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Pharmacology for Preterm Labor

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ABSTRACT

Preterm birth occurs with 10% of deliveries and yet accounts for more than 85% of perinatal morbidity and mortality. Management of preterm labor prior to delivery includes a multipronged pharmacologic approach targeting utilization of reproductive hormones for continuation of pregnancy, advancement of fetal lung maturity, and the decrease of uterine contractility (tocolysis). This article will review and compare guidelines on pharmacologic management of preterm labor as recommended by the American College of Obstetricians and Gynecologists and the European Association of Perinatal Medicine. The classifications of drugs discussed include exogenous progesterone, corticosteroids, and tocolytics (β-adrenergic agonists, magnesium sulfate, calcium channel blockers, prostaglandin inhibitors, nitrates, and oxytocin receptor blockers). For each of these drug classes, the following information will be presented: mechanism of action, maternal/fetal side effects, and nursing implications.

Key Words: pharmacology, preterm, tocolytics

Currently in the United States, preterm births account for 10% of live births.[1] Preterm birth is defined as birth between 20 weeks' gestation and less than 37 weeks' gestation and accounts for more than 85% of all perinatal morbidity and mortality.[2] Preterm labor usually precedes preterm birth and includes uterine contractions with accompanying cervical dilation greater than 2 cm or changes in dilation or effacement.[3] Many women presenting with preterm labor will give birth at term (50%); in addition, 30% of preterm labor resolves spontaneously.[4,5] Preterm labor is generally not treated prior to neonatal viability and only when delay of neonatal birth will benefit the newborn.[3] Current pharmacologic management for premature labor consists of advancing fetal lung maturity, decreasing uterine contractility, and utilizing reproductive hormones for continuation of pregnancy.[6] Guidelines on the use of pharmacologic management of preterm labor are disputed among obstetricians throughout the world and professional organizations have established various guidelines for practice.[6–8] This article will explore pharmacologic management for premature labor and compare pharmacologic guidelines written by the American College of Obstetricians and Gynecologists (ACOG) and the European Association of Perinatal Medicine.

EXOGENOUS PROGESTERONE TO MAINTAIN PREGNANCY

Maternal progesterone is vital to the establishment and continuation of pregnancy.[9] Progesterone increases blood flow to the uterus, stimulates the endometrium to thicken, and helps establish the placenta.[10] Progesterone also is necessary for fetal development, suppresses uterine contractions, and strengthens the pelvic wall. Low maternal progesterone is associated with preterm labor and exogenous progesterone is a prophylactic therapy used for pregnant women who have experienced a preterm birth prior.[11] Progesterone administration should be initiated between 16 and 20 weeks and only in women with intact membranes. Progesterone reduces the risk of preterm birth by maintaining uterine acquiescence.[12] Studies suggest that progesterone reduces the risk of preterm birth by up to 50%[13] and may decrease the incidence of respiratory distress, neonatal morbidity, and neonatal mortality in pregnant

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women with a shortened cervix. Confounding research suggests that in a subset of individuals, those with certain genetic factors or women with premature rupture of membranes, progesterone injections do not prolong pregnancy.[14] In addition, progesterone given intramuscularly has been found to increase the incidence of gestational diabetes by threefold.[15]

