17-Hydroxyprogesterone caproate (17OHP-C) coverage among eligible women delivering at 2 North Carolina hospitals in 2012 and 2013: A retrospective cohort study

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BACKGROUND: Although a weekly injection of 17-hydroxyprogestone caproate is recommended for preventing recurrent preterm birth, clinical experience in North Carolina suggested that many eligible patients were not receiving the intervention.

OBJECTIVE: Our study sought to assess how well practices delivering at 2 major hospitals were doing in providing access to 17-hydroxyprogesterone caproate treatment for eligible patients.

STUDY DESIGN: This retrospective cohort analysis studied all deliveries occurring between January 1, 2012, and December 31, 2013, at 2 large hospitals in North Carolina. Women were included if they had a singleton pregnancy and history of a prior spontaneous preterm birth. We extracted demographic, payer, and medical information on each pregnancy, including whether women had been offered, accepted, and received 17-hydroxyprogesterone caproate. Our outcome of 17-hydroxyprogesterone caproate coverage was defined as documentation of ≥1 injection of the drug.

RESULTS: Over the 2-year study period, 1216 women with history of a prior preterm birth delivered at the 2 study hospitals, of which 627 were eligible for 17-hydroxyprogesterone caproate eligible after medical record review. Only 296 of the 627 eligible women (47%; 95% confidence interval, 43—51%) received ≥1 dose of the drug. In multivariable analysis, hospital of delivery, later presentation for prenatal care, fewer prenatal visits, later gestation of prior preterm birth, and having had a term delivery immediately before the index pregnancy were all associated with failed coverage. Among those women who were "covered," the median number of 17-hydroxyprogesterone caproate injections was 9 (interquartile range, 4—15), with 84 of 296 charts (28%) not having complete information on the number of doses.

CONCLUSION: Even under our liberal definition of coverage, less than half of eligible women received 17-hydroxyprogesterone caproate in this sample. Low overall use suggests that there is opportunity for improvement. Quality improvement strategies, including population-based measurement of 17-hydroxyprogesterone caproate coverage, are needed to fully implement this evidence-based intervention to decrease preterm birth.

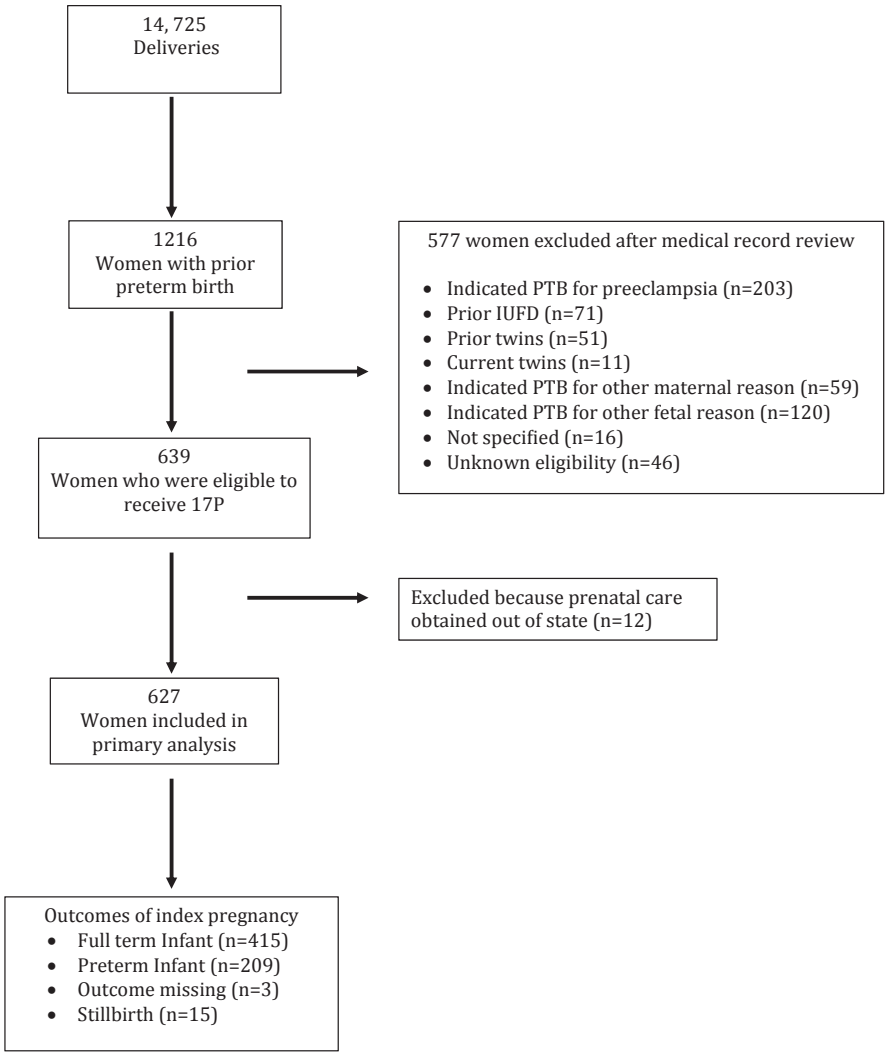
Key words: implementation, prematurity, prevention, 17OHP-C

