

Preventing Preterm Birth Through Progesterone:

How Medicaid Can Help Increase Access



May 2016

Background

The burden of preterm birth^I on the U.S. healthcare system is well documented. Pre-term birth is the leading cause of infant morbidity and mortality, and accounts for roughly 11.5 percent of all births and 50 percent of all pregnancy-related costs. It is also associated with increased probability of long-term health issues including digestive and respiratory problems, sight and hearing loss, cerebral palsy, and developmental and intellectual disabilities.^{II} Factors that can lead to preterm birth include smoking, obesity, drug or alcohol use, certain health conditions (e.g., blood pressure, diabetes, and blood clotting disorders), being pregnant with multiples, and improper birth spacing (i.e., becoming pregnant too soon following previous birth).

The Role of Medicaid

Medicaid agencies, which annually pay for nearly half of births nationwide^{III}, are responsible for a significant share of the burden of at-risk births. An analysis of preterm births and low-birth-weight births in Medicaid found that one in eight Medicaid-covered babies is born premature, and that Medicaid costs for premature or low-birth-weight infants were more than nine times as high as those for uncomplicated births (\$13,729 and \$1,498, respectively). Further, when matching mothers and babies, total Medicaid payments were \$19,971 if the baby was premature or of low birth weight, roughly \$14,000 more than the average cost for the pair when there was an uncomplicated delivery.^{IV} High costs for preterm births and other high-risk births are typically related to services provided through neonatal intensive care units—often referred to as NICUs.^V

In light of the impact on Medicaid-covered lives and the high costs associated with preterm births, state Medicaid agencies are pursuing various strategies for improving the rate of babies born to full term. Progesterone is one such method that has been proven to safely reduce the occurrence of preterm birth, and a strategy that many Medicaid agencies are increasingly covering and promoting through statewide interventions.

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Overview of Progesterone Use to Prevent Preterm Birth

A naturally occurring hormone, progesterone can be synthesized and administered as a weekly injection, a vaginal cream, or suppository. Progesterone administered through intramuscular injections, commonly referred to as 17-alpha-hydroxyprogesterone capote (or 17P), has been found to reduce the risk of recurrent preterm birth by up to 42 percent in women with singleton pregnancies (pregnancies where one fetus develops).^{VI} Analyses tracking the use of 17P during pregnancy have found that it costs between \$200 and \$440 per birth for the full course of the drug.^{VII}

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal and Fetal Medicine have recommended 17P use in women with singleton pregnancies with a prior spontaneous preterm singleton birth since 2008. As of August 2015, there is only one Food and Drug Administration (FDA) approved brand of 17P on the market—Makena. A generic version of 17P can also be produced by a licensed compounding pharmacy. Vaginal progesterone is also available as both a generic and branded FDA-approved drug and like the intramuscular version, can also be compounded.

In 2012, ACOG and the Society for Maternal and Fetal Medicine released updated clinical recommendations reaffirming their recommendations regarding 17P and further recommending the use of

vaginal progesterone for first-time pregnant women or women without a previous preterm birth, with singleton pregnancies and premature cervical shortening in the second trimester.^{VIII} Appropriate use of vaginal progesterone in women who meet these criteria has been found to reduce the risk of preterm birth by up to 50 percent.^{IX} Preterm birth presents complications for one in every eight births, and many of these complications could be mitigated through the use of progesterone-based treatment.^X Research has also shown that the use of I7P for women with high risk of a preterm pregnancy can result in a significant reduction in the rate of infant admission to NICUs.^{XI}

Federal Medicaid Policies Regarding Progesterone and Compounded Drug Products

There is limited federal Medicaid guidance from the Centers for Medicaid and Medicare Services (CMS) that specifically addresses coverage of I7P and/or vaginal progesterone, but Medicaid prescription drug regulations allow for the coverage of branded, generic and compounded synthetic progesterone. State Medicaid agencies typically reimburse for any FDA-approved drug, such as Makena or branded vaginal progesterone, as long as the physician prescribes the drug for its FDA-approved usage,^{XII} and the vaginal progesterone is administered in an inpatient or outpatient setting^{XIII}. Further, the manufacturers of the branded version of I7P and at least one manufacturer of vaginal progesterone participate in the federal Medicaid drug rebate program. As such, state Medicaid agencies are generally required to provide coverage for these drugs in exchange to access to the rebate funding.^{XIV}

