



PRETERM LABOR: IDENTIFICATION AND TREATMENT

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COVERAGE RATIONALE

Progesterone

Progesterone therapy is proven for preventing spontaneous preterm birth in women with a singleton pregnancy and a prior spontaneous preterm delivery in a singleton pregnancy.

Progesterone therapy is unproven for preventing spontaneous preterm birth in women with multiple gestations.

Several multicenter, randomized controlled trials fail to demonstrate that progesterone therapy reduces the rate of preterm birth in women with multiple gestations.

Tocolytic Therapy

The use of tocolytic therapy beyond 7 days is unproven for preventing spontaneous preterm birth by prolonging pregnancy.

Available studies fail to demonstrate any benefit of maintenance tocolysis in terms of gestational age at birth, pregnancy prolongation or birth weight.

Subcutaneous terbutaline pump maintenance therapy is unproven for preventing spontaneous preterm birth by prolonging pregnancy.

Terbutaline pump maintenance therapy has not been shown to decrease the risk of preterm birth by prolonging pregnancy.

Home Uterine Activity Monitoring

Home uterine activity monitoring (HUAM) is unproven for preventing spontaneous preterm birth.

There is insufficient clinical evidence that home uterine activity monitoring, as an independent variable, reduces the frequency of preterm births. Available studies fail to demonstrate that the use of HUAM reduces the rate of preterm delivery and neonatal complications or improves pregnancy outcomes.

Salivary Estriol

Salivary estriol testing is unproven for predicting preterm birth.

Salivary estriol testing has a high false-positive rate which can lead to unnecessary surveillance and use of tocolytic drugs, without change in perinatal outcome.

BACKGROUND

Preterm labor is defined as regular uterine contractions, associated with cervical change, before 37 weeks of gestation. Deliveries that are early by five weeks or more are the leading cause of infant morbidity and mortality in the United States. Preterm labor risk factors include, but are not limited to previous premature birth, current multiple gestation, previous preterm labor during current pregnancy, shortened cervix (15 mm or less) or uterine bleeding in the current pregnancy after 14 weeks.

Despite the introduction of new diagnostic and therapeutic technologies, there has been little reduction in the incidence of preterm birth over the past 30 years. While no treatment has proven highly effective in preventing preterm delivery in women who experience preterm labor, diagnosis at an early stage allows the use of interventions that may delay delivery for 48 hours or more.

Tocolytics are drugs given to inhibit uterine contractions. Acute tocolysis is used to decrease or stop uterine contractions and halt cervical change in women during active preterm labor. Maintenance tocolysis is administered after acute tocolysis, in women with arrested preterm labor, to prevent a recurrence of preterm labor.

CLINICAL EVIDENCE

Progesterone

The use of progesterone during pregnancy for the prevention of preterm birth in high-risk women is currently under intense investigation. Many questions remain regarding a number of issues, including long-term safety, optimal treatment protocols and appropriate patient selection criteria, as well as the mechanism of action of the treatment (Hayes, 2007).

Rode et al. (2009) conducted a meta-analysis of 6 randomized trials including singleton pregnancies with previous preterm birth. The data showed that in women with a singleton pregnancy and previous preterm delivery, progesterone reduced the rates of preterm delivery before 32 weeks, perinatal death, as well as respiratory distress syndrome and necrotizing enterocolitis in the newborn. Women with a short cervix or preterm labor may also benefit from progesterone, but further evidence is needed to support such a recommendation.

Rai et al. (2009) randomized 150 women with at least one preterm birth (PTB) to receive 100 mg of oral micronized progesterone (n=74) or placebo twice a day (n=74) from recruitment (18-24 weeks) until 36 weeks or delivery. PTB occurred in 29 (39.2%) women in the progesterone group compared with 44 (59.5%) in the control group. Mean gestational age at delivery was higher in the progesterone group. Progesterone reduced the risk of PTB between 28 and 31 weeks plus 6 days, NICU admissions and neonatal morbidity and mortality in high risk patients.

