Prenatal Drug Exposure and its Effects on Fetal Development:

Clinical and Health Education Implications

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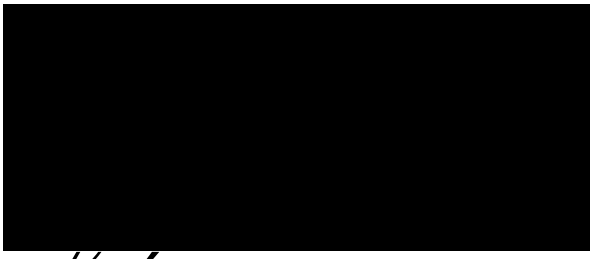

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Abstract

Prenatal drug exposure is a common clinical phenomenon in pregnancy cases. Pregnancy is a fragile period of time for both the mother and the fetus. Therefore, strict drug regulation is important to ensure the safety and wellbeing of the developing fetus. Certain drugs, once thought to be safe, have been found to have detrimental effects on the normal development of functioning organ systems in the fetus. Current research has identified drugs that when taken during pregnancy can result in the onset of fetal physical abnormalities, impaired brain development, and disrupted organogenesis and organ function. Thalidomide, losartan, opioids, alcohol, and caffeine are reviewed to identify the trends in the literature on prenatal drug exposure and the implications of drug usage during pregnancy. Although the Food & Drug Administration (FDA) are active in regulation, educational programs for pregnant/lactating women and epidemiological research on both prescribed and over-the-counter drugs on the fetus is necessary to preserve maternal health and, consequently, the health of the baby.

Prenatal Drug Exposure and its Effects on Fetal Development: Clinical and Health Education Implications

Pregnancy is one of the most dynamic stages of life for many women. When a woman becomes pregnant, her body undergoes an extensive number of physiological changes which are necessary to accommodate the growing baby. Critical and sensitive stages of development, most of which are foundational for growth outside of the womb, occur during pregnancy; therefore, any disruption to this process could detrimentally affect the overall health and wellbeing of the fetus. For this reason, the successful development of the fetus becomes the predominant goal. To accomplish this goal, the health of the mother is strictly monitored during pregnancy. Specifically, prenatal nutrition, drug intake, and lifestyle are observed and consistently supervised to facilitate a healthy pregnancy and normal fetal development. Prenatal drug exposure is a clinical phenomenon that has impacted the lives of mothers and children around the world. The NIH reported that about 5% of pregnant women use one or more addictive drugs as of 2012; this statistic increased over the years (NIDA, 2021). In the 2018 National Survey of Drug Use and Health, illicit drug use by pregnant women increased to 5.4% (SAMHSA, 2018). This steady increase of drug use by pregnant women has become a critical public health concern as more drugs have become more available to the public.

During pregnancy, drug intake/exposure is observed by the primary physician due to the adverse effects certain drugs may have on the fetus (Konijnenberg, 2015). Current research has found that major prescription and over-the-counter drugs that were considered to be safe, especially for daily use, can cause adverse effects on fetal development. The FDA has established a categorical index, and today, a new labeling system for pregnant women is used to

determine which medication is safe to take; however, if not being urgently tested or monitored, pregnant women are often left uneducated with respect to their medications and implications of safety that should be considered prior to intake. This literature review aims to explore select drugs that have been shown to adversely affect fetal development. The following drugs will be reviewed: thalidomide, losartan, opioids, alcohol, and caffeine. Each drug discussed represents a category established by the FDA that describes medications and their relative effects during pregnancy (see Appendix A). The following analysis will also highlight the urgent need of accurate testing/regulation to protect newborns from the onset of diseases and other dangerous conditions.

Maternal Nutrition

The survival of the fetus is largely dependent on maternal health because pregnancy accommodates the development of vital organ systems. The development of the integumentary and musculoskeletal systems begin at gestation (Leung et al., 2013; Yan et al., 2013). The epidermal layer of the skin continues to develop throughout pregnancy, and two layers, the basal layer and periderm, are formed at the first four weeks. At nine weeks, the skin has been keratinized; at thirteen weeks, the different layers that make up the skin can be differentiated (Leung et al., 2013). While the skin develops throughout gestation, the musculoskeletal system is developing consequently. During the embryonic stage, primary myogenesis occurs in which a small amount of muscle fibers begins to form. When the embryo enters the fetal stage, these muscle fibers serve as the framework for the additional muscle fibers that form which become the musculoskeletal system (Yan et al., 2013). The proliferation of these muscle fibers heavily relies on adequate nutrition. Fetal development is highly sensitive to maternal nutrient

deficiency, primarily during early gestation (Wu et al., 2012). If the mother is lacking nutrients or does not have a healthy diet, the peri-implantation and placenta formation stages are easily affected, resulting in the onset of disorders that hinder the growth of the fetus. Furthermore, the musculoskeletal system is dramatically affected by the lack of nutrients (Wu et al., 2012; Yan et al., 2013;). The diet of the mother, therefore, is incredibly important for the progression of normal fetal development. Maternal nutrition affects all stages of pregnancy and the development of all physiological systems. Diets composed of mostly sugar and fat are associated with the development of metabolic and cardiovascular diseases later in life (Lowensohn et al., 2016). Therefore, mothers are encouraged to have a diet rich in fruits, vegetables, grains, and fish to maintain optimal health during pregnancy. Supplemental folic acid, calcium, and iodine are also encouraged to protect against neural tube defects, asthma, and iodine deficiency. Nutrient-dense foods are preferred over calorically dense foods to support the pregnancy and maintain a healthy weight (Lowensohn et al., 2016). Maintaining this diet would prevent low birth weights which are associated with fetal growth impairment and later occurrence of other metabolic diseases.

