17 Alpha-Hydroxyprogesterone Caproate (17P) Usage in a Medicaid Managed Care Plan and Reduction in Neonatal Intensive Care Unit Days

Offering 17P as a benefit to pregnant women enrollees with a history of preterm delivery can reduce NICU days significantly for a Medicaid plan.

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ABSTRACT

Purpose: To evaluate whether providing 17 alpha-hydroxyprogesterone caproate (17P) to high-risk pregnant women who have a history of preterm delivery in a Medicaid managed care population reduces the rate of neonatal intensive care unit (NICU) admissions, NICU length of stay, and associated costs.

Design: A 2004–2005 longitudinal review of birth outcomes in 24 pregnant women with a history of preterm delivery who were treated with 17P versus a control group.

Methodology: Intervention included offering 17P as a benefit to pregnant women who had a history of preterm labor and delivery and who were deemed to be appropriate candidates for this treatment by their physicians. An educational program about 17P was developed that was aimed at physicians, their office staff, and plan members. A process of early identification of potential 17P candidates was also implemented.

Principal findings: NICU admission rates decreased to 14.3 percent in the control group and 8.3 percent in the 17P group. NICU length of stay decreased significantly from 231 days in the control group to 149 days in the 17P group. Overall costs for the control group were $568,462 versus $165, 487 in the treatment group — a significant savings of $402, 975.

Conclusion: Offering 17P as a benefit to pregnant women enrollees with a history of preterm delivery can decrease NICU days significantly for a Medicaid managed care plan.

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INTRODUCTION

Preterm delivery defined as a delivery before 37 weeks, represents a large portion of a managed Medicaid plan's medical expenses, due to high-dollar neonatal intensive care unit (NICU) claims. More than 480,000, or 12 percent, of live births in the United States are preterm births. According to the March of Dimes, in the past decade, there has been an increase in preterm labor and delivery in almost all states. Despite medical and technological advances, the preterm birth rate increased 27 percent from 1982 to 2002 (Martin 2003). The pathophysiological events that trigger preterm delivery are for the most part not known, but a history of spontaneous preterm delivery is one of the strongest risk factors for preterm birth in a subsequent pregnancy (Mercer 1999).

A multicenter, randomized controlled trial by the National Institute of Child Health and Human Development, published in the *New England Journal of Medicine*, showed a significant reduction in preterm labor and delivery for high-risk women with a history of spontaneous preterm delivery. These women received weekly injections of 17 alpha-hydroxyprogesterone caproate (17P) (Meis 2003).

A follow-up study estimated that if 17P therapy was offered to all high-risk women with a history of preterm delivery in 2002, 10,000 spontaneous preterm births would have been prevented, reducing the overall U.S. preterm birth rate by 2 percent (Petrini 2005). This therapy seems to have the same effect among women of diverse backgrounds and offers new hope for helping to slow the rising number of preterm births.

Following the publication of the results from the Meis study, Coventry Health Care began to provide 17P as a benefit to high-risk pregnant enrollees with a history of preterm delivery (Meis 2003). The greatest potential opportunity for 17P to improve birth outcomes within Coventry Health Care is through HealthCare USA of Missouri (HCUSA), the largest managed Medicaid plan in Missouri with 185,000 members throughout the state. Seventy percent of HCUSA's

members are children and pregnant women, and of 7,636 live births in 2004, 8.8 percent of these infants were admitted to the NICU.

Because many of HCUSA's members are from lower socioeconomic groups, much attention is focused on preventing poor birth outcomes and high-cost NICU expenses. Dedicated obstetric (OB) nurse case managers and special needs nurses attempt to identify and provide support for pregnant mothers who are identified as being at high risk for preterm delivery. Yet, despite aggressive efforts, the percentage of NICU admissions and days has remained steady.

The goal of this study was to determine whether weekly injections of 17P could affect the number of NICU admissions, NICU length of stay (LOS), and associated costs in a real Medicaid population.

What is 17P?

