An Overview: Extent of Teratogenicity of Common Medications in Fetal Development

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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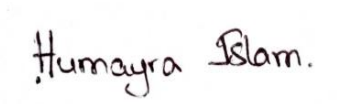

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Approval

The project titled “An Overview: Extent of Teratogenicity of Common Medications in Fetal Development” submitted by Humayra Islam (17346046) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Fetal development is regulated by several important factors, such as maternal physiology and health condition, lifestyle, use of different types of drugs and susceptibility to various chemical, physical, and biological agents. An imbalance, abuse, misuse, or undesirable exposure to these factors can prove to be teratogenic. Drugs can act as teratogens depending on its extent of use, gestational age at which the drug is administered and the drug's pharmacokinetics. This is possible since most drugs can cross the placental barrier and disrupt the optimal environment of the amniotic fluid, causing birth abnormalities. Some drugs can even cross the fetal blood brain barrier and cause neurological disorders. In this review paper, the extent of teratogenicity of common gestational drugs has been explored, along with their mechanisms of action that lead to congenital deformities.

Keywords: Fetal development; FDA classification; Common Drugs in Gestation; Teratogenicity; Placenta; Fetal BBB

"Dedicated to the children of the thalidomide tragedy who are a reminder of the importance of safe drug use in pregnancy"

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Finally, I would like to thank my parents for their constant prayers and support, which motivated me to take on challenges along the way and attain my utmost potential with success.

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List of Acronyms

ACE	Angiotensin-converting enzyme	ADA	American Dental Association
ARB	AII Receptor Blockers	ARIA	Allergic Rhinitis and its Impact on Asthma
BBB	Blood Brain Barrier	BCSFB	Blood-cerebrospinal fluid barrier
B12	Vitamin B12	COX	Cyclooxygenase
CYP450	Cytochrome P450	DHC	Dihydrocodeine
DHFR	Dihydrofolate reductase	DHM	Dihydromorphine
EDC	Endocrine-Disrupting Chemical	ER	Extraction ratio
GERD	Gastroesophageal reflux disorder	GFR	Glomerular filtration rate
HCG	Human chorionic gonadotropin	HDAC	Histone deacetylase
HMG-CoA	Hydroxymethylglutaryl-coenzyme A	ICS	Inhaled corticosteroids
IGF	Insulin-like growth factor	LABA	Long-acting beta-2 agonists
LMP	Last menstrual period	LSD	Lysergic acid diethylamide
MAC	Minimum alveolar concentration	MTHF	Methyltetrahydrofolate
MTHFR	Methyltetrahydrofolate reductase	NCC	Neural crest cell
NICE	National Institute for Health and Care Excellence	NICHD	National Institute of Child Health and Human Development
NSAID	Non-steroidal anti-inflammatory drug	NVP	Nausea and vomiting of pregnancy
NVU	Neurovascular unit	PPHN	Persistent pulmonary hypertension of the newborn
PPI	Proton pump inhibitors	REM	Rapid Eye Movement
ROS	Reactive oxygen species	SABA	Short-acting beta-2 agonists
SNRI	Serotonin and noradrenaline reuptake inhibitor	SSRI	Selective serotonin reuptake inhibitor

STI	Sexually transmitted infection	TERIS	Teratogen Information System
UGT	Uridine diphosphate glucuronosyltransferase	URTI	Upper respiratory tract infection
USFDA	US Food and Drug Administration	UTI	Urinary tract infection
V_d	Volume of distribution		

Chapter 1:

Introduction

1.1 Background of the review

The use of medications in pregnancy is almost inevitable, especially for underlying physiological disorders of the mother and the physiological changes that are brought about in gestation. More than 85% of pregnant women take medications during pregnancy (Kennedy, 2011). Amongst all these medications, the ones commonly used in pregnancy are antidepressants, antihypertensives, anesthetics, analgesics, medications for heartburn, antiemetics, antidiabetics, antibiotics, and statin drugs (Khedun et al., 2000; Black & Hill, 2003; Eltonsy et al., 2014; Dubovicky et al., 2017; Tsamantioti & Hashmi, 2021).

The administration of a drug in a pregnant woman is challenging owing to the pharmacokinetic changes that occur with pregnancy and the risk of harm to the developing fetus (Sachdeva et al., 2009). The need for medication cannot be completely ruled out since certain medical conditions (e.g., elevated blood pressure, asthma) can exacerbate the mother's health and consequently harm the fetus. On the other hand, some drugs can pose substantial risk to the fetus for their ability to cross the placental barrier and the fetal blood brain barrier. This is a matter of concern since most drugs cross the placenta and reach the fetal systemic circulation. Moreover, more than 10% of the congenital anomalies occur due to the maternal exposure to drugs during pregnancy (Black & Hill, 2003).

Some medications have been taken for such a long time that doctors are able to understand its level of safety and provide recommendations accordingly. For instance, it is generally safe to take acetaminophen, some antibiotics, some antihistamines, some antihypertensives, most asthma medications and most antidiabetics ("Medicines During Pregnancy; Michigan Medicine", 2020). However, some prescription medications and OTC medicines are not completely safe and need to be administered with caution since the safety profile of drugs can vary according to the gestational period and many other factors, which will be discussed in this paper (Black & Hill, 2003).

Drugs that hinder the natural development of a fetus and cause any type of fetal abnormality are known as teratogenic drugs. The extent of teratogenicity can vary depending on the pharmacokinetics of the drug, maternal physiology in gestation, dose of the drug, frequency of the drug, and most importantly the embryonic age. Teratogenic exposure two weeks before gestation has been shown to have no correlation with abnormalities (Alwan & Chambers, 2015). However, it is recommended to avoid all types of teratogenic drugs in the first trimester, especially during organogenesis, which is the most sensitive stage of fetal development (Donovan & Cascella, 2020).

Drugs have been classified by the U.S. Food and Drug Administration (FDA) into five risk categories (A, B, C, D, and X) depending on its potential to cause congenital abnormalities (Law et al., 2010). There is relevant literature that assesses the safety of a particular drug during pregnancy and categorizes every drug available into this FDA classification. This is due to the ethical considerations for conducting controlled clinical studies on pregnant women and the potential risk to the fetus and mother. However, data retrieved from animal studies can be useful for further evaluation of teratogenic potential in pregnancy. Furthermore, post-marketing surveillance is also beneficial in the case of drugs that have been in use since a very long time. Under such circumstances, the key decision to provide a particular medication therapy depends on whether the benefits of the therapy outweigh the risks for both the mother and the fetus (Law et al., 2010).

1.2 Rationale of the study

Pregnancy is a common natural phenomenon in the female reproductive cycle. Understanding the safe use of medications is a necessity, given the growing dependence on medications in both the prenatal and postnatal period. Due to the ethical considerations and lack of data of clinical studies involving pregnant women, the use of certain medications is controversial. This review highlights the possible areas of controversy and recommendations for clinical management of a disease during pregnancy that ensures the maximum safety for both the mother and the fetus as per the existing literature. In addition, it explores some of the key mechanisms of teratogenic drugs and how they interact with the fetal development and lead to congenital abnormalities.

1.3 Aim and objectives of the study

The aim of this review is to understand the critical stages of pregnancy and the safe practice of medication use with regard to its teratogenic potential.

The objectives of this study include:

- to understand the critical stages of fetal development and the practice of medication use during these stages
- to understand the extent of teratogenicity of common medications in pregnancy
- to know the possible mechanisms of action of teratogenic medications
- to identify the limitations of data for a certain drug that is commonly used in pregnancy
- to explore the recommendations for the safe use of medications in pregnancy according to the most recent literature

Chapter 2:

Methodology

This paper is an overview of the teratogenic potential of common medications used during pregnancy and its safe practice. The paper has been constructed based on an outline with relevant research questions per heading. The content for each heading was extracted by a thorough literature search. The information for this review paper was collected from primary sources such as NCBI, Springer, Science Direct, Wiley Online Library, Journal of the American Medical Association etc., secondary sources such as PubMed, Mayo Clinic, WebMD, Elsevier, Parents Magazine, etc., and tertiary sources such as University of Michigan Health, etc. The plethora of information was then summarized in tabular forms to organize the current data available. The mechanisms of action and anatomical structures pertaining to teratogenicity and fetal development were illustrated with appropriate citation of literature. The areas that need further research have been identified and discussed. The use of valid and reliable information with proper in-text citation and bibliography has been meticulously followed using APA 6th version referencing format.

Chapter 3:

Fetal development

3.1 Stages of fetal development

Gestational age is a measure of the progression of a pregnancy. It is calculated from the first day of a woman's last menstrual period (LMP) to the current date (Jukic et al., 2013). This means that the onset of pregnancy is marked by a women's last menstruation, and it occurs two weeks before conception. Conception, also known as fertilization, is the instance when a sperm penetrates an ovum and forms a zygote. At this point, the gender and genetic makeup of the fetus is fixed. Embryonic age is different from gestational age in the sense that unlike gestational age, it is a measure of the fetus' actual age and is calculated from the point of fertilization and is therefore also termed as fertilization age, conceptional age, or fetal age. It begins from approximately week 3 of pregnancy for a menstrual cycle that has a duration of 28 days (Jukic et al., 2013). Once fertilization has taken place, the zygote rapidly divides into a mass of cells known as a morula, which marks day 4 of the embryonic age and consists of 16-32 blastomeres. This morula stage is crucial for the formation of blastocyst, first cell-line and subsequently the entire development of the fetus (Coticchio et al., 2019). In terms of CNS development, the formation of synapse usually takes place in the later gestational period and takes 2-3 years postnatally to complete its development (Li et al., 2021).

Table 1: Stages of growth and development of the fetus

Trimester	**Age of gestation (in weeks)**	**Fetal size (in mm) [4]**	**Fetal weight (in gm) [4]**	**Development stage [1,2,3]**
First [1]	3	-	-	Fertilization has occurred; zygote travels to the uterus and forms a morula
	4	0.2-0.3 [1]	1-1.1	Implantation of blastocyst takes place on the endometrium of uterus

	5	1-1.5	1.1-1.2	HCG hormone levels increase; ovaries stop releasing eggs; production of estrogen and progesterone increases; menstruation is halted; embryo develops into three layers: ectoderm (outer layer), mesoderm (middle layer) and endoderm (inner layer)
	6	3-4	1.1-1.3	Rapid growth occurs; neural tube closes; heart and other major organs begin to form; heartbeat develops; anatomical features leading to the formation of eyes, ears and limbs begins to develop; C-shaped structure forms
	7	10-12	1.1-1.4	Growth of brain and facial features occurs; nostrils and retina begin to develop; arm buds become paddle-shaped
	8	12-16	1.1-1.5	Lower limb buds become paddle-shaped; fingers start to develop; ear structures grow outwards; eyes become conspicuous; upper lip and nose develop; torso straightens
	9	16-22	1.5-2.5	Arms grow, forming elbows; eyelids form; toes appear; slightly developed chin is visible
	10	29-33	3-4	Head becomes rounder; elbows can be bent; webbing of toes and fingers

				disappear to make them elongated; eyelids and outer part of ears develop further; umbilical cord is conspicuous
	11	48-52 [1]	6-10 [1]	Fetus is formed as per clinical description; head grows up to half its full body length; eye lids, ears, and eye spacing becomes more pronounced; teeth buds form; production of red blood cells begins in liver; genitalia start to develop as per the gender
	12	59-63 [1]	12-16 [1]	Fingernails develop; facial features become more prominent; intestines position themselves in the abdomen
Second [2]	13	72-76	21-25	Production of urine occurs; skull and long bones harden
	14	85-89 [1]	43-47 [1]	Neck becomes more distinct; production of red blood cells begins in the spleen; gender becomes obvious
	15	99-103	68-72	Bones become conspicuous in ultrasound imaging; pattern of the scalp becomes visible
	16	118-122 [1]	108-112 [1]	Head becomes erect; slight movement of eyes occurs; skin thickens; limb movements become detectable by USG but not actually felt by mother
	17	128-132	138-142	Toenails begin to form; fetal movement inside amniotic sac increases; heart

				pumps around 47.3 liters of blood per day
	18	138-142 [1]	198-202 [1]	Ears become straight and allow fetus to hear sounds; eyes face forward; digestive system becomes active;
	19	151-155	238-242	Growth slows down; outer coating known as vernix caseosa develops to cover and protect fetus from damage; uterus and vaginal passage develops (in females)
	20	162-166	298-302	Termed as the half-way point of pregnancy; mother can feel fetal movements; sleep-cycle becomes functional where maternal movement and external sound can awaken the fetus
	21	200-260	320-360	Layer of hair called lanugo covers the skin and holds the vernix caseosa in place; sucking reflex begins
	22	270-280	430-460	Hair and eyebrows become conspicuous; brown adipose tissue forms to provide warmth; testes grow downwards (in males)
	23	280-290	490-500	Eye movements become rapid; fingerprints and footprint begin to form; hiccups and twitchy movements occur