Fetal Development

Organogenesis commences and progresses from weeks three to eight of gestation. The digestive system of the fetus develops right after implantation of the blastocyst. After three weeks, the digestive tube differentiates, and gastrulation occurs in which three germ layers arise—mesoderm, endoderm, and ectoderm (Bhatia et al., 2021). The mesoderm later forms the connective tissue and smooth muscle that will become the gut tube. The endoderm constitutes the epithelial lining of the GI tract, pancreas, liver, and gall bladder which are essential for

digestion and nutrient absorption. The ectoderm composes the surface ectoderm, neural tube, and neural crest which gives rise to facial features, the brain and spinal cord, and the entirety of the peripheral nervous system consequently (Bhatia et al., 2021). Additionally, the formation of the respiratory system begins at the third week. The respiratory diverticulum is located posterior to the pharynx and at the ventral wall of the primitive foregut formed by the endoderm. A parallel tube, which later becomes the trachea anteriorly and esophagus posteriorly, is established after the ventral wall of the foregut buds off the dorsal wall of the respiratory diverticulum (Rehman & Bacha, 2021). By the fourth week, the caudal end of the trachea divides into the left and right primary bronchial buds which will differentiate into secondary bronchial buds, leading to the formation of the lobes of the lungs. Branching of these buds will continue until the end of the sixth week. During the fifth to seventh weeks, the visceral and parietal pleura of the lungs are constructed by the mesoderm. At the end of the embryonic stage, the trachea, larynx, primordium, lobes, and the ten bronchopulmonary segments of the lungs are completely formed; the lungs will continue to develop after birth (Rehman & Bach, 2021). While these two major, interconnected systems are being constructed, brain development also occurs with the rise of the three germ layers. During the third week, the neural progenitor cells divide into neurons and glia. By the ninth week, the brain is a small structure that will continue to grow and begin to have folds which are characteristic of certain brain regions (Konkel, 2018). This dramatic growth occurs on a cellular level while certain signaling molecules assist in communication between neurons. Later, the neocortex develops which is involved in senses, thought, reasoning, and language. The brain continues to develop and grow after the child is born (Konkel, 2018). These organ systems are only a portion of the systems that are being developed. However, each system

is equally important and are required for normal functioning after prenatal development. When the development of even one system is hindered, a resultant cascade of cellular changes can occur that could change the course of the life of the fetus.

FDA Drug Categories for Pregnant Women

For years, a growing concern for the regulation of prescription medications for pregnant women correlative to the discovery of more diseases and disorders has developed. In 1979, the FDA created pregnancy-risk letter categories (A, B, C, D, and X) that aimed to help pregnant women understand the risk of birth defects as a result of taking certain medications during pregnancy. Category A includes drugs that have not been found to cause birth defects. Drugs in category B are shown to have no adverse effects on the fetus in animal reproduction studies, however no controlled studies on pregnant women have been published. Category C includes drugs that have been found to cause birth defects in animal reproduction, but no controlled studies on pregnant women have been conducted. Category D includes drugs that are a risk to the human fetus. However, drugs in both categories C and D can still be used by pregnant women as prescribed and monitored by a physician. Drugs in category X pose dangerous health risks to the human fetus and are not prescribed to pregnant women in any case or during any term of pregnancy (FDA, 2014). These categories were established for the safety of the mother and child, however, the letter categories showed to be a cause of confusion when patients read the label on their medications. Effective starting on June 30, 2015, the FDA replaced the letters with a new system, called the Pregnancy and Lactation Rule, that clarifies not only the risks of exposure during fetal development, but also the risks during breastfeeding, testing for pregnancy, and fertility (FDA, 2014).The goals of this new rule are twofold; 1) to aid clinicians in

prescribing medications and 2) to improve the accessibility of the risks and benefits of certain drugs to the end of empowering pregnant and nursing women to make appropriate decisions regarding their health and the health of their children. Although labelling changes are seemingly miniscule in comparison to other forms of drug distribution regulations, it provides vital information for both the clinician and the patient that will assist in understanding how to treat the current condition of the mother. The effectiveness of this new regulation, however, requires time to determine its helpfulness to both the patient and the clinician.

The Case of Thalidomide

The stringency of modern drug testing, especially for pregnant women, is a result of modern research identifying links between drugs and certain disorders in developing children. Thalidomide, a category X drug, is one of many drugs that, while effective, was later found to pose a threat to proper fetal development. Thalidomide was introduced in the 1950s as a sedative, anti-emetic, and treatment for nausea in pregnant women (Kim & Scialli, 2011; Vargesson, 2015). It was globally marketed and distributed and resultantly became one of the best selling drugs in history.

Dangerous Birth Defects caused by Thalidomide

The dangerous aftereffects of using thalidomide were made apparent when the children of the thalidomide-using mothers were born; around 10,000 children were born with severe birth defects because of its usage (Kim & Scialli, 2011; Vargesson, 2015;). One of the most prominent outcomes of thalidomide exposure during fetal development is congenital malformation. In a study conducted by Hallene et al. (2006), the effects of thalidomide exposure on neural development of rat pups were studied. When exposed to thalidomide, the brain cortical thickness

increased due to the onset of interstitial edema. Exposure also had acute effects on the formation of cerebral blood vessels which decreased in the thalidomide-exposed group. Additionally, early exposure to thalidomide was correlated to altered vasculogenesis and angiogenesis as seen in the decreased growth of the bovine aortic endothelial cell tube and decrease in hemoglobin concentration. Consequently, a decline in vascular endothelial growth factors was confirmed 48 hours after exposure to thalidomide. This inhibition of growth resulted in altered developing cortexes characterized by cortical swelling, thicker cortexes, and edema. Postnatal effects include abnormalities in vascular profiles and white matter distribution of the cortical and hippocampal structures, leading to leaky vessels; these findings were observed 4-8 days after birth. The study also found that thalidomide exposure is associated with microcephaly and an increased chance of miscarriage or fetal resorption (Hallene et al., 2006). The changes in neuroarchitecture could also affect the neural pathways being formed. In humans, this damage to the brain may lead to the development of autism and epilepsy (Vargesson, 2015).

