

Characteristic	All Years (2004-2013)	Period 1 (2004-2006)	Period 2 (2011-2013)	p-value* (Period 1 vs. Period 2)
Total singleton births	754 763	219 233	225 429	
Maternal age (years)				<0.001
<20	57 042 (7.5)	18 454 (8.4)	13 603 (6.0)	
20-29	387 712 (51.4)	114 244 (52.1)	112 427 (49.9)	
30-39	287 479 (38.1)	80 300 (36.6)	92 175 (40.9)	
≥40	22 530 (3.0)	6 235 (2.8)	7 224 (3.2)	
Maternal BMI (kg/m^2)				<0.001
Underweight (<18.5)	21 563 (2.9)	6 467 (3.0)	6 477 (2.9)	
Normal (18.5-24.9)	324 689 (43.0)	91 968 (42.0)	97 451 (43.2)	
Overweight (25-29.9)	177 020 (23.5)	47 444 (21.6)	55 439 (24.6)	
Obese (≥30)	162 030 (21.5)	41 138 (18.8)	53 556 (23.8)	
Missing values	69 461 (9.2)	32 216 (14.7)	12 506 (5.6)	
Maternal race				<0.001
Non-Hispanic White	480 468 (63.7)	143 356 (65.4)	141 132 (62.6)	
African American	34 112 (4.5)	8 964 (4.1)	11 098 (4.9)	
Native American	14 962 (2.0)	4 503 (2.1)	4 265 (1.9)	
Hispanic	144 035 (19.1)	40 603 (18.5)	42 543 (18.9)	
Other	77 638 (10.3)	20 558 (9.4)	25 266 (11.2)	
Type of health insurance				<0.001
Medicaid	298 366 (39.5)	83 608 (38.1)	91 829 (40.7)	
Self-Pay	7 369 (1.0)	2 100 (1.0)	2 561 (1.1)	
Private	386 778 (51.2)	109 452 (49.9)	115 198 (51.1)	
Other**	42 500 (5.6)	13 375 (6.1)	12 013 (5.3)	
Maternal education (≤8 years)	27 731 (3.6)	9 958 (4.5)	6 334 (2.8)	<0.001
Smoking during pregnancy	72 846 (9.7)	22 073 (10.1)	20 339 (9.0)	<0.001
Unmarried	252 963 (33.5)	69 033 (31.5)	77 143 (34.2)	<0.001
No prior live births	310 297 (41.1)	88 552 (40.4)	92 232 (40.9)	<0.001
Chronic hypertension	9 669 (1.3)	2 650 (1.2)	3 002 (1.3)	0.003
Pre-pregnancy diabetes	5 472 (0.7)	1 367 (0.6)	1 755 (0.8)	<0.001
Assisted conception	6 887 (0.9)	1 551 (0.7)	2 487 (1.1)	<0.001
Gestational age (weeks)				<0.001
24-27	2 495 (0.3)	678 (0.3)	820 (0.4)	
28-31	4 649 (0.6)	1 299 (0.6)	1 520 (0.7)	
32-33	6 063 (0.8)	1 640 (0.8)	1 919 (0.9)	
34-36	41 775 (5.5)	12 808 (5.8)	12 072 (5.4)	
≥37	699 781 (92.7)	202 808 (92.5)	209 098 (92.8)	
SGA infant (<10th percentile)	6 590 (0.9)	1 767 (0.8)	2 122 (0.9)	<0.001
Infant sex (male)	386 468 (51.2)	112 128 (51.2)	116 049 (51.5)	0.026
Congenital anomalies***	3 656 (0.5)	996 (0.5)	1 133 (0.5)	0.066

BMI, pre-pregnancy body mass index; SGA, small-for-gestational-age

* p-value for Chi-square test comparing Period 1 and 2.

** Includes other government insurance, student insurance, Indian Health Care, and other programs.
*** Includes the following conditions observed within first 24 hours after birth: anencephaly, meningomyelocele or spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction, cleft lip, cleft palate, Down syndrome, chromosomal disorders, and hypospadias.
Note: Some percentages do not add up due to missing values; missing values <3% are not shown.

Preterm Birth Rates

There were 737 711 singleton live births between 2004 and 2013; out of these, 52 014 infants were born preterm (7.1%). Among the preterm infants, 16.4% were born following PPROM, 43.7% were born following spontaneous onset of labor, and 39.9% were born following clinician-initiated delivery (Appendix Table 2). The overall preterm birth rate declined from 7.3% in 2004-2006 to 7.0% of singleton live births in 2011-2013. This decline was attributed to the decline in spontaneous delivery following PPROM (1.3% to 1.1%), and spontaneous onset of labor (3.2% to 3.0%). In contrast, clinician-initiated preterm birth increased slightly from 2.7% to 2.9% (all p-values for trend <0.01; Figure 1).

Gestational age-specific trends in the type of preterm birth varied (Figure 2). There were 1 833 live births at 24-27 weeks (0.2%); of these 27.8% were PPROM, 29.0% were spontaneous onset of labor, and 43.2% were clinician-initiated delivery. At 28-31 weeks, there were 4 095 live births (0.6%); 22.3% were PPROM, 30.6% were spontaneous onset of labor, and 47.2% were clinician-initiated. At 32-33 weeks, there were 5 664 live births (0.8%); 22.7% were PPROM, 35.1% were spontaneous onset of labor, and 42.2% were clinician-initiated. At 34-36 weeks, there were 40,422 live births (5.5%); 14.4% were PPROM, 46.9% were spontaneous onset of labor, and 38.7% were clinician-initiated. The overall preterm birth rate increased in all gestational age categories except for late preterm births where the rate declined from 5.8% to

5.3% (all p<0.01). In each gestational age category, the clinician-initiated preterm birth rate increased, and the PPROM preterm birth rate declined over time (all p<0.05).

Neonatal Mortality

Neonatal mortality remained unchanged over time (1.3%, Table 2). Neonatal mortality increased among late preterm infants between 2004-06 and 2011-13 (RR 1.25, 95% CI 0.85-1.84; average change per year AOR 1.064, 95% CI 1.003-1.129; Table 2). Overall, higher neonatal mortality was among infants delivered following PPROM (1.7%) and clinician-initiated delivery (1.6%) as compared with spontaneous delivery (0.8%).

A significant decline in mortality was observed among infants born following clinician-initiated delivery at 32-33 weeks, from 2.5% in 2004-2006 to 1.0% in 2011-2013 (RR 0.40, 95% CI 0.17-0.95; AOR 0.85, 95% CI 0.74-0.97; Table 3). In contrast, neonatal mortality increased from 0.5% to 0.8% (RR 1.60, 95% CI 0.94-2.73; AOR 1.10, 95% CI 1.01-1.20) among infants following clinician-initiated delivery at 34-36 weeks.

Table 2. Gestational age-specific rates of adverse neonatal outcomes among singleton preterm infants, Washington State, U.S.A., 2004-2013.

Outcome and gestational age category	Rates per 100 live births			Adjusted odds ratio per 1-year change† (95% CI)
	N (Rate)		Rate ratio (95% CI)	
	2004-2006	2011-2013		
Neonatal death				
24-27 weeks	76 (15.5)	85 (14.2)	0.92 (0.67-1.25)	0.97 (0.92-1.03)
28-31	55 (4.9)	40 (3.0)	0.61 (0.41-0.92)	0.95 (0.89-1.01)
32-33	23 (1.6)	18 (1.0)	0.63 (0.34-1.16)	0.93 (0.84-1.02)
34-36	43 (0.4)	64 (0.5)	1.25 (0.85-1.84)	1.06 (1.00-1.13)
All (24-36)	197 (1.3)	207 (1.3)	1.00 (0.82-1.22)	0.99 (0.95-1.02)
Neonatal death/ severe morbidity				
24-27 weeks	353 (72.2)	429 (71.7)	0.99 (0.86-1.14)	1.00 (0.96-1.04)
28-31	383 (33.7)	496 (36.6)	1.08 (0.95-1.24)	1.03 (1.00-1.06)
32-33	166 (11.3)	302 (16.3)	1.44 (1.19-1.74)	1.05 (1.02-1.08)
34-36	307 (2.5)	639 (5.4)	2.16 (1.89-2.47)	1.10 (1.08-1.12)

All (24-36)	1 209 (7.9)	1 866 (11.9)	1.51 (1.40-1.62)	1.06 (1.05-1.08)

CI, confidence interval; severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.
Adjusted odds ratios express the average annual change in the odds of the outcome.
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Table 3. Gestational age-specific rates of neonatal death by subtype of preterm birth, Washington State, U.S.A., 2004-2013.

Gestational age category and preterm birth subtype	Neonatal death			Adjusted odds ratio per 1-year change† (95% CI)
	N (per 100 live births)		Rate ratio (95% CI)	
	2004-2006	2011-2013		
24-27 weeks				
PPROM	27 (14.9)	18 (13.9)	0.93 (0.51-1.69)	1.05 (0.94-1.17)
Spontaneous labor	21 (15.6)	26 (13.8)	0.88 (0.50-1.57)	0.95 (0.86-1.06)
Clinician-initiated	28 (16.2)	41 (14.7)	0.91 (0.56-1.47)	0.94 (0.86-1.03)
28-31 weeks				
PPROM	14 (4.8)	5 (1.9)	0.40 (0.14-1.10)	0.92 (0.78-1.07)
Spontaneous labor	11 (3.1)	9 (2.2)	0.71 (0.30-1.71)	0.91 (0.77-1.06)
Clinician-initiated	30 (6.2)	26 (3.8)	0.61 (0.36-1.04)	0.96 (0.88-1.06)
32-33 weeks				
PPROM	2 (0.5)	5 (1.2)	2.40 (0.47-12.37)	1.08 (0.80-1.45)
Spontaneous labor	7 (1.3)	5 (0.8)	0.62 (0.20-1.94)	0.97 (0.83-1.13)
Clinician-initiated	14 (2.5)	8 (1.0)	0.40 (0.17-0.95)	0.85 (0.74-0.97)
34-36 weeks				
PPROM	14 (0.7)	7 (0.4)	0.57 (0.23-1.42)	0.97 (0.84-1.12)
Spontaneous labor	7 (0.1)	22 (0.4)	4.00 (1.71-9.36)	1.08 (0.96-1.20)
Clinician-initiated	22 (0.5)	35 (0.8)	1.60 (0.94-2.73)	1.10 (1.01-1.20)
All (24-36 weeks)				
PPROM	57 (2.1)	35 (1.4)	0.67 (0.44-1.02)	1.00 (0.93-1.07)
Spontaneous labor	46 (0.7)	62 (0.9)	1.29 (0.88-1.88)	0.98 (0.92-1.04)
Clinician-initiated	94 (1.6)	110 (1.7)	1.06 (0.81-1.40)	0.98 (0.94-1.03)

PPROM, preterm premature rupture of membranes; CI, confidence interval
Adjusted odds ratios express the average annual change in the odds of neonatal death.
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Composite outcome: Neonatal Mortality or Severe Morbidity

The rate of combined mortality or severe morbidity increased from 7.9% in 2004-2006 to 11.9% in 2011-2013 (RR 1.51, 95% CI 1.40-1.62; average change per year AOR 1.06, 95% CI 1.05-1.08; Table 2). This increase was predominately due to an increase in combined mortality or severe morbidity among infants born at 32-33 weeks and 34-36 weeks' gestation (RR 1.44, 95% CI 1.19-1.74, and RR 2.16, 95% CI 1.89-2.47, respectively); the relative average increase in the odds of combined neonatal mortality or severe morbidity was 5% per year among infants born at 32-33 weeks (AOR 1.05, 95% CI 1.02-1.08), and 10% per year among infants born at 34-36 weeks (AOR 1.10, 95% CI 1.08-1.12). Rate differences are shown in Appendix Table 3.

The rate of composite neonatal mortality or severe morbidity increased in each preterm birth subtype (all $p<0.001$, Table 4). The rate was highest among infants born following PPROM (14.8%), and these infants had the largest relative increase (10% per year) in combined mortality or severe morbidity over the study period (AOR 1.10, 95% CI 1.07-1.13). Gestational age-specific analyses of trends in combined neonatal mortality or severe morbidity showed an increase in the rates among infants born at 34-36 weeks in all subtypes of preterm birth (PPROM: RR 2.20, 95% CI 1.64-2.96; spontaneous: RR 2.32, 95% CI 1.85-2.90; clinician-initiated: RR 2.04, 95% CI 1.65-2.51; Table 4), and increases in the rates among infants born following PPROM at 28-31 weeks (AOR 1.07, 95% CI 1.02-1.13) and 32-33 weeks (AOR 1.12, 95% CI 1.06-1.19). In addition, a significant increase in combined neonatal mortality or severe morbidity was observed among infants born following spontaneous onset of labor at 24-27 weeks' gestation (AOR 1.09, 95% CI 101-1.17). In contrast, clinician-initiated delivery at 24-27 weeks was associated with a decline in the rate of composite adverse outcome (AOR 0.93, 95% CI 0.87-0.99).

Table 4. Gestational age-specific rates of neonatal death/severe morbidity by subtype of preterm birth, Washington State, U.S.A., 2004-2013.

Gestational age category and preterm birth subtype	Neonatal death/severe morbidity			Adjusted odds ratio per 1-year change† (95% CI)
	N (per 100 live births)		Rate ratio (95% CI)	
	2004-2006	2011-2013		
24-27 weeks				
PPROM	133 (73.5)	98 (75.4)	1.03 (0.79-1.33)	1.01 (0.94-1.10)
Spontaneous labor	89 (65.9)	142 (75.1)	1.14 (0.87-1.49)	1.09 (1.01-1.17)
Clinician-initiated	131 (75.7)	189 (67.7)	0.89 (0.72-1.12)	0.93 (0.87-0.99)
28-31 weeks				
PPROM	101 (34.2)	112 (42.4)	1.24 (0.95-1.62)	1.07 (1.02-1.13)
Spontaneous labor	112 (31.4)	144 (34.6)	1.10 (0.86-1.41)	1.02 (0.98-1.08)
Clinician-initiated	170 (35.2)	240 (35.5)	1.01 (0.83-1.23)	1.02 (0.98-1.06)
32-33 weeks				
PPROM	42 (11.0)	90 (22.0)	2.00 (1.39-2.88)	1.12 (1.06-1.19)
Spontaneous labor	60 (11.3)	87 (13.4)	1.19 (0.85-1.65)	1.01 (0.96-1.07)
Clinician-initiated	64 (11.5)	125 (15.8)	1.37 (1.02-1.86)	1.04 (0.99-1.08)
34-36 weeks				
PPROM	67 (3.5)	129 (7.7)	2.20 (1.64-2.96)	1.13 (1.08-1.18)
Spontaneous labor	111 (1.9)	245 (4.4)	2.32 (1.85-2.90)	1.09 (1.06-1.13)
Clinician-initiated	129 (2.8)	265 (5.7)	2.04 (1.65-2.51)	1.10 (1.07-1.13)
All (24-36 weeks)				
PPROM	343 (12.4)	429 (17.3)	1.40 (1.21-1.61)	1.10 (1.07-1.13)
Spontaneous labor	372 (5.5)	618 (9.1)	1.65 (1.45-1.88)	1.06 (1.04-1.09)
Clinician-initiated	494 (8.6)	819 (12.9)	1.50 (1.34-1.68)	1.05 (1.03-1.07)

PPROM, preterm premature rupture of membranes; CI, confidence interval, severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.

Adjusted odds ratios express the average annual change in the odds of neonatal death and/or morbidity.

†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Additional analyses

The most prominent temporal trend in the rates of specific severe neonatal morbidities was an increase in the rate of neonatal sepsis, from 4.5% in 2004-06 to 8.5% in 2011-2013 (AOR 1.09, 95% CI 1.08-1.11). The rate of sepsis increased substantially among late preterm infants from 1.7% to 4.5% (AOR 1.12, 95% CI 1.10-1.14), infants born at 28-33 weeks (AOR 1.07, 95% CI

1.05-1.10), and those born at 24-27 weeks (AOR 1.05, 95% CI 1.01-1.09). In contrast, the rate of BPD among preterm infants decreased from 2.0% to 1.7% (AOR 0.95, 95% CI 0.93-0.98; Appendix Table 4), mainly in infants born at 28-33 weeks (AOR 0. 93, 95% CI 0.89-0.97).

DISCUSSION

Our findings show a decline in the preterm birth rate in Washington State between 2004 and 2013 that was predominately due to a decline in spontaneous preterm birth (PPROM and spontaneous preterm labor), while clinician-initiated preterm deliveries increased slightly. These changes were associated with increased mortality among late preterm infants born following clinician-initiated delivery and increased rates of the composite outcome of neonatal mortality or severe morbidity among all late preterm infants. The rise in neonatal morbidity was driven mainly by the increase in the rate of neonatal sepsis.

After a large increase in the preterm birth rate in the United States in the early 2000s, a decline was observed from 12.8% in 2006 to 9.8% in 2015.(4–8) A recent study by Gyamfi-Bannerman *et al*. showed a decline in both clinician-initiated and spontaneous preterm birth rates between 2005 and 2012.(10) Our study provides more detailed information on preterm birth categories and describes temporal trends in neonatal outcomes adjusted for changes in important risk factors.

