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Review

Physiological and Pharmacokinetic Alterations and Drug-Nutrient Interactions During Pregnancy

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Abstract

During pregnancy, many physiological and metabolic alterations occur to support the requirements of the developing fetus. Alterations associated with the respiratory, cardiovascular, hematological, urinary, and gastrointestinal systems (GIS) may result in pregnancy-related disorders and may change the pharmacokinetic or pharmacodynamic characteristics of received drugs; the pharmacokinetic phase of drugs include their absorption, distribution, metabolism, and excretion. This involves reduced plasma albumin concentrations, increased cardiac output, increased gastric pH, reduced intestinal motility, and increased glomerular filtration rate (GFR). Drug-nutrient interactions are defined as physicochemical, physiological, and physiopathological interactions between a drug and a nutrient as well as between a drug and food, multiple nutrients, other dietary components, or nutritional status of the body. Understanding the impact of these changes on drug pharmacokinetic properties and food, drug-nutrient interactions are essential to ensure/optimize maternal health and fetal development. As a consequence, drug-nutrient interactions over the course of the pharmacological treatment of complications and disease during pregnancy should be considered. The purpose of this review is to summarize physiological changes during pregnancy and their effects on pharmacokinetic properties and to evaluate potential food, nutrient, and drug interactions.

Keywords: Pregnancy, drug, nutrient, interaction, pharmacokinetics

Introduction

During pregnancy, a large part of the body is affected by the physiological and anatomical changes that start in early pregnancy. Many of these changes significantly affect the pharmacokinetic (absorption, distribution, metabolism, and excretion) and pharmacodynamic properties of different drugs (1-3). During treatment, the use of medicines with the content of only some active ingredients is important to ensure maternal and fetal safety during pregnancy (4-6).

Drug–nutritional element interactions are defined as the physicochemical, physiological, and pathophysiological relationships between a drug and nutritional element or between a drug and multiple nutritional elements, nutrients, and constituents or the nutritional status in a broader sense (6-8). Drug–nutritional element interactions can occur in four steps: extracellular bioinactivation, decrease/increase in absorption, decrease/increase in efficacy, and decrease/increase in excretion (elimination) (7). Therefore, the fact that health professionals consider the physiological changes and the factors affecting the distribution of the drug in the body during pregnancy is important to ensure the effectiveness of pharmacotherapy. In this review article, we aimed to investigate the effects of physiological changes during pregnancy on the pharmacokinetic properties of the drug and the interactions of drugs, nutrients, and nutritional elements.

Physiological Changes and Drug Metabolism in Pregnancy

Pregnancy is a process in which many physiological differentiations occur in the cardiovascular, respiratory, excretory, gastrointestinal, and circulatory systems, which alter the interactions of nutrition, nutritional element, and drug metabolism. In summary, the rate and volume of the heart increase, lung capacity decreases, glomerular filtration rate (GFR) increases, blood volume increases, blood circulation decreases, and gastrointestinal system (GIS) motility decreases; in addition, changes, such as nausea and vomiting, occur affecting nutrition. The physiological changes associated with pregnancy are summarized in Table 1.

During pregnancy, the interactions between drug metabolism and nutrition and nutritional element may be pharmaceutical, pharmacokinetic, and pharmacodynamic. The pharmaceutical interactions occur within the delivery medium, such as enteral tube or gastrointestinal lumen. This can affect the bioavailability of the drug or nutritional element (8). The pharmacokinetic interactions include the processes of absorption, distribution, metabolism, and excretion of the drug or nutritional element. The pharmacodynamic interactions include physiological changes

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Table 1. Physiological changes depending on pregnancy

System	Indicator	Change
Cardiovascular	Cardiac output	Increase
	Pulse volume	Increase
	Heart rate	Increase
	Systemic vascular resistance	Decrease
Respiratory	Pulmonary vascular resistance	Decrease
	Ventilation rate	Increase
	Total lung capacity	Decrease
	Respiratory volume	Increase
Excretion	Glomerular filtration rate	Increase
	Renal blood flow	Increase
	Serum creatinine	Decrease
Gastrointestinal	Gastric emptying	Decrease
	Small-bowel transit rate	Decrease
	Constipation	Increase
	Nausea	Increase
	Vomiting	Increase
Circulatory	Colloid osmotic pressure	Decrease
	Hemoglobin concentration	Decrease
	Coagulation	Increase
	Blood circulation	Decrease

