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September 2005 "Drug Considerations During Pregnancy" 707-000-05-009-H01

THIS MONTH
"Drugs During Pregnancy & Lactation

RENEWAL STATEMENTS FOR NEXT YEAR HAVE BEEN MAILED. SEND THEM BACK DURING SEPTEMBER & SAVE.

ALL STATEMENTS OF CREDIT FOR 2005 WILL BE MAILED NEAR THE END OF THE YEAR. IF YOU HAVE SPECIAL REQUIREMENTS, CONTACT US & WE WILL ACCOMMODATE YOUR STATE'S RULES.

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HAVE YOU RECENTLY MOVED? PLEASE NOTIFY US.

This month's lesson deals with a topic where we as pharmacists have a challenging responsibility to furnish information to patients. "*Drugs Used During Pregnancy & Lactation*" is a topic that we periodically cover because of its significance. Our goal is to discuss those issues that must be shared with patients. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

The program ID # for this lesson is 707-000-05-009-H01.

Pharmacists completing this lesson by September 30, 2008 may receive full credit.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. List the body systems affected by pregnancy.
2. Describe the physiology of pregnancy.
3. Discuss drugs that are often taken by pregnant women.
4. List the major effects of drugs on the fetus.
5. Discuss the common disorders that are associated with pregnancy.
6. Describe the affects of drugs upon lactation.

BACKGROUND

Studies indicate that about 86% of women take approximately 3 medications (range 1 to 15) during a pregnancy. Approximately 50% of pregnancies in the U.S. are unplanned, and women may take medications or other substances such as alcohol or nicotine. These may place the fetus at risk of developing malformation before pregnancy is realized.

The intake of drugs and their influence during pregnancy and lactation is compounded by the physiological and biochemical changes that take place in both mother and fetus. Most of these changes occur in practically all organ systems, and they return to normal after childbirth. However, some may continue during lactation. The body systems affected by pregnancy include the cardiovascular, renal, pulmonary, gastrointestinal, endocrine, as well as the skin.

CARDIOVASCULAR SYSTEM

The cardiac output (CO) gradually increases starting by the 6th week of pregnancy, and peaking in the 24th week. This may be due to uteroplacental circulation. An additional rise occurs during labor; however, after delivery the CO drops noticeably. It remains slightly elevated, but a gradual decline occurs until the 6th week postpartum, when it reaches normal level. As the CO increases, so does the heart rate and blood volume (body water). As the uteroplacental circulation increases, blood pressure usually decreases in the second trimester, but may reverse to normal during the third trimester. The presence of the fetus and the placenta, as well as the increased maternal red blood cells, all result in an increase in iron requirements.

RENAL SYSTEM

A significant increase in kidney function occurs during pregnancy. This activity gradually increases and peaks between the 16th and 24th week, and continues to be at this level until shortly prior to delivery. The increase in renal function is usually accompanied by a decrease in BUN and creatinine levels.

PULMONARY SYSTEM

The main changes in lung function include increased respiratory rate, plasma pH, and oxygen consumption, as well as a decrease in plasma PCO_2 as well as inspiratory and expiratory reserve. The nasal mucosa may become hyperemic, and the pregnant woman may complain of nasal stuffiness, mild dyspnea on exertion, and frequent deep respiration.

GASTROINTESTINAL SYSTEM

During pregnancy, the enlarged uterus tends to press against the rectum and adjacent portions of the colon. This often causes constipation and hemorrhoids. In addition, the increased level of progesterone results in a decrease in GI motility. Women often experience gastroesophageal reflux disease (heart burn) and belching, that may be due to delay in gastric emptying rate as well as relaxation of the esophageal sphincter. The incidences of gallbladder disorders are high during pregnancy.

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ENDOCRINE SYSTEM

An increase in thyroid function may occur during pregnancy. Symptoms of hyperthyroidism (i.e., tachycardia, palpitations, and nervousness) may be experienced. Similarly, adrenal hormone levels may increase, resulting in edema. The increased level of glucocorticoids along with estrogen and progesterone may alter glucose metabolism and increase insulin requirements. Insulinase produced by the placenta and the increased production of placental lactogen may modify the needs for insulin.

SKIN

The most noticeable change in the skin is the appearance of chloasma (mask of pregnancy), a condition that is described as a localized spotty brownish discoloration of the forehead, nose, and cheeks as a result of melanin production in these areas. Likewise, the nipples and the genitalia become darker. Capillaries of the lower legs may become discolored. Weight gain usually occurs as a result of fetal and placental growth, increased blood volume (fluid) and breast enlargement.

