Understanding if, How, and Why Women with Prior Spontaneous Preterm Births are Treated with Progestogens: A National Survey of Obstetrician Practice Patterns

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Abstract

Objective  In 2017, the Society for Maternal-Fetal Medicine (SMFM) Guideline Committee reaffirmed that 17α-hydroxyprogesterone caproate (17-OHPC) to prevent preterm birth (PTB) is underutilized. We sought to determine what drove progestogen treatment choice of obstetricians managing pregnant women with histories of 1+ singleton spontaneous PTBs (< 37 weeks) who then delivered singleton gestations within the previous 12 months.

Subjects  We recruited a nationally representative random sample of obstetricians to abstract medical records of study-qualified patients. Of the 423 study-qualified physicians contacted, 358 (85%) participated; 56 (16%) maternal fetal medicine specialists and 302 (84%) general obstetrician/gynecologists (OB/GYNs) extracted data from 991 eligible patient charts.

Results  Almost three-fourths of patients (73.6%) were treated with 17-OHPC; 18.6% received vaginal progesterone, and 11.8% were not treated. Key drivers of physicians’ choice to (1) prescribe branded 17-OHPC were “FDA (Food and Drug Administration) approval” (52% relative influence [RI]) and “SMFM guidelines” (24% RI); (2) prescribe vaginal progesterone were “ease of administration” (32% RI) and “shortened cervix” (16% RI); and (3) not provide prophylaxis were “patient not informed of risk” (35% RI) and “no shortened cervix” (29% RI).

Conclusion  Study findings support SMFM’s contention of continued 17-OHPC underutilization to prevent PTB. Need for additional physician education merits assessment along with appropriate follow-up actions.

About 380,000 neonates in the United States are born preterm (before 37 weeks of gestation).1 Preterm birth (PTB) is the leading cause of antenatal hospitalization, neonatal mortality, and perinatal morbidity.2 Prematurity continues to present a serious challenge because it is difficult to predict, prevent, and treat.3 Approximately 30% (135,000) of these women who deliver preterm had a history of a prior singleton spontaneous PTB. This subset of women is of particular interest because evidence-based treatment is available to prevent subsequent spontaneous PTB in this population.4

Keywords  ► Spontaneous Preterm Birth (SPTB) ► prematurity ► 17α-hydroxyprogesterone caproate (17-OHPC) ► progestogen ► vaginal progesterone ► maternal fetal medicine specialists (MFMs) ► shortened cervix

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In 2003, a landmark study conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the Maternal-Fetal Medicine Units (MFMU) Network demonstrated that recurrent PTB was reduced by about one-third with weekly injections of 17α-hydroxyprogesterone caproate (17-OHPC) in women with a history of singleton spontaneous PTB. The same year, the American College of Obstetricians and Gynecologists (ACOG) issued a Committee Opinion recognizing this intervention but also acknowledged that clinical study supplies had been specially formulated and were not currently commercially available. In the absence of a Food and Drug Administration (FDA) approved product, pharmacists compounded versions of 17-OHPC but utilization is presumed to have varied considerably, although there are no published estimates from that time. In February 2011, the U.S. FDA approved Makena (hydroxyprogesterone caproate injection); however, controversy ensued due to pricing concerns by the original manufacturer, KV Pharmaceutical (KV) (St. Louis, MO). In 2011, KV lowered the price of Makena and in 2012, the FDA stated that compounded versions of 17-OHPC should only be used when patients had clinical needs (e.g., allergy) that prohibited them from taking the FDA-approved drug. AMAG Pharmaceuticals (Waltham, MA) acquired Makena in 2014.

Vaginal progesterone also has been studied for the reduction of spontaneous PTB. Although several large placebo-controlled studies in women with histories of spontaneous PTB have been negative, other studies have indicated a benefit. Vaginal progesterone also has been studied with regard to treatment for an incidental short cervix and demonstrated a reduction in PTB; however, vaginal progesterone is not FDA approved to prevent PTB in women with a prior spontaneous PTB or an incidental short cervix.

In 2012, ACOG and the Society for Maternal-Fetal Medicine (SMFM) issued separate guidelines regarding the management of women at risk for PTB. In the SMFM guideline, an algorithm recommends the use of vaginal progesterone for women with an incidental short cervix and the use of 17-OHPC for women with histories of spontaneous PTB. The ACOG guideline was more general and stated only that “progesterone supplementation should be offered” to women with histories of spontaneous PTB.