Tita and Rouse (2009) systematically reviewed emerging data on the use of progesterone to prevent preterm birth (PTB). Seventeen relevant reports (8 RCTs, 6 meta-analyses and 3 national guidelines) were identified. Individual trials and meta-analyses support that synthetic intramuscular 17-alpha-hydroxyprogesterone effectively reduces the incidence of recurrent PTB in women with a history of spontaneous PTB. One trial found that vaginally administered natural progesterone reduced the risk of early PTB in women with a shortened cervix. The data are suggestive but inconclusive about the benefits of progesterone in the setting of arrested preterm labor and whether progesterone lowers perinatal morbidity or mortality. Further study is required to identify appropriate candidates and optimal formulations.

Borna and Sahabi (2008) conducted a randomized controlled trial to determine whether supplementation of vaginal progesterone after inhibition of preterm labor is associated with an increased latency period and a decreased recurrence of preterm labor. Seventy women were randomized to progesterone therapy (daily suppository) or no treatment. The authors concluded that the use of vaginal progesterone after successful parenteral tocolysis is associated with a longer latency preceding delivery but failed to reduce the incidence of readmission for preterm labor.

O'Brien et al. (2007) conducted a multinational randomized, double-blind, placebo-controlled trial of 659 pregnant women to determine whether prophylactic administration of vaginal progesterone reduces the risk of preterm birth in women with a history of spontaneous preterm birth. Patients were assigned randomly to once-daily treatment with either progesterone vaginal gel or placebo until either delivery, 37 weeks' gestation or development of preterm rupture of membranes. The primary outcome was preterm birth at ≤ 32 weeks of gestation. Progesterone did not decrease the frequency of preterm birth at ≤ 32 weeks. There was no difference between the groups with respect to the mean gestational age at delivery, infant morbidity or mortality or other maternal or neonatal outcome measures.

In a secondary analysis, the same authors investigated the efficacy of vaginal progesterone to prevent early preterm birth in women with sonographic evidence of a short cervical length in the midtrimester. In women with a cervical length < 28 mm, the rate of preterm birth at ≤ 32 weeks was significantly lower for those receiving progesterone than it was for those receiving the placebo. With progesterone, there were fewer admissions into the neonatal intensive care unit and shorter NICU stays. There was also a trend toward a decreased rate of neonatal respiratory distress syndrome (DeFranco, 2007).

Fonseca, et al. (2007) conducted a randomized trial of vaginal progesterone in asymptomatic women with a shortened cervix. Cervical length was measured by transvaginal ultrasonography at a median of 22 weeks of gestation (range, 20 to 25) in 24,620 pregnant women seen for routine prenatal care. Cervical length was 15 mm or less in 413 of the women (1.7%), and 250 (60.5%) of these 413 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (19.2% vs. 34.4%; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86). Progesterone was associated with a nonsignificant reduction in neonatal morbidity (8.1% vs. 13.8%; relative risk, 0.59; 95% CI, 0.26 to 1.25; P=0.17). In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.

Meis et al (2003) conducted an NICHD-sponsored, multicenter, double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery.

Women were randomly assigned, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P (Gestiva) (n=310) or weekly injections of a placebo (n=153). Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). A four-year follow-up study found no adverse health outcomes of surviving children (Northen 2007).

In a smaller study, da Fonseca, et al. (2003) conducted a randomized, double-blind, placebo-controlled study (n=142) of high-risk singleton pregnancies. Progesterone (n=72) or placebo (n=70) was administered daily by vaginal suppository and all patients underwent uterine contraction monitoring between 24 and 34 weeks of gestation. The preterm birth rate was 21.1% (30/142). Differences in uterine activity were found between the progesterone and placebo groups (23.6% vs 54.3%, respectively; $P < .05$) and in preterm birth between progesterone and placebo (13.8% vs 28.5%, respectively; $P < .05$). More women were delivered before 34 weeks in the placebo group (18.5%) than in the progesterone group (2.7%) ($P < .05$).

