PRETERM LABOR: IDENTIFICATION AND TREATMENT

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee’s specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Essential Health Benefits for Individual and Small Group:

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee’s specific plan document to determine benefit coverage.
**COVERAGE RATIONALE**

**Tocolytic Therapy**
The use of tocolytic therapy beyond 7 days is unproven and not medically necessary for preventing spontaneous preterm birth by prolonging pregnancy. See note below regarding terbutaline.
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 and not medically necessary for delaying or 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.

**Note:** On February 17, 2011, the U.S. Food and Drug Administration (FDA) notified healthcare professionals that treatment of preterm labor with terbutaline administered by injection or by continuous infusion pump should not be used beyond 48 to 72 hours in a hospital setting. In particular, injectable terbutaline should not be used in the outpatient or home setting. In addition, oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns. Death and serious maternal heart problems have been reported after prolonged administration of oral or injectable terbutaline to pregnant women. Additional information available at: [http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm243843.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm243843.htm). Accessed April 8, 2014.

**Home Uterine Activity Monitoring**
Home uterine activity monitoring (HUAM) is unproven and not medically necessary 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.

**APPLICABLE CODES**

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service 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 enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>J3105</td>
<td>Injection, terbutaline sulfate, up to 1 mg</td>
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<tr>
<td>S9001</td>
<td>Home uterine monitor with or without associated nursing services</td>
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<tr>
<td>S9208</td>
<td>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)</td>
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<tr>
<td>S9349</td>
<td>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</td>
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DESCRIPTION OF SERVICES

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, smoking, previous confirmed preterm labor during current pregnancy and/or shortened cervix.

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 slow or halt cervical change in women during preterm labor. Maintenance tocolysis refers to medication administered after acute tocolysis, in women with arrested preterm labor, to prevent a recurrence of preterm labor.

CLINICAL EVIDENCE

Tocolytic Therapy
Subcutaneous terbutaline (SQ terbutaline) infusion by pump is used as a prolonged (beyond 48–72 hours) maintenance tocolytic following acute treatment of preterm contractions. The effectiveness and safety of this maintenance tocolysis have not been clearly established. In an Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review, Gaudet et al. (2011) compared the benefits and harms of the SQ terbutaline pump with other tocolytics, conservative management or placebo in specific populations of women with arrested preterm labor. In women with recurrent preterm labor (RPTL) and singleton gestation, the strength of evidence favoring the SQ terbutaline pump over oral tocolytics or no treatment is low for the outcomes of incidence of delivery at <32 weeks and <37 weeks, and mean days of pregnancy prolongation. In women with RPTL and twin gestation, the strength of evidence favoring the pump over oral tocolytics is low for neonatal death, incidence of delivery at <32 weeks, and mean days of pregnancy prolongation. Strength of evidence is insufficient for bronchopulmonary dysplasia, incidence of delivery <28 weeks and <34 weeks, and withdrawals due to adverse events. Observational studies of medium to high risk of bias showed the benefit of the SQ terbutaline pump for other surrogate outcomes, such as birth weight and neonatal intensive care unit (NICU) admission. Absent or inconclusive evidence addressed all other neonatal health outcomes, neonatal harms, maternal harms and pump-related outcomes. Although evidence suggests that pump therapy is beneficial as maintenance tocolysis, confidence in its validity and reproducibility is low. While postmarketing surveillance has detected cases of serious harms, safety of the therapy remains unclear.

A meta-analysis by Han et al. (2010) did not show any differences between magnesium sulfate maintenance therapy and either placebo or beta-adrenergic receptor agonists in preventing preterm birth after an initial treated episode of threatened preterm labor.

In a Cochrane systematic review, Chawanpaiboon et al. (2014) evaluated the effectiveness of terbutaline pump maintenance therapy after threatened preterm labor in reducing adverse neonatal outcomes. This report replaces an earlier Cochrane review by Nanda et al. (2002). Four randomized controlled trials (n=234) comparing terbutaline pump therapy with alternative therapy, placebo or no therapy after arrest of threatened preterm labor were included in the review. The authors found no strong evidence that terbutaline maintenance therapy offered any advantages over saline placebo or oral terbutaline maintenance therapy in reducing adverse neonatal outcomes by prolonging pregnancy among women with arrested preterm labor.
In a Cochrane systematic review, Dodd et al. (2012) 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. Thirteen 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.