States have flexibility regarding the coverage of compounded drug products, such as compounded I7P and vaginal progesterone. (See pg. 4.) Medicaid agencies can opt to cover compounded drugs under their prescription drug benefit. Regulations differ, however, depending on whether the compounded drug product contains “active pharmaceutical ingredients” (APIs). APIs are defined by the FDA as



“any substance that is represented for use in a drug and that, when used in manufacturing, processing, or packaging of a drug, becomes an active ingredient.”^{XV} APIs are not generally considered a covered outpatient drug, as defined by the Medicaid program, which has led to confusion among states as to whether a compounded drug containing an API, such as compounded progesterone, can be covered under Medicaid. As clarified in a CMS notice, states are permitted to cover compounded drugs in their State plan if the coverage is related to another service category (e.g., home health, nursing, or other practitioner).^{XVI} CMS also notified states that compounded drugs can also be covered as a pharmacy service when they are included in an extemporaneously compounded prescription (See pg. 4.), is prescribed by an authorized medical provider, and is dispensed by an authorized pharmacy provider.^{XVII} Medicaid coverage of progesterone remains unclear and varies across states. Indeed, state Medicaid agencies differ in whether they consider compounded progesterone a pharmacy or medical benefit. (See pg. 4 and Table 1, pg. 6.)

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Major Causes of Confusion in Coverage of Branded and Compounded Progesterone

Two events in particular caused confusion for states regarding which forms of progesterone that are reimbursable under Medicaid: (1) the introduction of an FDA-approved brand of 17P (Makena) into the market; and (2) a 2012-2013 Meningitis outbreak linked to compounded drugs. This confusion has resulted in variability among states on Medicaid coverage of progesterone.

Branded Versus Compounded 17P

Even though progesterone has had FDA approval for over four decades, it was not until February 2011 that the FDA approved a branded form of 17P, known as Makena, for the reduction of the risk of preterm birth in women with a history of preterm birth. Makena's entrance into the market was immediately controversial due to its high, initial cost (\$1,440 per injection, \$30,000 per pregnancy) and the attention it brought to the practice of compounding 17P. Prior to Makena, 17P access was limited to the drug as compounded by a pharmacist in a certified compounding pharmacy.

KV Pharmaceuticals, the producer of Makena, reduced the list price of Makena by nearly 55 percent in April 2011 in response to public backlash and FDA pressure. Further reducing costs for states, state Medicaid agencies are also able to obtain a 23.1 percent price reduction due to the drug's inclusion in the federal Medicaid drug rebate program.

In spite of these advancements, compounded 17P was questioned in October 2011 when KV Pharmaceuticals sent a letter to the FDA claiming to have identified variability in the purity and potency of both bulk and compounded 17P products, essentially questioning the viability of compounded progesterone and ostensibly promoting Makena (FDA Notice November 2011). In response, the FDA conducted its own analysis of samples of compounded 17P, and did not identify any major safety problems. In the years following the release of FDA statements confirming safety, compounding pharmacies have continued to produce 17P, and as will be discussed below, many state Medicaid agencies have reimbursed for the compounded product.

Compounded Pharmaceuticals and the Meningitis Outbreak of 2012-2013

The issue of compounded pharmaceuticals was once again in the spotlight during 2012, when a Meningitis outbreak resulted in a number of deaths and was linked to contaminated compounded drugs administered by a compounding center.

Response to the outbreak resulted in an increased scrutiny and led to the signing of the Drug Quality and Security Act of 2013, which added Food, Drug and Cosmetic Act (FDCA) oversight provisions of all compounded drugs, which includes unbranded 17P.

Despite the new oversight, compounding remains a largely state-regulated industry. Certain states have passed new laws or are considering revisions to laws and regulations for compounding pharmacies, in part due to the recent events. As a result, these changes have affected and in many states, limited the ability to provide Medicaid reimbursement of non-branded (compounded) 17P.

State-specific Medicaid Coverage of I7P and Vaginal Progesterone

Although a complete state analysis of progesterone coverage under Medicaid has not been conducted, progesterone to prevent preterm birth, either in the form of intramuscular I7P or vaginal progesterone, is covered by at least 15 Medicaid agencies, including Alabama, California, Colorado, Indiana, Kentucky, Louisiana, Michigan, Mississippi, New York, North Carolina, Ohio, South Carolina, Texas, Virginia and Wisconsin.