	24	290-300	590-630	Creases appear on skin; skin becomes reddish and semi-transparent for underlying capillaries;
	25	340-345	660-670	Fetus responds to recognizable sounds; majority of the sleep-cycle consists of Rapid Eye Movement (REM)
	26	355-360	760-820	Lungs develop with the formation of surfactant layer
	27	365-370	860-890	Second semester is over; nervous system develops further; fat deposition under the skin continues
Third [3]	28	375-380	1005-1010	Eyelids open slightly; eye lashes develop; CNS controls mechanical breathing and body temperature
	29	385-390	1150-1155	Movements such as kicking, sprawling and clenching occur
	30	395-400	1300-1330	Eyes can be widely opened; hair growth is high; red blood cells are produced in the bone marrow
	31	405-410	1500-1510	Major development is complete; fetus gains weight rapidly
	32	420-425	1700-1705	Toenails become conspicuous; lanugo is shed
	33	435-440	1910-1920	Pupillary Light Reflex (PLR) develops;

				all bones except the skull hardens
	34	445-455	2100-2150	Fingernails become conspicuous and grow larger
	35	460-465	2380-2390	Skin smoothens; limbs become plump
	36	470-475	2600-2610	Most of the space inside amniotic sac is filled up; frequency of fetal movements increases
	37	485-490	2850-2870	Head may turn downwards facing the pelvis for delivery
	38	495-500	2900-3100	Head and abdomen have reached nearly the same diameter; toenails grow larger; most of the lanugo has fallen off
	39	505-510	3200-3300	Chest becomes more distinct; testes grow further downwards (in males); fat accumulation increases
	40	510-515	3400-3500	Estimated time of delivery, which varies amongst individuals

Note: From [1]"Fetal Development: The 1st Trimester - Mayo Clinic", 2021; [2]"Fetal Development: The 2nd Trimester - Mayo Clinic", 2021; [3]"Fetal Development: The 3rd Trimester - Mayo Clinic", 2021; [4]"Pregnancy Stages Week by Week - Parents", 2021.

3.2 Factors affecting fetal development

The rate of fetal growth increases exponentially during the last 20 weeks of gestation. On average, it reaches 95% of its weight. As its growth progresses, several factors play a crucial role

in its outcome. These factors can be (i) genetic, (ii) environmental, (iii) nutritional, (iv) uteroplacental, or (v) fetal. The uteroplacental and umbilical blood flow and transplacental glucose and fetal insulin are major determinants of fetal growth (H, 1982). The rate of uterine blood flow determines the amount of nutrients (e.g., glucose, fatty acids, and amino acids) and oxygen reaching the developing fetus. The uptake of these nutrients and presence of hormones (e.g., thyroid hormone, insulin, and cortisol) modulate the expression of genes in the developing fetus for certain fetal components such as glucose transporters, mechanism of ketogenesis, hexokinase, oxidation of fatty acids and so on (Mongelli, 2003).

The environmental factors include paternal and maternal genome, maternal weight, and uterine capacity to deliver oxygen and nutrients to the developing fetus. Genetic factors are the fetal genome that influences it growth pattern. Several genes from both parents are imprinted in the fetal genome, especially insulin-like growth factor I (IGF-I) and IGF-II. These genes control the maturation of trophoblast cells to form the placenta. A study with a cohort of 171 females pregnant with twins was conducted by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies. It was observed that the impact of environmental factors on fetal development is greater than genetic influence in early pregnancy and the effect of genetic influence is greater in later pregnancy (Workalemahu et al., 2018).

3.3 Critical stages susceptible to teratogenicity

Every stage of development has its own critical period, which is the time at which the fetus is most vulnerable to a teratogen (Donovan & Cascella, 2020).

The development of fetal CNS is the most sensitive stage in terms of the influence of environmental factors and drugs. The significant events of this stage occur during the mid-trimester. This stage is divided into 2 sub phases: (i) neurogenesis and (ii) neuronal migration. Both these phases are critical for the neurodevelopment of the fetus. Neurogenesis involves the formation of neurons via proliferation and differentiation of neural crest cells. Neuronal migration leads to the development of the neural tube and subsequent formation of synapse (Kummer et al., 2006).

In various animal studies, rodents have been used to study the effect of drugs in pregnancy. The events that occur in fetal rodent brains in day 14 to 16 of fetal period correspond to the events that occur in the 2nd trimester of the human fetal brain. Therefore, this period is used as the reference value for assessment of human fetal development (Clancy et al., 2007).

Drugs can affect the development of the fetus in 3 phases, as summarized in table 3 (Khedun et al., 2000).

Table 2: Summary of drug influence in three major stages of fetal development

Duration in gestation	**Name of the phase susceptible to drug**	**Effect of interference of the drug**
Day 0 to 17	Fertilization and implantation	Embryonic death and abortion
Day 18 to 55	Organogenesis, most sensitive stage	Functional and structural abnormalities
Day 56 to birth	Fetal period, least sensitive stage	Reduction of cell size and number leading to fetal deformities

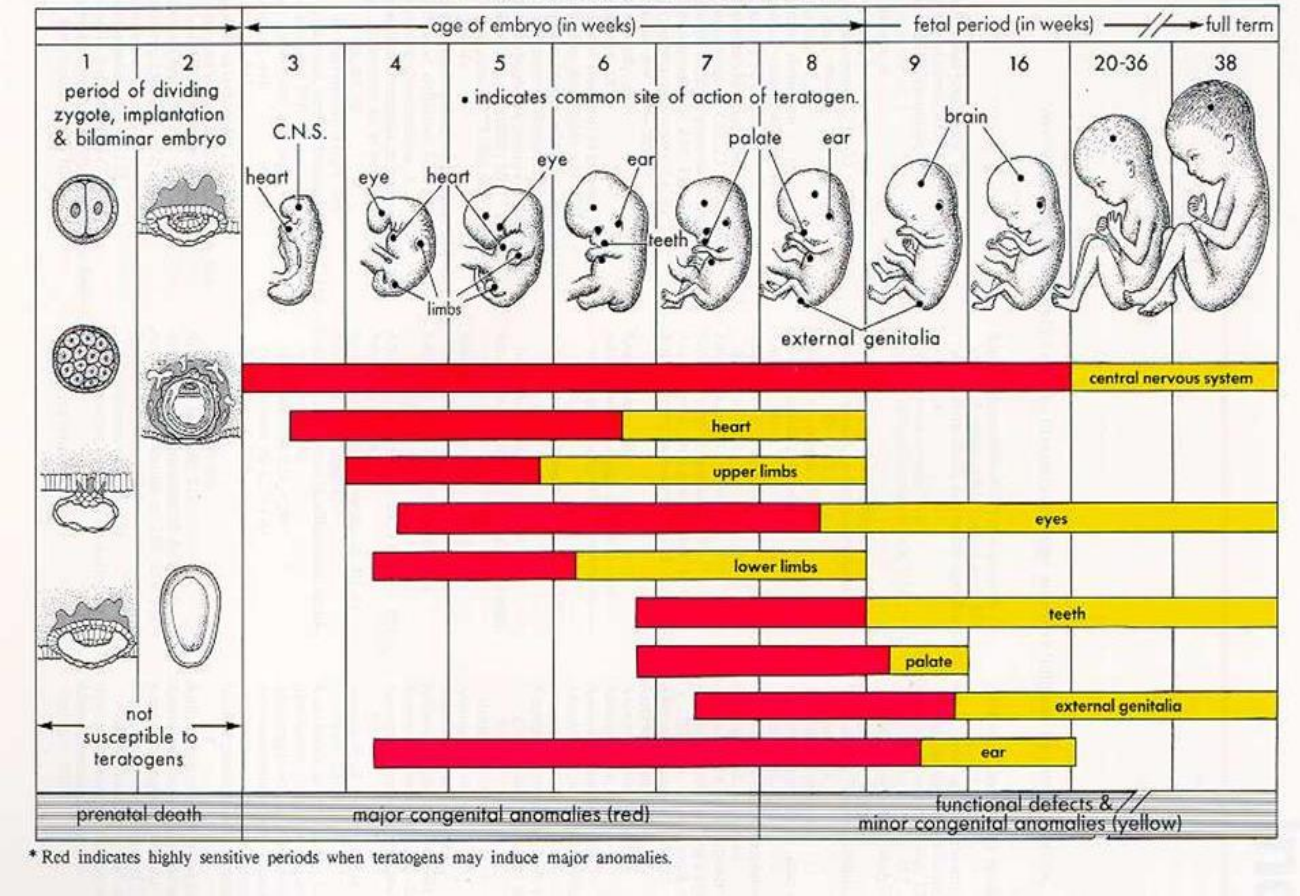

Figure 1: Critical periods in fetal development (Adapted from "Prenatal Stages of Development", 2020)

3.4 Fetal blood brain barrier

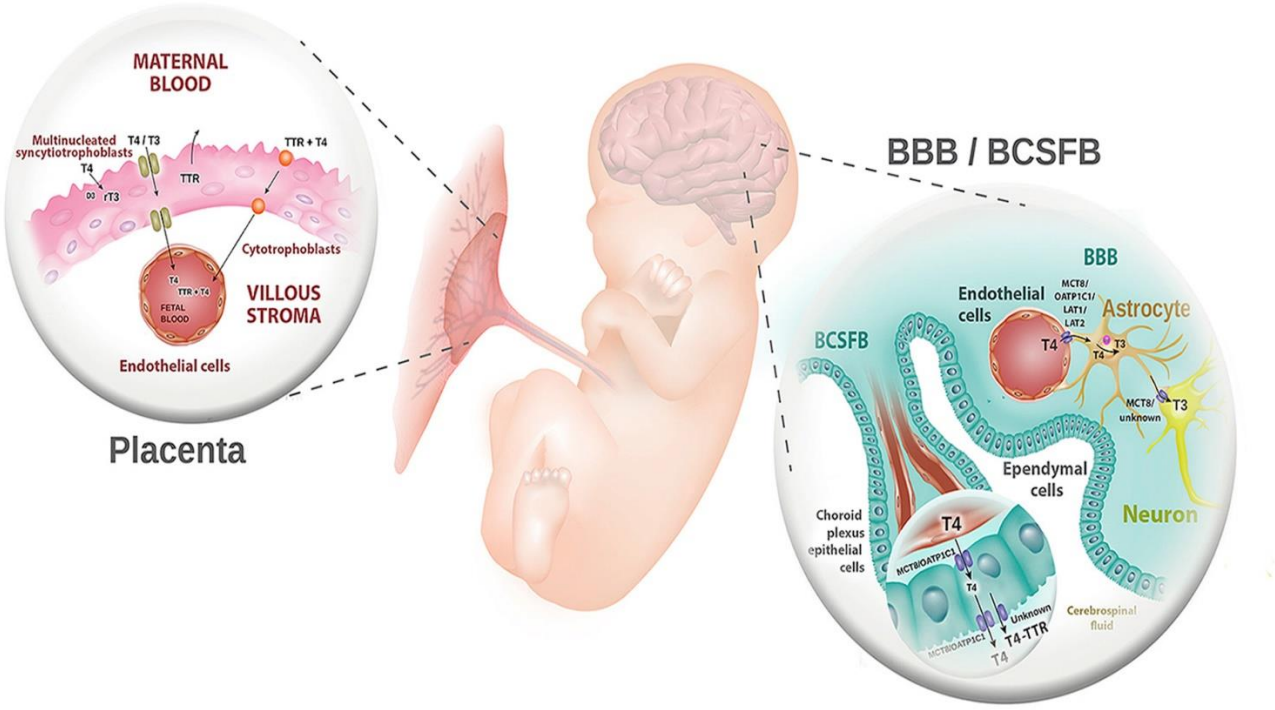

Figure 2: Fetal blood brain barrier (Adapted from Landers & Richard, 2017)

