Optimizing the Use of 17P In Pregnant Managed Medicaid Members

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ABSTRACT

Objective

To evaluate the effect of 17 alpha-hydroxyprogesterone caproate (17P) on reducing the rate of neonatal intensive care unit (NICU) admissions and premature births in a managed Medicaid population that has a history of preterm delivery.

Specifically, to measure the effect of initiating 17P treatment during the recommended time frame of 16–21 weeks gestation versus after 21 weeks gestation.

Design

A 2004–2007 observational, causal comparative study reviewed birth outcomes in 104 pregnant women with a confirmed history of preterm delivery. Women whose 17P treatment was initiated during the recommended time frame of 16–21 weeks gestation were compared to those whose treatment was initiated after 21 weeks gestation.

Methodology

Intervention included offering 17P as a benefit to pregnant women who had a history of preterm delivery and who were deemed to be appropriate candidates for this treatment by their physician.

Results

No significant changes in birth outcomes were noted when comparing those members whose treatment was initiated during the recommended time frame of 16–21 weeks versus those whose treatment began after 21 weeks gestation. Members who received therapy of at least five injections of 17P, as opposed to those receiving fewer than five injections, experienced a statistically significant reduction in NICU admissions and in preterm birth at fewer than 37 weeks and at fewer than 32 weeks.

Conclusion

The number of injections and not the time frame, which had been indicated by previous research, the initiation of 17P therapy is the factor in reducing preterm birth and decreasing NICU admissions for pregnant women with a history of preterm birth in a managed Medicaid population.

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Key Words

Managed Medicaid, preterm birth, 17P, NICU

INTRODUCTION

Preterm delivery, defined as a delivery before 37 weeks, and the resulting large NICU claims that follow these early births are a large portion of a managed Medicaid company's expenses. The National Center for Health Statistics' final birth data for 2005 showed that the preterm birth rate, the percentage of babies born at less than 37 weeks gestation, is continuing to rise, with more than 525,000 babies, or 12.7 percent, born prematurely. That's up from 12.5 percent in 2004. The 2006 preliminary report indicates that the preterm birth rate will continue its upward trend and reach 12.8 percent, about 543,000 babies (Martin 2005).

The pathophysiological events that trigger preterm labor are for the most part unknown, but a history of prior 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 (*Meis, 2003) showed that treatment with 17P led to a statistically significant

reduction in preterm labor and delivery for high-risk women with a history of spontaneous preterm delivery. In 19 clinical trial centers, the study enrolled 463 women with a confirmed history of preterm birth.

Patients were enrolled at 16–21 weeks of gestation and randomly assigned to receive weekly injections of 17P or placebo until delivery or until 37 weeks of gestation. This may have amounted to as many as 20 or more injections of 17P for the 16–21 week group as opposed to the group receiving injections only after 21 weeks gestation. The initiation of the treatment injections is confounded with the total amount of 17P the participants in the study received. Therefore, it is possible that the amount of 17P received is more valuable than the timing of its initiation.

In the study, treatment with 17P resulted in an overall reduction in the preterm birth rate of 34 percent and a reduction of 42 percent in the rate of preterm births before 32 weeks. In addition, infants born to women treated with 17P had significantly lower rates of serious complications such as necrotizing enterocolitis, intraventricular hemorrhage, use of supplemental oxygen, and mean number of days of post-delivery respiratory therapy.

A longitudinal review of birth outcomes in 24 pregnant women with a confirmed history of preterm birth in a managed Medicaid health plan revealed a significant decrease in NICU admissions as well as NICU length of stay, resulting in cost savings related to treatment with 17P (Mason 2005).

Obstetricians who treat women with high-risk pregnancy, such as those with a history of spontaneous preterm birth, will often initiate progesterone treatments.

A 2005 survey found that 67 percent of these obstetricians use the progesterone treatments, compared to 38 percent in 2003 (March of Dimes 2006).

The goal of this study is to determine whether delaying the initiation of weekly injections of 17P until 21 weeks gestation or later could affect the number of NICU admissions and premature births in a Medicaid population.

What is 17P?

The drug is a naturally occurring metabolite of progesterone, produced in large quantities during pregnancy. It is used to prevent recurrent miscarriages and for various menstrual disorders. This hormone has been indicated for amenorrhea, endometrial carcinoma, and uterine corpus adenocarcinoma.

Use of 17P in women who have had a previous premature birth (fewer than 37 weeks) has been endorsed by the American College of Obstetrics and Gynecology (2003).