A naturally occurring metabolite of progesterone, produced in large quantities during human pregnancy, 17P is used for recurrent miscarriages and various menstrual disorders. This hormone has been indicated for amenorrhea, endometrial carcinoma, and uterine corpus adenocarcinoma.

Attention has been focused on 17P since an article in the *New England Journal of Medicine* reported that a substantially reduced rate of recurrent preterm delivery was associated with its use in high-risk women (Meis 2003). Use of 17P in women who have had a previous premature birth (<37 weeks) has been endorsed by the American College of Obstetrics and Gynecology (2003), but the U.S. Food and Drug Administration does not recognize prevention of preterm delivery for high-risk women as an approved indication for 17P.

How does 17P work?

In animal models, progesterone appears to be responsible primarily for maintaining uterine quiescence during pregnancy. A drop in the progesterone levels normally occurs at the initiation of labor at term. Nevertheless, the physiological mechanism is not the same when considering the initiation of preterm labor, as this is not merely an early initiation of normal labor (ACOG 2003, Katz 1985, Varma 1982, Michaelis 1983, Raman-Wilms 1995, Resseguie 1985).

Substantial evidence suggests that preterm labor and preterm rupture of the membranes result from an inappropriate, inflammatory response. Weekly injections of 250 mg of 17P initiated in the second trimester of pregnancy may suppress this pathological labor (Mercer 1999).

The quantities of 17P produced naturally during pregnancy, predominately by the placenta, far exceed the recommended dose of 250 mg weekly by intramuscular injection during the last half of pregnancy. One would not expect any serious side effects from a nonandrogenic progestin, such as 17P, which is naturally produced in large quantities during pregnancy.

Results from several animal and clinical studies support the safety of 17P in pregnancy. According to information on Reprotox (1997), an online reproductive toxicology database, "There is no available evidence that the administration of this agent [17P] during pregnancy is harmful."

In 2003, Meis and colleagues published the results of their double blind, randomized, placebo-controlled trial involving pregnant women having a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16- to 20-weeks' gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or 36 weeks of gestation.

The primary outcome was preterm delivery prior to 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle. The baseline characteristics were similar for the 310 women who were in the progesterone group and the 153 women in the placebo group. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks' gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks' gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks' gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]).

Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. Reasons for exclusion from the trial were multi-fetal gestation, known fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension necessitating medication, and seizure disorder (Meis 2003).

METHODS

Availability of benefit

In 2004, 17P was not offered as a benefit in the fee-for-service Medicaid plan or the managed Medicaid plans in Missouri. The fee-for-service Medicaid program is prohibited from paying for any drug product for which a rebate agreement has not been signed. The Missouri Medicaid managed care plans provide coverage on a capitated rate, and therefore, they are not prohibited from paying for 17P. HCUSA's contract with the state of Missouri includes a requirement that any changes to the drug products covered by the health plan first must be submitted to the state for approval.

Only after submission and approval can the products or the criteria around the products be used. Coverage of 17P was submitted through this process, and we received approval to add this product to our prior authorization

process from the Division of Medical Services for the state of Missouri to make the product available as a benefit for our MCO.

Identification of high-risk members

To identify pregnant mothers at risk for preterm delivery and complicated pregnancies, we developed a 7-question risk assessment, which physician offices filled out and submitted with the OB global claim form. If the physician indicates that a member has a history of preterm labor and delivery, an OB nurse case manager reviews the case and a letter is sent to both the member and the physician explaining HCUSA's coverage of 17P (Table 1).

Providing the 17P benefit

If the physician identifies a member who is a suitable candidate for 17P, that member is instructed to call the HCUSA OB nurse case manager. The OB nurse case manager arranges for weekly delivery of 17P to either the physician's office or to the patient's home through a home health care agency. If a member is hospitalized during pregnancy, 17P is sent to the hospital for administration. Every member receiving 17P is assigned an OB case manager who keeps in regular telephonic contact to ensure compliance and to address issues that arise. Our contracted vendor for compounded 17P is Wedgewood Pharmacy, in Swedesboro, N.J.

