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Preventing Preterm Birth: An Update for Medicaid MCOs on Utilization of Progesterone

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Medicaid finances about 43% of all births in the United States (U.S.), including nearly half (49%) of preterm births.[1] Preterm birth, defined as delivery prior to 37 weeks of gestation, is the leading cause of neonatal mortality, morbidity, and neonatal intensive care (NICU) utilization.[2] Cost-effective, evidence-based interventions and care models are needed to prevent preterm birth in the Medicaid-insured population.

Over the past decade a large emphasis has been placed on the use of progesterone to prevent preterm birth in people with certain risk factors, based on promising initial trials and obstetric guidelines. As state Medicaid programs and Medicaid managed care organizations (MCOs) began to shift toward value-based payment models, assessing risk factors for preterm birth, including medical eligibility for progesterone treatment, has been a focus of many performance-based payment programs.[3] These efforts have increased the utilization of progesterone treatment and, due to the high cost of Food and Drug Administration (FDA) approved formulations, resulted in high costs to payers and purchasers. However, despite early promising evidence, increased utilization of and investment in progesterone has not been linked to reductions in preterm birth at the population level.[4, 5] State Medicaid programs and MCOs are in need of guidance to navigate the shifting clinical and regulatory landscape to rebalance prevention efforts in light of the evolving evidence base.

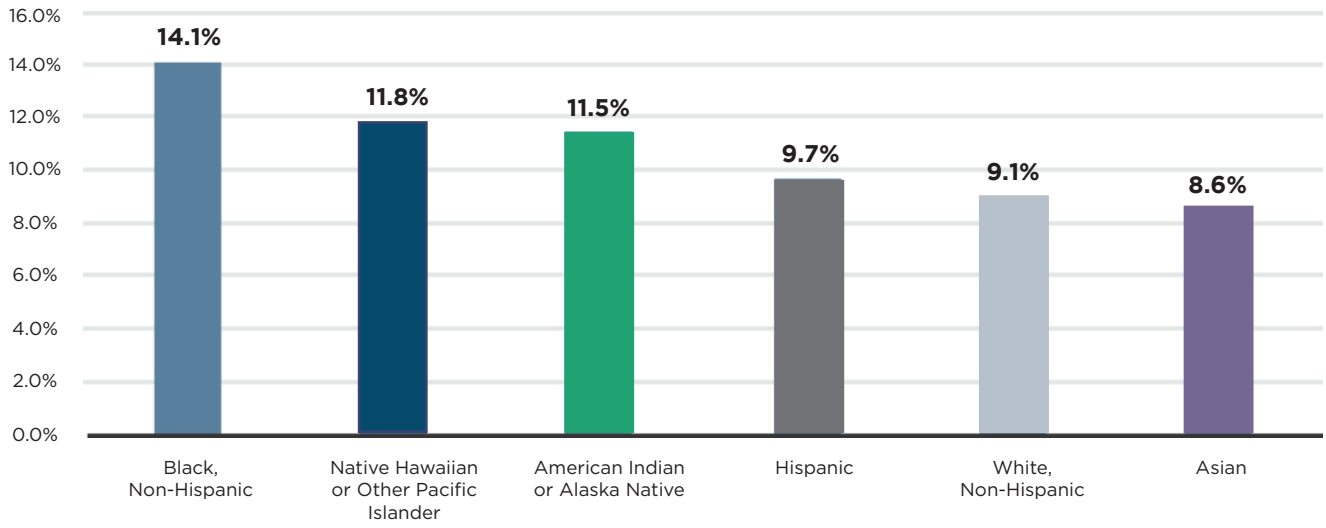
This report will review emerging evidence about the use of progesterone in preterm delivery prevention with updated position statements from professional organizations about the continued use of progesterone for that indication. It will also provide evidence on promising care models that MCOs might consider supporting within their networks to decrease the high rates of prematurity.

The mission of the Institute for Medicaid Innovation is to improve the lives of Medicaid enrollees through the development, implementation, and diffusion of innovative and evidence-based models of care that promote quality, value, equity and the engagement of patients, families, and communities.

