

# Outcomes of Admissions for Preterm Labor

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## Abstract

**Objective** This study aims to quantitate the incidence of preterm labor (PTL) admissions and determine the frequency and predictors of preterm delivery (PTD) during these admissions.

**Study Design** Retrospective cohort of singleton pregnancies within Kaiser Permanente Northern California, 2001 to 2011. PTL admissions were defined as inpatient encounters > 24 hours with an International Classification of Diseases, 9th Revision code for PTL.

**Results** Total study population was 365,897 with PTL admission rate 11%. PTD occurred in 85% of pregnancies with PTL admission. Delivery occurred within 48 hours of admission in 96%  $\geq$ 34 weeks, 67% 31 to 33 weeks, and 51.9% <31 weeks. Predictors of delivery during PTL admission included gestational age 34 to 36 weeks (adjusted odds ratio [aOR], 6.90), chorioamnionitis (aOR, 105.58), and preterm rupture of membranes (aOR 19.29).

**Conclusion** We demonstrate a high rate of PTD per PTL admission in a highly integrated health care system. More work is needed to determine optimal practices for hospitalization and treatment of women diagnosed with PTL.

## Keywords

- ▶ preterm labor
- ▶ maternal-fetal medicine
- ▶ labor and delivery
- ▶ neonatal outcomes

Preterm birth is associated with increased neonatal mortality and long-term morbidity.<sup>1–3</sup> Preterm delivery may occur due to maternal or fetal indications, or result from preterm premature rupture of membranes or after spontaneous preterm labor (PTL) with intact membranes. Approximately 32 to 50% of preterm births are the consequence of spontaneous PTL.<sup>4–7</sup> The etiology is often multifactorial and poorly understood. Contributory features include hormonal changes, uterine overdistension, cervical disease, infection/inflammation, uteroplacental ischemia/hemorrhage, or immunologic pathology.<sup>8,9</sup>

Substantial variation exists in the diagnosis and management of PTL.<sup>10</sup> A literature search for guidelines or best practice

recommendations for clinicians caring for patients who present with possible PTL yielded no comprehensive algorithm for the management of such patients. Unfortunately, current strategies such as tocolytic agents have shown limited efficacy and are associated with undesirable side effects.<sup>11–19</sup>

Not all women admitted with a diagnosis of PTL delivery prematurely, illustrating that it may be difficult to determine which women have true PTL initially.<sup>20,21</sup> Determining which women admitted with PTL who are most likely to deliver imminently may be helpful in defining the population most likely to benefit from new interventions or medications to prolong pregnancy.

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Few population-based studies have examined the outcomes of admissions for PTL.<sup>20,22–27</sup> The aims of the study were to quantitate the incidence of admissions for PTL, to examine maternal and neonatal outcomes, and evaluate predictors for delivery after PTL admission in a large population-based cohort.

## Methods

### Study Population and Design

We utilized a retrospective cohort design. The study cohort consisted of singleton pregnancies that resulted in a live birth between January 1, 2001 and December 31, 2011, at a Kaiser Permanente Northern California (KPNC) facility. KPNC serves a population of 3.7 million members, which constitutes nearly half of the insured population in Northern California. A total of 16 facilities were included in the study. KPNC facilities share the same common medical record numbers and database systems, which permits linkage of maternal and neonatal records to each other and to multiple information systems (e.g., laboratory and hospitalization data).<sup>28</sup> We excluded pregnancies with missing infant gestational age at birth, birth weight, or maternal discharge data.

The KPNC Institutional Review Board approved the study.

### Classification of Preterm Labor Admissions

We identified all maternal admissions that occurred between 20<sup>0/7</sup> and 36<sup>6/7</sup> weeks' gestation from the KPNC virtual data warehouse (VDW). The VDW contains electronic records of all patient encounters (inpatient and outpatient) at KPNC facilities, including health plan enrollment dates, encounter dates with location, dispositions, diagnostic and procedure codes, laboratory tests, and their results.<sup>29</sup> Gestational age was determined from the maternal record and defined according to the obstetrically assigned estimated date of confinement (EDC). For women with regular menstrual cycles, EDC was based on last menstrual period if in 7-day agreement with a first-trimester ultrasound. For women with irregular menstrual cycles, EDC was determined from first-trimester ultrasound results. We categorized encounters by completed weeks of gestation at admission:  $\leq 24$ , 25 to 27, 28 to 30, 31 to 33, and 34 to 36 weeks.