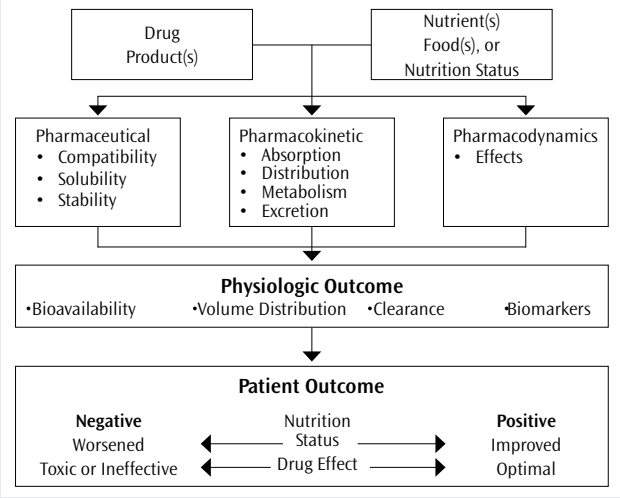

Figure 1. The diagram for the drug–nutritional element interactions (6)

in the mechanism of action of the drug or nutritional element (6). The physiological results of the drugs are obtained by evaluating bioavailability, distribution volume, excretion, and indicators. Accordingly, the nutritional status and drug effects can negatively or positively affect the patient. Although the nutritional status can worsen the patient's condition, it may also have a positive effect on the healing process. Similarly, the toxic effect of drugs and the reduced efficacy negatively affect the patient's health, and the ideal level of drug efficacy may contribute to the desired healing process. The mentioned interactions of the drug and nutritional element are shown in Figure 1.

Cardiovascular System

Pregnancy is related to significant anatomical and physiological restructuring of the cardiovascular system. Ventricular wall thickness, cardiac muscle contraction, and cardiac compliance increase. The increase in heart outflow reaches the highest level in the 28–32 weeks, and subsequently, it attains stability and does not change significantly until birth. In addition, the uterine blood circulation increases 10 times, and the blood circulation in the kidney increases at a rate of 50%. This is important particularly for patients who had hypertension prior to pregnancy and who use antihypertensive drugs (1, 9).

The increase in total body water, blood volume, and hydrostatic pressure in the capillary vessels significantly increase the distribution volume of hydrophilic substrates. In addition, an increase in the free forms and biological activities of protein-binding drugs can be observed due to the decrease in the concentration of serum albumin and other protein-binding drugs (1-3).

Respiratory System

Anatomical changes, such as increased vascularization in the respiratory system and edema in the upper respiratory tract, occur due to the elevation of progesterone level during pregnancy. The breathing volume (tidal volume) begins to increase as of the first trimester of the pregnancy and reaches up to 30%–50%. While the respiratory rate does not change during this period, the rate of ventilation per minute increases significantly (30%–50%). In addition, the diaphragm shifts 4–5 cm upward due to the growing intrauterine pressure caused by the growing fetus. This leads to a 10%–20% reduction in both functional residual capacity and total lung capacity (3, 10, 11).

Excretory System

Due to the effects of progesterone and relaxin hormones on smooth muscles, the urine collecting channels expand. Accordingly, the blood circulation in the urinary system slows down and pregnant women become prone to urinary tract infections. Increasing renal blood flow and GFR as of the fourteenth week of pregnancy causes a decrease in serum creatinine concentration. Hence, the elimination rate of the drugs that are excreted from the kidneys can increase at a rate of 20%–65% and cause the half-life of the drugs to decrease (1-3).

While prostaglandins facilitate atrial natriuretic factor and progesterone natriuresis, they cause the accumulation of aldosterone and estrogen sodium. Accordingly, while a significant level of water and sodium accumulation occurs during pregnancy, the total body water and plasma volume increase. Because of the increase in volume, the maximum concentration (C_{max}) of the hydrophobic drugs, which particularly have a very low volume of distribution, decreases (1, 2).

