Vaginal Versus Intramuscular Progestogen for Prevention of Recurrent Spontaneous Preterm Birth

A Pragmatic Study in a High-Risk Patient Population

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OBJECTIVE: To evaluate whether vaginal progestogen (VP) can be substituted for intramuscular (IM) progestogen for the prevention of recurrent spontaneous preterm delivery in a residency based high-risk obstetric clinic.

STUDY DESIGN: Retrospective study comparing delivery <37 weeks in women with a history of spontaneous preterm birth (SPTB) receiving vaginal versus IM progestogen. Outcomes were obtained via electronic medical record.

RESULTS: There was no significant difference between the IM (n=36) and VP (n=28) groups for delivery <37 weeks (23.5% vs. 46.4%, p=0.067). A statistically significant increase in the number of additional gestational days compared to their earliest SPTB was seen in individuals with 17α-hydroxyprogesterone caproate (17α-OHP) versus VP (9.0±5.8 days vs. 5.3±6.0 days; p=0.036). There were no differences between the groups for other secondary outcomes.

CONCLUSION: Our study supports the use of either VP or 17α-OHP for prevention of SPTB; however, there was an increase in the number of gestational days versus earliest SPTB in the 17α-OHP group. (J Reprod Med 2019;64:395–400)

This study suggests that vaginal progestogen can be substituted for 17α-OHP for the prevention of recurrent SPTB in our patient population.

Keywords: 17 alpha-hydroxyprogesterone caproate; gestational age; intramuscular; intramuscular absorption; intramuscular injections; obstetric labor, premature; premature birth; pregnancy; preterm birth; preterm labor; progestogens; risk assessment; tocolytic agents; vaginal; vaginal absorption.

Preterm birth, or delivery between 20 and 37 weeks, is responsible for more than one-third of infant deaths and is the number one cause of neonatal death.[1,2] In addition, premature infants require greater use of medical interventions, resulting in costs of approximately $51,000 per infant annually.[1] One million neonatal deaths each year are secondary to preterm delivery, and there is often significant morbidity associated with the survivors of early delivery.[3] Women with a history of spontaneous preterm birth (SPTB) have an increased risk for cardiovascular disease, coronary heart disease, and stroke.[4] While there are many risk factors for SPTB, a history of SPTB is the most predictive for recurrent SPTB, with a recurrence rate of 22%.[5]

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Meis et al in 2003 demonstrated in a randomized placebo-controlled trial that weekly intramuscular administration of 17α-hydroxyprogesterone caproate (17α-OHP) from 16–36 weeks' gestation significantly reduced recurrent SPTB in singleton gestations.[6] Currently the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend 17α-OHP for all women with a history of SPTB.[2,7] However, there are numerous system, provider, and patient level barriers that impede the ability to enact these recommendations.[8] A meta-analysis performed in 2017 by Saccone et al reported that vaginal progestogen (VP) was more beneficial for preventing SPTB versus 17α-OHP; however, they were limited by low quality evidence.[9]

The impact of cost and availability cannot be overlooked, particularly in a low-income area. Although prices are variable, the retail cost of 17α-OHP is $963.60 per injection versus $3.89–9.82 per 200 mg of VP for a maximum cost of $68.74/week.[10,11] It is important to note that most of our patient population has government-based insurance, which completely covers 17α-OHP or VP.[12] Additionally, the maker of 17α-OHP has programs to cover the cost for the uninsured, and the cost of VP is often less than the retail cost pending pharmacy coverage and discounts.[13]

Even though ACOG and SMFM endorse 17α-OHP for women with a history of SPTB, in practice this often does not occur.[8] Our clinical practice has been to initiate the process for prescribing 17α-OHP for women with a history of SPTB; however, if the medication is not available in a timely manner, then VP is substituted until 17α-OHP is available or for the remainder of pregnancy. The objective of this study is to compare the pregnancy and neonatal outcomes of women who received 17α-OHP versus those who received VP.

Materials and Methods

This is a pragmatic retrospective study of women receiving progestogen for the prevention of recurrent SPTB in a low income, high-risk patient population. Women who received only weekly injections of 250 mg 17α-OHP, the current standard of care, were compared to women who were prescribed 200 mg micronized VP administered daily as a substitution for 17α-OHP. Many women in our clinic switched from 17α-OHP to VP or vice versa at undetermined points of time; those cases were excluded from the final dataset. The study received approval from the institution's human subjects committee (SC# 6231).