The Burden of Preterm Birth

In 2018, ten percent of U.S. births were preterm, the third straight year the rate has increased after several years of decline.[6] In 2018, the preterm birth rate for black non-Hispanic newborns was 14.1%, an increase of nearly a full percentage point in only four years, from 13.2% in 2014 (Figure 1).[6]

Figure 1. Preterm Birth Rates by Race and Ethnicity, 2018



Source: Martin, J.A, Hamilton, B.E., Osterman, M.J.K, & Driscoll, A.K. (2019). Births: Final Data for 2018. NVSS, 68(13), 1-47. https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf

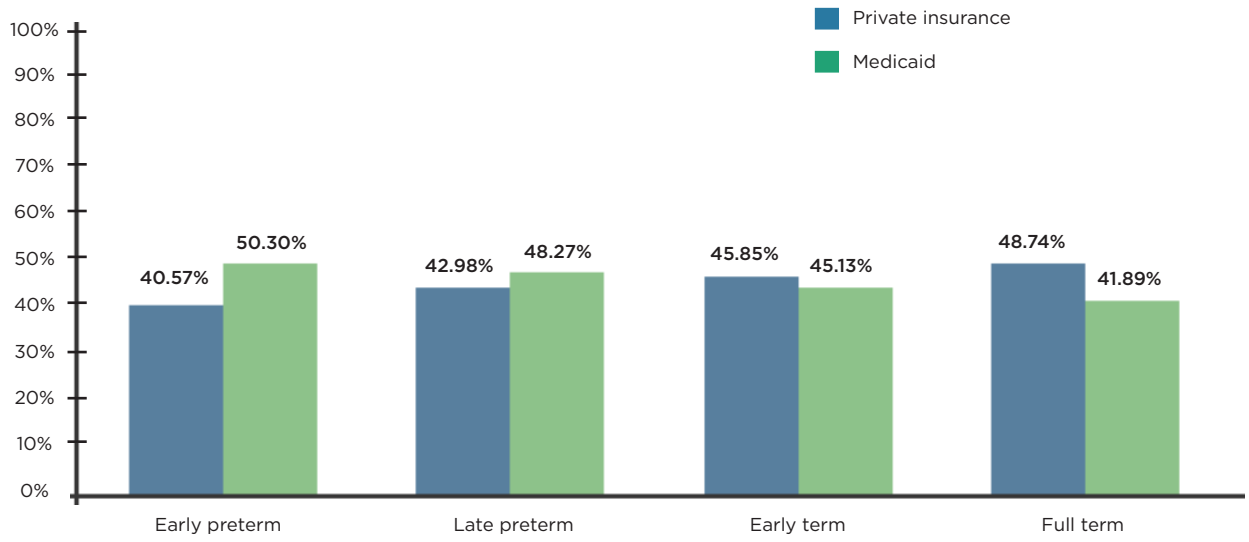
Infants born prematurely are at higher risk for short-term health complications including respiratory distress and infection and chronic conditions such as asthma, cognitive development disorders, and motor function problems.[2] Preterm newborns are also more likely than full-term newborns to have longer hospital stays in the NICU and increased hospital readmissions. As a result, preterm infants account for half of all annual infant hospitalization costs, and one quarter of subsequent pediatric hospitalization costs.[7] Recent estimates indicate that preterm births account for over $20 billion in U.S. health care costs.[8]

Prevalence in Medicaid

Enrollment in Medicaid is an independent predictor of preterm delivery as people insured under Medicaid are more likely to have risk factors for adverse birth outcomes including younger age with a higher prevalence of smoking and illicit drug use and late entry into prenatal care.[9, 10] Within the Medicaid insured population, there are disparities as well. One study of 457,200 Medicaid-enrolled women found that black women had a 35% higher odds of preterm birth than white women, even when controlling for age, number of prenatal visits, and major medical comorbidities. This same study found continued evidence for the "Hispanic paradox:" Hispanic women had the lowest number of prenatal visits yet had the lowest percentage of preterm births of all racial/ethnic groups in the study.[11]

State Medicaid programs and Medicaid MCOs pay for a disproportionate number of preterm births and associated poor outcomes, with a gap that is inversely proportional to gestational age (Figure 2).[1] This indicates that more of the short and long-term effects of extreme prematurity accumulate to Medicaid programs, MCOs, and their beneficiaries.