PREGNANCY

Pregnancy is a natural event that occurs as a result of fertilization of the mature ovum. Following its release from one of the two ovaries, the mature egg travels through the fallopian tubes toward the uterus where it meets one of the millions of sperms found in the ejaculate. A single sperm will be able to penetrate the cell wall of the ovum. The nuclei of both the sperm and the ovum bind, resulting in fertilization. The fertilized egg implants itself in the uterus lining and slowly and gradually divides to form an embryo and placenta. Following implantation, the embryo receives its nourishment by digesting the endometrial cells, but by the second month, the placenta assumes the role of oxygen and nutrient provider. It also expels away embryonic metabolic wastes into the mother's blood system. The formation of the placenta is an extension of the implantation process. The placenta is a temporary organ that is formed from embryonic (trophoblastic) and endometrial tissue. As they proliferate, the embryonic tissues develop a layer of mesoderm at the inner surface. This new structure becomes the chorion with vascularized fingerlike bodies known as chorionic villi that interlock with the decidua basalis (the endometrium during pregnancy, the decidua basalis is the part of the decidua that unites with the chorion to form the placenta), and constitutes the maternal portion. The blood vessels of the villi extend to the embryo as umbilical arteries and veins. Eventually a hollow space (lacunae) filled with blood forms where the villi immerse in maternal blood. The chorionic villi and part of the endometrium form the placenta, a discord spongy structure that is attached to the membrane and encloses the embryo. The umbilical cord, which is 50 cm long, is attached to the center of the placenta. The umbilical vessels (2 arteries and one vein) pass to the fetus, which is connected to the placenta by the umbilical cord. The placenta is expelled after childbirth. Nutrients, oxygen, and antibodies diffuse from the mother into fetal blood, and the metabolic waste products pan from fetal blood into the mother's blood. Although maternal blood and fetal blood are in very close proximity, they do not mix. Other functions of the placenta include the secretion of estrogen, progesterone, and chorionic gonadotropins. In spite of the presence of placental barriers, which prevent the passage of harmful substances from entering fetal blood, certain substances, some of which are harmful to the fetus, have the ability to cross such barriers.

INTAKE OF DRUGS DURING PREGNANCY

Medications are taken by pregnant women to manage symptoms associated with pregnancy such as pain, anxiety, nausea, vomiting, and heartburn. Other medications, which may be used, are vitamins and mineral supplements, or medications to treat diabetes, asthma, rheumatoid arthritis, and hypertension. Until the 1950's, it had been assumed that the uterus and placenta act as barriers against adverse effects. However, the thalidomide disaster has shown that drugs and other substances could cross the placental barrier, causing serious fetal damage. This drug, which was used during pregnancy as a sedative to alleviate morning sickness, had been declared to be safe in several species. Its teratogenicity was not suspected for many years. Fetal exposure to thalidomide during the period of limb bud differentiation (approximately days 26-56) caused severe limb defects and other fetal malformations. Unfortunately, it took many years of thalidomide use and the birth of hundreds of thousands of victims to realize the relationship between the use of the drug and the resultant problems. The post-thalidomide era has witnessed an increased concern for the safety of using drugs during pregnancy and lactation. This concern led to the 1962 drug regulation act in the USA, which states that a drug must be safe and effective for its intended uses

designated on the label. It is difficult to predict teratogenicity to humans from studies performed on animals. Teratology is the science that deals with structural (e.g., limbs, kidneys, heart) or functional (e.g., brain function, behavioral changes) fetal defects. A drug that may be proven safe in animals does not ensure safety in humans. For example, the initial safety data of thalidomide was based on animal studies. The reverse is also true. A number of drugs that caused fetal malformation in animals, failed to give the same results in humans. For example, corticosteroid compounds are teratogens in animals but not in humans. About 30 drugs have been proven to be significant teratogens to humans; however, the vast majority of drugs used in the US carry a disclaimer in their package inserts and in published literature indicating that the safe use of this drug in pregnancy has not been established and should be used only if the anticipated benefits outweigh the potential risk to the fetus. Pharmaceutical manufacturers simply are reluctant to engage in efficacy and safety studies during pregnancy in light of the current ethical, regulatory and legal environment. Even though animal studies have provided a vast wealth of information concerning teratogenicity of drugs, the conclusions of these studies cannot be extrapolated from one species to another or from animals to humans. For example, thalidomide causes fetal malformation in humans and rabbits, but not in rodents. To help physicians in the decision-making process, in 1979 the FDA established the following five categories of drugs based on the potential benefits and risks for a pregnant woman and the fetus.

