



# Teratogenic effect of different drug at a different stages of Pregnancy

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## Abstract

Development begins the day of fertilization, when one sperm penetrates the ovum (egg) and unites with it to form one cell. The process of inauguration and development of an embryo from zygote (zygotic embryogenesis) or a physical cell (physical embryogenesis). It's also known as period of organogenesis. Gestations live for 9 weeks which is divided into three trimesters. Gestation and lactation is a unique clinical situation where medicine treatment presents a special concern because all the medicines taken by the lady have a eventuality to produce dangerous goods in the growing fetus or lactating baby. First trimester of gestation is most susceptible to medicines. Since important of this period occurs before a opinion of gestation is made, care must be used in treatment of common ails in all women susceptible to getting pregnant. Roughly 3- 5 of live births are complicated by a birth disfigurement each time totaling around,000 babies. Colorful medicines similar as tetracycline, Warfarin, Thalidomide, Cholramphenicol produces abnormalities similar as teratogenicity, microcephaly, hydrocephalus, spina bifida and colorful runs.

The purpose of this composition is to give an up to date source of information about drug use in gestation, to review the US Food and Drug Administration (FDA) gestation and lactation orders.

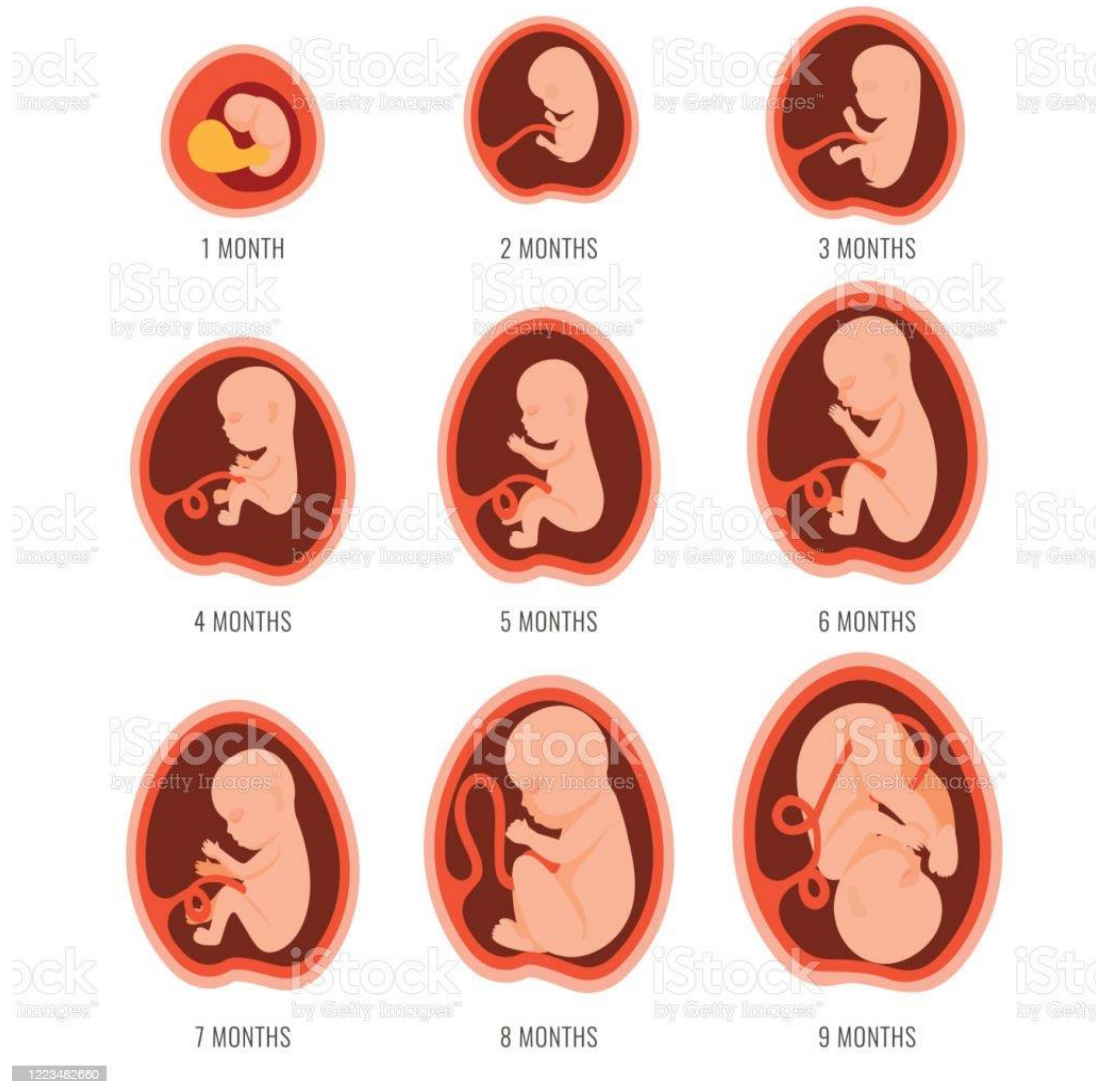
**Keywords:** fertilization, fetus Teratogenic drug, history of pregnancy, drug used in pregnancy