Obstetric interventions, changes in practice patterns, and implementation of specific evidence-based guidelines for high-risk women may be reasons behind the decline in preterm birth following spontaneous onset of labor. The use of 17 α-hydroxyprogesterone caproate (17P) for women with previous spontaneous preterm births, and the use of vaginal progesterone for select women with short cervical length and without prior preterm birth progressively increased

between 2006 and 2013 and may have led to a decline in spontaneous preterm births.(6,25–29) More aggressive pursuit of expectant management in PPROM, preeclampsia and intrauterine growth restriction may have led to a delivery at later gestation in high-risk mothers.(30–32) Other changes including declines in births to teenage mothers may have contributed to an overall decline in the preterm birth rate, while increases in maternal age, obesity, and assisted conception have likely contributed to an increase in clinician-initiated delivery in general.(33–35)

In 1999 and 2009, the American College of Obstetrics and Gynecologists (ACOG) advocated against elective deliveries under 39 weeks of gestation in an effort to prevent non-medically-indicated preterm births and the potentially avoidable morbidity associated with these deliveries.(36,37) Previous studies have shown that timely medically-indicated clinician-initiated delivery can prevent stillbirth and reduce neonatal mortality.(23,38,39) A population-based study of all births in the United States showed that the 68% increase in clinician-initiated preterm births between 1995 and 2005 was not associated with increased rates of neonatal mortality/morbidity.(5) In our study, the small increase in clinician-initiated interventions was associated with reduced mortality at 32-33 weeks and reduced mortality/severe morbidity at 24-27 weeks. However, at late preterm, declines in spontaneous and PPROM birth and increases in clinician-initiated delivery were associated with increased rates of mortality/severe morbidity. This may be due temporal increase in maternal chronic morbid conditions that we did not adjust for in our study, for example, asthma, autoimmune conditions, or respiratory morbidity.

The increase in neonatal sepsis was observed in all subtypes of late preterm birth, which points to possible common causes relatively independent of delivery type. However, the pathology of neonatal sepsis can vary by preterm birth subtype (for example, originating from

the effects of chorioamnionitis in PPROM, or IUGR in clinician-initiated delivery), and the uniform increase may be due to the broad definition of sepsis in our study, which included early and late onset sepsis. This unfavorable trend in adverse neonatal outcomes in our study thus warrants further investigation, as prior studies of clinical sepsis (defined broadly as 'other infection specific to neonatal period') in the first 3 months after birth showed a small decline between 1988 and 2006 among preterm infants in the U.S.A.(40) The reasons behind the increased rates of sepsis in our study may include temporal changes in the proportion of vulnerable infants, increased use of antenatal steroids, or changes in antibiotic use and antibiotic resistance.(40,41) Currently, there is lack of clinical diagnostic criteria or ideal laboratory marker for neonatal sepsis with excellent sensitivity for daily clinical operations, rendering the assessment of variation in the incidence rates of neonatal sepsis difficult.(41–43) Antibiotics are essential in the treatment of bacterial sepsis, and are the most commonly used medications in neonatal intensive units; however, overly liberal antimicrobial use has been associated with increased adverse neonatal outcomes.(44) A large population study in California showed substantial variations in antibiotic use that was not related to proven infection, NEC, surgical case volume, or Neonatal Intensive Care Unit (NICU) mortality, especially among community and intermediate NICUs.(44) Unified diagnostic criteria and antimicrobial policies are needed to further examine and address this issue.

The strengths of our study include a large population-based database with detailed information on demographic and clinical risk factors (e.g., BMI, assisted conception) and obstetric history (e.g., parity, prior adverse outcomes). We were, therefore, able to adjust for temporal changes in a large spectrum of known risk factors for preterm birth. Data on pregnancy and birth outcomes were collected consistently over the study period, and neonatal morbidity

was also coded consistently using exclusively ICD-9-CM during the entire study period. The ICD-9-CM code for neonatal sepsis did not change over the study period, and there was no indication of any major changes in clinical diagnostic criteria.

This study has a few limitations. First, clinical details on severity of some neonatal morbidity were not available, for example, the NEC Stage I or ROP Grade I, both of which can be treated conservatively. This led to the inclusion of infants with less severe NEC and ROP or other components of the composite outcome. Second, the ICD-9-CM code for neonatal sepsis did not differentiate between sepsis confirmed by blood or cerebrospinal fluid culture and a clinical diagnosis of sepsis without microbiological confirmation, or between early-onset and late-onset sepsis. This could lead to over-diagnosis of neonatal infection. Third, information on iatrogenic termination of pregnancy was not available, thus we could not account for these temporal changes. However, the vast majority of iatrogenic pregnancy terminations is likely to occur prior to 24 weeks gestation; terminations beyond 23 weeks would be included as stillbirths in this study. Temporal changes in gestational age-specific stillbirth rates showed small increases in stillbirth rates at 24-27 weeks and 28-31 weeks, which augments the upward trend in adverse neonatal outcome (mortality or severe morbidity) at 28-31 weeks gestation. Fourth, potential errors and omissions are inevitable in large databases; these may have led to non-differential misclassification, which may have resulted in the underestimation of temporal trends. Fifth, the data sources had detailed information on mode of delivery that allowed accurate categorization of preterm birth subtypes; however, this categorization may have overestimated the proportion of deliveries following PPROM.(45) Data collection had not changed over the study period, however, changes in physician's preferences for specific mode of delivery (e.g., trial of labor before cesarean delivery) may be responsible for year-to-year fluctuation in temporal trends in

preterm birth subtypes. Lastly, a relatively large number of temporal trends were assessed, possibly rendering some trends statistically significant due to chance. In addition, singleton infants excluded due to out-of-hospital delivery or missing values may have impacted our results, however, non-hospital births are more likely to be term deliveries without complications requiring hospitalization.

Washington State has one of the lowest preterm birth rates in the USA, and lowest infant mortality rates;(46) however, the ranking is very much dependent on the ethnicity, age, and socioeconomic status composition of the obstetric population.(46) We adjusted for a number of these indices thus our results are relevant to other states in the U.S.A. and high-income countries in general.

CONCLUSION

Our objectives were to assess temporal trends in gestational age-specific rates of neonatal mortality and a composite outcome of neonatal mortality or severe morbidity among preterm infants. The small decline in the preterm birth rate in Washington State from 2004 to 2013 was predominantly due to a decline in the rates of spontaneous onset of labor and PPROM at late preterm. This was associated with increased neonatal mortality among late preterm infants born following clinician-initiated delivery, and increased rate of composite outcome including neonatal death or severe morbidity among all late preterm infants. The increase in adverse neonatal outcomes among late preterm infants and increase in sepsis rates among all preterm infants warrant further investigation. Our results are important for identifying areas for improvement in obstetric and neonatal health care, and serve as hypothesis generating findings to direct further research.

List of tables:

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Supplement:

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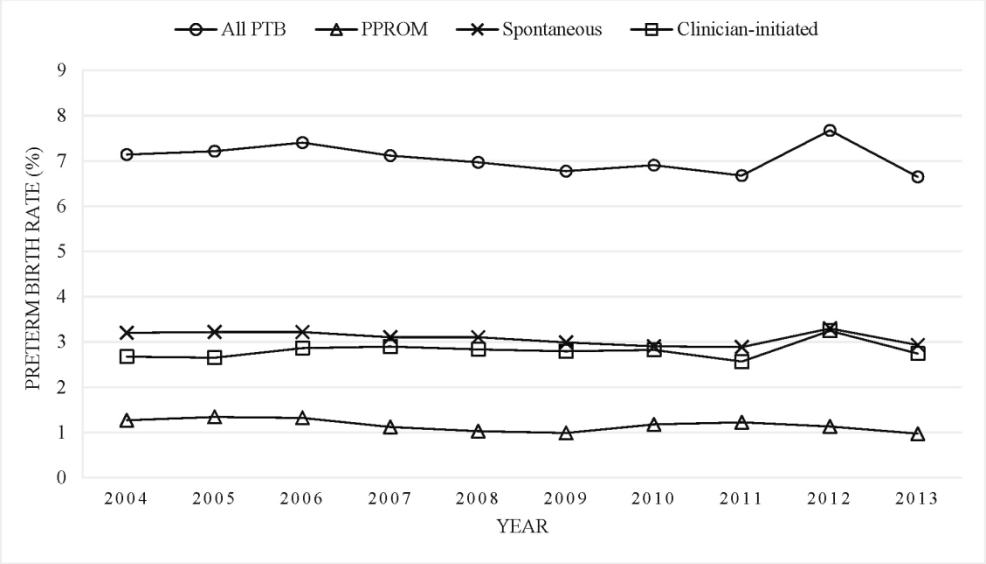


Figure 1. Temporal trends in the rates of singleton preterm birth following preterm premature rupture of membranes (PPROM), spontaneous labor and clinician-initiated delivery, Washington State, U.S.A., 2004-2013.

163x93mm (300 x 300 DPI)

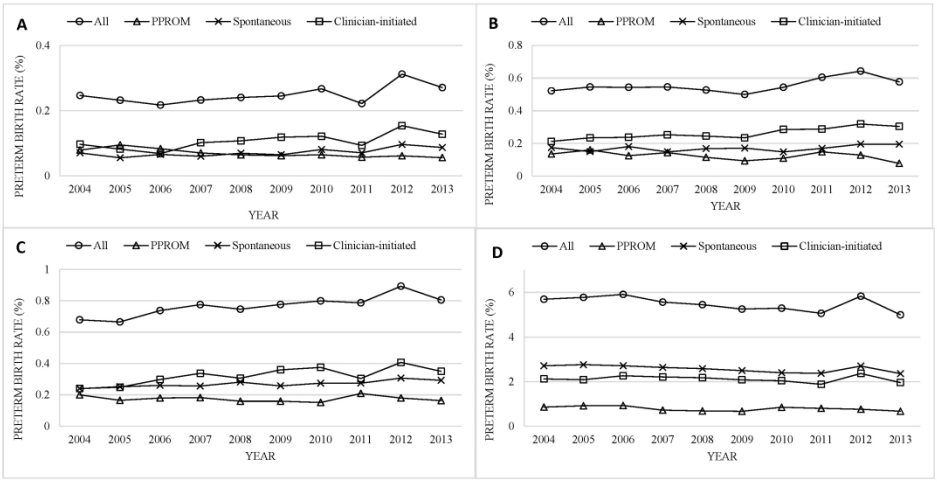


Figure 2. Temporal trends in gestational-age specific preterm birth rates following preterm premature rupture of membranes (PPROM), spontaneous labor and clinician-initiated delivery; at 24-27 weeks (Panel A), 28-31 weeks (Panel B), 32-33 weeks (Panel C), and 34-36 weeks (Panel D); Washington State, U.S.A., 2004-2013.

279x215mm (300 x 300 DPI)

Washington State Department of Health

Washington State Birth Filing Form

For Hospital Use Only

Mother's Medical Record #:	Child's Medical Record #:

Plurality: ☐ 1- single birth ☐ 2- twin ☐ 3- triplet ☐ Other _____

If multiple, this worksheet is for child: ☐ 1- first born ☐ 2- second born ☐ 3- third born ☐ Other _____

Child's Information

*1. Child's Name First	Middle	Last
*2. Child's Date of Birth (MM/DD/YYYY) / /	*3. Time of Birth	*4. Child's Sex ☐ Male ☐ Female

5. Type of Birthplace
☐ Hospital ☐ Home
☐ Enroute ☐ Clinic/Doctor's Office
☐ Freestanding Birth Center ☐ Other (specify):

6. Planned Birth Place, if different (specify):

*7. Name of Facility (If not a facility, enter name of place and address)	*8. County of Birth	*9. City of Birth

Mother's Information

10. Mother's Current Legal Name First	Middle	Last
*11. Mother's Name on her Birth Certificate First	Middle	Last/Maiden
*12. Date of Birth (MM/DD/YYYY) / /	*13. Birthplace (State, Territory, or Foreign Country)	14. Social Security Number

15. Do you want to get a Social Security Number for your child? ☐ Yes ☐ No

16a. Residence: Number and Street (e.g., 624 SE 5th St.)	Apt No.

16b. If not U.S.; Country	16c. State	16d. County

16e. If you live on Tribal Reservation, give name	16f. City or Town	16g. Zip Code + 4

16h. Inside City Limits? ☐ Yes ☐ No ☐ Unknown	17. How Long at Current Residence? Years: Months:	18. Telephone Number ( )

19a. Mailing Address, if different: Number and Street, or PO Box	Apt. No.

19b. If not U.S.; Country	19c. State	19d. City	19e. Zip Code + 4

20. Occupation (type of work done during last year)	21. Kind of Business/Industry (do not use company name)

22. Mother's Education
(Check the box that best describes the highest degree or level of school completed at the time of delivery.)

1 ☐ 8th grade or less (specify):_____
2 ☐ 9th – 12th grade; no diploma
3 ☐ High school graduate or GED
4 ☐ Some college credit, but no degree
5 ☐ Associate degree (AA, AS, etc.)
6 ☐ Bachelor's degree (BA, AB, BS, etc.)
7 ☐ Master's degree (MA, MS, MEd, MSW, MBA, etc.)
8 ☐ Doctorate (PhD, EdD, etc.) or professional degree (MD, DDS, DVM, LLB, JD, etc.)

23. Mother of Hispanic Origin?
(Check the box that best describes whether the mother is Spanish/Hispanic/Latina or check "No" box if not Spanish/Hispanic/Latina.)

1 ☐ No, not Spanish/Hispanic/Latina
2 ☐ Yes, Mexican, Mexican American, Chicana
3 ☐ Yes, Puerto Rican
4 ☐ Yes, Cuban
5 ☐ Yes, Other Spanish/Hispanic/Latina (specify):

24. Mother's Race (check one or more)

1 ☐ White
2 ☐ Black or African American
3 ☐ American Indian or Alaska Native
(Name of enrolled or principal tribe)

4 ☐ Asian Indian 5 ☐ Chinese
6 ☐ Filipino 7 ☐ Japanese
8 ☐ Korean 9 ☐ Vietnamese
10 ☐ Other Asian (specify):
11 ☐ Native Hawaiian 12 ☐ Guamanian or Chamorro
13 ☐ Samoan
14 ☐ Other Pacific Islander (specify):
15 ☐ Other (specify):

Continue on next page

Mother's Information

25. Mother's Height Feet: Inches:	26. Mother's Pre-Pregnancy Weight (pounds)	27. Did Mother get WIC food for herself during pregnancy? ☐ Yes ☐ No

28. Cigarette Smoking Before and During Pregnancy ☐ Yes ☐ No

Average number of cigarettes or packs per day:

	# of cigarettes		# of packs
Three months before pregnancy		or	
First three months of pregnancy		or	
Second three months of pregnancy		or	
Last three months of pregnancy		or	

Mother's Marital Status

Mother's Marital Status

29. Is mother married? (Check only one box)

Important - Read before responding to marital status question:
If you were married at any time during your pregnancy, your spouse or partner is considered the other legal parent unless he or she completes a denial of paternity and another man acknowledges that he is the father (chapter 26.26 RCW). To add someone other than your spouse or partner to the birth certificate, an acknowledgment and denial of paternity needs to be completed by all parties (DOH form 422-032). Under Washington State law, a state-registered domestic partnership is considered the same as a marriage (chapter 26.60 RCW).

If you were not married at any time during the pregnancy, an acknowledgment of paternity needs to be completed to add the father to the birth certificate.

Married - Yes	Married - No
29a. ☐ Yes, I am married to the other parent identified in box #30.	29d. ☐ No, I am not married and I am providing information about the father in box #30. *Ask hospital staff for a Paternity Acknowledgment form (#DOH 422-032). If you were married any time during the pregnancy and your previous spouse is not the parent identified in box #30, the spouse's Denial of Paternity must also be completed.*
29b. ☐ Yes, I am married but not to the other person identified in box #30. *Ask hospital staff for a Paternity Acknowledgment form (# DOH 422-032).You must complete this form, including the spouse's Denial of Paternity.*	29e. ☐ No, I am not married now, but I was married to the other parent identified in box #30 at some time during this pregnancy.
29c. ☐ Yes, I am married but I refuse to provide the spouse or partner's information. *If this box is checked, the other parent will be listed on the birth certificate as "None Named".*	29f. ☐ No, I am not married and I refuse to provide the father's information. *If this box is checked, the other parent will be listed on the birth certificate as "None Named".*

Father/ Parent's Information

Father/Parent's Information

*30. Current Legal Name First	Middle	Last
*31. Date of Birth (MM/DD/YYYY) / /	*32. Birthplace (State, Territory, or Foreign Country)	33. Social Security Number

34. Occupation (type of work done during last year.)	35. Kind of Business/Industry (do not use Company Name)

36. Father/Parent Education
(Check the box that best describes the highest degree or level of school completed at the time of delivery.)

1 ☐ 8th grade or less (specify):_____
2 ☐ 9th – 12th grade; no diploma
3 ☐ High school graduate or GED
4 ☐ Some college credit, but no degree
5 ☐ Associate degree (AA, AS, etc.)
6 ☐ Bachelor's degree (BA, AB, BS, etc.)
7 ☐ Master's degree (MA, MS, MEd, MSW, MBA, etc.)
8 ☐ Doctorate (PhD, EdD, etc.) or professional degree (MD, DDS, DVM, LLB, JD, etc.)

