Published in final edited form as:

J Perinatol. 2019 September ; 39(9): 1182–1189. doi:10.1038/s41372-019-0401-2.

Practical Considerations with 17-Hydroxyprogesterone Caproate for Preterm Birth Prevention: Does timing of initiation and compliance matter?

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Abstract

Objective: Determine whether gestational age of 17-hydroxyprogesterone caproate (17-OHPC) initiation is associated with preterm birth (PTB) risk.

Study Design: We performed a retrospective cohort study using MarketScan® data. The primary outcome was PTB<37 weeks. Rates of PTB were compared between medication initiation

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AUTHOR CONTRIBUTIONS

Ebony B. Carter, MD, MPH: Conceived and designed the work that led to the submission, played an important role in interpreting the results, drafted and revised the manuscript, and approved the final version. She has had full access to the data in the study and final responsibility for the decision to submit for publication

Alison G. Cahill, MD, MSCI: Played an important role in interpreting the results, revised the manuscript, and approved the final version.

Margaret A. Olsen, PhD, MPH: Helped to design the work that led to the submission, acquired data, revised the manuscript, and approved the final version.

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Molly J. Stout, MD, MSCI: Conceived and designed the work that led to the submission, played an important role in interpreting the results, revised the manuscript, and approved the final version. She has had full access to the data in the study and final responsibility for the decision to submit for publication

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CONFLICT OF INTEREST

Ebony B. Carter, MD, MPH: Reports no conflicts of interest or financial disclosures.

Alison G. Cahill, MD, MSCI: Reports no conflicts of interest or financial disclosures.

Margaret A. Olsen, PhD, MPH: Reports no conflicts of interest or financial disclosures.

George A. Macones, MD, MSCE: Reports no conflicts of interest or financial disclosures.

Methodius G. Tuuli, MD, MPH: Reports no conflicts of interest or financial disclosures.

Molly J. Stout, MD, MSCI: Dr. Stout has research support from AMAG pharmaceuticals. AMAG pharmaceuticals had no role in the planning, execution, analysis, or interpretation of these results.

This study was conducted at Washington University School of Medicine

at 16.0– 21 weeks versus 21.0–29.0 weeks. The effect of compliance with weekly 17-OHPC injections was tested after adjusting for potential confounding variables.

Result: 3374 pregnancies met inclusion criteria. Women with an early 17-OHPC start were less likely to deliver preterm than those with a late start (aRR 0.88; 95% CI 0.79–0.97; $p=0.02$). Less compliant patients receiving <25% of recommended doses had a higher PTB rate than those receiving > 85% of recommended doses (aRR 1.5; 95% CI 1.2–1.7; $p<0.01$).

Conclusion: There is an association between both early 17-OHPC initiation and compliance with reduced rates of PTB.

Keywords

17-hydroxyprogesterone caproate; preterm birth; prevention; compliance; prophylaxis; recurrence; treatment outcome

INTRODUCTION

The preterm birth (PTB) rate in the United States decreased slightly in recent years. (2) Potential explanations include demographic changes in the obstetric population including reduced rates of teen pregnancies and multiple gestations as well as medical evidence to support use of progestins in high-risk groups.(1)

Weekly treatment with 17-hydroxyprogesterone caproate (17-OHPC) from 16–36 weeks of gestation became the standard of care for spontaneous preterm birth (PTB) prevention after Meis and colleagues demonstrated that it decreased the risk of recurrent PTB by 34% among women with a prior spontaneous PTB.(2) The Meis trial used observational data to inform their choices for timing of medication initiation, dosing, and dosing interval. Clinical practice guidelines for the use of 17-OHPC were modeled according to use of the drug in the clinical trial;(3) yet little subsequent evidence exists for whether strict adherence to the trial protocol is required for clinical effect. While 17-OHPC has no known long-term adverse side effects, the drug is not innocuous with possible injection site reactions, high cost, and inconvenient weekly injections. If a more liberal gestational age of initiation or dosing strategy is effective for PTB prevention, then patient compliance may be improved and health care costs could be decreased.

17-OHPC use is the standard of care for women with a prior spontaneous preterm birth and thus it is not ethical to randomize women to different dosing intervals or gestational ages of treatment initiation. Instead, observational epidemiologic data must be examined to infer how clinical use of this drug impacts rates of recurrent PTB. The aim of this study was to examine the timing of 17-OHPC initiation and compliance with the recommended 17-OHPC dose schedule on the risk for recurrent preterm birth. We hypothesized that women initiating 17-OHPC prior to 20 weeks and having high compliance with the recommended dose schedule, would have significantly reduced rates of recurrent PTB compared to those who did not.