We identified admissions for PTL by selecting inpatient encounters that had an International Disease Classification (ICD-9) code for PTL (644.0, 644.00, 644.03, 644.20, 644.21, V23.41) assigned. Admissions for observation less than 24 hours were not included ( $n = 23,282$ ). PTL admissions were classified as spontaneous PTL if there were no other complicating diagnoses such as preterm premature rupture of membranes (658.1, 658.10, 658.11, 658.13), chorioamnionitis (658.4x), preeclampsia/eclampsia (642.5x, 642.6x, 642.7x), cervical incompetence (622.5, 654.5x, 654.6x), or bleeding/placenta previa/abruption (641.1x, 641.2x, 641.3x, 641.8x, 641.9x). We examined these spontaneous PTL admissions separately with the hypothesis that these otherwise uncomplicated pregnancies may have different outcomes than more complicated PTL admissions.

### Maternal and Infant Characteristics and Outcomes

KP administrative databases supplied data on maternal race/ethnicity, maternal age at delivery, and mode of delivery.

Small for gestational age (SGA) was determined by plotting the infant's weight and gestational age on the Fenton curves, using  $<$ fifth percentile as a cutoff for SGA.<sup>30</sup> Postpartum hemorrhage was determined from discharge diagnosis ICD-9 codes. The KPNC VDW provided data on inpatient, 30-day, and 1-year mortality as well as infant or maternal intensive care unit admission. If a mother required a transfer between KP facilities, we analyzed the combined hospital stays as a single hospitalization.

### Statistical Analysis

We performed comparisons of characteristics, maternal outcomes, and neonatal outcomes, using chi-square or Fisher's exact test, as appropriate. For PTL admissions, multivariate logistic regression models assessed the association between gestational age at admission, maternal age, and maternal race/ethnicity, additional maternal diagnoses, and the number of admissions and the outcome of delivery. The models included the birth year and facility as covariates, with adjustment for clustering by a woman, as some women had multiple pregnancies.