37. Father/Parent of Hispanic Origin?
(Check the box that best describes whether the father/parent is Spanish/Hispanic/Latino or check "No" box if not Spanish/Hispanic/Latino.)

1 ☐ No, not Spanish/Hispanic/Latino
2 ☐ Yes, Mexican, Mexican American, Chicano
3 ☐ Yes, Puerto Rican
4 ☐ Yes, Cuban
5 ☐ Yes, other Spanish/Hispanic/Latino (specify):

38. Father/Parent Race (check one or more)

1 ☐ White
2 ☐ Black or African American
3 ☐ American Indian or Alaska Native (Name of enrolled or principal tribe)

4 ☐ Asian Indian 5 ☐ Chinese
6 ☐ Filipino 7 ☐ Japanese
8 ☐ Korean 9 ☐ Vietnamese
10 ☐ Other Asian (specify):

11 ☐ Native Hawaiian 12 ☐ Guamanian or Chamorro
13 ☐ Samoan
14 ☐ Other Pacific Islander (specify):
15 ☐ Other (specify):

For Hospital Use Only

Mother's Statistical Information

39. Date of First Prenatal Care Visit (MM/DD/YYYY) / / ☐ No Prenatal Care

40. Date of Last Prenatal Care Visit (MM/DD/YYYY) / /

41. Total Number of Prenatal Visits for this Pregnancy (If none, enter '0') _____

42. Number of Previous Live Births (Do not include this child)
Number Now Living _____ ☐ None
Number Now Dead _____ ☐ None

43. Date of Last Live Birth (MM/YYYY) (Do not include this child) / /

44. Number of Other Pregnancy Outcomes (Spontaneous or induced losses or ectopic pregnancies)
Number of Other Outcomes _____ ☐ None

45. Date of Last Other Pregnancy Outcome (MM/YYYY) / /

46. Date Last Normal Menses Began (MM/DD/YYYY) / /

47. Mother's Weight at Delivery(pounds)

48. Was mother transferred to higher level care for maternal medical or fetal indications for delivery? ☐ Yes ☐ No
If yes, name of facility mother was transferred from:

49. Principal Source of Payment for this Delivery
☐ Medicaid ☐ Self-Pay ☐ Private Insurance
☐ Other Gov't ☐ Tricare ☐ Indian Health
☐ Charity Care ☐ Other _____

Child's Statistical Information

50. Birth Weight
lbs: ozs: **or** grams:

51. Infant Head Circumference (cm)

52. Obstetric Estimate of Gestation (completed weeks)

53. Apgar score at 5 minutes _____ If score is less than 6, score at 10 minutes _____

54. Plurality: ☐ Single ☐ twins ☐ triplets ☐ other _____

55. If not single birth; birth order: ☐ first ☐ second ☐ third ☐ other _____

56. Was infant transferred within 24 hours of delivery? ☐ Yes ☐ No
If yes, name of facility infant was transferred to:

57. Is infant living at the time of report?
☐ Yes ☐ No ☐ Transferred, status unknown

58. Is infant being breastfed?
☐ Yes ☐ No

Medical and Health Information

59. Risk Factors in this Pregnancy (check all that apply):

1 Diabetes
- ☐ Prepregnancy (Diagnosis prior to this pregnancy)
- ☐ Gestational (Diagnosis in this pregnancy)

2 Hypertension
- ☐ Prepregnancy (Chronic)
- ☐ Gestational (PIH, preeclampsia)
- ☐ Eclampsia

3 ☐ Previous preterm births
4 ☐ Other previous poor pregnancy outcome (includes perinatal death, small-for-gestational age/intrauterine growth restricted birth)
5 ☐ Vaginal bleeding during this pregnancy prior to the onset of labor
6 ☐ Pregnancy resulted from infertility treatment - If yes-check all that apply:
- ☐ Fertility-enhancing drugs, artificial insemination or intrauterine insemination
- ☐ Assisted reproductive technology [e.g., in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT)]

7 ☐ Mother had a previous cesarean delivery? If Yes, how many_____
8 ☐ Group B Streptococcus culture positive
9 ☐ None of the above

60. Infections Present and/or Treated During this Pregnancy (check all that apply):

1 ☐ Gonorrhea
2 ☐ Syphilis
3 ☐ Herpes Simplex Virus (HSV)
4 ☐ Chlamydia
5 ☐ Hepatitis B
6 ☐ Hepatitis C
7 ☐ HIV Infection
8 ☐ Other Specify:_____
9 ☐ None of the above

61. Maternal Morbidity (complications associated with labor and delivery) (Check all that apply):

1 ☐ Maternal transfusion
2 ☐ Third or fourth degree perineal laceration
3 ☐ Ruptured uterus
4 ☐ Unplanned hysterectomy
5 ☐ Admission to intensive care unit
6 ☐ Unplanned operating room procedure following delivery
7 ☐ None of the above

62. Method of Delivery

A. Was delivery with forceps attempted but unsuccessful? ☐ Yes ☐ No

B. Was delivery with vacuum extraction attempted but unsuccessful? ☐ Yes ☐ No

C. Fetal presentation at birth ☐ Cephalic ☐ Breech ☐ Other

D. Final route and method of delivery (Check One)
Vaginal: ☐ Spontaneous ☐ Forceps ☐ Vacuum
OR
Cesarean: ☐
If cesarean, was a trial of labor attempted? ☐ Yes ☐ No

63. Obstetric procedures (Check all that apply):

1 ☐ Cervical cerclage
2 ☐ Tocolysis
3 ☐ External cephalic version:
- ☐ Successful
- ☐ Failed

4 ☐ None of the above

64. Onset of Labor (Check all that apply):

1 ☐ Premature rupture of the membranes (Prolonged, ≥ 12hr)
2 ☐ Precipitous Labor (< 3hr)
3 ☐ Prolonged Labor (≥ 20hr)
4 ☐ None of the above

65. Characteristics of Labor and Delivery (Check all that apply):

1 ☐ Induction of labor
2 ☐ Augmentation of labor
3 ☐ Non-vertex presentation
4 ☐ Epidural or spinal anesthesia during labor
5 ☐ Steroids (glucocorticoids) for fetal lung maturation received by the mother prior to delivery
6 ☐ Antibiotics received by the mother during labor
7 ☐ Clinical chorioamnionitis diagnosed during labor or maternal temperature ≥38°C (100.4°F)
8 ☐ Moderate/heavy meconium staining of the amniotic fluid
9 ☐ Fetal intolerance of labor such that one or more of the following actions was taken: in-utero resuscitation measures, further fetal assessment, or operative delivery
10 ☐ None of the above

66. Abnormal Conditions of the Newborn (Occurring within 24 hours of delivery) (check all that apply):

1 ☐ Assisted ventilation required immediately following delivery
2 ☐ Assisted ventilation required for more than six hours
3 ☐ NICU admission
4 ☐ Newborn given surfactant replacement therapy
5 ☐ Antibiotics received by the newborn for suspected neonatal sepsis
6 ☐ Seizure or serious neurologic dysfunction
7 ☐ Significant birth injury (skeletal fracture(s), peripheral nerve injury, soft tissue or solid organ hemorrhage which requires intervention)
8 ☐ None of the above

67. Congenital Anomalies of the Newborn (Observed within 24 hours of delivery) (Check all that apply)

1 ☐ Anencephaly
2 ☐ Meningomyelocele / Spina bifida
3 ☐ Cyanotic congenital heart disease
4 ☐ Congenital diaphragmatic hernia
5 ☐ Omphalocele
6 ☐ Gastroschisis
7 ☐ Limb reduction defect (excluding congenital amputation and dwarfing syndrome)
8 ☐ Cleft Lip with or without Cleft Palate
9 ☐ Cleft Palate alone
10 Down Syndrome
- ☐ Karyotype confirmed
- ☐ Karyotype pending

11 Chromosomal disorder
- ☐ Karyotype confirmed
- ☐ Suspected, Karyotype pending

12 ☐ Hypospadias
13 ☐ None of the above

Attendant and Certifier Information

68. Certifier – Name and Title

69. Date Certified (MM/DD/YYYY) / /

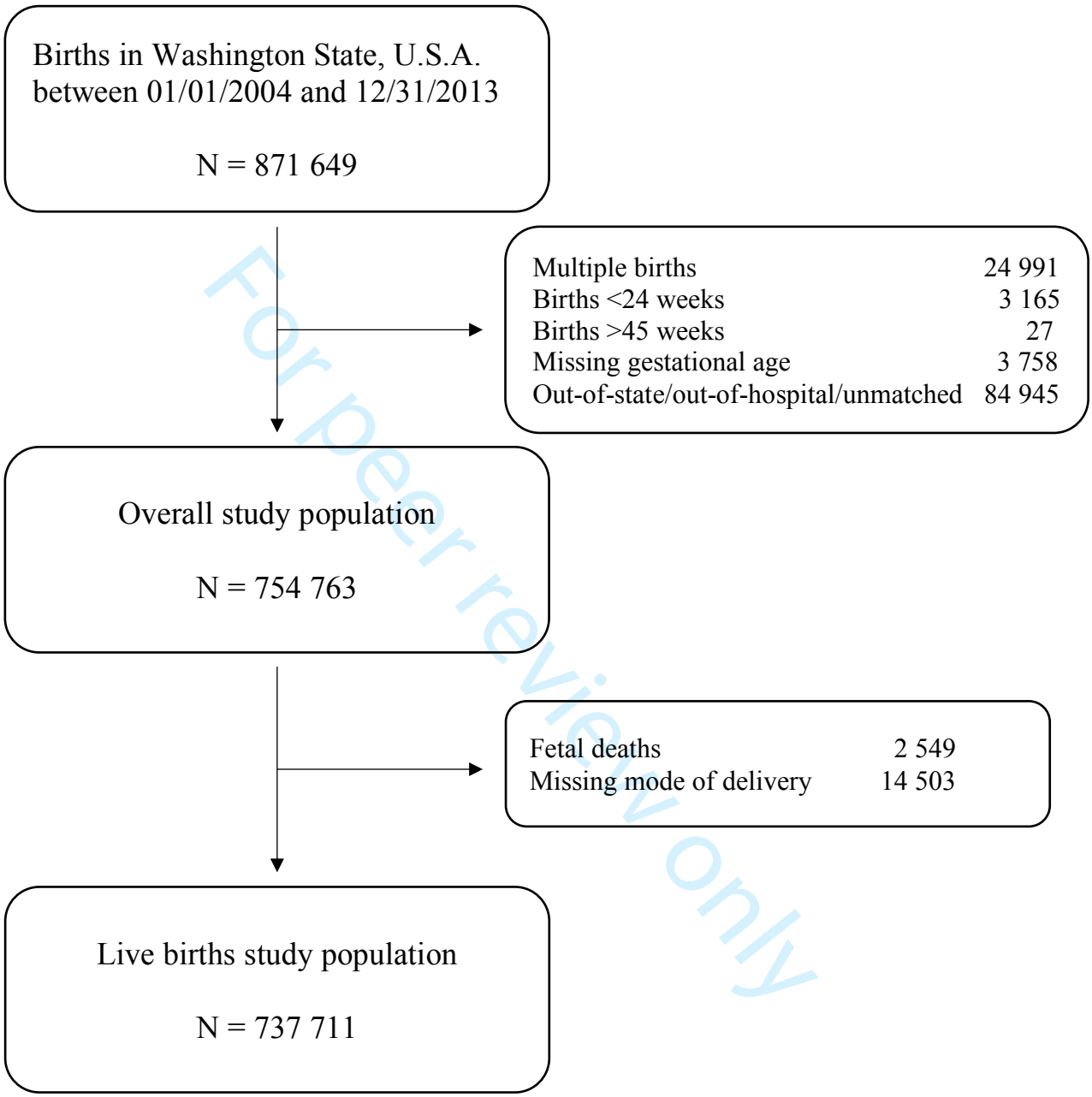
70. Attendant – Name and Title (If other than Certifier)

71. NPI of person delivering the baby:

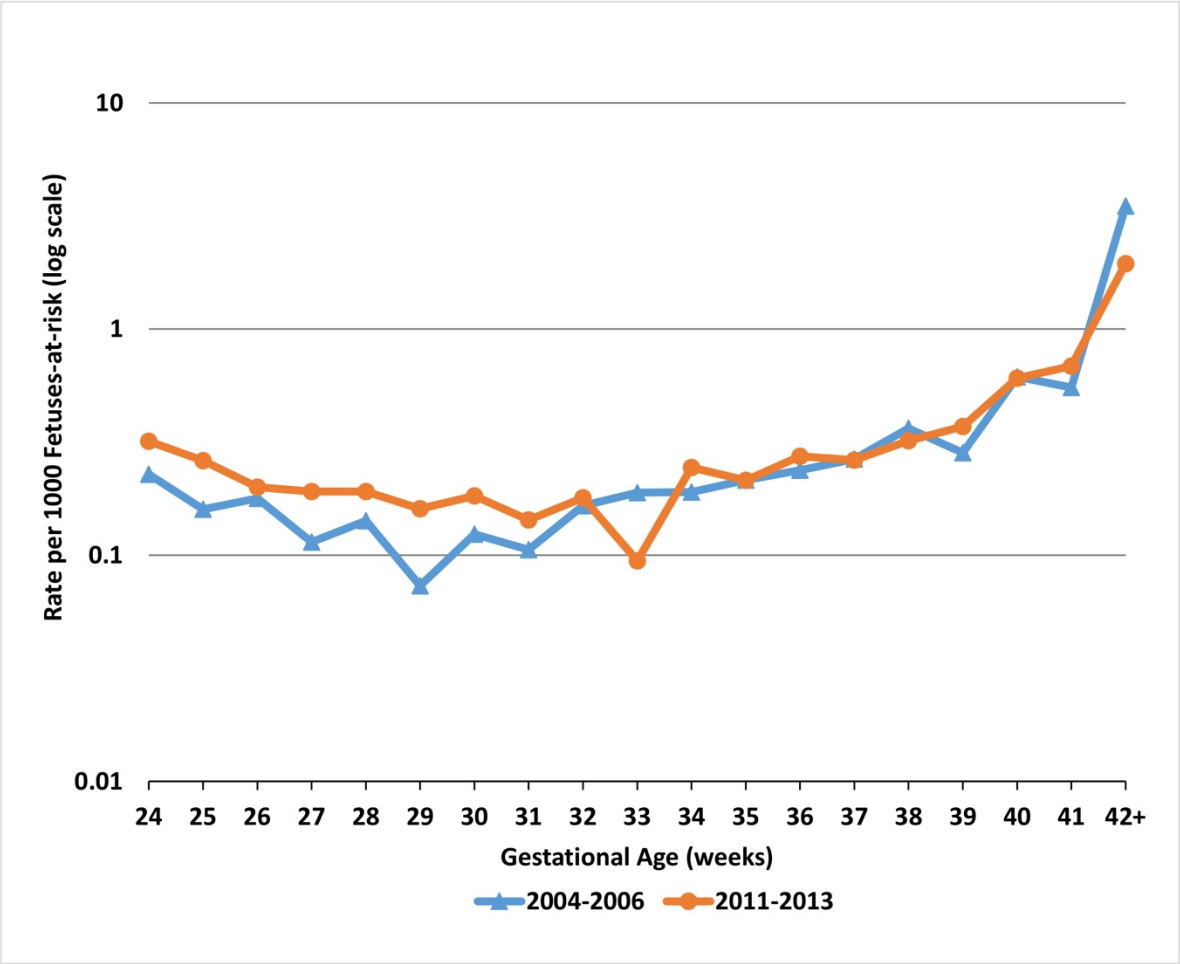
Appendix Table 1. Severe neonatal morbidity components and ICD-9-CM codes.

Neonatal morbidity	ICD-9-CM code
Bronchopulmonary dysplasia	770.7
Intraventricular hemorrhage	
Grade III – bleeding with enlargement of ventricle	772.13
Grade IV – bleeding into cerebral cortex	772.14
Periventricular leukomalacia	779.7
Retinopathy of prematurity	362.2
Necrotizing enterocolitis	777.5
Sepsis	
Septicemia of newborn	771.81
Convulsions	
Fits in newborn; seizures in newborn	779.0
Severe birth trauma	
Subdural and cerebral hemorrhage (whether described as due to birth trauma or to intrapartum anoxia or hypoxia; subdural hematoma (localized); tentorial tear	767.0
Epicranial subaponeurotic hemorrhage (massive); subgaleal hemorrhage	767.11
Injury to spine and spinal cord including:	767.4
Dislocation of spine or spinal cord due to birth trauma	
Fracture of spine or spinal cord due to birth trauma	
Laceration of spine or spinal cord due to birth trauma	
Rupture of spine or spinal cord due to birth trauma	

Appendix Figure 1. Study population flow chart, Washington State, U.S.A., 2004-2013.



Appendix Figure 2. Gestational age-specific rates of stillbirths calculated using the fetuses-at-risk (FAR) approach, Washington State, U.S.A., 2004-2013.



Appendix Table 2. Preterm live births by gestational age categories and clinical subtype, Washington State, U.S.A., 2004-2013.