The choice of progestogen initiated was determined by the clinic's ability to obtain 17α-OHP in a timely manner, defined as between 16$^0/_7$ to 23$^6/_7$ weeks' gestation or by women's preferences. Some women declined treatment with one type of progestogen but were willing to use the other. Eligible women were those who were receiving their prenatal care at the institution's resident clinic, had a history of a SPTB, and were identified from the patient logs developed for the Ohio Perinatal Quality Collaborative's Progestogen Project.[14] A screening transvaginal cervical length was measured at 16$^0/_7$ to 23$^6/_7$ weeks, and cervical cerclage was recommended if there was a prior SPTB at less than 34$^0/_7$ weeks and the transvaginal cervical length was less than 25 mm.[15]

Inclusion criteria consisted of singleton gestation, a history of SPTB between 16$^0/_7$ and 36$^6/_7$ weeks' gestation, and initiation of progestogen treatment between 16$^0/_7$ to 23$^6/_7$ weeks of gestation. Exclusion criteria consisted of initiating treatment after 24 weeks of gestation, or if a progestogen was prescribed for an indication other than a history of SPTB, e.g., an ultrasound diagnosis of an asymptomatic short cervix. The unique patient identifier, indication for progestogen, method of progestogen administration, and treatment initiation date were recorded. Compliance with progestogen treatment was assessed at each prenatal visit and recorded in the electronic medical record (EMR) by either note by the nurse administering the injection or patient reported compliance with VP. Due to discrepancies with refills, the medication list was unable to be utilized to determine patient compliance, therefore compliance was based solely on record or nurse intake at each injection. Patients were placed in 2 estimated categories of <75% or >75% compliance. Demographics, presence of cerclage, prior pregnancy information regarding the number and gestational age at delivery of prior SPTB, and maternal outcome data were obtained from the hospital's EMR.

Neonatal outcomes were obtained from the hospital's neonatal intensive care unit (NICU) database used for reporting to the Vermont Oxford Network.[16] Neonatal morbidity was defined as the occurrence of bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, retinopathy of prematurity, intraventricular hemorrhage, or respira-

tory distress syndrome per established Vermont Oxford Network criteria.[16] Each morbidity was assigned 1 point, and a composite index was used to compare the groups.

Statistical Analysis

Analysis of the data was conducted using SPSS (IBM, version 23.0). Continuous parameters were summarized as mean±standard deviation, and 95% confidence intervals were provided. The *t* test was used for analysis of continuous data. Categorical data were compared using Pearson's χ^2 and Fisher's exact test. A p value for all data was deemed statistically significant if <0.05.

Results

From September 2014 through March 2017, there were 64 women who met the inclusion criteria: 36 in the 17α-OHP group and 28 in VP group. The average gestational age of initiation of progestogen was not different: 18.3±2.3 weeks for 17α-OHP and 18.4±2.8 weeks for VP (p=0.84) (Table I). Women on 17α-OHP were more likely to have a history of an earlier SPTB, but this was not statistically significant (28.5 weeks vs. 31.0 weeks, p=0.06). The 17α-OHP group were also more likely to have greater than 75% compliance with the progestogen treatment versus the VP group (91.2% vs. 50.0%, p=0.001) and less likely to have government insurance or be self-pay (82.4% vs. 100%, p=0.028). All other maternal characteristics to include race, education, insurance, indication for delivery, shortest screening transvaginal cervical length, number of prior SPTB, and mode of delivery were comparable (Table I). However, data were not reported regarding the number of term deliveries each individual had versus preterm deliveries.

Table II contains the primary and secondary outcomes. The primary outcome of delivery at less than 37 weeks of gestation was not different between the groups, though a trend in favor of VP was noted (23.5% for 17α-OHP vs. 46.4% for VP, p=0.067). Secondary outcomes were also shown to be equivalent between the 2 groups in all areas except when comparing the difference between the patient's earliest delivery versus current delivery. The 17α-OHP group had 9.0±5.8 greater gestational days versus only 5.3±6.0 days for VP (p=0.018) (Table II). When analyzing this group further and comparing only individuals who had a positive latency (i.e., those who delivered at a later gestational age than their earliest SPTB, n=57), 17α-OHP again showed an increased latency period at 9.6±5.3 days versus 5.3±6.0 days for VP (p=0.032) (Table II).