## Introduction

In case of pregnancy a special concern of the drug treatment should be presents due to the threat of potential teratogenic effects of the drug and physiologic adjustments in the mother in response to the pregnancy[. 1]The physiology of pregnancy affects the pharmacokinetics of medications used and these medications can reach the fetus and cause harm. A teratogenesis is any agent that physically or chemically alters developmental processes and produces congenital deformities. A teratogen is any agent that causes an abnormality following fetal exposures during pregnancy. [2 ].Teratogens are usually discovered after an increased prevalence of a particular birth defects. For example, in the early 1960's,a drug known as thalidomide was used to treat morning sickness The embryonic period, during which organogenesis takes place, occurs between implantation at around 14 days to around 60 days post conception. This is usually the most sensitive period to teratogenesis when exposure to a teratogenic agent has the greatest like hood producing

Medical science cannot always predict how exposure to a teratogenic drug will affect a fetus. [3]

## History and development of pregnancy:



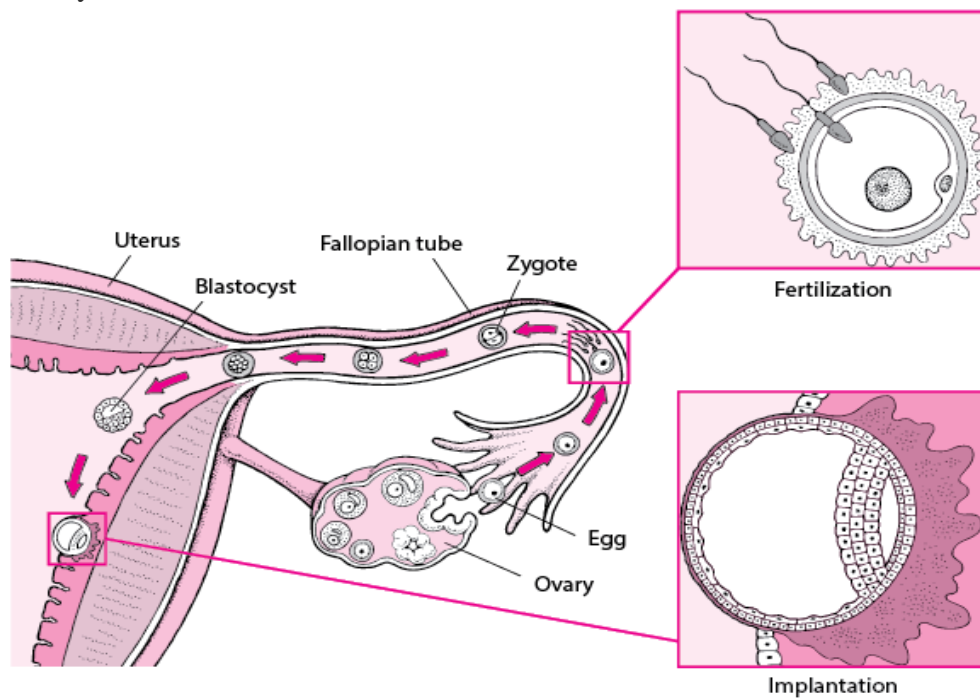
There are four stages of development of pregnancy in every woman which are as follow