In 2006, the Reproductive Health Drugs Advisory Committee of the Food and Drug Administration (FDA) recommended that the data presented by a particular biotech company in its new drug application (NDA) for a 17P-type product supports the efficacy of 17P treatments in preventing preterm birth prior to 35 weeks. This committee also agreed that overall safety data are adequate and sufficiently reassuring to support use of these treatments in women with a history of preterm delivery.

How does 17P work?

In animal models, progesterone appears to be primarily responsible for maintaining uterine quiescence during pregnancy. A drop in progesterone levels normally occurs at the initiation of labor at term. However, the mechanism is not the same for preterm labor and preterm rupture of the membranes; evidence suggests this is the result of an inappropriate, inflammatory response. Weekly injections of 17P starting at 16–21 weeks until 35 weeks gestation (totaling as many as 20 injections) may suppress this pathological labor (Mercer 1999).

The quantities of 17P produced naturally during pregnancy, predominantly by the placenta, far exceed the recommended dose of 250 mg weekly by intramuscular injection during the last half of pregnancy. Based on the animal and clinical studies that support the safety of 17P in pregnancy, and on the fact that large quantities are produced naturally by the body during pregnancy, one would not expect any serious side effects from initiation of 17P. Indeed, Reprotox (1997), an online reproductive toxicology database, states that "there is no available evidence that the administration of this agent (17P) during pregnancy is harmful."

Based on this information, we hypothesized that an adequate number of injections of 17P, even after 21 weeks gestation, could help to reduce negative pregnancy outcomes associated with preterm delivery in a managed Medicaid environment.

METHODS

Environment

Centene Corp. is a large company with many products, including insurance, nursing services, disease management, and behavioral health management, for people receiving benefits under state Medicaid programs, including Supplemental Security Income (SSI) and the State Children's Health Insurance Program (SCHIP). Centene operates health plans in Georgia, Indiana, New Jersey, Ohio, South Carolina, Texas, and Wisconsin and manages over 1.1 million Medicaid members. These Centene health plans had 63,895 deliveries in the past 12 months. Approximately 12 percent of these deliveries resulted in NICU admissions.

Because the majority of our members are from lower income

socioeconomic groups, considerable attention is focused on preventing poor birth outcomes and NICU admissions. Centene health plans have obstetric nurse case managers and social workers who provide support for pregnant mothers who are identified as being at high risk for complications during pregnancy.

A notification system is in place to allow our health plans to identify members as early as possible in their pregnancy. However, because of a number of factors including members not accessing prenatal care in a timely manner, delays in state eligibility processes, and noncompliance with notification requirements, our plans frequently do not identify a woman's pregnancy until she is well into her second or third trimester. For example, in 2006 over 15 percent of the pregnant mothers in Superior Health Plan, Centene's Texas subsidiary health plan, joined after 21 weeks gestation.

Availability

From 2004 to 2007, 17P was not offered as a covered benefit in fee-for-service Medicaid in any of the states (Georgia, Indiana, New Jersey, Ohio, Texas and Wisconsin) where Centene currently operates health plans. The fee-for-service Medicaid program is prohibited from paying for any drug product for which a rebate agreement has not been signed. Centene has verbiage in its contracts that allows its health plans to provide 17P as a benefit for the managed Medicaid population.

The use of 17P treatment is voluntary, and physicians have adopted its use at varying rates. Therefore, determining whether or not the introduction of the use of 17P, after the time period recommended by previous studies (16–21 weeks gestation), would benefit these higher risk cases was a key motivating factor in conducting the present study.

Indeed, if it could be demonstrated that 17P injections after 21 weeks gestation could have the same beneficial effects as revealed in other studies, better health outcomes could be provided to plan members, and plan care costs could be reduced.

Identification of high risk members

For this review, members who received 17P during their pregnancy were identified by reviewing claims and by collecting data from the obstetric (OB) case managers in each of the Centene health plans.

Providing the 17P benefit

Once a physician identified a member who is a candidate for 17P, the health plan made arrangements to administer the injections in the physician's office or through a home health agency. Frequent contact with the health plan's OB case managers provided the members with information and support to facilitate education and compliance with the treatment. The time frame for initiation of 17P treatment was determined by member enrollment in managed Medicaid, timing of the initial prenatal care visit, and when the health plan learned of the member's pregnancy.

Statistical test

A chi-square analysis (2 x 2 contingency table), commonly used when comparing the number of occurrences between two groups or time frames, was conducted to determine the significance of reduction in NICU admissions and pregnancy outcomes between the two groups.

Using statistical tests rules out the risk of chance being the contributing factor to reductions and/or improvements in outcomes and also accounts for variations in sample sizes. The p-value assigned to determine statistical significance and account for sample size variation at 95 percent confidence is less than 0.05.

