OPTIMIZING USE OF LOW-DOSE ASPIRIN AND PROGESTERONE (17P) FOR PRETERM BIRTH PREVENTION

A TOOLKIT FOR PRENATAL CARE PROVIDERS IN CALIFORNIA

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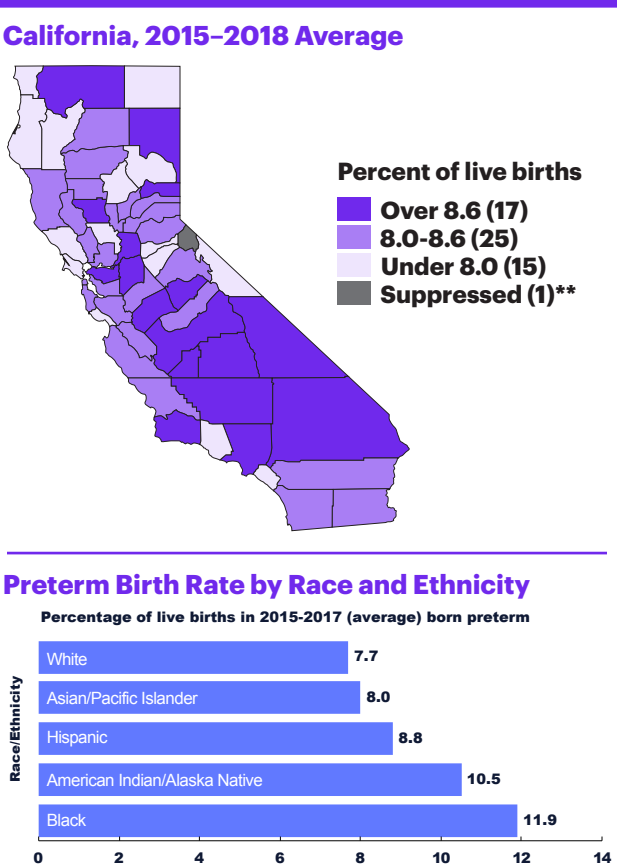
INTRODUCTION

Preterm birth (birth before 37 weeks of pregnancy) is a reflection of America's health. It contributes to infant death within the first year of life, childhood disease and disability, and adult chronic disease. After steadily declining from 2007-2014, the preterm birth rate in the U.S. increased for the fourth year in a row to 10.0% in 2018. Each year in the U.S., approximately 1 in 10 babies are born preterm (380,000 babies) and more than 22,000 infants die[1]. In addition to the human toll, the societal cost of premature birth is at least $25.2 billion per year.[2]

In California, the preterm birth rate in 2018 was 8.7%, and has been steadily rising since 2014. Preterm birth rates vary by county and by race; the highest rates are seen in Black and American Indian/Alaska Native populations (Figure 1).

FIGURE 1. Preterm birth in California



Significant disparities exist for women of color and their babies across the state of California. Higher rates of preterm birth are seen in inland and more rural counties. Black and American Indian/Alaska Native women experience the highest rates of preterm birth in California. Source: National Center for Health Statistics, 2015-2018 Final Natality Data.

Our unequal society has negative consequences for health, and there are significant disparities between birth outcomes of White women and those of Black, American Indian/Alaska Native and other women of color. Although declines in the infant mortality rate have been observed for both Black and White infants over the past few decades, the 2013 infant mortality rate for Black infants in the U.S. was higher than the rate for White infants 30 years ago.[3] In the U.S., women of color are up to 50% more likely than White women to give birth prematurely, and their children can face a 130% higher infant death rate than children born to White women.[1]

Socioeconomic factors and health behaviors, such as education, income, health insurance coverage, and smoking do not fully explain racial disparities in preterm birth.[4-6] Black women consistently have higher preterm birth rates than their White counterparts regardless of education attainment and income.[7] Furthermore, Black women are more likely to die from pregnancy-related conditions than White women.[8] Researchers have identified exposure to racism, disrespectful care, and chronic toxic stress compounded by socioeconomic challenges, such as unemployment and unstable housing as some of the reasons for the racial disparities in health outcomes.[9-13] It will require significant time and work at many levels to make improvements to these social and structural determinants of health. March of Dimes is committed to collaborating with partners to alleviate the negative impacts of racism and inequities. While this work is underway, we must also optimize the use of clinical interventions we currently have to decrease preventable preterm birth.

There are only a few clinical treatments that have been found to effectively improve maternal and birth outcomes among women with known risk factors. Two of these evidence-based interventions are 17 alphahydroxyprogesterone caproate (17P), a synthetic form of progesterone, for recurrent preterm birth prevention, and low-dose aspirin to prevent preeclampsia, which accounts for 15% of preterm births in the U.S. each year.[6] Unfortunately, both interventions are underutilized, especially for those pregnant people who need it the most.[14-18]

The goal of this toolkit is to provide strategies for optimizing the use of 17P and low-dose aspirin among eligible pregnant patients. Studies have shown

a 34% reduction in recurrent preterm birth with use of 17P and 24% reduction in preeclampsia with use of low-dose aspirin.[14,15] This toolkit provides resources and tools for prenatal care providers, nursing staff, and clinic and office managers to expand equitable access to and utilization of these two prevention opportunities in California.

To maximize the number of eligible patients receiving these treatments, timely screening and identification, and patient-centered, motivational counseling is needed. The development of this toolkit has been led by **March of Dimes California** and informed by the work of the **California 17P Workgroup**.

The toolkit will highlight the following key practices for preterm birth prevention.