Each year in the United States, nearly half a million infants are born before 37 weeks gestation.[1,2] In 2006, the US preterm birth (PTB) rate reached a record high of 12.8%.[3] Since that time, it has declined significantly to 11.32% in 2014,[4] with the reductions thought to be due to changes in elective deliveries before 37 weeks.[5-8] The number of early preterm term births (<34 weeks) has not seen significant improvement in the past 20 years, and it is these infants who experience the highest rates of morbidity and mortality.[3,9]

Ambitious goals have been adopted by the Association of State and Territorial Health Officials (ASTHO)[10] and the March of Dimes[11] for reducing the disease burden caused by prematurity. Central to these goals is a reduction in the national PTB rate to 8.1% by 2020. North Carolina, which has a preterm birth rate of 9.7%, received a grade "C" on its 2015 March of Dimes report card, which refers to states with a preterm birth rate between 9.3% and 10.3%.[10] A national target of 8.1% can be achieved only through a systematic, multifaceted, and coordinated effort. Although there has been reasonable recent progress made toward mitigating some PTB risk factors (smoking in pregnancy, elective late preterm births),[8] other areas still need attention. These include the complexity of addressing racial/ethnic inequalities in perinatal care[12,13] and increasing coverage of known effective interventions such as use of 17-hydroxyprogesterone caproate (17OHP-C).

A history of a prior PTB is among the most important risk factors for spontaneous PTB in a subsequent pregnancy.[14,15] Thus, women with a history of PTB have been the focus of interventions. In 2003, Meis and colleagues published the results of a multicenter randomized trial showing that, among women with singleton gestations and history of a prior spontaneous PTB, a weekly intramuscular injection of 17OHP-C (starting between 16 and 20 weeks and administered through delivery or 36 weeks' gestation) reduced the risk of recurrent PTB by 34%.[16] Numerous professional organizations in the United States, including the Society for Maternal—Fetal Medicine, the American College of Obstetricians and Gynecologists (ACOG), and the American Association of Midwives, have endorsed the use of 17OHP-C treatment in eligible women.[17-19] The most recent 2012 ACOG Practice Bulletin on preterm birth recommends tracking the "percentage of women with a prior spontaneous preterm birth who are offered progesterone supplementation" as a way to monitor implementation of

FIGURE 1
Flowchart of potential patients for 17OHP-C prophylaxis



A cohort of women potentially eligible to receive 17OHP-C prophylaxis and delivering at 2 North Carolina Hospitals between January 1, 2012, and December 31, 2013.

IUFD, intrauterine fetal demise; *PTB*, preterm birth; *17P*, 17OHP-C.

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17OHP-C. Yet, the document does not specify how to carry out such monitoring, which populations to evaluate, or appropriate data sources.

North Carolina has had a strong, statewide 17OHP-C initiative for almost 9 years, and the UNC Center for Maternal and Infant Health has disseminated guidelines for the use of 17OHP-C based on the ACOG/SMFM eligibility criteria on the Center's website (www.mombaby.org). However, there are no coordinated efforts to monitor statewide coverage of the intervention. In an effort to characterize 17OHP-C use in NC, we sought to assess what percentage of eligible women had received at 17OHP-C at 2 major hospitals.

Material and Methods

We conducted a retrospective review of all deliveries 20 weeks and above occurring between January 1, 2012, and December 31, 2013, at the University of North Carolina (UNC) Women's Hospital (Chapel Hill, NC) and at Mission Hospital (Asheville, NC). Both facilities have perinatal databases that can be queried for basic indicators, such as parity, gestational age, and birth history. We used these databases as a first pass through the study population to identify women whose medical records should be further evaluated, specifically those deliveries occurring during the study period to women whose obstetric history indicated a prior preterm birth ($\leqq$37 weeks). We then evaluated the full (paper) medical record for all women who were identified as potentially eligible for 17OHP-C through this initial screening process.

We define index pregnancy as the pregnancy that occurred between January 1, 2012, and December 31, 2013, and the pregnancy in which the woman would have been eligible for 17OHP-C. Our study cohort included women whose index pregnancy was a singleton gestation and who had a history of $\geq$1 singleton birth characterized by either premature rupture of membranes or spontaneous labor, occurring between $20^0/_7$ weeks and $36^6/_7$ weeks' gestation. We excluded women whose only "qualifying" prior preterm birth was indicated for maternal reasons (eg, induction for preeclampsia), indicated for fetal reasons (eg, fetal growth restriction with abnormal testing), or associated with placental abruption. We also excluded those whose index fetus had a major structural anomaly. Finally, we excluded from our primary analysis those women whose prenatal care for the index pregnancy was provided outside North Carolina, because we had limited access to those prenatal records. We categorized cases in which there was not enough available information to determine the cause of the prior PTB as "unknown."