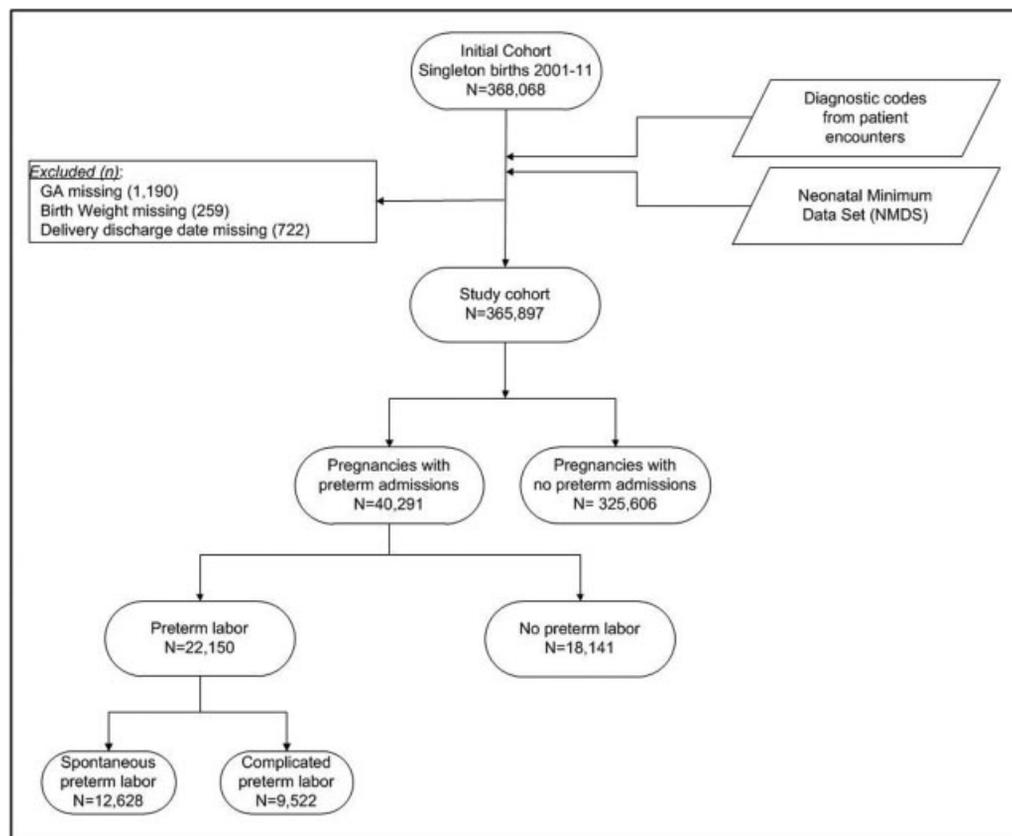
## Results

We identified 368,068 singleton pregnancies and excluded records missing infant gestational age ( $n = 1,190$ ), birth weight ( $n = 259$ ), or maternal discharge date ( $n = 722$ ). The study cohort consisted of 365,897 pregnancies. At least one preterm inpatient admission occurred in 11% ( $n = 40,291$ ) of pregnancies. Of these admissions, 52% had a diagnosis of PTL. Thus, 6% of all pregnancies were complicated by PTL. The majority (55%) of PTL admissions had no other complications (**Fig. 1**).

We compared women with PTL admission to those without a PTL admission (**Table 1**). Women with a PTL admission were more likely to be Black, at the extremes of age ( $<18$  or  $\geq 40$ ), and to have another pregnancy complication. These women were also more likely to deliver by cesarean section and to have infants that were SGA or had a congenital anomaly.

Overall, 85% of pregnancies with PTL admissions resulted in the delivery of a preterm infant. The proportion was higher for complicated PTL (93%) compared with spontaneous PTL (79%),  $p < .0001$ . We examined the time to delivery from first PTL admission, stratified by gestational age at admission (**Fig. 2**). The delivery curves were similar for all PTL admissions and spontaneous PTL admissions. Time to delivery differed substantially depending on gestational age at admission. For PTL admissions  $\geq 34$  weeks, delivery occurred within 48 hours in 96% of the admissions. For infants 31 to 33 weeks, 67% delivered before 48 hours. Infants admitted  $< 31$  weeks showed similar delivery curves, with 51.9% delivering within 48 hours and 77.6% within 7 days after admission.

Maternal and infant outcomes of pregnancies with a PTL admission were significantly worse than pregnancies without a PTL admission. There were elevated rates of maternal intensive care unit admission, inpatient maternal mortality, and 30-day maternal mortality. As expected, with a higher rate of preterm delivery, neonatal intensive care unit admissions, inpatient infant mortality, and 1-year mortality were also



**Fig. 1** Study population.

higher. These differences persisted even in the spontaneous PTL subset (► **Table 2**).

We evaluated predictors for delivery using multivariate logistic regression in the PTL admission cohort (► **Table 3**). Admissions at 34 to 36 weeks were strongly associated with delivery. Compared with admission at 31 to 33, all gestational groups < 31 weeks were statistically less likely to deliver during the admission. Women older than 34 years were more likely to have an admission that resulted in delivery than women younger than 30 years. Diagnoses of chorioamnionitis or preterm premature rupture of membranes (PPROM) was strong predictors of delivering during that admission. Placental abruption/previa also increased the risk of delivering but to a lesser degree. If an admission was the first preterm admission for the mother, there was a reduced risk of delivery, compared with subsequent preterm admissions. Restricting the analysis to spontaneous PTL showed similar results

## Discussion

This population-based study shows that 11% of singleton pregnancies result in at least one preterm admission. Over half of preterm admissions related to a diagnosis of PTL, of which over half are uncomplicated. A population-based study from New South Wales, Australia (2001–2008) showed that 4.2% (28,796/688,902) of singleton pregnancies were admitted with a diagnosis of PTL between 20 and 36 weeks

gestation,<sup>20</sup> similar to our results in which there were 5.6% of singleton pregnancies with at least one admission for PTL.