MATERIALS AND METHODS

We performed a retrospective cohort study using the Truven Health Analytics MarketScan® Commercial Claims and Encounters Database (Truven Health Analytics, Ann Arbor, MI) from 2006–2014. MarketScan is an administrative, commercial health insurance database including medical and prescription drug claims from approximately 100 large employer and private health plans across the United States. Inpatient, outpatient and pharmacy patient level data are included. Institutional Review Board approval was not required for analysis of this de-identified limited dataset.

Inclusion criteria included women aged 13–45 years with prescription drug coverage and treated with 17-OHPC in at least one pregnancy within 150 days of delivery, and gestational age at delivery for the index 17-OHPC pregnancy available either through maternal or linked infant data, as described in the *Assigning Gestational Age of Delivery* section. Pregnancies with multiple gestations or major fetal anomalies were excluded. The first pregnancy meeting study criteria was considered the index pregnancy if a woman had multiple pregnancies in the database; thus, only one pregnancy per patient was included in the study.

Definitions of Exposures and Outcomes of Interest

The primary exposures examined were gestational age of initiation of 17OHPC as well as compliance with the weekly recommended 17OHPC dose schedule. 17OHPC initiation was dichotomized into “early start” (16–20 6/7 weeks) or “late start” (21–28 6/7 weeks). Gestational age of initiation was also stratified in 4 week ranges to explore the effect of timing of initiation across gestation on rates of PTB. To examine the effect of weekly compliance, separate from the timing of initiation we calculated “% compliance” based on number injections received divided by the number of injections for which the patient was eligible. For example, a patient who started weekly injections at 16 weeks, but delivered at 33 weeks would be 100% compliant (17 injections of a possible 17), but had the same patient stopped the injections after week 33 and carried to term, she would only be 85% compliant (17 injections of a possible 20). The primary outcome of interest was preterm birth <37 weeks.

Identification of Study Population in MarketScan®

We identified the target cohort in the MarketScan data using the International Classification for Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes, Current Procedural Terminology (CPT) codes, and the Healthcare Common Procedure Coding System (HCPCS) in a stepwise fashion to maximize the reliable capture of the target population of pregnant women using 17-OHPC for PTB prevention. Reproductive age women (13–45 years old) who received an injectable progestin (as defined by HCSPCS codes J1725 and J2675) during pregnancy were included. The delivery date was identified using ICD-9-CM diagnosis, procedure, and CPT codes associated with delivery, as previously described.⁽⁴⁾ If the only progestin exposure occurred less than 16 weeks of gestation or > 150 days from delivery, these women were excluded as they were assumed to be treated with progestin for reasons other than PTB prevention, such as in vitro fertilization luteal support.

Assigning Gestational Age of Delivery

In order to define the delivery date, essential to calculate the timing of 17OHPC start, a hierarchical system with the following criteria was employed: The matching delivery record for the newborn was prioritized, since it allowed identification of the exact delivery date. In the absence of a matching newborn delivery record, the delivery date was defined based on all claims within a range of 7 days during an inpatient hospitalization with a service date coded for delivery (CPT-4 codes for vaginal or CPT-4/ICD-9-CM procedure codes for cesarean delivery). If the range of dates consistent with delivery was too broad, it was limited by considering sequentially: UB-04 revenue codes for labor and delivery services (0720–0729), ICD-9-CM diagnosis codes V27.x (outcome of delivery) or 650 (normal delivery), and finally ICD-9-CM diagnosis codes 651.x–669.x with a 5th digit of 1 or 2 (conditions existing with delivery). If inpatient claims were not available to help narrow the potential delivery date, provider claims with a CPT-4 code for delivery were used alone to define the delivery date.