Gastrointestinal System

The increase of progesterone hormone during pregnancy causes a delay of gastric emptying and the prolongation of the transit time of the small intestine. These changes affect the bioavailability-related variables, such as C_{max} and maximum concentration time (T_{max}) of orally administered drugs. The decrease in C_{max} and increase in T_{max} are important for single-dose medicines. In addition, nausea and vomiting in the early period of pregnancy decrease the drug absorption and cause the plasma drug concentration to

decrease. In addition, increased constipation prevalence and the use of pain relievers slow down GIS movements and may delay the absorption of drugs in the small intestine (1-3).

Circulatory System

The number of white and red blood cells increase during pregnancy. An increase in the plasma volume (45%) at a rate higher than that of the mass of red blood cells leads to the appearance of physiological anemia particularly at the beginning of the third trimester (thirtieth to thirty-second weeks) (1, 2).

In addition to slowing blood circulation, changes in coagulation and fibrinolytic pathways lead to an increase in coagulation during pregnancy. Plasma levels of clotting factors, fibrinogen, and the von Willebrand factor begin to increase in the first trimester and reach the highest level in the third trimester. This leads to minimal blood loss after birth, but causes pregnant women to be at high risk for thromboembolism (1, 3).

Pharmacokinetic Changes and Drug Metabolism During Pregnancy

In a healthy pregnancy, there are various changes in the mother's body in response to the stimuli generated by the fetus. These changes are important for the growth and development of the fetus and for the development of placenta, and they change the disease process and treatment significantly. In this regard, the pharmacokinetic properties of the drug play an effective role. Maternal and fetal changes during pregnancy cause the differentiation of pharmacokinetic properties (8).

The pharmacokinetic process is defined as the parameters, such as absorption, distribution, metabolism, and excretion, which the body shows against a drug or any component. The properties of these parameters ensure an appropriate and effective dose to be determined. Bioavailability is defined as a measure of both the relative amount getting into the general circulation and the momentary rate of the drug that is administered (12).

Based on these physiological processes and interaction mechanisms that occur following drug ingestion, the interaction of drug and nutritional element is examined in four main groups: ex vivo bioinactivation, interactions related to the absorption process, interactions related to the physiological effect, and interactions related to the excretory process. Interactions generally occur during absorption, distribution, placental passage, and protein binding of the drug and during the effects of the enzymes involved in food–drug interactions; they vary depending on the physiological and anatomical characteristics in the pregnancy period as summarized below (7).

Drug Absorption

Drug absorption is the passage of the drug from the administration site to the systemic circulation. Intravenous (IV) drugs are completely absorbed after directly entering into the bloodstream, and intramuscular (IM) or subcutaneous administration may delay the time to reach C_{max}. However, orally administered drugs are exposed to many factors, such as GIS pH, nutrients, intestinal transit time, and bowel metabolism, and the bioavailability is affected at a level that cannot be compared with the IV mode (4, 12).

Symptoms of nausea and vomiting during pregnancy decrease the bioavailability of the drug because they shorten the duration of absorption after oral administration. It is thought that hormonal changes, such as the increase in progesterone especially during gestation, are effective on the smooth muscle cells by decreasing intestinal motility and by prolonging gastric emptying time and the duration of intestinal transit. This reduces drug efficacy, prolongs T_{max} value, and is an important interaction in medications for which the effect begins rapidly. In the first and second trimesters, due to the increase in gastric mucus secretion and the decrease in acid secretion, gastric pH increases and symptoms, such as nausea and reflux, may occur (4, 13).

The increase in pulmonary blood circulation and cardiac output and respiratory rate, which causes hyperventilation, are observed in early gestation. In this case, the alveolar absorption of the drug administered through inhalation can increase. Increased perfusion in skin and mucosal membranes causes the absorption of locally administered drugs to increase (4, 13).

Distribution of Drugs

Drug distribution, which is also defined as reversible circulation after the drugs entering the systemic circulation, is influenced by the factors, such as cell perfusion, cell binding, fat solubility, and binding to plasma proteins. With the increased cardiac outflow, uterine and renal perfusion significantly increase in pregnant women. With the increased plasma volume in the third trimester, the distribution of many drugs, particularly water-soluble drugs, increases and their plasma concentrations decrease (4, 13, 14).