Of the pregnancies with at least one PTL admission, 85.0% delivered preterm. Our data demonstrate that the majority of women who deliver during PTL admission have a short latency between time of admission and time of delivery despite presumptive receipt of tocolytics and other standard interventions in use at KPNC, consistent with prior studies demonstrating a lack of substantial pregnancy prolongation with interventions such as tocolysis.<sup>10,11,14–16</sup>

When latency is shorter, there may be insufficient time to enable the maximal benefit of antenatal steroids, which have been proven to accelerate fetal lung maturity, and are most effective when administered at least 48 hours before delivery.<sup>31–33</sup> It appears current strategies are failing to have a significant impact on prolonging pregnancy in women with PTL. Unfortunately, this leads to worse neonatal outcomes. Numerous studies have documented the benefit of each additional week of gestational age on neonatal morbidity and mortality.<sup>34</sup>

Older studies have suggested that over half of the women diagnosed with PTL will deliver at term.<sup>24,25</sup> Our study shows this percentage to be much lower. In our study, 15.1% of mothers admitted for PTL ultimately delivered at term. The higher delivery rate after PTL admission in our study may be explained by more selective admission of patients with suspected PTL. In KPNC, more patients with suspected PTL

**Table 1** Characteristics and outcomes of mothers with at least one PTL admission, compared with mothers with no PTL admission

Characteristic	PTL admission ( <i>n</i> = 22,150)		No PTL admission ( <i>n</i> = 343,747)		<i>p</i> Value
	<i>n</i>	%	<i>n</i>	%	
<b>Race/ethnicity</b>					
White	8,087	36.5	138,101	40.2	< 0.0001
Black	2,420	10.9	25,996	7.6	
Asian	4,946	22.3	74,567	21.7	
Hispanic	5,286	23.9	86,717	25.2	
Other/unknown	1,411	6.4	18,366	5.3	
<b>Maternal age (y)</b>					
< 18	477	2.2	4,526	1.3	< 0.0001
18–29	9,995	45.1	155,830	45.3	
30–39	10,426	47.1	167,142	48.6	
40+	1,252	5.7	16,249	4.7	
More than one preterm admission	3,339	15.1	1,162	0.3	< 0.0001
No major pregnancy complications <sup>a</sup>	12,038	54.4	296,170	86.2	< 0.0001
Maternal diabetes	3,642	16.4	34,062	9.9	< 0.0001
Preterm rupture of membranes	4,310	19.5	18,948	5.5	< 0.0001
Chorioamnionitis	1,470	6.6	19,781	5.8	< 0.0001
Hypertension/preeclampsia	2,855	12.9	6,529	1.9	< 0.0001
Incompetent cervix	776	3.5	1,578	0.5	< 0.0001
Placental abruption or previa	2,177	9.8	4,033	1.2	< 0.0001
<b>Delivery mode</b>					
Cesarean	7,444	33.6	80,542	23.4	< 0.0001
Vaginal	14,656	66.2	262,667	76.4	
Preterm (<37 wk) delivery	18,816	85.0	5,698	1.7	< 0.0001
Infant small for gestational age	685	3.1	5,713	1.7	< 0.0001
Major congenital anomaly <sup>b</sup>	1,299	5.9	4,459	1.3	< 0.0001

Abbreviation: PTL, preterm labor.