Gestational age at delivery was defined using a hierarchical algorithm, prioritizing gestational age based on ICD-9-CM diagnosis codes 765.20–765.29 coded on the matching newborn record, when available. If the matching newborn record was not available or did not include diagnosis codes in the range 765.20–765.29, gestational age was estimated using service dates for antenatal testing, as described by Wallace et al.(5) The midpoint of the recommended testing intervals was used to estimate the gestational age at testing. For example, nuchal translucency screening was considered second in the algorithm and any patient with this testing was assigned an estimated gestational age of 12.5 weeks at screening as the midpoint in the recommended screening range of 11+0 weeks to 13+6 weeks gestation with a maximum estimated margin of error of 1.5 weeks. Next, any of four tests: chorionic villus sampling (CVS), pregnancy-associated plasma protein A (PAPP-A), inhibin-A, and alpha-fetoprotein (AFP). CVS was assumed to have been performed at 11 weeks, PAPP-A at 12 weeks, and inhibin-A and AFP at 17 weeks gestation. If more than one of the four tests was performed and there was agreement in the gestational age with at least two tests, then that gestational age was used as the gestational age at delivery. If more than one of the four tests was performed and there was disagreement among the calculated gestational age at delivery, the patient was dropped from analysis. Finally, if none of the above information was available, but the mother's delivery record indicated full or post-term delivery (ICD-9 645.1, 645.2, 649.8, or 650), and the matching infant's birth record did not have a diagnosis code for gestational age, the infant was considered to be full term.

Assigning Gestational Ages of Progestin Injections

The gestational age at which 17OHPC was initiated was assigned by subtracting the estimated gestational age on the date of first progestin injection from the estimated gestational age at delivery. Patients who were identified as progestin users by outpatient pharmacy claims were excluded from the analysis because the primary exposures of number of injections, timing and compliance were not possible to track precisely with the outpatient prescriptions.

Analysis

Demographic characteristics, including number of prior preterm births (among women with at least one prior delivery captured in the data during the study period), mode of delivery, hypertension, diabetes, obesity, tobacco use, intrauterine growth restriction, and preterm premature rupture of membranes were defined using ICD-9-CM diagnosis and other codes (see Supplemental Table 1). These characteristics were compared between early-start and late-start groups using descriptive statistics, including chi-square test and Student's t-test, as appropriate. Unadjusted analyses were used to calculate the relative risk for PTB at <37 weeks and <34 weeks in early versus late start of progestin groups. Lastly the effect of compliance with weekly progestin injections on the risk for PTB was examined using >85% compliance as the reference group. Potential confounding variables including gestational age of earliest prior PTB, number of prior PTB's, and obesity were assessed after considering significant differences between groups, known predictors of PTB, and the reliability of diagnostic codes in MarketScan. All analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

RESULTS

HCPCS codes identified 238,496 women in the MarketScan database who were 13 years old and received a progestin (Figure 1). ICD-9 diagnosis, procedure and CPT codes were used to identify 61,281 women from this group who also had a delivery during the study period. Maternal and infant records were able to be linked in MarketScan for 78% of the sample. After limiting the sample to only those women with an identifiable delivery date, use of injectable progestins at gestational age ranges plausible for PTB prevention, maternal age 13–45 years at delivery, singleton pregnancies, initiation of progestin between 16–28+6 weeks, and those who received injectable progestin in an office setting, the final study population for analysis was 3,374 women (Figure 1). Maternal records could be linked to infant records for 2,639/3,374 (78.2%) women in the sample and there were no significant differences in characteristics of women with a linked record compared to those who could not be linked. With regard to gestational age determination, 20% of gestational ages in the sample were defined by the infant record, 37% by timing of the nuchal translucency ultrasound, 28% by CVS, PAPP-A, inhibin-A or AFP, and the remaining 15.3% were defined as full-term by the absence of any indicators for PTB. Women who received progestin from an outpatient pharmacy (n=5,823) were excluded from analysis since the timing of injections could not be determined precisely. They were more likely to be > 35 years of age and primiparous than women who received their progestin at office visits (Supplemental Table 2).

The overall rate of preterm birth in the cohort was 27.4%. Women with an early 17-OHPC start (prior to 21 weeks) had similar demographic characteristics to women who started 17-OHPC later (≥ 21 weeks). The average duration of enrollment of a woman in MarketScan was 2.5 years; therefore, information on prior preterm births in the dataset was limited. Of 3,374 women meeting inclusion criteria, 2,622 (78%) had a diagnosis code during pregnancy for prior preterm birth (supervision of pregnancy with history of preterm labor (V23.41) or poor obstetric history (V23.49)). For women with information available for

gestational age of prior PTB available in MarketScan, women in the early start group had their earliest prior preterm birth recorded at an earlier gestational age (30.6 ± 4.8 weeks) than those with a late start (31.6 ± 4.7 weeks) ($p=0.05$) (Table 1). Most women in both groups delivered at term with similar obstetric outcomes with regard to mode of delivery, hypertensive disorders of pregnancy, fetal growth abnormalities, and preterm prelabor rupture of membranes (Table 2).