Although the 2012 SMFM guideline specifically recommended the use of 17-OHPC for women with a prior spontaneous PTB, several recent publications (which retrospectively assessed utilization of 17-OHPC in indicated women) found that the rate of treatment with 17-OHPC varied from less than 10% among medicaid beneficiaries in Louisiana to 75% at a dedicated PTB clinic in Philadelphia. In 2017, the SMFM Guideline Committee conducted a review of various studies of prostegens for history of spontaneous preterm birth (SPTB) because there had been some conflicting results and reaffirmed its recommendation that all women with prior singleton, spontaneous PTB be offered 17-OHPC therapy in subsequent pregnancies with singleton gestations. The committee also reported that data from several sources suggested that despite their recommendations, underutilization of 17-OHPC for eligible patients continued. To further understand why this underutilization persists, this study sought to determine (1) the practice patterns of obstetricians across the United States with regard to the extent and type of progesterone they use to treat women with histories of singleton spontaneous PTB and (2) the type of provider/patient factors that influence treatment decisions.

Materials and Methods
To conduct a nationally representative, retrospective, observational study of OB/GYN who manage pregnant women with histories of spontaneous PTB, we recruited maternal-fetal medicine specialists (MFMs) and general OB/GYNs using the American Medical Association (AMA) Physician Masterfile supplemented by a national list of MFMs developed by Medefield, Inc. (New York, NY), a global physician research company. Randomly selected physicians in the targeted specialties were contacted via email or telephone and screened for eligibility.

Inclusion/Exclusion Criteria
A study-eligible obstetrician was required to have managed at least one patient with a history of prior spontaneous PTB (singleton) less than 37 weeks of gestation and then delivered a singleton pregnancy for that patient in the past 12 months. The obstetrician was required to have been the primary decision maker for that pregnancy’s prenatal care. An eligible physician was asked to extract information from the medical records of the last four patients who met study criteria. The physician was required to have access to all required information from each study patient’s medical record that would be needed to complete the study.

Study data were weighted to help minimize systematic sample-selection error by adjusting for over or under-representation of the sampled population against the expected corresponding distributions of the national population of high-risk pregnant patients by applying a methodology that has been used in several national and multinational surveys similar to our study here and was similar in aim to propensity score weighting. The factors influencing a patient’s weight were: (1) specialty of the treating physician, and (2) self-estimated patient volume of the treating physician. The expected distributions of these characteristics in the target population nationally were informed by the prevalence of patient-care MFM and OB/GYN physicians in the AMA Physician Masterfile and study participating physicians’ self-estimates of their respective volume of study-target patients managed during the preceding 12 months.

Fig. 1 contains a diagram of the overall design of the study. Note that 358 of the 423 qualified physicians contacted were participated in the study, providing 991 study-eligible cases. The first 966 cases were a probability sample of physicians and corresponding cases provided by OB/GYNs and MFMs. An additional 25 cases of patients managed by MFMs were obtained by oversampling.

Data Weighting Procedure
Data were weighted to statistically adjust for this oversampling. The purpose of weighting is to correct for over or
under-representation in the sample of key segments in the universe. Patient-based weights were necessary to properly adjust this survey.

Each patient’s raw weight was determined by the relative proportion of target patients seen by the patient’s physician (S8 in questionnaire). The steps we used to determine these proportions are presented in Table 1. As this table indicates, patients of MFMs collectively account for 7.9% of all target patients and OB/GYNs, 92.1%. Raw patient data were weighted to sum collectively to these specialty proportions. This procedure also adjusted for the oversampling of 25 patient cases by MFMs that occurred after completion of the probability sample to obtain a predetermined desired number for analysis.

**Efforts to Minimize Study Bias**

A basic challenge of national retrospective chart studies is systematic (confounding) error caused by differences in baseline characteristics between a study sample and the universe of patients, the sample is expected to represent. Such systematic error can cause over or under-representation of certain patient segments. We tried to minimize these effects in part by obtaining a national probability sample which requires that each potentially qualified physician and each patient whose case is selected for the study have a nonzero and a known probability of study selection. This was accomplished by random selection of general OB/GYNs and MFMs from the AMA Physician Masterfile supplemented by a national list of MFMs developed by a specialized physician research company (Medefield, Inc.) and subsequently weighting data to reflect each physician’s and patient’s probabilities of study selection.

The electronic data collection instrument was programmed into an online format with safeguards to (1) prevent missing data, (2) disallow entries outside of reasonable preset ranges (determined in physician pretesting and with the aid of literature review), (3) require that the patient’s chart be checked to verify or correct the initial response when a response was out of range, and (4) automatically calculate time period ranges, dosing conversions and other values that would require calculation by the physician for the target patient. Further, we conducted pretests of the instrument with qualified physicians to test the case report form with real-world cases. We believe that the feedback and suggested improvements we received from these physicians helped to minimize incorrectly entered data. To minimize missing data, physicians also were instructed on the types of information they would need to extract before beginning the study and were allowed to stop and start their input over several days if necessary to locate and obtain needed data from a patient’s chart. Data collection took place from April 21 to June 17, 2017.