Recent studies have demonstrated that the fetal BBB not only exists in the development stage for as early as 8 weeks of gestation, but also possesses physiological functionality. Moreover, the fetal BBB has also been shown to have many of the characteristics of a completely developed adult BBB (Sanders et al., 2014). The blood-brain barrier (BBB) is a crucial part of the fetal anatomy and physiology, which plays an important role in the normal functioning of the fetal central nervous system (CNS). It acts as a barrier between systemic circulation and the parenchyma of the brain and regulates the movement of various substances between them. It comprises compact endothelial cells such as astrocytes, microglia, pericytes, together with neuron and form the neurovascular unit (NVU). In addition, there are various protein complexes that form cell-cell junctions. These junctions allow the diffusion of selective substances into the brain, restricting the free movement of large molecules such as proteins, charged molecules and polar molecules such as water. This helps to maintain fetal homeostasis and provides protection to the developing fetal brain from various toxins, which can be either endogenous or exogenous and can have long term pathological implications (Goasdoué et al., 2017).

Apart from fetal anatomy, there are certain transport mechanisms in the fetal BBB that acts as a medium of nutrient transfer to the brain as well as a medium of harmful substances away from the brain. The types of transport mechanisms include: (i) free diffusion, (ii) carrier-mediated transport, (iii) receptor-mediated transport, and (iv) active efflux transport. The active efflux mechanism is a key process that regulates the movement of drugs into the fetal BBB. These transporters also remove metabolic waste products and xenobiotics from the brain (Hawkins, 2009).

Some transport systems are present in both the placenta and the fetal BBB. However, the placenta does not provide the optimum protection to the fetus because drugs can permeate the placenta with adequate time of exposure and dosage of the drug. Small and lipophilic drugs can freely diffuse through the placenta and enter fetal blood, which increases the risk of teratogenicity to the fetal CNS. On the other hand, fetal BBB is more selective and restrictive and is largely dependent on the size and lipophilicity of the drug. Despite this meticulously maintained barrier, it can be disrupted and lead to long-term neurological diseases such as multiple sclerosis and Alzheimer's disease (Stolp et al., 2013). This is because fetal development not only depends on the anatomical structures or transporters in the BBB, but also on drug metabolizing enzymes, mainly glutathione S-transferases and cytochrome P450 (Agúndez et al., 2014). Moreover, drugs can reach the fetal brain via other routes such as the blood-CSF barrier between systemic circulation and choroid plexus, meningeal barrier, and the fetal-specific CSF-brain barrier (CJ et al., 2012).

3.5 Placenta

The human placenta is composed of 3 layers: (i) amniotic layer, (ii) chorionic layer, and (iii) decidual layer. The amniotic layer is composed of a layer of single-celled epithelium and a deeper layer of mesoderm. The chorionic layer has a mesoderm and trophoblast layer. Trophoblast cells are derived from the outer layer of blastocyst and form the larger portion of the placenta (Herrick & Bordoni, 2021). Trophoblast cells provide nutrients to the developing fetus (Soares & Varberg, 2018). The decidual layer is found between the fetal membrane and myometrium (Castillo-Castrejon et al., 2018).

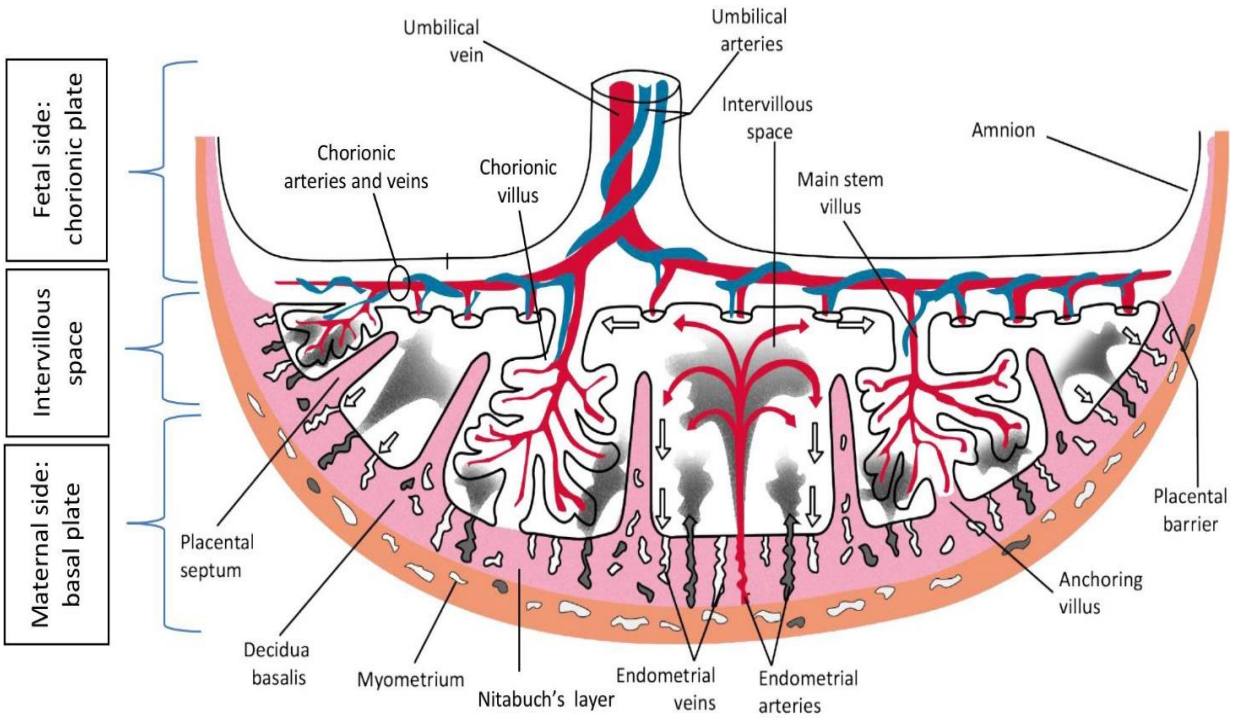

Figure 3: Structure of the placenta (Adapted from Jansen et al., 2020)

The chorionic villus is the basic structural unit of the placenta. The maternal blood reaches the uterus via endometrial arteries. The two umbilical arteries carry deoxygenated blood of the fetus to the placenta through the umbilical cord. Various substances present in the maternal blood diffuse into the intervillous space and combine with the fetal blood. The average rate of maternal blood flow to the uterus at term is 600 ml per minute. 80% of this blood reaches the placenta (Griffiths & Campbell, 2015).

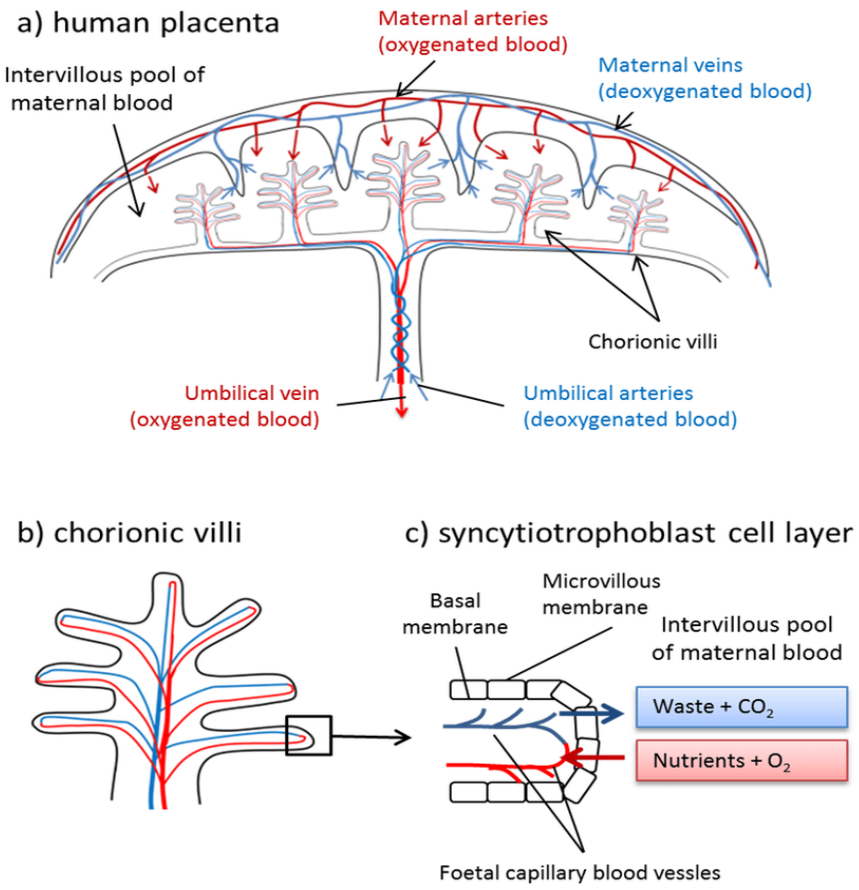

Figure 4: Blood flow across the placenta (Adapted from Barman, 2015)

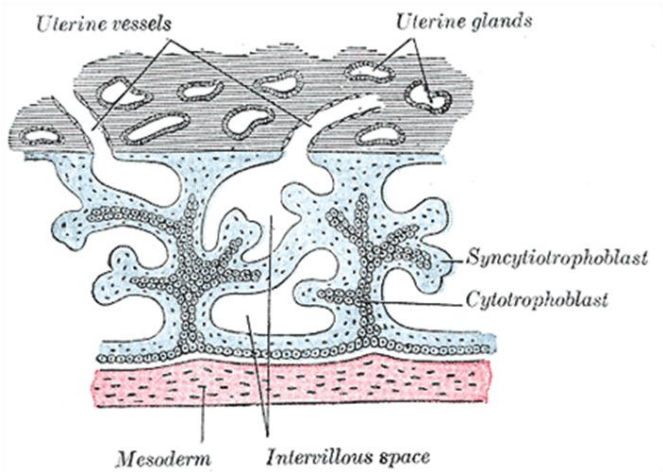

Figure 5: Chorionic villus in the placenta (Adapted from Aplin et al., 2018)

The chorionic villus is composed of two layers: (i) The syncytiotrophoblast layer, which is which forms rapidly and ruptures the capillaries of the endometrium to form a connection with the fetus, and (ii) cytotrophoblast layer, which develops into the early-stage chorionic villi (Aplin et al., 2018)

Drugs are carried from the maternal to the fetal blood in a number of stages. The drug must first be released into the intervillous space. Then it is transferred to the layer of syncytiotrophoblast cells of the chorionic villi. The drug then progresses into the fetal capillary blood vessels. In this overall process, the transfer of drugs across the syncytiotrophoblast cell layer acts as the rate-limiting step (Griffiths & Campbell, 2015).