- Part 1: Strategies for identifying patients at risk for preterm birth
- Part 2: Progesterone for preterm birth prevention
- Part 3: Low-dose aspirin for preeclampsia prevention
- Part 4: Organizational culture change and clinic education

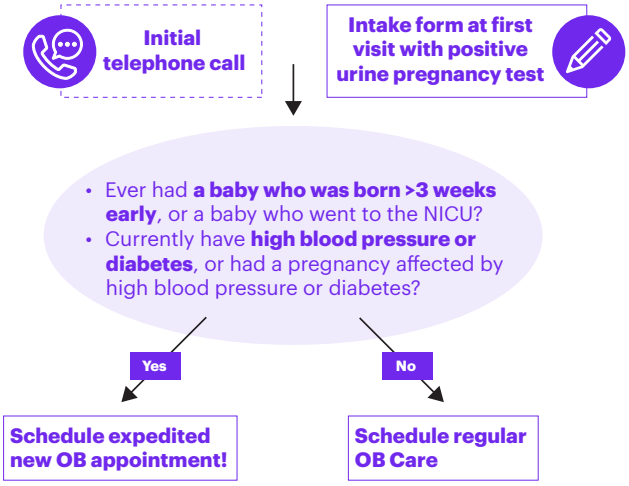
PART 1. STRATEGIES FOR IDENTIFYING PATIENTS AT RISK FOR PRETERM BIRTH

Early Screening

Screening for preterm birth risk in early pregnancy is crucial because one of the major risk factors for preterm birth is history of a prior spontaneous preterm birth. Maternal history of preterm birth confers a 1.5-2.0 increased risk in subsequent pregnancies.[19, 20]

A 2019 March of Dimes survey conducted with almost 80 obstetric providers in California showed that most patients are screened for a prior preterm birth *during* the first prenatal appointment with their provider. However, screening patients *before* this visit is ideal to facilitate treatment as early as possible for eligible people. Early screening can be done over the phone at the time of scheduling the initial prenatal appointment, or via updated standard intake forms to ensure that the screening questions are asked before the first encounter with the provider (see Figure 2).

FIGURE 2: Triaging patients for preterm birth risk



Telephone Screening

At the time of scheduling the new OB visit, the following questions can be asked:

- "I have two questions to ask you about your pregnancy history, so that we can give you the best possible care.
  - — Have you ever had a baby who was born more than three weeks before your due date, or a baby who was cared for in the neonatal intensive care unit (NICU)?
  - — Do you have high blood pressure or diabetes now or prior to pregnancy, or did you have high blood pressure or diabetes during previous pregnancies?"

If yes to either of these questions, the patient should receive an expedited first prenatal appointment.

Written Screening Questions for First Prenatal Appointment Forms

For written forms, include the two questions above, and consider including the following:

- — Have you ever had a baby who did not go home with you from the hospital?
- — Have you ever received progesterone injections or vaginal progesterone cream?
- — Have you ever been told your cervix was short?
- — Have you ever had a cerclage (stitch) placed in your cervix during a pregnancy?
- — Have you ever had high blood pressure, preeclampsia, or toxemia during a pregnancy?

Postpartum Visit Best Practices:

- Ensure that every patient who experienced a preterm birth or preeclampsia has the opportunity to "debrief" with her delivering provider to ensure she understands any diagnoses and is advised and empowered to share this information with future providers.
- Educate eligible patients about 17P and low-dose aspirin for future pregnancies and the importance of seeking care early.
- Advise patients that waiting 18 months before becoming pregnant again will reduce preterm birth risk. Discuss contraception. (Resource: March of Dimes Health Action Sheet: **"How long should you wait before getting pregnant again?"**)
- Encourage healthy habits (such as exercise, healthy diet, folic acid supplementation, and smoking cessation).

PART 2: PROGESTERONE FOR PRETERM BIRTH PREVENTION

A. Increasing 17P Utilization for Prevention of Recurrent Preterm Birth

Progestins include both vaginal progesterone and 17 alpha-hydroxyprogesterone caproate (17P) in an injectable format. This toolkit is focused on injectable 17P which has been best studied for prevention of recurrent preterm birth. Based on current research, women with a short cervix, but no prior preterm birth history, are eligible to receive vaginal progesterone.

Weekly intramuscular administration of 17P for pregnant women with a previous spontaneous preterm birth has shown to significantly reduce the risk of recurrent preterm delivery by 34%.[14] Data from multiple studies suggest that despite recommendations from national organizations such as the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, there is continued underutilization of 17P for eligible patients.[16,17] Best estimates of 17P utilization in California show 34% penetration, leaving tremendous room for improvement (T. Horton, AMAG email communication, April 2017).

FIGURE 3. 17P treatment cascade

Figure adapted from Stringer EM, Vladutiu CJ, Batra P, et al. Operationalizing 17α-Hydroxyprogesterone Caproate to Prevent Recurrent Preterm Birth: Definitions, Barriers, and Next Steps. *Obstet Gynecol.* 2016;128(6):1397-1402.

Adherence to weekly progesterone treatment remains one of our most important tools to combat recurrent preterm birth, but **many progesterone-eligible patients are not offered 17P or do not complete the treatment**.[16,17] Stringer, et al described the "17P cascade" – critical steps to ensure successful treatment – as depicted in Figure 3.[21]

When prescribing and administering 17P, there are common challenges to address at each step of the treatment cascade:

1. **Attend antenatal care in the 1st trimester:** Lack of insurance prior to pregnancy and lack of patient education after the prior preterm birth to emphasize importance of 1st trimester prenatal care can contribute to low participation in early prenatal care.
2. **Identify as eligible:** Incomplete medical records, gaps in providers' understanding of eligibility criteria and prescribing process, and patients' unawareness of their eligibility can contribute to missed treatment opportunities.
3. **Offer 17P:** The complexities of insurance and prior authorization processes can cause delays in treatment initiation.
4. **Accept 17P:** Patients decline treatment for various reasons including lack of understanding about the treatment benefits and fear or distrust about the medication and its potential side effects.
5. **Receive 17P:** Challenges include difficulty attending weekly injection appointments due to childcare or transportation issues, or inability to take time off from work.

17P Administration

As of August 2020, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) support the use of 17P for prevention of recurrent spontaneous preterm birth in a singleton pregnancy.*[19,22] Algorithms illustrating these published practice guidelines are provided in Figures 4 and 5.