**Statistical Analysis**

Statistical analysis included $t$-tests for comparisons of interval-scale data and Chi-square tests of independence and 2-tests for column proportions (with Bonferroni’s method used to correct for multiple comparisons) for categorical data comparisons. Logistic regression analysis (LRA) with proportional odds was used to identify which of the more than 100 physician and patient variables tested in our survey were significant individual (isolated) predictors of whether prophylactic treatment was received and if so, the significant predictors of the specific treatment option received. We augmented this analysis with a relatively new supplemental analytical tool for logistic regression (relative weights analysis–RWA). RWA enables researchers to draw more accurate inferences concerning the relative contribution or relative importance among multiple predictor

### Table 1 Steps in determining proportion of target patients in national universe by specialty

| Metric Descriptor | Type of specialty |
|-------------------|-------------------|
| 1. Number of target specialists nationally in active patient care\(^a\) | 1,355 | 43,423 |
| 2. Percentage of physicians by specialty who have managed a target patient in past 12 mo | 98% | 65% |
| 3. Number of physicians by specialty who have managed a target patient in past 12 mo (1 × 2) | 1,328 | 28,225 |
| 4. Ratio of target patients treated annually per physician by MFMs compared with OB/GYNs | 1.75 | 1 |
| 5. Percentage of national patient universe treated by physicians in specialty | 7.9% | 92.1% |

Abbreviations: OB/GYN, obstetricians/gynecologists; MFMs, maternal-fetal medicine specialist.

\(^a\)American Medical Association (AMA) Physician Masterfile supplemented by national list of MFMs developed by Medefield, Inc., a global physician research company.
variables in a regression analysis. This methodology (termed LRA/RWA) helps minimize the long recognized problem in regression analysis of unstable parameter estimates due to multicollinearity by removing all correlations between the significant predictor variables. For each of the four simulation models presented here, 15,000 bootstrap replications were conducted ($\alpha < 0.05$).

All analysis was done using IBM SPSS Statistics 23.0 at Clarity Pharma Research, Spartanburg, SC, and with a Microsoft R server at Davidson College, Davidson, NC.

**Results**

A total of 358 of the 423 study-qualified physicians contacted chose to participate in the study (302 general OB/GYNs and 56 MFM) and extracted data from the medical records of 991 qualified patient cases (913 by general OB/GYNs and 78 by MFM). The first 966 patient cases came from a probability sample and the final 25 were an oversample of MFM patients to reach a predetermined minimal number. Sample data were adjusted to correct for the oversampling of MFM patients (15.6% of study physician sample vs. 7.9% of universe).

As -Fig. 2 indicates, 545 (55%) patients received FDA-approved (17-OHPC), 184 (19%) received pharmacy compounded 17-OHPC, 117 (12%) received vaginal progesterone, and 145 (15%) received no therapy.

The MFM who participated in the study were more likely than general OB/GYNs to be hospital based (43% vs.14%, $p < 0.001$) either in a university or community hospital system and less likely to be in private practice (43 vs. 72%, $p < 0.001$). The MFMs and general OB/GYNs were similar with respect to U.S. census region, gender, and age. Approximately half of all physicians who were included in the study used a combination of ACOG and SMFM guidelines to guide treatment for women at risk for PTB. More MFMs than general OB/GYNs used a combination of both ACOG and SMFM guidelines (68 vs. 49%, $p = 0.003$). General OB/GYNs were more likely to only use ACOG guidelines to guide treatment practices (30 vs. 9%, $p = 0.003$; -Table 2).

Patients of MFMs and OB/GYNs were similar with regard to race/ethnicity, type of geographic setting in which patients live (rural, urban, suburban) maternal age at time of first prenatal visit, number of PTBs, and number of miscarriages. MFM patients, however, were more likely to have four or more full-term live births (11 vs. 5%, $p = 0.05$). Women with a term birth after a prior PTB were less likely to be treated with a progestogen (28% not treated vs. 17% treated, $p = 0.02$).

Patients who did not receive 17-OHPC were more likely than those who received 17-OHPC to be Hispanic or Latino (28 vs. 17%, $p < 0.001$), be between 31 to 35 years of age at the time of first prenatal visit (32 vs. 20%, $p < 0.001$), and less likely to have been informed of their increased risk of PTB (91 vs. 97%, $p < 0.001$; -Table 3).

- Fig. 3 contains the results of LRA supplemented RWA which indicates the amount of the total model variance explained when the influence of other variables in the model is eliminated. The RWA metric is a measure of relative influence (RI) of the variable on the dependent variable. LRA/RWA metrics are presented for each treatment option and the option of no treatment.

The greatest predictor of whether a patient received commercially available 17-OHPC was the attribute that it is “approved by the FDA” (52% RI). A combination of “physician compliance with SMFM guidelines” (16% RI) and that SMFM guidelines support use of this treatment (8% RI), as well as compliance of physician’s institution or practice with treatment guidelines (7% RI) accounted for most of the remaining influence of physician selection of this treatment.