The placenta is responsible for carrying out several functions, including: (i) gaseous exchange between mother and fetus, (ii) transfer of nutrients from mother to fetus, (iii) transfer of metabolic wastes from fetus to mother, (iv) passive immunity, and (v) hormonal secretion, mainly thyroid hormone essential for fetal development. The mechanisms of placental transfer include: (i) passive diffusion, (ii) facilitated diffusion, (iii) active transport, (iv) endocytosis, (v) exocytosis (Griffiths & Campbell, 2015).

Table 3: Mechanisms of placental transfer (Murphy et al., 2006)

Substance transferred	**Mechanism of transfer**	**Dependent factors**
Oxygen	Passive diffusion	Oxygen partial pressure gradient between maternal blood in the intervillous space and fetal blood in the umbilical arteries (4 kPa); Bohr effect; placental exchange area and blood flow
Carbon dioxide	Passive diffusion	Partial pressure gradient for carbon dioxide between fetal blood in the umbilical arteries and maternal blood in the intervillous space (1.8 kPa); Haldane effect; placental exchange area and blood flow

Glucose	Facilitated diffusion	--------
Amino acids	Active transport. Co-transport of sodium down the concentration gradient cause influx of amino acids	--------
Fatty acids and glycerol	Simple diffusion; fatty acid binding proteins	--------
Electrolytes	Sodium, chloride: passive diffusion	--------
	Calcium, iron: active carrier mediated transport	--------
Vitamins	Active carrier mediated transport	--------
Water	Simple diffusion; water channel proteins in trophoblast	Osmotic pressure and hydrostatic gradients
Immunoglobulins	Pinocytosis; exocytosis; endocytosis	--------

As previously mentioned, organogenesis, which occurs during the 1st trimester, is the most susceptible stage. The fetus is directly or indirectly affected. For instance, changes in uteroplacental blood flow can expose the fetus to adverse effects. Therefore, placental blood flow and its components being transferred are crucial for the fetal development.

Table 4: Classification of drug transfer across the placenta (Griffiths & Campbell, 2015)

Type of drug transfer	**Description**	**Examples**
Type 1	Complete; concentration of drug in maternal blood quickly equilibrates with the concentration of the drug in the fetal blood	Thiopental drugs
Type 2	Incomplete; concentration of drug is higher in the fetal blood than in the maternal blood	Ketamine
Type 3	Exceeding; drug partially crosses the placenta so that the concentration of drug in the maternal blood is higher than in the fetal blood	Succinylcholine

There are several factors affecting the drug transfer across the placenta (Griffiths & Campbell, 2015). These include:

- Physical placental surface area
- Placental thickness
- pH of maternal and fetal blood
- Placental metabolism
- Uteroplacental blood flow
- Protein binding
- pKa
- Lipid solubility
- Pharmacological molecular weight of drug
- Presence of placental drug transporters
- Concentration gradient across placenta
- Degree of ionization

Chapter 4:

Pharmacokinetic changes in pregnancy

Clinical management in pregnancy with medications requires adequate understanding of maternal physiology, pathophysiology, and pharmacology of the medications used during gestation. The primary goal is to optimize the therapeutic efficacy of the treatment with minimal risk to both the mother and fetus. One major limitation of ensuring this is the lack of pharmacological studies involving pregnant women due to preconceived concerns regarding fetal safety. In addition, the majority of studies on gestation-specific medications have been done involving healthy adult males and non-pregnant women (Feghali et al., 2015).

Comprehension of the pharmacokinetic parameters must be evaluated by considering the pregnancy-related changes. The parameters of interest are absorption, distribution, metabolism, elimination, and transport of drugs.

4.1 Drug absorption

Absorption of drugs is defined as the movement of drugs from the site of administration into the blood. This is expressed by bioavailability, which is the amount of active ingredient absorbed into the bloodstream to produce the desired therapeutic effect (Alagga & Gupta, 2021). In early pregnancy, oral bioavailability is reduced by nausea and vomiting. Therefore, drugs must be administered when these conditions are minimal to achieve the optimum therapeutic effect. Moreover, during gestation, production of gastric acid is reduced, and secretion of mucus is elevated, which raise the stomach pH. This in turn may reduce the absorption of weak acids and weak bases. Lower GI motility may also affect oral bioavailability. On the other hand, increased cardiac output and blood perfusion to the intestines may increase drug bioavailability (Costantine, 2014). However, there is limited data to confirm these assumptions for both oral and non-oral routes of administration (Feghali et al., 2015).

4.2 Drug distribution

Distribution is the perfusion of drugs into different tissues after being absorbed into the bloodstream. This is expressed by volume of distribution (Vd), which is a theoretical volume

occupied by a drug, assuming it is uniformly distributed at a certain plasma concentration. This parameter is crucial for determining a drug's loading dose required to attain the desired therapeutic effect. The higher the value of Vd, the higher the proportion of drugs bound to tissues. Conversely, plasma protein-bound drugs will have a lower Vd. Such variations Vd ultimately affect the therapeutic efficacy and safety profile of a drug. For instance, the heart rate in the third trimester is about 90 bpm at rest, which implies higher cardiac output and stroke volume (Feghali et al., 2015). The plasma volume also increases during pregnancy with approximately 3.5 L at 38 gestational weeks. An increase in total body water increases the Vd of hydrophilic drugs. On the other hand, an increase in total maternal body fat increases the Vd of lipophilic drugs. In case of plasma-protein binding, the concentration of albumin and alpha 1-acid glycoprotein decreases throughout gestation, and this increases the plasma concentration and Vd of unbound drugs (Hayashi et al., 2002). This is crucial for administration of drugs with a narrow therapeutic index (e.g. phenytoin). A small increase in the unbound fraction of such drugs can increase the possibility of adverse effects. Therefore, it is crucial to monitor the plasma concentration of unbound drugs and make strategic dosing adjustments to avoid subsequent toxicity (Feghali et al., 2015).

Uterine blood increases by 10 times at term, which increases the Vd of certain drugs and may lead to drug accumulation in the fetus as well as the amniotic fluid (Feghali et al., 2015).

4.3 Drug metabolism

Metabolism of drugs is defined as the modification of drugs via certain enzyme systems mainly found in the liver. During pregnancy, the placenta also plays a role in drug metabolism as it contains certain drug-metabolizing enzymes, and their levels fluctuate throughout gestation (Syme et al., 2004).

Both the liver and the placenta involve phase I and phase II metabolic reactions.

Table 5: Comparative metabolism of drugs in liver and placenta (Jeong, 2010; Syme et al., 2004)

Drug metabolism reactions	**Normal hepatic metabolism and altered metabolism in pregnancy**	**Placental metabolism**
Phase I reactions	Oxidation, reduction, and hydrolysis	Synthesis and catabolism of a wide range of drugs and toxic substances, including steroid hormones, fatty acids, and metabolizing vitamins
Phase II reactions	Conjugation of glucuronic acid to various substrates	i. conjugation of glucuronic acid to xenobiotics ii. conjugation of glutathione to bioactive electrophiles iii. conversion of epoxides into trans-glycols or trans-dihydrodiols
Enzymes involved in phase I	Cytochrome P450 (CYP) family	Cytochrome P450 (CYP) family, namely CYP1A1, CYP1A2, CYP1B1, CYP2E1, CYP3A
Enzymes involved in phase II	Uridine 5'-diphosphate glucuronosyltransferases (UGTs)	Uridine 5'-diphosphate glucuronosyltransferases (UGTs); Glutathione S-Transferases; Epoxide Hydrolase; Sulfotransferases
Enzymatic activity of phase I enzymes	CYP3A4, CYP2A6, CYP2D6, and CYP2C9 show increased activity in gestation; CYP1A2 and CYP2C19 show decreased activity in gestation	CYP1, CYP2, CYP3, and CYP4 show increased activity in the 1st trimester and decreased activity in the later trimesters

Enzymatic activity of phase II enzymes	Overall, enzymes show increased activity, with a higher activity in the 3rd trimester compared to the 1st and 2nd trimesters	i. UGTs catalyze conjugation of glucuronic acid to xenobiotics ii. Glutathione S-Transferases catalyze conjugation of glutathione to bioactive electrophiles iii. Epoxide Hydrolase convert epoxides into trans-glycols or trans-dihydrodiols
Factors affecting enzyme activity	Ethnicity, age, gender, pathophysiological conditions	

Once drugs cross the placental barrier, they travel through the umbilical vein and perfuse into the fetal liver tissues where they undergo fetal first pass effect. The drugs then subsequently reach the fetal systemic circulation. The enzymatic activity of liver enzymes in the fetus is lower than that in the adult liver. Occasionally, fetal hepatic enzymes remain inactive as well. Moreover, the fetal renal clearance is ineffective since the excreted products in the amniotic fluid are taken in by fetal swallowing. However, presence of placental metabolism reduces the exposure of the fetus to potentially teratogenic drugs. In addition, hepatic first-pass effect of the fetus contributes further to drug metabolism and inhibits transfer of unchanged drug (Muller et al., 2010).

4.4 Drug elimination

Drug clearance is defined as the volume of plasma that is completely eliminated of a drug via different organs, e.g., mainly liver and kidneys. This is in turn depends on extraction ratio (ER), which is the amount of drug that is absorbed by the liver and metabolized. The clearance of drugs with high ER depends on the hepatic blood flow. On the other hand, the clearance of low ER depends on metabolizing capacity of the liver and the amount of free drug in the plasma, regardless of the hepatic blood flow (Feghali et al., 2015).

Renal clearance is dependent on GFR, secretion via renal tubules, reabsorption. The GFR is a measure of the amount of blood that is filtered by the kidney per unit time (usually in minutes).

The GFR increases by 50% within the 1st trimester, which continues till the last week of gestation. Drugs that undergo renal clearance will have a higher rate of elimination after the 1st trimester since the GFR is higher (e.g., cefazolin, clindamycin, digoxin, atenolol). Furthermore, changes in renal tubular secretion and tubular reabsorption also affect the rate of renal clearance of drugs in pregnancy (Feghali et al., 2015).

Chapter 5:

Teratogenicity in gestation

5.1 Types of teratogenicity

Teratogenicity can be of five types, which are: (i) infectious agents (e.g., pathogenic viruses and bacteria), (ii) physical agents (e.g., ionizing agents), (iii) maternal health factors (e.g., chronic diseases), (iv) environmental chemical substances (e.g., organic mercury compounds, herbicides, and (v) drugs (medicinal or recreational) ("Teratogens/Prenatal Substance Abuse", 2017) .

5.2 Factors determining teratogenic potential

Apart from the type of teratogen, the extent of teratogenicity and congenital abnormality depends on factors including duration of exposure to teratogen, embryonic age, dose of teratogen, genetic susceptibility of the fetus, combination therapies, maternal pharmacokinetics, and variations in maternal metabolism. For instance, the risk of teratogenicity is greatest in the first trimester compared to the later gestational period (Gelder et al., 2010).

5.3 Pregnancy risk classification for medicines

After the thalidomide tragedy in 1961, the U.S. Food and Drug Administration (FDA) developed a system of labelling medications in 1979. Five risk categories (A, B, C, D or X) were established to promote safe use of medications during pregnancy. It is important to note that drugs must only be administered if they pose no evidence-based risk to the fetus, or as clearly needed if the benefits outweigh the risks (Law et al., 2010).

Table 6: FDA risk classification for gestational drugs (Law et al., 2010)

Category	**Broad description**	**Examples**
A	No fetal risks found in the 1st trimester of gestation in sufficient and well-controlled studies have been conducted in pregnant women (and there is no evidence of risk in later trimesters)	Levothyroxine, Folic acid, liothyronine
B	No fetal risks found in animal reproduction studies;	Metformin, hydrochloro-

	sufficient and well-controlled studies in pregnant women have not been conducted	thiazide, cyclobenzaprine , amoxicillin
C	Adverse effects found on the fetus in animal reproduction studies; sufficient and well-controlled studies have not been conducted in humans; benefits in gestation may allow use of the drug despite the risks	Gabapentin, amlodipine, trazodone
D	Fetal risks found based on adverse reaction data from investigational or post-marketing experience or human studies; potential benefits in gestation may allow use of the drug despite the risks	Losartan
X	Fetal abnormalities found in animal or human studies based on adverse reaction data from investigational or post-marketing experience; risks in gestation outweigh the benefits; contraindicated in pregnancy	Atorvastatin, simvastatin, methotrexate, finasteride

The table below summarizes the main medications that are contraindicated in pregnancy.