Figure 2. Coverage of Preterm Birth by Payer Type, 2013



Source: Markus, A.R., Krohe, S., Garro, S., Gerstein, M., & Pellegrini, C. (2017). Examining the association between Medicaid coverage and preterm birth using 2010-2013 National Vital Statistics Birth Data. Journal of Children and Poverty, 23(1), 79-94. DOI: 10.1080/10796126.2016.1254601

To address the increased prevalence of preterm birth and other comorbidities, Medicaid MCOs utilize many approaches to provide access to and coverage for optimal maternity care. These approaches include promotion of early access to both preconception and maternity care, individualized case management for high risk pregnancies, phone apps to remind all pregnant members about recommended care at each stage of pregnancy, web-based education, and community outreach. Many MCOs also provide information on the use of effective contraception to increase the interpregnancy interval, as short interpregnancy intervals are associated with higher preterm birth risk. MCOs also partner with nutrition programs like WIC and local community-based food banks to promote healthy pregnancies. Additionally, they support access and coverage for tobacco cessation and substance use disorder programs as a critical cornerstone of strategies to promote healthy pregnancies and prevent preterm birth.

What Causes Preterm Birth?

The causes of preterm birth are multifactorial and not completely understood. There are two main types of preterm birth: spontaneous and medically indicated. The constellation of causes and potential solutions for each subtype are different.

Spontaneous preterm birth occurs when labor begins on its own or when membranes rupture before the 37th completed week of gestation. The cause is often unclear, but infectious and inflammatory processes are both known to trigger spontaneous preterm birth. Health-related and social risk factors for preterm birth[12] include smoking in the current pregnancy, underweight or obesity based on body mass index, short inter-pregnancy interval, food insecurity, and unstable housing.[2, 13] Preterm birth is also associated with community risk factors including pollution and area-level deprivation, an index variable that assesses

sociodemographic domains by ZIP code, including education, employment, housing, occupation, poverty, racial composition, and residential stability.[14, 15] However, the strongest risk factor for preterm birth is a history of a previous spontaneous singleton preterm birth.[16]

Medically indicated preterm birth occurs when a provider recommends induction of labor or cesarean before 37 weeks' gestation to manage maternal complications such as pre-eclampsia, concerns about fetal well-being, or placental problems. Evidence for optimal timing of birth for pregnancy complications is limited and there is wide variation in practice, suggesting some of these preterm births are preventable.[17]

History of Progesterone to Prevent Preterm Birth

Progesterone is a hormone produced by the placenta that is thought to have an important role in sustaining gestation: progesterone activity rises rapidly in early pregnancy and remains high until the onset and progression of labor. Based on its role in supporting normal gestation, researchers several decades ago began to evaluate the potential value of progesterone supplementation in the prevention of spontaneous preterm birth. Although a clear pharmacological mechanism for action of progesterone has not been identified, it has been theorized that progesterone supplementation may prevent "functional withdrawal," a sequence of changes in progesterone receptors and local hormone activity that has been observed at the onset of labor, or that progesterone may have anti-inflammatory properties.[18, 19]

17 alpha-hydroxyprogesterone caproate (17-OHP)

In 2003, the National Institute of Child Health and Human Development (NICHD) funded a multi-center randomized controlled trial that found benefits in weekly injections of 17 alpha-hydroxyprogesterone caproate (17-OHP) from 16-36 weeks of gestation.[20] The researchers observed a significant ($p < 0.001$) one-third reduction in recurrent preterm delivery and a significant improvement in several neonatal complications. The evidence suggested that progesterone treatment may be beneficial in two specific high-risk populations: those with a prior spontaneous preterm birth and those with short cervical length, based on ultrasound measurements in the second trimester. For other subgroups, such as those with twin pregnancies or prior cervical surgery, progesterone treatments were not found to be effective.[20]