For patients who received compounded OHPC, cost-related factors accounted for four-fifths of the RI. The RI of “favorable cost for this particular patient” and favorable cost of product “in general” were 52 and 29%, respectively. For patients who received vaginal progesterone, “ease of administration” had the greatest influence (RI 32%) on treatment selection. Three other highly important predictors were “shortened cervix” (RI 16%), “patient preference” (RI 15%), and “favorable cost for this particular patient” (RI 13%).

The single greatest influence on the decision as to why a patient did not receive any treatment was “patient not informed of increased risk for a preterm birth.” A patient was more than six times as likely to not receive treatment if she was not informed of the increased risk based upon her obstetrical history (proportional odds ratio of 6.6), representing an RI of 35. The second most influential variable was that the patient did not have a shortened cervix (RI 29%). Two other significant influences were “the immediately preceding birth was term” (RI 14%) and “the patient had no health care insurance” (RI 14%). The detailed metrics for LWA and RWA analyses are presented in -Table 4.

**Comment**

Though we tried to minimize the sample biases, it is not possible for a population sample of a retrospective observational study to mirror accurately the national universe of patients on all important baseline characteristics. With study limitations in mind, we report that our study supports
SMFM’s recognition that 17-OHPC is underutilized. We found 55% of the patients in our target cohort (women with a history of spontaneous PTB) received FDA-approved 17-OHPC, and 19% received compounded versions. This means that three-fourths of patients received 17-OHPC treatment consistent with SMFM guidelines which do not differentiate between compounded and the FDA-approved versions. An eighth (12%) of women received vaginal progesterone and 15%, no progestogen. While 96% of our study patients were offered some form of treatment, only 83% of untreated patients were offered therapy, a statistically significant difference.

The women who were not treated were of particular interest. A variety of factors were found to influence a provider’s decision to not treat a patient who had a documented history of spontaneous PTB. First, women with a term birth after the prior PTB were less likely to be treated with a progestogen, although risk does remain

Table 2 Physician demographics and practice characteristics

| Practice setting                      | MFMs n = 56 column A n (%) | OB/GYNs n = 302 column B n (%) | All physicians n = 358 column C n (%) |
|---------------------------------------|-----------------------------|---------------------------------|----------------------------------------|
| Hospital based                        | 24 (43) [B]                 | 42 (14)                         | 66 (18)                                |
| Solo private practice                 | 4 (7)                       | 66 (22) [A]                    | 70 (20)                                |
| Single specialty group                | 14 (25)                     | 131 (43) [A]                   | 145 (41)                               |
| Multispecialty group                 | 12 (21)                     | 56 (19)                        | 68 (19)                                |
| Medicaid-based clinic (e.g., FQHC)    | 2 (4)                       | 7 (2)                          | 9 (3)                                  |

Practice ownership

| Practice ownership                     | MFMs n = 56 column A n (%) | OB/GYNs n = 302 column B n (%) | All physicians n = 358 column C n (%) |
|---------------------------------------|-----------------------------|---------------------------------|----------------------------------------|
| Community hospital system             | 12 (21) [B]                 | 16 (5)                          | 28 (8)                                 |
| Corporate owned group                 | 8 (14)                      | 47 (16)                        | 55 (15)                                |
| Private practice                      | 24 (43)                     | 216 (72) [A]                   | 240 (67)                               |
| University hospital system            | 12 (21) [B]                 | 23 (8)                         | 35 (10)                                |

Region

| Region       | MFMs n = 56 column A n (%) | OB/GYNs n = 302 column B n (%) | All physicians n = 358 column C n (%) |
|--------------|-----------------------------|---------------------------------|----------------------------------------|
| Northeast    | 17 (30)                     | 81 (27)                         | 98 (27)                                |
| Midwest      | 11 (20)                     | 56 (19)                        | 67 (19)                                |
| South        | 16 (29)                     | 101 (33)                       | 117 (33)                               |
| West         | 12 (21)                     | 64 (21)                        | 76 (21)                                |

Gender

| Gender       | MFMs n = 56 column A n (%) | OB/GYNs n = 302 column B n (%) | All physicians n = 358 column C n (%) |
|--------------|-----------------------------|---------------------------------|----------------------------------------|
| Male         | 37 (66)                     | 180 (60)                       | 217 (61)                               |
| Female       | 19 (34)                     | 122 (40)                       | 141 (39)                               |

Age range

| Age range | MFMs n = 56 column A n (%) | OB/GYNs n = 302 column B n (%) | All physicians n = 358 column C n (%) |
|-----------|-----------------------------|---------------------------------|----------------------------------------|
| ≤ 34      | 1 (2)                       | 12 (4)                          | 13 (4)                                 |
| 35–44     | 13 (23)                     | 72 (24)                         | 85 (24)                                |
| 45–54     | 29 (52)                     | 125 (41)                        | 154 (43)                               |
| 55–64     | 11 (20)                     | 80 (26)                         | 91 (25)                                |
| ≥ 65      | 2 (4)                       | 13 (4)                          | 15 (4)                                 |