Thalidomide exposure is also associated with the onset of congenital heart disease. Cardiac development is key for the formation of organs in the womb. This period of prenatal development is considered one of the most sensitive stages (Kumar et al., 2018; Vargesson, 2015). Thalidomide intake during pregnancy was shown to correlate to heart abnormalities, such as pulmonary stenosis, patent ductus arteriosus, ventricular septal defect , and atrial septal defect (Smithells & Newman, 1992). A study performed by Kumar et al. (2018) utilized chick embryos to identify the cardiac effects of thalidomide exposure. Lump formation in the heart wall was prominent in the left ventricle later affecting cardiac looping. Continuous observation of the lump had also shown that thalidomide led to blood hemorrhage. The lumps that were formed

were non-muscular and resembled a blood clot containing a high concentration of hemoglobin. When the tissue of the lump was isolated, the expression of immune genes was found to be downregulated in the lump. Furthermore, the movement of cardiac progenitor cells (CPCs) was inhibited by thalidomide. When RNA was isolated from the heart tissue, *bcl2*, a gene responsible for regulating apoptosis, and Fgfr3, a growth factor involved in cardiac remodeling, are upregulated; the *tbx5* gene which is important for septum formation and coordination of heart contractions is downregulated (Hardwick & Soane, 2013; Itoh & Ohta, 2013; Khalil et al., 2017; Kumar et al. 2018). The unusual morphology in cardiac looping may have resulted from inhibited migration of the CPCs in which apoptosis was induced. The study also indicated that this looping defect may have led to unusual fluid pressure distribution that resulted in the formation of the lump in the hearts of the chick embryos. Furthermore, the anatomical anomalies may have also arisen from the inhibition of CPC migration which compromises cardiac wall development (Kumar et al. 2018). Therefore, thalidomide is recognized as a cardiac teratogen.

The American Heart Association (as cited in Jenkins et al., 2007) released a statement saying that during the period of gestation, there is no safe dose of thalidomide treatment for pregnant women. Defects in the development of the limbs, eyes, ears, face, genitalia, vertebral column, and/or internal organs were observed; this widespread effect of thalidomide use is now termed thalidomide embryopathy. This critical condition can result in infant mortality because of the damage present in the internal organs (Smithells & Newman, 1992; Vargesson, 2015). Malformations of the urinary tract, kidneys, genitals, and gastrointestinal tract are associated with thalidomide embryopathy. However, the rate of incidence of these defects are unknown due to the inability to track the large number of affected individuals that were affected by the

thalidomide phenomenon (Smithells & Newman, 1992; Vargesson, 2015). Notable defects that are characteristic of this condition include small eyes, eyeball absence, and poor vision. Ocular defects, such as aberrant coloboma and strabismus, are common in thalidomide survivors; some survivors also report deafness and other hearing deficits (Smithells & Newman, 1992; Vargesson, 2015). As found in heart formation, the *tbx5* gene plays a vital role in teratogenicity as it interacts with thalidomide. The drug binds to R81, R82, and K226, in the T-box domain which is essential for the interaction of TBX5 with DNA. TBX5 is also heavily involved in limb development during gestation; when bound to thalidomide, the gene is downregulated, potentially leading to physical deformities in the developing fetus (Khalil et al., 2017). The mechanism and effects of thalidomide binding on the gene for cardiac and limb development, however, are still being studied. In 1961, the drug was eventually banned due to reports of peripheral neuropathy and other birth defects in multiple organ systems (Vargesson, 2015). Recent literature suggests that the window in which thalidomide exposure happens may be a factor in determining the level of damage to the developing fetus (Kim & Scialli, 2011; Vargesson, 2015). Although thalidomide causes significant damage during days 20-36 after fertilization, recent studies indicate that the drug may not be safe during any period of gestation with the increased incidence of miscarriage and subsequent organ damage (Khalil et al., 2017; Kim & Scialli, 2011; Kumar et al., 2018; Smithells & Newman, 1992; Vargesson, 2015). The dangerous aftermath of thalidomide changed the way drugs are tested, resulting in stricter drug regulation and distribution especially for pregnant and reproductive-aged women. Despite the grave effects of its use in the past, thalidomide has been shown to be an effective treatment for leprosy, cancer, multiple myeloma, HIV, and other diseases. Its use as a treatment for these

conditions is continuously being closely regulated and monitored to ensure the safety and well-being of those exposed to the drug; specifically, pregnant women are discouraged from thalidomide intake (Rajkumar et al., 2003; Singhal et al., 1999; Vargesson, 2015). The case of thalidomide is unique; however, it exemplifies the positive role of drug safety research and strict drug regulation in the protection of the most vulnerable.

Losartan

As seen in the example of thalidomide, everyday drugs/medications have the potential to be a danger for pregnant women if not exhaustively tested and strictly regulated. Losartan, classified as a category D drug, is a common antihypertensive drug . The drug is a nonpeptide angiostenin II (AII) receptor antagonist that will selectively bind to AT-1 receptors, lowering blood pressure (Alwan et al., 2005; Goa & Wagstaff, 1996; Mata-Greenwood et al., 2018). AII is a key player in the renin-angiotensin (RAS) system which regulates blood pressure in the body. RAS also plays a vital role in the formation of intrauterine tissue, directly regulating uteroplacental blood flow necessary for nutrient transport to the fetus (Lumbers & Pringle, 2014). Binding to AT-1 receptor is involved in increasing blood pressure and vasoconstriction, however when inhibited, blood flow decreases which can be a major concern during pregnancy. During the first few weeks of pregnancy, AT-2 receptors are more highly expressed than AT-1 receptors for kidney development; however, expression of AT-1 receptors increases during the later stages of pregnancy (Alwan et al., 2005). The adverse effects of losartan and other AT-1 receptor antagonist treatment are more obvious during the second and third trimesters. One of the main outcomes of losartan intake during pregnancy is the reduction of amniotic fluid which is essential for protecting the fetus, lung development, and the formation of other organ systems.