We examined the prenatal records of the index pregnancy to determine whether the patient had been offered 17OHP-C by evidence of documentation of a provider discussing 17 P with the patient. We also documented whether the patient who had been offered 17 P accepted or declined it. We extracted information on the number of documented 17OHP-C injections received by

TABLE 1

Characteristics of 17OHP-C–eligible women delivering at 2 North Carolina hospitals between January 1, 2012, and December 31, 2013, who received ≥1 dose of 17OHP-C

Characteristic	Total		Covered		Not covered		*P* value
Age, y, n (%)							.59
<24	130	22%	61	22%	69	22%	
25–29	165	27%	75	26%	90	28%	
30–34	191	32%	97	34%	94	29%	
≥35	118	10%	51	18%	67	21%	
Missing	23		12		11		
Race/ethnicity, n (%)							.03
White	314	52%	153	53%	161	50%	
African American	114	19%	65	23%	49	15%	
Other	20	3%	8	3%	12	4%	
Hispanic	161	26%	63	22%	98	31%	
Missing	18		7		11		
Type of insurance, n (%)							.48
Medicaid	352	56%	166	56%	186	57%	
BC/BS	70	11%	32	11%	38	12%	
Tricare	9	1%	5	2%	4	1%	
Self-pay	101	16%	42	14%	59	18%	
Other	92	15%	50	17%	42	13%	
Missing	3		1		2		
Gravidity, n (%)							.38
<3	133	21%	66	22%	67	20%	
3 or 4	286	46%	140	47%	146	44%	
≥5	208	33%	90	30%	118	36%	
Smoker, n (%)							.83
Yes	121	20%	59	20%	62	20%	
No	487	80%	232	80%	255	80%	
EGA at first prenatal visit, weeks, n (%)							.0001
<14	373	64%	204	72%	169	57%	
14–20	117	20%	53	19%	64	22%	
>20	92	16%	28	10%	64	22%	
Missing	45		11		34		
Prenatal visits, n (%)							<.0001
<4	55	10%	18	6%	37	12%	
4–10	259	44%	94	33%	165	55%	
>10	268	46%	172	61%	96	32%	
Missing	45		12		33		
GA (weeks) at delivery of index pregnancy, mean (SD)	36.2 (4)		35.7 (4)		36.7 (4)		.002

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(continued)

TABLE 1

Characteristics of 17OHP-C–eligible women delivering at 2 North Carolina hospitals between January 1, 2012, and December 31, 2013, who received ≥1 dose of 17OHP-C *(continued)*

Characteristic	Total		Covered		Not covered		*P* value
Delivery type of index pregnancy, n (%)							.01
Vaginal	441	72%	192	66%	249	77%	
Cesarean	165	275	95	33%	70	22%	
Assisted vaginal	10	2%	5	2%	5	2%	
Missing	11		4		7		
Place of delivery, n (%)							.002
UNC	346	55%	144	49%	202	61%	
Asheville	281	45%	152	51%	129	39%	
County of residence							.002
Urban	454	77%	238	82%	216	71%	
Rural	139	23%	52	18%	87	29%	
Missing	34		6		28		
Any prior full-term births, n (%)							<.0001
Yes	343	55%	131	44%	212	64%	
No	284	45%	165	56%	119	36%	
Number of prior full-term births, n (%)							<.0001
0	284	45%	165	56%	119	36%	
1	181	29%	78	26%	103	31%	
2	105	17%	39	13%	66	20%	
Number of prior preterm births, n (%)							<.0001
1	477	765	206	70%	271	82%	
2	106	17%	62	21%	44	13%	
≥3	44	7%	28	10%	16	5%	
Earliest GA of prior preterm births, n (%)							<.0001
20 to <28	156	25%	117	40%	39	12%	
28 to <32	57	9%	31	11%	26	8%	
32 to <36	247	39%	121	41%	126	38%	
≥36	167	27%	27	9%	140	42%	
GA of most recent pregnancy before index pregnancy, n (%)							<.0001
<20	89	14%	40	14%	49	15%	
20–36	370	60%	207	70%	163	50%	
≥37	163	26%	47	16%	116	35%	
Missing	5		2				

Columns may not add up to 100% due to rounding.

BC/BS, Blue Cross/Blue Shield; *EGA*, estimated gestational age; *GA*, gestational age; *UNC*, University of North Carolina Women's Hospital.