1. Fertilization
2. Development of the blastocyst
3. Development of embryo
4. Development of fetus and placenta.

### 1. Fertilization

During each menstrual cycle in the women one egg is usually released from one ovary, about 14 days after the last menstrual period. Ovulation is the process of release of egg from ovary. The egg is shifted into funnel shaped end of fallopian tube. At the time of ovulation the mucus in the cervix becomes more fluid and elastic which becomes more capable of allowing the sperm to enter into uterus. Within 5 minutes sperm enters into the fallopian tube which is the important site for fertilization. [4]

The cell lining present in the fallopian tube increases the process of the fertilization. Here the fertilization of egg with the sperm is occurs. If this fertilization does not occurs then the egg will moves down the fallopian tube to the uterus .In the uterus egg is degenerate and then pass through the uterus with the next menstrual period. The fertilized egg which is also called as zygote divides repeatedly as it moves down the fallopian tube to the uterus. Firstly the zygote becomes a solid ball of cells and then it becomes a hollow ball of cells which is called as blastocyst. [5]



## 2. Development of the blastocyst :-

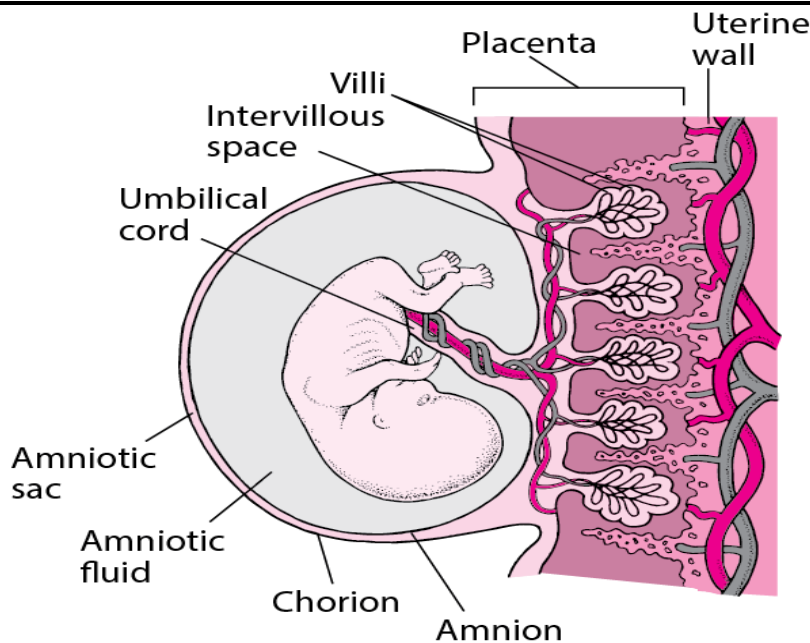
The 6 days after the fertilization the blastocyst links to the uterus linings usually near to the top. This is the process of the implantation . This implantation process is completed by 9 to 10 days.

The wall of blastocyst is one cell thick where it is three to four cells thick. The thickened are of inner cells develop into the embryo whereas the outer cells enter into the wall of the uterus and there is development of placenta. The various hormones are produced by placenta which are helpful in the maintaining of pregnancy. [7]

## 3. Development of embryo :-

Development of embryo is the next step in the development of pregnancy. This development occurs in the amniotic sac, under the lining of the uterus on one side. This stage results into formation of internal organs and external body structure of the fetus. The period of development of organ is about 3 weeks after the fertilization that the period is equal to 5 weeks of pregnancy. Firstly there is development of shape of body and thereafter it results into development of brain and the spinal cord are developed.[8] The development of heart and major blood vessel are developed by about day 16.The pumping of the fluid through the blood vessel is occurs at the day of 20.