Before the fetal kidneys can secrete urine into the amniotic fluid, most of the fluid will be coming from the maternal blood. Renal perfusion is low during the beginning of fetal development. Therefore, when losartan inhibits the function of AT-1 receptors, fetal hypotension and renal hypoperfusion may occur and blood flow decreases to the fetus. Furthermore, low levels of amniotic fluid, below 5 cm, usually indicates a birth defect or maternal illness. When the fetus experiences a prolonged inadequate amount of amniotic fluid that is required for being in the gestational stage, the condition is called oligohydramnios (Alwan et al., 2005; Jabeen et al., 2021; Rosenthal & Oparil, 2002). This decrease in amniotic fluid is due to the reduction of urine output caused by the renal system being suppressed by losartan. A recent study found a low pulsatility index (PI) for the middle cerebral artery and a high PI for the umbilical artery associated with oligohydramnios, demonstrating redistribution of blood flow and possible brain-sparing effects (Jabeen et al., 2021). The high PI value indicates impaired placentation and increased risks for preeclampsia, abruption, fetal growth restriction, and stillbirth. Additionally, in cases of isolated term oligohydramnios, maternal vascular malperfusion lesions occur at a higher rate. Isolated term oligohydramnios is the condition in which amniotic fluid in the womb is reduced at term in the absences of fetal growth restriction, maternal illness, or chromosomal irregularities (Miremberg et al., 2020; Rosenthal & Oparil, 2002). Therefore, the womb becomes more toxic for the developing fetus. Due to the imbalance of blood flow and its consequent effects on the amount of amniotic fluid produced for the fetus caused by exposure to losartan, the fetus is more sensitive to the onset of birth defects.

Physical Signs of Prenatal Losartan Exposure

Prenatal exposure to losartan is also associated with physical anomalies. Oligohydramnios increases the chance of the fetal pulmonary and/or skull hypoplasia. The prolonged lack of amniotic fluid and impairment of the kidneys, associated with inhibition of RAS, can severely affect lung development by inhibiting lung growth and restricting breathing (Alwan et al., 2005; Pipkin et al., 1981; Rosenthal & Oparil, 2002; Weber-Schoendorfer et al., 2020). In skull development, the mechanism by which skull hypoplasia occurs has not been explained. This condition is characterized by a widened skull or tower skull and is associated with impaired learning. However, some researchers suggest that the defect originated from maternal intake of angiotensin receptor blockers, such as losartan, resulting in RAS being inhibited, and complications due to fetal hypotension and oligohydramnios (Alwan et al., 2005; Shankar et al., 2019; Weber-Schoendorfer et al., 2020). Fetal growth restriction (FGR) is also a common outcome of exposure to losartan. FGR is a term used to describe the failure of a fetus to reach optimal growth in utero, harming overall fetal development. It is usually associated with incidences of preeclampsia and other events that make an adverse or unsafe prenatal environment (Bullo et al., 2012; Delforce et al., 2019; Diav-Citrin et al., 2011; Lumbers & Pringle, 2014; Miremberg et al., 2020; Richter et al., 2020; Rosenthal & Oparil, 2002). The condition is associated with irregular RAS signaling in the placenta, severe fetal hypotension, and/or maternal vascular malperfusion lesions. Although the defects involved in this condition can vary, the main characteristic of FGR is lower birthweight (Delforce et al., 2019; Miremberg et al., 2020; Rosenthal & Oparil, 2002; Zygula et al., 2020). The fetus could have facial and limb deformities due to exposure to losartan. These deformities usually arise from cases of oligohydramnios. For labor, stillbirth and/or pre-term birth is common in fetuses exposed to

antihypertensive drugs (Alwan et al., 2005). Complications in the baby's health in later development due to maternal intake of losartan and other similar medications may also occur. Specifically, the late onset of medical conditions involving blood pressure and renal perfusion can occur (Rosenthal & Oparil, 2002). Introducing losartan in the prenatal environment, in turn, affects multiple organ systems of the body, endangering fetal development and nutrient intake. Because of its dangerous side-effects for both the mother and the baby, controversial losartan is not recommended for use during pregnancy.

Opioids

The recent opioid crisis has introduced a new public health issue of opioid-dependency that is not limited to the pregnant population. Opioids, a category C or D drug, are a class of drugs derived from opium that is used to treat severe pain by binding to μ-, δ-, and κ-receptors (Zöllner & Stein, 2007). The opioid epidemic saw drastic growth from 2005-2014; during that time, opioid-associated hospitalization increased 64%, reaching all parts of the United States (Lyden & Binswanger, 2019). Correlative to that, opioid abuse among pregnant women became a prevalent concern. The number of pregnant women using opioids quadrupled from 1999-2014 (Grossman & Berkwitt, 2019). From 2000-2007, one in five American women were prescribed opioids during pregnancy (Desai et al., 2014). A more recent study reported 6,065 prenatal hospitalizations due to opioid-related conditions, and 751,037 birth hospitalizations; these numbers are expected to steadily increase (Hirai et al., 2021). Common opioid use has proven to be a major concern for fetal development because of the risk of the onset of addiction that is sometimes undetected.

Codeine and Hydrocodone

Two of the most common opioids prescribed to pregnant women are codeine (6.1% of prescribed opioids) and hydrocodone (6.8% of prescribed opioids) (Bateman et al., 2014). The effects of codeine exposure are inconclusive and difficult to define. Some studies associated prenatal codeine exposure with congenital cardiac malformation, gastrointestinal anomalies, and defects in neural tube formation, while other studies found no significant correlation (Bowie et al., 2022; Fishman et al, 2019; Lind et al., 2017). The trimester during which these drugs are administered is also vital in understanding its effects (Bowie et al., 2022); however, the severity of the effects of prenatal opioid exposure in each trimester has not been defined. Codeine is a major drug interest for research aimed at investigating prenatal opioid use due to its ability to cross the placenta and be extensively distributed in the tissue. Hydrocodone has been associated with an increased risk of spina bifida, heart malformations, and club foot (Broussard et al., 2011; Werler et al., 2014; Yazdy et al., 2013). However, studies focused on hydrocodone exposure during pregnancy are limited. Opioids are a difficult group of drugs to test due to their common, unregulated use in over-the-counter medicines, such as cough and cold medications. From an ethical standpoint, a sufficient sample is also difficult to obtain for these studies. More longitudinal epidemiological studies need to be conducted to understand the long-term effects of opioid use during pregnancy.