RESULTS

We measured the effectiveness of 17P by analyzing and comparing results under two comparative conditions, onset of treatments (gestation) and number of treatments (injections). The first condition consisted of a two-group comparison between those members who were 1) treated with injections between 16 and 21 weeks gestation and 2) those members treated after 22 weeks gestation. The second condition consisted of a comparison between 1) those members who received fewer than five injections and 2) those members who received more than five injections during their pregnancy.

To assess treatment effectiveness, we used a) the NICU admission rate, b) the rate of preterm delivery prior to 32 weeks, c) the rate of preterm delivery between 33 and 37 weeks gestation, and d) the total infant deaths related to preterm delivery.

All members were enrolled in case management, as they had been identified by prenatal risk assessments as being at risk for preterm delivery. In addition to educational material, members in OB case management received ongoing follow-up services and support to help them comply with treatment and for continued prenatal care.

Initiation of treatment comparison

The sample consisted of 47 women who were administered 17P within the recommended time frame of 16–21 weeks gestation and 57 women who were administered treatment after 22 weeks gestation. Table 1 demonstrates the results.

NICU admissions

The group initiating 17P between

TABLE 1
Initiation of treatment

	15–21 weeks gestation		22–34 weeks gestation		P-value
	N	*%*	*N*	*%*	*Significance (2 × 2 chi-square one tailed statistical test)*
N	47	100	57	100	
NICU admits	18	38.2	18	31.5	None
Delivery <37 weeks	22	46.8	27	47.3	None
Delivery <32 weeks	12	25.5	8	14.0	None

16 and 21 weeks gestation had a 38.2 percent NICU admission rate while the group initiating treatment with 17P after 21 weeks gestation had 31.50 percent NICU admissions. The mean NICU rate for the whole population was 34.6 percent. This result reflects no significant changes in outcome based on time of initiation of treatment and does not show significant variation from the mean rate of NICU admissions for this population.

Preterm birth

The group initiating 17P between 16 and 21 weeks gestation had a 46.8 percent rate of preterm birth between 33 and 37 weeks and 25.5 percent rate of preterm birth before 32 weeks. The group initiating treatment with 17P after 21 weeks gestation had a 47.30 percent rate of preterm birth between 33 and 37 weeks and 14 percent rate of preterm birth before 32 weeks. This result reflects no significant changes in outcome based on time of initiation of treatment.

Total injection comparison

We treated 104 members with 17P; they were the subjects of this review. Thirteen received fewer than five injections (12.5 percent), and 91 received five or more (87.5 percent).

Table 2 depicts the results of comparing pregnancy outcomes between the two groups.

NICU admissions

The application of five or more 17P injections (as opposed to fewer than five injections) is associated with a reduction of NICU admissions from 61.6 percent to 30.7 percent. This drop of 30.9 percentage points is on the order of that found and reported in earlier studies. Specifically, of the 13 members who received fewer than five injections, over 60 percent delivered prematurely. Of these deliveries, 76.9 percent were between 32 and 37 weeks gestation, and over 61 percent of these deliveries were prior to 32 weeks gestation, with fetal demise accounting for one delivery in each category.

Ninety-one members received more than five weekly injections of 17P. Of that group, 30.7 percent resulted in an NICU admission. The reduction in NICU admissions, compared to members who received fewer than five injections, meets the test of statistical significance.

Preterm birth

The use of five or more 17P injections is associated with statistically significant reductions in the number of preterm births at fewer than 32 weeks (from 61.5 percent to 13.1 percent) and between 33 and 37 weeks (from 76.9 percent to 42.8 percent). Note that 42.8 percent of members had a preterm birth between 33 and 37 weeks and 13.10 percent had a preterm birth at fewer than 32 weeks.

Member compliance

Of the 1,064 doses scheduled in this series, only 24 doses were missed. A total of 12 members missed the doses. While the 12 accounted for only 2.2 percent of the total number of doses given, they account for over 19 percent of members who delivered and who had infants admitted to the NICU. Note that three members in the non-compliant group were also identified as having received fewer than five injections of the 17P therapy. All three (100 percent) of these members delivered and had infants admitted to the NICU. We find this result compelling.

Complications

Review of the clinical records for the 104 women in the study group show no complications associated

TABLE 2
Total Injections

	< 5 Injections		≥ 5 Injections		P-value
	N	*%*	*N*	*%*	*Significance (2 × 2 chi-square one tailed statistical test)*
N	13	100	91	100	
NICU admits	8	61.5	28	30.7	P = 0.029
GA < 37 weeks	10	76.9	39	42.8	P = 0.021
GA < 32 weeks	8	61.5	12	13.1	P = 0.000

with the initiation of the 17P medication therapy.