Women who initiated 17-OHPC early were less likely to deliver prior to 37 weeks after adjusting for obesity (25.9% early start vs. 29.5% late start, aRR 0.88; 95% CI 0.79–0.97; $p=0.02$) (Table 3). There was not a statistically significant difference in rates of preterm birth prior to 34 weeks. In stratified analysis examining timing of initiation of 17-OHPC across gestation (16– <21 weeks, 21– <25 weeks, and 25– <29 weeks), the preterm birth rate prior to 37 weeks progressively increased at rates of 25.9%, 28.5%, and 31.1%, respectively (Table 4). However, this difference only became statistically significant at 25– <29 weeks with the early start group (<21 weeks) used as the referent (aRR 1.20; 95% CI 1.03–1.37).

Women who received >85% of recommended 17-OHPC injections had significantly decreased rates of preterm birth compared to those with 61–85%, 26–60%, and <25% compliance (Table 5). The rate of preterm birth in patients receiving <25% of recommended 17-OHPC injections was 50% higher than in patients who received >85% of recommended injections (RR 1.4; 95% CI 1.2–1.7).

DISCUSSION

Our results suggest the timing of initiation and compliance with 17-OHPC has a significant impact on its effectiveness for recurrent preterm birth prevention. The risk of preterm birth was lowest in women starting the medication earlier in pregnancy (16– <21 weeks) and those who achieved greater than 85% compliance with recommended doses. Earlier start of 17-OHPC prophylaxis was associated with significantly decreased risk for PTB at <37 weeks. There was no difference in the risk of PTB at <34 weeks; however, a post-hoc calculation revealed that we had only 31% power to detect a difference in preterm birth rates with $\alpha=0.05$. When we explored the effect of gestational age of initiation by stratifying into smaller gestational age groups, we found that those who started 17OHPC <21 weeks had a significantly decreased risk for recurrent PTB at <37 weeks compared to those who started at 25–<29 weeks. The absolute risk of preterm birth <37 weeks was increased from baseline in the later start groups, however the risk of PTB <34 weeks risk did not increase with each subsequent delay of initiation in a dose-response fashion. These data suggest that earlier initiation, preferably at <21 weeks of gestation confers the most protective effect.

Because clinical care may be associated with unavoidable delays in initiation of 17OHPC, we then sought to examine whether compliance with weekly dosing schedule was important for effect, regardless of when the patient was able to start the medication. We accounted for compliance by calculating the proportion of doses received compared to the total number of doses for which she was eligible starting from the time of initiation. We found that PTB rates at both <37 and <34 weeks were significantly higher in women with poorer

compliance with injections, with a 50% increased risk for PTB < 37 weeks and nearly 2-fold increased risk for PTB <34 weeks in the least compliant group. This finding suggests that women can be counseled that compliance with the weekly dosing schedule increases the protective effect of the medication.

In 2007, How et al. reported that later gestational age of initiation of 17-OHPC was as effective as earlier initiation, which differs from our findings.(6) Additionally, recent data from a single institution examined the clinical effect of 17-OHPC prophylaxis by examining the trend in each patient's PTB history in pregnancies with and without treatment with 17-OHPC. They found that 17-OHPC prophylaxis did not alter the rates of recurrent PTB <35 weeks nor was there a change in severity of PTB (gestational weeks achieved in treated pregnancy) in women treated with 17-OHPC. The authors conclude that they were not to demonstrate any benefit for 17-OHPC to prevent recurrent preterm birth.(7) In contrast, our data suggest that the 17-OHPC prophylaxis does have an effect. Both the gestational age of initiation and the compliance analysis suggest that earlier gestational age of initiation and increased number of injections are associated with decreased rates of PTB, suggesting that 17-OHPC does have a prophylactic effect at least in some subset of patients. Lack of understanding of the mechanism of effect of 17-OHPC, and whether the protective effect differs according to clinical characteristics, limits the ability to ascertain why data from both randomized control trials and observational studies are conflicting.(2, 6–11)