Neonatal Abstinence Syndrome

One common condition associated with opioid use during pregnancy is neonatal abstinence syndrome. Habitual maternal use of opioids often leads to infant withdrawal characterized by blood hypertonicity, poor feeding, tremors, and irritability—a condition called Neonatal Abstinence Syndrome (NAS). With an increased number of pregnant women who

regularly intake opioids, the number of infants born with NAS has also increased. The physiological mechanisms behind the onset of NAS remains unclear. Recent animal studies have indicated that the onset of withdrawal is different from the adult's. In gestation, brain development is highly sensitive, and the growing neurons are still immature. The combination of developing neurons, levels of opiate receptor-binding, and actions of neurotransmitters occurring at the same time during fetal development are correlated with withdrawal occurring to the newborn (Grossman & Berkwitt, 2019; Kinnunen et al., 2019; Kocherlakota, 2014). It is hypothesized that NAS primarily relies on noradrenergic output of the locus coeruleus which produces norepinephrine in the pons of the brain. Opiate drugs easily pass through the placenta due to their low molecular weight and water solubility (lipophilic) (Kocherlakota, 2014). When μ-opiate receptors are consistently bound to opioids, the locus coeruleus increases production of cyclic adenosine monophosphate (cAMP) which will activate cAMP-mediated cellular processes. These processes are essential for maintaining body homeostasis, and with this increase in cAMP, respond with increased production of norepinephrine. This increase in cellular activity is hypothesized to be the mechanism of withdrawal symptoms that characterize NAS (Grossman & Berkwitt, 2019; Kocherlakota, 2014). Additionally, the dopaminergic mesolimbic pathway decreases dopamine release from the ventral tegmental area into the nucleus accumbens, and the dorsal raphe nucleus decreases serotonin levels as withdrawal occurs. The symptoms of NAS, irritability and trouble sleeping, may be associated with these sudden declines (Grossman & Berkwitt, 2019). The autonomic nervous system can also be affected by NAS. These effects include changes in breathing rate, unstable body temperature, and skin perfusion which is usually mistaken for sepsis. In withdrawal, the infant experiences poor feeding, failure to meet the

caloric needs that hypermetabolism requires. Infants with NAS may also suffer symptoms of vomiting and diarrhea which complicate their problem with nutritional intake (LaGasse et al., 2003). These symptoms indicate that the compromised health and postnatal development may be hindered. However, seizures are the most dangerous outcome of NAS; they are associated with tremors and sudden jerks (Herzlinger et al., 1977). Moreover, being born into withdrawal is dangerous and can further delay development that occurs outside the womb.

Other neurological outcomes of opioid exposure include volumetric alterations in multiple cortical and subcortical regions which are involved in higher-executive functioning, learning, information-processing, and emotional regulation (Peterson et al., 2020). These effects imply that cognitive processes may also be affected by opioid exposure. One study found that white matter integrity and connectivity decreased in the neonatal brain due to opioid exposure (Monnelly et al., 2018). These cognitive delays may not seem apparent during the first year. A study by Benninger et al. (2020) found that children who were treated for NAS were at the same cognitive level as unexposed children during the first year. However, at the second year, exposed children had significantly lower language and cognitive scores in comparison to the unexposed children. This finding indicates that the severity of the damage may not be apparent until later in life. Current research on prenatal opioid exposure is limited due to sample size and an inability to replicate experiments, especially in human models. However, these findings illustrate that the opioid exposure during pregnancy places the mother and baby at risk. It is likely that fastidious drug regulation and testing could prevent the onset of NAS. Yet, a significant number of over-the-counter medications contain opioids. With an increased population of consumers of over-the-

counter medications containing opioids, education on drug use during pregnancy is required so that soon-to-be mothers are made well-aware of the risks that opioid exposure may cause.

Alcohol

Prenatal exposure to alcohol (PAE) is one of the leading causes of preventable congenital conditions (Vorgias & Bernstein, 2021). The CDC (2022) reported that from 2011-2018, alcohol consumption during pregnancy increased from 9.2% to 11.3% and binge drinking increased from 2.5% to 4.0%. Although the number of individuals affected by fetal alcohol exposure remains unknown, the CDC found that for every 1,000 live births, 0.2-1.5 infants are born with a fetal alcohol spectrum disorder. Other environmental/situational factors may affect drinking habits to varying degrees, and fetal exposure to alcohol can be life-threatening; therefore, alcohol consumption is discouraged during pregnancy. Alcohol is not categorized and regulated under the FDA, however for the following review, its prevalent use in pregnant populations is significant to discuss because of its unregulated use and dangerous side effects on the developing fetus.

Alcohol is a teratogen that causes permanent damage to the brain and its structures. During the first trimester, PAE increases the likelihood of physical deformity. High levels of exposure are associated with occurrences of spontaneous abortion. Decreases in brain volume, height, and weight result from high levels of exposure during the third trimester (Hasken et al., 2021; Vorgias & Bernstein, 2021). PAE is also associated with disrupted insulin levels. A study by Kable, et al. (2021) assessed the intellectual functioning and measured the level of dysmorphia caused by alcohol exposure of African American adults whose mothers consumed alcohol and drugs during the first trimester of pregnancy. The researchers found that their insulin

levels and body-mass index (BMI) was correlated; individuals who had a BMI below threshold of overweight or normal had lower insulin levels and higher insulin sensitivity. Moreover, individuals with above threshold or overweight BMI were more insulin resistant. The researchers speculate that this relationship between BMI and stage of diabetes development may explain the increased risk for obesity development with increased insulin sensitivity (Guiducci et al., 2014; Kable, et al., 2021). Additional research on the cellular development of diabetes in relation to PAE needs to be conducted, however one group of disorders have been identified due to PAE. Fetal alcohol spectrum disorders (FASDs) include four main disorders that arise due to alcohol consumption during pregnancy. This group includes the following disorders: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), static encephalopathy/alcohol exposed (SE/AE), and neurobehavioral disorder/alcohol exposed (ND/AE).