*Guidance from ACOG and SMFM in response to findings from the Makena (17P) PROLONG study can be found here: www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/10/clinical-guidance-for-integration-of-the-findings-of-the-prolong-study and www.smfm.org/publications/280-smfm-statement-use-of-17-alpha-hydroxyprogesterone-caproate-for-prevention-of-recurrent-preterm-birth

- **Discuss 17P with all patients** with a history of a previous singleton spontaneous preterm birth (20 0/7– 36 6/7 weeks) who have a current singleton pregnancy.
- **Initiate treatment** between 16^0 – 23^6 weeks gestation, ideally.
- **Continue 17P injections** weekly until 36^6 weeks gestation or delivery.
- **Emphasize importance of 17P** to your eligible patients and have an open dialogue about their concerns and barriers to obtaining treatment.

"I'm not an MFM. I don't feel comfortable prescribing 17P."
*Advanced practice providers and **all** obstetrical providers can prescribe 17P for their eligible patients! Even if you plan to refer to a high-risk OB provider, as the primary care clinician, you can simultaneously start patient counseling and prescribe 17P to ensure timely initiation of the medication.*

In addition to treating with 17P for prevention of recurrent preterm birth, it is important to screen low- and high-risk patients with cervical length surveillance by use of transvaginal ultrasound assessment. See Figures 4 and 5 for universal and targeted cervical length screening guidelines.

B. Clinic Workflow for 17P

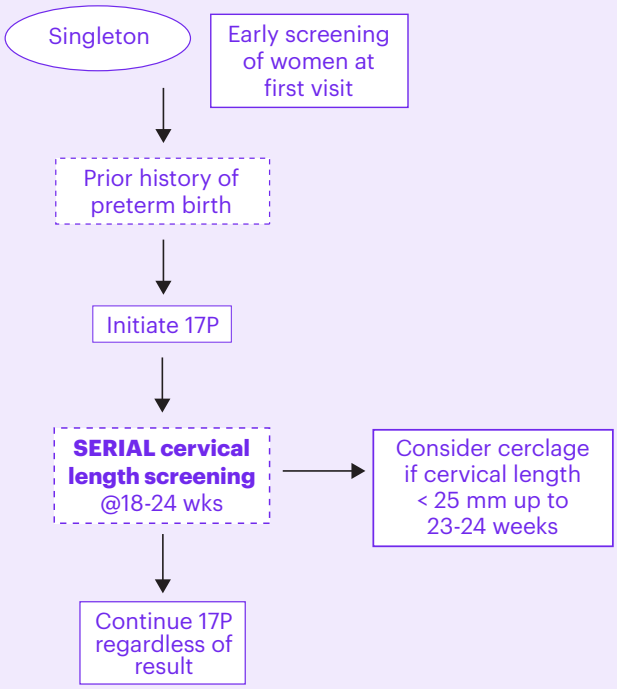
17P is administered weekly as follows:
- **Intramuscular (IM) injection** (several generic formulations available)
- **Makena® subcutaneous auto-injector** (branded formulation)

Challenges for clinics that administer 17P include completing the prior authorization forms in a timely manner, cost to the patient and coordination of weekly clinic visits or home visits for injections. Training dedicated staff to complete prior authorizations and gain familiarity with workflow can improve efficiency. Tips for currently available 17P formulations are included below.

Process and Steps in 17P Prior Authorization and Initiation

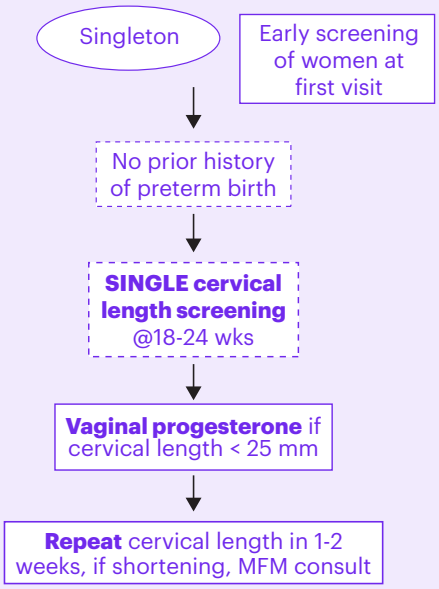
Both the IM and auto-injector formulations of 17P are considered "specialty injectables" and will require a prior

FIGURE 4. Algorithm: patients with prior history of spontaneous singleton preterm birth



Source: Society for Maternal-Fetal Medicine. Preterm Birth Toolkit. https://www.smfm.org/publications/231-smfm-preterm-birth-toolkit

FIGURE 5. Algorithm: patients with no prior history of preterm birth



Source: Society for Maternal-Fetal Medicine. Preterm Birth Toolkit. https://www.smfm.org/publications/231-smfm-preterm-birth-toolkit

authorization by most insurers in California. Any patient co-pay, co-insurance, or deductible expense is dependent on their insurance coverage. The patient's insurance plan also determines the pharmacy that is assigned to fill the prescription. The medication can be sent to the provider office or directly to the patient.

For prior authorization purposes, consider using the following ICD-10 codes

- O09.212 Supervision of pregnancy with history of preterm labor, second trimester
- O09.213 Supervision of pregnancy with history of preterm labor, third trimester
- O09.219 Supervision of pregnancy with history of preterm labor, unspecified trimester

Medi-Cal: In California, patients with Medi-Cal coverage receive 17P (generic IM or Makena Auto-Injector) at no cost to the patient (i.e., no co-pay). Health plans may require additional clinical information to determine medical necessity for the branded product. Provider offices can follow the steps as outlined below to obtain either 17P formulation for patients with Medi-Cal.

If Prescribing Generic IM Progesterone:

- Contact the patient's insurance provider (either private insurance or Medi-Cal) to verify coverage, ascertain if injections at home are covered, determine cost to patient (for private insurance), and start the prior authorization process for that plan.
- Continue to follow-up with the insurance plan every 2 days until the medication is approved to ensure timely initiation.
- Once the medication is approved, send the prescription to the pharmacy that the payer has identified to dispense the medication.
- It is important to determine what the insurance plan's preferred pharmacy is (not the patient's preferred pharmacy) because if a non-preferred pharmacy is used, the patient will pay more than is necessary, often the full cost of the drug (similar to what happens if a patient uses an out-of-network provider). Additionally, a non-preferred pharmacy may not have a reliable system in place to notify you that they are unable to dispense the medication.
- For Medi-Cal fee-for-service patients, submit a Treatment Authorization Request (TAR) to Medi-Cal which serves as a prior authorization.