A 2006 Cochrane Review reported that for all women administered progesterone, there was a reduction in the risk of preterm birth less than 37 weeks (six studies, 988 participants, relative risk (RR) 0.65, 95% confidence interval (CI) 0.54 to 0.79) and preterm birth less than 34 weeks (one study, 142 participants, RR 0.15, 95% CI 0.04 to 0.64). Infants born to mothers administered progesterone were less likely to have birthweight less than 2500 grams (four studies, 763 infants, RR 0.63, 95% CI 0.49 to 0.81) or intraventricular hemorrhage (one study, 458 infants, RR 0.25, 95% CI 0.08 to 0.82). There was no difference in perinatal death between women administered progesterone and those administered placebo (five studies, 921 participants, RR 0.66, 95% CI 0.37 to 1.19). Intramuscular progesterone is associated with a reduction in the risk of preterm birth less than 37 weeks' gestation, and infant birthweight less than 2500 grams. However, other important maternal and infant outcomes have been poorly reported to date, with most outcomes reported from a single trial only (Meis, 2003). It is unclear if the prolongation of gestation translates into improved maternal and longer-term infant health outcomes. Similarly, information regarding the potential harms of progesterone therapy to prevent preterm birth is limited. Further information is required about the use of vaginal progesterone in the prevention of preterm birth (Dodd, 2006a).

Sanchez-Ramos, et al. (2005) performed a systematic review with meta-analysis and reported that compared with women allocated to receive placebo, those who received progesterone agents had lower rates of preterm delivery (26.2% versus 35.9%; OR 0.45, 95% CI 0.25-0.80). Similar results were noted when comparing patients who were specifically treated with 17alpha-hydroxyprogesterone caproate (29.3% versus 40.9%; OR 0.45, 95% CI 0.22-0.93). Additionally, subjects allocated to receive 17alpha-hydroxyprogesterone caproate had lower rates of birth weights less than 2,500 g (OR 0.50, 95% CI 0.36-0.71). The team concluded that the use of progesterone agents and 17alpha-hydroxyprogesterone caproate reduced the incidence of preterm birth and low birth weight newborns.

Mackenzie, et al (2006) concluded that progesterone agents, initiated in the second trimester of pregnancy, may reduce the risk of delivery less than 37 weeks' gestation, among women at increased risk of spontaneous preterm birth, but the effect on neonatal outcome is uncertain. Larger randomized controlled trials are required to determine whether this treatment reduces perinatal mortality or serious neonatal morbidity.

Several clinical trials are in progress.

Progesterone in Multiple Gestations

Caritis et al. (2009) conducted a randomized, double-blind, placebo-controlled trial in 14 centers. Healthy women with triplets were randomly assigned to weekly intramuscular injections of either

250 mg of 17 alpha-hydroxyprogesterone caproate (n=71) or placebo (n=63), starting at 16-20 weeks and ending at delivery or 35 weeks of gestation. Treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with triplet gestations.

In a multicenter, double-blind, placebo-controlled trial, Norman et al. (2009) randomized 500 women with twin pregnancy to daily vaginal progesterone gel (n=250) or to placebo gel (n=250) for 10 weeks from 24 weeks' gestation. Progesterone, administered vaginally, did not prevent preterm birth. The authors also conducted a meta-analysis of published and unpublished data to establish the efficacy of progesterone in prevention of early (<34 weeks' gestation) preterm birth or intrauterine death in women with twin pregnancy. The meta-analysis confirmed that progesterone does not prevent early preterm birth in women with twin pregnancy.

Rouse, et al. (2007) performed a multicenter, randomized, double-blind, placebo-controlled trial (n=661) of healthy women pregnant with twins and found that treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with twin gestations.

Tocolytic Therapy

Evidence to support the use of tocolytic therapy shows that tocolytic drugs do not prolong pregnancy beyond seven days. Specific evidence on the use of subcutaneous terbutaline shows that subcutaneous terbutaline given after acute tocolysis does not prolong pregnancy by any measurable length of time.

In a Cochrane systematic review, Dodd et al. (2006b) assessed the effects of oral betamimetic maintenance therapy after threatened preterm labor for preventing preterm birth. Randomized controlled trials comparing oral betamimetic with alternative tocolytic therapy, placebo or no therapy for maintenance following treatment of threatened preterm labor. Eleven randomized controlled trials (RCTs) were included. The authors concluded that the available evidence does not support the use of oral betamimetics for maintenance therapy after threatened preterm labor.