Fetal Alcohol Spectrum Disorders

FAS is a permanent birth defect that is characterized by minor abnormalities of the face, central nervous system (CNS) or brain, and prenatal and/or postnatal growth deficiency. For this disorder to be diagnosed, the presence of all three characteristics is necessary (Davies, 2021). This growth restriction of the fetus can manifest as low birthweight, being small for their gestational age, and failure to thrive. In a study of children in South Africa, in comparison to children with PFAS, children with FAS were reported to be lighter, more dysmorphic, and shorter in height (Hasken et al., 2021). These physical signs of FAS differentiate this disorder from the FASDs. Facial characteristics of children with FAS and PFAS include a smaller smooth philtrum, narrower vermilion, and smaller maxillary and mandibular arcs in addition to their

short stature (May et al., 2020). FAS, therefore, is a condition that describes permanent physical abnormalities in comparison to the partial and/or mainly neural damage present in other FASDs.

PFAS has similar physical cranial anomalies as FAS. The major difference is that PFAS does not consist of all the physical manifestations of FAS; children with PFAS either have moderate facial structures or do not have impaired growth (Davies, 2021). Notably, the facial features resulting from FAS and PFAS, specifically, were found to evolve or slightly diminish as the child aged in one study and indicate inhibited forebrain development (Jacobson et al., 2020). Additionally, neural damage is common for both cases of FAS and PFAS.

SE/AE is the condition in which there is evidence of structural damage in the brain and/or severe neural dysfunction. Individuals with this condition usually have a smaller head circumference or cranial structure abnormality. Their severe brain damage results in the onset of a seizure disorder and/or hard neurological signs of damage. The CNS experiences significant damage due to this condition in three or more parts of the brain (Darbinian et al., 2021; Davies, 2021). In prenatal ethanol exposure cases, the oligodendrocyte cell populations experience inhibited growth, slowing the process of maturation and affecting apoptosis (Darbinian et al., 2021). In the future, research should focus on the relationship between the occurrence of apoptosis and SE/AE to understand this inhibiting effect in brain maturation.

Individuals with ND/AE have a moderate dysfunction that suggests possible CNS damage. The dysfunction apparent in this condition is primarily identified interview data, observational study, and other psychological/psychometric tests. The level of damage occurs in either one or two domains (Davies, 2021). These critical, four main FASDs are also associated with cognitive impairment and other physiological complications that can develop postnatally

reaching adulthood for those who are diagnosed with one of the disorders. Therefore, more studies focused on each of the FASDs is required to determine the pathways and physiological changes associated with each disorder.

The actual mechanism behind FASDs has not been determined, however there are significant neurological effects associated with FASDs that may develop into the onset of other disorders/disabilities. A major part of the development of these disorders involves brain dysmyelination, affecting the concentration of white matter in the brain. Microglia in the CNS play a role in the immune response and maintenance of homeostasis. They perform phagocytosis, antigen reception, and the production of cytokines and chemokines; overall, microglia remove pathogens that can damage cells of the CNS (Kane & Drew, 2020; Ransohoff & Brown, 2012). When microglia are exposed to ethanol, a set of downstream signaling pathways resulting in microglial activation whereby oxygenated species are produced, and the neurons undergo apoptosis. In rodent and human FAS studies, apoptosis of oligodendrocyte precursor cells and repressed differentiation of oligodendrocytes occurred, accompanied by reduced or delayed myelin production. This phenomenon results in synaptic loss, leading to the onset of fatal FASDs (Darbinian et al., 2021; Kane & Drew, 2020). The postnatal, early stage of rodents is equivalent to the third trimester of human pregnancy. When ethanol is introduced during this period, increased expression of certain chemokines (CCL2 and CCL4), which function in directing white blood cell activity, and pro-inflammatory cytokines (TNF-α and IL-1β), which function in chemical messaging, were found to be involved in this process of demyelination as the structure of the hippocampus was altered (Niedzwiedz-Massey et al., 2021). The dysfunction of cytokines and chemokines in the brain through ethanol exposure induces neuroinflammation.

Moreover, the white matter development in the brain is negatively affected. White matter is heavily involved in learning and other executive brain functions. It is an area of the brain that has high connectivity and is known for its large concentration of myelin. FASDs and ethanol exposure are significantly correlated with less white matter in the brain (Darbinian et al., 2021; Kane & Drew, 2020; Niedzwiedz-Massey et al., 2021; Stephen et al., 2021). Less white matter also entails less myelin. Myelin is a lipid-rich sheath originating from the oligodendrocytes and surround axons; it functions in communication between neurons. Therefore, if there is less myelin, communication between neurons is impaired which translates into cognitive disabilities and poor adaptive ability (Brown & Reynolds, 2021; Niedzwiedz-Massey et al., 2021). The consequence of alcohol exposure disturbs appropriate executive function, resulting in the development of emotional and behavioral disorders. Children with white matter abnormality also have impaired connectivity between the hemispheres of the brain, inhibiting efficient flow of information (Stephen et al., 2021). Impaired connectivity affects reasoning, memory, and other skills required as the child begins to attend school and learn. This brain damage can, therefore, develop into learning disorders, autism spectrum disorders, and other difficulties in cognitive ability as a child continues to develop postnatally (Brown & Reynolds, 2021; Khalifa et al., 2021; Stephen et al., 2021). Furthermore, prenatal exposure to alcohol has far-reaching effects as the child grows that can extend to postnatal development and evolve into serious behavioral disorders.