Type of guidelines in place at practice/institution for use of progestogens to manage preterm birth in at risk patients

| Type of guidelines | MFMs n = 56 column A n (%) | OB/GYNs n = 302 column B n (%) | All physicians n = 358 column C n (%) |
|--------------------|-----------------------------|---------------------------------|----------------------------------------|
| ACOG               | 5 (9)                       | 86 (30)                         | 91 (27)                                |
| SMFM               | 4 (7)                       | 3 (< 1)                         | 7 (2)                                  |
| Combination of ACOG and SMFM | 38 (68)                   | 140 (49)                        | 178 (52)                               |
| Other type         | 1 (2)                       | 3 (< 1)                         | 4 (< 1)                                |
| No guidelines      | 8 (14)                      | 55 (22)                         | 63 (21)                                |

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; FQHC, Federally Qualified Health Center; SMFM, Society for Maternal-Fetal Medicine.

Note: Data provided in parentheses (%) = % of total n for each column.

Comparison Group: Columns AB: When a percentage is followed by a column letter in brackets [], that percentage is significantly greater than the corresponding percentage in the other column (at the 95% confidence level).
elevated in subsequent pregnancies. Second, a history of late PTB was associated with decreased treatment. While earlier PTB has been shown to confer a greater risk of recurrent PTB, the risk for recurrence is elevated among women with histories of late PTBs compared with women with no PTBs.26,27 In the original study by Meis et al, women on average had a prior GA of approximately 31 weeks.5 A 2005 post hoc analysis stratified women

### Table 3: Patient demographic and baseline characteristics

|                      | MFM patients | OB/GYN patients | 17-OHPC received | 17-OHPC not received | Total patients |
|----------------------|--------------|-----------------|------------------|----------------------|---------------|
|                      | n = 78       | n = 913         | n = 729          | n = 262              | n = 991       |
| **Race/ethnicity**   |              |                 |                  |                      |               |
| American Indian or   | 0 (0)        | 15 (2)          | 8 (1)            | 8 (3)                | 15 (2)        |
| Alaska Native        |              |                 |                  |                      |               |
| American               | 5 (7)        | 41 (5)          | 32 (4)           | 14 (5)               | 46 (5)        |
| Asian                | 23 (30)      | 239 (26)        | 204 (28)         | 58 (22)              | 262 (24)      |
| Black or African      | 31 (40)      | 445 (49)        | 366 (50)         | 110 (42)             | 476 (48)      |
| African American     |              |                 |                  |                      |               |
| Caucasian/Non-        | 17 (22)      | 178 (20)        | 122 (17)         | 73 (28)              | 195 (20)      |
| Hispanic or Latino   |              |                 |                  |                      |               |
| Native Hawaiian or   | 0 (0)        | 4 (< 1)         | 4 (< 1)          | 0 (0)                | 4 (< 1)       |
| other Pacific Islander|             |                 |                  |                      |               |
| **Setting in which** |              |                 |                  |                      |               |
| patient lives        |              |                 |                  |                      |               |
| Rural                | 10 (13)      | 86 (9)          | 70 (10)          | 26 (10)              | 96 (10)       |
| Urban                | 32 (40)      | 339 (37)        | 266 (36)         | 105 (40)             | 371 (37)      |
| Suburban             | 37 (47)      | 488 (53)        | 394 (54)         | 130 (50)             | 524 (53)      |
| **Patient’s age**    |              |                 |                  |                      |               |
| at time of first     |              |                 |                  |                      |               |
| prenatal visit       |              |                 |                  |                      |               |
| < 20                 | 3 (3)        | 45 (5)          | 29 (7)           | 19 (4)               | 48 (5)        |
| 20–25                | 20 (26)      | 176 (19)        | 146 (19)         | 50 (20)              | 196 (20)      |
| 26–30                | 17 (22)      | 286 (31)        | 216 (33)         | 87 (30)              | 303 (31)      |
| 31–35                | 22 (28)      | 267 (29)        | 236 (20)         | 52 (32)              | 288 (29)      |
| 36–40                | 16 (20)      | 128 (14)        | 95 (19)          | 49 (13)              | 144 (15)      |
| > 40                 | 0 (0)        | 12 (1)          | 7 (2)            | 5 (1)                | 12 (1)        |
| **Number of full-**  |              |                 |                  |                      |               |
| term live births     |              |                 |                  |                      |               |
| 1                    | 29 (38)      | 325 (36)        | 254 (35)         | 100 (38)             | 354 (36)      |
| 2                    | 29 (38)      | 363 (40)        | 297 (41)         | 94 (36)              | 391 (40)      |
| 3                    | 10 (13)      | 173 (19)        | 132 (19)         | 50 (19)              | 183 (19)      |
| 4 or more            | 8 (11)       | 45 (5)          | 37 (5)           | 16 (6)               | 53 (5)        |
| **Number of pre-**   |              |                 |                  |                      |               |
| term live births     |              |                 |                  |                      |               |
| 1                    | 50 (66)      | 684 (76)        | 539 (75)         | 195 (75)             | 734 (745)     |
| 2 or more            | 26 (34)      | 220 (24)        | 181 (25)         | 66 (25)              | 246 (25)      |
| **Number of still**  |              |                 |                  |                      |               |
| births/fetal deaths  |              |                 |                  |                      |               |
| (< 20 wk)            | 0 (0)        | 3 (< 1)         | 2 (< 1)          | 1 (< 1)              | 3 (< 1)       |
| None                 | 50 (68)      | 701 (78)        | 547 (76)         | 204 (78)             | 751 (77)      |
| 1                    | 24 (32)      | 201 (22)        | 170 (24)         | 55 (21)              | 225 (23)      |
| 2 or more            | 9 (12)       | 131 (15)        | 102 (14)         | 38 (15)              | 140 (14)      |
| **Number of miscar-**|              |                 |                  |                      |               |
| rriages (< 20 wk)    |              |                 |                  |                      |               |
| None                 | 42 (56)      | 498 (55)        | 399 (56)         | 141 (56)             | 540 (56)      |
| 1                    | 24 (32)      | 269 (30)        | 218 (30)         | 75 (30)              | 293 (30)      |
| 2 or more            | 9 (12)       | 131 (15)        | 102 (14)         | 38 (15)              | 140 (14)      |
| **Documentation**    |              |                 |                  |                      |               |
| that patient was     | 76 (97)      | 869 (95)        | 706 (97)         | 238 (91)             | 945 (95)      |
| informed of increased|              |                 |                  |                      |               |
| risk for spontaneous |              |                 |                  |                      |               |
| preterm birth        |              |                 |                  |                      |               |