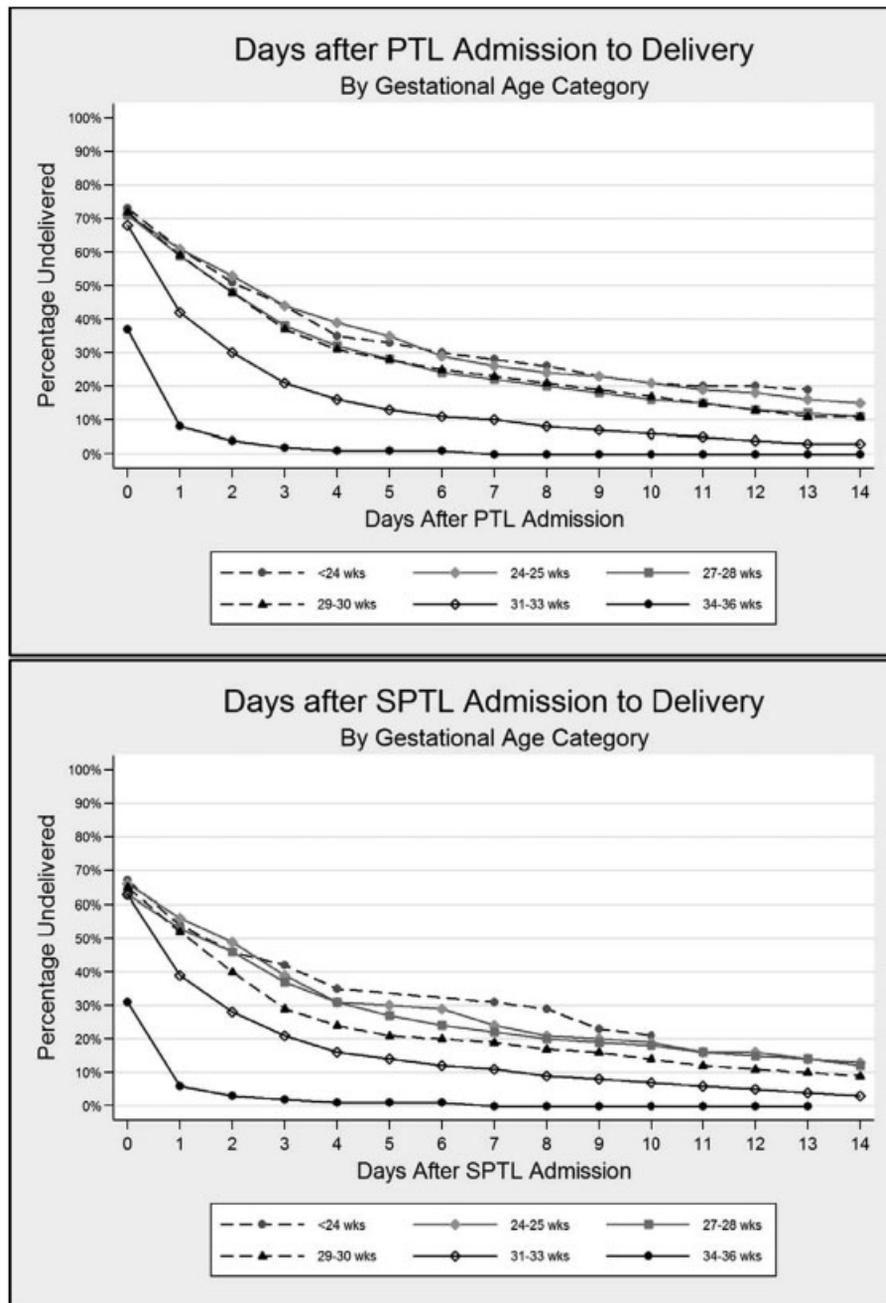
<sup>a</sup>No diagnosis of premature rupture of membranes, chorioamnionitis, hypertension/preeclampsia, incompetent cervix, placental abruption/previa.

<sup>b</sup>Major anomalies include cardiovascular, chromosomal, central nervous system, gastrointestinal, urinary tract.

may be evaluated and monitored in outpatient settings, due to the robust integration of services. What is unclear in these cases of nondelivery after PTL admission is whether they represent the successful resolution of preterm labor or an incorrect assignment of a diagnostic code for PTL. Since our study was retrospective and relied on administrative data, the specific clinical data required to classify true PTL were not available.