In a Cochrane systematic review, Nanda et al. (2002; updated 2010) evaluated terbutaline pump maintenance therapy after threatened preterm labor in preventing preterm birth and its complications. The authors found that terbutaline pump maintenance therapy did not appear to offer any advantages over the saline placebo pump or oral terbutaline maintenance therapy in preventing preterm births by prolonging pregnancy or its complications among women with arrested preterm labor. Terbutaline pump therapy also did not result in a lower rate of infant complications.

Home Uterine Activity Monitoring (HUAM)

Home uterine activity monitoring (HUAM) uses a device to measure uterine activity away from the clinic or hospital. It is used to detect early-stage uterine contractions suggestive of preterm labor.

According to a multicenter study by the National Institute of Child Health and Human Development (NICHD), portable monitors that detect contractions of the uterus do not appear to be useful for identifying women likely to have a preterm delivery. "Although they are widely prescribed for women at risk of giving birth prematurely, the monitors are not useful for predicting or preventing preterm birth" (Iams, 2002).

There is some evidence that HUAM may allow earlier detection of uterine contractions than patient recognition; however, it remains unclear whether the reported benefits in patient management are due to the use of the monitoring device or to the accompanying nursing support. Furthermore, the available studies fail to prove that the use of HUAM reduces the rate of preterm delivery and its consequent neonatal complications, and thereby improves pregnancy outcomes (Hayes, 2007). A January 2010 update found no new evidence that would impact the Hayes rating for this technology.

Reichmann (2009) systematically reviewed 3 Level I randomized, controlled trials; 1 level II matched cohort trial; and 5 level III case series evaluating home uterine activity monitoring in multiple gestations and found that contractions in multiple gestations are not predictive of preterm birth. In an earlier review, the same author analyzed published clinical trials examining HUAM for the management of current preterm labor. He concluded that HUAM has no clinical value, has virtually no scientific support and constitutes a gross deviation from evidence-based medicine (Reichmann, 2008).

The US Preventive Services Task Force recommendation now has inactive status and states that home uterine monitoring is no longer considered a part of standard obstetrical care and is not relevant to clinical practice. The USPSTF will not update its 1996 recommendation and directs readers to consult current literature for updated information on the topic.

Salivary Estriol

Salivary estriol testing measures the concentration of a fetal hormone, estriol, in the saliva of a pregnant woman. In the majority of pregnant women, plasma estriol levels rise at an increased rate 2 to 3 weeks before delivery, whether at term or preterm.

There is evidence from two published studies that salivary estriol testing may be more accurate in predicting which women will or will not experience preterm delivery than is the Creasy score, particularly in women with known risk factors. However, there are two major problems with the use of salivary estriol as a screening test to aid in the detection of women at risk for premature delivery. First, the proportion of pregnant women with singleton pregnancies who are at risk for spontaneous premature delivery is small, and the sensitivity of the test is approximately 42% to 64%, which results in low positive predictive value for the test, even for women with known risk factors. Second, no currently approved treatment has been proven to prevent the onset of labor or to significantly prolong gestation; thus, even accurate detection of women at high risk for preterm delivery would be unlikely to alter pregnancy outcome. Although a negative salivary estriol test might provide reassurance for women who have had previous preterm deliveries and could potentially reduce unnecessary tocolytic therapy, it is also possible that salivary estriol screening would lead to increased unnecessary surveillance and use of tocolytic drugs, without change in perinatal outcome (Hayes, 2006).

Periodontal Disease

Some studies have shown an association between periodontal disease and an increased risk of preterm low birth weight (Vergnes, 2007). However, this association was weaker in higher quality studies.

The results of a meta-analysis suggest that oral prophylaxis and periodontal treatment may in fact reduce the rate of preterm low birth weight but may not significantly reduce the rates of preterm birth or the rate of low birth weight (Xiong, 2007). Another multicenter, randomized controlled trial reported that although periodontal treatment improved periodontitis measures, it did not significantly alter rates of preterm birth (Michalowicz, 2006).

Further studies have failed to demonstrate an association between periodontal disease and adverse pregnancy outcomes (Macones, 2010; Newnham, 2009; Offenbacher, 2009; Srinivas, 2009).