Category A: Indicates drugs for which well-controlled studies in pregnant women have failed to show a risk to the fetus. Even though one cannot entirely rule out a risk, it is assumed that when a drug is placed in this category, its use during pregnancy is relatively safe.

Category B: Refers to drugs that show no evidence of risk to humans. Animal studies may have failed to demonstrate a fetal risk in animals, and there are no adequate studies in humans; **or** animal studies have shown some fetal risk that has not been demonstrated in humans.

Category C: Also has two meanings. This category indicates that risk cannot be excluded. Either animal study has shown fetal risk and there are not adequate studies in humans, or studies in humans and animals are lacking. However, potential benefits may outweigh the potential risk.

Category D: Applies to drugs that show positive evidence of risk in humans. Data indicates that drugs in this category show risk of birth defects in humans, but the potential benefits of the drugs may justify the potential risk. These drugs are usually used in life-threatening circumstances or in diseases for which safer drugs cannot be used or are ineffective.

Category X: Applies to drugs that are contraindicated during pregnancy. Studies in both humans and animals have demonstrated fetal risk that clearly outweighs the potential benefits. The FDA advises that physicians should inform the pregnant patient of the potential risk to the fetus.

Suggestions have been made that the FDA should modify this classification system to a more meaningful and evidence-based system. A modified system has been instituted in Europe.

DRUG TRANSPORT

Drugs are transferred from the mother to the fetus through the placenta, which acts as a lipoprotein membrane. Following its intake, a drug circulates between mother and fetus in the same way as nutrients, oxygen, and other substances needed for growth, and then waste products are expelled. As stated earlier, this process takes place in the placenta. Exchange of solutes takes place across fetal capillaries contained in the villi. The driving force behind the diffusion of the drug through the placenta is the concentration gradient. Drugs having low molecular weight, lipid solubility, neutral polarity, and low protein binding properties, favor diffusion through the placenta. Most drugs have molecular weight that ranges from 250 to 400. Such drugs are capable of crossing the placenta without difficulty. However, compounds having molecular weight over 1000 can cross the placenta causing fetal abnormalities, whereas heparin, which has a molecular weight of 20,000, cannot cross the placenta, and consequently will not cause any fetal malformation. Because of these characteristics, heparin is the recommended anticoagulant during pregnancy. Highly lipid soluble drugs, such as thiopental, can reach fetal circulation within a short period of time. Due to its polarity, the muscle relaxant vecuronium diffuses through the placenta slowly.

A number of physical and physiologic changes take place during pregnancy that may change the pharmacokinetics of drugs, and ultimately change the quantity of the drug reaching the fetus. Pregnancy is usually accompanied by a delay in gastric emptying rate and a decreased GI motility. These changes result in slow but thorough absorption of drugs from the GI tract and, in turn, a lower peak plasma concentration. It appears that the decrease in plasma albumin during pregnancy, along with increased binding competition and decreased hepatic metabolism during the latter phases of pregnancy may increase the amount of circulating free drug.

EFFECT OF DRUGS ON FETUS

Many drugs taken during pregnancy may cross placental barriers and enter the fetal blood. Some of these drugs are potentially harmful to the fetus. A drug may affect the fetus by several ways:

1) **Direct action**, which may result in toxicity or teratogenicity. A teratogen is an agent that causes congenitally deformed fetuses. Established teratogenic agents include antineoplastics, antimetabolites (i.e., amethopterin and fluorouracil), alkylating agents (i.e., cyclophosphamide) and amphotericin, estrogens (diethylstilbestrol), thalidomide, and organic mercury. Possible teratogens include LSD and sulfonylureas. Others are narcotics, heroin, morphine, excessive salicylates, coumarin, and excessive phenobarbital.
2) **Constriction of the blood vessels in the placenta**, resulting in reduction or deprivation of nutrients and oxygen as well as accumulation of waste materials.
3) **Effects on the myometrium** that may cause physiological changes. For example, oxytocin, which stimulates contraction of the uterus, may cause fetal asphyxia.
4) **Indirectly affecting the fetus** by altering the bio-chemical dynamics of the mother. The extent of the effects depends on dosage, duration of use, potency of the drug and stage of pregnancy. During the early stages after conception (first 3 weeks), teratogenic drugs may have minimal deleterious effects, but these effects become crucial between the 3rd and 8th weeks of pregnancy. In this period, drugs that cross the placental barrier may have no detrimental effect, or may result in spontaneous abortion, true teratogenicity, or slow, permanent functional or metabolic defect that may appear years later. Teratogenicity does not appear as a threat when drugs are used in the 2nd and 3rd trimester. However, physiologic and biochemical function may be altered.