Placental Transition of Drug

Many drugs, which are in a double-layered lipid structure, pass through the placenta and reach the fetus easily. In general, it is thought that the drugs with a small molecule structure pass through the placenta via passive diffusion, and those with a large molecular structure pass via active transport, facilitated diffusion, phagocytosis, and pinocytosis. These mechanisms also play an important role in the transport of nutritional elements through the placenta (12-14).

Protein Binding of Drugs

Since the increase in plasma volume and the increase in albumin synthesis does not show parallelism during pregnancy, plasma albumin concentration decreases. In addition, since albumin is usually under the control of hormones during pregnancy, it leads to a decrease in the binding capacity of drugs to proteins and an increase in the free drug concentration. It has been determined that the usable active drug is balanced with the decrease in albumin against the increase in biotransformation and excretion. The levels of α1-acid glycoprotein, which is another plasma protein, remain at a stable level during pregnancy (6, 13).

Enzymes in Food-Drug Interactions in Drug Metabolism

Rapid changes in the estrogen and progesterone levels during healthy pregnancy have multiple effects on liver metabolism. Progesterone regulates microsomal enzyme activity and causes the metabolism of drugs with phenytoin active ingredient to increase. In contrast, progesterone and estradiol inhibit microsomal oxidases; thus, the excretion of the other drugs, such as theophylline and caffeine, decreases (6, 14).

Table 2. Changes occurring in certain enzymes due to pregnancy

Enzyme	Change	Possible substrate-active ingredient
CYP3A4	Increase	Glyburide, nifedipine, indinavir
CYP2D6	Increase	Metoprolol, paroxetine, duloxetine, flocetine, cytolopram
CYP2C9	Increase	Glyburide, phenytoin, fuloxetine
CYP2C19	Decrease	Glyburide, citalopram, diazepam, omeprazole, pantoprazole, propranolol
CYP1A2	Decrease	Theophylline, clozepine, olanzepine, ondansetron, cyclobenzapyrine
UGT1A4	Increase	Lamotrigine
UGT1A1/9	Increase	Acetaminophen
NAT2	Decrease	Caffeine

CYP3A4: Cytochrome 3A4; CYP2D6: Cytochrome 2D6; CYP2C9: Cytochrome 2C9; CYP2C19: Cytochrome 2C19; CYP1A2: Cytochrome 1A2; UGT1A4: uridine diphosphate glucuronyltransferase 1A4; UGT1A1/9: uridine diphosphate glucuronyltransferase 1A1/9; NAT2: N-acetyl transferase 2.

The enzymes that enable the metabolism of the drug are mainly found in the liver and intestine and in the systemic circulation, lung, skin, central nervous system, and kidneys. Through the blood circulation, the lipophilic drugs passing through these organs that are involved in excretion and are converted into hydrophilic compounds, which facilitates the excretion of the drug from the body (12).

The enzymes that enable the metabolism of the drug in the liver are divided into two groups as phase I enzymes (oxidation, reduction, hydroxylation, and demethylation) and phase II enzymes (conjugation and acetylation). The reactions that include the phase I enzymes are in the more polar or reactive portion of the drug molecules, whereas the reactions that include phase II enzymes conjugate with compounds, such as glucuronic acid, sulfate, amino acid, and glutathione and involve the excretion process via urine or bile.