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each woman. In cases in which there was no documentation of whether or not a woman had been offered the drug, but there was evidence of her having received injection(s), we assumed that it had been offered. In some cases, women opted to self-inject 17OHP-C at home, and in those instances we assumed that she received it because in most cases there was no record of actual receipt in the chart.

We also extracted characteristics potentially associated with non-receipt

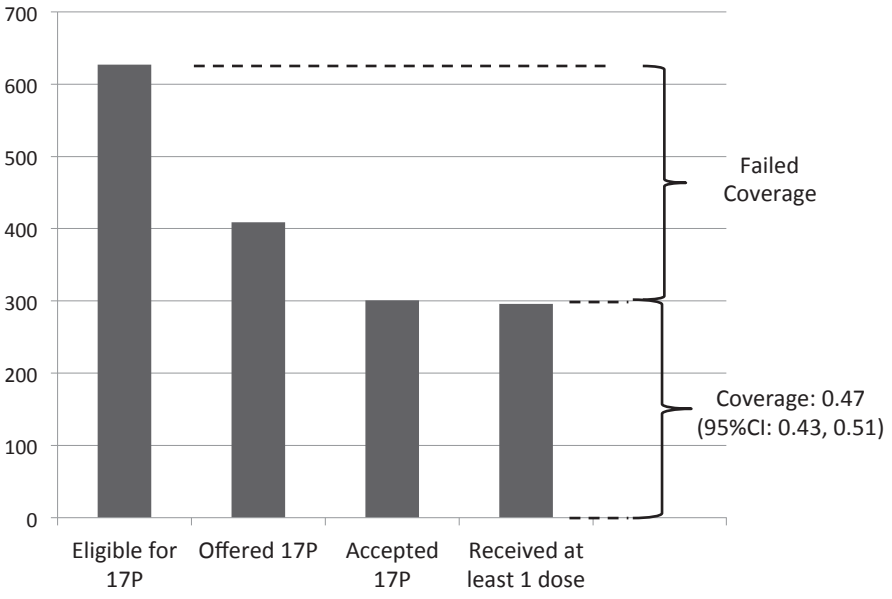
of 17OHP-C, such as maternal age, race/ethnicity, gravidity, smoking status, and type of insurance from each chart. Prenatal care data from the index pregnancy, including gestational age at the start of prenatal care and number of prenatal visits were collected. Finally, we extracted detailed available information on all prior pregnancies. We classified each participant represented in the sample as urban or rural according to her county of residence using definitions from the North Carolina Rural Economic Development Center.[20]

Our primary outcome was "17OHP-C failed coverage" defined as the proportion of eligible women who had not received ≥1 dose of 17OHP-C. We also investigated in additional analysis the outcome of "not offered 17OHP-C," which we defined as the proportion of eligible women who were not offered the drug by their provider and "refused 17OHP-C," which we defined as the proportion of women who refused the medication.

We fit logistic regression models to estimate odds ratios (OR) for the association between selected correlates and 3 dichotomous outcomes: failed 17OHP-C coverage, not offered 17OHP-C, and refused 17OHP-C. We used a stepwise regression approach with backward elimination to select an adjusted model. Main effects were retained in the model if *P* values were <.2. We performed all analyses with SAS version 9.4 software (SAS Institute, Cary, NC).

We planned our sample size around a balance between precision of the primary outcome estimate and projected feasibility of the medical record review. We anticipated that our time and resources available would allow detailed record extraction from approximately 600 charts. Assuming 50% 17OHP-C coverage among participants, a sample size of 600 eligible patients would provide 5% precision around this estimate (ie, 17OHP-C coverage = 0.50; 95% confidence interval [CI], 0.45–0.55). We estimated from prior experience that approximately 5% of women in the hospitals' birth cohort would be eligible for 17OHP-C,[21] and selected our study period to provide approximately 600 eligible patients. The study was approved by the Institutional Review Boards of the 2 delivery hospitals.

FIGURE 2
Eligibility for 17OHP-C intervention



Critical path that must be negotiated by eligible gravidas in order to receive the 17OHP-C intervention.

17P, 17OHP-C.

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Results

Between January 1, 2012, and December 31, 2013, a total of 14,725 women delivered at the 2 hospitals (Supplemental Table). Of those women, 1216 (8.2%) women had a prior preterm birth. We excluded 577 women (47%) for 17OHP-C noneligibility or unknown eligibility after medical record review (Figure 1). Once exclusions were applied, we were left with 627 women who were classified as 17OHP-C eligible.

Characteristics of women with a prior spontaneous preterm birth are presented in Table 1. Of the women who were eligible to receive 17OHP-C, the majority were of white ethnicity, and more than half (56%) were covered by Medicaid in the index pregnancy. Approximately two-thirds (64%) presented to their first prenatal visit before 14 weeks' gestation, and nearly half (46%) had >10 prenatal visits. The mean gestational age at delivery of the index pregnancy was 36 weeks (interquartile range [IQR], 35–39). Slightly more than half of the women (55%) had ≥1 prior full-term birth, whereas 25% reported ≥1 prior extremely preterm birth (≤28 weeks).