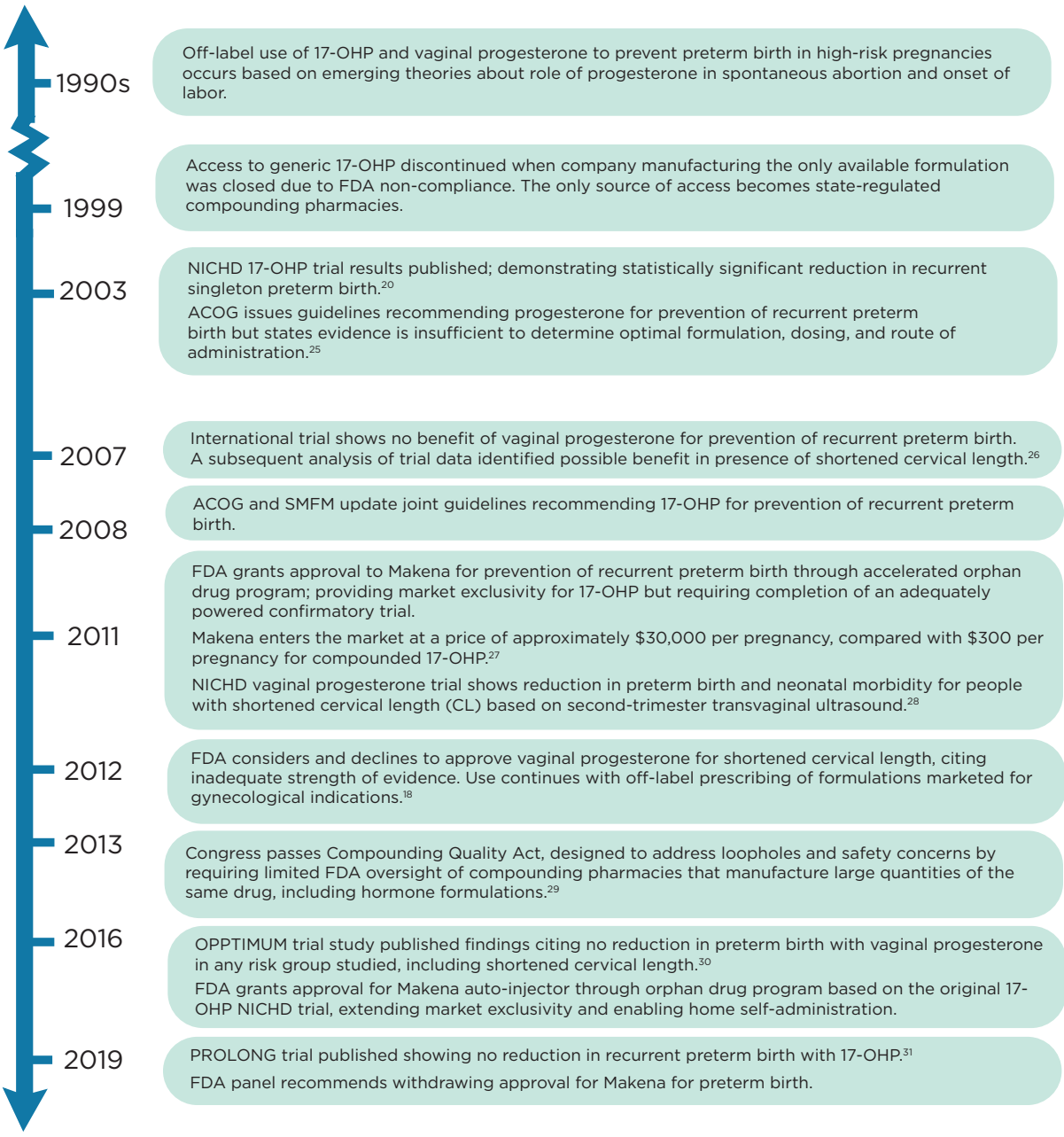
The study had some limitations, including an unexplained, very high rate of preterm birth (>50%) in the placebo group, as well as differences in the baseline characteristics of the two groups that might have affected outcomes. Despite these limitations, physician organizations including American College of Obstetricians and Gynecologists (ACOG), American Academy of Family Physicians (AAFP), and Society for Maternal Fetal Medicine (SMFM) endorsed the use of 17-OHP, and guidelines were published in support.[21, 22] However, prior to 2011, there were no FDA-approved formulations for 17-OHP and the drug was sourced from compounding pharmacies when indicated.

In 2011, the Food and Drug Administration (FDA) granted expedited approval for 17-OHP under the "orphan drug" pathway based on the results of the NICHD trial. The orphan drug pathway, designed for products that demonstrate promise for the diagnosis and treatment of rare diseases, allows for lower levels of evidence than regular FDA approval, such as smaller population sizes and use of less rigorous statistical methods.[23] To maintain FDA approval, companies must complete confirmatory trials that are large enough and designed appropriately to detect clinically significant differences in outcomes. The 2011 approval provided market exclusivity to Makena™, a branded formulation of 17-OHP, while the confirmatory trial was underway.