The cytochrome P450 (CYP) enzyme system, which is responsible for the metabolism of many drugs and endogenous substrates (steroids, fatty acids, and eicosanoids), is the most important enzyme system for phase I reactions and catalyzes different types of oxidative reactions (4, 11, 15). Due to the phase I oxidative metabolic reactions, drugs and chemical components dissolve more in water and convert into a form that generates less toxic intermediates. The phase II enzymes catalyze conjugation reactions involving the binding of intracellular polar groups, such as glucuronate, glutathione, and sulfate, to foreign molecules. In addition, the protection of the organism is provided through the elimination of reactive oxygen species that develop as a result of phase I reactions. Of the most important phase II enzymes, microsomal uridine diphosphate glucuronyltransferase (UGT) and cytosolic glutathione S-transferase catalyze the conjugation reactions. As a result, the excretion of xenobiotics is facilitated by the formation of water-soluble glucuronate and glutathione (11, 15). The levels of phase I and phase II enzymes involved in the metabolic process of drugs vary during pregnancy (4). The enzymes that are most frequently affected in nutrient, nutritional element, and drug interactions are those of the CYP enzyme system (CYP3A, CYP2E1, CYP2D6, CYP2C9, CYP2C19, and CYP1A2), UGT1A4, and carbonyl reductase 1 (CBR1). In this process, while an increase in the activity of some enzymes (CYP3A, CYP2E1, CYP2D6, CYP2C9, and UGT1A4) is observed, the activity of other enzymes (CYP1A2 and CBR1) has been reported to decrease (4, 11, 15). The changes that occur in the CYP3A enzyme is involved in drug metabolism among the P450 enzyme systems. The induction of this enzyme in the three trimesters of pregnancy changes at a rate of 40%-100%. During pregnancy, the CYP3A enzyme is stimulated by an increase in the cortisol concentration, and the enzyme activity can increase at a rate of 35%-38% in this period. The CYP2D6 enzyme is another enzyme active in metabolism and is involved in the metabolism of 25% of the drugs. The oral clearance value of the phenotype that moderately metabolizes is lower than the common phenotype in both the pregnancy period and the postpartum period. The requirement level of CYP2D6 substrates increases during pregnancy (16).

The CYP2C9 enzyme is involved in the metabolism of fewer drugs than the CYP3A and CYP2D6 enzymes. It metabolizes phenytoin, with a poor impact area, and glyburide, which is one of the commonly used drugs. Due to an increased oral clearance of the drugs of phenytoin and glyburide during pregnancy, an increase in maternal dose increases fetal exposure (17). The enzyme CYP2C19 is involved in the metabolism of fewer drugs, and the substrates of this enzyme include proton pump inhibitors (omeprazole, esomeprazole, and lansoprazole), antidepressants (citalopram and sertraline), and antiviral drugs (etravirine). The CYP1A2 enzyme is responsible for the metabolism of many drugs, such as caffeine, clozapine, duloxetine, melatonin, triamterene, and olanzapine. The enzyme activity decreases at a rate of 30% in the fourteenth-eighteenth weeks, at a rate of 50% in the twenty-fourth-twenty-eighth weeks, and at a rate of 65% in the thirty-sixth-fortieth weeks of pregnancy (16). The CYP2E1 enzyme is involved in the metabolism of several compounds, such as acetaminophen, some anesthetic drugs (halothane), and ethanol. In addition, it causes the metabolic activation of many carcinogenic and toxic compounds. Increased levels of placental lactogen in humans enable the stimulation of CYP2E1 activity (19). The CYP2B6 enzyme metabolizes many drugs, such as bupropion, efavirenz, methadone, and propofol. Unlike the other enzymes in the P450 enzyme system, the CYP2B6 enzyme is not affected by physiological and metabolic changes developing during pregnancy (20).

The UGT1A4 enzyme, which is among the phase II enzymes, plays a role in the metabolism of many antiepileptic and antidepressant drugs, such as lamotrigine and imipramine, and the UGT1A4 enzyme activity increases during pregnancy (21). CBR1, another important phase II enzyme, is involved in the metabolism of several compounds, such as doxorubicin, daunorubicin, vitamin E, and coenzyme Q. The activity of this enzyme is inhibited by 17β-estradiol during pregnancy (22).

Drug Excretion

The excretion of the drug from the kidneys occurs depending on the GFR, tubular secretion, and reabsorption. From the sixth week of gestation to the last week, no change in renal tubular reabsorption is observed despite increased GFR. In this period, an increase in GFR may result in an increased excretion of drugs whose clearance is realized by the kidneys and in a decreased steady-state concentration of the drug (6, 13).