**Abbreviations:** 17-OHPC, 17α-hydroxyprogesterone caproate; OB/GYN, obstetricians/gynecologists; MFM, maternal-fetal medicine specialist.

**Note:** Data provided in parentheses ( ) = % of total n for each column.

**Comparison Groups:** Columns AB and CD: When a percentage is followed by a column letter in brackets [], that percentage is significantly greater than the corresponding percentage in the other column (at the 95% confidence level).
based upon prior GA. Although women in the late PTB history cohort were not found to have a statistically significant reduction in recurrent preterm birth, the authors cautioned that the analysis was not powered sufficiently. Current guidelines, as well as FDA-approved labeling, state that all women with a history of a prior singleton spontaneous PTB < 37 weeks should receive 17-OHPC treatment. Moreover, a substantial amount of literature recognizing the risks associated with late preterm birth has been generated in recent years.\textsuperscript{28}

### Table 4 Significant predictors/drivers of treatment choice

| Treatment | p-Value\textsuperscript{a} | Proportional OR Exp. (B)\textsuperscript{a} | 95% CI for Exp. (B)\textsuperscript{a} | RI (% of total model variance)\textsuperscript{b} |
|-----------|-----------------|-------------------------------|--------------------------------|-----------------------------------------------|
| **Branded 17-OHPC** | | | | |
| FDA approval of branded 17-OHPC | < 0.0005 | 2.4 | 1.7–3.3 | 52% |
| SMFM guideline compliance (physician) | 0.0026 | 1.6 | 1.2–2.3 | 16% |
| SMFM guideline support for branded 17-OHPC | < 0.0005 | 13.4 | 9.3–19.5 | 8% |
| Patient health insurance coverage | 0.0013 | 1.8 | 1.3–3.5 | 8% |
| Institutional guideline compliance | 0.0006 | 1.9 | 1.3–2.7 | 7% |
| **Compounded 17-OHPC** | | | | |
| Cost (favorable) for this patient | < 0.0005 | 2.5 | 1.7–3.8 | 52% |
| Favorable cost in general | 0.0006 | 2 | 1.3–2.9 | 29% |
| **Vaginal progesterone** | | | | |
| Ease of administration | 0.0163 | 1.8 | 1.1–3.0 | 32% |
| Shortened cervix | < 0.0005 | 3.4 | 2.1–5.7 | 16% |
| Patient preference | 0.0012 | 2.6 | 1.5–5.0 | 15% |
| Cost (favorable) for this patient | < 0.0005 | 3.4 | 2.2–5.03 | 13% |
| Fewer logistical barriers to/from HCP office | < 0.0005 | 6.2 | 2.7–13.5 | 7% |
| **No treatment** | | | | |
| Patient not informed of increased risk for a preterm birth | < 0.0005 | 6.6 | 3.4–12.8 | 35% |
| Shortened cervix not a comorbidity | 0.0016 | 3.4 | 1.6–7.4 | 29% |
| Preceding birth was term | 0.0035 | 1.9 | 1.2–3.0 | 14% |
| Not insured (health care) | < 0.0005 | 7.5 | 3.2–17.2 | 14% |

Abbreviations: 17-OHPC, 17α-hydroxyprogesterone caproate; CI, confidence interval; HCP, hydroxyprogesterone caproate; Exp, exponentiation; FDA, Food and Drug Administration; RI, relative influence; SMFM, Society for Maternal-Fetal Medicine.