State Medicaid agency reimbursement of I7P or vaginal progesterone is varied, and is influenced by many factors such as state regulatory oversight of compounding pharmacies, policies regarding coverage of generic and branded drugs, and the cost of particular therapies. Variation also exists regarding the types of providers that can bill for progester-



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one, the settings in which it can be administered, prior authorization policies, and whether progesterone to prevent preterm birth is considered a medical or pharmacy benefit.

State Strategies to Increase Progesterone Access and Treatment

While Medicaid agencies have had the ability to cover progesterone to prevent preterm birth for several years, treatment levels remain low due to the relatively new nature of the research demonstrating its efficacy. In many states, this has meant progesterone is not yet the standard of care for at-risk women. A growing number of Medicaid agencies are implementing progressive strategies in order to increase the level of progesterone treatment and reduce the number of preterm births and high costs associated with those births. The following approaches provide examples for other states that may seek to increase access to progesterone.

Innovative Reimbursement Models

New reimbursement models can support further growth of progesterone use through incentives to increase both plan and provider awareness of the efficacy of the drug.

In 2014, Louisiana established the nation’s first statewide pay-for-performance program for I7P and is considered a leader with this approach. Managed care organizations that serve Medicaid

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Table I. Medicaid Coverage of I7P and Vaginal Progesteroneⁱ

State	Medicaid reimburses for:			Prior Authorization (PA) Required
	Compounded I7P	Branded I7P: Makena	Vaginal progesterone (all types)	
AL	X	X		
CA	X	X		Yes. PA required for compounded I7P. To be dispensed, providers are required to provide medical justification establishing its clinical necessity.
CO	X			No. No PA is required but clinical records must document that the client meets all eligibility criteria for coverage of I7P for the prevention of preterm birth.
IN	X	X		Yes. PA for Makena requires prescriber confirmation that the member is pregnant with a history of preterm delivery and receiving the product to prevent preterm delivery.
KY	X	X		Yes. For Makena, must show that a woman has had a bad reaction to the compounded version – or had previously tried it and delivered prematurely.
OH	X	X	X	Yes and No. Pharmacy claims (patient to administer in the home): Yes, compounded or prior vaginal progesterone preferred Medical claims (administered in the provider office): No Branded I7P: Varies by MCO. Branded Vaginal Progesterone: Varies by Medicaid MCO. Compounded I7P: Varies by Medicaid MCO. Compounded vaginal progesterone: Varies by Medicaid MCO.
LA	X	X	X	Yes. PA for Makena.
MI			X	
MS	X*	X*		Yes. Provider must complete a Certificate of Medical Necessity for I7P Injections.
NC	X	X	X	Yes. Some formulations of vaginal progesterone require PA.
NY	X	X		Yes. MMC and FHPlus plans may require preauthorization of these drugs based on medical necessity and cost effectiveness.
SC	X	X		Yes and No. PA not needed in FFS Medicaid or Medical Home Network. Medicaid MCOs use a Prior Authorization Request form for both Makena and I7P.
TX	X	X		Yes. Doctor show there is no pharmacy able to make or deliver the drug to their offices to get coverage.
VA		X*	X (compound)*	
WA				Yes and No. PA not required for compounded I7P. PA required for Makena. PA for reimbursement to a dispensing pharmacy for Makena requires documented medical justification of the reason an individually compounded form of I7P is not appropriate.
WI	X	X		Yes. Doctors explain why a woman might need compounded drug

*Mississippi provider manual does not differentiate between branded or compounded I7P.

ⁱThis table was developed by performing an internet search for state policies related to Medicaid reimbursement of various progesterone products (compounded I7P, branded I7P, and vaginally-administered progesterone). The chart represents publicly available information as of September 2015. Part 2 of this issue brief (forthcoming) will include additional information regarding state reimbursement for I7P.

patients in the state are ineligible for full payment by the state for billed expenses unless they meet a progesterone-specific managed care measure that requires an increase from five percent to 20 percent of I7P usage rate in its eligible pregnancy population. The program places a total of \$2.5 million in reimbursement at risk, with each of 5 plans subject to losing up to \$250,000 for failing to meet the measure.^{xviii} Data is not currently available on the success of this initiative, but should become available in the coming year.^{xix}