Neuroprotective Effects of Magnesium Sulfate

Doyle et al. (2009) systematically reviewed rates of neurologic outcomes reported in childhood for preterm fetus exposed to antenatal magnesium sulfate. Five eligible randomized controlled trials (RCTs) with 6,145 fetuses were identified; in four studies (4,446 fetuses) the primary intent was neuroprotection of the fetus. Antenatal magnesium sulfate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their children. Moreover, there was a significant reduction in the rate of substantial gross motor dysfunction. No statistically significant effect of antenatal magnesium sulfate therapy was detected on pediatric mortality, or on other neurologic impairments or disabilities in the first few years of life. There were no

significant effects of antenatal magnesium sulfate on combined rates of mortality with neurologic outcomes, except in the studies where the primary intent was neuroprotection, where there was a reduction in death or cerebral palsy. Two subsequent meta-analyses of similar design confirmed these results (Conde-Agudelo, 2009; Costantine, 2009).

In a multicenter, placebo-controlled, double-blind trial, Rouse et al. (2008) randomly assigned 2241 women at imminent risk for delivery between 24 and 31 weeks of gestation to receive intravenous magnesium sulfate or matching placebo. The primary outcome was a total of stillbirth or infant death by 1 year or moderate or severe cerebral palsy at or beyond 2 years. Fetal exposure to magnesium sulfate before anticipated early preterm delivery did not reduce the combined risk of moderate or severe cerebral palsy or death, although the rate of cerebral palsy was reduced among survivors.

Marret et al. (2007) evaluated whether magnesium sulphate (MgSO₄) given to women at risk of very-preterm birth would be neuroprotective in preterm newborns and would prevent neonatal mortality and severe white matter injury (WMI). 564 gravid women (688 infants) with fetuses of gestational age < 33 weeks whose birth was planned or expected within 24 hours were randomly assigned to receive a single infusion of MgSO₄ or a placebo. The primary outcome was infant death or severe WMI. The investigators found no significant differences in total infant death or severe WMI or both between the two treatment groups and acknowledged that more research is needed to assess the protective effect of MgSO₄ alone or in combination with other neuroprotective molecules.

Crowther et al. (2003) reported the results of a multicenter randomized controlled study evaluating the effectiveness of magnesium sulfate given for neuroprotection to women at risk of preterm birth. A total of 1062 women (1255 infants) with fetuses younger than 30 weeks' gestation for whom birth was planned or expected within 24 hours were enrolled. Women were randomly assigned to receive an infusion of magnesium sulfate or a placebo for 20 minutes followed by a maintenance infusion for up to 24 hours. Primary outcomes included infant death or cerebral palsy or both at a corrected age of 2 years. No significant reductions in the occurrences of infant death or cerebral palsy or both were seen with the magnesium sulfate treatment. In a secondary analysis, the researchers demonstrated significantly less frequent substantial gross motor dysfunction (inability to walk without assistance) or death or both in the infants exposed to magnesium sulfate. Magnesium sulfate given to women immediately before very preterm birth may improve important pediatric outcomes. No serious harmful effects were seen.

Professional Societies

American College of Obstetricians and Gynecologists

A 2008 ACOG Committee Opinion states that recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women. However, despite the apparent benefits, the ideal progesterone formulation is unknown. ACOG, jointly with the Society for Maternal-Fetal Medicine, believes that further studies are needed to evaluate the optimal preparation, dosage, route of administration and other indications for the use of progesterone for preventing preterm delivery. Based on current knowledge, the two societies believe it is important to offer progesterone for pregnancy prolongation to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation. Current evidence does not support the routine use of progesterone in women with multiple gestations.

The 2003 ACOG Practice Bulletin on management of preterm labor states that neither maintenance treatment with tocolytic drugs nor repeated acute tocolysis improve perinatal outcomes and neither should be undertaken as a general practice. Tocolytic drugs may prolong gestation for two to seven days, which can provide time for administration of steroids to improve fetal lung maturity and the consideration of maternal transport to a facility with a neonatal intensive care unit. The benefits of prolonging pregnancy for two to seven days are otherwise unclear. Studies of maintenance therapy in women who present with symptoms of preterm labor and receive tocolysis acutely show no differences in effectiveness between treatment and control groups. Meta-analysis likewise fails to demonstrate any benefit of maintenance tocolysis in terms

of gestational age at birth, pregnancy prolongation or birth weight. Prolonged oral, subcutaneous, or intravenous tocolytic treatment is not effective, and cautions that prolonged use of any tocolytic may potentially increase the maternal-fetal risk without offering a clear benefit.