Of the 627 women eligible to receive 17OHP-C for prematurity prevention, only 296 (47%; 95% CI, 43–51%) met our definition for coverage (ie, documented receipt of ≥1 dose of the drug). 17OHP-C coverage varied significantly by hospital of delivery: at UNC Women's Hospital, 144 of 346 of eligible women (42%) were covered, compared to Mission Hospital, where 152 of 281 eligible women (54%) were covered ($P = .002$).

We recreated and quantified the steps along the critical path that each woman with a prior PTB must negotiate to benefit from 17OHP-C (Figure 2). Of 627 women who were eligible to receive 17OHP-C, 409 (65%) were offered it. Of the 409 women who were offered the drug, 301 (74%) accepted it, and of those 301 who accepted, 296 (98%) received ≥1 dose of the medication (Figure 2).

TABLE 2

Correlates of overall failed 17OHP-C coverage and not having been offered 17OHP-C among eligible women delivering at 2 North Carolina hospitals between January 1, 2012, and December 31, 2013

	Not covered (vs covered)				Not offered (vs offered)				Not accepted (vs accepted)			
	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI
Age, y												
<25	1.00	Reference			1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
25–29	1.06	0.67–1.68			1.42	0.87–2.32	1.55	0.74–3.24	0.71	0.38–1.32	0.54	0.24–1.22
30–34	0.86	0.55–1.34			1.11	0.68–1.80	1.00	0.49–2.01	0.73	0.41–1.32	0.51	0.23–1.12
≥35	1.16	0.70–1.92			1.97	1.17–3.33	1.95	0.89–4.27	0.60	0.29–1.25	0.24	0.08–0.72
Race/ethnicity												
White	1.00	Ref			1.00	Ref			1.00	Ref		
African American	0.72	0.47–1.10			0.84	0.52–1.34			0.58	0.31–1.10		
Other	1.43	0.57–3.58			1.43	0.57–3.60			0.96	0.25–3.75		
Hispanic	1.48	1.00–2.18			1.65	1.11–2.44			0.97	0.56–1.68		
Type of insurance												
BC/BS	1.00	Ref	1.00	Ref	1.00	Ref			1.00	Ref	1.00	Ref
Medicaid	0.94	0.56–1.58	0.99	0.48–2.06	1.10	0.63–1.91			0.76	0.39–1.48	0.94	0.38–2.31
Tricare	0.71	0.38–1.32	0.84	0.36–1.93	0.91	0.46–1.78			0.55	0.24–1.27	0.70	0.25–1.97
Self-pay	1.18	0.64–2.19	0.49	0.19–1.25	1.75	0.93–3.32			0.55	0.23–1.31	0.16	0.04–0.61
Other	0.67	0.17–2.72	—	—	1.75	0.43–7.14			—	—	—	—
Gravidity												
<3	1.00	Ref	1.00	Ref	1.00	Ref			1.00	Ref		
3–4	1.03	0.68–1.55	0.74	0.39–1.39	1.16	0.74–1.80			0.98	0.56–1.74		
≥5	1.29	0.83–2.00	1.41	0.68–2.93	1.54	0.97–2.45			1.02	0.55–1.87		
Smoker												
Yes	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref		
No	1.05	0.70–1.56	1.63	0.89–3.00	1.42	0.92–2.20	2.17	1.11–4.26	0.76	0.45–1.29		
EGA at first prenatal visit of index pregnancy												
<14	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
14–20	1.46	0.96–2.21	1.10	0.59–2.05	1.41	0.91–2.20	0.93	0.48–1.81	1.23	0.69–2.19	0.69	0.32–1.51
>20	2.76	1.69–4.50	3.08	1.49–6.37	2.99	1.87–4.77	3.47	1.72–7.00	1.55	0.77–3.12	2.00	0.81–4.93

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(continued)

TABLE 2

Correlates of overall failed 17OHP-C coverage and not having been offered 17OHP-C among eligible women delivering at 2 North Carolina hospitals between January 1, 2012, and December 31, 2013 *(continued)*