In addition to the work being done related to the pay-for-performance measure, Louisiana also had a Medicaid State Plan Amendment approved in July of 2015 that increased the reimbursement rate for compounded I7P from \$17 per dose to \$69 per dose.^{xx} The state hopes that increased reimbursement will incentivize providers to order and prescribe the drug to at-risk women.^{xxi}

Allowing for Home Administration

One of the largest patient barriers for use of I7P is that the drug must be administered weekly, which has traditionally been done in a medical office. In some states, Medicaid only reimburses for I7P or vaginal progesterone administered in a particular setting or provided by a particular provider-type. This approach presents several barriers to progesterone use including for women, particularly those who are low-income, in making weekly appointments, provider administration and being lost to follow-up. In states where progesterone is considered a pharmacy benefit, such as Louisiana, the re-

imbursement model provides the opportunity and flexibility for states, plans and providers to move to home administration, which would help increase access to progesterone for low-income women.

State policies on prior authorization (PA) can also limit access to home administration of progesterone. Some states show preference for office administration by not requiring PA if progesterone is provided in a medical office.

Several states are beginning to address this barrier with innovative programs:

- In **South Carolina**, 90 percent of Medicaid births are covered by one of the state's five MCOs, each of which contract individually with one to two home nurse administered companies for providing home I7P administration.
- In **Louisiana**, all five Medicaid MCOs either reimburse for home health agency administration of I7P or are in the process of instituting this coverage. In these cases, home health nurses administer I7P.^{xxii}
- **Iowa** has convened an Obstetrical Care State-wide Task Force with Medicaid serving as one of the primary members. The task force has developed an "Obstetrical Care Statewide Strategic Plan" that includes the goal of eliminating the patient barrier to appropriate progesterone and the creation of a protocol recommendation for home health nurse administration of progesterone by 2018. To date, the task force has been able to eliminate the prior authorization barrier that had been in place with Medicaid related to coverage for Makena. The state was also able



to work within the existing Medicaid policy to include administration of I7P by home health nurses as part of the maternal and child health services. With Iowa's transition to managed care in Medicaid effective April 1, the state will be continuing to work with Medicaid and the managed care organizations to ensure the barriers to progesterone access remain lifted for Iowa's Medicaid members.

- In **Ohio**, Medicaid reimburses for home health delivery of I7P.

Identifying At-Risk Moms

With the significant costs and health complications related to pre-term birth, universal screening of pregnant women for risk factors has been recommended as a cost-effective and important component of pre-partum treatment. In 2012, ACOG and SMFM included expanded pre-term birth risk screening in their updated clinical guidelines. Several states have identified the issue of screening as a barrier to increased progesterone utilization and have incorporated comprehensive risk assessments in their approach to care of pregnant women.

- **North Carolina.** The state has a quality improvement initiative focused on I7P utilization, which is a part of its Pregnancy Medical Home program. The program launched in 2011 and now includes the majority of maternity care providers in the state, including over 380 practices and 1,800 individual providers. To participate in the Pregnancy Medical Home model, providers must agree to offer and provide I7P to all eligible patients. State officials have indicated that outside of the increased access, the inclusion of progesterone in the Pregnancy Medical Home program has increased provider awareness of the benefits of progesterone.
- **Ohio.** The state's Departments of Medicaid and Health are funding a Progesterone Quality Improvement Project that aims to reduce the rate of premature births in Ohio by increasing the screening, identification and treatment of pregnant women who are at-risk for pre-term

birth and will benefit from progesterone. The project's goal is to reduce the rate of premature births in Ohio at less than 37 weeks by 10 percent and births at less than 32 weeks by 10 percent by July 1, 2016.

- **New York:** As part of the state's Medicaid Prenatal Care Standards, all pregnant women are expected to receive an assessment, which includes risk for preterm birth and eligibility for progesterone per ACOG recommendations.

Conclusion

Increased use of progesterone for at-risk mothers represents an evidence-based approach to preventing dangerous and costly preterm births as well as reducing NICU admissions. Medicaid, as a payer of a disproportionate percentage of these births, is an important stakeholder and partner in developing policies and reimbursement strategies that increase women's access to progesterone and support healthier moms and babies.