COMMON DISORDERS IN PREGNANCY

Anemia: The food taken by pregnant women also provides nourishment to the fetus. Regular meals that consist of a well-balanced diet are of paramount importance. Meat, fish, dairy products, beans, peas (as a good source of protein) are essential. Dairy products and vitamin A & D fortified milk will supply calcium and vitamins A and D. Eggs, liver, enriched bread or cereal and green vegetables provide iron, a component of hemoglobin, which carries oxygen to various parts of the body. A pregnant woman with a hemoglobin concentration of <10gm/dl is considered anemic. It is estimated that about 80% of women during pregnancy suffer from anemia. Another cause of anemia is deficiency of vitamin B_{12} and folic acid.

Nausea: Nausea and vomiting, especially in the morning, are experienced often during pregnancy. This condition continues during the first month until the 14th to 16th week of pregnancy. Then they usually subside. These symptoms are unpleasant, but usually harmless. However, in some cases the vomiting can be frequent and intense (hyperemesis). This may lead to dehydration and deprivation of nutrients.

Gastroesophageal Reflux Disease: GERD is common during pregnancy, and it is caused by relaxation of the esophageal sphincter allowing gastrointestinal fluid to re-enter the esophagus. This activity results in irritation of the esophageal mucosa. With advancing pregnancy, the weight of the enlarged uterus places pressure on the stomach, causing increased episodes of GERD. This condition usually disappears at the end of pregnancy.

Weight Gain: Normal weight gain during pregnancy is 2 to 3 lbs. per month. Both excessive weight gain or meager weight gain can harm the fetus. The increase in weight is due to the fetus, edema, placenta, engorged uterus and breasts. Edema occurs mostly in the legs due to stasis. Elastic support hose as well as lying on the left side and elevation of the legs are helpful in reducing edema.

Constipation: Constipation may be encountered during pregnancy mainly due to the decreased GI motility and increased intestinal transit time. This, along with increased downward pressure from the uterus, may cause hemorrhoids. Expectant mothers should be encouraged to increase the amount of fiber in the diet. Bulk-forming laxatives containing psyllium are recommended because of their safety and efficacy. Irritant laxatives should be avoided. Stool softeners such as docusate sodium provide relief of constipation and may be used during pregnancy. Caution should be exercised when using mineral oil, since it may interfere with absorption of lipid soluble vitamins. It is always best to recommend that the patient speak with their physician prior to taking any of the above.

Backache: Backache in pregnancy is common and may range from mild to severe. Ligaments and the fibrous tissue that control the joints, especially the pelvis, tend to relax during pregnancy to allow expansion of the pelvis during delivery. However, this characteristic, with the weight gain, allows the hip to be more vulnerable to strain. In addition, the change in center of balance that results can alter posture. All of these factors can contribute to backache.

DRUGS IN PREGNANCY

Antiemetics: Mild to severe nausea and vomiting occur in up to 90% of pregnancies. These bothersome symptoms take place mainly during the period from the third to seventh weeks, and usually cease by the end of the fourth month. Many pregnant women take antiemetics for relief. Although the symptoms are annoying, they do not pose severe consequences. The exact mechanism that triggers nausea and vomiting is not clear. However, the increased plasma concentration of chorionic gonadotropin hormone and progesterone is believed to play a role in the etiology of these symptoms. Nonpharmacologic measures such as eating small frequent meals high in carbohydrates or protein may reduce the intensity. Avoidance of spicy food, noxious odors, and fatty food is recommended. If these measures fail to provide relief, then the use of drugs may be recommended. (Always under physician guidance).