Educational program

We encourage physicians to follow the guidelines in the aforementioned *New England Journal of Medicine* study (Meis 2003). The guidelines include initiation of 17P at 16- to 21-weeks' gestation and continuation through 36 weeks' gestation or up to delivery. The study's clinical exclusions were women with multi-fetal gestation, known fetal anomaly, progesterone or heparin treatment, current or planned cervical cerclage, hypertension necessitating medication, and seizure disorder (Meis 2003).

TABLE 1 Obstetric risk screening form

Date of first visit	
EDC	
History that may affect current pregnancy (Circle all that apply)	PTL or delivery HTN Asthma Sickle Cell DM Mental illness STD Smoker Alcohol Drugs Other _____
Pregnancy history	
Multiple gestation this pregnancy?	
Enrolled in WIC?	
Lead test on mother?	

DM=diabetes mellitus, EDC=estimated date of confinement, HTN=hypertension, PTL=preterm labor, STD=sexually transmitted disease, WIC=Women, Infants, and Children.

Statistical test

A chi-square analysis (2x2 contingency table) was conducted to determine the significance of reduction in admissions, NICU LOS, and cost savings. This statistical test is used commonly when determining the frequency of an occurrence, such as comparing one year or one group to another.

RESULTS

The measurement of the 17P program's effectiveness is the NICU admission rate and the LOS for babies born to the women enrolled in the program as compared to a control group. The control group consisted of 14 identified members who did not receive 17P treatment during their recent pregnancy and who had a history of preterm delivery within the last 36 months. The members who were selected for the control group also were enrolled in the OB case management program, as they were identified as being at high risk; they received ongoing follow-up services and were monitored for treatment compliance.

Initiation of 17P injections ranged from 15 weeks' gestation to 33 weeks' gestation in the 24 patients. In the intervention group, 15 patients (62.5 percent) started the weekly injections within the treatment initiation window described in the Meis study (2003) of 16- to 21-weeks' gestation. Reasons for delay in initiation of 17P therapy were not identified in this review. Ten patients in the intervention group did not miss any weekly injections of 17P. Five members missed more than 2 doses (Table 2). Reasons for noncompliance were not evaluated for this review (Table 3).

NICU admissions

The control group had 14.3 percent NICU admissions, and the group treated with 17P only had 8.33 percent NICU admissions. This result is not a significant reduction according to the chi-square analysis (Table 4).

NICU length of stay

An analysis of the length of stay is used also to measure successful interventions with improving pregnancy

TABLE 2 Patient compliance with 17P weekly injections

Number of missed doses	Number of patients	Percentage of group
0	10	41.60
1	4	16.70
2	4	16.70
5	3	12.50
6	2	8.33
>6	1	4.17

TABLE 3 Week of initiation of 17P injections

Week of gestation	Number of patients
15	1
16	5
17	2
18	2
19	2
20	2
21	1
22	1
23	1
24	1
28	3
30	1
32	1
33	1

outcomes. The length of treatment for both the intervention group and the control group was analyzed, and a significant reduction in the NICU LOS occurred for members who received the injection versus those members in the control group. Compared to those in the control group who delivered preterm, members in the intervention group who delivered preterm delivered at a later gestational age and remained hospitalized for fewer days. The financial impact resulted in savings of more than $402,975 in inpatient-related costs, which was also statistically significant (Table 5). The financial result is dependent on contracted rates of the facilities accessed by our members, and our members have open access. The savings could vary based on place of service.

Member compliance

Only 1 of 5 NICU/special care nursery deliveries received 100 percent of 17P prescribed treatments. Two patients began 17P treatment after 20 weeks' gestation; two in this group began treatment at 16 weeks' gestation.