**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 et al., 2002).

In a Cochrane systematic review, Urquhart et al. (2012) evaluated whether home uterine activity monitoring is effective in improving outcomes for women and their infants considered to be at high risk of preterm birth. Fifteen studies (n=6008) were included in the review. The authors found that home uterine monitoring may result in fewer admissions to a neonatal intensive care unit but more unscheduled antenatal visits and tocolytic treatment. The report concluded that home uterine activity monitoring had no impact on maternal and perinatal outcomes such as perinatal mortality or incidence of preterm birth.

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 U.S. Preventive Services Task Force (USPSTF) recommendation 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 does not plan to update its 1996 recommendation and directs readers to consult current literature for updated information on the topic.

A National Institute for Health and Care Excellence (NICE) guideline on multiple pregnancies recommends against the use of home uterine activity monitoring to predict the risk of spontaneous preterm birth in twin or triplet pregnancies (NICE, 2011).

**Periodontal Disease**

Some studies have shown an association between periodontal disease and an increased risk of preterm low birth weight (Vergnes et al., 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 et al., 2007). Another multicenter, randomized controlled trial reported that although periodontal treatment improved periodontitis measures, it did not significantly alter rates of preterm birth (Michalowicz et al., 2006).
Further studies have failed to demonstrate an association between periodontal disease and adverse pregnancy outcomes (Fogacci et al., 2011; Polyzos et al., 2010; Macones et al., 2010; Newnham et al., 2009; Offenbacher et al., 2009; Srinivas et al., 2009).

Neuroprotective Effects of Magnesium Sulfate
Based on the 2 largest trials studying magnesium sulfate for neuroprotection, Reeves et al. (2011) developed a treatment algorithm that identifies specific patients who are appropriate for magnesium sulfate therapy.

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 and Romero, 2009; Costantien and Weiner, 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 (ACOG)
A practice bulletin on the management of preterm labor makes the following recommendations based on good and consistent scientific evidence:

- No evidence exists to support the use of home uterine activity monitoring to prevent preterm delivery in women with contractions but no cervical change.

- Accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation.

- Evidence supports the use of first-line tocolytic treatment for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.

- Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose (ACOG, 2012a).

A committee opinion on oral health care during pregnancy states that although some studies have shown a possible association between periodontal infection and preterm birth, evidence has failed to show any improvement in outcomes after dental treatment during pregnancy. These studies did not raise any concern about the safety of dental services during pregnancy (ACOG, 2013a).

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 (SMFM) 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; reaffirmed 2013).

Following the FDA’s safety announcement regarding the use of magnesium sulfate to stop preterm labor, ACOG and SMFM released a committee opinion on the use of magnesium sulfate in obstetrics (ACOG, 2013b). The two professional societies continue to support the short-term (usually less than 48 hours) use of magnesium sulfate in obstetric care for appropriate conditions and for appropriate durations of treatment. These conditions include the following:

- Prevention and treatment of seizures in women with preeclampsia or eclampsia
- Fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery
- Short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women between 24 and 34 weeks of gestation who are at risk of preterm delivery within seven days.

### U.S. FOOD AND DRUG ADMINISTRATION (FDA)

**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:
On May 30, 2013, the FDA issued a safety announcement advising health care professionals against using magnesium sulfate injection for more than 5-7 days to stop preterm labor in pregnant women. Administration of magnesium sulfate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems in the developing baby or fetus, including osteopenia and fractures. The shortest duration of treatment that can result in harm to the baby is not known. Magnesium sulfate injection should only be used during pregnancy if clearly needed. If the drug is used during pregnancy, the health care professional should inform the patient of potential harm to the fetus. Additional information available at:


CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for identification and treatment of preterm labor. Local Coverage Determinations (LCDs) do not exist at this time. (Accessed April 9, 2014)

REFERENCES


Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of


POLICY HISTORY/REVISION INFORMATION

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| 07/01/2014 | • Reorganized policy content  
|           | • Added benefit considerations language for Essential Health Benefits for Individual and Small Group plans to indicate:  
|           |   ○ For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”)  
|           |   ○ Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs; however, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans  
<p>|           |   ○ The determination of which benefits constitute EHBs is made on a state by state basis; as such, when using this guideline, it is important to refer to the enrollee’s specific plan document |</p>
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<td>to determine benefit coverage</td>
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<td>• Updated coverage rationale; added language to indicate the unproven services are “not medically necessary”</td>
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<td>• Updated supporting information to reflect the most current clinical evidence, FDA and CMS information, and references</td>
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<td>• Archived previous policy version 2013T0352L</td>
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