Drugs Used in Pregnancy and Drug–Nutritional Element Interactions

Nutrients, nutritional elements, and dietary components taken with drugs can alter the process of absorption, distribution, metabolism, and excretion of the drug through physiological mechanisms (delayed gastric emptying, acidity of the environment, and flora changes) and physicochemical mechanisms (binding of the drug to the nutrient and nutritional element). Thus, the side effects may increase due to the increase or decrease of systemic drug exposure, or the treatment process may be adversely affected (20, 23). For example, grapefruit juice, which is one of the most investigated foods, holds an important place in literature on nutrient–drug interactions because it inhibits the activity of cytochrome enzymes in the small intestine through furanocoumarins in its composition (24, 25). While grapefruit juice consumption increases the oral bioavailability of some drugs (atorvastatin and sildefanil) due to the long duration of this effect, oral bioavailability of some drugs (etoposide and L-tyroxine) decreases and this may lead to adverse health outcomes (26).

The following information on active substances and nutrients, nutritional element–drug interaction used in the treatment of symptoms and diseases in pregnancy are summarized in Table 3 (24, 27-39). The reliability, prescription, and food interactions of these drugs should be assessed individually considering the risk classification (A, B, C, D, and X) of the US Food and Drug Administration (FDA), which has been organized according to the results of the studies of fetal drug exposure and toxicity relationship (40).

Analgesic Drugs

Paracetamol (acetaminophen), which has both analgesic and antipyretic properties, is the first preferred in pregnancy period and can be used more reliably than other drugs in all trimesters (41). There are studies on acetylsalicylic acid, non-steroidal anti-inflammatory drugs (ibuprofen and diclofenac), and the drugs with sumatriptan used in the treatment of migraine, and the reliability of use should be evaluated specifically to the patient (5). In a study that investigated the effect of foods on the rate of absorption of commonly used paracetamol, it has been reported that the plasma concentration of the drug is lower because a high-energy meal prolongs the gastric emptying time compared to a low-energy meal (28). In a study conducted with laboratory animals investigating the effect of grapefruit juice on the pharmacokinetics of paracetamol, the increase in the frequency of consumption of grapefruit juice was reported to significantly decrease the bioavailability of the active ingredient in paracetamol (24).

Antihistamine Drugs

Antihistamines used in the treatment of allergy symptoms during pregnancy can also be preferred in the case of nausea, vomiting, dizziness, insomnia, and hyperemesis gravidarum. Studies have reported that the use of intranasal steroids (fluticasone, mometasone, budesonide, flunisolide, and triamcinolone active ingredient) and orally taken second-generation antihistamines (cetirizine and loratadine) is safe during pregnancy in the treatment of allergies (27, 40). In a study, it has been shown that the drugs with the active ingredient of loratadine, whose absorption was determined to considerably decrease when taken with food, are more appropriate for the bioavailability when taken before a meal (29).

Asthma and Antitussive Drugs

In terms of maintaining maternal health as well as ensuring fetal oxygen, asthma treatment is important during pregnancy. Low-dose short- and long-acting orally inhaled β2 agonists (albuterol, salmeterol, and formoterol), orally inhaled corticosteroids (budesonide), or if necessary, leukotriene receptor antagonists and oral corticosteroids (prednisone, prednisolone, and methylprednisolone) can be used in the long-term treatment (42,43). In a study conducted using the oral form of albuterol, which is one of the commonly used medications, it was determined that the T_{max} value was delayed by 1 hour due to the ingestion of the drug with nutrition (30). In another study, it was reported that the intake of caffeine with albuterol increased the metabolic rate in humans and in vitro, and it reduced fat mass and fat-free tissue mass in rats (31). In a study of budesonide, another commonly used drug, it has been reported that regular consumption of grapefruit juice inhibits CYP3A activity in the gastrointestinal mucosa, resulting in a doubling of both controlled and slow-release budesonide bioavailability (32).

Gastrointestinal System Drugs

Nutritional and lifestyle changes as well as pharmacological treatment can be initiated in conditions, such as nausea, vomiting, gastroesophageal reflux, constipation, and diarrhea, which occur due to physiological changes in the maternal period (44).