Our study builds upon prior literature on 17-OHPC for preterm birth prevention by using a large, validated, nationwide cohort to address nuanced differences in effectiveness based on both timing of initiation and weekly compliance. MarketScan provides a unique advantage of linked maternal and neonatal records, allowing us to examine critical obstetric characteristics such as gestational age of delivery as well as injection history in a large administrative dataset. The size of the sample available for analysis allowed a detailed examination of smaller gestational age subgroups. Additionally, we provide an analysis of compliance that informs patient counseling regardless of the often-fixed gestational age of initiation based on when a patient presents for care. Because injections are reliably coded, as they are billable encounters, we are confident that 17OHPC use is accurately ascertained from this dataset with less risk for misclassification than interventions that may not be reimbursed or traceable through pharmacy data. Lastly because this is population data from an administrative data source, not data from an interventional research trial, these data may better reflect real world population effectiveness.(12)

However, our findings should be viewed in the context of the following limitations. MarketScan is an administrative claims database so outcomes associated with payment, such as 17-OHPC injection, are coded more reliably than demographics or clinical outcomes. While this was a strength for reliability of capturing 17-OHPC injections, it is a significant limitation for assessment of other pertinent demographic factors. The use of an administrative database also precluded collection of more nuanced clinical details, such as whether prior or current preterm births were spontaneous or medically indicated, although appropriate clinical use of 17-OHPC implies that the prior preterm birth was spontaneous. The utility of our adjusted analysis was limited by several factors. The most important is that MarketScan lacks information on race; thus, race could not be included as a covariate for

outcomes in our population. Because race may be associated both with gestational age of treatment start, compliance, and the outcomes of PTB, it is likely that race is an important confounder that is missing in this dataset. The adjusted analysis did not include number of prior preterm births or gestational age of prior preterm births because there was no way to be certain that every pregnancy a woman had was captured in MarketScan, as patients may move in and out of private insurance plans. However, the high rate of Vcodes for prior PTB in our study population are reassuring, since Vcodes are not associated with reimbursement and they are historically undercoded. In addition, demographics such as obesity are undercoded in administrative data;(13) thus, our findings and adjusted analysis likely under-represents the true prevalence of obesity.

We used a previously validated coding algorithm to determine gestational ages for included subjects,(5) but we still had a margin of error of exact gestational age of delivery due to, 1.)The way ICD-9-CM diagnosis codes capture preterm gestational ages in 2 week ranges on the infant claim, and 2.) The hierarchy we used to assign gestational ages for those that could not be defined using infant claims. For example, if an ideal interval for performing an antenatal test was a 4 week period and we assigned the midpoint of this period as the gestational age at the time of screening, we would introduce up to a 2 week error in the gestational age calculated using antenatal testing. A large number of subjects were eliminated from this analysis because they had outpatient 17-OHPC claims with inadequate data to determine timing of initiation or compliance; however, analysis comparing these groups showed that most baseline demographics were similar to patients included in the analysis, with the exception of advanced maternal age and parity (Supplemental Table 2).

In conclusion, these data support that starting 17-OHPC prophylaxis prior to 21 weeks and taking 85% of recommended doses is associated with a significant impact on reducing the risk of recurrent preterm birth. Future studies are needed to address whether 17-OHPC preterm birth prevention is more effective in certain demographic groups of patients than others. Clinicians and health care administrators should develop efficient mechanisms to provide access to this medication for on-time initiation of therapy and to improve compliance with weekly injection schedules to maximize prevention of recurrent preterm birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Dr. Carter is supported by a Robert Wood Johnson Grant #74250. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the Robert Wood Johnson Foundation. Dr. Stout has research support from The March of Dimes, Washington University in St. Louis Prematurity Research Center and AMAG pharmaceuticals. The Center for Administrative Data Research is supported in part by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR002345 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) and Grant Number R24 HS19455 through the Agency for Healthcare Research and Quality (AHRQ).