Of those 18 patients with well deliveries, 13 (72.2 percent) were at 90 percent or better with compliance with prescribed 17 P treatment. Only five (27.7 percent) patients received less than 90 percent of prescribed treatment. All delivered well babies at full-term. Nine (50 percent) patients started 17P treatment before gestational week 20, nine (50 percent) patients after gestational week 20, and only three patients in this group began treatment at or before 16 weeks. Thirteen women received 17P during the 16- to 20- weeks' gestation window described in the Meis study (2003). Three of these patients were in the group that delivered preterm. Nevertheless, none were less than 32 weeks' estimated gestational age, and they each had a relatively short LOS (5, 5, 10 days). Ten patients received 17P later than 20 weeks' gestation, after the timeframe for initiation of 17P described in Meis et al (2003). Two of these patients delivered preterm, with one delivering twins. The lengths of stay were 66 days, 66 days, and 3 days. The twins were delivered at 30 weeks; the other delivery was at 37 weeks' gestation (Table 6).

Complications

Of 24 women receiving 17P, 1 had an allergic reaction at the injection site after 10 injections, resulting in an abscess. A second patient had an allergic reaction at the injection site after treat-

TABLE 4 NICU admissions: 17P group versus control group

	17P group		Control group		Variance percentage points	Significance
Well delivery	19	79.1%	11	78.6%	-0.50	None
NICU	2	8.3%	2	14.3%	+5.97	None
SCN	3	12.5%	1	7.1%	–5.36	None
Total sample	24	100%	14	100%		

NICU=neonatal intensive care unit, SCN=special care nursery.

TABLE 5 NICU length of stay and financial impact

	17P group	Control group	Variance	Significance
Length of stay	149	231	–21.66 percentage points	*P*<.000 Chi-square = 34.531
Financial impact	$165,486.75	$586,461.78	–56.00 percentage points	*P*=.000 Chi-square = 471,358.9 DF=1

DF=degree of freedom, NICU=neonatal intensive care unit.

TABLE 6 Patient compliance with administration of 17P

EGA treatment began	No. of injections authorized	No. of injections completed	Delivery outcome		No. of days in SCN/NICU	Cost
33	3	3 (100%)	39 weeks	Well	N/A	
21	15	10	37 weeks	SCN	3	$4124.00
19	17	17 (100%)	37 weeks	Well	N/A	
18	18	13 (72%)	32 weeks	SCN	10	$18,041.30
17	19	3 (15%)	38 weeks	Well	N/A	
23	13	1 (7%)	40 weeks	Well	N/A	
28	7	1 (14%)	39 weeks	Well	N/A	
16	21	20 (95%)	38 weeks	Well	N/A	
18	18	18 (100%)	38 weeks	Well	N/A	
32	8	8 (100%)	39 weeks	Well	N/A	
24	12	11 (92%)	35 weeks	Well	N/A	
22	14	14 (100%)	37 weeks	Well	N/A	
20	16	15 (94%)	37 weeks	Well	N/A	
28	9	3 (33%)	37 weeks	Well	N/A	
30	5	5 (100%)	39 weeks	Well	N/A	
19	15	13 (87%)	38 weeks	Well	N/A	
28	8	3 (38%)	30 weeks	SCN	63	$67,647.03
16	20	18 (90%)	35 weeks	NICU	5	$7,086.55
16	20	20 (100%)	38 weeks	Well	N/A	
19	17	17 (100%)	38 weeks	Well	N/A	
17	19	19 (100%)	37 weeks	Well	N/A	
15	20	20 (100%)	37 weeks	Well	N/A	
16	18	18 (100%)	35 weeks	NICU	5	$6,089.00

EGA=estimated gestational age, N/A=not available, NICU=neonatal intensive care unit, SCN=special care nursery.

ment week 3. These complications responded to outpatient treatment. Both patients discontinued 17P injections.

DISCUSSION

Although the intervention group is small, this study shows evidence of a significant reduction in both NICU bed days and cost. Other than offering 17P as a benefit, we are not aware of any external reasons that would have caused decreases in the NICU admission rate and LOS, such as coding changes, changes in NICU admission or discharge criteria, or new interventions that decrease preterm labor.

