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Review Article

Teratogenic Effect Of Various Medication During Various Phases Of Pregnancy

A. D. Khajekar*, A. P. Aher, G. V. Salunke, R. M. Kawade

Nandkumar Shinde College of Pharmacy, Aghur, Vaijapur 423701 Dist: Aurangabad, Maharashtra India.

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ABSTRACT

Although prescription drug use is prevalent during pregnancy, but for over 90% of medication approved in USA over a previous few decade, the teratogenic risk to human are unknown. A particular birth defect may have its origins through multiple mechanism and possible exposures, including medications. This review focuses on the teratogenic mechanism associated with a number of medication (understanding of teratogenic background risk and specific risk associated with in utero exposure to 12 different drugs generally approached the established knowledge). Environmental teratogenic factor [E.g. : Alcohol]are preventable .we focus our analysis on human teratogenic drug which are not used frequently during pregnancy.[1]

INTRODUCTION

Pregnancy is the beginning of new life as well as most important and unique period in a woman`s life which result into the continuation of the species. This entire period of pregnancy which is 36-40 weeks leads to many physical and chemical changes in a woman`s body. To deal with those changes there are lots of medication /drugs prescribed by doctors / physician to pregnant women. sometime such medication can cause harmful teratogenic effect on developing fetus.

Teratogen is any disease drug or other environmental agent that causes abnormal fetal development. Teratogens discovered after increased in rate of abnormality and birth defect. For example: in 1960's drug [thalidomide] causing teratogenic effect was used to treat morning sickness. To avoid or reduce the rate of teratogenic effect there must be proper understanding of teratogenic background and risk. [1,2]

***Corresponding Author:** A. D. Khajekar
Address: *Nandkumar Shinde College of Pharmacy, Aghur, Vaijapur 423701 Dist: Aurangabad , Maharashtra India.*
Email : angelkhajekar8856@gmail.com

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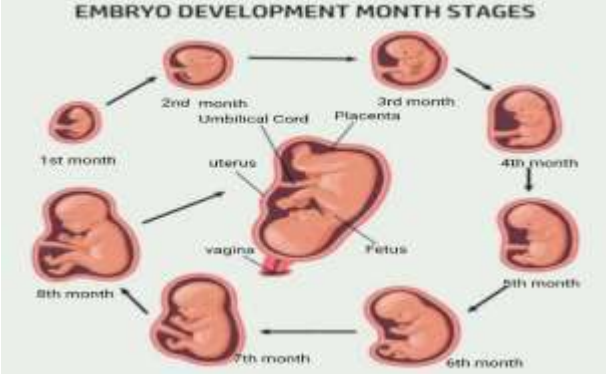


Figure: Stages Of Developing Fetus

During each menstrual cycle is women one egg usually released the egg release from ovary (ovulation). This releases the egg from the ovary. The sperm fertilize it in the fallopian tube. Fertilization: fusion of haploid male gametes (Spermatozoa) and haploid female gametes (Ovum).

Initial /1st Trimester (0-14 weeks)

After the process of fertilization fertilized egg start to divided and form a ball cell.

(3–4 weeks following the final menstrual cycle)

- The ball of cells burrows into the uterine lining
- The cell ball starts to take the shape of layers and fluid-filled cavities.
- The first segment of the afterlife starts forming.
- The ball of cells at this stage of development is known as a "embryo."
- The embryo develops to a 0.2 mm (or 1 /100 inch) length. [3,4,5,6]

(5–6 weeks following the final menstrual cycle)

The embryo develops into a curved, C-shaped form from a flat disc. Organ formation starts. the menstrual period is missed at this point. Along the length of the embryo, a tube forms. This develops into the spinal cord and brain.The heart is initially just a tube that beats as it expands.

• On the sides of the head, simple structures develop. With time, they will become eyes and ears.

• The formation of limb buds, or bumps, begins. They'll develop into arms and legs later.

• The embryo develops to a 6 mm (or 1/4 inch) length.

(7-8 weeks following the last menstrual cycle, or 5–6 weeks from conception)

Because of the brain's a rapid expansion, the head makes up about half of the embryo's length. The heart begins to develop the typically four Chamber. An ultrasound can show the heartbeat.

(9–10 weeks following the last menstrual cycle)

The embryo undergoes shape changes as the face develops. It starts to break free from the C-shape. The tiny tail bud starts to disappear. Now, every vital organ is developed, including the fundamental components of the heart and brain.