Almost all organs are completely formed in about 10 weeks after the fertilization occurs .i, e, 12 weeks of pregnancy. [9]



#### 4. Development of fetus and placenta :-

After fertilization, at the end of 8 weeks (10 week of pregnancy) ,the embryo is considered a fetus. During this stage, the structure of embryo, that has already grown and develops. This structure provides oxygen and nutrient to growing baby. The following are markers during pregnancy

- By 12 weeks of pregnancy: The fetus fills the entire uterus.
- By about 14 weeks: The sex can be identified.
- By about 16 to 20 weeks: Typically, the pregnant woman can feel the fetus moving. Women who have been pregnant before typically feel movements about 2 weeks earlier than women who are pregnant for the first time.
- By about 24 weeks: The fetus has a chance of survival outside the uterus.[10]

#### ❖ List of some of the drugs whose use is contraindicated during pregnancy which may effects they may produce on the fetus

##### 1. Alcohol:

**Introduction:** Antenatal alcohol exposure (AAE) can have immediate and long- lasting poisonous and teratogenic goods on an existent’s development and health. As a toxic, alcohol can lead to a variety of physical and neurological anomalies in the fetus that can lead to behavioral and other impairments which may last a continuance. [11]Recent studies have concentrated on relating mechanisms that intervene the immediate teratogenic goods of alcohol on fetal development and mechanisms that grease the patient poisonous goods of alcohol on health and predilection to complaint latterly in life. The teratogenicity of alcohol has been demonstrated in humans through laboratory studies, epidemiologic studies, and in creatures through controlled laboratory trials. [12]

**Mechanism of Action:** The enzyme alcohol dehydrogenises (ADH) converts alcohol to acetaldehyde, which inhibits DNA synthesis, amino acid transport from placenta to the fetus, besides interfering in brain development. The susceptibility is related to the amount of ADH, which have variations in their expression due to genetic differences in ADH alleles. [13]

**Teratogenic effect:** Deficiency in intrauterine growth and postnatal growth, cognitive abnormalities, leading to a set of characteristics called fetal alcohol syndrome (FAS), characterized by: alterations in facial appearance such as small palpebral fissures, large epicanthic folds, small head, small upper jaw, smooth philtrum, thin upper lip etc , decreased muscle tone, poor coordination, heart defects (ventricular and atrial septal defects), late reasoning, speech, movement and social skills development. FAS is the main cause of intellectual disability.[14]

## 2. Marijuana:

**Introduction:** Marijuana is the lawless medicine most generally used during gestation. The tone- reported frequency of marijuana use during gestation ranges from 2 to 5 in utmost studies but increases to 15 – 28 among youthful, civic, socioeconomically underprivileged women 1 2 3 4 5. Advanced rates of use are set up when querying women at the time of delivery rather than at antenatal visits because some druggies may not seek antenatal care. (15)

**Mechanism of Action:** It's major psychoactive element, Marijuana crosses the placenta and accumulates in fetal brain, potentially harming CNS development, marijuana use in early gestation is associated with confinement and cognitive abnormalities at age 10 in the seed, similar as lower Command and literacy disabilities, memory impairment. [15]

**Teratogenic effect:** Intrauterine growth restriction, cognitive and neurobehavioral imbalance respiratory and hormonal disorders [16]

## 3. LSD:

**Introduction:** Lysergic acid diethylamide (LSD) is a medicine that causes an altered state of mind (visions). Some physical goods of LSD on the body can include increased blood pressure, fast heart rate, and dilated pupils. This medicine is generally taken by mouth, but can also be taken by injection (using a needle) or by inhalation (breathing it into lungs)[17]

**Mechanism of Action:** LSD (lysergic acid diethylamide) produces a series of disort in the functioning of the brain, changing the psychic, circulatory and thermal functions

**Teratogenic effect:** Brain damage, abnormalities in the lower jaw, modification of facial contours, defects in the limbs and eyes, joint problems and miscarriage. [18]