Gestational age and clinical preterm birth subtype	All Years (2004-2013)	Period 1 (2004-2006)	Period 2 (2011-2013)	p-value* (Period 1 vs. Period 2)
24-27 weeks	1 833	489	598	<0.001
PPROM	509 (27.8)	181 (37.0)	130 (21.7)	
Spontaneous labor	532 (29.0)	135 (27.6)	189 (31.6)	
Iatrogenic	792 (43.2)	173 (35.4)	279 (46.7)	
28-31	4 095	1 135	1 357	<0.001
PPROM	909 (22.2)	295 (26.0)	264 (19.5)	
Spontaneous labor	1 255 (30.6)	357 (31.5)	416 (30.7)	
Iatrogenic	1 931 (47.2)	483 (42.6)	677 (49.9)	
32-33	5 664	1 469	1 848	0.006
PPROM	1 288 (22.7)	383 (26.1)	410 (22.2)	
Spontaneous labor	1 988 (35.1)	530 (36.1)	649 (35.1)	
Iatrogenic	2 388 (42.2)	556 (37.8)	789 (42.7)	
34-36	40 422	12 249	11 821	0.001
PPROM	5 809 (14.4)	1 912 (15.6)	1 673 (14.2)	
Spontaneous labor	18 973 (46.9)	5 770 (47.1)	5 530 (46.8)	
Iatrogenic	15 640 (38.7)	4 567 (37.3)	4 618 (39.1)	
All (24-36)	52 014	15 342	15 624	<0.001
PPROM	8 515 (16.4)	2 771 (18.1)	2 477 (15.9)	
Spontaneous labor	22 748 (43.7)	6 792 (44.3)	6 784 (43.4)	
Iatrogenic	20 751 (39.9)	5 779 (37.7)	6 363 (40.7)	

PPROM, preterm premature rupture of membranes

* p-value for Chi-square test comparing Period 1 and 2

Appendix Table 3 Gestational age-specific rates of adverse neonatal outcomes among singleton preterm infants, Washington State, U.S.A., 2004-2013.

Outcome and gestational age category	Rates per 100 live births		
	N (Rate)		Rate difference
	2004-2006	2011-2013	(95% CI)
Neonatal death			
24-27 weeks	76 (15.5)	85 (14.2)	-1.33 (-5.59, 2.93)
28-31	55 (4.9)	40 (3.0)	-1.90 (-3.44, -0.36)
32-33	23 (1.6)	18 (1.0)	-0.59 (-1.37, 0.19)
34-36	43 (0.4)	64 (0.5)	+0.19 (0.02, 0.36)
All (24-36)	197 (1.3)	207 (1.3)	+0.04 (-0.21, 0.29)
Neonatal death/ severe morbidity			
24-27 weeks	353 (72.2)	429 (71.7)	-0.45 (-5.82, 4.92)
28-31	383 (33.7)	496 (36.6)	+2.81 (-0.95, 6.57)
32-33	166 (11.3)	302 (16.3)	+5.04 (2.70, 7.38)
34-36	307 (2.5)	639 (5.4)	+2.90 (2.41, 3.39)
All (24-36)	1 209 (7.9)	1 866 (11.9)	+4.06 (3.40, 4.73)

CI, confidence interval; severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.

Appendix Table 4. Temporal trends in gestational-specific rates of severe neonatal morbidity components, Washington State, U.S.A., 2004-2013.

Neonatal Morbidity	Rates of Outcome by Period [N (per 100 live births)]		Adjusted Odds Ratio† (95% CI)
	2004-2006	2011-2013	
All PTB (24-36 weeks)			
BPD	306 (2.0)	269 (1.7)	**0.95 (0.93-0.98)**
IVH (grade ≥3)	72 (0.5)	61 (0.4)	**0.95 (0.90-1.00)**
PVL	13 (0.1)	27 (0.2)	1.10 (1.00-1.22)
ROP	60 (0.4)	86 (0.6)	1.02 (0.98-1.07)
NEC	129 (0.8)	173 (1.1)	1.02 (0.99-1.06)
Sepsis	686 (4.5)	1 331 (8.5)	**1.09 (1.08-1.11)**
Convulsions	53 (0.4)	62 (0.4)	1.00 (0.94-1.04)
Severe birth trauma	29 (0.2)	26 (0.2)	0.96 (0.89-1.04)
Late PTB (34-36 weeks)			
BPD	6 (0.1)	4 (0.0)	0.96 (0.81-1.12)
IVH (grade ≥3)	3 (0.0)	3 (0.0)	0.97 (0.78-1.21)
PVL	0 (0.0)	0 (0.0)	1.05 (0.64-1.72)
ROP	0 (0.0)	2 (0.0)	1.56 (0.85-2.87)
NEC	16 (0.1)	21 (0.2)	1.04 (0.95-1.14)
Sepsis	211 (1.7)	530 (4.5)	**1.12 (1.10-1.14)**
Convulsions	26 (0.2)	28 (0.2)	1.01 (0.93-1.09)
Severe birth trauma	16 (0.1)	14 (0.1)	0.97 (0.87-1.08)
PTB at 28-33 weeks			
BPD	121 (4.7)	95 (3.0)	**0.93 (0.89-0.97)**
IVH (grade ≥3)	24 (0.9)	19 (0.6)	0.92 (0.84-1.01)
PVL	8 (0.3)	15 (0.5)	1.06 (0.93-1.21)
ROP	35 (1.3)	63 (2.0)	1.05 (0.99-1.11)
NEC	76 (2.9)	89 (2.8)	1.00 (0.95-1.05)
Sepsis	306 (11.8)	554 (17.3)	**1.07 (1.05-1.10)**
Convulsions	19 (0.7)	20 (0.6)	0.96 (0.87-1.05)
Severe birth trauma	9 (0.4)	9 (0.3)	0.95 (0.82-1.11)
PTB at 24-27 weeks			

BPD	179 (36.6)	170 (28.4)	0.97 (0.94-1.01)
IVH (grade ≥3)	45 (9.2)	39 (6.5)	0.95 (0.88-1.01)
PVL	5 (1.0)	12 (2.0)	1.13 (0.96-1.32)
ROP	25 (5.1)	21 (3.5)	0.95 (0.87-1.02)
NEC	37 (7.6)	63 (10.5)	1.04 (0.98-1.10)
Sepsis	169 (34.6)	247 (41.3)	**1.05 (1.01-1.09)**
Convulsions	8 (1.6)	14 (2.3)	1.02 (0.91-1.14)
Severe birth trauma	4 (0.8)	3 (0.5)	0.94 (0.76-1.15)

CI, confidence interval; PTB, preterm birth; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.
Adjusted odds ratios express the average annual change in the odds for each morbidity.
Bolded value indicates statistical significance at $p<0.05$
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies. NOTE: some covariates were excluded from the regression models due to collinearity.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract **This was done, title page; "a population-based study"**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **This was done, abstract, page 2; "We described concomitant changes in…"**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **This was done, page 4-5; "However, it is unknown whether the temporal decline in preterm birth is associated with…"**
Objectives	3	State specific objectives, including any prespecified hypotheses **This was done, page 5; "Our aim was to describe temporal trends in …"**
Methods		
Study design	4	Present key elements of study design early in the paper **This was done, page 5; "We carried out a population-based study including…"**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **This was done, page 5; "… all singleton hospital births to mothers aged 15 to 60 in Washington State, U.S.A., between January 1, 2004, and…"**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **This was done, page 5-6; "We used information from two linked population databases…"**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **This was done, page 6-7; "The primary outcomes were neonatal mortality and a composite adverse outcome including…"**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **This was done, page 5-6; "…diagnosis and procedure codes related to each hospitalization episode coded by the International Classification of…"**
Bias	9	Describe any efforts to address potential sources of bias **This was done, page 6-7; inclusion/exclusion criteria, consistent use of case ascertainment by ICD-9-CM codes from administrative data to avoid recall bias**

		or diagnostic bias
Study size	10	Explain how the study size was arrived at **This was done, page 5; population-based; "… all singleton hospital births to mothers aged 15 to 60 in Washington State, U.S.A., between January 1, 2004, and…"**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **This was done, page 8-9; "The preterm birth rate was calculated as a proportion of live births…"**
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding **This was done, page 8; "Logistic regression was used to assess temporal trends…adjusted for temporal changes in risk factors…"**
		(b) Describe any methods used to examine subgroups and interactions **This was done, page 8-9; "Temporal trends in the individual components of the composite outcome were examined… using logistic regression models…"**
		(*c*) Explain how missing data were addressed **This was done; page 9; "Missing values for BMI… were imputed using multiple imputation… other missing values were <3% of the total, and the complete case multivariable analysis included 93% of preterm births…"**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **n/a**
		(*e*) Describe any sensitivity analyses **not included**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **This was done, page 10; "Overall, 871 649 singleton births occurred…the study population included 754 763 singleton infants born in hospital…"**
		(b) Give reasons for non-participation at each stage **This was done, page 10; "We excluded births at <24 or >45 weeks' gestation, multiple births, births that occurred outside of Washington State…"**
		(c) Consider use of a flow diagram **This was done, Appendix Figure 2**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **This was done, Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **This was done, Table 1**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **This was done; Table 2, Table 3, Table 4, Figure 1, Figure 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **This was done; Table 2, Table 3, Table 4**
		(*b*) Report category boundaries when continuous variables were categorized **This was done, Table 1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **This was done, page 16, Appendix Table 4**
Discussion		
Key results	18	Summarise key results with reference to study objectives **This was done, page 17; "Our findings show a decline in the preterm birth rate…"**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **This was done, page 20; "This study has a few limitations. First, clinical details on the severity of some…"**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **This was done, page 22; "The small decline in the preterm birth rate…was predominately due to…"**
Generalisability	21	Discuss the generalisability (external validity) of the study results **This was done, page 21; "We adjusted for a number of these indices thus our results are fairly generalizable to other states…or high-income countries…"**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **This was done, title page; "This work was supported by…"**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Temporal trends in neonatal mortality and morbidity following spontaneous and clinician-initiated preterm birth in Washington State, U.S.A.: a population-based study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023004.R2
Article Type:	Research
Date Submitted by the Author:	04-Dec-2018
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology, Paediatrics
Keywords:	Preterm Birth, Neonatal Mortality, Neonatal Morbidity, Trend, United States

Temporal trends in neonatal mortality and morbidity following spontaneous and clinician-initiated preterm birth in Washington State, U.S.A.: a population-based study

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Word count: Abstract 300; Text 4178.
Funding statement: This work was funded by the Canadian Institutes of Health Research (F17-02161), University of British Columbia Department of Obstetrics and Gynaecology, and the BC Women's Health Research Institute.
Competing interests statement: None declared.
Authors' contribution statement: SL and LR designed the study, LR and SL performed data analysis, and LR and SL wrote the first draft of the manuscript. GM, JT, AS and KL contributed to the interpretation of the results and critically revised the first draft. LR, SL, GM, JT, AS and KL approved the final version of the manuscript.
Ethics approval: All analyses were performed on publicly accessible de-identified data. An exemption from ethics approval was granted by the Department of Social and Health Services, State of Washington.
Data sharing statement: Analyses were based on administrative data collected and maintained by the Department of Health, State of Washington. The availability of the data is restricted. Permission for data access can granted after verification of the research goals by the Department of Social and Health Services, State of Washington.
Acknowledgements: SL is supported by a Michael Smith Foundation for Health Research Scholar Award. JT is supported by the Investigator Grant Award Program from British Columbia Children's Hospital Research Institute. GMM is supported by a Vanier Canada Graduate Scholarship.
Abbreviations: PPROM preterm premature rupture of membranes, AOR adjusted odds ratio, CI confidence interval.
Key words: Preterm Birth, Neonatal Mortality, Neonatal Morbidity, Trend, United States

ABSTRACT

Objective: After a decade of increase, the preterm birth (PTB) rate has declined in the United States since 2006, with the largest decline at late preterm (34-36 weeks). We described concomitant changes in gestational age-specific rates of neonatal mortality and morbidity following spontaneous and clinician-initiated PTB among singleton infants.

Design, Setting, and Participants: This retrospective population-based study included 754,763 singleton births in Washington State, U.S.A., 2004-2013, using data from birth certificates and hospitalization records. PTB subtypes included preterm premature rupture of membranes (PPROM), spontaneous onset of labor, and clinician-initiated delivery.

Outcome Measures: The primary outcomes were neonatal mortality and a composite outcome including death or severe neonatal morbidity. Temporal trends in the outcomes and individual morbidities were assessed by PTB subtype. Logistic regression yielded adjusted odds ratios (AOR) per 1-year change in outcome and 95% confidence intervals (CI).

Results: The rate of PTB following PPROM and spontaneous labor declined, while clinician-initiated PTB increased (all p-values<0.01). Overall neonatal mortality remained unchanged (1.3%; AOR 0.99, CI 0.95-1.02), though gestational age-specific mortality following clinician-initiated PTB declined at 32-33 weeks (AOR 0.85, CI 0.74-0.97), and increased at 34-36 weeks (AOR 1.10, CI 1.01-1.20). The overall rate of the composite outcome increased (from 7.9% to 11.9%; AOR 1.06, CI 1.05-1.08). Among late preterm infants, combined mortality or severe morbidity increased following PPROM (AOR 1.13, CI 1.08-1.18), spontaneous labor (AOR 1.09, CI 1.06-1.13), and clinician-initiated delivery (AOR 1.10, CI 1.07-1.13). Neonatal sepsis rates increased among all preterm infants (AOR 1.09, CI 1.08-1.11).

Conclusions: Timing of obstetric interventions is associated with infant health outcomes at preterm. The temporal decline in late PTB among singleton infants was associated with increased mortality among late preterm infants born following clinician-initiated delivery and increased combined mortality or severe morbidity among all late preterm infants, mainly due to increased rate of sepsis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large population-based database with detailed demographic and clinical information which allowed adjustment for temporal changes in many known risk factors for preterm birth
- Major clinical preterm birth subtypes were identified and subsequent neonatal outcomes were described by gestational age categories to provide clinically-relevant information
- Data on pregnancy and birth outcomes were collected and coded consistently over the study period
- Clinical details on severity of some neonatal morbidities including necrotizing enterocolitis and retinopathy of prematurity were not available
- Coding for neonatal sepsis did not differentiate between sepsis confirmed by blood or cerebrospinal fluid culture and a clinical diagnosis of sepsis without microbiological confirmation, or between early-onset and late-onset sepsis

INTRODUCTION

Preterm birth, defined as birth before 37 weeks' gestation, is the leading cause of neonatal mortality and morbidity, and a major risk factor for long-term neurological and respiratory morbidity and neurodevelopmental impairment.(1–3) In the United States, the rate of preterm birth increased by 24% between 1990 and 2006, from 10.6 to 13.1 per 100 live births, mainly due to an increase in obstetric intervention at late preterm (34-36 weeks' gestation).(4–6) More recently, preterm birth rates declined to 9.8 per 100 live births in the United States in 2015.(7,8) Nevertheless, the high rate of preterm birth remains a considerable concern.

Preterm birth can result from many possible etiologies.(9) The three major clinical subtypes of preterm birth include: clinician-initiated preterm birth, preterm birth following preterm premature rupture of membranes (PPROM), and preterm birth following spontaneous labor with intact membranes.(1,9) Clinician-initiated preterm birth, including labor induction and cesarean delivery without labor, constitutes about 30-40% of all preterm births, and pre-eclampsia/eclampsia and severe intrauterine growth restriction are the common indications.(9–11) Spontaneous preterm birth can result from multiple causes, including infection or inflammation, incompetent cervix, vascular/placental disorders (other than preeclampsia), and uterine over-distension.(9)

While gestational age at birth is the strongest predictor of adverse neonatal outcomes, the subtype of preterm birth is also important. Preterm infants born to women with spontaneous onset of labor have a better prognosis than infants born following clinician-initiated delivery.(5,12–15) However, it is unknown whether the temporal decline in preterm birth is associated with changes in neonatal mortality and morbidity among preterm infants.

Our aim was to describe temporal trends in gestational age-specific rates of neonatal mortality and a composite adverse outcome, defined as neonatal death or any severe morbidity, among preterm infants born following PPROM, spontaneous onset of labor and clinician-initiated delivery. We further examined gestational age-specific rates in the specific neonatal morbidity components included in the composite outcome.

METHODS

Study Population

We carried out a population-based study including all singleton hospital births to mothers aged 15 to 60 years in Washington State, U.S.A., between January 1, 2004, and December 31, 2013. We used information from two linked population databases: (1) live birth, fetal and infant death certificates with data on maternal demographic characteristics, obstetric history, and pregnancy and birth factors, from the Birth Events Record Database (BERD); and (2) hospitalization files with information on specific infant morbidities from the Comprehensive Hospital Abstract Reporting System (CHARS). The BERD included information abstracted by trained abstractors using standardized forms about maternal characteristics (e.g., maternal age, pre-pregnancy body mass index [BMI], race, education, marital status, smoking status, chronic hypertension, pre-pregnancy diabetes, and the type of health care insurance provider); obstetric history (e.g., parity, assisted conception); and pregnancy, labor, and birth characteristics (e.g., gestational age at delivery, use of tocolytics, use of steroids at delivery, mode of delivery, prolonged labor, congenital anomalies, neonatal death and birth outcomes). The CHARS database included information on all newborn hospitalizations in Washington State with diagnosis and procedure codes related to each hospitalization episode coded by the International Classification of

Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The completeness and accuracy of these databases was monitored by the Washington State Department of Health with annual assessments and consistency checks.(16–18) Records flagged with inconsistent or out-of-range entries were addressed systematically through hospital review and correction. The frequency of diagnostic and procedure codes was monitored in annual reports.(18) Previous validation studies of the linked dataset showed that the positive and negative predictive values (PPV and NPV) for delivery characteristics were above 80% and 98%, respectively; (19,20) for example, labor induction had PPV 89.0% and NPV 94.5%.(20) Gestational age at delivery was based on ultrasound dating, and last menstrual period dating was used for women with missing ultrasound data. We excluded infants born at less than 24 weeks' and greater than 45 weeks' gestation, and those with missing data on gestational age from the overall study population. After analysis of temporal trends in stillbirth, we excluded stillborn infants and those with missing mode of delivery to limit the analyses of neonatal outcomes following various types of preterm birth to live births only.