CORTICOSTEROIDS TO IMPROVE FETAL LUNGS

Corticosteroids are a class of steroid hormones naturally produced in the adrenal cortex.[16] Corticosteroids are anti-inflammatory, immunosuppressant and used to treat a wide range of conditions.[16] Corticosteroids, such as betamethasone or dexamethasone, are recommended for pregnant women between 24 and 33$^6/_7$ weeks' gestation and may be considered for pregnant women 34$^0/_7$ to 36$^6/_7$ weeks' gestation who are at risk of delivery within 7 days.[17] Corticosteroids promote fetal lung maturity[18] and consistently improve outcomes of preterm birth such as reduction and severity of respiratory distress syndrome, decreased mortality, improved stability of neonates, reduced rates of intraventricular hemorrhage, and decreased rates of necrotizing enterocolitis compared with preterm neonates not exposed to corticosteroids.[19] Corticosteroids' mechanism of action includes the accelerated development of type 1 and type 2 pneumocytes, which improves lung mechanics and gas exchange.[20] In addition, corticosteroids increase surfactant production, surfactant release, and upregulation of epithelial Na^+ channels that absorb lung fluid after birth.[8,21] Corticosteroids increase the number of β receptors in the lung, aiding in the lungs transition to air breathing.[20] Although the positive effects of lung maturity with corticosteroids are well established, negative effects of corticosteroids pose risks to the developing neonate.[22] The most prominent negative effect of corticosteroid treatment on lung development is the decrease in numbers of alveoli and decrease in lung growth.[22] This adverse effect has been studied in the animal model using rats, sheep, and monkeys but not extensively studied in humans.[23–25] It has been posited that mechanical ventilation and prematurity also contribute to the decrease in pulmonary growth.[26] Current recommendations specifically state using a single course of corticosteroids in pregnant women as cumulative treatment remains speculative.[21] Further concern on antenatal corticosteroid use and its effects on brain development and neuromotor function is evidenced in animal models with mice, rats, and sheep.[27–29] However, in human studies, antenatal corticosteroids decrease the incidence of intraventricular hemorrhage and improve neurodevelopmental outcomes.[30] Limited data on long-term follow-up leave questions related to effects of corticosteroids in pregnancy and long-term infant health outcomes. Corticosteroids are considered an adjunct to other therapies targeted to prolong pregnancy and stop preterm labor.[21] Appropriate use of corticosteroids for preterm lung development should also consider potential short- and long-term outcomes.

TOCOLYTICS TO DECREASE UTERINE CONTRACTIONS

Tocolytics are a group of medications used to decrease uterine contractions in women experiencing preterm labor between 23 and 34 weeks' gestation, though they have not been proven to stop preterm labor.[31] Tocolytic therapy is not considered in all preterm labor patients due to maternal and fetal complications.[32] Maternal contraindications to tocolytics include chorioamnionitis, placental abruption, severe preeclampsia, cardiac disease, poorly controlled diabetes or hypertension, and medical conditions necessitating pregnancy termination.[32] Fetal contraindications to tocolytics include intrauterine growth restriction, intrauterine fetal demise, and lethal fetal anomalies.[31] Tocolytics include β-adrenergic agonists (terbutaline, ritodrine), magnesium sulfate, calcium channel blockers (nifedipine), prostaglandin inhibitors (indomethacin, ketorolac), nitrates (nitroglycerine), and oxytocin receptor blockers (atosiban).[8,33,34] Recent meta-analysis suggests prostaglandin inhibitors (indomethacin, ketorolac) as the best first-line tocolytic therapy,[35] though experts in the field do not all agree on the most effective tocolytic for delaying preterm birth.[21] Tocolytic therapy is recommended only for short prolongation of pregnancy to allow for the administration of corticosteroids.[4] Long-term tocolytic therapy is not effective in preventing preterm birth or improving neonatal outcomes.[35]

β-Adrenergic agonists stimulate the β receptors in smooth muscle cells causing uterine relaxation.[36] β-Adrenergic agonists mostly affect β_2 receptors in smooth muscle of the myometrium (middle layer of uterine wall), bronchioles, and blood vessels, though they may also exhibit a small effect on β_1 receptors in the heart and small intestines causing cardiovascular and metabolic responses.[8,33] Caution should be exercised with administration of β-adrenergic agonists to mothers with cardiovascular disorders, glaucoma, diabetes mellitus, placenta previa, and placental abruption.[37] In fetuses, the density of β-adrenergic receptors is low compared with adults, resulting in a less powerful fetal cardiovascular response.[38] These fetal cardiovascular effects present as fetal tachycardia and decreased fetal heart rate variability.[38] In some cases of maternal β-adrenergic agonist administration,

neonatal hyperinsulinemia has been observed and prolonged treatment is associated with significant cardiotoxic effects.[39] β-Adrenergic agonists are contraindicated in fetal heart rate disorders and some fetal anomalies. β-Adrenergic agonists have potent effects on delaying delivery for 48 hours and a slight reduction in preterm delivery but no significant effects on perinatal mortality or prevention of severe neonatal respiratory distress.[39] The utility of β-adrenergic agonists is to provide time for corticosteroids for lung maturation or potential transfer of patient to a tertiary hospital, though, after long-term therapy, β receptors desensitize and downregulate in addition to causing an increase of prostaglandin production, which results in myometrial contraction.[39]