The mechanism by which alcohol affects fetal development and determines occurrence of FASDs is still being researched. One study by Fischer et al. (2021) used in vitro human pluripotent stem cells as a model of corticogenesis to understand the molecular and genetic

mechanisms behind development of FAS. The cortical neurons were exposed to 50 mM ethanol for 50 days. The researchers identified that pathways involved in cell specification, axon and synapse differentiation and growth, and gene patterns were affected, specifically the WNT signaling pathway. A shift in gene expression caused the genes involved with caudal forebrain formation and growth to be upregulated in comparison to the anterior (Fischer et al., 2021). Their findings indicate that the effect of alcohol on fetal development is widespread; furthermore, prenatal alcohol exposure, if not prevented, may be more dangerous to the overall development of the fetus. Further research is required to understand the long-term effects of alcohol exposure on development, however finding a sufficient sample and producing longitudinal epidemiological studies have become a challenge in studying the occurrence of FASDs.

Caffeine

The most widely used drug in the world is caffeine. Caffeine is a stimulant that induces wakefulness. It is commonly found in coffee, teas, and other beverages. Caffeine is also widely used by women during pregnancy; however, it is not regulated by the FDA and does not have a classification (Mioranzza et al., 2014). Caffeine is an antagonist to the A1 and A2 adenosine receptors that will become G-protein coupled during the postnatal stage in the cortex and hippocampus. This stimulant can easily pass through the fetal brain and placental barrier. Rodent model studies on caffeine revealed that mice exposed to high dosages of caffeine, equivalent to 6-12 cups of coffee for a human being, experienced delayed conception and placenta weight; furthermore, there was an increased risk for intrauterine growth retardation, fetal resorption, and low birth weight. Female rats who were not pregnant were exposed to the same dosage of caffeine for four days and subsequently experienced reduced fertility due to disrupted embryo

implantation (Huang et al. 2012; Pollard et al., 1999; Qian et al., 2020). In addition, neural tube growth was inhibited in the presence of caffeine (Jacombs et al., 1999). This finding implies that, due to neural tube growth being prevented, the formation and development of the brain and spinal cord is delayed for which the neural tube is the basis. In rat models, prenatal exposure to caffeine increased the frequency of physical malformations of the limbs and palate. High doses of the drug used on mother rats was correlated with growth retardation, skull structure abnormality, and fetal death (Brent et al., 2011). Although findings on growth retardation due to caffeine is similar for both animal and human studies, the effects of caffeine on human fetal development, especially in prenatal and postnatal brain development, is poorly researched. The human studies on prenatal caffeine exposure are inconclusive due to small sample sizes and failures to account for other variables (Brent et al., 2011; Schmidt et al., 2009). The results of animal studies cannot be ultimately used to understand the effects of caffeine exposure on human fetal development. Future studies will need to focus on human populations to establish clinical significance. Furthermore, if conducted accurately and ethically, future research should attempt to explain the mechanism by which caffeine directly causes birth defects. For the present pregnant population, ongoing studies on caffeine and other stimulants should increase awareness and serve as a basis of extreme caution for prenatal drug use.

Implications for Pharmaceutical Procedures and Pregnant Women

The sensitive period of pregnancy is characterized by the development of essential organ systems. Each stage of development heavily interacts with the mother and relies on the ability of the body to maintain conditions that are most conducive to the successful growth and development of the baby in the womb. Furthermore, as the population of pregnant women with

underlying health conditions increases and more medications are prescribed to relieve the outcomes of being pregnant, prescription and over-the-counter drug usage has increased as well. From past events, the scientific community has witnessed the mass effects of lenient drug testing and regulation, especially on pregnant women and their offspring. As seen with the case of thalidomide, drug regulation became a primary concern for the safety of both the mother and the developing fetus. This issue was addressed by the FDA with their labelling systems; however, this solution has become a cause of confusion for mothers and the medical personnel involved. Clarification of these labels was established, however due to the urgency of the issue at hand, a faster solution is required to maintain the maternal and fetal health.

The development of more educational programs that target pregnant/lactating women should be developed to increase awareness of drug use during pregnancy and its risks and benefits, especially for women with underlying health conditions. Although programs that serve to assist mothers suffering from drug addiction or alcoholism are established, education on common drugs, such as opioids and losartan, that are used to treat a variety of symptoms/illnesses and are easily accessible is lacking in the United States. In a clinical setting, a soon-to-be mother may not fully understand the risks of certain medications and make hasty health decisions. Programs that aim to teach pregnant women the importance of maintaining their physical health and being involved in communication with their doctor would empower them to make the best medical judgment for them and their children.

The increasingly common use of drugs to treat a variety of symptoms and conditions requires researchers to urgently test and study the effects of prolonged usage of these drugs on target populations. Unregulated drugs, such as caffeine, have been found to cause detrimental

developmental delay *in utero* in rodent and human studies (Brent et al., 2011; Huang et al. 2012; Jacombs et al., 1999; Pollard et al., 1999; Qian et al., 2020). Longitudinal effects of caffeine intake on pregnancy outcomes require more research, yet the current findings are pointing towards possible health complications in fertility, implantation, and organogenesis that can affect the outcome of the pregnancy and development of the fetus. Thus, this trend in the literature indicates that unregulated and/or addictive drugs are also important future research topics, as seen with the studies on alcohol. Pregnant women are a highly sensitive population. The clinicians that serve this group are challenged with maintaining the mother's physical health necessary for the baby's normal development and/or developing a treatment plan for any current health issue she may be experiencing without jeopardizing her pregnancy. Because pregnancy involves both the mother and the child, more research on both regulated and unregulated drugs used by pregnant and lactating women needs to be conducted so that clinicians can better inform mothers on how to best approach their current health status. Epidemiological research on the prolonged effects of these common drugs will be beneficial for educational programs in better informing future mothers. Though research in this field has improved over the years, limitations in experimental methods are still apparent. Finding sufficient samples, producing controlled studies, and following ethical standards are vital to gain significant findings. Moreover, longitudinal research studies are the most suitable in understanding the health risks associated with prenatal drug exposure. The critical period of pregnancy that drug exposure may cause more severe outcomes in has not been determined. Future research should focus on the trimester in which fetal development is the most sensitive to drug exposure specific to each drug. The literature, then, on this subject can expand to determining the molecular/cellular pathways *in*

utero that are affected by these drugs. Furthermore, with this in-depth understanding, clinicians and mothers are able to make more well-informed health decisions that will be able to preserve the optimal conditions for normal pregnancy to occur and proceed.