If Prescribing Makena Auto-Injector:

Providers can contact Makena Care Connection to obtain assistance with prescription and prior authorization processing for Medi-Cal and commercial insurance. Makena Care Connection (MCC) can be called at (800) 847-3418 and provides the following:

- patient benefits investigation and prior authorization processing; follow-up with payer and pharmacy to ensure timely initiation of medication
- processing prescriptions through the payer-preferred pharmacy
- checking patient benefit coverage for home healthcare administration, and if covered, coordination of home healthcare administration
- language translation services in 250 languages

To begin the process, follow instructions on the Makena Referral/Prescription Form. This form can be accessed from **www.makenahcp.com/Rx** . Here are some tips to streamline the process:

1. It is important to fully complete the form. Ideally, you will have the patient sign the form before faxing, but fax it anyway if she has not yet signed it (1-800-847-3413). MCC will work with the provider and patient to ensure the form is signed.
2. If a woman needs to start the medication immediately, enter today's date in the "desired start date" section of the form. This will trigger MCC to expedite the process.
3. If your patient is difficult to reach by phone, make a note when completing the form. Prior to approving, the Makena Care Connection team must speak with the patient. You can call the MCC team while faxing in the prescription form so that the patient can speak with customer assistance right away.
4. The provider should provide a specific contact name, direct phone number and email address to facilitate and expedite communication from MCC to the office.
5. For patients with Medi-Cal fee-for-service coverage, the TAR can be sent directly to Makena Care Connection to process.

(continued on page 7)

6. For patients who are uninsured: The Makena Patient Assistance Program will help to obtain medication for patients without insurance. On the Makena Referral Form, in the patient information section, there is a box that should be checked that states: "Patient does not have insurance and should be evaluated for patient assistance program."
7. Makena educational materials are available in several languages: **makena.com/resources**.

C. Tracking High-Risk Patients and Outcomes

Think about how you manage other patients with high-risk conditions complicating pregnancy (e.g., diabetes, hypertensive disorders) and create similar workflows for patients at-risk for preterm birth.

- Once patients are identified, flag their chart with ICD-10 codes such as "History of preterm delivery, currently pregnant". In the EMR, utilize sticky notes, episodes or problem-based charting to track progress.
- Many clinics use new OB "facesheets" or worksheets to facilitate scheduling of appointments. Consider adding preterm birth information to these sheets.
- Consider keeping a paper or electronic log book for tracking 17P patients (see Figure 6). Patients who miss 17P injection appointments should be contacted to reschedule and address any barriers.
- Consider tracking outcomes and gestational age at birth and share data with staff every 3-6 months for reinforcement and follow-up.

D. Person-Centered Care and Patient Counseling

Patient adherence to treatment recommendations can be affected by the quality of the relationship they feel they have with their provider. Establishing a positive clinician-patient relationship early on can have a significant impact on adherence over the many months a patient is treated with 17P.

In 2019, March of Dimes conducted a focus group in Los Angeles, California with Black women who had experienced a preterm birth. Most participants reported that they did not receive education about being at higher risk for a subsequent preterm birth nor were they informed about or prescribed 17P or low-dose aspirin, even if eligible for these treatments. Women reported that they only became aware of their higher risk status when they were admitted to the hospital for delivery.

Goals of patient counseling are to:

- Clarify patient history of preterm birth.
- Discuss the definitions of preterm birth by gestational age. Patients who had a late preterm birth in the past may be less likely to accept 17P, so it is important to emphasize that a subsequent preterm birth could be earlier.
- Talk about the difference between birthweight and gestational age.
- Combat beliefs about repeat preterm birth being inevitable. Emphasize that since there is a higher risk for delivering early, it is crucial to keep all appointments for 17P shots and routine prenatal care.
- Emphasize 17P shots can reduce risk of another preterm birth significantly.
- Ensure you allow time to address patients' questions and concerns. Adherence will improve as a patient's understanding about treatment increases.

Furthermore, the focus groups identified distrust of the health care system as a significant stressor when seeking care during pregnancy. Factors leading to this distrust include racism, disrespect, and previous poor experiences of their own or a loved one with the health care system. To deliver respectful, patient-centered care, it is critical

FIGURE 6. Example 17P tracking log

Name	MRN	Age	G/P	EDD	GA at prior birth	Date screened	Date offered 17P	First dose (GA)	Cervical lengths y/n	Insurance	Subsequent doses	Notes
Patient Name	1234	28	2/0101	2/29/20	33 wk	6/7/19	12w2d	9/3/19 (16w1d)	y	Medi-Cal	9/10, 9/17	Prefers walk in clinic, Tuesdays

that health care providers build trust through listening, acknowledging patient and family member experiences, and empowering patients through shared decision-making.

Decreasing barriers to initiation and completion of treatment is important to help all eligible patients receive and complete 17P treatments. Advocate for your patients and help them overcome common 17P barriers using the following recommendations.