Neonatal outcomes consisting of APGAR score <7 at 5 minutes, mean birth weight, NICU admission and length of stay, mortality, and composite morbidity did not differ between the groups (Table III). Due to inaccurate reporting surrounding time of delivery, data were not consistently available regarding indication for delivery.

Discussion

Vaginal progestogen is often substituted for 17α-

Table I *Maternal Demographics*

Characteristic	17α-OHP (n=34) N (%)	Vaginal progesterone (n=28) N (%)	95% Confidence interval	p Value
Maternal age (yrs)	27.60±3.52	28.96±4.61	(–3.43; 0.70)	0.191
GA at initiation (wks)	18.29±2.36	18.42±2.76	(–1.43; 17)	0.844
Cerclage	5 (14.7)	3 (10.7)	0.70** (0.15; 3.21)	0.719*
No. of SPTBs	1.44±0.66	1.50±0.64	(–0.39; 0.27)	0.724
Shortest transvaginal cervical length	2.86±1.04 (n=26)	3.03±1.08 (n=26)	(–0.75; 0.42)	0.580
Transvaginal length ≥25 mm	20 (74.1) (n=27)	21 (80.8) (n=26)	NA	0.745*
Transvaginal length <25 mm	7 (25.9%) (n=27)	5 (19.2%) (n=26)	NA	0.745*
GA at earliest SPTB, (N=88)	28.5±5.0	31.0±5.3	(–5.13; 0.11)	0.060
Race: black	17 (50.0)	13 (46.4)	NA	0.511
Sexual partner	7 (20.6)	7 (25.0)	NA	0.765*
Insurance: government/self-pay	28 (82.4)	28 (100.0)	NA	**0.028***
Compliance (>75%)	31 (91.2)	14 (50.0)	NA	**0.001**

17α-OHP = 17α-hydroxyprogesterone caproate, GA = gestational age, SPTB = spontaneous preterm birth.
*2-sided Fisher's exact test.
**Odds ratio.

Table II *Primary and Secondary Outcomes*

Outcome	17α-OHP (n=34) N (%)	Vaginal progesterone (n=28) N (%)	95% Confidence interval	p Value
Delivery ≥37 wks	26 (76.5)	31 (53.6)	NA	0.067*
Delivery ≥34 wks	31 (91.2)	25 (89.3)	NA	1.00*
No. of days' difference between current delivery and earliest SPTD	9.0±5.8	5.3±6.0	(0.66; 6.67)	**0.018**
Difference in positive latency between earliest SPTD and current pregnancy	9.6±5.3 (n=32)	6.6±5.0 (n=25)	(0.3; 5.8)	**0.032**
Earlier delivery in current pregnancy vs. earliest SPTD	2 (5.9)	3 (10.7)	NA	0.65*
Later delivery in current pregnancy vs. earliest SPTD	32 (94.1)	25 (89.3)	NA	0.65*
Mode of delivery: LTCS	11 (32.4)	8 (28.6)	NA	0.788*
No. of antepartum admissions	1.29±1.87	2.35±3.66	(–2.50; 0.38)	0.145
No. of triage visits	2.44±3.09	2.04±2.78	(–1.10; 1.91)	0.593

17α-OHP = 17α-hydroxyprogesterone caproate, LTCS = low transverse cesarean section, SPTB = spontaneous preterm birth.
*2-sided Fisher's exact test.

OHP in individuals with a prior history of SPTB, and our results showed no difference in the rate of recurrent SPTB, although the p value approached significance at p=0.067. Secondary outcomes including SPTB <34 weeks, NICU admission rate, and composite neonatal morbidity did not differ between the groups. In the subpopulation of individuals who delivered at a later gestational age during their current pregnancy as compared to their earliest SPTB and current delivery, 17α-OHP had approximately 4 additional gestational days.

There is very little evidence to guide the use of VP as an alternative to 17α-OHP when the latter is not available. A randomized controlled trial (RCT) was performed by El-Gharib and El-Hawary in 2013 that compared the use of VP and intramuscular progestogen (Proluton Depot). They found no difference in the rate of SPTB; however, they administered intramuscular injections every 3 days and started treatment between 20–24 weeks.[17] Maher et al also compared the use of VP and intramuscular progestogen (Proluton Depot) in a prospective randomized trial, which resulted in a statistically significant decrease in delivery <34 weeks in the group randomized to VP when initiated treatment from 14–18 weeks.[18] In 2017 a meta-analysis was conducted by Saccone et al that included 3 RCTs comparing the use of VP versus 17α-OHP, with varying doses of VP. The primary outcome was SPTB <34 weeks, in which VP was shown to have a statistically significant lower rate of SPTB of 17.5% versus