DISCUSSION

These findings indicate that the number of 17P weekly injections is a factor for better pregnancy outcomes. High risk members with a confirmed previous history of preterm birth who have at least five injections during the course of their pregnancy benefit from 17P therapy. There was no noted significant difference in outcomes between members who received the injections from 16 to 21 weeks and members who received the injections from 22 to 34 weeks in this study.

The strength of this study is its design, which includes patients who are typical members in a managed Medicaid population. The results are statistically significant for reduction in NICU admissions, and the population size is sufficient to make this conclusion.

There is potential for bias in this study. Specifically, members who were compliant with their 17P injections may also have tended to be more compliant with other aspects of prenatal care, compared to those members who were not compliant and as a result received fewer than five injections. Whether the differences in the birth outcomes of members who received five or more injections versus those who received fewer than five injections are attributable to inherent differences between the groups' general approaches to pregnancy or differences in prenatal care are not addressed by this study.

The literature shows that offering 17P as a benefit to pregnant women enrollees with a history of preterm birth can decrease NICU days significantly for a Medicaid managed care population (Mason 2005).

Our results are consistent with the results of a double blind, randomized, placebo-controlled trial completed by Meis and colleagues (2003). In the Meis study, treatment with 17P significantly reduced the risk of delivery to 36.3 percent at fewer than 37 weeks and to 11.4 percent at fewer than 32 weeks. In the present study, the intervention group which had at least five injections of 17P had a 42.8 percent rate of preterm birth between 33 and 37 weeks and a preterm birth rate of 13.1 percent at fewer than 32 weeks, despite the significant challenges that exist in extending the 17P benefit to this population. Delays in approval and notification of eligibility for managed Medicaid for pregnant women and in getting access to prenatal care make it difficult to initiate 17P injections in high-risk women who are suitable candidates for such treatment within the recommended time frames. The injections are scheduled weekly, so compliance also becomes an issue because of social barriers encountered by this population.

Other than offering 17P as a covered benefit, we are not aware of any external reasons that might have caused any decreases in the rate of NICU admission or the rate of preterm delivery.

The effects of delaying the initi-

FIGURE 1
Initiation of treatment

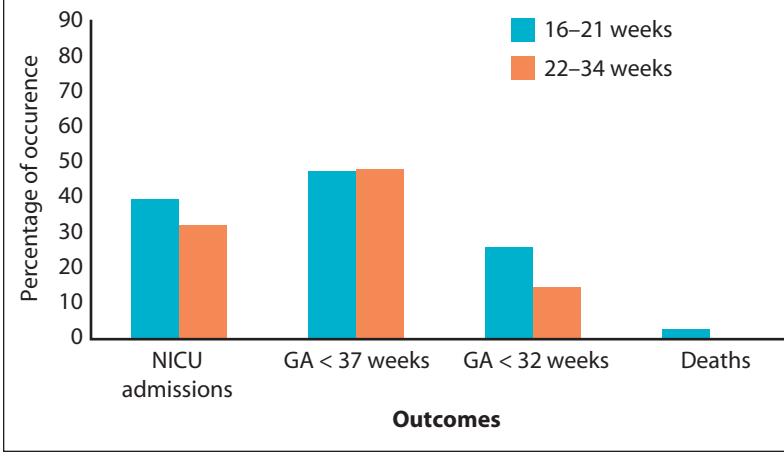
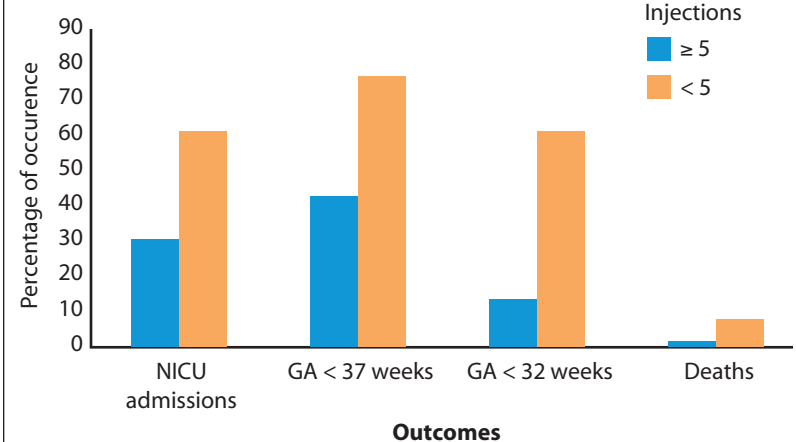


FIGURE 2
Total Injections



ation of 17P beyond the 16–21 weeks' gestation time line studied by Meis and colleagues has not been fully studied or reported in the literature. It is suggested that the optimal time frame for initiation of 17P treatment can be extended late into the 2nd trimester, as long as the woman receives at least the five weekly injections. Furthermore, the issue of dosage is still open for investigation.