Antiemetics such as meclizine, dimenhydrinate and certain phenothiazines may be used. Meclizine has been shown to be teratogenic in animals, but apparently not in humans. No evidence has been found to suggest a relationship between the used of dimenhydrinate and fetal malformation. The use of promethazine appears to have no adverse effects on the fetus. Prochlorperazine use has been linked to increased risk of cardiovascular abnormalities. Jaundice and extrapyramidal symptoms have occurred in neonates of mothers who have taken chlorpromazine during pregnancy. Even though meclizine and promethazine appear to have no fetal effects in humans, their use during the last weeks of pregnancy should be avoided.

In the 1960's, a combination of the antihistamine doxylamine and pyridoxine was the most widely used drug for nausea and vomiting during pregnancy. The combination of these two drugs was marketed under the trade name Bendectin®, and was the only medication approved by the FDA for nausea and vomiting associated with pregnancy. However, in the 1970's lawsuits alleging that Bendectin® is teratogenic were filed against the manufacturer, in spite of many case reports and epidemiologic studies that showed no increased risk of teratogenicity following the use of the drug. In 1982, to avoid added mounting costs in litigation, the drug was withdrawn from the market by the manufacturer, leaving pregnant women without the only drug approved by the FDA for managing nausea and vomiting during pregnancy. On the other hand, a Canadian panel concluded that the drug is safe, and as a result, the combination medication continues to be marketed in Canada under a different trade name.

Antacids: Antacids, which are primarily available as OTC drugs, are used by 30 to 50% of pregnant women to relieve symptoms of gastroesophageal reflux disorders. The use of aluminum, magnesium, and calcium salts is believed to be safe during the last two trimesters. Sodium bicarbonate should not be used as it may lead to metabolic alkalosis. In high doses, magnesium trisilicate use may cause silicaceous nephroliasis, and thus it should be avoided.

Analgesics: Aspirin, as well as acetaminophen, are commonly used drugs for headache and pain relief. Although the use of aspirin for rheumatoid arthritis has diminished since the introduction of the non-steroidal anti-inflammatory drugs, aspirin is frequently used during pregnancy. Its use was once believed to cause fetal malformations such as cleft palate and congenital heart disease. However, in subsequent and more comprehensive studies, aspirin has been shown to be safe. Aspirin is capable of crossing the placenta and causing birth defects in animals, but rarely in humans.

Acetaminophen is recommended for use during all stages of pregnancy. Its short-term use in therapeutic doses appears to be safe. Certain non-steroidal anti-inflammatory drugs may cause constriction of the ductus arteriolus, when used during pregnancy.

Caffeine: Caffeine is a naturally occurring substance found in coffee, tea and cocoa. It is often included in OTC medications for the common cold, appetite suppression and CNS stimulation. It is also found in many beverages. Depending on the way it is brewed, 5 ounces of coffee may contain from 30 to 180 mg of caffeine. Stimulants usually contain from 100 to 200 mg of caffeine per tablet, whereas anorexics may contain up to 120 mg of caffeine per tablet. Because of its presence in popular drinks and chocolate bars, as well as in coffee and tea, caffeine is believed to be the most widely ingested chemical during pregnancy. Conflicting results from studies concerning the effects of caffeine consumption by expectant mothers have been reported. It appears that the relationship between low to moderate consumption of caffeine and fetal abnormalities or complications of pregnancy have not been established. However, low birth weight infants and spontaneous abortions may be associated with caffeine ingestion. Pregnant mothers should be advised to refrain from heavy intake of coffee, tea, beverages and foods that yield 300 mg of caffeine daily. In 1980, the FDA recommended that pregnant women avoid the ingestion of caffeine.

Smoking: It has been estimated that over fourteen million women between the ages of 18 and 44 smoke cigarettes. Studies have shown that cigarette smoking may result in increased fetal, neonatal and infant mortality, low birth weight of infants and complications of pregnancy. The detrimental effects of smoking appear to be dose-

related. Smoking less than one pack a day resulted in 20% increase in the risk of fetal mortality, whereas smoking more than one pack a day caused an increase of 35%. An increase in low birth weight is associated with the degree of smoking. Pregnant women should be advised as to the importance of smoking cessation at least while pregnant.