There are no current data to support the use of salivary estriol or home uterine activity monitoring as strategies to identify or prevent preterm birth (ACOG, 2001).

Numerous large clinical studies have evaluated the evidence regarding magnesium sulfate, neuroprotection and preterm births. The Committee on Obstetric Practice and the Society for Maternal-Fetal Medicine recognize that none of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis and monitoring in accordance with one of the larger trials (ACOG, 2010).

Society of Obstetricians and Gynaecologists of Canada (SOGC)

1. Women at risk for preterm labor (PTL) should be encouraged to participate in studies on the role of progesterone in reducing the risks of preterm labor. (I-A)
2. Women should be informed about the lack of available data for many neonatal outcome variables and about the lack of comparative data on dosing and route of administration. Women with short cervix should be informed of the single large RCT showing the benefit of progesterone in preventing PTL. (I-A)
3. Women and their caregivers should be aware that a previous spontaneous preterm labor and/or short cervix (< 15 mm at 22-26 weeks' gestation) on transvaginal ultrasound could be used as an indication for prophylactic progesterone therapy. The therapy should be started after 20 weeks' gestation and stopped when the risk of prematurity is low. (I-A)
4. On the basis of the data from the RCTs and metaanalysis, it is recommended that in cases where the clinician and the patient have opted for the use of progesterone the following dosages should be used:
 - For prevention of PTL in women with history of previous PTL: 17 alpha-hydroxyprogesterone 250 mg IM weekly (I-B) or progesterone 100 mg daily vaginally. (I-A)
 - For prevention of PTL in women with short cervix of \leq 15 mm detected on transvaginal ultrasound at 22-26 weeks: progesterone 200 mg daily vaginally. (I-A) (Farine, 2008)

Additional search terms

17-alpha hydroxyprogesterone caproate, 17-hydroxyprogesterone, hydroxyprogesterone, hydroxy-progesterone, hydroxy progesterone

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Progesterone Therapy

Currently, no progestins have received approval by the FDA for the prevention of preterm labor or preterm birth.

In October 2006, Adeza Biomedical received an approvable letter from the FDA for Gestiva (17-alpha hydroxyprogesterone) (drugs.com, 2006).

On January 31, 2007, the FDA granted orphan drug status for Gestiva (17-alpha hydroxyprogesterone) for the prevention of recurrent preterm birth. On October 30, 2007, a private industry representative requested that this status be revoked. This petition is still pending. The FDA has assigned docket number 2007P-0455 to this matter.

Adeza Biomedical Corporation has since been acquired by Cytoc Corporation, which was then acquired by Hologic. KV Pharmaceutical Company was to acquire the rights to Gestiva in January 2008 and was set to begin marketing it upon getting FDA approval for their New Drug Application (NDA). In January 2009, the pending NDA for Gestiva was not approved, and the FDA requested that additional data and information be submitted. Additional information available at:

http://www.kvpharmaceutical.com/news_center_article.aspx?articleid=279

Accessed March 10, 2010.

Home Uterine Activity Monitoring

The FDA describes HUAM as a prescription only electronic system (comprising of a tocotransducer, an at-home recorder, a modem and a monitor to receive, process, and display the data) for at-home antepartum measurement of uterine contractions and data transmission by telephone to a clinical setting where it will be displayed. The FDA also states that HUAM is indicated for use, in conjunction with current high-risk care, for the daily at home measurement of uterine activity in pregnancies > 24 weeks of gestation for women with a history of previous preterm birth, to aid in the early detection of preterm labor. Available at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM073596.pdf>. Accessed March 10, 2010.

Salivary Estriol Testing

In April 1998, the FDA approved SalEst an enzyme-linked immunosorbent assay (ELISA) designed to measure the levels of salivary estriol in pregnant women. The SalEst system is approved for use in women between their 22nd and 36th week of pregnancy and is intended as an aid in identifying risk of spontaneous preterm labor and delivery in singleton pregnancies.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for preterm labor. Local Coverage Determinations (LCDs) do not exist at this time. Accessed March 11, 2010.

APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

CPT [®] Code	Description
99500	Home visit for prenatal monitoring and assessment to include fetal heart rate, non-stress test, uterine monitoring, and gestational diabetes monitoring

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HCPCS Code	Description
J3105	Injection, terbutaline sulfate, up to 1 mg
S3652	Saliva test, hormone level; to assess preterm labor risk
S9001	Home uterine monitor with or without associated nursing services
S9208	Home management of preterm labor, including administrative services, professional pharmacy services, care coordination, and all necessary supplies or equipment (drugs and nursing visits coded separately), per diem (do not use this code with any home infusion per diem code)
S9349	Home infusion therapy, tocolytic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded

	separately), per diem
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ICD-9 Code	Description
644.00	Threatened premature labor, unspecified as to episode of care
644.03	Threatened premature labor, antepartum
V23.41	Supervision of pregnancy with history of pre-term labor

REFERENCES

- American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 455. Magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstet Gynecol.* 2010 Mar;115(3):669-71.
- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 31. Assessment of risk factors for preterm birth. *Obstet Gynecol.* 2001 Oct;98(4):709-16. (reaffirmed 2008)
- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 43. Management of preterm labor. *Obstet Gynecol.* 2003 May;101(5 Pt 1):1039-47. (reaffirmed 2008)
- American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 419. Use of progesterone to reduce preterm birth. *Obstet Gynecol.* 2008 Oct;112(4):963-5.
- American College of Obstetricians and Gynecologists. ACOG Patient Education brochure. Preterm Labor. 2004 Available at: http://www.acog.org/publications/patient_education/bp087.cfm. Accessed March 10, 2010.
- Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labor: a randomized controlled trial. *Aust N Z J Obstet Gynaecol.* 2008 Feb;48(1):58-63.
- Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *Obstet Gynecol.* 2009 Feb;113(2 Pt 1):285-92.
- Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2009 Jun;200(6):595-609.
- Costantine MM, Weiner SJ; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis. *Obstet Gynecol.* 2009 Aug;114(2 Pt 1):354-64.
- Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA.* 2003 Nov 26;290(20):2669-76.
- da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol.* 2003 Feb;188(2):419-24.
- DeFranco EA, O'Brien JM, Adair CD, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a

secondary analysis from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.* 2007 Oct;30(5):697-705.

Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth. *Cochrane Database Syst Rev.* 2006a Jan 25;(1):CD004947.

Dodd JM, Crowther CA, Dare MR, Middleton P. Oral betamimetics for maintenance therapy after threatened preterm labour. *Cochrane Database Syst Rev.* 2006b Jan 25;(1):CD003927.

Doyle LW, Crowther CA, Middleton P, Marret S. Antenatal magnesium sulfate and neurologic outcome in preterm infants: asystematic review. *Obstet Gynecol.* 2009 Jun;113(6):1327-33.

Drugs.com. [Internet] Adeza Receives FDA Approvable Letter for Gestiva. Available at: http://www.drugs.com/nda/gestiva_061023.html. Accessed March 10, 2010.

ECRI Institute. Home uterine activity monitoring in women at risk for preterm birth. January 2010.

ECRI Institute. Hotline Service. Progesterone for prevention of preterm birth. December 2009.

Farine D, Mundle WR, Dodd J, et al. The use of progesterone for prevention of preterm birth. *J Obstet Gynaecol Can.* 2008 Jan;30(1):67-77.

Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med.* 2007 Aug 2;357(5):462-9.

Hayes, Inc. Hayes Directory. Home uterine activity monitoring. Lansdale, PA: Hayes, Inc.; January 2008. Updated January 2010.

Hayes, Inc. Hayes Directory. Salivary estriol test for preterm labor. Lansdale, PA: Hayes, Inc.; October 2005. Updated October 2009.

Hayes, Inc. Hayes Directory. Progesterone for the prevention of preterm birth. Lansdale, PA: Hayes, Inc.; July 2007. Updated June 2009.