	Not covered (vs covered)				Not offered (vs offered)				Not accepted (vs accepted)			
	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI
Prenatal visits												
>10	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
4–10	3.14	2.20–4.49	3.85	2.35–6.31	3.02	2.05–4.44	3.19	1.86–5.48	2.38	1.47–3.87	3.11	1.67–5.81
<4	3.68	1.99–6.82	4.47	1.95,10.26	4.11	2.24–7.54	5.09	2.21,11.76	2.24	0.94–5.37	3.50	1.20–10.21
Place of delivery												
Asheville	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
UNC	1.65	1.20–2.27	2.41	1.42–4.10	1.72	1.23–2.41	1.46	0.86–2.47	1.20	0.77–1.87	3.15	1.58,6.28
County of residence												
Urban	1.00	Ref			1.00	Ref	1.00	Ref	1.00	Ref		
Rural	1.84	1.25–2.72			2.32	1.57–3.43	1.80	0.97–3.35	1.07	0.60–1.92		
Any prior full-term births												
No	1.00	Ref			1.00	Ref			1.00	Ref	1.00	Ref
Yes	2.24	1.63–3.09			2.39	1.69–3.38			1.63	1.04–2.54	3.31	0.87–12.54
Number of full-term births												
0	1.00	Ref			1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
1	1.83	1.26–2.67			1.75	1.16–2.62	0.91	0.47–1.79	1.57	0.94–2.62	0.33	0.09–1.22
2	2.35	1.48–3.72			3.06	1.91–4.89	2.90	1.36–6.18	1.30	0.65–2.60	0.32	0.07–1.35
≥3	4.26	2.23–8.14			3.99	2.21–7.19	2.15	0.83–5.60	2.85	1.21–6.70	1.00	1.00–1.00
Number of prior preterm births												
≥3	1.00	Ref			1.00	Ref			1.00	Ref		
2	1.24	0.60–2.57			1.33	0.57–3.12			1.25	0.44–3.52		
1	2.30	1.21–4.37			2.40	1.13–5.11			1.93	0.77–4.83		

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(continued)

TABLE 2

Correlates of overall failed 17OHP-C coverage and not having been offered 17OHP-C among eligible women delivering at 2 North Carolina hospitals between January 1, 2012, and December 31, 2013 *(continued)*

	Not covered (vs covered)				Not offered (vs offered)				Not accepted (vs accepted)			
	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI
Earliest GA of prior preterm births												
20 to <28	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
28 to <32	2.52	1.33–4.75	1.71	0.65–4.50	2.04	1.00–4.20	1.13	0.36–3.53	3.20	1.27–8.09	2.08	0.58–7.45
32 to <36	3.12	2.01–4.85	6.37	3.33,12.20	2.07	1.70–2.77	3.95	1.87–8.35	4.19	2.13–8.25	7.21	2.99–17.37
≥36	15.56	8.99,26.93	38.3	17.5–83.7	9.34	5.49–15.91	20.31	9.24,44.64	11.33	5.19,24.74	22.98	8.52–61.96
GA of most recent pregnancy before index pregnancy												
<20	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
20–36	0.64	0.40–1.02	0.44	0.22–0.88	0.55	0.34–0.89	0.27	0.13–0.53	0.95	0.48–1.89	0.92	0.36,2.38
≥37	2.01	1.18–3.45	3.22	1.50–6.93	1.64	0.97–2.77	1.45	0.66–3.19	1.93	0.89–4.18	4.35	1.35–14.03

AOR, adjusted odds ratio; *BC/BS*, Blue Cross/Blue Shield; *CI*, confidence interval; *EGA*, estimated gestational age; *GA*, gestational age; *OR*, odds ratio; —, sample size too small to calculate AOR; *Ref*, reference; *UNC*, University of North Carolina Women's Hospital.

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In multivariate regression, factors associated with failed 17OHP-C coverage included the following: delivery at UNC Women's Hospital compared to Mission Hospital (adjusted odds ratio [AOR], 2.4); presenting at >20 weeks' gestation for the first prenatal visit compared to <14 weeks' gestation (AOR, 3.1); attending <4 prenatal visits (AOR, 4.5) versus >10, and attending between 4 and 10 prenatal visits compared to >10 (AOR, 3.9) (Table 2).

The covariate most strongly associated with failed 17OHP-C coverage was the severity of a woman's prior preterm birth, in which we found evidence of a dose–response relationship, with increasingly later prior preterm births associated with lower odds of 17OHP-C coverage. Compared to women whose earliest prior preterm birth was at 20 to <28 weeks, there were successively higher odds of failed 17OHP-C coverage among women whose prior preterm birth occurred at 32 to <36 weeks (AOR, 6.4) and >36 weeks (AOR, 38.3). Women whose most recent pregnancy before the index was >37 weeks also had a higher odds of failed coverage when compared to women whose most recent pregnancy was <20 weeks (AOR 3.2) (Table 2).

Among those women who were "covered," the median number of 17OHP-C injections was 9 (IQR, 4–15), with 84 of 296 charts (28%) not having complete information on the number of doses. The median number of doses among women delivering at UNC Women's Hospital was 11 (IQR, 4–15) and in Ashville it was 7 (IQR, 3–16).