Alcohol: Alcohol consumption during pregnancy can produce a group of fetal abnormalities known collectively as fetal alcohol syndrome (FAS). This syndrome is characterized by intrauterine and postnatal growth retardation, characteristic pattern of facial features (short palpebral fissures, flattened maxilla, hypoplastic philtrum and cleft palate), CNS abnormalities (microcephaly, behavioral abnormalities, and mental retardation). As the infant becomes older, the facial changes may become less apparent, but short stature, microcephaly and behavioral abnormalities may persist. These anomalies are usually seen in infants of women who, during pregnancy, consumed the equivalent of 2-3 ounces of absolute alcohol (4-6 drinks of hard alcoholic beverages) per day throughout pregnancy or with frequent binge drinking (6 or more drinks on one occasion per month). Moderate consumption (more than one ounce of absolute alcohol per week) may result in low birth weight, spontaneous abortion and impaired motor and mental development. Consumption of one to two drinks daily may be associated with growth-retarded babies. It has been estimated that about 20% of pregnant women consume some alcoholic beverages during pregnancy, and only 1-2% consume 4 or more drinks daily. The incidence of FAS is 1 per 1000 live births, and about 4% of women who consume alcohol heavily may give birth to infants with FAS.

The mechanism of fetal abnormalities induced by alcohol is unknown. It is possible that ethanol or its metabolite acetaldehyde may directly or indirectly affect neuronal and nonneuronal brain cells.

Opioids: The incidence of opioid intake during pregnancy is relatively significant. About 0.2% of pregnant women are heroin or methadone users, and up to 75,000 babies annually receive opioids in utero. Growth retardation involving weight and length are encountered in infants exposed to opioids. Additionally, neonatal withdrawal syndrome characterized by hyperirritability, GI disturbances, respiratory distress, and seizures may be encountered. Acute heroin withdrawal symptoms occur within 24 hours, whereas that of methadone is mostly delayed in nature.

Cocaine: It is estimated that 1% of pregnant women in the US use cocaine. In certain segments of the population, estimates may be as high as 15%. It is believed that about 100,000 babies are exposed to cocaine in utero. The most commonly encountered obstetric complications among users include placental abruption, premature delivery, and uterine rupture. Other effects include cerebral infarction, seizures and intrauterine growth retardation. Congenital malformation especially those involving the cardiovascular and genitourinary systems have been reported.

USE OF DRUGS DURING LACTATION

Over the last 30 years, breast-feeding has gained vast popularity, and currently it is more prevalent than in past years. This has been recommended by pediatricians and other health professionals as the method of choice of nutrition for infants. Breast-feeding provides nutritional, immunologic and psychological advantages over bottle-feeding. In addition, it is advantageous in medically underserved areas of the country where nutrition and sanitation are inadequate. In 1995, about 60% of new mothers in the US were breast-feeding at hospital discharge. Breast-feeding plays an important role not only in preventing infant mortality, but in morbidity from infectious diseases and in decreasing the risk of immunologically mediated disorders. Even though human milk is ideal for providing total nutritional needs to the growing infant, there are certain conditions that may require the use of formulas. Refraining from breast-feeding should be based on the fact that the risk to the infant outweighs the advantage of breast-feeding.

The increasing prevalence of breast-feeding has caused clinicians to direct their attention to the potential of harmful effects to infants from drugs taken by the nursing mother. There are several factors that play a role in determining the amount of drugs excreted in the mother's milk.

1. **Characteristics of the drug:** Most drugs cross-mammary alveolar membranes by passive diffusion; others may pass through the aqueous-filled pores or by carrier mediated transport. The factors that determine the extent of diffusion of the drug into the breast milk include plasma protein binding, molecular weight of the drug, or ionization and degree of lipophilicity. In order for a drug to cross any biological membrane, it must be present in the free form. Thus, drugs that are highly protein bound, may be excreted in breast milk in low quantities. Highly protein bound drugs, such as warfarin, are incapable of crossing the mammary membrane in appreciable amounts. Drugs whose molecular weight is large (i.e., insulin, heparin) will not be excreted into breast milk.

The pH of breast milk, which is about 7.00, is somewhat more acidic than plasma. Consequently, acidic drugs will occur as ionized molecules in the plasma and will fail to diffuse into breast milk. In contrast, basic drugs will be available as non-ionized molecules in the plasma and will be able to cross the membrane and reach the milk compartment.

In addition to protein, minerals and lactose, the milk of nursing mothers is rich in fat. Lipophilic drugs may bind to milk causing accumulation of the drug in the milk.