Magnesium sulfate decreases myometrial contractions through inhibition of calcium entry into the myometrial cells, resulting in a tocolytic effect.[8,33,39] Magnesium sulfate is primarily used to decrease seizure potential in patients with preeclampsia, but it also provides fetal neuroprotection and may decrease the severity of cerebral palsy in surviving infants when administered prior to 32 weeks' gestation.[8] Magnesium sulfate has fewer side effects than β-adrenergic agonists and can arrest uterine contractions, but limited randomized clinical trials are available to determine its efficacy in treating preterm birth.[40] Magnesium sulfate affects smooth muscle, including the myometrium and the blood vessels, leading to decreased uterine contractions and vasodilation.[39] Magnesium sulfate crosses the placental barrier and can result in decreased fetal movements and heart rate. In the neonate, exposure to magnesium may result in hypotonia, drowsiness, decreased sucking, or need for assisted ventilation.[33]

Calcium channel blockers act similarly to magnesium sulfate, in that they inhibit the influx of calcium into the myometrial smooth muscle cell, decreasing uterine contractions.[39,41] Calcium channel blockers have similar effectiveness compared with β-adrenergic agonists with fewer side effects.[42] Calcium channel blockers are contraindicated in maternal hypotension and maternal heart disease. Calcium channel blockers relax smooth muscle causing a relaxation of the uterine artery, decreasing placental perfusion pressure, though this does not appear to affect fetal heart rate or variability.[42] Fetal contraindications to calcium channel blockers include disorders affecting uteroplacental blood flow and fetal tachycardia and distress.[43]

Prostaglandin synthetase inhibitors decrease the actions of prostaglandins' effect on the uterus.[33] Prostaglandins allow for electrical coupling of myometrial cells and stimulate influx of intracellular calcium needed for muscle contractions. In addition, prostaglandin levels increase during labor; therefore, inhibition of prostaglandins reduces uterine contractions.[39] Prostaglandin inhibitors inhibit the renin-angiotensin system and constrict the renal arteries, resulting in decreased amniotic fluid[44] and can be utilized only with normal amniotic fluid and not in cases with oligohydramnios. Prostaglandin synthetase inhibitors are nonsteroidal anti-inflammatory drugs and have not been proven to improve short -or long-term neonatal outcomes.[45] If needed, the treatment may be repeated after a 5-day break if effective. Prostaglandin inhibitors are recommended as a first-line tocolytic therapy though caution in needed due to maternal and fetal effects.[21] Maternal contraindications include coagulation disorders, abnormal liver function, or asthma. Prostaglandin synthetase inhibitors cross the placenta and can cause constriction of the ductus arteriosus and oligohydramnios with prolonged use and are not recommended after 32 weeks' gestation, though some institutions use prostaglandin synthetase inhibitors up to 34 weeks' gestation.[8] Significant neonatal adverse effects include necrotizing enterocolitis, intracranial hemorrhage, patent ductus arteriosus, and bronchopulmonary dysplasia.[46]

The evidence to support nitroglycerine as a tocolytic treatment is conflicting. In a Cochrane analysis of 5 randomized controlled trials, nitroglycerine did not delay delivery and its use was not supported. In contrast, in a double-blind placebo trial, neonates born to mothers treated with nitroglycerine had a reduced neonatal morbidity and mortality compared with the placebo-treated mothers.[35] In addition, nitroglycerine patch has been found to reduce neonatal intensive care unit cost and improve neonatal outcomes.[47]

Oxytocin is a potent stimulator of uterine contractions. Oxytocin antagonist, atosiban, binds with oxytocin receptors in the myometrium decreasing uterine contractility.[33,39] Oxytocin antagonists show great promise as they have little effects on renal, cardiopulmonary, and central nervous system functions and are highly specific to the uterus.[41] Atosiban is currently used in Europe as a treatment for preterm labor but not approved in the United States. Administration of atosiban is through a bolus injection, followed by an infusion.[48] Research on oxytocin antagonists is continuing, and changes to practice may include atosiban in the future.

GUIDELINES

The ACOG defines preterm labor as uterine contractions with a dilated cervix greater than 2 cm or uterine contractions with cervical dilation or effacement changes. Current practice guidelines from ACOG recommend pharmacologic treatment of preterm labor for women between 24 and 34 weeks' gestation.[21] The ACOG does