This means 17P can be effectively used in the Medicaid population, where there is often late initiation of prenatal care.

The effect of missed weekly injections of 17P has not been previously reported in the literature. There is a suggestion that there is an impact on birth outcomes, as documented above. The women who missed doses of 17P contributed disproportionately to the overall NICU admission rate. However, these results should be interpreted with caution, as more study is needed.

It is of note that the 17P treatment was well tolerated within the group and that there were no documented complications.

CONCLUSION

This comparative, observational study of birth outcomes in 104 pregnant women who had a confirmed history of preterm birth and were prescribed 17P showed that there were no significant differences in the birth outcomes between those who received the 17P injections from 16 to 21 weeks gestation compared to 22–34 weeks gestation. The high risk pregnant members with a previous confirmed history of preterm birth who had at least five injections during the course of their pregnancy had lower NICU admissions and premature births before 32 and before 37 weeks of gestation.

The optimal time frame for initiation of 17P treatment and the effect of missed weekly 17P injections on birth outcomes requires additional study. Use of 17P on a broader scale should be a strong consideration in treating high-risk pregnant women with a confirmed history of preterm birth, even if presenting after 21 weeks of gestation.

REAL WORLD IMPLICATIONS

As health care professionals continue to focus on reducing health care costs attributed to negative pregnancy outcomes, findings such as these provide additional support to the managed Medicaid industry in helping to identify better ways to reduce cost associated with preterm delivery while improving quality of care for pregnant women at risk.

Treatment with 17P, initiated at 16–21 weeks gestation, has been shown to reduce the premature birth rate and NICU admission rate in women who have had a history of preterm birth. The effects of delaying 17P beyond the 16–21 weeks gestation time frame has not been studied or reported in the literature.

This study clearly demonstrates that:

The optimal (effective) time for initiation of 17P treatment can be extended beyond 16–21 weeks gestation. As long as the women receive at least five weekly injections, it appears that they will obtain the typical benefits of receiving 17P treatments.

This hormone can still be used effectively in managed Medicaid populations, which are notorious for late initiation of prenatal care.

REFERENCES

ACOG (American College of Obstetrics and Gynecology). Progesterone recommended in certain high-risk pregnancies to help prevent preterm birth. Press release. Oct. 31, 2003.

Katz A, Lancet M, Skornik J, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. *Obstet Gynecol.* 1985;65(6):775–780.

March of Dimes. "Drug to Prevent Preterm Birth Needs Prompt FDA Approval." Press release, Aug. 26, 2006.

Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2002. *Natl Vital Stat Rep.* 2003;52(10):1–113.

Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2003. *Natl Vital Stat Rep.* 2005;54(2): 1–116.

Mason MV, House KM, et al. 17 alpha-hydroxyprogesterone caproate usage in a Medicaid managed care plan and reduction in NICU days. *Managed Care* 2005;14(10):58–63.

Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17-alpha hydroxyprogesterone caproate. *N Engl J Med* 2003;349(13):1299.

Mercer BM, Goldenberg RI, Moawad AH, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol.* 1999;18(5 Pt 1):1216–1221.

Michaelis J, Michaelis H, Gluck E, Keller S. Prospective studies of suspected association between certain drugs administered in early pregnancy and congenital malformations. *Teratology.* 1983;27:57–64.

Petrini JR, Callaghan WM, Klebanoff M, et al. Estimated effect of 17-alpha hydroxyprogesterone caproate on preterm birth in the United States. *Obstet Gynecol.* 2005;105(2):267–272.

Raman-Wilms L, Tseng AL, Wighardt S, et al. Fetal genital effects of first trimester sex hormone exposure: a meta-analysis. Obstet Gynecol. 1995;85(1):141–149.

Anonymous. Reprotox. 1997, vol:92. Micromedix Inc. Available at: «http://www.reprotox.org». Verified Dec. 6, 2007.

Resseguie LJ, Hick JF, Bruen JA, et al. Congenital malformations among offspring exposed *in utero* to progestins. Olmsted County, Minn., 1936–1974. *Fertil Steril.* 1985;43(4):514–519.

Varma T, Morsman J. Evaluation of the use of hydroxyprogesterone hexanate in early pregnancy. *Int J Gynecol Obstet.* 1982;20:13–17.