In additional analysis, we examined covariates associated with not having been offered 17OHP-C. In multivariable analysis, we found factors associated with the primary outcome to also be associated with this secondary outcome, with very similar strengths of association. Two exceptions included non-smokers, who had lower odds of being offered 17OHP-C than did smokers (AOR, 2.2) and women living in rural areas, who trended toward higher odds of not being offered the drug than did women living in urban areas (AOR, 1.8) (Table 2). Finally, we examined

covariates associated with refusing 17OHP-C. In multivariable analysis, we found that women who delivered at UNC Women's Hospital were 3.2 times as likely to refuse 17OHP-C as women delivering in Asheville. Women were also much more likely to refuse 17OHP-C if their prior preterm birth was a late preterm birth and if the most recent pregnancy prior to the index pregnancy was a term delivery.

Comment

In this retrospective cohort study conducted at 2 large regional perinatal centers in North Carolina, we found unacceptably low coverage of 17OHP-C among eligible women. Only 47% of eligible women in our cohort had documentation of a single dose of the drug, which was lower than we had expected. This finding confirms our hypothesis that many women at risk for recurrent preterm birth are not accessing 17OHP-C, despite its almost universal availability in our state through both private and public payers, and through a donation program sponsored by the manufacturer.

Our primary failed coverage outcome was strongly associated with key clinical factors, including later presentation to prenatal care, fewer prenatal visits, and severity of the prior "qualifying" preterm birth. Failed coverage also varied between the delivery hospitals, which, because of their geographic separation, serve largely distinct antenatal practices at which 17OHP-C would be prescribed and administered.

Our study shows not only that a gap in 17OHP-C coverage exists, but that there are problems with failure of providers to offer the treatment as well as failure of patients to accept the intervention. A previous survey among obstetricians on the use of 17OHP-C reported that only 59% of the physicians surveyed prescribed 17OHP-C to their eligible patients.[22] Logistical reasons and financial reasons were cited as the 2 most common reasons for not prescribing the drug. A secondary aim of our study was to develop methods that might be used for ongoing monitoring and quality assurance. We found that identifying a woman as eligible for 17OHP-C through chart review is not always as straightforward as one might assume, and we hypothesize that prenatal providers are faced with similar ambiguous clinical situations in the real world. The ACOG/SMFM guidelines advise that "a woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16−24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth," leaving room for interpretation in several situations.[17,18] For instance, the guidelines are silent on whether 17OHP-C should be prescribed when (1) the prior preterm birth was associated with placental abruption, (2) the prior preterm birth was a twin gestation, (3) the index pregnancy is a twin gestation, (4) the prior preterm birth occurred before 20 weeks' gestation, and (5) the clinical circumstances of the prior preterm birth are unclear/ambiguous. It likely that this lack of clarity is contributing to failed coverage. Iams and other experts have argued for expanded coverage of 17OHP-C to include women with a prior preterm birth as early as 16 weeks, when feasible, as well as offering it to women when the etiology is unclear.[23,24] Although we decided to define eligibility based on ACOG and SMFM guidelines, it is not unreasonable to advocate for revisions to this advice. Based on our data, we think that expanding potential indications for offering 17OHP-C may help with coverage.

North Carolina was an early adopter of 17OHP-C, with Medicaid paying for the drug as early as 2008.[16] Our study is among 1 of the first reports on the actual implementation of 17OHP-C among eligible women and is, to our knowledge, the only one that actually quantifies 17OHP-C coverage, 17OHP-C offered, and 17OHP-C received in a representative sample. Orsulak and colleagues have previously reported that the only 7.4% of eligible women covered by Medicaid received 17OHP-C in Louisiana in 2010.[25] We chose a retrospective cohort design because we wanted to understand the pragmatic issues around measuring 17OHP-C coverage before launching a larger prospective effort.

Interestingly, women who received 17OHP-C delivered at an earlier gestational age than those women who did not receive 17OHP-C. These women were more likely to have had an earlier prior preterm birth, which we think explains why they delivered at an earlier gestational age. It is possible that women who received 17OHP-C, although many still delivered preterm, delivered at later gestational ages than they would have had they not received 17OHP-C. More studies are needed to determine differences between women who respond to 17OHP-C and those who do not.[26] In addition, our hypothesis for the differences between coverage at Mission Hospital and UNC is that Mission has a more defined outreach area compared to UNC and the Mission catchment area includes a single maternal−fetal medicine group giving a consistent message on 17OHP-C.

Our study suffers from the usual challenges of a retrospective cohort analysis, including potential ascertainment bias and misclassification bias.[27] We were limited by the available information in the charts and the nonsystematic way in which information is captured. It was not uncommon to encounter a medical record in which 17OHP-C had been administered but in which there was no documentation that the patient was offered it. It is therefore possible that ascertainment error has been introduced at the individual points of attrition along the 17OHP-C cascade (offered, accepted). However, we are confident that the actual administration of drug is being accurately documented when it is administered in the clinic setting. When the 17OHP-C was administered at home, we were not able to quantify the number of injections that the patient actually received because it was not well documented in the chart.