Table III *Neonatal Outcomes*

Outcome	17α-OHP (n=34) N (%)	Vaginal progesterone (n=28) N (%)	95% Confidence interval	p Value
APGAR of <7 at 5 min	2 (5.9)	1 (3.6)	NA	1.00*
Infant weight (g)	3,083.94±819.44	2,856.14±932.01	(–217.28; 672.88)	0.310
NICU admission rate, N=24	10 (29.4)	14 (50)	2.4** (0.84; 6.83)	0.121*
NICU length of stay, N=24	12.7±14.6 days	36.14±131.15 days	(–38.1; 135.8)	0.256
Neonatal mortality	1 (2.9)	0 (0)	NA	1.00*
Composite neonatal outcomes	12 (35.3)	15 (53.6)	2.12** (0.76; 5.88)	0.200*

17α-OHP = 17α-hydroxyprogesterone caproate, NICU = neonatal intensive care unit.
*2-sided Fisher's exact test.
**Odds ratio.

25.0% (CI 0.53–0.95).[9] No difference was seen in the rate of SPTB or neonatal outcomes when analyzing 17α-OHP versus VP.[9] Similar results were seen in another recent meta-analysis of 3 RCTs on individuals with a history of SPTB, where there was a significant improvement in delivery <34 weeks and <32 weeks for the VP group versus 17α-OHP.[19]

Although some RCTs and meta-analyses comparing VP versus 17α-OHP have been undertaken, limited substantial research has been available to draw firm recommendations for administration and timing of progestogen. As previously mentioned, the RCTs that have been completed varied in their results from VP being equivalent to superior for the prevention of SPTB. Due to low quality of evidence, VP cannot be recommended until well-designed RCTs are conducted.[9] In our case, it may be more prudent to compare to smaller retrospective/prospective studies due to our unique patient population and overall poor adherence to medication dosing. Haidar et al in 2016 reported in a secondary analysis that analyzed compliance with 17α-OHP of >80% (n=370) versus 40–80% (n=35), in which they determined there was no difference in the adjusted odds ratio of recurrent SPTB.[20] It is unknown if these data could be extrapolated to VP.

A similar prospective cohort study performed at a large tertiary center in Texas looked specifically at their current rate of SPTB at 16.8% and then followed 430 patients with a history of SPTB.[21] These individuals were given only 17α-OHP, and 267 of them initiated prior to 18 weeks; no data were provided on the remaining 163 patients. They saw no improvement in the rate of SPTB in this cohort of patients (25%) at <35 weeks. In their article they noted the importance of single study prospective trials that highlight a "real world" scenario that is often not exemplified in traditional RCTs.[21]

A strength of this study is that it evaluated a high-risk patient population with significant financial and social barriers to accessing care and medications, as well as the estimation of compliance. This is representative of the population of women at substantial risk for recurrent SPTB. Several potential weaknesses exist, including the non-randomization of treatment, a lack of blinding to the treatment, and recall bias from both the patients and providers when determining compliance with medication. Women in the 17α-OHP group had a history of an earlier delivery than the VP group. The 17α-OHP group also had a higher rate of compliance; however, this piece of data was based on the completeness of the EMR and patient/physician reports, not on conclusive medication monitoring. Another limitation is the lack of power with a small sample size. Missing and incomplete data are always a challenge in research involving chart review; therefore the ability to determine the reason behind delivery was not always clear. This paper shines further light on research in low funding, resident-run clinics, where patients may not fully comprehend the necessity of treatment; thus, poor compliance to medication and misuse of progestogens is seen more often than in RCTs.

This study suggests that VP can be substituted for 17α-OHP for the prevention of recurrent SPTB in our patient population. In populations with limited resources and limited access to care, the ability to utilize an inexpensive medication that is readily available has a significant impact. It is also important to note that more gestational days were gained when compared to their earliest SPTB in those who had 17α-OHP, which may have clinical significance. Therefore, these findings can be discussed with our patients when determining options. This retrospective cohort study adds to the limited quality literature that is available when comparing 17α-OHP versus VP for prevention of SPTB for individuals with a history, yet at this time it may be applicable only to our unique patient population. It also sheds light that higher-quality randomized controlled studies are needed to compare not only the type of progestogen, but also the optimal dosing, as compliance is often problematic.

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