Classification of Preterm Birth

Preterm birth was defined as a live birth at 24 to 36 completed weeks' gestation. Preterm birth subtypes were categorized using the following algorithm: (1) first, spontaneous preterm births following PPROM (≥12 hours); (2) second, clinician-initiated preterm births following labor induction or cesarean delivery without labor; and (3) third, all other births were classified as spontaneous preterm births following spontaneous labor onset with intact membranes (Supplementary File 1, items no 62, 64, 65).

Outcome Measures and Covariates

The primary outcomes were neonatal mortality and a composite adverse outcome including death or severe neonatal morbidity. Neonatal mortality was defined as death of an infant that occurred within the first 28 days after birth, including deaths in the delivery room, in-hospital deaths, and deaths after hospital discharge. Severe neonatal morbidity was identified using ICD-9-CM codes and included (a) bronchopulmonary dysplasia (BPD); (b) intraventricular hemorrhage grade ≥3 (IVH); (c) periventricular leukomalacia (PVL); (d) retinopathy of prematurity (ROP); (e) necrotizing enterocolitis (NEC), (f) neonatal sepsis; (g) convulsions of newborn; and (h) severe birth trauma (Appendix Table 1).

Temporal changes in maternal characteristics over the study period were examined, including maternal age (<20, 20-29, 30-39, 40+ years); pre-pregnancy BMI (underweight <18.5 kg/m^2, normal BMI 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, and obese ≥30 kg/m^2); race (non-Hispanic White, African American, Native American, Hispanic, and other); maternal education (≤8 years vs. >8 years); smoking during pregnancy (yes/no); marital status (married/common law vs. other); parity (prior live births, yes/no); chronic hypertension (yes/no); pre-pregnancy diabetes (yes/no); assisted conception (yes/no); use of antenatal steroids (yes/no); use of tocolytics (yes/no); and type of health insurance coverage (Medicaid, self-pay, private, other). We also examined temporal trends in infant characteristics including gestational ages in completed weeks (within gestational age categories), small-for-gestational age infant (SGA, <10th percentile (21); yes/no), infant's sex (male/female), congenital anomalies, and stillbirths. Congenital anomalies were identified from BERD and included the following conditions observed within the first 24 hours after birth: anencephaly, meningomyelocele or spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis,

limb reduction, cleft lip, cleft palate, Down syndrome, chromosomal disorders, and hypospadias. We adjusted for temporal trends in these conditions as a potential risk factor for adverse outcomes. Stillbirth was defined as spontaneous intrauterine death of a fetus. Gestational age-specific rates of stillbirths were calculated using the fetuses-at-risk (FAR) approach.(22) Under this approach, ongoing pregnancies (fetuses in-utero) at each gestation were used as denominators (the appropriate at-risk population) for the calculation of gestational age-specific stillbirth rates.(22,23)

Statistical Analyses

The preterm birth rate was calculated as a proportion of live births at 24 to 36 weeks' gestation among infants born alive at ≥24 weeks. Gestational age-specific temporal trends were described as proportions of extremely preterm births (24-27 weeks), very preterm (28-31 weeks), moderately preterm (32-33 weeks), and late preterm births (34-36 weeks). The Cochran-Armitage test was used to assess the statistical significance of temporal trends over the years. The rates of neonatal mortality and the composite outcome of neonatal death or severe morbidity were also contrasted between years 2004-2006 vs. 2011-13, using rate ratio (RR) and rate difference (RD) and 95% confidence intervals (CI).

Logistic regression was used to assess temporal trends in adverse neonatal outcomes adjusted for temporal changes in risk factors that may have changed over the study period: maternal age, pre-pregnancy BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies. Calendar year was modelled as a continuous variable. Temporal trends in adverse outcomes were expressed as the average annual change in

the odds of neonatal mortality and combined neonatal death or severe neonatal morbidity with adjusted odds ratios (AOR) and 95% CI.

Additional Analyses

Temporal trends in the individual components of the composite outcome were examined as secondary outcomes using logistic regression models as described above. These analyses were performed including all preterm live born infants, and also for subgroups of infants born at late preterm, at 28-33 weeks, and at 24-27 weeks' gestation.

All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). Missing values for BMI (approximately 10%) were imputed using multiple imputation (PROC MI). Other missing values were <3.0% of the total, and the complete case multivariable analysis excluded 7.0% of preterm births. All p-values are reported as recommended by the American Statistical Association.(24) All analyses were performed on publicly accessible de-identified data. An exemption from ethics approval was granted by the Department of Social and Health Services, State of Washington.

Patient and Public Involvement

No patients or public were directly involved in this study.

RESULTS

Study Population

Overall, 871 649 singleton births occurred in Washington State from 2004 to 2013. We excluded births at before 24 weeks or after 45 weeks' gestation, multiple births, births that occurred outside of Washington State and out-of-hospital births, as well as births that could not be matched with hospital records (N=116 886, 13.4%). The study population included 754 763 singleton infants born in hospital at ≥24 weeks; of these, 2 549 infants were stillborn (0.34%). Further, births with missing information on mode of delivery (N=14 503, 1.9%) were excluded for analyses of preterm birth rates by type of delivery (live births included 737 711 infants; Appendix Figure 1).

The rate of stillbirth increased slightly from 3.2 per 1000 total births in 2004-2006 to 3.7 in 2011-2013 (p=0.002). Stillbirth rates increased at 24-27 weeks (from 0.7 to 1.0 per 1000 fetuses-at-risk (FAR), p=0.003), and at 28-31 weeks' gestation (from 0.4 to 0.7 per 1000 FAR, p=0.002; Appendix Figure 2).

Maternal characteristics changed over the study period; women who delivered in 2011-2013 were older, more educated, and had higher pre-pregnancy BMI than those who gave birth in 2004-2006 (Table 1). The proportions of births to mothers of Hispanic and African American origin, unmarried mothers, and nulliparous mothers increased, while the proportions of mothers who smoked during pregnancy decreased over time. More mothers had chronic hypertension or pre-pregnancy diabetes, and more pregnancies occurred from assisted conception in 2011-2013 than in 2004-2006. The use of antenatal steroids for lung maturation at delivery increased over the study period, while the use of tocolytics declined. All temporal changes were statistically significant (p<0.001, Table 1).

Table 1. Maternal and infant characteristics among all singleton infants born at ≥24 weeks' gestation), Washington State, U.S.A., 2004-2013.

Characteristic	All Years (2004-2013)	Period 1 (2004-2006)	Period 2 (2011-2013)	p-value* (Period 2 vs. Period 1)
Total singleton births	754 763	219 233	225 429	
Maternal age (years)				<0.001
<20	57 042 (7.5)	18 454 (8.4)	13 603 (6.0)	
20-29	387 712 (51.4)	114 244 (52.1)	112 427 (49.9)	
30-39	287 479 (38.1)	80 300 (36.6)	92 175 (40.9)	
≥40	22 530 (3.0)	6 235 (2.8)	7 224 (3.2)	
Maternal BMI (kg/m^2)				<0.001
Underweight (<18.5)	21 563 (2.9)	6 467 (3.0)	6 477 (2.9)	
Normal (18.5-24.9)	324 689 (43.0)	91 968 (42.0)	97 451 (43.2)	
Overweight (25-29.9)	177 020 (23.5)	47 444 (21.6)	55 439 (24.6)	
Obese (≥30)	162 030 (21.5)	41 138 (18.8)	53 556 (23.8)	
Missing values	69 461 (9.2)	32 216 (14.7)	12 506 (5.6)	
Maternal race				<0.001
Non-Hispanic White	480 468 (63.7)	143 356 (65.4)	141 132 (62.6)	
African American	34 112 (4.5)	8 964 (4.1)	11 098 (4.9)	
Native American	14 962 (2.0)	4 503 (2.1)	4 265 (1.9)	
Hispanic	144 035 (19.1)	40 603 (18.5)	42 543 (18.9)	
Other	77 638 (10.3)	20 558 (9.4)	25 266 (11.2)	
Type of health insurance				<0.001
Medicaid	298 366 (39.5)	83 608 (38.1)	91 829 (40.7)	
Self-Pay	7 369 (1.0)	2 100 (1.0)	2 561 (1.1)	
Private	386 778 (51.2)	109 452 (49.9)	115 198 (51.1)	
Other**	42 500 (5.6)	13 375 (6.1)	12 013 (5.3)	
Maternal education (≤8 years)	27 731 (3.6)	9 958 (4.5)	6 334 (2.8)	<0.001
Smoking during pregnancy	72 846 (9.7)	22 073 (10.1)	20 339 (9.0)	<0.001
Unmarried	252 963 (33.5)	69 033 (31.5)	77 143 (34.2)	<0.001
No prior live births	310 297 (41.1)	88 552 (40.4)	92 232 (40.9)	<0.001
Chronic hypertension	9 669 (1.3)	2 650 (1.2)	3 002 (1.3)	0.003
Pre-pregnancy diabetes	5 472 (0.7)	1 367 (0.6)	1 755 (0.8)	<0.001
Assisted conception	6 887 (0.9)	1 551 (0.7)	2 487 (1.1)	<0.001
Gestational age (weeks)				<0.001
24-27	2 495 (0.3)	678 (0.3)	820 (0.4)	
28-31	4 649 (0.6)	1 299 (0.6)	1 520 (0.7)	
32-33	6 063 (0.8)	1 640 (0.8)	1 919 (0.9)	
34-36	41 775 (5.5)	12 808 (5.8)	12 072 (5.4)	
≥37	699 781 (92.7)	202 808 (92.5)	209 098 (92.8)	
SGA infant (<10th percentile)	6 590 (0.9)	1 767 (0.8)	2 122 (0.9)	<0.001
Infant sex (male)	386 468 (51.2)	112 128 (51.2)	116 049 (51.5)	0.026
Congenital anomalies***	3 656 (0.5)	996 (0.5)	1 133 (0.5)	0.066

BMI, pre-pregnancy body mass index; SGA, small-for-gestational-age
* p-value for Chi-square test comparing Period 1 and 2.
** Includes other government insurance, student insurance, Indian Health Care, and other programs.
*** Includes the following conditions observed within first 24 hours after birth: anencephaly, meningomyelocele or spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction, cleft lip, cleft palate, Down syndrome, chromosomal disorders, and hypospadias.
Note: Some percentages do not add up due to missing values; missing values <3% are not shown.

Preterm Birth Rates

There were 737 711 singleton live births between 2004 and 2013; out of these, 52 014 infants were born preterm (7.1%). Among the preterm infants, 16.4% were born following PPROM, 43.7% were born following spontaneous onset of labor, and 39.9% were born following clinician-initiated delivery (Appendix Table 2). The overall preterm birth rate declined from 7.3% in 2004-2006 to 7.0% of singleton live births in 2011-2013. This decline was attributed to the decline in spontaneous delivery following PPROM (1.3% to 1.1%), and spontaneous onset of labor (3.2% to 3.0%). In contrast, clinician-initiated preterm birth increased slightly from 2.7% to 2.9% (all p-values for trend <0.01; Figure 1).

Gestational age-specific trends in the type of preterm birth varied (Figure 2). There were 1 833 live births at 24-27 weeks (0.2%); of these 27.8% were PPROM, 29.0% were spontaneous onset of labor, and 43.2% were clinician-initiated delivery. At 28-31 weeks, there were 4 095 live births (0.6%); 22.3% were PPROM, 30.6% were spontaneous onset of labor, and 47.2% were clinician-initiated. At 32-33 weeks, there were 5 664 live births (0.8%); 22.7% were PPROM, 35.1% were spontaneous onset of labor, and 42.2% were clinician-initiated. At 34-36 weeks, there were 40,422 live births (5.5%); 14.4% were PPROM, 46.9% were spontaneous onset of labor, and 38.7% were clinician-initiated. The overall preterm birth rate increased in all

gestational age categories except for late preterm births where the rate declined from 5.8% to 5.3% (all p<0.01). In each gestational age category, the clinician-initiated preterm birth rate increased, and the PPROM preterm birth rate declined over time (all p<0.05).

Neonatal Mortality

Neonatal mortality remained unchanged over time (1.3%, Table 2). Neonatal mortality increased among late preterm infants between 2004-2006 and 2011-2013 (RR 1.25, 95% CI 0.85-1.84; average change per year AOR 1.064, 95% CI 1.003-1.129; Table 2). Overall, higher neonatal mortality was among infants delivered following PPROM (1.7%) and clinician-initiated delivery (1.6%) as compared with spontaneous delivery (0.8%).

A significant decline in mortality was observed among infants born following clinician-initiated delivery at 32-33 weeks, from 2.5% in 2004-2006 to 1.0% in 2011-2013 (RR 0.40, 95% CI 0.17-0.95; AOR 0.85, 95% CI 0.74-0.97; Table 3). In contrast, neonatal mortality increased from 0.5% to 0.8% (RR 1.60, 95% CI 0.94-2.73; AOR 1.10, 95% CI 1.01-1.20) among infants following clinician-initiated delivery at 34-36 weeks.

Table 2. Gestational age-specific rates of adverse neonatal outcomes among singleton preterm infants, Washington State, U.S.A., 2004-2013.

Outcome and gestational age category	Rates per 100 live births			Adjusted odds ratio per 1-year change† (95% CI)
	N (Rate)		Rate ratio (95% CI)	
	2004-2006	2011-2013		
Neonatal death				
24-27 weeks	76 (15.5)	85 (14.2)	0.92 (0.67-1.25)	0.97 (0.92-1.03)
28-31	55 (4.9)	40 (3.0)	0.61 (0.41-0.92)	0.95 (0.89-1.01)
32-33	23 (1.6)	18 (1.0)	0.63 (0.34-1.16)	0.93 (0.84-1.02)
34-36	43 (0.4)	64 (0.5)	1.25 (0.85-1.84)	1.06 (1.00-1.13)
All (24-36)	197 (1.3)	207 (1.3)	1.00 (0.82-1.22)	0.99 (0.95-1.02)
Neonatal death/ severe morbidity				
24-27 weeks	353 (72.2)	429 (71.7)	0.99 (0.86-1.14)	1.00 (0.96-1.04)
28-31	383 (33.7)	496 (36.6)	1.08 (0.95-1.24)	1.03 (1.00-1.06)

32-33	166 (11.3)	302 (16.3)	1.44 (1.19-1.74)	1.05 (1.02-1.08)
34-36	307 (2.5)	639 (5.4)	2.16 (1.89-2.47)	1.10 (1.08-1.12)
All (24-36)	1 209 (7.9)	1 866 (11.9)	1.51 (1.40-1.62)	1.06 (1.05-1.08)

CI, confidence interval; severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.
Adjusted odds ratios express the average annual change in the odds of the outcome.
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Table 3. Gestational age-specific rates of neonatal death by subtype of preterm birth, Washington State, U.S.A., 2004-2013.

Gestational age category and preterm birth subtype	Neonatal death			Adjusted odds ratio per 1-year change† (95% CI)
	N (per 100 live births)		Rate ratio (95% CI)	
	2004-2006	2011-2013		
24-27 weeks				
PPROM	27 (14.9)	18 (13.9)	0.93 (0.51-1.69)	1.05 (0.94-1.17)
Spontaneous labor	21 (15.6)	26 (13.8)	0.88 (0.50-1.57)	0.95 (0.86-1.06)
Clinician-initiated	28 (16.2)	41 (14.7)	0.91 (0.56-1.47)	0.94 (0.86-1.03)
28-31 weeks				
PPROM	14 (4.8)	5 (1.9)	0.40 (0.14-1.10)	0.92 (0.78-1.07)
Spontaneous labor	11 (3.1)	9 (2.2)	0.71 (0.30-1.71)	0.91 (0.77-1.06)
Clinician-initiated	30 (6.2)	26 (3.8)	0.61 (0.36-1.04)	0.96 (0.88-1.06)
32-33 weeks				
PPROM	2 (0.5)	5 (1.2)	2.40 (0.47-12.37)	1.08 (0.80-1.45)
Spontaneous labor	7 (1.3)	5 (0.8)	0.62 (0.20-1.94)	0.97 (0.83-1.13)
Clinician-initiated	14 (2.5)	8 (1.0)	0.40 (0.17-0.95)	0.85 (0.74-0.97)
34-36 weeks				
PPROM	14 (0.7)	7 (0.4)	0.57 (0.23-1.42)	0.97 (0.84-1.12)
Spontaneous labor	7 (0.1)	22 (0.4)	4.00 (1.71-9.36)	1.08 (0.96-1.20)
Clinician-initiated	22 (0.5)	35 (0.8)	1.60 (0.94-2.73)	1.10 (1.01-1.20)
All (24-36 weeks)				
PPROM	57 (2.1)	35 (1.4)	0.67 (0.44-1.02)	1.00 (0.93-1.07)
Spontaneous labor	46 (0.7)	62 (0.9)	1.29 (0.88-1.88)	0.98 (0.92-1.04)
Clinician-initiated	94 (1.6)	110 (1.7)	1.06 (0.81-1.40)	0.98 (0.94-1.03)

PPROM, preterm premature rupture of membranes; CI, confidence interval
Adjusted odds ratios express the average annual change in the odds of neonatal death.
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Composite outcome: Neonatal Mortality or Severe Morbidity

The rate of combined mortality or severe morbidity increased from 7.9% in 2004-2006 to 11.9% in 2011-2013 (RR 1.51, 95% CI 1.40-1.62; average change per year AOR 1.06, 95% CI 1.05-1.08; Table 2). This increase was predominately due to an increase in combined mortality or severe morbidity among infants born at 32-33 weeks and 34-36 weeks' gestation (RR 1.44, 95% CI 1.19-1.74, and RR 2.16, 95% CI 1.89-2.47, respectively); the relative average increase in the odds of combined neonatal mortality or severe morbidity was 5% per year among infants born at 32-33 weeks (AOR 1.05, 95% CI 1.02-1.08), and 10% per year among infants born at 34-36 weeks (AOR 1.10, 95% CI 1.08-1.12). Rate differences are shown in Appendix Table 3.