Several states have begun to implement new models that increase identification of pregnant women at-risk for preterm birth, support the ability to administer I7P injections, increase access to progesterone (e.g., home-based administration), and develop cost structures that incentivize providers and payers to provide progesterone. As these models mature, additional lessons learned will likely be identified for spread across states seeking to implement similar initiatives. As demonstrated by the research and early lessons from the states, efforts to increase progesterone coverage and use can lead to healthier babies and help avert Medicaid costs related to medical interventions for high-risk moms and preterm births.

Author's Note:

“Preventing Preterm Birth Through Progesterone: How Medicaid Can Help Increase Access” is a joint publication of the National Academy for State Health Policy (NASHP) and the National Institute for Children’s Health Quality (NICHQ). This brief was written by Tamara Kramer and Kimm Mooney of NASHP. The authors thank Karen VanLandeghem of NASHP and Elaine Fitzgerald and Zhandra Ferreira-Cesar Levesque of NICHQ for their guidance and support in the development of this brief.

Acknowledgement:

This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) (under grant # UF3MC26524, Providing Support for the Collaborative Improvement and Innovation Network (CoIIN) to Reduce Infant Mortality, \$2,918,909, no NGO sources). This information or content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.

- ⁱ Preterm birth is generally defined as a birth that occurs prior to 37 weeks of gestation. A pregnancy is considered full-term when a baby is delivered after 40 weeks of gestation.
- ⁱⁱ Medicaid Health Plans of America: Center for Best Practices, “Preterm Birth Prevention: Evidence-Based Use of Progesterone Treatment, Issue Brief and Action Steps for Medicaid Health Plans”, November 2014. Available at: http://www.mhpa.org/_upload/PTBIssueBrief111714MHPA.pdf.
- ⁱⁱⁱ Medicaid Covered Births, 2008 Through 2010, in the Context of the Implementation of Health Reform. Markus, Anne Rossier et al., Women’s Health Issues, Volume 23 , Issue 5 , e273 - e280.
- ^{iv} *Id.*
- ^v *Id.*
- ^{vi} *Id.*
- ^{vii} Norwitz ER, Caughey AB. Progesterone Supplementation and the Prevention of Preterm Birth. *Reviews in Obstetrics and Gynecology*. 2011;4(2):60-72.
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- ^{xii} Englehardt, Christin. “Getting Insurance Coverage for a Newly Approved Drug”, 2014.
- ^{xiii} Cahill, Alison G. et al. “Universal Cervical Length Screening and Treatment with Vaginal Progesterone to Prevent Preterm Birth: A Decision and Economic Analysis.” *American journal of obstetrics and gynecology* 202.6 (2010): 548.e1–548.e8. PMC. Web. 21 Sept. 2015.
- ^{xiv} See 42 U.S.C. 1396r-8.
- ^{xv} See 21 CFR 207.3.
- ^{xvi} The June 2012 CMCS Informational Bulletin on Compounded Versions of 17P can be viewed here: <http://medicaid.gov/Federal-Policy-Guidance/Downloads/CIB-2-06-15-12.pdf>. An accompanying Question & Answer Document produced by the U.S. Food and Drug Administration can be found here: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310215.htm>.
- ^{xvii} CMS notice 155.158.
- ^{xviii} Association of State and Territorial Health Officers, “Louisiana Public Health and Medicaid Team Up to Increase 17P Access and Reduce Preterm Birth Rate”, 2015. Available at: <http://www.astho.org/Maternal-and-Child-Health/Louisiana-Public-Health-and-Medicaid-Team-Up-to-Increase-17P-Access-and-Reduce-Preterm-Birth-Rate/>.
- ^{xix} *Id.*
- ^{xx} CMS’ approval of the 17P rate increase can be viewed here: <http://www.dhh.state.la.us/assets/medicaid/StatePlan/Amend2015/15.0015CMSApproval.pdf>.
- ^{xxi} Association of State and Territorial Health Officers, “Louisiana Public Health and Medicaid Team Up to Increase 17P Access and Reduce Preterm Birth Rate”, 2015. Available at: <http://www.astho.org/Maternal-and-Child-Health/Louisiana-Public-Health-and-Medicaid-Team-Up-to-Increase-17P-Access-and-Reduce-Preterm-Birth-Rate/>.
- ^{xxii} Aetna’s policy on 17P reimbursement and home administration in its Louisiana Medicaid Managed Care program can be viewed here: <http://www.aetnabetterhealth.com/louisiana/assets/pdf/providers/17P-Makena-LA.pdf>