Antiemetic drugs (trimethobenzamide), phenothiazines (prochloroperazine and promethazine), histamine receptor blockers (ondansetron), antacids (calcium carbonate, aluminum hydroxide, and magnesium trisilate), sucralfate, histamine type 2 receptor antagonists (cimetidine and ranitidine), proton pump inhibitors (omeprazole and lansoprazole), and dopamine antagonists (methochloropamide) can be used in the treatment of GIS symptoms in the early stages of pregnancy (44). In a systematic review and meta-analysis conducted to evaluate the relationship between the use of gastric acid inhibitors (proton pump inhibitors, H_2 receptor antagonists) and vitamin B_{12}, a statistically significant positive correlation was found between the long-term use of these drugs and the deficiency of vitamin B_{12} (33).

If the constipation developing due to maternal physiological and hormonal changes cannot be controlled with sufficient fluid consumption and a fiber-rich diet, osmotic laxatives (lactulose and polyethylene glycol), which are the drugs increasing fecal mass, can be prescribed. In the pharmacologic treatment of diarrhea, which is more rarely seen than the other GIS diseases during pregnancy, the use of loperamide as a motility reducing agent, erythromycin, and ampicillin active ingredient if infection accompanies, should be evaluated by the physician. Although irritable bowel syndrome is rarely encountered during pregnancy, antispasm medications, tricyclic antidepressants, and selective serotonin reuptake inhibitors may be used for severe symptoms (44, 46). In a study conducted, increased absorption of calcium and magnesium was reported due to the use of lactulose (47).

Antibacterial Drugs

Drugs with penicillin and cephalosporin active ingredients can be used in the treatment of bacterial infections, which may cause negative effects on maternal and fetal health. In case of *Helicobacter pylori* infection during pregnancy, antibiotic treatment, including amoxicillin and clarithromycin active ingredient, can be

Table 3. Some pharmacological active ingredients, classification, and possible interactions of nutrients, nutritional elements, and drugs

Active ingredient	FDA classification	Nutrition–nutritional element interaction
Analgesic drugs		
Paracetamol	B	High-energy meal reduces the plasma concentration of the drug
		Increased frequency of consumption of grapefruit juice was reported to significantly reduce the bioavailability of paracetamol
Allergy and asthma medications		
Antihistamines		
Cetirizine	B	Administration with alcohol increases side effects of the drug
Loratadine	B	When taken together with food, absorption is significantly reduced
Antiasthmatics (Bronchodilators)		
Albuterol	C	Intake along with food increases the duration of absorption
		Intake along with caffeine causes sensitization, nervousness, and tachycardia
Budesonide	B	Consumption with grapefruit juice increases the bioavailability of the drug
		Gastroesophageal reflux
Antacids		
Calcium carbonate	C	Long-term use causes the deficiency of B12 vitamins
Aluminum hydroxide and zinc	B	It causes the deficiency of folic acid, calcium, copper, iron, magnesium, phosphate,
Sodium bicarbonate	C	It causes the deficiency of folic acid, calcium, copper, iron, magnesium, phosphate, and zinc
Non-absorbed drug		
Sucralfate	B	The activity of the drug decreases due to binding to the protein found in foods
H_2 receptor antagonists/Proton pump inhibitors		
Cimetidine	B	It causes the deficiency of vitamin B12
Ranitidine	B	It causes the deficiency of vitamin B12
Lansoprazole	B	It causes the deficiency of vitamin B12
Omeprazole	C	It causes the deficiency of vitamin B12
Antibacterial drugs		
Cephalosporin	B	It causes the deficiency of vitamins B1, B2, B3, B6, B12, and K; calcium; magnesium; and iron
		When taken together with food, its absorption increases
Drugs used in cardiovascular diseases		
β-blockers		
Labetalol	C	When taken together with food, its absorption increases
Metoprolol	C	When taken before a meal, it reduces blood pressure
		Amino acids reduce the plasma concentration of the drug
Calcium channel blockers		
Nifedipine	C	Bioavailability increases in the case of satiety, but when a high-fat meal is consumed, absorption is delayed
α-methyldopa	C	It causes hyperglycemia
Antidiabetic drugs		
Insulin	B	Protein alone has been shown to increase postprandial blood glucose
Metformin	B	It causes insufficiency of vitamin B12
Antiepileptic drugs		
Phenobarbital	B	It causes folic acid insufficiency
Phenytoin	D	Deficiency of folic acid, vitamin B12, vitamin D, and calcium and hyperglycemia
Carbamazepine	D	It causes folic acid insufficiency