- Late to prenatal care: 17P can be started up to 24 weeks.
  - Goal is to initiate at 16 -20 weeks, but patients late to care or who occasionally have no show visits should still be encouraged to start 17P.
- Home visits for difficulty in keeping a weekly appointment:
  - Some Medi-Cal managed care plans and commercial insurance plans cover home health visits for 17P shots. As you start the prior authorization process, find out if this service is available for your patient.
- For transportation concerns:
  - Medi-Cal offers transportation benefits which patients can use to travel to the clinic for weekly shots.
- Offer nurse walk-in visits for 17P administration, and consider early/late hours once a week to accommodate patients' schedules.
- Alleviate child care concerns by allowing children at injection clinic visits.
- Injection site pain and discomfort can be reduced using the following approaches:
  - As possible, have the same person administer 17P in the clinic and ensure they are well trained.
  - The pain of IM injections can be minimized by applying pressure to the area of administration prior to giving the injection and administering the drug slowly.
  - For any injection, applying ice before or after can help with post injection pain.
  - Oral Benadryl can be given before or after injection site reactions are noted.
- Strengthen the provider – patient relationship.
  - Support adherence by emphasizing trust and communication.
  - Use a shared decision-making approach or provide tools to help patients make informed decisions about the benefits/risks of 17P.
  - Maintain continuity of care and consistently emphasize the safety and efficacy of 17P.
  - Praise patients for coming and continuing with injections. *"I am proud of you for doing everything you can to have a healthy pregnancy!"* Be a coach and support progress.

A Patient's Perspective: Raena's Story

After a stillbirth and cervical issues in my second pregnancy, my doctor didn't need to do much to convince me to take 17P. She presented it as an option that would give me the best chance at a full-term pregnancy. I had some questions about how progesterone works to prevent preterm labor and the side effects of taking it. My doctor tried to explain, but her wording wasn't very easy to understand for someone without a medical background. However, I appreciated her informative approach compared to the fear tactics and coercion from my previous physician.

A barrier to 17P was getting injections from a specialist quite far from my home and traveling there weekly in a three hour round-trip. I was also on strict bedrest and I had to get a ride. Another barrier was not having the relationship with the specialist that I did with my doctor. Eventually, I became comfortable with the nurse who administered the shot. The nurse made an effort to form a relationship with me. She asked about how this entire process had been for me and how I was holding up. We'd talk about our families and how our weeks were going. It made our interactions less transactional and more familiar. It helped that she wasn't just fishing for information about me but also sharing about herself. That way we got to know each other and find commonalities and shared experiences.

It's sometimes difficult to rely on science with the long history of obstetric racism that is still alive in the U.S. But, I'm a loud and proud spokesperson for 17P because without it, I don't believe my beautiful 4- and 7-year old children would be here.

17P Patient Education Talking Points

- Progesterone shots may help prevent preterm birth for some women who have had a premature birth before.
- Progesterone is a hormone that helps your uterus grow during pregnancy and keeps it from having contractions. If you've had a prior premature birth (before 37 weeks of pregnancy) progesterone shots called 17P may help prevent another early birth if both of these describe you:
  - You had a spontaneous premature birth when you were pregnant with just one baby. Spontaneous means labor began on its own, without drugs or other methods. Or the sac around your baby broke early.
  - You're pregnant with just one baby. Progesterone shots don't work if you're pregnant with twins, triplets or more.
- Since you have had a prior preterm baby, your chance of this baby coming early is higher. And, it is possible that this baby could be born even earlier than your other baby. This is true even if you've had a full term baby more recently than your earlier preterm baby.
- Every day your baby is in the womb is important for the development of their organs like the brain and lungs. Babies born preterm can have problems that are so serious that they may not survive. In addition, some preterm babies may have problems with learning, breathing, and/or vision.
- Progesterone shots are given to you once a week starting at 16 weeks of pregnancy until you reach 37 weeks.
- Progesterone can lower the chance of a preterm birth by one-third (33%).
- Studies show that 17P is safe for you and your baby.
- You can get the shots here in the clinic/office or it may be that a nurse can come to your home or work to give them to you. We know that getting to weekly appointments can be challenging and will work with you and your insurance provider to find the best option for you.
- You may have some discomfort at the injection site (the place on your body where you get the shot). We will use ice and other techniques to help reduce that discomfort.
- Your health insurance may help pay for the shots. (Note: Medi-Cal patients will have no cost to them). You may get a generic form, or may get brand name shots called Makena®.
- 17P stands for 17 alpha-hydroxyprogesterone caproate. Look for this name on the product label.
- Depending on which formulation you are prescribed, you will get the shot in the back of your arm (Auto-injector) or on your outer thigh/gluteal area (IM).
- Call your provider if you have even one of the following signs or symptoms of preterm labor:
  - Change in your vaginal discharge (watery, mucus or bloody) or more vaginal discharge than usual
  - Pressure in your pelvis or lower belly, like your baby is pushing down
  - Constant low, dull backache
  - Belly cramps with or without diarrhea
  - Regular or frequent contractions that make your belly tighten like a fist. The contractions may or may not be painful.
  - Your water breaks.

Common Questions & Answers:

What is progesterone?
Progesterone is known as the "hormone of pregnancy." It is a natural and important hormone because of the role it plays in getting pregnant and carrying a baby to full term.

How does progesterone work?
During pregnancy, progesterone levels naturally increase. Research has shown that people who had a baby born more than three weeks early may benefit from extra progesterone in a future pregnancy.

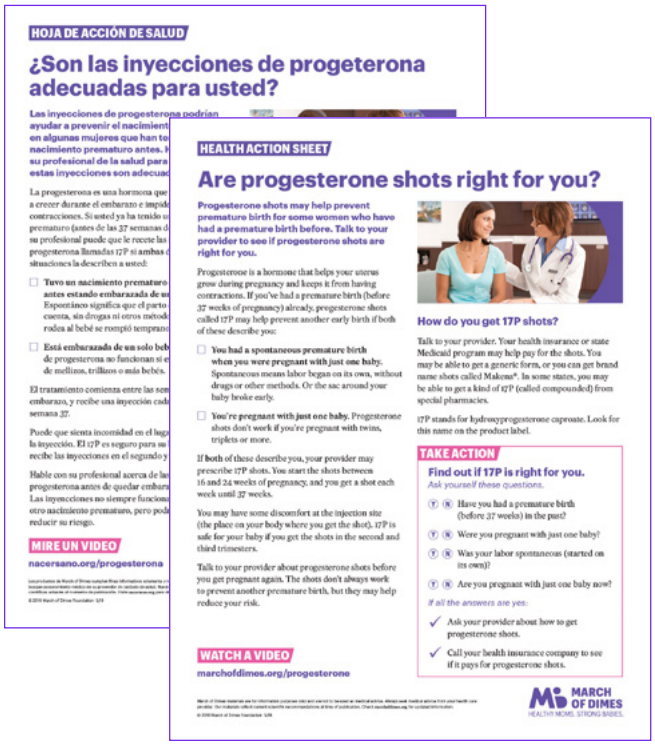
What are progesterone shots?
Progesterone shots are approved by the FDA, meaning that they are not experimental. However, your mom, grandma, or other family members might not have heard of it because only some pregnant persons need it.