A small prospective study (*n* = 234) from North Carolina showed a delivery rate after PTL admission of 38.5%; however, when PTL was diagnosed at < 33 weeks, the delivery rate was 17.1%, and when diagnosed at ≥ 33 weeks, the rate was 64.8%.<sup>35</sup> Our data also shows that delivery rates differ by gestational age at admission. As a result, caution must be taken in comparing the delivery rate after PTL across studies, as gestational age at presentation has a significant impact on the rates.

Examining the predictors of delivery during PTL admission, later gestational age at presentation (34–36 weeks) was a strong predictor. The higher delivery rate and short latency periods in admissions ≥ 34 weeks may reflect decreased efforts on behalf of the obstetricians to prolong labor. The American College of Obstetricians and Gynecologists (ACOG) does not currently recommend the use of tocolytics after 34 weeks given their limited efficacy, side effects, and reduced neonatal morbidity, and mortality at this gestational age.<sup>36</sup> However, if effective and safe interventions were available, there may be utility in treating PTL at this later gestational age, since late preterm infants have increased morbidity compared with term infants.<sup>37–42</sup> Alternatively, the lower rate of delivery per preterm admission seen earlier in the third trimester may represent a lower threshold to admit for suspected PTL at earlier gestational ages, resulting in a higher false-positive rate of PTL diagnosis in this subgroup.



**Fig. 2** Days from PTL admission to delivery, all PTL, and spontaneous PTL. PTL, preterm labor.

The main limitation of our study was reliance on administrative data to define PTL. Most past studies have this same limitation. A large number of patients in this population-based study made it impractical to perform chart review on all PTL admissions to confirm the diagnosis. While some of our PTL admissions may not have met clinical criteria, the finding of a higher delivery rate after PTL admission than prior studies may suggest that we had fewer inclusions of false labor in our PTL admissions than other studies.

In our study, we also do not have data on the interventions the women received while admitted for PTL in terms of tocolytics, fluids, etc. As a result, we do not have the ability to differentiate if one treatment or management strategy was

superior in prolonging the time to delivery. However, such questions are better answered using randomized controlled trials. We were also unable to detangle the temporal relationship between PTL, PPROM, and chorioamnionitis.

Given the short latency and high delivery rate after PTL admission, a better understanding of the regulation of myometrial contractility is still needed. Development of agents that target the process leading to myometrial activation may prove to be more effective in prolonging time to delivery, providing additional time for fetal maturation as well as an expanded timeframe for clinical interventions (steroids, magnesium, and antibiotics) known to improve maternal and infant outcomes.

**Table 2** Maternal and infant outcomes, pregnancies with all PTL and spontaneous PTL, compared with pregnancies with no PTL

	All PTL (n = 22,150)		Spontaneous PTL (n = 12,628)		No PTL (n = 343,747)	
	n	%	n	%	n	%
<b>Maternal outcomes</b>						
Postpartum hemorrhage	517	2.3	284	2.2	8,434	2.5
ICU admission	134	0.6 <sup>a</sup>	36	0.3 <sup>b</sup>	467	0.1
Inpatient mortality	6	0.0 <sup>a</sup>	3	0.0 <sup>b</sup>	6	0.0
30-d mortality	12	0.1 <sup>a</sup>	7	0.1 <sup>b</sup>	14	0.0
<b>Infant outcomes</b>						
Level-3 NICU admission	10,089	45.5	4,318	34.2 <sup>b</sup>	19,623	5.7
SGA (<fifth percentile)	685	3.1	351	2.8 <sup>b</sup>	5,713	1.7
Inpatient mortality	442	2.0 <sup>a</sup>	185	1.5 <sup>b</sup>	245	0.1
One-year mortality	468	2.1 <sup>a</sup>	200	1.6 <sup>b</sup>	411	0.1

Abbreviations: ICU, intensive care unit; NICU, neonatal intensive care unit; PTL, preterm labor; SGA, small for gestational age.