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Appendix A

FDA Drug Classification by Letter Category and New Label.

Drug	Letter Category	New Label
Thalidomide	X	Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to THALOMID during pregnancy as well as female partners of male patients who are exposed to THALOMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to THALOMID to the FDA via the MedWatch program at 1-800-FDA-1088 and to Celgene Corporation at 1-888-423-5436. Risk Summary Based on the mechanism of action [see Clinical Pharmacology (12.1)], human and animal data (see Data), THALOMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy [see Boxed Warning, Contraindications (4.1), and Warnings and Precautions (5.1)]. THALOMID is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants. Even a single dose taken by a pregnant woman can cause birth defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus. If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to THALOMID to the FDA via the MedWatch program at 1-800-FDA1088 and also to Celgene Corporation at 1-888-423-5436. Thalidomide crossed the placenta after administration to pregnant hamsters (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk in the U.S. general population

		of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies. Data Animal Data A pre- and postnatal reproductive toxicity study was conducted in pregnant female rabbits. Compound-related increased abortion incidences and elevated fetotoxicity were observed at the lowest oral dose level of 30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA) and all higher dose levels. Neonatal mortality was elevated at oral dose levels to the lactating female rabbits ≥150 mg/kg/day (approximately 7.5-fold the maximum human dose based upon BSA). No delay in postnatal development, including learning and memory functions, were noted at the oral dose level to the lactating female rabbits of 150 mg/kg/day (average thalidomide concentrations in milk ranged from 22 to 36 mcg per mL). In a study conducted in pregnant rabbits, thalidomide levels in fetal plasma were approximately 11% to 73% of the maternal Cmax. In a study conducted with 14C-thalidomide (150 mg/kg orally) in pregnant hamsters, radioactivity was detected in the embryo, and the relative concentrations of radioactivity in the embryo and maternal plasma were about the same at 4, 12 and 24 hours after dosing. Based on the radioactivity data, thalidomide crossed the placental barrier, and the fetal levels of drug-related material were approximately similar to those of maternal levels.[1]
Losartan	C or D	COZAAR can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the reninangiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the reninangiotensin system from other antihypertensive agents. When pregnancy is detected, discontinue COZAAR as soon as possible (see Clinical Considerations). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations Disease-associated Maternal and/or Embryo/Fetal Risk Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g.,

		need for cesarean section, post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly. Fetal/Neonatal Adverse Reactions Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the reninangiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. In patients taking COZAAR during pregnancy, perform serial ultrasound examinations to assess the intraamniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue COZAAR, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe neonates with histories of in utero exposure to COZAAR for hypotension, oliguria, and hyperkalemia. In neonates with a history of in utero exposure to COZAAR, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function. Data Animal Data Losartan potassium was administered orally to rats during the period of late gestation through lactation (Gestation Day 15 through Lactation Day 20) at doses of 10, 25, and 100 mg/kg/day. Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m2 basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.[2]
Alcohol	N/A	N/A

Opioids	B; D for prolonged use	Risk Summary: Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.5)]. Available data with Codeine Sulfate Tablets are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, codeine administration during organogenesis has been shown to produce delayed ossification in the offspring of mice at 1.4 times maximum recommended human dose (MRHD) of 360 mg/day, embryolethal and fetotoxic effects in the offspring of rats and hamsters at approximately 2 to 3 times the MRHD, and cranial malformations/cranioschisis in the offspring of hamsters between 2 and 8 times the MRHD [see Data]. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations: Fetal/Neonatal Adverse Reactions: Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.5)]. Labor or Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Codeine Sulfate Tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Codeine Sulfate Tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression. Reference ID: 4756502

		Data: Animal Data: Studies on the reproductive and developmental effects of codeine have been reported in the published literature in hamsters, rats, mice and rabbits. In a study in which pregnant hamsters were administered 150 mg/kg twice daily of codeine (oral; approximately 7 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m2 basis) during organogenesis cranial malformations (i.e., meningoencephalocele) in several fetuses were reported; as well as the observation of increases in the percentage of resorptions per litter. Doses of 50 and 150 mg/kg, bid resulted in fetotoxicity as demonstrated by decreased fetal body weight. In an earlier study in hamsters, single oral doses of 73 to 360 mg/kg level on Gestation Day 8 (oral; approximately 2 to 8 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m2 basis), reportedly produced cranioschisis in all of the fetuses examined. In studies in rats, doses at the 120 mg/kg level (oral; approximately 3 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m2 basis) during organogenesis, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In pregnant mice, a single 100 mg/kg dose (subcutaneous; approximately 1.4 times the recommended daily dose of 360 mg/day for adults on a mg/mg2 basis) administered between Gestation Day 7 and 12 reportedly resulted in delayed ossification in the offspring. No teratogenic effects were observed in rabbits administered up to 30 mg/kg (approximately 2 times the maximum recommended daily dose of 360 mg/day for adults on a mg/m2 basis) of codeine during organogenesis. Codeine (30 mg/kg) administered subcutaneously to pregnant rats during pregnancy and for 25 days after delivery increased neonatal mortality at birth. This dose is 0.8 times the maximum recommended human dose of 360 mg/day on a body surface area comparison.[3]
Caffeine	N/A	N/A

Note. The following table describes the letter category and the section of the label discussing pregnancy risks as established by the FDA for the drugs described in this review.
[1]The following description is of Thalomid (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020785s069lbl.pdf)
[2]The following description is of Cozaar. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020386s064lbl.pdf)
[3]The following description is of Codeine Sulfate. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022402s014lbl.pdf)