By this time, weekly 17-OHP injections were the standard of care for preventing recurrent preterm birth in the U.S. and other countries. Therefore, arranging a clinical trial with a placebo was ethically and pragmatically challenging. As a result, the confirmatory trial, known as Progestin's Role in Optimizing Neonatal Gestation (PROLONG), took eight years to complete, and required international recruitment, with 77% of participants enrolled outside the United States. In 2019, the trial results were published, showing no benefit to 17-OHP compared with placebo.[24] There were no differences for 17-OHP compared with placebo in preterm birth or neonatal morbidity. There were also no differences seen in the subpopulation from the United States (n=391), although the study was underpowered to detect differences in subpopulations.

The timeline in Figure 3 highlights key events over the last 30 years that have shaped the current practice of prescribing intramuscular and vaginal progesterone for the prevention of spontaneous preterm delivery.

Figure 3. Timeline of 17-OHP and Vaginal Progesterone to Prevent spontaneous Preterm Birth



Source: Institute for Medicaid Innovation. (2020). Preventing Preterm Birth: An Update for Medicaid MCOs on Utilization of Progesterone.

Based on the findings of the PROLONG trial and testimony from clinical and statistical experts, an FDA panel recommended withdrawing approval of Makena by a vote of 9 to 7. A final decision is pending as of April 2020.

At the time of publication, ACOG and SMFM have not changed their clinical guidelines in support of the use of 17-OHP in the context of shared medical decision making between providers and women at high risk for recurrent preterm delivery. However, both organizations have raised concerns that individuals enrolled in the PROLONG trial were at lower risk of preterm delivery and postulate selection bias that precluded those at highest risk of preterm delivery from enrollment in the PROLONG trial. SMFM states that it is "reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial." Table 1 provides a comparison of the two landmark studies, Meis and PROLONG, highlighting the differences between the populations studied and the outcomes.

Table 1. Comparison of Initial and Confirmatory 17-OHP Trials for Prevention of Recurrent Spontaneous Preterm Birth (SPTB)

Study Characteristics	Initial trial (Meis et al., 2003)	Confirmatory trial PROLONG (Blackwell et al., 2019)*
Number of participants	463	1708 (including 391 from the United States)
Setting	19 U.S. academic medical centers	93 sites in 9 countries
Population characteristics	59% black, 24% white, 15% Hispanic, 0.6% Asian 32% had > 1 prior SPTB, although the rate differed between 17-OHP (27.7%) and placebo (41.2), and the average number of prior preterm births was significantly higher in the placebo group (1.6 vs. 1.4, p=.007) 21.6% smoked cigarettes 50% were married or lived with a partner	87% white, 9% Hispanic / Latino, 7% black, 3% Asian 12% had >1 prior SPTB 7% smoked cigarettes 89% were married or lived with partner
Preterm birth < 37 weeks	36.3% 17-OHP vs. 54.9% placebo, RR = 0.66 (0.54–0.81), p<0.001	23.1% 17-OHP vs. 21.9% placebo, RR = 1.06 (0.88–1.28)*
Preterm birth < 35 weeks	20.6% 17-OHP vs. 30.7% placebo, RR = 0.67 (0.48 - 0.93), p=0.02	11.0% 17-OHP vs. 11.5% placebo RR = 0.95 (0.71–1.26)*
Preterm birth < 32 weeks	11.4% 17-OHP vs. 19.6% placebo, RR = 0.58 (0.37 - 0.91), p=0.02	4.8% 17-OHP vs. 5.2% placebo, RR = 0.92 (0.60–1.42)*

*Note: The PROLONG trial did not show statistically significant differences for preterm birth at < 37weeks, <35 weeks, or <32 weeks as indicated by the confidence intervals that do not cross 1.

**Note: Includes neonatal death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis.

Source: Institute for Medicaid Innovation. (2020). Preventing Preterm Birth: An Update for Medicaid MCOs on Utilization of Progesterone.

Vaginal Progesterone

While most efforts to decrease spontaneous preterm birth have focused on prevention of recurrent preterm birth, another strategy has been to prevent the initial preterm birth.[32] A risk factor for preterm birth that has emerged is a shortened cervix (<25 mm before 24 weeks gestation) as detected by transvaginal ultrasound measurement in the midtrimester.[33, 34]

Asymptomatic women without a history of preterm birth who are found on ultrasound to have a shortened cervix (< 20mm) are sometimes treated with off label use of vaginal progesterone. Several randomized controlled trials all found a significant decrease in the rate of preterm delivery in women treated with vaginal progesterone compared to placebo.[28, 35, 36] However, another study by Norman et. al. showed that vaginal progesterone was not associated with reduced risks of preterm birth or composite neonatal adverse outcomes.[30]