not recommend exclusively utilizing fetal fibronectin test results or short cervix assessment to direct management of preterm labor with acute symptoms. Timing of pharmacologic management and assessment for preterm labor is currently debatable. The European Association of Perinatal Medicine recommends ultrasound cervical length measurements in all pregnant patients between 19 and 24 weeks' gestation to assess risk of preterm birth and potential preventive measures such as progesterone therapy.[8] For women in preterm labor, a single course of corticosteroids is recommended for women who are at risk of delivery within 1 week.[21] A single repeated course of corticosteroids should be considered in women less than 34 weeks' gestation, who are at risk of delivery within 1 week, and whose prior course of corticosteroids was greater than 14 days prior. Tocolytic treatment with β-adrenergic agonists, calcium channel blockers, or prostaglandin inhibitors for prolongation of pregnancy up to 48 hours for administration of corticosteroids is recommended. The ACOG and the European Association of Perinatal Medicine recommend different medications only for first-line tocolytic therapy. The European Association of Perinatal Medicine recommends using oxytocin receptor antagonist due to its absence of systemic effects on mothers and fetuses.[8] Oxytocin receptor antagonists are not mentioned in the most recent ACOG recommendations for the management of preterm labor. Extended tocolytic therapy is not recommended for preventing preterm birth or improving neonatal outcomes. Antibiotics are not recommended to prolong gestation or improve neonatal outcomes in women with intact membranes. Bed rest and hydration are also not recommended for routine treatment of preterm labor.[21]

DISCUSSION

Upon entry to care, nurses are responsible for completing a thorough patient history, paying special attention to preexisting conditions (eg, diabetes, hypertension, or cardiac arrhythmias) and any home medications or supplements (eg, aspirin) that may interfere with the treatment plan.[49] Before administering medication for preterm labor, a baseline head-to-toe physical assessment should be completed.[33] Fetal well-being assessments such as external fetal monitoring and imaging should be performed, as well as completion of a chart review to understand the course of pregnancy.[49] As therapy is administered, nurses should continue to perform timely and accurate assessments including vital signs, intake and output records, and safety management.[33,50] Fetal heart rate patterns and uterine activity should be assessed every 30 minutes for uncomplicated patients in the first stage of labor, and for the complicated patient, evaluation should occur every 15 minutes.[51–53] Afors and Chandraharan[54] have questioned whether continuous fetal heart rate monitoring practice guidelines for term pregnancies apply to preterm fetuses, given the physiologic changes associated with gestational age. In the absence of clear adaptations to recommendations, nurses should follow the fetal monitoring protocols at their institution of practice and should stay current on evidence by engaging in continuing education.[53] Psychosocial support should be offered as this may be a trying time for patients, partners, and family.[55] Emotional support can allow these individuals to express their feelings regarding the situation and/or the events leading up to it. This could come from the nurse directly or through an empowered partner—higher levels of paternal support have been associated with lower levels of preterm birth.[56] Informational support means providing evidence, feedback, and guidance.[55] Nurses are opportunely poised to provide ongoing education pertinent to patients' condition and received therapy.[33] In addition, should this current episode of preterm labor result in a preterm birth, neonatal nurses can be unique educational resources, providing information to patients that may impact future pregnancies.[57] In cases when the labor stabilizes and less acute management is acceptable, discharge teaching may be necessary and follow-up care or services should be arranged.[49]

Progesterone (intramuscular injection, vaginal suppository or gel) is a therapy for preventing preterm labor. Researchers are trying to determine the population in which this medication would be most effective.[13] Nursing considerations for patients receiving this therapy surround the methods of administration—weekly injections may be a detriment to some patients, whereas vaginal suppositories may result in pruritus or increased secretions.[58,59] A recent systemic review and meta-analysis reveals vaginal progesterone as the only route with consistent benefits in preventing preterm birth.[60]

The most common corticosteroid administered in this population is either betamethasone or dexamethasone. Betamethasone has suggested dosing of two 12-mg doses intramuscularly 24 hours apart; dexamethasone is administered in four 6-mg doses every 12 hours.[19] Corticosteroids have few side effects, especially due to the short course of treatment. However, blood glucose monitoring may be necessary for those women whose condition is complicated by preexisting or gestational diabetes. In addition, the injection site should be rotated to decrease irritation.