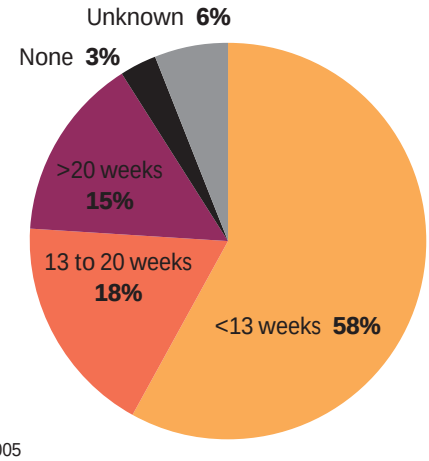
Among this study's strengths are its design, which included patients who would be typical candidates in a managed Medicaid population. Though the sample size and control group are small, the study yielded a statistically significant result for a reduction in the NICU LOS.

A longitudinal review of birth outcomes of 24 pregnant women with a history of preterm delivery prescribed 17P as compared to a control group does have shortcomings. Due to the low number of potential candidates for the control group, demographics could not be taken into consideration when selecting the control group. There is also the potential for risk bias, as the members who are most compliant (at less risk) might be those who agreed to take the weekly injections of 17P. Whether the differences in the birth outcomes of the intervention group versus the control group are attributable to inherent differences between the groups' general approaches to pregnancy or differences in prenatal care was not addressed by this study.

Challenges exist in extending the 17P benefit to a managed Medicaid population. The effects of delaying initiation of 17P and missing weekly injections are neither fully studied nor understood. The *New England Journal of Medicine* study (Meis 2003) initiates the weekly injections between 16 and 21 weeks' gestation. Unfortunately, many obstacles exist that delay the first prenatal visit of Medicaid enrollees, often too late in the second trimester. The process of Medicaid eligibility is complicated. In our Missouri service area, once a woman has a positive pregnancy test, she is immediately eligible for fee-for-service Medicaid. Nonetheless, she must wait for processing to be complete before she is able to choose a managed Medicaid plan. Often, pregnant women signing up for our plan are beyond 20 weeks' gestation. This delay in eligibility and in the start of prenatal care makes it difficult to initiate 17P weekly injections in high-risk women who are suitable candidates for such treatment.

We completed a focus study in 2004

FIGURE Gestational age at start of prenatal care



SOURCE: HCUSA 2005

that analyzed demographic data including the gestational age when prenatal care was initiated. According to the analysis, more than 15 percent of members who become eligible under Medicaid managed care receive prenatal care after 20 weeks' gestation, and more than 15 percent receive prenatal care between 13 and 20 weeks' gestation (Figure).

While only 62.5 percent of the women started 17P injections before gestational week 21, a reduction in NICU bed days still was seen, evidence that 17P can be used successfully in a population that is notorious for late prenatal care.

Once the patient was identified, administration of 17P on a weekly basis was a simple process. Because a physician could arrange to administer the injection in the office or through home health, a high level of compliance with the weekly injection was reported. Frequent contact with our OB nurse case managers most likely contributed to compliance with the weekly injection. The injection was well tolerated, with only two patients discontinuing treatment, due to minor adverse reactions.

To date, there are no widely established treatments to prevent preterm delivery. The reduction in NICU days and cost savings demonstrated in this study by offering 17P as a benefit in a managed Medicaid population is substantial. Use of 17P deserves further investigation, especially for application on a much broader scale.

In conclusion, a 2004 longitudinal review of birth outcomes in 24 pregnant women who had a history of preterm delivery and were prescribed 17P versus a control group showed a significant decrease in NICU LOS for a Medicaid managed care plan. The evidence provided by these results is consistent with those of a double blind, randomized, placebo-controlled trial by Meis and colleagues (2003). The 17P was well tolerated, with only a small abscess and allergic reaction noted at the injection site, both treated on an outpatient basis. The optimal time frame for initiation of 17P treatment as well as the effect of missed weekly injections on outcomes need further study. Use of 17P on a broader scale should be a strong consideration in treating high-risk pregnant women with a history of preterm delivery.

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