## 3. Cocaine :

**Introduction:** Cocaine is a Schedule II medicine and a important goad with a high eventuality for abuse. Though pharmaceutical cocaine continues to see limited use as a original anesthetic and vasoconstrictor, the maturity of cocaine use takes place illicitly. Cocaine is use by pregnant women by wide goods of embryo and fetus, ranging from colorful gastro- intestinal and cardiac blights to towel death from inadequate blood force. These agent produces a teratogen and produces blights in fetuses during antenatal development.[19]

**Mechanism of Action:** Cocaine has vasoconstrictor exertion, which may affect in an interruption of blood inflow to the fetus. When someone uses cocaine, the time it takes for them to feel its goods depend on the system of ingestion. Edging in and smoking cocaine give the most rapid-fire high since they give the fastest delivery of the medicine to the brain. still, this also means that the high produced by edging in or smoking cocaine subsides more snappily. **Teratogenic effect:** Placental abruption, intrauterine growth deceleration, branch blights, vascular diseases, punctuality, respiratory problems, ilea artesian, blights in brain growth and central nervous system( CNS), neurobehavioral disease.[20]

#### 4. Thalidomide:

**Introduction:** Thalidomide was an extensively used medicine in the late 1950 and early 1960s for the treatment of nausea in pregnant women. Thalidomide was a extensively used medicine in the late 1950s and early 1960s for the treatment of nausea in pregnant women. It came apparent in the 1960s that thalidomide treatment redounded in severe birth blights in thousands of children. Occasionally when people find out they're pregnant, they suppose about changing how they take their drug, or stopping their drug altogether. The product marker for thalidomide recommends people who are pregnant not use this drug. But, the benefit of using thalidomide may overweigh possible pitfalls. It's important to talk with your healthcare providers before making any changes to how you take this drug. They can talk with you about the benefits of treating your condition and the pitfalls of undressed illness during gestation.[21]

##### **Mechanism of Action:**

It is the most notorious human teratogen .The enantiomer of thalidomide is an angiogenesis inhibitor, affecting the following pathway: growth factor I (IGF-I), and fibroblast growth factor 2 (FGF-2). Stimulation of integrin` subunit B3 genes transcription, which are responsible for stimulation of angiogenesis in the developing limb buds, which promotes the growth from the root.[22]

**Teratogenic effect:** Phocomelia of upper and lower limbs, pre-axial polydactyl, trifalangeal thumb, facial hemangiomas, esophageal and duodenal artesian, cardiac defects, renal agenesis, urinary tract anomalies, genital defects, dental anomalies, ear anomalies, facial palsy, ophthalmoplegia, exophthalmia and microphthalmia.[23]

#### 4. Tobacco :

**Introduction:** Tobacco in gestation is one of the leading preventable causes of adverse health issues, including preterm birth, low birth weight and birth. still, the pitfalls related to smoking in gestation are well known, 16 of all pregnant Danish women smoked in 2005, which is among the loftiest rates in the western world. Tobacco in gestation may also be associated with natural deformations, presumably due to a teratogenic effect. A many epidemiological studies have delved the implicit association between motherly smoking and threat for natural deformations [24]

##### **Mechanism of Action:**

Nicotine is a vasoconstrictor interfering in intrauterine growth due to decreased perfusion fetal tissues, which may lead to placental abruption. Carbon monoxide present in the smoke of the cigarette also crosses the placenta, producing an increase in carboxyhemoglobin in blood.

**Teratogenic effect:** Oral clefts, low birth weight, intrauterine growth retardation, CNS abnormalities, CVS abnormalities, spontaneous abortion, premature birth, Low birth weight, Microcephaly. [25]

#### 7. Caffeine:

**Introduction:** Caffeine is a chemical found in numerous foods and drinks, including coffee, tea and cola. It affects the nervous system and can beget perversity, unease and sleeplessness. However, consuming up to 200 mg a day is safe for your baby, If you're pregnant or breastfeeding. The impact of caffeine on the course of gestation and the development of the fetus is largely dependent on motherly input and, apparently, also on the speed of caffeine metabolism in the mama's body. Until lately, utmost experts believed that diurnal motherly input of caffeine shouldn't exceed 300 mg. Although recent recommendations of the European Food Safety Authority (EFSA)[26]

##### **Mechanism of action:-**

Caffeine is a xanthine alkaloid, which readily crosses the human placenta, entering the fetal circulation during its development. Drug effect occurs on the CNS stimulation, such as increased motor activity, catecholamine release, adrenaline and noradrenaline release, serotonin turnover in selected areas, inhibition of phosphodiesterase activity.