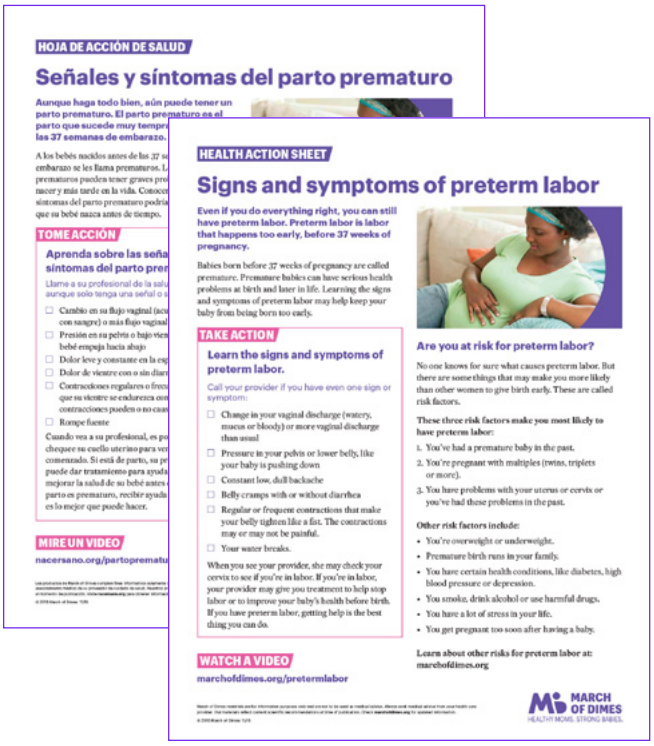
Adapted from The Progesterone Messaging Toolkit developed by the Ohio Collaborative to Prevent Infant Mortality. Available at **gowhenyouknow.org**.

Resources

March of Dimes

- Websites:
  - English: **marchofdimes.org/progesterone**
  - Spanish: **https://nacersano.marchofdimes.org/progesterona**
- Health Action Sheet: Are Progesterone Shots Right for You?
  - Available in English and Spanish at: **marchofdimes.org/progesterone**
- Health Action Sheet: Signs and Symptoms of Preterm Labor
  - Available in English and Spanish at: **marchofdimes.org/pretermlabor**





PART 3: LOW-DOSE ASPIRIN FOR PREECLAMPSIA PREVENTION

Preeclampsia, a condition in pregnancy that results in high blood pressure with swelling in the body and increased protein excretion in the urine, is one of the most serious health problems affecting pregnant women. It is a complication in 2% to 8% of pregnancies worldwide and contributes to both maternal and infant morbidity and mortality.[15] In the U.S., preeclampsia accounts for 15% of preterm births and 8% of maternal deaths each year.[15,23]

The United States Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) recommend the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high-risk for preeclampsia (see Table 1).[15,24] Aspirin–well-known for it's anti-inflammatory, antithrombotic, and antiplatelet properties–has shown to have beneficial effects in prevention of preeclampsia. The active ingredient of aspirin is acetylsalicylic acid.

The USPSTF found adequate evidence of reduction in risk for preeclampsia, preterm birth, and intrauterine fetal growth restriction (IUGR) in women at increased risk for preeclampsia who received low-dose aspirin (Grade B recommendation). In clinical trials, low-dose aspirin (60-150 mg) reduced the risk for: preeclampsia by 24%, preterm birth by 14%, and IUGR by 20%.[15] Despite USPSTF and ACOG guidelines, the use of low-dose aspirin in clinical practice remains varied.[24] In one study examining low-dose aspirin prescription rates among nearly 1,100 eligible patients at an urban safety-net hospital, only 40% of the women meeting high-risk eligibility criteria and only 10% of women meeting moderate-risk eligibility criteria were provided with prenatal low-dose aspirin prescriptions.[18]

Provider Guidelines for Prescribing Low-Dose Aspirin

- ACOG and the USPSTF recommend starting daily low-dose aspirin between 12 and 28 weeks of pregnancy. Recent evidence shows that low-dose aspirin is most effective when initiated between weeks 12 and 16 of pregnancy.
- Low-dose aspirin is also known as baby aspirin or prenatal aspirin. Aspirin is low cost over the counter, but a prescription can be written to provide no-cost aspirin if covered by insurance.

TABLE 1. Clinical risk assessment for preeclampsia

Risk Level	Risk Factors	Recommendation
High	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (systemic lupus erythematous, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate	• Nulliparity (never having given birth) • Obesity (body mass index >30 kg/m^2) at first visit • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age ≥35 years • Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)	Consider low-dose aspirin if the patient has two or more of these moderate-risk factors
Low	Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Sources: LeFevre ML; U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(11):819-826; Low-dose aspirin use during pregnancy. ACOG Committee Opinion No. 743. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e44–52.

- In the U.S., 81mg of low-dose aspirin daily is recommended for the prevention of preeclampsia.[15,24] However, the results of the ASPRE trial showed the effectiveness of aspirin at a dose equivalent to 150mg daily (a dose that is not currently available in the U.S.).[25]
- To prevent preeclampsia and hypertensive disorders of pregnancy, women with one or more high-risk factors should take low-dose aspirin. Patients with two or more moderate-risk factors may also benefit from low-dose aspirin (see Table 1).
- Providers should be especially aware that a Black woman having her first baby has two risk factors and should be carefully screened for other risk factors and strongly considered a candidate for low-dose aspirin.