β-Adrenergic agonist is typically terbutaline (intravenous, subcutaneous, or oral routes) or ritodrine (intravenous progressing to oral routes). These medications require cardiac monitoring. Side effects may

range from tachycardia, palpitations, and tremors to pulmonary edema, chest pain, and heart failure.[31,33,47] Because of potentially rare but serious complications, this therapy should be contraindicated for patients with cardiac history.[39] Nurses should follow the institution's protocol, assessing cardiac and respiratory status frequently and monitoring intake/output. Fetal tachycardia is possible as well, necessitating fetal heart rate monitoring to observe for baseline changes.[39] In addition to cardiac effects, β-adrenergic agonists have metabolic effects, namely, hyperglycemia. If patients are receiving corticosteroids concurrently, the effect of glucose increase may be potentiated; nurses should perform routine blood glucose checks.[39] Hypokalemia is possible though it is usually transient and does not require therapy.[33,47]

Magnesium sulfate is typically administered as an intravenous infusion beginning with an initial 6-g loading dose progressing to a 2- to 3-g maintenance dose.[33] This medication can have systemic effects and is excreted through the kidneys. Although rare, nurses should observe for serious effects of magnesium toxicity—respiratory depression, neurologic sedation, and muscular weakness may occur at high doses. Hourly assessments of breath sounds, deep tendon reflexes, hand grasp, intake and output, and level of consciousness should be completed by the nurse. Magnesium sulfate infusion can also cause a number of uncomfortable side effects as a result of vasodilation. The patient may report feeling flushed and warm, light-headed, nauseous, and lethargic. Nurses should promote safety and assist patients out of bed. Patients may appreciate interventions to increase comfort such as cool compresses and linen changes.[33,39] Maternal magnesium sulfate can also impact the fetus; this drug has been shown to decrease fetal heart rate baseline and variability due to central nervous system depressant effects.[50,61] After delivery, neonatal effects of magnesium persist. Nurses should be alert for signs and symptoms of hypocalcemia, poor muscular tone, and respiratory depression in the newborn.[50] In the event that magnesium sulfate is administered for cerebral palsy neuroprotection, the same nursing implications would be applicable.

Calcium channel blockers, such as nifedipine, are administered orally with an initial dose of 10 to 20 mg with a second loading dose possible within the first 30 minutes. Maintenance is 10 to 20 mg every 6 to 8 hours, depending on the institution.[33] Calcium channel blockers may also result in vasodilation, causing side effects such as flushing, nausea, and headache.[39] Nurses should monitor heart rate for tachycardia and blood pressure for hypotension. Precautions such as gradual position changes and dangling should be taken to prevent postural hypotension. Patients managed on cimetidine should discontinue use of this drug as it can lead to higher circulating levels of nifedipine.[62] Digoxin levels may require monitoring for therapeutic level per institution policy, though several researchers have indicated that nifedipine can be safely coadministered.[34]

Prostaglandin synthetase inhibitor, indomethacin, is administered orally with a loading dose of 50 to 100 mg, followed by maintenance dosing of 25 to 50 mg every 6 hours for 48 hours.[33] This medication has few maternal side effects but complaints include nausea, vomiting, headache, and dizzy spells.[39] This medication interferes with platelet activity and thus is contraindicated in patients with histories of coagulation disorders, gastrointestinal ulcerative disease, and renal and hepatic dysfunction. Prostaglandin synthetase inhibitors can have significant fetal effects with long-term use. Ductus arteriosus constriction or closure and oligohydramnios caused by decreases in fetal urine output can result from administration of this medication.[33,39] The effects are greater at later gestation; recommendations are to avoid administration after 32 weeks.[18] In addition to fetal monitoring, nurses may assist with fetal imaging such as an amniotic fluid index or ultrasonography.

The following tocolytic therapies are being investigated or are employed internationally; however, they are not yet used clinically with wide support in the United States. Nurses should still be educated on ways to care for patients who would be administered these potential therapies. Nitroglycerine may be administered as a transdermal patch and side effects include headache and hypotension.[63] Nurses should monitor blood pressure and heart rate, as well as the topical site for irritation.[47] Oxytocin antagonists, such as atosiban, are administered by intravenous infusion. They are a promising therapy as they have been tolerated well. Reported side effects include nausea, vomiting, and headache.[8]

CONCLUSION

Management of preterm labor happens in conjunction with interdisciplinary teams; nursing can contribute to positive outcomes for both mothers and babies. Nursing responsibility includes understanding relevant pharmacological treatment of preterm labor, pharmacologic mechanisms of action, and potential side effects of pharmacologic therapy. It is crucial that nurses are knowledgeable of the breadth of preterm labor management including pharmacologic contraindications for both mothers and babies. Current and evolving evidence-based guidelines are available and practicing nurses are responsible for staying abreast of changes in order to contribute to the management of preterm

labor. As with other conditions, patient education is an ongoing task of the nurse. Nurses should teach signs and symptoms of preterm labor and for possible side effects of treatment, where appropriate.

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