**Teratogenic effect:** CNS defects, orofacial clefts, structural skeletal defects, cardiovascular malformations, adactyly and absence of thumbs.[27]

## List of some of the commonly used drugs used in pregnancy along with their categories

### 1. Hydantoin:

Hydantoin taken by pregnant women to help seizures are among the most common causes of implicit detriment to the fetus. Hydantoin crosses the placenta in such a way that the developing fetus receives a much advanced cure of the drug than the mama is taking the medicine is metabolized else by the fetus. This is especially true when the drug is used during the first trimester of gestation. Despite these pitfalls, seizure control during gestation is veritably important. Fetal hydantoin pattern associated with in utero Hydantoin exposure.[28] It's an antiepileptic medicine that decreases the neuronal excitation. It stabilizes the neuronal membrane by inhibiting the sodium channel, snooping in the psychomotor performance **Teratogenic effect :-** Delayed Internal development, craniofacial dysmorphism, hypoplasia of the distal phalanges, cardiac, cadaverous and eye blights, imbalance in the vulnerable system. Can beget a number of dislocations, known as the fetal hydantoin pattern.[29]

### 2. Angiotensin converting enzyme (ACE) inhibitors:

The angiotensin-converting enzyme (ACE) inhibitors are contraindicated during the second and third trimesters of pregnancy because of increased risk of fetal renal damage.. Angiotensin-converting enzyme (ACE) inhibitors are widely used as first-line therapy for chronic hypertension. They are frequently used in women of reproductive age; consequently, some women are bound to be taking ACE inhibitors at the time of conception, as more than half of all pregnancies are unplanned.

It is an antihypertensive that has an action in ACE inhibition, which is an enzyme responsible for converting angiotensin I to angiotensin II, acting on the renin angiotensin aldosterone system.

**Teratogenic effect:** Small formation of amniotic fluid (oligohydramnios), spontaneous abortions, intrauterine and neonatal deaths, neonatal respiratory distress, central nervous system and limb defects, calcarial hypoplasia and renal disorders (intrauterine renal failure, renal tubular dysplasia)[30].

### 3. NSAIDs, Aspirin and other Salicylates :

Non-steroidal anti-inflammatory medicines (NSAIDs) are among the extensively used medicines and are frequently used by pregnant women. Still, they can have significant teratogenic goods. Non-steroidal anti-inflammatory medicines are among the extensively used medicines and are frequently used by pregnant women especially during first trimester of gestation. The main medium of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is needed to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The remedial goods of NSAIDs are attributed to the lack of these eicosanoids.

#### **Teratogenic effect:**

Delay in start of labor, premature closing of ducts arteriosus, jaundice, brain damage in the fetus and bleeding problems in the woman during and after delivery and in the newborn.[31]

#### 4. Antidepressants- Lithium:

Lithium is an effective treatment in gestation and postpartum for the forestallment of relapse in bipolar complaint. Still, lithium has also been associated with pitfalls during gestation for both the mama and the future child. In summary, first and alternate trimester are characterized by a significant drop of lithium blood situations with a threat of sub remedial situations. In third trimester and the postpartum, lithium situations gradationally return to their prepossession position which implicates that in this period clinicians need to be apprehensive of the threat of lithium intoxication.[32]

**Teratogenic effect:** Cardiac deformations and babies with increased birth weight, Cohort, prospective, retrospective and increased birth weight[33]

#### 5. Anticoagulants- Warfarin :

Warfarin use in I trimester produces blights like nasal hypoplasia and a depressed nasal ground; nominated as Fetal Warfarin Pattern and also use during II and III trimesters is associated with increased threat of fetal deformations. Warfarin, which is considered the first- line remedy for thrombosis prophylaxis outside gestation, readily crosses the placenta and renders the fetus unfit to synthesize vitamin K-dependent proteins.