The rate of composite neonatal mortality or severe morbidity increased in each preterm birth subtype (all $p<0.001$, Table 4). The rate was highest among infants born following PPROM (14.8%), and these infants had the largest relative increase (10% per year) in combined mortality or severe morbidity over the study period (AOR 1.10, 95% CI 1.07-1.13). Gestational age-specific analyses of trends in combined neonatal mortality or severe morbidity showed an increase in the rates among infants born at 34-36 weeks in all subtypes of preterm birth (PPROM: RR 2.20, 95% CI 1.64-2.96; spontaneous: RR 2.32, 95% CI 1.85-2.90; clinician-initiated: RR 2.04, 95% CI 1.65-2.51; Table 4), and increases in the rates among infants born following PPROM at 28-31 weeks (AOR 1.07, 95% CI 1.02-1.13) and 32-33 weeks (AOR 1.12, 95% CI 1.06-1.19). In addition, a significant increase in combined neonatal mortality or severe morbidity was observed among infants born following spontaneous onset of labor at 24-27 weeks' gestation (AOR 1.09, 95% CI 1.01-1.17). In contrast, clinician-initiated delivery at 24-27 weeks was associated with a decline in the rate of composite adverse outcome (AOR 0.93, 95% CI 0.87-0.99).

Table 4. Gestational age-specific rates of neonatal death/severe morbidity by subtype of preterm birth, Washington State, U.S.A., 2004-2013.

Gestational age category and preterm birth subtype	Neonatal death/severe morbidity			Adjusted odds ratio per 1-year change† (95% CI)
	N (per 100 live births)		Rate ratio (95% CI)	
	2004-2006	2011-2013		
24-27 weeks				
PPROM	133 (73.5)	98 (75.4)	1.03 (0.79-1.33)	1.01 (0.94-1.10)
Spontaneous labor	89 (65.9)	142 (75.1)	1.14 (0.87-1.49)	1.09 (1.01-1.17)
Clinician-initiated	131 (75.7)	189 (67.7)	0.89 (0.72-1.12)	0.93 (0.87-0.99)
28-31 weeks				
PPROM	101 (34.2)	112 (42.4)	1.24 (0.95-1.62)	1.07 (1.02-1.13)
Spontaneous labor	112 (31.4)	144 (34.6)	1.10 (0.86-1.41)	1.02 (0.98-1.08)
Clinician-initiated	170 (35.2)	240 (35.5)	1.01 (0.83-1.23)	1.02 (0.98-1.06)
32-33 weeks				
PPROM	42 (11.0)	90 (22.0)	2.00 (1.39-2.88)	1.12 (1.06-1.19)
Spontaneous labor	60 (11.3)	87 (13.4)	1.19 (0.85-1.65)	1.01 (0.96-1.07)
Clinician-initiated	64 (11.5)	125 (15.8)	1.37 (1.02-1.86)	1.04 (0.99-1.08)
34-36 weeks				
PPROM	67 (3.5)	129 (7.7)	2.20 (1.64-2.96)	1.13 (1.08-1.18)
Spontaneous labor	111 (1.9)	245 (4.4)	2.32 (1.85-2.90)	1.09 (1.06-1.13)
Clinician-initiated	129 (2.8)	265 (5.7)	2.04 (1.65-2.51)	1.10 (1.07-1.13)
All (24-36 weeks)				
PPROM	343 (12.4)	429 (17.3)	1.40 (1.21-1.61)	1.10 (1.07-1.13)
Spontaneous labor	372 (5.5)	618 (9.1)	1.65 (1.45-1.88)	1.06 (1.04-1.09)
Clinician-initiated	494 (8.6)	819 (12.9)	1.50 (1.34-1.68)	1.05 (1.03-1.07)

PPROM, preterm premature rupture of membranes; CI, confidence interval, severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.

Adjusted odds ratios express the average annual change in the odds of neonatal death and/or morbidity.

†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies.

Additional analyses

The most prominent temporal trend in the rates of specific severe neonatal morbidities was an increase in the rate of neonatal sepsis, from 4.5% in 2004-2006 to 8.5% in 2011-2013 (AOR 1.09, 95% CI 1.08-1.11). The rate of sepsis increased substantially among late preterm infants from 1.7% to 4.5% (AOR 1.12, 95% CI 1.10-1.14), infants born at 28-33 weeks (AOR 1.07, 95%

CI 1.05-1.10), and those born at 24-27 weeks (AOR 1.05, 95% CI 1.01-1.09). In contrast, the rate of BPD among preterm infants decreased from 2.0% to 1.7% (AOR 0.95, 95% CI 0.93-0.98; Appendix Table 4), mainly in infants born at 28-33 weeks (AOR 0. 93, 95% CI 0.89-0.97).

DISCUSSION

Our findings show a decline in the preterm birth rate in Washington State between 2004 and 2013 that was predominately due to a decline in spontaneous preterm birth (PPROM and spontaneous preterm labor), while clinician-initiated preterm deliveries increased slightly. These changes were associated with increased mortality among late preterm infants born following clinician-initiated delivery and increased rates of the composite outcome of neonatal mortality or severe morbidity among all late preterm infants. The rise in neonatal morbidity was driven mainly by the increase in the rate of neonatal sepsis.

After a large increase in the preterm birth rate in the United States in the early 2000s, a decline was observed from 12.8% in 2006 to 9.8% in 2015.(4–8) A recent study by Gyamfi-Bannerman *et al*. showed a decline in both clinician-initiated and spontaneous preterm birth rates between 2005 and 2012.(10) Our study provides more detailed information on preterm birth categories and describes temporal trends in neonatal outcomes adjusted for changes in important risk factors.

Obstetric interventions, changes in practice patterns, and implementation of specific evidence-based guidelines for high-risk women may be reasons behind the decline in preterm birth following spontaneous onset of labor. The use of 17 α-hydroxyprogesterone caproate (17P) for women with previous spontaneous preterm births, and the use of vaginal progesterone for select women with short cervical length and without prior preterm birth progressively increased

between 2006 and 2013 and may have led to a decline in spontaneous preterm births.(6,25–29) More aggressive pursuit of expectant management in PPROM, preeclampsia and intrauterine growth restriction may have led to a delivery at later gestation in high-risk mothers.(30–32) Other changes including declines in births to teenage mothers may have contributed to an overall decline in the preterm birth rate, while increases in maternal age, obesity, and assisted conception have likely contributed to an increase in clinician-initiated delivery in general.(33–35)

In 1999 and 2009, the American College of Obstetrics and Gynecologists (ACOG) advocated against elective deliveries under 39 weeks of gestation in an effort to prevent non-medically-indicated preterm births and the potentially avoidable morbidity associated with these deliveries.(36,37) Previous studies have shown that timely medically-indicated clinician-initiated delivery can prevent stillbirth and reduce neonatal mortality.(23,38,39) A population-based study of all births in the United States showed that the 68% increase in clinician-initiated preterm births between 1995 and 2005 was not associated with increased rates of neonatal mortality/morbidity.(5) In our study, the small increase in clinician-initiated interventions was associated with reduced mortality at 32-33 weeks and reduced mortality/severe morbidity at 24-27 weeks. However, at late preterm, declines in spontaneous and PPROM birth and increases in clinician-initiated delivery were associated with increased rates of mortality/severe morbidity. This may be due temporal increase in maternal chronic morbid conditions that we did not adjust for in our study, for example, asthma, autoimmune conditions, or respiratory morbidity.

The increase in neonatal sepsis was observed in all subtypes of late preterm birth, which points to possible common causes relatively independent of delivery type. However, the pathology of neonatal sepsis can vary by preterm birth subtype (for example, originating from

the effects of chorioamnionitis in PPROM, or IUGR in clinician-initiated delivery), and the uniform increase may be due to the broad definition of sepsis in our study, which included early and late onset sepsis. This unfavorable trend in adverse neonatal outcomes in our study thus warrants further investigation, as prior studies of clinical sepsis (defined broadly as 'other infection specific to neonatal period') in the first 3 months after birth showed a small decline between 1988 and 2006 among preterm infants in the U.S.A.(40) The reasons behind the increased rates of sepsis in our study may include temporal changes in the proportion of vulnerable infants, increased use of antenatal steroids, or changes in antibiotic use and antibiotic resistance.(40,41) Currently, there is lack of clinical diagnostic criteria or ideal laboratory marker for neonatal sepsis with excellent sensitivity for daily clinical operations, rendering the assessment of variation in the incidence rates of neonatal sepsis difficult.(41–43) Antibiotics are essential in the treatment of bacterial sepsis, and are the most commonly used medications in neonatal intensive units; however, overly liberal antimicrobial use has been associated with increased adverse neonatal outcomes.(44) A large population study in California showed substantial variations in antibiotic use that was not related to proven infection, NEC, surgical case volume, or Neonatal Intensive Care Unit (NICU) mortality, especially among community and intermediate NICUs.(44) Unified diagnostic criteria and antimicrobial policies are needed to further examine and address this issue.

The strengths of our study include a large population-based database with detailed information on demographic and clinical risk factors (e.g., BMI, assisted conception) and obstetric history (e.g., parity, prior adverse outcomes). We were, therefore, able to adjust for temporal changes in a large spectrum of known risk factors for preterm birth. Data on pregnancy and birth outcomes were collected consistently over the study period, and neonatal morbidity

was also coded consistently using exclusively ICD-9-CM during the entire study period. The ICD-9-CM code for neonatal sepsis did not change over the study period, and there was no indication of any major changes in clinical diagnostic criteria.

This study has a few limitations. First, clinical details on severity of some neonatal morbidity were not available, for example, the NEC Stage I or ROP Grade I, both of which can be treated conservatively. This led to the inclusion of infants with less severe NEC and ROP or other components of the composite outcome. Second, the ICD-9-CM code for neonatal sepsis did not differentiate between sepsis confirmed by blood or cerebrospinal fluid culture and a clinical diagnosis of sepsis without microbiological confirmation, or between early-onset and late-onset sepsis. This could lead to over-diagnosis of neonatal infection. Third, information on termination of pregnancy was not available; thus, we could not account for these temporal changes. However, the vast majority of pregnancy terminations are likely to occur prior to 24 weeks' gestation; terminations beyond 23 weeks would be included as stillbirths in this study. Temporal changes in gestational age-specific stillbirth rates showed small increases in stillbirth rates at 24-27 weeks and 28-31 weeks, which augments the upward trend in adverse neonatal outcome (mortality or severe morbidity) at 28-31 weeks' gestation. Fourth, potential errors and omissions are inevitable in large databases; these may have led to non-differential misclassification, which may have resulted in the underestimation of temporal trends. Fifth, the data sources had detailed information on mode of delivery that allowed accurate categorization of preterm birth subtypes; however, this categorization may have overestimated the proportion of deliveries following PPROM.(45) Data collection had not changed over the study period, however, changes in physician's preferences for specific mode of delivery (e.g., trial of labor before cesarean delivery) may be responsible for year-to-year fluctuation in temporal trends in preterm birth

subtypes. Lastly, a relatively large number of temporal trends were assessed, possibly rendering some trends statistically significant due to chance. In addition, singleton infants excluded due to out-of-hospital delivery or missing values may have impacted our results, however, non-hospital births are more likely to be term deliveries without complications requiring hospitalization. Washington State has one of the lowest preterm birth rates in the USA, and lowest infant mortality rates;(46) however, the ranking is very much dependent on the ethnicity, age, and socioeconomic status composition of the obstetric population.(46) We adjusted for a number of these indices thus our results are relevant to other states in the U.S.A. and high-income countries in general.

CONCLUSION

Our objectives were to assess temporal trends in gestational age-specific rates of neonatal mortality and a composite outcome of neonatal mortality or severe morbidity among preterm infants. The small decline in the preterm birth rate in Washington State from 2004 to 2013 was predominantly due to a decline in the rates of spontaneous onset of labor and PPROM at late preterm. This was associated with increased neonatal mortality among late preterm infants born following clinician-initiated delivery, and increased rate of composite outcome including neonatal death or severe morbidity among all late preterm infants. The increase in adverse neonatal outcomes among late preterm infants and increase in sepsis rates among all preterm infants warrant further investigation. Our results are important for identifying areas for improvement in obstetric and neonatal health care, and serve as hypothesis generating findings to direct further research.

List of tables:

List of figures:

Supplement:

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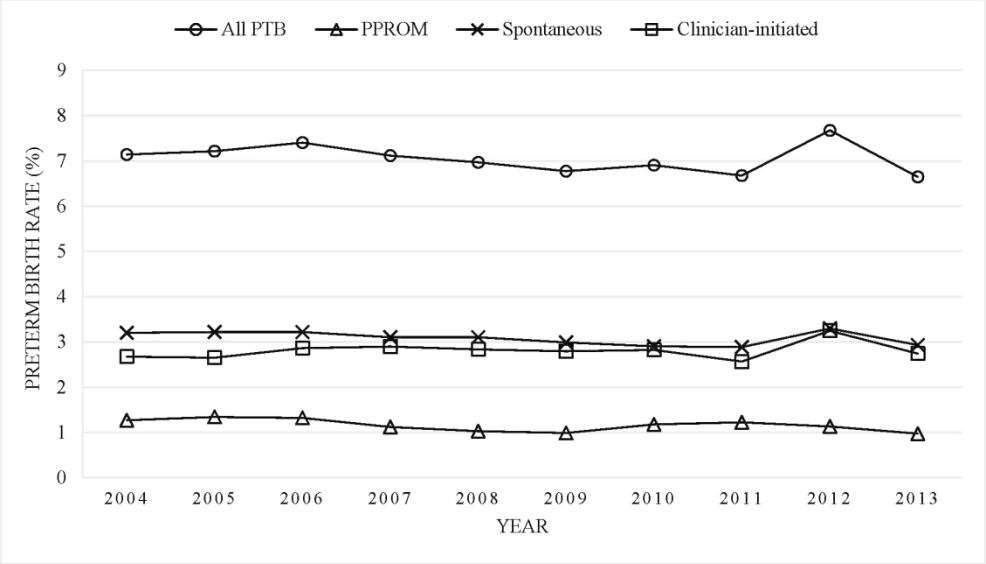

Figure 1. Temporal trends in the rates of singleton preterm birth following preterm premature rupture of membranes (PPROM), spontaneous labor and clinician-initiated delivery, Washington State, U.S.A., 2004-2013.

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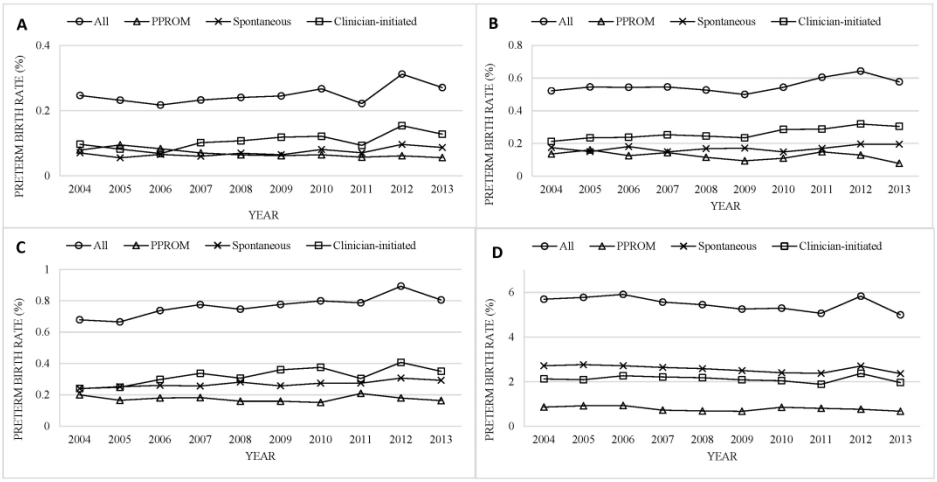

Figure 2. Temporal trends in gestational-age specific preterm birth rates following preterm premature rupture of membranes (PPROM), spontaneous labor and clinician-initiated delivery; at 24-27 weeks (Panel A), 28-31 weeks (Panel B), 32-33 weeks (Panel C), and 34-36 weeks (Panel D); Washington State, U.S.A., 2004-2013.