Safety of Low-Dose Aspirin During Pregnancy

The potential benefits greatly outweigh the minimal risks of aspirin use in pregnancy. There are few contraindications to low-dose aspirin use. Aspirin should be avoided in patients with aspirin allergy, patients with aspirin-sensitive asthma, or in patients with gastrointestinal bleeding. As part of its assessment, the USPSTF reported the following:

- No increase in infant loss, growth problems, or cognition harm to the baby;
- No statistically significant impact on risk of placental abruptions, postpartum hemorrhage (bleeding), or miscarriage to the mother;
- No differences in developmental outcomes of the infants up to age 18 months.
- Data on the long term effects beyond 18 months is being collected in The Preeclampsia Registry (**www.preeclampsiaregistry.org**).

Low-Dose Aspirin Patient Education Talking Points

- For some people, taking low-dose aspirin during pregnancy may help reduce your risk for serious problems for you and your baby, like preeclampsia and premature birth.
- Preeclampsia is when you have high blood pressure and signs that some of your organs, like your kidneys and liver, may not be working right. Preeclampsia can happen after the 20th week of pregnancy or up to six weeks after delivery.
- If not treated, preeclampsia can cause serious problems for you and your baby, including premature birth (before 37 weeks of pregnancy). Babies born early may have more health problems than babies born on time.
- These are your personal factors which increase your risk for developing preeclampsia:

  _____
- One way to reduce the chance that you get preeclampsia is for you to take a low-dose aspirin every day starting at 12 weeks of pregnancy.
- Low-dose aspirin also is called prenatal aspirin, baby aspirin, or 81 mg (milligrams) aspirin.
- You can buy low-dose aspirin over-the-counter, or your provider can write a prescription for aspirin for you so that you can get it at low cost or no cost, depending on your health insurance.

Common Questions & Answers:

Where can I get low-dose aspirin?
Low-dose, 81-mg tablet aspirin is available over the counter at pharmacies and grocery stores. Your doctor also may write you a prescription for low-dose aspirin for you to have filled at your pharmacy so that you can get it at no cost or very low cost. Your health insurance may pay for all or some of your aspirin prescription.

Does low-dose aspirin increase risk of miscarriage?
Research suggests the use of aspirin during pregnancy does not increase the risk of miscarriage.

Will taking aspirin when I'm pregnant hurt the baby?
Low-dose aspirin is safe for mom and safe for baby. Aspirin does not increase the chance of birth defects.

What time of day should I take my dose?
Research shows that aspirin is most effective at bedtime when compared to morning, afternoon, and evening dose times.

When should I stop taking low-dose aspirin?
It is very important that you ask your doctor when you should stop taking aspirin, as recommendations may differ depending on your medical history.

Adapted from Preeclampsia Foundation: **preeclampsia.org/aspirin**

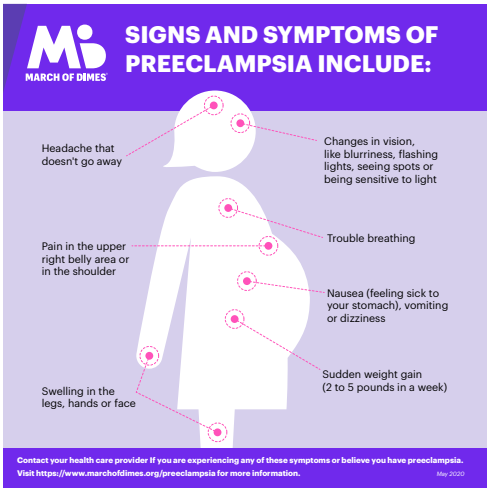
- Low-dose aspirin is safe during pregnancy and won't harm you or your baby.
- Setting a calendar alert on your cell phone can be an easy way to remember to take your pill each day before bedtime.
- Go to all your prenatal care checkups, even if you're feeling fine. You can have preeclampsia and not know it.
- What questions or concerns do you have about taking low-dose aspirin during your pregnancy?

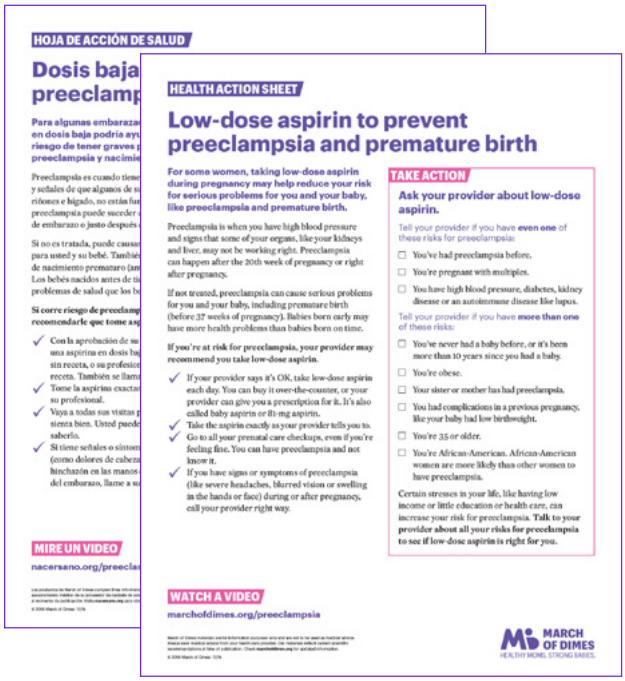
- These are some symptoms that could mean you have preeclampsia. If you experience any of them, call your provider right away or go to the hospital:
  - Changes in vision, like blurriness, flashing lights, seeing spots or being sensitive to light
  - Headache that doesn't go away
  - Nausea, vomiting or dizziness
  - Pain in the upper right belly area or in the shoulder
  - Sudden weight gain (2 to 5 pounds in a week)
  - Swelling in the legs, hands or face
  - Trouble breathing