Some researchers advocate for routine universal screening of cervical length by ultrasound measurement to identify those at risk based on shortened cervical length, but this method is controversial and currently not recommended routinely by ACOG or SMFM.[37, 38, 39] The prevalence of shortened cervix in the overall population is about 2%. Screening for conditions that have low prevalence in a population leads to high false positive rates, and higher use of treatment among people unlikely to benefit, reducing cost effectiveness and exposing mothers and newborns to potential side effects. Screening is performed by transvaginal ultrasound, which is invasive and adds cost and complexity to the routine mid-trimester ultrasound. As a result of these challenges, although shortened cervical length is correlated with preterm birth, the best approach to identifying the population to screen and treat has not been determined.

Promising Best Practices

At the state level, expansion of Medicaid through the Affordable Care Act has been shown to have reduced the racial disparity in preterm birth rates and low birthweight infants for non-Hispanic black infants in expansion states.[40] Beyond expanding access, states and MCOs have invested in various initiatives aimed at reducing preterm birth, including preconception and interconception care programs, new care delivery models, and care management programs, frequently emphasizing coordination of access to progesterone treatments when indicated.

At the national level, the Centers for Medicare and Medicaid Services (CMS) in partnership with the Health Resources and Services Administration (HRSA) and the Administration on Children and Families (ACF) recently concluded a large, 4-year program known as "Strong Start for Mothers and Newborns Initiative" to evaluate the potential impact of innovative care models to reduce preterm birth and other high priority outcomes, such as low birth weight, cesarean birth, and hospital utilization for women enrolled in Medicaid or Children's Health Insurance Program (CHIP).[41] Over 45,000 women at high-risk for preterm delivery were enrolled. The care models evaluated included:

- **maternity care homes** (provide care coordination, sometimes with other enhanced services);
- **group prenatal care** (prenatal visits provided in a group format enhanced with health education and facilitated discussion); and
- **midwife-led birth centers** (freestanding birth centers led by midwives with community health workers who assisted with care navigation and education).

Outcomes from the Strong Start initiative found significantly better outcomes for women receiving care in midwifery-led birth centers compared with matched population controls. The evaluation of the five year program found a decrease in the cesarean birth rate (17.5% vs. 29%, $p<0.01$), preterm birth rate (6.3% vs. 8.5%, $p<0.01$), and low-birthweight rate (5.9% vs. 7.4% $p<0.01$).[41] Participants in midwifery-led birth centers were also more likely to report being "very satisfied" with their care experience compared to participants in traditional clinical settings.[41] To learn more about midwifery-led and birth center care models specific to the Medicaid population, visit the Institute for Medicaid innovation's website.

MCOs are uniquely positioned to develop and employ multiple approaches to increase the overall health and care of their members of childbearing age and to prevent preterm birth. This may include promoting preconception care, interconception care programs, new care delivery models such as Strong Start, and individualized care management. However, a limiting factor for Medicaid MCOs is that many pregnant members only become Medicaid-eligible once they are pregnant, delaying their entry to care. Furthermore, they may lose coverage within 60 days postpartum, limiting the ability of the care team to adequately treat and manage comorbidities long-term to prevent its potential impact on preterm birth.

Implications and Next Steps for Medicaid Programs and MCOs

The landscape for preterm birth prevention is shifting, as evidence continues to evolve and state Medicaid programs and MCOs evaluate the impact and cost-effectiveness. Many state Medicaid programs and MCOs developed protocols for use of 17-OHP to prevent preterm birth for women with a previous singleton preterm delivery and included screening for prior preterm birth before initiating Makena therapy as a quality measure. With the recent studies and the FDA panel recommendation against this use of 17-OHP, clinicians, state Medicaid programs, and MCOs may want to evaluate the evidence and reevaluate their approach to its use.

However, there are still unanswered questions, and ongoing research may demonstrate whether there might be a subpopulation of people for whom this treatment could be useful.[42] Therefore, maternity care providers may choose to individualize their approach to preterm birth prevention. ACOG and SMFM recommend shared decision-making regarding the use of progesterone to make an informed decision for each individual. MCOs with current policies and quality initiatives that include incentivizing or otherwise promoting the use of 17-OHP for prevention of preterm delivery may want to disseminate information about the new evidence to their members and clinicians.

This report is dedicated to Cindy Pellegrini, a former IMI committee member and champion for maternal child health, especially the prevention of preterm birth, in the Medicaid population.

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