**Teratogenic effect:** robotic revocations; can beget the fetal warfarin pattern( cadaverous abnormalities, nasal hypoplasia, narrow nasal ground, scoliosis, spinal calcifications, femur and heel bone calcifications, low birth weight, and experimental disabilities.[34]

#### 6. Antibiotic -Tetracycline:-

##### Introduction:

Tetracycline is one of the antibiotic that treat infections that are spread by ticks, lice, diminutives, and infected creatures. It can also be used in cases who can not be treated with penicillin to treat certain types of food poisoning, and anthrax. Tetracycline is in a class of specifics called tetracycline antibiotics. It works by precluding the growth and spread of bacteria..

Tetracyclines are teratogens due to the liability of causing teeth discolouration in the fetus as they develop in immaturity. For this same reason, tetracyclines are contraindicated for use in children less than 8 times of age. Some grown-ups also witness teeth abrasion (mild slate tinge) after use.

**Teratogenic effect:** Impaired teeth and bone development, Yellow brown discoloration of teeth [35]

#### Reference:

1. Appolinary Kamuhabwa and Rashida Jalal Drug use in pregnancy: Knowledge of drug dispensers and pregnant women in Dar as Salaam, Tanzania 2011 May-Jun
2. Punam Sachdeva,\* B. G. Patel, and B. K. Patel<sup>1</sup> Drug Use in Pregnancy; a Point to Ponder! 2009 Jan-Feb
3. Brittney D Bastow, MD; Chief Editor: Christine Isaacs, MD Teratology and Drug Use during Pregnancy Nov 09, 2022
4. Raul Artal-Mittelmark , MD Stages of Development of the Fetus May 2021
5. Raul Artal-Mittelmark , MD Stages of Development of the Fetus May 2021
6. Lorenzo Crumbie MBBS, BSc Embryology: 2nd week of development July 19, 2022
7. Larissa Hirsch, MD Female Reproductive System June 2019