279x215mm (300 x 300 DPI)

Washington State Department of Health

Washington State Birth Filing Form

For Hospital Use Only

Mother's Medical Record #:	Child's Medical Record #:

Plurality: ☐ 1- single birth ☐ 2- twin ☐ 3- triplet ☐ Other _____

If multiple, this worksheet is for child: ☐ 1- first born ☐ 2- second born ☐ 3- third born ☐ Other _____

Child's Information

*1. Child's Name First	Middle	Last
*2. Child's Date of Birth (MM/DD/YYYY) / /	*3. Time of Birth	*4. Child's Sex ☐ Male ☐ Female

5. Type of Birthplace
☐ Hospital ☐ Home
☐ Enroute ☐ Clinic/Doctor's Office
☐ Freestanding Birth Center ☐ Other (specify):

6. Planned Birth Place, if different (specify):

*7. Name of Facility (If not a facility, enter name of place and address)	*8. County of Birth	*9. City of Birth

Mother's Information

10. Mother's Current Legal Name First	Middle	Last
*11. Mother's Name on her Birth Certificate First	Middle	Last/Maiden
*12. Date of Birth (MM/DD/YYYY) / /	*13. Birthplace (State, Territory, or Foreign Country)	14. Social Security Number

15. Do you want to get a Social Security Number for your child? ☐ Yes ☐ No

16a. Residence: Number and Street (e.g., 624 SE 5th St.)	Apt No.

16b. If not U.S.; Country	16c. State	16d. County

16e. If you live on Tribal Reservation, give name	16f. City or Town	16g. Zip Code + 4

16h. Inside City Limits? ☐ Yes ☐ No ☐ Unknown	17. How Long at Current Residence? Years: Months:	18. Telephone Number ( )

19a. Mailing Address, if different: Number and Street, or PO Box	Apt. No.

19b. If not U.S.; Country	19c. State	19d. City	19e. Zip Code + 4

20. Occupation (type of work done during last year)	21. Kind of Business/Industry (do not use company name)

22. Mother's Education
(Check the box that best describes the highest degree or level of school completed at the time of delivery.)

1 ☐ 8th grade or less (specify):_____
2 ☐ 9th – 12th grade; no diploma
3 ☐ High school graduate or GED
4 ☐ Some college credit, but no degree
5 ☐ Associate degree (AA, AS, etc.)
6 ☐ Bachelor's degree (BA, AB, BS, etc.)
7 ☐ Master's degree (MA, MS, MEd, MSW, MBA, etc.)
8 ☐ Doctorate (PhD, EdD, etc.) or professional degree (MD, DDS, DVM, LLB, JD, etc.)

23. Mother of Hispanic Origin?
(Check the box that best describes whether the mother is Spanish/Hispanic/Latina or check "No" box if not Spanish/Hispanic/Latina.)

1 ☐ No, not Spanish/Hispanic/Latina
2 ☐ Yes, Mexican, Mexican American, Chicana
3 ☐ Yes, Puerto Rican
4 ☐ Yes, Cuban
5 ☐ Yes, Other Spanish/Hispanic/Latina (specify):

24. Mother's Race (check one or more)

1 ☐ White
2 ☐ Black or African American
3 ☐ American Indian or Alaska Native
(Name of enrolled or principal tribe)

4 ☐ Asian Indian 5 ☐ Chinese
6 ☐ Filipino 7 ☐ Japanese
8 ☐ Korean 9 ☐ Vietnamese
10 ☐ Other Asian (specify):
11 ☐ Native Hawaiian 12 ☐ Guamanian or Chamorro
13 ☐ Samoan
14 ☐ Other Pacific Islander (specify):
15 ☐ Other (specify):

Continue on next page

Mother's Information

25. Mother's Height Feet: Inches:	26. Mother's Pre-Pregnancy Weight (pounds)	27. Did Mother get WIC food for herself during pregnancy? ☐ Yes ☐ No

28. Cigarette Smoking Before and During Pregnancy ☐ Yes ☐ No

Average number of cigarettes or packs per day:

	# of cigarettes		# of packs
Three months before pregnancy		or	
First three months of pregnancy		or	
Second three months of pregnancy		or	
Last three months of pregnancy		or	

Mother's Marital Status

Mother's Marital Status

29. Is mother married? (Check only one box)

Important - Read before responding to marital status question:
If you were married at any time during your pregnancy, your spouse or partner is considered the other legal parent unless he or she completes a denial of paternity and another man acknowledges that he is the father (chapter 26.26 RCW). To add someone other than your spouse or partner to the birth certificate, an acknowledgment and denial of paternity needs to be completed by all parties (DOH form 422-032). Under Washington State law, a state-registered domestic partnership is considered the same as a marriage (chapter 26.60 RCW).

If you were not married at any time during the pregnancy, an acknowledgment of paternity needs to be completed to add the father to the birth certificate.

Married - Yes	Married - No
29a. ☐ Yes, I am married to the other parent identified in box #30.	29d. ☐ No, I am not married and I am providing information about the father in box #30. *Ask hospital staff for a Paternity Acknowledgment form (#DOH 422-032). If you were married any time during the pregnancy and your previous spouse is not the parent identified in box #30, the spouse's Denial of Paternity must also be completed.*
29b. ☐ Yes, I am married but not to the other person identified in box #30. *Ask hospital staff for a Paternity Acknowledgment form (# DOH 422-032).You must complete this form, including the spouse's Denial of Paternity.*	29e. ☐ No, I am not married now, but I was married to the other parent identified in box #30 at some time during this pregnancy.
29c. ☐ Yes, I am married but I refuse to provide the spouse or partner's information. *If this box is checked, the other parent will be listed on the birth certificate as "None Named".*	29f. ☐ No, I am not married and I refuse to provide the father's information. *If this box is checked, the other parent will be listed on the birth certificate as "None Named".*

Father/ Parent's Information

Father/Parent's Information

*30. Current Legal Name First	Middle	Last
*31. Date of Birth (MM/DD/YYYY) / /	*32. Birthplace (State, Territory, or Foreign Country)	33. Social Security Number

34. Occupation (type of work done during last year.)	35. Kind of Business/Industry (do not use Company Name)

36. Father/Parent Education
(Check the box that best describes the highest degree or level of school completed at the time of delivery.)

1 ☐ 8th grade or less (specify):_____
2 ☐ 9th – 12th grade; no diploma
3 ☐ High school graduate or GED
4 ☐ Some college credit, but no degree
5 ☐ Associate degree (AA, AS, etc.)
6 ☐ Bachelor's degree (BA, AB, BS, etc.)
7 ☐ Master's degree (MA, MS, MEd, MSW, MBA, etc.)
8 ☐ Doctorate (PhD, EdD, etc.) or professional degree (MD, DDS, DVM, LLB, JD, etc.)

37. Father/Parent of Hispanic Origin?
(Check the box that best describes whether the father/parent is Spanish/Hispanic/Latino or check "No" box if not Spanish/Hispanic/Latino.)

1 ☐ No, not Spanish/Hispanic/Latino
2 ☐ Yes, Mexican, Mexican American, Chicano
3 ☐ Yes, Puerto Rican
4 ☐ Yes, Cuban
5 ☐ Yes, other Spanish/Hispanic/Latino (specify):

38. Father/Parent Race (check one or more)

1 ☐ White
2 ☐ Black or African American
3 ☐ American Indian or Alaska Native (Name of enrolled or principal tribe)

4 ☐ Asian Indian 5 ☐ Chinese
6 ☐ Filipino 7 ☐ Japanese
8 ☐ Korean 9 ☐ Vietnamese
10 ☐ Other Asian (specify):

11 ☐ Native Hawaiian 12 ☐ Guamanian or Chamorro
13 ☐ Samoan
14 ☐ Other Pacific Islander (specify):
15 ☐ Other (specify):

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Mother's Statistical Information

39. Date of First Prenatal Care Visit (MM/DD/YYYY) / / ☐ No Prenatal Care

40. Date of Last Prenatal Care Visit (MM/DD/YYYY) / /

41. Total Number of Prenatal Visits for this Pregnancy (If none, enter '0') _____

42. Number of Previous Live Births (Do not include this child)
Number Now Living _____ ☐ None
Number Now Dead _____ ☐ None

43. Date of Last Live Birth (MM/YYYY) (Do not include this child) / /

44. Number of Other Pregnancy Outcomes (Spontaneous or induced losses or ectopic pregnancies)
Number of Other Outcomes _____ ☐ None

45. Date of Last Other Pregnancy Outcome (MM/YYYY) / /

46. Date Last Normal Menses Began (MM/DD/YYYY) / /

47. Mother's Weight at Delivery(pounds)

48. Was mother transferred to higher level care for maternal medical or fetal indications for delivery? ☐ Yes ☐ No
If yes, name of facility mother was transferred from:

49. Principal Source of Payment for this Delivery
☐ Medicaid ☐ Self-Pay ☐ Private Insurance
☐ Other Gov't ☐ Tricare ☐ Indian Health
☐ Charity Care ☐ Other _____

Child's Statistical Information

50. Birth Weight
lbs: ozs: **or** grams:

51. Infant Head Circumference (cm)

52. Obstetric Estimate of Gestation (completed weeks)

53. Apgar score at 5 minutes _____ If score is less than 6, score at 10 minutes _____

54. Plurality: ☐ Single ☐ twins ☐ triplets ☐ other _____

55. If not single birth; birth order: ☐ first ☐ second ☐ third ☐ other _____

56. Was infant transferred within 24 hours of delivery? ☐ Yes ☐ No
If yes, name of facility infant was transferred to:

57. Is infant living at the time of report?
☐ Yes ☐ No ☐ Transferred, status unknown

58. Is infant being breastfed?
☐ Yes ☐ No

Medical and Health Information

59. Risk Factors in this Pregnancy (check all that apply):

1 Diabetes
- ☐ Prepregnancy (Diagnosis prior to this pregnancy)
- ☐ Gestational (Diagnosis in this pregnancy)

2 Hypertension
- ☐ Prepregnancy (Chronic)
- ☐ Gestational (PIH, preeclampsia)
- ☐ Eclampsia

3 ☐ Previous preterm births
4 ☐ Other previous poor pregnancy outcome (includes perinatal death, small-for-gestational age/intrauterine growth restricted birth)
5 ☐ Vaginal bleeding during this pregnancy prior to the onset of labor
6 ☐ Pregnancy resulted from infertility treatment - If yes-check all that apply:
- ☐ Fertility-enhancing drugs, artificial insemination or intrauterine insemination
- ☐ Assisted reproductive technology [e.g., in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT)]

7 ☐ Mother had a previous cesarean delivery? If Yes, how many_____
8 ☐ Group B Streptococcus culture positive
9 ☐ None of the above

60. Infections Present and/or Treated During this Pregnancy (check all that apply):

1 ☐ Gonorrhea
2 ☐ Syphilis
3 ☐ Herpes Simplex Virus (HSV)
4 ☐ Chlamydia
5 ☐ Hepatitis B
6 ☐ Hepatitis C
7 ☐ HIV Infection
8 ☐ Other Specify:_____
9 ☐ None of the above

61. Maternal Morbidity (complications associated with labor and delivery) (Check all that apply):

1 ☐ Maternal transfusion
2 ☐ Third or fourth degree perineal laceration
3 ☐ Ruptured uterus
4 ☐ Unplanned hysterectomy
5 ☐ Admission to intensive care unit
6 ☐ Unplanned operating room procedure following delivery
7 ☐ None of the above

62. Method of Delivery

A. Was delivery with forceps attempted but unsuccessful? ☐ Yes ☐ No

B. Was delivery with vacuum extraction attempted but unsuccessful? ☐ Yes ☐ No

C. Fetal presentation at birth ☐ Cephalic ☐ Breech ☐ Other

D. Final route and method of delivery (Check One)
Vaginal: ☐ Spontaneous ☐ Forceps ☐ Vacuum
OR
Cesarean: ☐
If cesarean, was a trial of labor attempted? ☐ Yes ☐ No

63. Obstetric procedures (Check all that apply):

1 ☐ Cervical cerclage
2 ☐ Tocolysis
3 ☐ External cephalic version:
- ☐ Successful
- ☐ Failed

4 ☐ None of the above

64. Onset of Labor (Check all that apply):

1 ☐ Premature rupture of the membranes (Prolonged, ≥ 12hr)
2 ☐ Precipitous Labor (< 3hr)
3 ☐ Prolonged Labor (≥ 20hr)
4 ☐ None of the above

65. Characteristics of Labor and Delivery (Check all that apply):

1 ☐ Induction of labor
2 ☐ Augmentation of labor
3 ☐ Non-vertex presentation
4 ☐ Epidural or spinal anesthesia during labor
5 ☐ Steroids (glucocorticoids) for fetal lung maturation received by the mother prior to delivery
6 ☐ Antibiotics received by the mother during labor
7 ☐ Clinical chorioamnionitis diagnosed during labor or maternal temperature ≥38°C (100.4°F)
8 ☐ Moderate/heavy meconium staining of the amniotic fluid
9 ☐ Fetal intolerance of labor such that one or more of the following actions was taken: in-utero resuscitation measures, further fetal assessment, or operative delivery
10 ☐ None of the above

66. Abnormal Conditions of the Newborn (Occurring within 24 hours of delivery) (check all that apply):

1 ☐ Assisted ventilation required immediately following delivery
2 ☐ Assisted ventilation required for more than six hours
3 ☐ NICU admission
4 ☐ Newborn given surfactant replacement therapy
5 ☐ Antibiotics received by the newborn for suspected neonatal sepsis
6 ☐ Seizure or serious neurologic dysfunction
7 ☐ Significant birth injury (skeletal fracture(s), peripheral nerve injury, soft tissue or solid organ hemorrhage which requires intervention)
8 ☐ None of the above

67. Congenital Anomalies of the Newborn (Observed within 24 hours of delivery) (Check all that apply)

1 ☐ Anencephaly
2 ☐ Meningomyelocele / Spina bifida
3 ☐ Cyanotic congenital heart disease
4 ☐ Congenital diaphragmatic hernia
5 ☐ Omphalocele
6 ☐ Gastroschisis
7 ☐ Limb reduction defect (excluding congenital amputation and dwarfing syndrome)
8 ☐ Cleft Lip with or without Cleft Palate
9 ☐ Cleft Palate alone
10 Down Syndrome
- ☐ Karyotype confirmed
- ☐ Karyotype pending

11 Chromosomal disorder
- ☐ Karyotype confirmed
- ☐ Suspected, Karyotype pending

12 ☐ Hypospadias
13 ☐ None of the above

Attendant and Certifier Information

68. Certifier – Name and Title

69. Date Certified (MM/DD/YYYY) / /

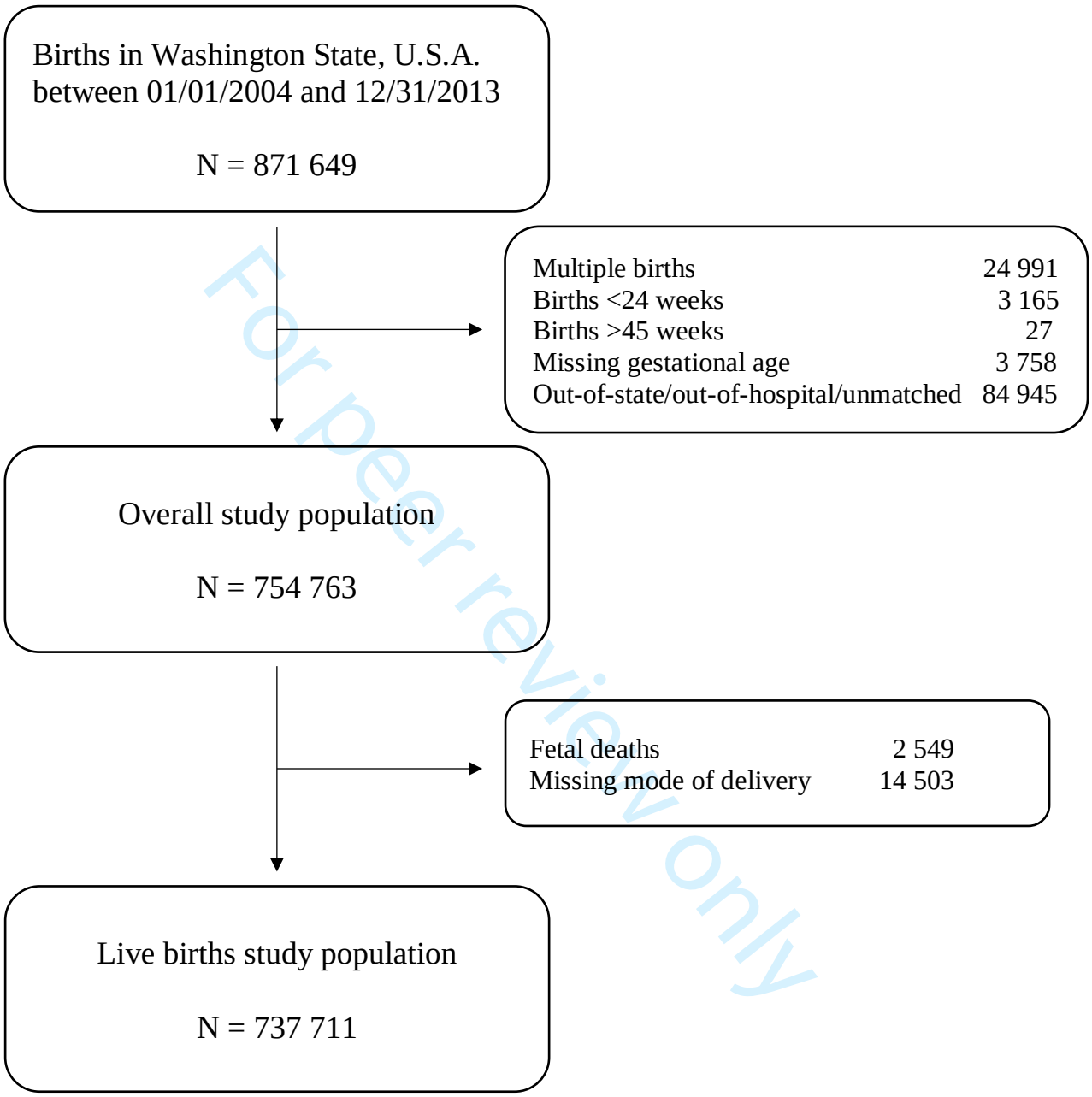
70. Attendant – Name and Title (If other than Certifier)