Table 7: Category X medications in pregnancy (Hall, 2016; "Medicines During Pregnancy - Michigan Medicine", 2020)

ACE inhibitors (angiotensin converting enzyme)	Efarvirenz
Anticonvulsants	Etretinate
Carbamazepine (carbimazole)	Fluconazole
Dilanten, Phenytoin	Heroin/methodone
Phenobarbital	Isotretinoin (13-cis-retinoic acid)
Tegretol	Lamotrigine
Trimethadione/paramethadione	Lithium
Valproic acid	LSD (lysergic acid diethylamide)
Cocaine	Methotrexate (aminopterin)
Coumarin derivatives e.g., warfarin	Misoprostol (prostaglandin E_1)

Cyclosporin	Mycophenolate mofetil
Tetracycline	Statin drugs
Thalidomide	Anxiety medications Alprazolam, Diazepam
Vitamin A in large doses/ retinoid containing drugs	Antidepressant Paroxetine
Antitussives containing guaifenesin	Decongestants Phenylephrine or pseudoephedrine
Bismuth subsalicylate	

5.4 Mechanism of action of teratogenic drugs

The risk of teratogenicity is unknown for 90% of the medication treatments in the US alone. In addition, the etiological pathways of the congenital abnormalities are mostly unknown, although some mechanisms through which drugs may lead to fetal abnormalities have been identified (Gelder et al., 2010).

5.4.1 Folate Antagonism

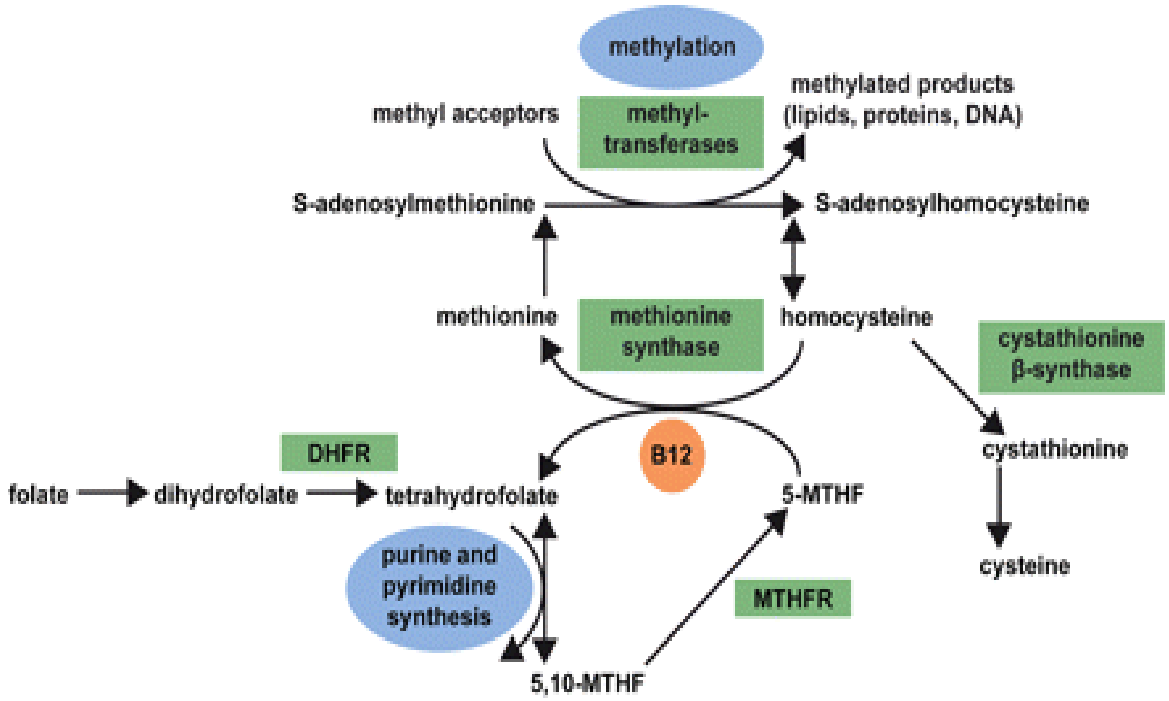

Figure 6: The inhibition of folate-methylation cycle (Adapted from Gelder et al., 2010)

Folate–homocysteine–methionine metabolism. B12, vitamin B12; DHFR, dihydrofolate reductase; MTHF, methyltetrahydrofolate; MTHFR, methyltetrahydrofolate reductase (Gelder et al., 2010).

Drugs following this mechanism either competitively inhibit the conversion of folate to tetrahydrofolate by binding irreversibly to the enzyme dihydrofolate reductase (DHFR), bind antagonistically with the enzymes involved in folate metabolism, reduce folate absorption, or facilitate folate degradation (Gelder et al., 2010).

5.4.2 Endocrine Disruption

Some drugs inhibit or mimic the action of hormones and consequently disrupt the release, metabolism or binding of endogenous hormones. The extent to which this is achieved depends

on the drug's affinity and specificity towards the hormone. In addition, such interference either activates the hormone or inhibit its action and hinders the natural physiological processes. These are known as endocrine-disrupting drugs or endocrine-disrupting chemicals (Gelder et al., 2010).

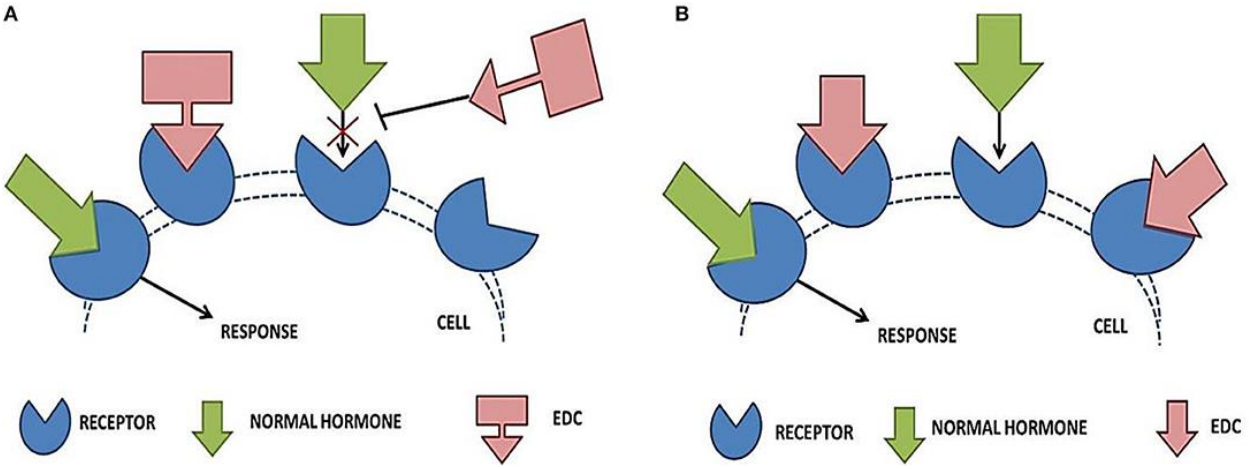

Figure 7: Teratogenesis via endocrine disrupting drugs (Adapted from Priyam et al., 2018)

EDC= Endocrine-Disrupting Chemical

5.4.3 Vascular Disruption

The arteries, veins, and capillaries, i.e., the vasculature of the fetus can be disrupted by certain factors such as lower uterine blood flow to the fetus, infection, maternal anatomical abnormalities, blockage of the vessels, constriction of the vessels can impair the proper transfer of nutrients and oxygen to the fetus and hinder its growth. This can lead to structural abnormalities in the fetus which in turn depends on gestational age, location, and extent of vascular damage. The congenital defects that arise through vascular disruption are usually observed in distal extremities and fetal intestines (Gelder et al., 2010).

5.4.4 Disruption of Neural Crest Cells

Neural crest cells (NCCs) are a group of multi-potent cells that originate from the neural tube present at the border of the ectoderm during the embryonic development. The neural tube is the foundation of the spinal cord. The NCCs then differentiate into different kinds of cells (Shakhova & Sommer, 2010).

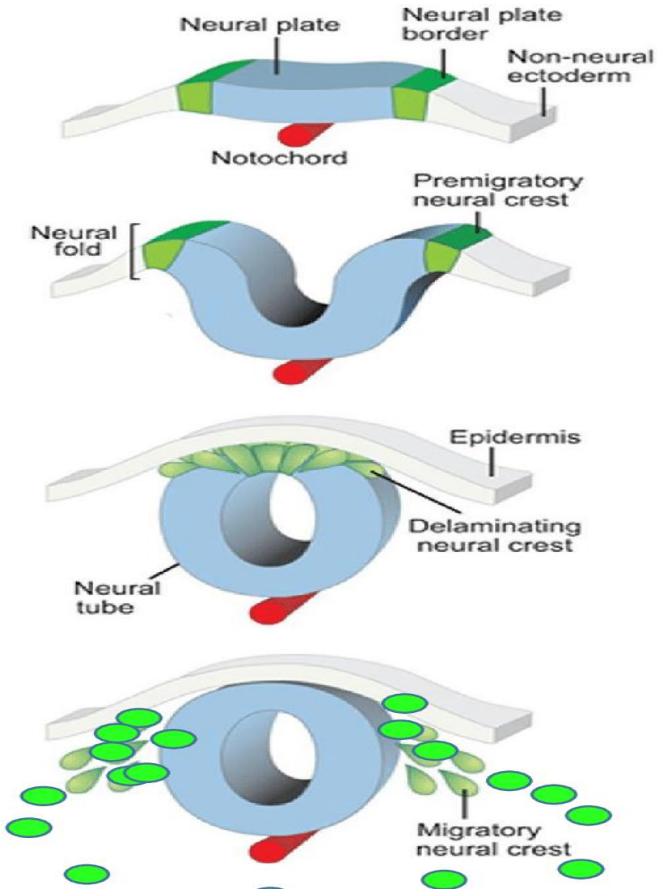

Figure 8: Formation and proliferation of neural crest cells (Adapted from "Anatomical Embryological Development of Neural Crest", 2021)

Some drugs can hinder the normal formation, proliferation, and migration of NCCs. They can do so by interfering with the growth factors involved in NCC formation. They may also interfere with the natural interaction of peptides called endothelins with their corresponding receptors, a process essential for the migration and proliferation of NCCs (Hu et al., 2006). Birth anomalies via neural disruption include cardiovascular and non-cardiovascular defects (Gelder et al., 2010).

5.4.5 Oxidative Stress

The developing embryo has a weak defense mechanism against oxygen free radicals. Any imbalance in the amount of these radicals creates an oxidative stress. The radicals, also termed as Reactive Oxygen Species (ROS), can be from exogenous sources (e.g., ionizing radiation) or endogenous sources (fetal metabolic changes). An increase in ROS levels can hinder the organogenesis of the fetus. For instance, changes in the embryonic metabolism can form ROS

via oxidation-reduction interaction between the fetal enzymes and the non-toxic pro-teratogen. The resulting ROS consequently hinder the natural formation of fetal DNA, RNA, proteins, and lipids, causing birth defects such as skeletal anomalies, neural tube anomalies, cleft lip, cardiovascular abnormalities, and defects of the extremities (Mazzu-Nascimento et al., 2017).