8. Raul Artal-Mittelmark, MD Stages of Development of the Fetus May 2021
9. Australas J Ultrasound Med. The development, structure and blood flow within the umbilical cord with particular reference to the venous system
10. Tan C.M.J. · Lewandowski A.J. the Transitional Heart: From Early Embryonic and Fetal Development to Neonatal Life Ther 2020
11. Dae D. Chung, Marisa R. Pinson, Lokeshwar S. Bhenderu, Michael S. Lai, Rhea A. Patel, and Rajesh C. Miranda \* Toxic and Teratogenic Effects of Prenatal Alcohol Exposure on Fetal Development, Adolescence, and Adulthood Aug; 22
12. M H Kaufman<sup>1</sup> the teratogenic effects of alcohol following exposure during pregnancy, and its influence on the chromosome constitution of the pre-ovulatory egg 1997 Mar-Apr
13. Keshav K. Gupta, Vinay K. Gupta, and Tomohiro Shirasaka an Update on Fetal Alcohol Syndrome—Pathogenesis, Risks, and Treatment August 2016
14. Basil J. Zitelli MD, in Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, Genetic Disorders and Dysmorphic Conditions, 2018
15. Review Rebecca Thompson, MD,\* Katherine DeJong, MD,<sup>†</sup> and Jamie Lo, MD<sup>‡</sup>; Marijuana Use in Pregnancy: 2019 Jul
16. Francisco Navarrete,<sup>1,2</sup> María Salud García-Gutiérrez,<sup>1,2</sup> Ani Gasparyan,<sup>1,2</sup> Amaya Austrich-Olivares,<sup>1</sup> Teresa Femenía,<sup>1,2</sup> and Jorge Manzanares<sup>1,2</sup> Cannabis Use in Pregnant and Breastfeeding Women: Behavioral and Neurobiological Consequences 2020 Nov 2.
17. Kristine Anne J. Hwang; Abdolreza Saadabadi. Lysergic Acid Diethylamide (LS) July 11, 2022.
18. Danilo De Gregorio,<sup>1</sup> Stefano Comai,<sup>2</sup> Luca Posa,<sup>1</sup> and Gabriella Gobbi<sup>1</sup> D-Lysergic Acid Diethylamide (LSD) as a Model of Psychosis: Mechanism of Action and Pharmacology 2016 Nov 23.
19. Stacy Mosel, L.M.S.W.: Sco Thomas, MD Dangers of Using Cocaine During Pregnancy Sep 14, 2022
20. Robert E. Arendt, PhD, Sonnia Minnes, and Lynn T. Singer Fetal Cocaine Exposure: Neurologic Effects and Sensory-Motor Delays 1996 Jan.
21. James H Kim<sup>1</sup>, Anthony R Scialli Thalidomide: the tragedy of birth defects and the effective treatment of disease 2011 Jul
22. T D Stephens<sup>1</sup>, C J Bunde, B J Fillmore Mechanism of action in thalidomide teratogenesis 2000 Jun
23. Main teratogen categories and respective embryo-fetal effects during pregnancy. (Scholl and Johnson 2000; HernándezDíaz et al., 2001)
24. Mathias Mund,<sup>1</sup> Frank Louwen,<sup>2</sup> Doris Klingelhofer,<sup>1,\*</sup> and Alexander Gerber<sup>1</sup> Smoking and Pregnancy — A Review on the First Major Environmental Risk Factor of the Unborn 2013 Nov 29
25. Shannon A Bainbridge<sup>1</sup>, Graeme N Smith The effect of nicotine on in vitro placental perfusion pressure 2006 Aug-Sep
26. Kamil Rodak,<sup>1,\*</sup> Izabela Kokot,<sup>2</sup> and Ewa Maria Kratz<sup>2,\*</sup> Caffeine as a Factor Influencing the Functioning of the Human Body—Friend or Foe? 2021 Sep 2
27. Vadivel Ganapathy<sup>1</sup> Drugs of abuse and human placenta 2011 May 23

28. Bogdan J. Wlodarczyk,<sup>1</sup> Ana M. Palacios,<sup>1</sup> Timothy M. George,<sup>2</sup> and Richard H. Finnell Antiepileptic Drugs and Pregnancy Outcomes 2012 Aug
29. Ranju Singh, Nishant Kumar,\* Sakshi Arora, Ritu Bhandari, and Aruna Jain Fetal Hydantoin Syndrome and Its Anaesthetic Implications: A Case Report 2012 Oct 2
30. Joel G. Ray, MD MSc FRCPC, Marian J. Vermeulen, MHSc, and Gideon Koren, Taking ACE inhibitors during early pregnancy 2007 Sep
31. Chalelgn Kassaw and Nasir Tajure Wabe<sup>1</sup> Pregnant Women and Non-Steroidal Anti-Inflammatory Drugs: Knowledge, Perception and Drug Consumption Pattern during Pregnancy in Ethiopia 2012 Feb
32. Hailing Shao, Shichu Gao, Qiuqing Lu, Xiaomin Zhao, Ying Hua & Xiaomei Wang Effects of delayed cord clamping on neonatal jaundice, phototherapy and early hematological status in term cesarean section 26 May 2021
33. Eline M. P. Poels,<sup>1</sup> Hilmar H. Bijma,<sup>2</sup> Megan Galbally,<sup>3</sup> and Veerle Bergink Lithium during pregnancy and after delivery: a review 2018; 6: 26.
34. Luke D Starling,<sup>1</sup> Ashutosh Sinha,<sup>2</sup> Duncan Boyd,<sup>3</sup> and Anke Furck Fetal warfarin syndrome 2012 Jul 27
35. Ian Chopra<sup>1</sup> and Marilyn Roberts<sup>2</sup> Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance 2001 Jun;