Iams JD, et al. Frequency of uterine contractions and the risk of spontaneous preterm delivery. *N Engl J Med.* 2002 Jan 24;346(4):250-5.

Mackenzie R, Walker M, Armson A, Hannah ME. Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. *Am J Obstet Gynecol.* 2006 May;194(5):1234-42.

Macones GA, Parry S, Nelson DB, et al. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). *Am J Obstet Gynecol.* 2010 Feb;202(2):147.e1-8.

Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomized controlled PREMAG trial*. *BJOG.* 2007 Mar;114(3):310-8.

Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med.* 2003 Jun 12;348(24):2379-85.

Meis PJ. 17 hydroxyprogesterone for the prevention of preterm delivery. *Obstet Gynecol.* 2005 May;105(5 Pt 1):1128-35.

Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med.* 2006 Nov 2;355(18):1885-94.

Nanda K, Cook LA, Gallo MF, Grimes DA. Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth. *Cochrane Database of Systematic Reviews* 2002;(4):CD003933. Updated 2010;(3) with no change to conclusions.

Newnham JP, Newnham IA, Ball CM, et al. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstet Gynecol.* 2009 Dec;114(6):1239-48.

Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomized, double-blind, placebo-controlled study and meta-analysis. *Lancet.* 2009 Jun 13;373(9680):2034-40.

Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. *Obstet Gynecol.* 2007 Oct;110(4):865-72.

O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.* 2007 Oct;30(5):687-96.

Offenbacher S, Beck JD, Jared HL, et al. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstet Gynecol.* 2009 Sep;114(3):551-9.

Rai P, Rajaram S, Goel N, et al. Oral micronized progesterone for prevention of preterm birth. *Int J Gynaecol Obstet.* 2009 Jan;104(1):40-3.

Reichmann JP. Home uterine activity monitoring: an evidence review of its utility in multiple gestations. *J Reprod Med.* 2009 Sep;54(9):559-62.

Reichmann JP. Home uterine activity monitoring: the role of medical evidence. *Obstet Gynecol.* 2008 Aug;112(2 Pt 1):325-7.

Rode L, Langhoff-Roos J, Andersson C, et al. Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. *Acta Obstet Gynecol Scand.* 2009;88(11):1180-9.

Rouse DJ, Hirtz DG, Thom E, Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med.* 2008 Aug 28;359(9):895-905.

Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med.* 2007 Aug 2;357(5):454-61.

Sanchez-Ramos L, Kaunitz AM, Delke I. Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol.* 2005 Feb;105(2):273-9.

Srinivas SK, Sammel MD, Stamilio DM, et al. Periodontal disease and adverse pregnancy outcomes: is there an association? *Am J Obstet Gynecol.* 2009 May;200(5):497.e1-8.

Tita AT, Rouse DJ. Progesterone for preterm birth prevention: an evolving intervention. *Am J Obstet Gynecol.* 2009 Mar;200(3):219-24.

U.S. Preventive Services Task Force (USPSTF). Agency for Healthcare Research and Quality, Rockville, MD. Screening for Home Uterine Activity Monitoring. Available at: <http://www.ahrq.gov/clinic/uspstf/uspshuam.htm>. Accessed March 10, 2010.

Vergnes JN, Sixou M. Preterm low birth weight and maternal periodontal status: a meta-analysis. Am J Obstet Gynecol. 2007 Feb;196(2):135.e1-7.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
10/01/2010	<ul style="list-style-type: none"> • Revised coverage rationale; added language to indicate the following services are unproven: <ul style="list-style-type: none"> ○ Progesterone therapy is unproven for preventing spontaneous preterm birth in women with multiple gestations. ○ The use of tocolytic therapy beyond 7 days is unproven for preventing spontaneous preterm birth by prolonging pregnancy. ○ Subcutaneous terbutaline pump maintenance therapy is unproven for preventing spontaneous preterm birth by prolonging pregnancy. ○ Home uterine activity monitoring (HUAM) is unproven for preventing spontaneous preterm birth. • Updated list of applicable HCPCS codes: <ul style="list-style-type: none"> ○ Added J3105 ○ Removed J3490 removed • Removed 644.10, 644.13, 644.20 and 644.21 from list of applicable ICD-9 Diagnosis codes