2. **Characteristics of Infant:** Age of an infant is an important consideration. The younger the infant, the more potential for a stronger response to drugs, especially when the kidneys and liver are not functioning effectively.
3. **Frequency of feeding the infant** has an effect on the amount of drug reaching the milk. Infants, who are breast fed frequently and for long periods, as it happens in the early neonatal stage, will be more exposed to drugs than infants who are breast fed less frequently, as is the case with older infants or infants who receive solid food supplements.

4. **Another important consideration is the gastric emptying rate** of infants. Infants who are breast-fed have a considerably shorter gastric emptying rate than infants who are bottle-fed. This results in reduction of exposure time of the drugs. The drug regimen of the nursing mother may contribute to the amount of drug reaching milk. Feeding the infant one-hour after drug intake when it is at peak level in the mother's plasma and milk compartment, will result in exposing the infant to larger quantities of the drug. Another consideration is whether the drug product ingested by the lactating mother is a long or short acting medication. Long-acting drugs pose more risk to infants than short-acting medications.

5. **Nature of the drugs** can play a role in drug effect. If the drug taken by the nursing mother can be given to infants, then it is unlikely that the amount of drug reaching milk will exceed the pediatric therapeutic dose. Such drugs are safe to use during lactation. However, if the drug taken by the mother is not recommended for infants, then there is risk potential for harmful effects to breast-feeding the baby.

This concludes our lesson on drug considerations during pregnancy and lactation. The decision to take medications (both OTC or by prescription) is one that must be evaluated carefully. The physician, patient and pharmacist must work together in order to evaluate these difficult considerations. This is another area where the pharmacist's knowledge, experience, education and judgment must come into play.

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REMAINING TOPICS FOR 2005	
▪ **OCTOBER—**MS & ALS	▪ **NOVEMBER/DECEMBER—** Food/Drug Interactions

Fill in the information below, answer questions and return **Quiz Only** for certification of participation to:
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LESSON EVALUATION

Please fill-out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

List the body systems affected by pregnancy	Yes	No
Describe the physiology of pregnancy	Yes	No
Discuss drugs that are often taken during pregnancy	Yes	No
List the major effects of drugs on the fetus	Yes	No
Discuss the common disorders that are associated with pregnancy	Yes	No
Describe the affects of drugs upon lactation	Yes	No

2. Was the program independent & non-commercial? Yes No

	Poor			Average			Excellent
3. Relevance of topic to your practice	1	2	3	4	5	6	7
4. Author's ability to communicate	1	2	3	4	5	6	7

5. What did you like most about this lesson?_____
6. What did you like least about this lesson?_____
7. How would you improve this lesson?_____
8. Further comments or suggestions for future programs_____

(WATCH OUR WEBSITE FOR RESULTS OF PARTICIPANT EVALUATIONS)

Quiz—Please Select the Most Correct Answer

1. Pregnant women often experience gastroesophageal reflux disease.
   A. True
   B. False
2. Teratology is defined as the science that deals with:
   A. Structural or functional fetal defects
   B. Carcinogenesis
   C. Geriatrics
   D. Dyskeratosis
3. Which of these is incapable of crossing the placenta?
   A. Fluorouracil
   B. Vaccuronium
   C. Thiopental
   D. Heparin
4. Which of these is correct regarding the way a drug may affect the fetus?
   A. Dilation of the myometrium
   B. Dilation of blood vessels in the placenta
   C. Indirectly affect fetus by altering biochemical dynamics during pregnancy
   D. Drugs are always useful during pregnancy
5. Which of these is not considered to be an antiemetic?
   A. Meclizine
   B. Progesterone
   C. Promethazine
   D. Prochlorperazine
6. Which is uncommon in pregnancy?
   A. Constipation
   B. Nausea
   C. Hallucinations
   D. Backache
7. In 1980 the FDA recommended that pregnant women:
   A. May take 500 mg of caffeine daily
   B. Should drink 3 cups of coffee daily
   C. Drink coffee only in the morning
   D. Should avoid intake of caffeine
8. Consumption of 1 or 2 alcoholic drinks per day during pregnancy may be associated with:
   A. Growth-retarded babies
   B. Spontaneous abortion
   C. Low birth babies
   D. Neonatal withdrawal symptoms
9. Breast-feeding is not recommended by physicians as the method of choice
   A. True
   B. False
10. Which of these is not a factor that determines the extent of diffusion of a drug into breast milk?
    A. Age of the lactating mother
    B. Plasma protein binding
    C. Molecular weight of the dru
    D. Degree of lipophilicity of the drug

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