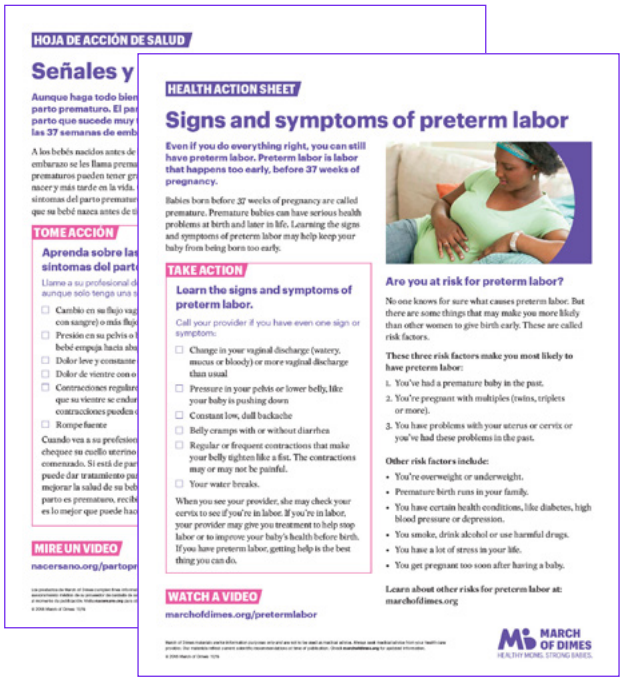
Resources

March of Dimes

- Websites:
  - English: **marchofdimes.org/preeclampsia**
  - Spanish: **https://nacersano.marchofdimes.org/preeclampsia**
- Health Action Sheet: Low-Dose Aspirin
  - Available in English and Spanish at: **marchofdimes.org/preeclampsia**
- Health Action Sheet: Signs and Symptoms of Preterm Labor
  - Available in English and Spanish at: **marchofdimes.org/pretermlabor**







PART 4: ORGANIZATIONAL CULTURE CHANGE AND CLINIC EDUCATION

Organize a movement in your clinic to adopt early screening and advocate for patients at-risk for preterm birth and preeclampsia. This may require planning, creativity, and new processes:

- Find ways to change the tide against the culture of "Because this is how we've always done it".
- Reframe changes for staff by focusing on the potential downstream benefit to moms and babies.
- Emphasize your clinic mission and community engagement which can be rewarding for employees.

Identify a champion(s) in your clinic to coordinate efforts on screening and coaching high-risk patients, and tracking their progress with 17P and low-dose aspirin. Once your champions are identified, emphasize continued education for all employees for buy-in and support.

Adopt an "all hands on deck" approach. Train front desk staff, patient scheduling representatives, or when applicable, staff delivering the Comprehensive Perinatal Services Program (CPSP) to screen new OB patients for preterm birth and preeclampsia risk.

- Educate your providers and staff with an in-service to overview the importance of 17P and low-dose aspirin and the signs and symptoms of preterm labor and preeclampsia.
- Train paraprofessional staff to serve in a peer mentor role for patients. There are resources available for training, like the "Credible Messengers" videos about how to talk to people about preterm birth, called "Talking With Your Clients About Progesterone" **gowhenyouknow.org**
- Ensure that your in-house or local pharmacists are part of the team as well by sharing this 2-hour on-line CE program with them. The training provides an overview of 17P, low-dose aspirin and birth spacing/ birth control. Any provider can view the training, but CEs are only available for pharmacists. Access the training at: **birthcontrolpharmacist.com/ healthypreg**

ENDNOTES

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ADDITIONAL RESOURCES

March of Dimes

Health Action Sheets
marchofdimes.org/professionals/information-for-your-patients.aspx

Our bilingual health action sheets are available for free download for your patients:

- Are progesterone shots right for you?
- Are you taking any of these prescription painkillers?
- How long should you wait before getting pregnant again?
- Low-dose aspirin to prevent preeclampsia and premature birth
- Signs and symptoms of preterm labor

Implicit Bias Training (CNE and CME Available):
marchofdimes.org/implicitbias

"Breaking Through Bias in Maternity Care," is an implicit bias training course that provides health care professionals with important insights to recognize and remedy implicit bias in maternity care settings. This unique learning experience, delivered live or through a self-paced, e-learning platform, provides authentic and compelling content for health care providers caring for women before, during, and after pregnancy. The training includes 4 key components:

- Overview of implicit bias and personal assessment.
- Historical overview of structural racism in the U.S.
- Strategies to mitigate racial bias in maternity care.
- Building a culture of equity within an organization.

Preeclampsia and Low-Dose Aspirin:
https://marchofdimes.org/preeclampsia
and
https://nacersano.marchofdimes.org/preeclampsia

Progesterone:
https://marchofdimes.org/progesterone
and
https://nacersano.marchofdimes.org/progesterona

Signs and Symptoms of Preterm Labor:
https://marchofdimes.org/pretermlabor

Other Resources

Boston Medical Center – Prenatal Aspirin Project:
https://www.prenatalaspirin.com/

California Department of Health Care Services - All Plan Letter to Medi-Cal Managed Care Plans on Proper Use and Billing for Makena:
www.dhcs.ca.gov/formsandpubs/Documents/MMCDAPLsandPolicyLetters/APL2015/APL15-009.pdf

Indiana Perinatal Quality Improvement Collaborative – Recommendations to Increase the Use of Progesterone to Prevent Prematurity:
in.gov/laboroflove/files/Progesterone_to_Prevent_Prematurity.pdf

Ohio Collaborative to Prevent Infant Mortality – Progesterone Messaging Toolkit:
GoWhenYouKnow.org

Ohio Perinatal Quality Care Collaborative – Progesterone Project:
opqc.net/projects/progesterone

Preeclampsia Foundation – Prenatal Aspirin:
preeclampsia.org/prenatal-aspirin

Society for Maternal-Fetal Medicine – Preterm Birth Toolkit:
smfm.org/publications/231-smfm-preterm-birth-toolkit

UNC School of Medicine Center for Maternal and Infant Health – 17P Clinical and Patient Education Resources:
mombaby.org/17-progesterone

Utah Women and Newborns Quality Care Collaborative – 17P and Preterm Birth Prevention Resources:
https://mihp.utah.gov/uwnqc/reduce-preterm-birth