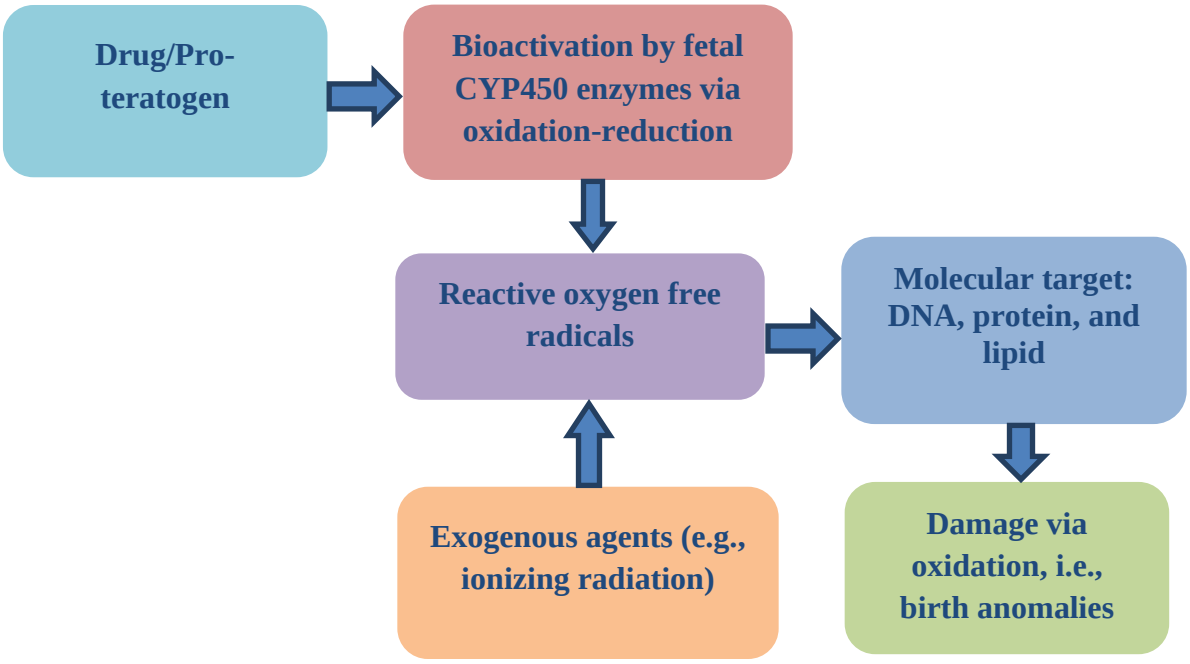

Figure 9: Teratogenesis via reactive oxygen species (Gelder et al., 2010)

5.4.6 Enzyme-mediated Teratogenesis

i. Angiotensin Converting Enzyme (ACE) inhibitors and AII Receptor Blockers (ARBs) may interfere with the RAAS mechanism of the fetus and impair its growth. A recent study has demonstrated that this can lead to cardiac and CNS anomalies in the developing fetus (Gelder et al., 2010).

ii. Cholesterol-lowering drugs can inhibit the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which is essential for the production of mevalonic acid via the mevalonate pathway. This inhibition can lead to birth defects since statins are essential for the normal development of the fetus (Gelder et al., 2010).

iii. Histone deacetylases (HDACs) are essential for the control of gene expression via chromatin remodeling. The inhibition of HDACs may hinder cell proliferation, division,

and apoptosis (Gelder et al., 2010). The HDAC activity is vital for the proper development of the fetus and its inhibition can lead to axial skeletal anomalies (Di Renzo et al., 2007) and neural tube defects (Daniel Eikel et al., 2006) as per animal studies. Drugs and substances that exhibit teratogenesis in this mechanism include valproic acid (Göttlicher et al., 2001), salicylates and boric acid (Gelder et al., 2010).

iv. Cyclooxygenase-1 (COX-1) is responsible for the production of prostaglandins required for a number of physiological processes (e.g., maintenance of blood pressure and platelet aggregation). Cyclooxygenase-2 (COX-2) also produces prostaglandins for inflammatory action. Selective NSAIDs inhibit COX-2 and non-selective NSAIDs inhibit both COX-1 and COX-2. The resulting COX-1 inhibition can cause cardiovascular, diaphragm and midline defects. However, inhibition of COX-2 has not been observed to cause teratogenic effects because the expression of this enzyme has not been found during the process of embryogenesis in rats. Aspirin irreversibly inhibits the COX enzymes via acetylation and is linked to greater incidence of teratogenic effect in preclinical studies (Gelder et al., 2010).

v. Carbonic anhydrase catalyzes the reversible hydration of carbon dioxide to bicarbonate ion and protons. This enzyme is expressed in several developing embryos and plays a crucial role in various physiological reactions, such as homeostasis, respiration, and bone resorption. Drugs that inhibit this enzyme (e.g., acetazolamide) have been reported to cause congenital anomalies and defects of the extremities. The main mechanism that is suspected to cause this teratogenic effect is the decrease in intracellular pH of the embryo, which consequently hampers glycolysis and synthesis and proliferation of important proteins. However, there is insufficient evidence of this mechanism in humans (Gelder et al., 2010).

5.4.7 Receptor-mediated Teratogenesis

i. Angiotensin-converting enzyme (ACE) and angiotensin II receptors: Blood pressure is regulated in the human body via a mechanism of homeostasis known as renin-angiotensin system (RAAS). The hormone angiotensin II increases the blood pressure by causing vasoconstriction of the smooth vascular muscles. The human fetus contains the elements of RAAS, but its composition varies from that of an adult. ACE inhibitors and

angiotensin II receptor antagonists can adversely affect the fetal RAAS and cause fetal abnormalities by affecting renal function, fetal blood pressure and vascular tone. For instance, ACE inhibitors can cause human malformation syndrome if taken in the 2nd or 3rd trimester. The adverse effects associated with this are oligohydramnios, dysgenesis of the proximal renal tubules, limb contractures, hypoplasia of the lungs, and incomplete formation of the skull bones (Gelder et al., 2010). In the case of Angiotensin II receptor antagonists, there is a higher risk of developing fetal cardiovascular and CNS abnormalities with 1st semester exposure according to a recent study (Cooper et al., 2009).

ii. N-methyl-D-aspartate receptors: N-methyl-D-aspartate (NMDA) receptors play a crucial role in the fetal brain development via migration of the NCCs. If these receptors are blocked, the fetal brain and blood brain barrier would not develop properly. NMDA receptor blockers can affect the fetal brain after 20 weeks of gestation. However, it is controversial whether NMDA receptor blockers cause neural tube defects, since this has not been proven in clinical trials with mice. Moreover, dextromethorphan, which is an NMDA blocker, is extensively used and has not been reported to cause birth defects (Gelder et al., 2010).

iii. 5-Hydroxytryptamine receptors and transporters: 5-hydroxytryptamine (5-HT) receptors play an important role in the structural development of several tissues of the embryo. Therefore, higher stimulation or inhibition of these receptors can lead to congenital abnormalities. Moreover, the reuptake of 5-HT by serotonin transporters imply that SSRIs can also cause birth anomalies. For instance, fluoxetine, paroxetine, and sertraline, have been observed to cause cranial and facial defects, although the risk does not appear to be significantly high. Fluoxetine in particular has been associated with cardiac anomalies when taken in the 1st trimester. In addition, since 5-HT is also involved in the development of the fetal heart, its inhibition can lead to cardiac defects (Gelder et al., 2010).

iv. G-Aminobutyric acid receptors: G-aminobutyric acid (GABA) is an inhibitory neurotransmitter which is believed to be involved in embryonic morphogenesis and palate formation, although its exact function is not yet known. Benzodiazepines act via GABA receptors and is reported to cause floppy infant syndrome. In addition, according

to some studies, use of benzodiazepines in the 1st trimester has been linked to orofacial clefts, cardiac defects, and GI tract atresia, although other studies are not consistent with these findings (Gelder et al., 2010).

The mechanism of action of certain number of drugs have been speculated till date. The table below summarizes this information.

Table 8: Summary of suspected mechanism of teratogenesis in certain drugs till date (Gelder et al., 2014)

Suspected mechanism of action	**Examples of drugs**
Folate antagonism	Several anti-epileptic drugs, methotrexate (immunosuppressant), metformin (antidiabetic agent), sulfasalazine (disease-modifying anti-rheumatic drug), trimethoprim (antibiotic)
Disruption of neural crest cells (NCCs)	Bosentan (treats pulmonary artery hypertension), etretinate (treats severe psoriasis), isotretinoin (13-cis-retinoic acid, which treats severe acne), ketoconazole (antifungal agent)
Endocrine disruption	Medications used to improve fertility, oral contraceptives
Oxidative stress	Class III antiarrhythmic drugs, iron supplements, phenytoin (anti-seizure medication), terbutaline (β2 adrenergic receptor agonist used to relieve asthma), tetracyclines (antibiotics), thalidomide (treats several forms of cancer and skin diseases), valproic acid (anti-seizure medication)
Vascular disruption	Antihypertensive medications, aspirin (NSAID and blood thinner) and other NSAIDs, ephedrine (CNS stimulant)
Enzyme-mediated teratogenesis	
(i) HMG-CoA reductase	Statins (cholesterol lowering drugs)
(ii) HDAC	Boric acid (when used as an inactive excipient)

	salicylates (mostly used to treat pain, fever, and inflammation), valproic acid (anti-seizure medication)
(iii) COX	NSAIDs
(iv) Carbonic anhydrase	Acetazolamide (anti-epileptic drug), topiramate (anti-epileptic drug)
Receptor-mediated teratogenesis	
(i) ACE and Angiotensin II receptors	ACE inhibitors, Angiotensin II receptor inhibitors
(ii) NMDA receptors	Amantadine (antiviral medication; also used to treat symptoms of parkinsonism), dextromethorphan (cough suppressant), ketamine (anesthetic agent)
(iii) 5-HT receptors and transporters	Risperidone (antipsychotic agent used to treat bipolar disorder and schizophrenia), SSRIs (antidepressants), sumatriptan (used to treat severe headaches)
(iv) GABA receptors	Barbiturates (sedative-hypnotics), benzodiazepines (CNS depressants)

Chapter 6:

Teratogenic potential of common medications

6.1 Antihypertensives

Hypertension is one of the most prevalent diseases during pregnancy, contributing approximately 7 to 15% to all the pregnancy related complications with 0.05% incidence rate in developed countries and a staggering 27% in developing countries (Khedun et al., 2000).

Antihypertensive drugs, which are hydrophobic, cross the placental barrier easily; unlike the hydrophilic ones which mostly cannot pass through. The placental transfer of antihypertensives administered during pregnancy can be classified as follows (Khedun et al., 2000):

- Complete - an equilibrium is set between the maternal and fetal plasma, due to significant concentration of the drug (e.g., methyldopa and clonidine)
- Incomplete - the drug concentration is higher in the maternal plasma than in the fetal plasma (e.g., isradipine, prazosin, propranolol and sotalol)
- undefined - the mechanism of drug transfer is not defined due to a lack of data and most of the drugs fall in this category (e.g., atenolol and acebutolol)

Antihypertensive drugs that reduce cardiac output to lower the maternal blood pressure (i.e. calcium channel blockers) will also reduce the uterine blood flow. As a result, the transfer of nutrients and oxygen will be hindered to some extent. Therefore, antihypertensives that are administered during gestation must be able to cause uterine vasodilation, preferably lower uterine vascular resistance and increase uterine blood flow, regardless of the blood pressure alterations. However, the safety assessment of these drugs is challenging because only a few randomized trials involving a small sample size have been conducted with a short-term treatment, which is usually less than 6 weeks (Khedun et al., 2000).

In terms of teratogenicity, ACE inhibitors fall under category X of the FDA risk classification and are contraindicated in the 2^{nd} and 3^{rd} trimesters. In case of combination therapy, nifedipine and $MgSO_4$ pose some fetal risk secondary to evidence of severe hypotension, cardiac depression, and neuromuscular blockade (Khedun et al., 2000).