We were particularly limited in our ability to discern the number of doses of 17OHP-C that a patient received, because repeat injection data are not well captured in the records. The few patients who self-administer 17OHP-C do not typically have all doses recorded in the medical record. Patients covered by North Carolina Medicaid for Pregnant

Women must have 17OHP-C administered at the clinic. Although this may help in capturing data about doses administered, it may be another barrier to receipt. A study that includes focus groups with pregnancy medical home care coordinators and with women eligible for 17OHP-C was recently conducted in North Carolina to explore individual patient barriers to uptake of the intervention. Finally, our study was conducted only among women who delivered at 2 large medical centers in North Carolina and may not be representative of all women across the state of North Carolina.

This study confirmed our anecdotal experience of significant gaps in 17OHP-C coverage, but also taught us that retrospective review of paper records is labor intensive and is not a feasible solution to monitor population coverage. We believe that developing a better methodology for measuring 17OHP-C coverage, such as linking electronic birth records with claims data, will be necessary for success, and should be a key research priority. We also found that reasons for failed coverage likely are due to a multitude of different reasons, and that to have a meaningful population increase in 17OHP-C, the solutions will need to be individualized for patients, clinics, and communities. Improving coverage of 17OHP-C will not only result in improved patient care and birth outcomes but also tremendous savings to the health care system.[28]

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SUPPLEMENTAL TABLE

Characteristics of eligible women delivering at the University of North Carolina at Chapel Hill and Mission Hospital in Asheville

Characteristic	UNC		Mission Hospital		*P* value
Age, years, (n%)					<0.0001
<24	46	14.2	84	29.9	
25-29	96	29.7	69	24.6	
30-34	109	33.8	82	29.2	
35+	72	22.3	46	16.4	
Missing	23		0		
Race/Ethnicity, n (%)					<0.0001
Caucasian	105	31.5	209	75.7	
African American	82	24.6	32	11.6	
Other	11	3.3	9	3.3	
Hispanic	135	40.5	26	9.4	
Missing	13		5		
Type of insurance, n (%)					<0.0001
Medicaid	158	46.1	194	69.0	
BC/BS		10.2	35	12.5	
Tricare	8	2.3	1	0.4	
Self-pay	90	26.2	11	3.9	
Other	52	15.2	40	14.2	
Missing	3	35	0		
Gravidity, mean (SD) n (%)					0.02
<3	70	20.2	63	22.4	
3-4	145	41.9	141	50.2	
≥ 5	131	37.9	77	27.4	
Smoker, n (%)					<0.0001
Yes	37	11.3	84	30.0	
No	291	88.7	196	70.0	
Missing	18		1		
EGA at 1st prenatal visit, n (%)					
<14					<0.0001
14-20	189	62.6	184	65.7	
>20	79	26.2	38	13.6	
Missing	34	11.3	58	20.7	
Prenatal visits, n (%)					0.002
<4	17	5.7	38	13.5	
4-10	148	49.2	111	39.5	
>10	136	45.2	132	47.0	
Missing	45		0		

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(continued)

SUPPLEMENTAL TABLE

Characteristics of eligible women delivering at the University of North Carolina at Chapel Hill and Mission Hospital in Asheville *(continued)*

Characteristic	UNC		Mission Hospital		*P* value
GA at delivery of index pregnancy, mean (SD)	36.5 (4.0)		35.9 (4.5)		0.06
Delivery Type of index pregnancy, n (%)					0.85
Vaginal	237	70.8	204	72.6	
Cesarean delivery	92	27.5	73	26.0	
Assisted vaginal delivery	6	1.8	4	1.4	
Missing	11		0		
County of residence					<0.0001
Urban	211	67.0	243	87.4	
Rural	104	33.0	35	12.6	
Missing	31		3		
Any prior full term births, n (%)					0.08
Yes	200	57.8	143	50.9	
No	146	42.2	138	49.1	
Number of prior full term births, n (%)					0.02
0	146	42.2	138	49.1	
1	96	27.8	85	30.3	
2	63	18.2	42	15.0	
Number of prior preterm births, n (%)					0.02
1	276	79.8	201	71.5	
2	53	15.3	53	18.9	
3+	17	4.9	27	9.6	
Earliest GA of prior preterm births, n (%)					0.003
20-<28	101	29.2	55	19.6	101
28-<32	38	11.0		19	6.8
32-36	109	31.5		138	49.1
36+	98	28.3	69	24.6	98
GA of most recent pregnancy prior to the index pregnancy, n (%)					0.55
<20	45	13.2	44	15.7	45
20-36	202	59.2	168	59.8	202
37+	94	27.6	69	24.6	94
Missing	5		0		5

EGA, estimated gestational age.

Stringer et al. 17OHP-C coverage among women delivering at 2 North Carolina hospitals. Am J Obstet Gynecol 2016.