\textsuperscript{a}Values derived from logistic regression analysis with proportional odds.

\textsuperscript{b}Values derived from relative weights analysis.
Third, women with prior spontaneous PTBs were less likely to be treated with progestogen if they had normal cervical lengths in the current pregnancies. Although robust data are lacking to understand the efficacy of progestogen in this patient population (prior SPTB and short cervix), the SMFM guidelines state that in patients with a history of a prior spontaneous PTB, if short cervix is also identified, 17-OHP should be used. Lastly, cost concerns were another important barrier to appropriate treatment. The manufacturer of the FDA-approved form of 17-OHCP provides patient assistance, both for women with no health insurance and to lower out-of-pocket costs for women with commercial insurance. To be eligible, patients must meet the FDA-approved indication (i.e., federal restrictions preclude manufacturer assistance for off-label indications, including starting after 26 weeks).

Of women who were treated with progestogen, we found it interesting that although most MFMs in the study utilized both SMFM and ACOG guidelines when deciding treatment regimens for women with histories of prior spontaneous PTB, most general OB/GYNs (the majority of the physicians sampled) only used ACOG guidelines. Given that the ACOG guideline stated that “progesterone supplementation should be offered” to women with histories of spontaneous PTB and did not specify which type of progestogen, this lack of specificity may have been a guiding factor in why some physicians chose vaginal progesterone for their patients. Although there may be a perception that all forms of progestogens are acceptable for women with histories of prior spontaneous PTBs, different results have been demonstrated in clinical studies.

“Progesterone” is sometimes used to describe 17-OHPC, although this is technically inaccurate. 17-OHPC is a progestin, a synthetic form of progesterone and has a different chemical structure which confers different pharmacological profiles and efficacy (Fig. 4).

In 1990, Keirse et al recognized that prior meta-analyses had included various progestational agents and concluded no benefit in PTB reduction. As chemical structural differences may confer varying pharmacological profiles, Keirse subsequently restricted his meta-analysis to seven studies using 17-OHPC only and found a significant reduction of preterm birth but not of miscarriage. These data in part informed the selection of IM 17-OHPC for the NICHD MFMU trial by Meis et al.

In addition to the specific chemical structure of the drug, drug formulation is also important. For instance, compounded drugs including 17-OHPC are made under different oversight, typically by individual state boards of pharmacy, compared with FDA-approved medications which must be made in accordance with Current Good Manufacturing Practices (CGMP). Concerns about patient safety are not hypothetical; in 2012, a fungal meningitis outbreak occurred due to a contaminated methylprednisolone made at a compounding pharmacy. Sixty-four patients died, and more than 750 were sickened. As a result, Congress passed the Drug Quality and Security Act (DQSA) in 2013. Although efforts are under way to help ensure better oversight for pharmacy compounding, a report issued in January 2017 acknowledged that the FDA has identified unsanitary conditions at the majority of sterile compounders it has inspected since enactment of DQSA. While managed care organizations previously had policies that sometimes required “failure” on compounded drug before covering branded 17-OHPC, these restrictions have nearly unanimously been modified following DQSA’s passage, allowing providers to prescribe the FDA-approved version for indicated patients.

Patient acceptance and ease of administration were also found to be significant factors regarding 17-OHPC utilization. The recommended 17-OHPC intervention requires weekly injections by a health care provider. Some patients may refuse to accept weekly injections or their providers may believe they are unlikely to accept or comply with weekly injections. In such cases, providers may view vaginal progesterone as a feasible alternative. Although providers may deem vaginal progesterone and 17-OHPC as interchangeable, three placebo-controlled studies of vaginal progesterone in women with prior spontaneous PTBs found no benefit relative to placebo. In the first study by O’Brien et al, 659 women were randomized to vaginal progesterone gel; PTB < 37 weeks was 41.7% in the vaginal progesterone group versus 40.7% placebo; 95% CI 1.08 (range: 0.76–1.52). In the second study by Norman et al (2016), 1,228 in the United Kingdom were randomized to vaginal progesterone 200 mg or placebo. Seventy-five percent of these women had histories of spontaneous PTBs (n = 921), with other risk groups including short cervix and positive fetal fibronectin. In both the overall results, as well as the prespecified subgroup analysis restricted to spontaneous PTB history, vaginal progesterone had no effect on any of the primary obstetric, neonatal, or childhood outcomes. Lastly, a study conducted in Australia, New Zealand, and Canada among 787 women with prior histories of spontaneous PTBs randomized women to vaginal progesterone 100 mg or placebo and found no benefit (PTB < 37 weeks: 36.5% vaginal progesterone vs. 37.2% placebo; p = 0.765).