The use of diuretics in gestation and its effect on the fetus is controversial. These are used during pregnancy to treat hypertension and cardiac disorders. Some studies have indicated that diuretics cause an increase in birth weight, growth retardation, neonatal diabetes, neonatal jaundice, and an imbalance in electrolytes. This is linked to the decrease in plasma volume after the administration of diuretics in the 2^{nd} and 3^{rd} trimesters. However, they have not been proved to be teratogenic and are classified as category C (Olesen et al., 2001).

6.2 Antidepressants, sedatives, and hypnotic drugs

Approximately 9-20% of pregnancies are accompanied with depressive disorders. Moreover, nearly 2–3% of pregnant females take medications for depression during (Dubovicky et al., 2017).

The common antidepressants used in the gestational period are serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). Since these drugs inhibit the reuptake of monoamines in the presynaptic neuron, they raise the concentration of monoamines in the developing fetal brain and hinder its natural functional maturation (Oyebode et al., 2012).

The clinical management of depression during pregnancy with antidepressants is challenging and its efficacy without significant fetal risk is debatable. This is mainly because all antidepressants can cross the placental barrier and most of them can traverse the fetal BBB as well as get transferred via breast milk. Some studies indicate that the use of antidepressants is associated with preterm deliveries, unprecedented abortions, neonatal adaptive syndrome, reduction in birth weight, intrauterine growth retardation, neonatal persistent lung hypertension, immediate postnatal irritability, hypoglycemia, bradycardia, reduced muscle tone, cyanosis, apnea, and stillbirth. For instance, a study has found that paroxetine treatment is correlated to fetal cardiovascular disorders (Oyebode et al., 2012).

On the other hand, untreated depression can create a number of complications such as maternal suicidal ideation, preeclampsia, eclampsia, postpartum depression, and a higher possibility of preterm labor. In addition, it can adversely affect the emotional and cognitive functioning of the developing fetus (Kinsella & Monk, 2009; Oberlander, 2012).

Recent data from meta-analyses and reviews indicate that the risk of teratogenicity in fetal development secondary to antidepressant therapy is minimal to non-existent. However, there have not been adequate well-controlled studies to evaluate the extent of teratogenicity of antidepressants in fetal development. Therefore, it is recommended to treat mild to moderate depression with psychotherapy and severe depression with antidepressants (Dubovicky et al., 2017).

According to one review, the risks of teratogenicity include omphalocele (1 per 5386 births), gastroschisis (1 per 2229 births), anencephaly (1 per 4859 births), and craniosynostosis (4–10 per 10,000 births) (Ram & Gandotra, 2015).

Table 9: Antidepressants and their comparative extent of teratogenicity (Ram & Gandotra, 2015)

Sub-class	**Pregnancy loss due to miscarriage**	**Risk of teratogenesis**	**Neonatal toxicity**
Tricyclic antidepressants	Most reports do not indicate miscarriage	Risk of organ dysgenesis in 400+ cases as per 3 prospective and 10+ retrospective studies. Medications of choice include desipramine and nortriptyline due to lower anticholinergic activity	Anticholinergic effects such as functional bowel obstruction and urinary retention. Withdrawal syndrome including jitteriness, irritability, and seizure with clomipramine use
Selective serotonin reuptake inhibitors (SSRIs)	Higher risk of spontaneous abortion with 1st trimester use	No increased risk of birth defects in 1100 fluoxetine-exposed infants but risk of several minor abnormalities is present.	A prospective study with 55 neonates exposed to paroxetine developed respiratory distress, hypoglycemia, and jaundice, and they

		Data from 2500 cases indicate no risk of major birth anomalies. A prospective study comprising 531 infants indicated no risk with 1st -trimester exposure to SSRIs (mostly citalopram). One meta-analysis found a higher risk of cardiac anomalies in infants with paroxetine exposure in the 1st -trimester	resolved in 1–2 weeks. PPHN is associated with exposure to SSRIs, mainly paroxetine, fluoxetine, and venlafaxine
Monoamine oxidase inhibitors	Comparative risk of 3.4 for birth anomalies found with monoamine oxidase inhibitors in 21 prenatal exposures. A population-based prospective cohort study indicated a higher risk of PPHN for early exposure in pregnancy.	Has not been reported	Has not been reported
Bupropion	A study with 136 women in 1st trimester found no	Has not been reported	Has not been reported

	major anomalies. A report by GlaxoSmithKline indicated 3.6% incidence of congenital defects and 1.3% incidence of congenital cardiovascular anomalies		
Venlafaxine	One study with 150 women found the incidence of major anomalies to be 1–3%. Another study with 10 subjects found no such incidence. A prospective cohort study found the rate of cardiac anomalies to be 0.6%	Has not been reported	Has not been reported

Nearly 15% pregnant women have anxiety (Wang et al., 2020). The medications prescribed in these cases are usually sedatives like benzodiazepines and hypnotics. The use of sedatives during gestation is 1-14% (Silvestri & Aricò, 2019). The maximum usage has been observed in Eastern Europe, while the minimum usage has been observed in Asia (Björkstedt et al., 2021).

Similar to antidepressants, benzodiazepines and hypnotics can cross the placental barrier and fetal BBB. However, unlike antidepressants, they do not cause any significant adverse neurodevelopmental changes to the growing fetus, especially in the first week of gestation, as per the most recent literature (Vigod & Dennis, 2019; Björkstedt et al., 2021).

6.3 Anesthetics

The extent of teratogenicity of anesthetics has been assessed in about 65 preclinical trials but no clinical trials have been conducted. In all the preclinical trials, it has been consistently found that anesthetics administered in animal models induced neurotoxicity in the fetus (e.g., memory impairment and learning disabilities). However, some limitations of these preclinical trials include longer duration of exposure to anesthetics, higher frequency of doses administered, and suboptimal regulation of physiological homeostasis. Moreover, most of the animal models used were rodents which have a different mechanism of CNS maturation compared to humans. This implies that there is limited information regarding the pharmacokinetics and transport mechanism of anesthetics in the fetus. Therefore, well-controlled clinical studies are required to conclude the teratogenic extent of anesthetics (Bleeser et al., 2021).

Considering the aforementioned evidence, the USFDA alerts pregnant women since 2017 against the use of general anesthetics due to its neurotoxic potential, especially in the later gestational period. Since majority of anesthetics are lipid-soluble, they can traverse the placental barrier with ease. (Tina et al., 2017). For instance, propofol can easily permeate the placental barrier and lead to elevated levels in the plasma. A study done with 1.3% isoflurane anesthesia exposed for six hours found elevated concentrations of the anesthetic in the fetal brain (0.40 mmol/g) (Li et al., 2021). Moreover, an abnormal heart rate was observed in the fetus in an actual clinical setting, secondary to anesthetic exposure. Another clinical study demonstrated a correlation with general anesthesia and higher frequency of low birth babies. However, they have not been explicitly addressed as a teratogen (Li et al., 2021).

Minimum alveolar concentration (MAC) is the minimum concentration of an inhalant anesthetic agent in the alveoli of the lungs that is required to prevent the responsive movement of 50% patients after applying a surgical stimulus (Lobo et al., 2021). In pregnancy, the MAC value is lower and the sensitivity to the anesthetic is higher (Li et al., 2021). Therefore, the MAC value of anesthetics is crucial for evaluating the fetal safety of exposure during pregnancy. A high MAC may ensure sufficient cervical relaxation, but it is not necessarily safe for the neurodevelopment of the fetus, especially in the 2nd trimester when the fetus is most vulnerable to inhalation anesthetics. This has been established after a study on rat babies demonstrated that one-time exposure to 1.4% isoflurane for four hours in the 2nd trimester hindered fetal long-term memory,

emotional and personality disorders (Kong et al., 2011). The mechanism of this adverse effect was studied by a group of scientists who concluded that general anesthesia in the 2nd trimester induces apoptosis and hinders the proliferation of NSCs (Wang et al., 2018).

6.4 Analgesics and NSAIDs

Approximately 50-60% pregnant women use analgesics for pain management. Analgesics are the second most prevalently used medication in gestation, the first one being vitamins (Kennedy, 2011). However, there is a lack of well-controlled and prospective clinical trials evaluating the safety of majority of this category of drugs (Price et al, 2017).

Occasionally, low-dose aspirin is prescribed in pregnancy for mild pain and fever management in pregnant women who have antiphospholipid syndrome and history of recurrent miscarriages. Apart from this, aspirin is generally considered to be safe for use in gestation (Kennedy, 2011).

NSAIDs such as ibuprofen, indomethacin, diclofenac, and naproxen are extensively used for mild to moderate pain and fever management. It is well known that NSAIDs inhibit the cyclo-oxygenase enzymes. A Scandinavian cohort, population-based, retrospective study indicated that the risk of spontaneous abortion was higher with the exposure to prescribed NSAID treatment in the 1st trimester. The major limitation of this study was the lack of a control group with NSAID indications. Another study in California also demonstrated that there is an 80% higher risk of miscarriage secondary to NSAID and aspirin use in the 1st trimester (Kennedy, 2011).

NSAIDs are contraindicated after 30 weeks of gestation due to the possibility of causing persistent lung hypertension and unprecedented closure of fetal ductus arteriosus. Moreover, it has been speculated that elevated doses of NSAIDs in the 3rd trimester decreases the fetal renal perfusion and subsequently reduces urine output of the fetus. and High doses of NSAIDs in the third trimester may also reduce perfusion of the fetal kidneys and decrease fetal urine output, which can lead to renal failure (Kennedy, 2011).

Opioids including oxycodone, codeine, hydrocodone, morphine, pethidine, and tramadol are indicated for moderate to severe pain management. Continuous use of opioids is associated with neonatal abstinence syndrome (Kennedy, 2011).

More than 50% of pain medications used in gestation have been classified as category C, and a higher percentage has been classified as category D, especially for the 3rd trimester (Price et al, 2017).

Table 10: Summary of analgesics and their teratogenicity (Bisson et al., 2019)

Name/ Category of analgesic	**Sub-category**	**Mechanism of action**	**Effect before 30 weeks of gestation**	**Effect after 30 weeks of gestation**	**Recommendation as per FDA**
Paracetamol		weak inhibitor of prostaglandin synthesis; selective COX-2 inhibitor	Safe to use	Safe to use	Safe to use in any trimester
NSAIDs		inhibition of cyclooxygenase	Conflicting evidence of higher risk of 1st trimester miscarriage	Risk of neonatal pulmonary hypertension and premature closure of fetal ductus arteriosus; lower fetal renal blood flow; reduced volume of amniotic fluid	Avoid use after 30 weeks; administer in minimum effective dose with shortest duration before 30 weeks
Opioid	Codeine	conversion to	Higher risk	Neonatal	Avoid

		active metabolites, mainly morphine; activity is dependent on an individual's metabolizing capacity	of neural tube abnormalities in 1st trimester	respiratory depression; neonatal withdrawal symptoms	indiscriminate use; administer in minimum effective dose with shortest duration
	Dihydro-codeine (DHC)	pro-drug that is metabolized to dihydromorphine (DHM) by CYP2D6			
	Tramadol	opioid and monoaminergic-mediated mechanism; also metabolized by CYP2D6 to an active O-desmethyl metabolite			
	Morphine	opioid receptor agonist in the CNS;			
Gabapentin			Limited evidence for use in pregnancy; no	Risk of neonatal withdrawal	Concomitant administration of high dose folic acid before

			association with higher risk of miscarriage		conception and in 1st trimester; inform neonatology beforehand about previous use in mother

6.5 Antihistamines

The prevalence of antihistamines in pregnancy is between 4-10% in the 1st trimester and 8-15% at any point in pregnancy (Källén, 2009; Shawky & Seifeldin, 2015). Their major indications include pruritis, atopic dermatitis, allergic conjunctivitis, upper respiratory tract infections, vomiting, nausea, dizziness, sleeping difficulties, urticaria, allergic rhinitis, or angioedema (KeleSl, 2018; Shawky & Seifeldin, 2015).