FDA: Food and Drug Administration; A: Drugs for which there are adequate studies showing that they do not create a risk when used in the first trimester of pregnancy and that there is no evidence of risk in the subsequent trimesters; B: Drugs that do not create a risk for the fetus in animal studies; however, no studies were conducted on humans or although adverse side effects were identified in studies of laboratory animals, there are not a sufficient number of studies on humans in terms of the risk for the fetus in the first trimester of pregnancy; C: Drugs that were found to have adverse effects on the fetus in studies with laboratory animals, but there are not adequate human studies showing that it is beneficial in pregnancy, or drugs for which no studies were conducted on animals and humans; D: Drugs that were proven to bear a risk for the fetus in humans; however, they are the drugs whose potential benefit in gestational use was accepted despite the known risks

applied (5). In a review published in this issue, it was reported that the absorption of penicillin, thus the bioavailability, increased when taken before a meal (34).

Drugs related to Cardiovascular Diseases

Drugs with the active ingredient of β-blockers (labetotol, metoprolol), calcium channel blockers (nifedipine and α-methyldopa), dihydralazine/hydralazine, and magnesium sulfate can be used in the treatment of pre-pregnancy hypertension, gestational hypertension, preeclampsia, and other hypertensive disorders [48]. In a laboratory study conducted on animals, it was determined that amino acids reduced the rate of metoprolol to reach the plasma concentration (V_{max}) (35). In a study that examined the effects of nutrients on nifedipine, it was reported that while the intake of the drug on a full stomach increased its bioavailability, the absorption was delayed when taken with a high-fat meal (36). It was reported in another study that the efficacy of methylprednisone taken with a protein-containing meal was reduced (37).

Antidiabetic Drugs

Insulin, long-acting analog detemir, and short-acting glargine may be used in the pharmacological treatment of diabetes mellitus during pregnancy. As an alternative, metformin and glyburide, whose short-term use is believed to be safe, may be preferred by some clinicians (49). In a cross-sectional study, it was determined that the use of metformin resulted in the deficiency of vitamin B_{12} in patients with type 2 diabetes mellitus (38). In a study that investigated the effect of dietary protein on postprandial blood glucose, it was reported that the protein alone increases postprandial blood glucose in type 1 diabetes mellitus patients receiving intensive insulin therapy (39).

Antiepileptic Drugs

Antiepileptic drugs, such as phenobarbital, phenytoin, and kabazepine, pass the placenta and stimulate hepatic microsomal enzymes in the fetal liver, resulting in decreased vitamin K levels (5, 50). To prevent this situation, it is suggested in literature that vitamin K supplementation should be given to pregnant women using antiepileptic drugs, and additionally, prophylactic vitamin K should be given immediately after birth to protect the newborn against bleeding-related diseases. In a study conducted on the effect of antiepileptic drug use on micronutrients, phenytoin and carbamazepine use was reported to reduce the serum folic acid levels (50).

Conclusion and Recommendations

Significant levels of physiological and metabolic changes occur in the maternal system during pregnancy. The pharmacokinetic and pharmacodynamic properties of various drugs used by pregnant women can vary due to these changes. Although foods and medicines are two important factors for the protection of health and the treatment of diseases, an undesirable interaction between the two can cause adverse health outcomes. Hence, to achieve optimal drug treatment, the determination of probable drug–nutrient interactions and establishment of the correct treatment protocol are of great importance for both pregnant women and fetal health. Considering the nature of the drug and gastrointestinal symptoms, consuming drugs and food at different times can be generally recommended to minimize food and drug interactions.

It is ethically difficult to perform interventions in pregnant women. Hence, data based on observational studies, retrospective studies, case reports, or case series are very limited. When the drug–nutrition interactions are evaluated during pregnancy period, it should be ensured that unwanted health outcomes are prevented by considering the physiological changes. To prevent possible interactions during this period, it may be advisable that pregnant women consume medicines and food at different times and keep the nutritional status at optimum level.

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