<sup>a</sup>p < 0.001 (All PTL compared with No PTL).

<sup>b</sup>p < 0.001 (Spontaneous PTL compared with No PTL).

**Table 3** aOR for delivery during PTL admission

	All PTL admissions (n = 23,919)			Spontaneous PTL admissions (n = 13,678)		
	aOR <sup>a</sup>	95% CI	p	aOR <sup>a</sup>	95% CI	p
<b>GA at admission (wk)</b>						
< 24	0.54	0.41–0.69	<0.0001	0.71	0.49–1.03	0.0716
24–25	0.72	0.60–0.87	0.0005	0.72	0.56–0.93	0.0106
26–28	0.70	0.63–0.81	<0.0001	0.70	0.59–0.84	<0.0001
29–30	0.71	0.63–0.81	<0.0001	0.66	0.56–0.77	<0.0001
31–33	Reference			Reference		
34–36	6.90	6.29–7.57	<0.0001	8.68	7.81–9.66	<0.0001
<b>Maternal age (y)</b>						
< 18	0.64	0.50–0.83	0.0005	0.65	0.49–0.86	0.0042
18–24	0.84	0.75–0.95	0.0035	0.86	0.75–0.98	0.0241
25–29	0.83	0.75–0.92	0.0005	0.83	0.73–0.93	0.0045
30–34	Reference			Reference		
35–39	1.18	1.05–1.33	0.0052	1.20	1.04–1.38	0.0138
40+	1.49	1.23–1.80	<0.0001	1.43	1.13–1.81	0.0045
<b>Maternal race/ethnicity</b>						
White	Reference			Reference		
Black	1.06	0.92–1.21	0.4273	0.96	0.82–1.13	0.6554
Asian	0.99	0.89–1.10	0.8204	1.07	0.94–1.21	0.3304
Hispanic	1.08	0.98–1.20	0.1301	1.11	0.99–1.26	0.0928
Other/unknown	1.71	1.40–2.08	<.0001	1.83	1.48–2.28	<0.0001
<b>Clinical characteristics</b>						
Chorioamnionitis	105.58	52.30–213.17	<0.0001	N/A	N/A	N/A
Preterm rupture of membranes	19.29	14.91–24.96	<0.0001	N/A	N/A	N/A
Incompetent cervix	0.61	0.50–0.74	<0.0001	N/A	N/A	N/A
Placental abruption/previa	1.75	1.53–2.00	<0.0001	N/A	N/A	N/A
First preterm admission	0.78	0.69–0.87	<0.0001	0.84	0.73–0.97	0.0282

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; GA, gestational age; N/A, not applicable; PTL, preterm labor.

<sup>a</sup>Adjusted for birth year, facility, and clustering by the mother.

In summary, in a contemporaneous, diverse patient population in a highly integrated health care system, we demonstrate a high rate of preterm delivery per PTL admission. Factors associated with a short latency to delivery included later gestational age and presence of comorbid conditions, such as chorioamnionitis and PPROM. How can we make clinical use of this data? On the one hand, our high rate of preterm delivery per PTL admission represents an appropriate use of inpatient services, and further characterization of our practices may serve as a good model for systems with a higher false-positive rate per PTL admission. On the other hand, it does indicate that any interventions applied to the hospitalized patient at risk of preterm delivery within our health care system infrequently result in substantial pregnancy prolongation. This is reflective of previously published data detailing the lack of efficacy of pharmacologic and nonpharmacological strategies to prolong pregnancy in the setting of PTL and reinforces the need for further development of such strategies.

#### Authors' Contribution

1. M.K. discloses grants from GlaxoSmithKline during the conduct of this study.
2. L.B. reports personal fees from GlaxoSmithKline during the conduct of this study and outside the submitted work.
3. E.W., S.L., and M.G. report grants from GlaxoSmithKline during the conduct of this study.

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