Table 11: FDA risk classification of antihistamines (Shawky & Seifeldin, 2015)

Antihistamine class	**Name of drug**	**Category as per FDA risk classification**	**Adverse effects reported so far**
First generation	cyproheptadine	A	Chlorpheniramine is linked to eye and ear defects, spina bifida and cleft lip with or without cleft palate. Doxylamine linked to oral clefts, pyloric stenosis, hypoplastic left heart syndrome, spina bifida and neural tube defects
	Chlorpheniramine, Diphenhydramine, Dexchlorpheniramine, Clemastine, and Tripelennamine	B	
	Promethazine and Hydroxyzine	C	

Second generation	Cetirizine, Loratadine, Levocetirizine	B	
Third generation	Fexofenadine, Desloratadine	C	Mild glandular hypospadias in infants with early gestational use, although the finding is controversial

The teratogenic potential of antihistamines is not explicitly defined, and neither are they classified as category A of FDA risk classification. However, the relatively safe and extensively studied antihistamines are first generation antihistamines. As per National Asthma Education recommendation, chlorpheniramine and tripelennamine are safe to use due to clear evidence derived from preclinical and clinical trials. However, as per Allergic Rhinitis and its impact on Asthma (ARIA) guidelines, 1st generation antihistamines have poor selectivity with associated sedative and anticholinergic activity. In the case of 2nd generation antihistamines, loratadine or cetirizine is the drug of choice in the 2nd and 3rd trimesters (Shawky & Seifeldin, 2015).

6.6 Drugs for hyperlipidemia (statin drugs)

As a normal physiological process, cholesterol levels increase in the maternal serum by 25–90% relative to the pre-gestational period. It is well established that cholesterol is required for optimum development of the fetus. Therefore, cholesterol lowering drugs (i.e., statins) are contraindicated during pregnancy. Moreover, these are recommended to be discontinued prior to being pregnant due to potential risk to the fetus. If a pregnant woman has a history of hyperlipidemia, this discontinuation for a short period of time has been speculated to have no significant negative impact on her hyperlipidemia or risk of developing Coronary Heart Disease (Ofori et al., 2007).

The extent of teratogenicity of statins has not been explored in clinical trials. However, one FDA case report has pointed out 22 cases of congenital abnormalities with statin treatment during pregnancy, with an incidence rate of 3.2% with simvastatin and lovastatin treatment (Pollack et al., 2005; Ofori et al., 2007).

6.7 Antibiotics

Approximately 80% of the medications prescribed during pregnancy are antibiotics. Moreover, 20-25% pregnant women are prescribed antibiotics for indications including urinary tract infections (UTIs), sexually transmitted infections (STIs), and upper respiratory tract infections (URTIs). Teratogenic effects of antibiotics include both prenatal and post-natal effects. (e.g., alterations in gut flora, asthma, atopic dermatitis). However, about 10% of the antibiotics have sufficient data related to safe and effective use in pregnancy. Beta-lactams, vancomycin, nitrofurantoin, metronidazole, clindamycin, and fosfomycin are deemed as safe in gestation, unlike fluoroquinolones and tetracyclines, which are risky for the fetus (Bookstaver et al., 2015).

6.8 Antidiabetic drugs

The treatment of choice for gestational diabetes mellitus is insulin therapy mostly due to the fact that it does not traverse the placental barrier. However, recent studies have indicated that oral antidiabetic medications (e.g., metformin and glyburide, which are most commonly taken in pregnancy) serve as safe, effective, less costly, and more patient compliant alternatives, although one study found that antenatal metformin exposure is linked to higher birth weight (Weelden et al., 2018). While metformin is safe despite its ability to cross the placenta, glibenclamide has a higher efficacy and lower rate of treatment failure than metformin. However, some studies have demonstrated an increased incidence of neonatal jaundice, stay in the neonatal intensive care unit, and neonatal hypoglycemia with glibenclamide treatment (Kalra et al., 2015).

The use of oral hypoglycemic medications in gestation is not advised by the American Dental Association (ADA) (Kitzmiller et al., 2008). In addition, the USFDA has not approved any oral antidiabetic agent for treating gestational diabetes (Berggren et al., 2013). However, as per UK National Institute for Health and Care Excellence (NICE) guidelines, metformin and glyburide are safe to use (Group, 2008).

Table 12: Antidiabetic medications commonly used in pregnancy (Kalra et al., 2015)

Type of antidiabetic agent	**Class of antidiabetic agents it belongs to**	**Mechanism of hyperglycemic control**	**Recommendations**
Metformin	bigaunide	Inhibition of gluconeogenesis and increased peripheral glucose uptake; reduces intestinal glucose absorption and increases insulin sensitivity	Not FDA approved for gestational use
Glyburide	second generation oral sulfonylurea	Induces the release of insulin from the pancreatic beta cells	Not FDA approved for gestational use
Acarbose	a-glucosidase inhibitors	Decreases the intestinal absorption of carbohydrate by inhibiting the cleavage of disaccharides and oligosaccharides to monosaccharides in the small intestine, and lowers post-prandial rise of glucose	Use is not recommended due to lack of safety data in human pregnancies
Insulin	hormone	Increases glucose absorption by cells	Optimal anti-diabetic treatment

6.9 Antiepileptics

Antiepileptic medications are one of the most prevalent medications prescribed during gestation for management of seizures, nerve pain, migraines, and other psychotic diseases. In higher doses, these medications have the potential to cause structural defects. In lower doses, they can cause cognitive abnormalities (Tsamantioti & Hashmi, 2021).

Table 13: Summary of some antiepileptics and their teratogenic potential (Tsamantioti & Hashmi, 2021)

Name of antiepileptic	**Mechanism of action**	**Teratogenic effect**
Phenobarbital	Inducer of CYP450 2B and 3A genes, producing free radicals and transversion of DNA bases	Growth impairment, motor function impairment, fetal death.
Valproate	The inhibitory actions of folate and histone deacetylase and subsequently high accumulation in fetal circulation in addition to formation of reactive oxygen species (ROS)	Most teratogenic, cardiovascular defects, neural tube abnormalities, spina bifida, growth delay, fetal valproate syndrome, lip/cleft palate, impaired urinary tract, defects of the extremities
Carbamazepine	Metabolized to carbamazepine-10, 11-epoxide	DNA destruction, craniofacial anomalies, facial cleft, growth retardation
Lamotrigine	--------	Safest anticonvulsant despite risk of fetal facial malformations
Topiramate	--------	Neonatal hypospadias and oral clefts in higher doses
Phenytoin	Bioactivated by fetal prostaglandin H synthase to a free radical, leading to DNA oxidative damage	Fetal phenytoin syndrome

6.10 Antiemetics

Nausea and Vomiting of Pregnancy (NVP) is a common disorder in gestation, affecting 70-80% of all pregnant females (Taylor, 2014). It is not interchangeable with morning sickness since it persists throughout the day in the majority of pregnancies. The onset of NVP symptoms is usually between two to four weeks after conception. It is maximum in 9-16 weeks of pregnancy and finally gets alleviated by week 22 (Lee & Saha, 2011), (Taylor, 2014).

A severe form of NVP can develop in pregnancy, which is known as hyperemesis gravidarum, affecting about 0.3–2% of pregnant women (Lee & Saha, 2011).

Table 14: FDA risk assessment and recommendations of antiemetic treatments (Taylor, 2014)

Antiemetic therapy	**Category as per FDA risk classification**	**Adverse effects reported**	**Comments**
Pyridoxine	Uncategorized	--------	--------
Prochlorperazine	C	--------	--------
Phenothiazines	C	High doses in late gestation caused prolonged neurological disorder	--------
Metoclopramide	A	--------	Limited safety and efficacy data
Ondansetron	B	Constipation in mother; 7.9% risk of fetal death in a large multi-cohort study (Dormuth et al., 2021)	Not recommended as first-line therapy; co-administration of laxatives is recommended
Mirtazapine	--------	--------	Alternative for treating hyperemesis gravidarum when other

			medications failed
Corticosteroid	--------	Cleft lip and palate	Recommended only for intractable nausea and vomiting; best to avoid in the first 10 weeks of gestation
Antacids, ranitidine, and proton pump inhibitors	--------	--------	To relieve exacerbating symptoms, e.g., bloating or heartburn
Thiamine replacement (100 mg daily via oral or IV route)	--------	--------	To treat thiamine deficiency

6.11 Medications for GERD

Approximately 30–50% of pregnant females suffer from gastroesophageal reflux disorder (GERD) or commonly termed as heartburn (Gerson, 2012).

All proton pump inhibitors (PPIs) fall under category B of the USFDA classification of drugs. However, only omeprazole is classified as a category C drug, although most recent studies have found no association of omeprazole use with congenital anomalies. In general, all PPIs have been considered to be safe for use during pregnancy. However, a recent study conducted in Denmark indicated a higher risk of congenital abnormalities secondary to PPI therapy before conception. This led to the recommendation of avoiding PPI use in women considering getting pregnant, although further research is needed to assess this recommendation (Gerson, 2011).

The recommended treatment of choice for GERD or associated symptoms is antacid or H_2-receptor antagonists (e.g., famotidine, ranitidine). Otherwise, PPI therapy should only be provided if the heartburn is severe. In case of an ineffective PPI therapy, a prokinetic agent (e.g., as metoclopramide, which is a category B medication) could be prescribed (Gerson, 2012).

In the case of treating symptoms of GERD, antacids are often prescribed. It is important to ensure that they do not contain aspirin, sodium bicarbonate, or magnesium trisilicate since these can have adverse effects on the fetus ("Gastroesophageal Reflux Disease (GERD) During Pregnancy", 2020)

6.12 Medications for asthma

Approximately 4 to 8% of the pregnant women in the United States suffer from asthma, making it one of the most prevalent diseases in gestation (Eltonsy et al., 2014). It has been established that uncontrolled and exacerbated asthma can lead to pregnancy complications and hinder fetal development. Persistent asthma is managed mainly with inhaled corticosteroids (ICS), but the use of beta-2 agonists is equally important. While short acting beta-2 agonists (SABA) are used for treating mild to severe asthma, long-acting beta-2 agonists (LABA) are used for treating moderate to severe consistent asthma in conjunction with low to moderate dose of ICS. Among these two modes of treatment, SABA is more commonly used. However, both the categories of beta-2 agonists are classified as Category C in the FDA risk classification. Furthermore, as per the Teratogen Information System (TERIS), the teratogenic potential of these beta-2 agonists is not yet defined due to lack of sufficient and qualitative data. According to the evidence gathered so far in 21 studies, treatment with beta-2 agonists is associated with a higher risk of fetal abnormalities and a reduction in birth weight secondary to gestational LABA treatment (Eltonsy et al., 2014).

Chapter 7:

Conclusion and Future Recommendations

7.1 Conclusion

Most of the common drugs have been studied in this review paper to assess their current safety profile in pregnancy and relevant recommendations that have been provided by the USFDA and other drug regulatory authorities. However, some drugs still require further study to evaluate the teratogenicity and ensure their safe use. For instance, there is inadequate data on the safety assessment on diuretics, anesthetics, analgesics, statin drugs, antibiotics, and some antiemetic drugs. According to the most recent literature, most of the medications commonly prescribed in pregnancy are safe if taken in the later gestation periods and are best to be avoided in the first trimester, which is the most susceptible stage of pregnancy. Since the safe use of drugs during pregnancy is of utmost importance for the normal fetal development, this review paper will help in awareness creation among the pregnant women.

7.2 Future recommendations

For better understanding the adverse effects of a medication in fetal development, more studies are needed on a clinical level as well as through post-marketing surveillance. For this reason, federal regulations could include pregnant women in clinical studies, after thorough assessment of the safety data obtained from animal trials. Moreover, enhanced scientific knowledge regarding the complex physiology of pregnancy and the mechanism of action of drugs administered during pregnancy will further help to optimize the medication practice in gestation with minimal to negligible adverse effect on the fetus.

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