Fig. 4 Chemical structures of selected progestogens (Sources: Can Stock Photo/logos2012, AMAG Pharmaceuticals, Inc.).
Proponents of vaginal progesterone cite a 2003 Brazilian study by Da Fonseca in which 142 high-risk women (more than 90% of whom had prior spontaneous PTBs) were randomized to vaginal progesterone 100 mg or placebo, with a significant reduction of PTB < 37 weeks (13.8% vs. 28.5%; \( p = 0.05 \)). In addition, a study by Maher in Saudi Arabia reported that vaginal progesterone was more effective than IM 17-OHPC in reducing PTB. This study enrolled 520 women with histories of one or more midtrimester PTBs or use of cerclage in a prior pregnancy, a heterogeneous population recognized by SMFM as being different from the typical 17-OHPC candidate in the U.S. After evaluation of the current available literature on vaginal progesterone, the SMFM statement reaffirmed its current recommendations: in women with a singleton gestation and a history of prior spontaneous PTB between 20 and 36\( \frac{1}{7} \) weeks of gestation, SMFM recommends 17-OHPC at 250 mg intramuscular weekly, starting at 16 to 20 weeks of gestation until 36 weeks of gestation or delivery, and vaginal progesterone should not be considered a substitute for 17-OHPC in these patients.

In February 2018, the FDA approved an alternative delivery method of the commercially available 17-OHPC which includes an autoinjector to deliver the medication subcutaneously. This device allows for a shorter, smaller, and nonvisible needle which may be beneficial for patients who express apprehension regarding injections and report discomfort of an intramuscular injection. The site of administration also changed from the upper, outer gluteus maximus to the back of the upper arm, which coupled with a device ready-to-administer out of the box, may ease the administration of the injection. This new delivery method has demonstrated comparable bioavailability, or systemic drug exposure, to the intramuscular injection formulation. The introduction of this new device and its ease of administration will hopefully support higher rates of treatment acceptance and compliance.

In conclusion, the main findings of this study suggest several factors could be improved to ensure all women with a prior spontaneous PTB receive appropriate treatment to decrease their risk of PTB in subsequent pregnancies. First, since our findings suggest most general OB/GYNs utilize ACOG statements to guide treatment choices, assessment of general OB/GYN awareness of SMFM guidelines on preterm birth prevention would be beneficial. If awareness is lacking, increasing education regarding the SMFM guidelines may be useful. Second, until further robust data exist on the utility of 17-OHPC in women who have a prior spontaneous late PTB or a prior spontaneous PTB and then a subsequent delivery at term, providers should note that current SMFM guidelines state 17-OHPC should be recommended and started between 16 to 20 weeks of gestation for women with a history of singleton, SPTB less than 37 weeks of gestation. Third, increasing awareness regarding the new patient/user friendly 17-OHPC may also increase provider/patient adherence to current recommended guidelines. Lastly, while research into additional causes of preterm birth and potential new treatments should continue to evolve, incorporation of recognized standard of care pharmacological treatment and nonpharmacological care (i.e., improve access to preconception care services, discourage nonmedically indicated deliveries before 39 weeks, prevent unintended pregnancies and use optimal birth spacing, transfer of single embryo for pregnancies achieved by assisted reproductive technology) must continue to be improved.

Conflict of Interest
Author J.R.G. is an employee of Clarity Pharma Research, LLC, Spartanburg, SC, and declares that he has no conflicts of interest. Author J.G. is an employee of AMAG Pharmaceuticals, Inc., Waltham, MA, and declares that she has no conflicts of interest. Author K.H. is an employee of Clarity Pharma Research, LLC, Spartanburg, SC, and declares that she has no conflicts of interest. Author J.V. is an employee of Columbia University Irving Medical Center (CUIMC), New York, NY, and is the Co-Director of the Preterm Birth Prevention Center at CUIMC. This Center has received unrestricted funds from AMAG Pharmaceuticals; however, these funds had no association with this study. Author S.C. is an employee of Clarity Pharma Research, LLC, Spartanburg, SC, and declares that she has no conflicts of interest. Physician participants in the study received an honorarium.

Ethics Approval and Consent to Participate
This article is based on previously existing observational data (i.e., retrospective chart information). Our research did not involve interventional studies of human or animal subjects performed by any of the authors. This retrospective study used anonymized, deidentified data, and no personal, individually identifiable health information was collected. Data were reported in the aggregate. Formal consent was not required for this study which was classified as exempt under 45CFR46. 101(b)(4) by Solutions IRB (Little Rock, AR).

Availability of Data and Materials
The dataset generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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interpretation of the data. All authors contributed to the drafting and critical review of the manuscript.

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