References

1. Schoen CN, Tabbah S, Iams JD, Caughey AB, Berghella V. Why the United States preterm birth rate is declining. *Am J Obstet Gynecol*. 2015 Aug;213(2):175–80. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25511243> [PubMed: 25511243]
2. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. *N Engl J Med*. 2003 6 12;348(24):2379–85. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa035140> [PubMed: 12802023]
3. Practice Bulletin No. 130. *Obstet Gynecol*. 2012 Oct;120(4):964–73. Available from: <http://insights.ovid.com/crossref?an=00006250-201210000-00042> [PubMed: 22996126]
4. Bommarito KM, Gross GA, Willers DM, Fraser VJ, Olsen MA. The Effect of Clinical Chorioamnionitis on Cesarean Delivery in the United States. *Health Serv Res*. 2016;51(5):1879–95. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26841089> [PubMed: 26841089]
5. Wallace A, Lee B, Selvam N, Tabb L, Yudell M, Turchi R, et al. Estimation of Gestational Age at Birth Using Claims-Based Algorithms in a Commercially Insured US Population. *Pharmacoepidemiol Drug Saf*. 2016 Aug;25:3–679. Available from: <http://doi.wiley.com/10.1002/pds.4070>. (abstract 512).
6. How HY, Barton JR, Istwan NB, Rhea DJ, Stanziano GJ. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? *Am J Obstet Gynecol*. 2007 9 1;197(3):260.e1–260.e4. Available from: <https://www.sciencedirect.com/science/article/pii/S0002937807008800?via%3Dihub> [PubMed: 17826411]
7. Nelson DB, McIntire DD, McDonald J, Gard J, Turrichi P, Leveno KJ. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. *Am J Obstet Gynecol*. 2017 6 1;216(6):600.e1–600.e9. Available from: <https://www.sciencedirect.com/science/article/pii/S0002937817302946?via%3Dihub> [PubMed: 28223163]
8. Markham KB, Walker H, Lynch CD, Iams JD. Preterm Birth Rates in a Prematurity Prevention Clinic After Adoption of Progestin Prophylaxis. *Obstet Gynecol*. 2014 Jan;123(1):34–9. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006250-201401000-00007> [PubMed: 24463661]
9. Heyborne KD, Allshouse AA, Carey JC. Does 17-alpha hydroxyprogesterone caproate prevent recurrent preterm birth in obese women? *Am J Obstet Gynecol*. 2015 12 1;213(6):844.e1–844.e6. Available from: <https://www.sciencedirect.com/science/article/pii/S0002937815008650?via%3Dihub> [PubMed: 26275354]
10. Meis PJ, Klebanoff M, Dombrowski MP, Sibai BM, Leindecker S, Moawad AH, et al. Does Progesterone Treatment Influence Risk Factors for Recurrent Preterm Delivery? *Obstet Gynecol*. 2005 Sep;106(3):557–61. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006250-200509000-00018> [PubMed: 16135587]
11. Yemini M, Borenstein R, Drazan E, Apelman Z, Mogilner BM, Kessler I, et al. Prevention of premature labor by 17 α -hydroxyprogesterone caproate. *Am J Obstet Gynecol*. 1985 3 1;151(5):574–7. Available from: <https://www.sciencedirect.com/science/article/pii/0002937885901413?via%3Dihub> [PubMed: 3976757]
12. Nallamothu BK, Hayward RA, Bates ER. Beyond the Randomized Clinical Trial. *Circulation*. 2008 9 16;118(12):1294–303. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.107.703579> [PubMed: 18794402]
13. Nickel KB, Wallace AE, Warren DK, Ball KE, Mines D, Fraser VJ, et al. Modification of claims-based measures improves identification of comorbidities in non-elderly women undergoing mastectomy for breast cancer: a retrospective cohort study. *BMC Health Serv Res*. 2016 12 16;16(1):388 Available from: <http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-016-1636-7> [PubMed: 27527888]

Figure 1:
Study Flow Diagram

Table 1.

Demographic Characteristics of Patients With Early Start (<21 weeks) Compared to Those With Late Start (≥ 21 weeks) of 17-OHPC

Characteristic	Early Start of 17OHPC (<21 weeks) (N=2,032)	Late Start of 17OHPC (≥ 21 weeks) (N=1,342)	P value
Maternal age, years (SD)	31.8 ± 4.9	31.5 ± 5.3	0.051
Maternal age ≥ 35 years	613 (30.2%)	397 (29.6%)	0.73
Primiparous	247 (12.2%)	189 (14.1%)	0.10
Number of prior PTBs (in MarketScan) in women with at least one prior delivery	0.70 ± 0.49 1 (0,1)	0.59 ± 0.52 1 (0,1)	<0.01 0.002
Liveborn in index pregnancy	2,018 (99.3%)	1,334 (99.4%)	0.83
GA of earliest prior PTB (in MarketScan) in women with at least one prior delivery	30.6 ± 4.8	31.6 ± 4.7	0.05
Chronic Hypertension	179 (8.8%)	112 (8.4%)	0.66
Pre-existing diabetes	105 (5.2%)	75 (5.6%)	0.64
Obesity	232 (11.4%)	128 (9.5%)	0.09
Tobacco use during pregnancy	57 (2.8%)	41 (3.1%)	0.67

Table 2.