71. NPI of person delivering the baby:

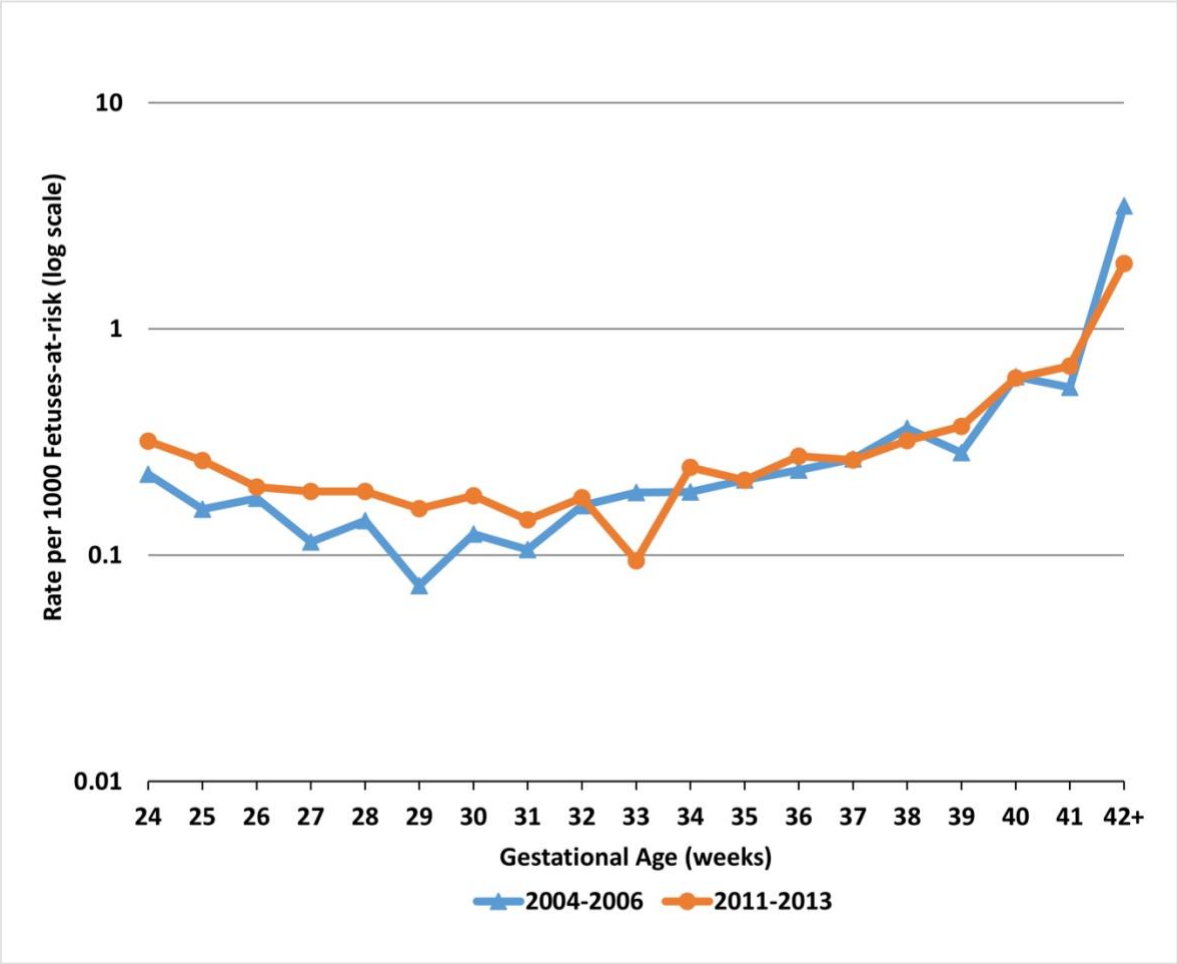
Appendix Table 1. Severe neonatal morbidity components and ICD-9-CM codes.

Neonatal morbidity	ICD-9-CM code
Bronchopulmonary dysplasia	770.7
Intraventricular hemorrhage	
Grade III – bleeding with enlargement of ventricle	772.13
Grade IV – bleeding into cerebral cortex	772.14
Periventricular leukomalacia	779.7
Retinopathy of prematurity	362.2
Necrotizing enterocolitis	777.5
Sepsis	
Septicemia of newborn	771.81
Convulsions	
Fits in newborn; seizures in newborn	779.0
Severe birth trauma	
Subdural and cerebral hemorrhage (whether described as due to birth trauma or to intrapartum anoxia or hypoxia; subdural hematoma (localized); tentorial tear	767.0
Epicranial subaponeurotic hemorrhage (massive); subgaleal hemorrhage	767.11
Injury to spine and spinal cord including:	767.4
Dislocation of spine or spinal cord due to birth trauma	
Fracture of spine or spinal cord due to birth trauma	
Laceration of spine or spinal cord due to birth trauma	
Rupture of spine or spinal cord due to birth trauma	

Appendix Figure 1. Study population flow chart, Washington State, U.S.A., 2004-2013.



Appendix Figure 2. Gestational age-specific rates of stillbirths calculated using the fetuses-at-risk (FAR) approach, Washington State, U.S.A., 2004-2013.



Appendix Table 2. Preterm live births by gestational age categories and clinical subtype, Washington State, U.S.A., 2004-2013.

Gestational age and clinical preterm birth subtype	All Years (2004-2013)	Period 1 (2004-2006)	Period 2 (2011-2013)	p-value* (Period 2 vs. Period 1)
24-27 weeks	1 833	489	598	<0.001
PPROM	509 (27.8)	181 (37.0)	130 (21.7)	
Spontaneous labor	532 (29.0)	135 (27.6)	189 (31.6)	
Iatrogenic	792 (43.2)	173 (35.4)	279 (46.7)	
28-31	4 095	1 135	1 357	<0.001
PPROM	909 (22.2)	295 (26.0)	264 (19.5)	
Spontaneous labor	1 255 (30.6)	357 (31.5)	416 (30.7)	
Iatrogenic	1 931 (47.2)	483 (42.6)	677 (49.9)	
32-33	5 664	1 469	1 848	0.006
PPROM	1 288 (22.7)	383 (26.1)	410 (22.2)	
Spontaneous labor	1 988 (35.1)	530 (36.1)	649 (35.1)	
Iatrogenic	2 388 (42.2)	556 (37.8)	789 (42.7)	
34-36	40 422	12 249	11 821	0.001
PPROM	5 809 (14.4)	1 912 (15.6)	1 673 (14.2)	
Spontaneous labor	18 973 (46.9)	5 770 (47.1)	5 530 (46.8)	
Iatrogenic	15 640 (38.7)	4 567 (37.3)	4 618 (39.1)	
All (24-36)	52 014	15 342	15 624	<0.001
PPROM	8 515 (16.4)	2 771 (18.1)	2 477 (15.9)	
Spontaneous labor	22 748 (43.7)	6 792 (44.3)	6 784 (43.4)	
Iatrogenic	20 751 (39.9)	5 779 (37.7)	6 363 (40.7)	

PPROM, preterm premature rupture of membranes

* p-value for Chi-square test comparing Period 1 and 2

Appendix Table 3 Gestational age-specific rates of adverse neonatal outcomes among singleton preterm infants, Washington State, U.S.A., 2004-2013.

Outcome and gestational age category	Rates per 100 live births		
	N (Rate)		Rate difference (95% CI)
	2004-2006	2011-2013	
Neonatal death			
24-27 weeks	76 (15.5)	85 (14.2)	-1.33 (-5.59, 2.93)
28-31	55 (4.9)	40 (3.0)	-1.90 (-3.44, -0.36)
32-33	23 (1.6)	18 (1.0)	-0.59 (-1.37, 0.19)
34-36	43 (0.4)	64 (0.5)	+0.19 (0.02, 0.36)
All (24-36)	197 (1.3)	207 (1.3)	+0.04 (-0.21, 0.29)
Neonatal death/ severe morbidity			
24-27 weeks	353 (72.2)	429 (71.7)	-0.45 (-5.82, 4.92)
28-31	383 (33.7)	496 (36.6)	+2.81 (-0.95, 6.57)
32-33	166 (11.3)	302 (16.3)	+5.04 (2.70, 7.38)
34-36	307 (2.5)	639 (5.4)	+2.90 (2.41, 3.39)
All (24-36)	1 209 (7.9)	1 866 (11.9)	+4.06 (3.40, 4.73)

CI, confidence interval; severe morbidity includes BPD, IVH grade≥3, PVL, ROP, NEC, neonatal sepsis, convulsions of newborn, and severe birth trauma.

Appendix Table 4. Temporal trends in gestational-specific rates of severe neonatal morbidity components, Washington State, U.S.A., 2004-2013.

Neonatal Morbidity	Rates of Outcome by Period [N (per 100 live births)]		Adjusted Odds Ratio† (95% CI)
	2004-2006	2011-2013	
All PTB (24-36 weeks)			
BPD	306 (2.0)	269 (1.7)	**0.95 (0.93-0.98)**
IVH (grade ≥3)	72 (0.5)	61 (0.4)	**0.95 (0.90-1.00)**
PVL	13 (0.1)	27 (0.2)	1.10 (1.00-1.22)
ROP	60 (0.4)	86 (0.6)	1.02 (0.98-1.07)
NEC	129 (0.8)	173 (1.1)	1.02 (0.99-1.06)
Sepsis	686 (4.5)	1 331 (8.5)	**1.09 (1.08-1.11)**
Convulsions	53 (0.4)	62 (0.4)	1.00 (0.94-1.04)
Severe birth trauma	29 (0.2)	26 (0.2)	0.96 (0.89-1.04)
Late PTB (34-36 weeks)			
BPD	6 (0.1)	4 (0.0)	0.96 (0.81-1.12)
IVH (grade ≥3)	3 (0.0)	3 (0.0)	0.97 (0.78-1.21)
PVL	0 (0.0)	0 (0.0)	1.05 (0.64-1.72)
ROP	0 (0.0)	2 (0.0)	1.56 (0.85-2.87)
NEC	16 (0.1)	21 (0.2)	1.04 (0.95-1.14)
Sepsis	211 (1.7)	530 (4.5)	**1.12 (1.10-1.14)**
Convulsions	26 (0.2)	28 (0.2)	1.01 (0.93-1.09)
Severe birth trauma	16 (0.1)	14 (0.1)	0.97 (0.87-1.08)
PTB at 28-33 weeks			
BPD	121 (4.7)	95 (3.0)	**0.93 (0.89-0.97)**
IVH (grade ≥3)	24 (0.9)	19 (0.6)	0.92 (0.84-1.01)
PVL	8 (0.3)	15 (0.5)	1.06 (0.93-1.21)
ROP	35 (1.3)	63 (2.0)	1.05 (0.99-1.11)
NEC	76 (2.9)	89 (2.8)	1.00 (0.95-1.05)
Sepsis	306 (11.8)	554 (17.3)	**1.07 (1.05-1.10)**
Convulsions	19 (0.7)	20 (0.6)	0.96 (0.87-1.05)
Severe birth trauma	9 (0.4)	9 (0.3)	0.95 (0.82-1.11)
PTB at 24-27 weeks			

BPD	179 (36.6)	170 (28.4)	0.97 (0.94-1.01)
IVH (grade ≥3)	45 (9.2)	39 (6.5)	0.95 (0.88-1.01)
PVL	5 (1.0)	12 (2.0)	1.13 (0.96-1.32)
ROP	25 (5.1)	21 (3.5)	0.95 (0.87-1.02)
NEC	37 (7.6)	63 (10.5)	1.04 (0.98-1.10)
Sepsis	169 (34.6)	247 (41.3)	**1.05 (1.01-1.09)**
Convulsions	8 (1.6)	14 (2.3)	1.02 (0.91-1.14)
Severe birth trauma	4 (0.8)	3 (0.5)	0.94 (0.76-1.15)

CI, confidence interval; PTB, preterm birth; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.
Adjusted odds ratios express the average annual change in the odds for each morbidity.
Bolded value indicates statistical significance at $p<0.05$
†Calendar year was modelled as a continuous variable; adjusted for temporal changes in maternal age, BMI, race, education, smoking, marital status, parity, chronic hypertension, pre-pregnancy diabetes, assisted conception, health insurance provider, gestational age, SGA infant, sex, and congenital anomalies. NOTE: some covariates were excluded from the regression models due to collinearity.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract **This was done, title page; "a population-based study"**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **This was done, abstract, page 2; "We described concomitant changes in…"**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **This was done, page 4-5; "However, it is unknown whether the temporal decline in preterm birth is associated with…"**
Objectives	3	State specific objectives, including any prespecified hypotheses **This was done, page 5; "Our aim was to describe temporal trends in …"**
Methods		
Study design	4	Present key elements of study design early in the paper **This was done, page 5; "We carried out a population-based study including…"**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **This was done, page 5; "… all singleton hospital births to mothers aged 15 to 60 in Washington State, U.S.A., between January 1, 2004, and…"**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **This was done, page 5-6; "We used information from two linked population databases…"**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **This was done, page 6-7; "The primary outcomes were neonatal mortality and a composite adverse outcome including…"**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **This was done, page 5-6; "…diagnosis and procedure codes related to each hospitalization episode coded by the International Classification of…"**
Bias	9	Describe any efforts to address potential sources of bias **This was done, page 6-7; inclusion/exclusion criteria, consistent use of case ascertainment by ICD-9-CM codes from administrative data to avoid recall bias**

		or diagnostic bias
Study size	10	Explain how the study size was arrived at **This was done, page 5; population-based; "… all singleton hospital births to mothers aged 15 to 60 in Washington State, U.S.A., between January 1, 2004, and…"**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **This was done, page 8-9; "The preterm birth rate was calculated as a proportion of live births…"**
Statistical methods	12	*(a)* Describe all statistical methods, including those used to control for confounding **This was done, page 8; "Logistic regression was used to assess temporal trends…adjusted for temporal changes in risk factors…"**
		(b) Describe any methods used to examine subgroups and interactions **This was done, page 8-9; "Temporal trends in the individual components of the composite outcome were examined… using logistic regression models…"**
		(*c*) Explain how missing data were addressed **This was done; page 9; "Missing values for BMI… were imputed using multiple imputation… other missing values were <3% of the total, and the complete case multivariable analysis included 93% of preterm births…"**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **n/a**
		(*e*) Describe any sensitivity analyses **not included**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **This was done, page 10; "Overall, 871 649 singleton births occurred…the study population included 754 763 singleton infants born in hospital…"**
		(b) Give reasons for non-participation at each stage **This was done, page 10; "We excluded births at <24 or >45 weeks' gestation, multiple births, births that occurred outside of Washington State…"**
		(c) Consider use of a flow diagram **This was done, Appendix Figure 2**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **This was done, Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **This was done, Table 1**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **This was done; Table 2, Table 3, Table 4, Figure 1, Figure 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **This was done; Table 2, Table 3, Table 4**
		(*b*) Report category boundaries when continuous variables were categorized **This was done, Table 1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **This was done, page 16, Appendix Table 4**
Discussion		
Key results	18	Summarise key results with reference to study objectives **This was done, page 17; "Our findings show a decline in the preterm birth rate…"**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **This was done, page 20; "This study has a few limitations. First, clinical details on the severity of some…"**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **This was done, page 22; "The small decline in the preterm birth rate…was predominately due to…"**
Generalisability	21	Discuss the generalisability (external validity) of the study results **This was done, page 21; "We adjusted for a number of these indices thus our results are fairly generalizable to other states…or high-income countries…"**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **This was done, title page; "This work was supported by…"**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.