Pregnancy Outcomes of Patients With Early Start (<21 weeks) Compared to Those With Late Start (≥ 21 weeks) of 17-OHPC

Characteristic	Early Start of 17OHPC (<21 weeks) (N=2,032)	Late Start of 17OHPC (≥ 21 weeks) (N=1,342)	P value
Gestational age at delivery Median weeks (IQR)	38.5 (36.6–38.9)	38.5 (36.0–38.9)	0.049
Vaginal Delivery	1,294 (63.7%)	875 (65.2%)	0.38
Cesarean Delivery	738 (36.3%)	467 (34.8%)	0.38
Hypertensive disease of pregnancy (Preeclampsia or Hypertension in pregnancy)	164 (8.1%)	116 (8.6%)	0.57
Poor fetal growth	307 (15.1%)	236 (17.6%)	0.06
Excessive fetal growth	253 (12.5%)	185 (13.8%)	0.27
Preterm Prelabor rupture of membranes	145 (7.1%)	92 (6.9%)	0.78

Table 3.

Preterm Birth Outcomes by Early and Late Start of 17-OHPC Injections

PTB	Start <21 weeks (n=2,032)	Start ≥21 weeks (n=1,342)	Relative Risk (RR) (95%CI)	p-value	* Adjusted RR (95% CI)	p-value
<37 weeks	527 (25.9%)	396 (29.5%)	0.88 (0.79, 0.98)	0.02	0.89 (0.80–0.97)	0.02
<34 weeks	219 (10.8%)	166 (12.4%)	0.85 (0.71, 1.03)	0.09	0.85 (0.69–1.00)	0.07

* Adjusted for obesity; Bolded items denote significance to p<0.05.

Table 4.

Preterm Birth Outcomes Stratified by Gestational Age of First 17-OHPC Injection

Gestational Age of 1 st Injection in weeks	Term Birth N=2,451 (72.6%)	Preterm Birth <37 weeks N=923 (27.4%)	RR (95%CI)	*aRR (95% CI)	Preterm Birth <34 weeks N=385 (13.6%)	RR (95%CI)	*aRR (95% CI)
16.0-<21 (N=2,032)	1,505 (74.1%)	527 (25.9%)	REF	REF	219 (12.7%)	REF	REF
21.0-<25 (N=815)	583 (71.5%)	232 (28.5%)	1.10 (0.96–1.25)	1.10 (0.96–1.24)	107 (15.5%)	1.22 (0.99–1.51)	1.23 (0.98–1.48)
25.0-<29 (N=527)	363 (68.9%)	164 (31.1%)	1.20 (1.04–1.39)	1.20 (1.03–1.37)	59 (14.0%)	1.10 (0.84–1.44)	1.11 (0.82–1.40)

* Adjusted for obesity; Bolded items denote significance to $p < 0.05$.

Table 5.

Preterm Birth Outcomes by Compliance with 17-OHPC Injections

Compliance (Injections received / possible)	Term Birth	Preterm Birth <37 weeks	RR (95%CI)	aRR (95% CI)	Preterm Birth <34 weeks	RR (95%CI)	aRR (95% CI)
<25% (N=923)	633 (68.6%)	290 (31.4%)	1.5 (1.2–1.7)	1.4 (1.2–1.7)	126 (16.6%)	1.9 (1.4–2.6)	1.9 (1.3–2.5)
26–60% (N=619)	400 (64.6%)	219 (35.4%)	1.7 (1.4–2.0)	1.6 (1.4–1.9)	112 (21.9%)	2.5 (1.9–3.5)	2.5 (1.7–3.2)
61–85% (N=742)	513 (69.1%)	229 (30.9%)	1.4 (1.2–1.7)	1.4 (1.2–1.6)	89 (14.8%)	1.7 (1.2–2.3)	1.6 (1.1–2.2)
>85% (N=1,090)	905 (83.0%)	185 (17.0%)	reference		58 (6.0%)	reference	

* Adjusted for obesity; Bolded items denote significance to $p < 0.05$.