- The hands have fingers;
- The toes are nearly formed.
- The eyelids cover the eyes, but they are not yet able to open.
- The first hair buds appear and the breasts are visible. Muscle formation starts. Bones begin to form early. The intestines expand quickly, and the arms can bend at the elbow.
- The embryo measures about 1¼ inches (31 mm) in length**.**

(11–12 weeks following the final menstrual cycle)

All of the major body parts have developed and are present at this point. The embryo is now referred to as a "fetus." Growth takes center stage. Fetal length is measured (crown-rump)—that is, from the top of the head to the curve of the rump.

- The ears elevate to their typical position from the area surrounding the neck.
- Ultrasonography shows the heartbeat and movements of the fetus.
- Different glands start to function.
- Urine production starts in the kidneys.
- The length from crown to rump is 61 mm, or roughly 21/3 inches.

- Less than an ounce, or 14 grams, makes up the fetus.

(13-14 weeks following the last menstrual cycle)

At this stage, the fetus's sex is frequently visible. The fluid in the amniotic sac (bag of waters) starts to be swallowed by the fetus. The kidneys' production of urine replaces the fluid. The placenta is finished developing.

The neck is clearly visible between the head and body, the bone marrow produces blood cells, and the length of the crown to rump is 86 mm, or approximately 3½ inches.

• The fetus is 45 grams-roughly an ounce and a half—in weight.

Second Trimester:

(15–16 weeks following the last menstrual cycle)

The body straightens out, but the fetal head remains large. The limbs are shaped and capable of bending.

- Sexual organ development is nearly complete.
- The growth of fingernails and toenails starts.
- The gaze advances. Ears return to their typical position. The face is now sculpted nicely.
- For the baby teeth, tooth buds may erupt.
- The length from crown to rump is 120 mm, or 4½ inches.
- The weight of the fetus is 110 grams, or 4 ounces.
- The eyes shut.

(17-18 week after the last menstrual period)

Some women experience what is known as "quickening," or the first fetal movements, 17–18 weeks after the last menstrual cycle. Growth starts to pick up speed. The fetal head appears smaller as the legs get longer. Ultrasound can detect slow movements of the fetus's eyes. The lips start to move in a sucking motion.

• The bones grow calcium quickly.

• The ears protrude from the skull.

• The length from crown to rump is 140 mm, or roughly 5½ inches.

• The fetus is 200 grams, or roughly 7 ounces, in weight.

• The skin is nearly clear.

• The fetus may regularly go to sleep and wake up.

(19–20 weeks following the last menstrual cycle)

By this point in the pregnancy, many women experience "quickening" or fetal movement. There is a substance known as "vernix caseosa" that covers the fetal skin. Visually, vernix caseosa resembles cream cheese. This is roughly where a typical pregnancy ends.

- The fetal body is covered in a very fine hair known as "lanugo."
- The length from crown to rump is 160 mm, or roughly 6¼ inches.
- The fetus is 320 grams, or roughly 7 ounces, in weight.

(21-22 weeks after the last menstrual period)

The skin is red and wrinkled. Blood vessels can be seen very clearly beneath it.

- Eyebrow and eyelashes start to form.
- Fingerprints begin to form.
- The crown-rump length is 190 mm (about 7¾ inches).
- The fetus weighs 460 grams (just over a pound).

(23–24 weeks following the final menstrual cycle)

At this time, fetal weight gain occurs quickly. Vibrant eye movements are visible with ultrasonography.

• The formation of certain gas exchange sacs is reached by lung growth.

• A stethoscope can be used to listen for the heartbeat.

• The length from crown to rump is 210 mm, or 8½ inches.

• The fetus is one pound, six ounces (1 630 grams) in weight.

• If the fetus is delivered at this point, there's a chance it will survive.

(25-26 weeks following the final menstrual cycle)

The lungs keep expanding. The production of a substance known as "surfactant" by lung cells starts. After birth, the lungs require a lot of surfactant to stay open in between breaths. Fat accumulating beneath the skin over time.

- The fetus starts to store fat beneath the skin.
- It can suckle on hands or fingers.
- When there are loud noises close to the woman's belly, the fetus will blink and show signs of shock.
- The length from crown to rump is 230 mm, or roughly 9 inches.
- The fetus is 820 grams—just under two pounds—in weight.

Third Trimester:

(27-28 weeks following the final menstrual cycle)

The lungs keep expanding. The fetus keeps gaining mass. The brain develops and becomes capable of more difficult tasks.

- The fetal eyes will slightly open.
- Eyelashes develop.
- The length from crown to rump is 250 mm, or roughly 10 inches.
- The weight of the fetus is 1000 grams, or roughly 2 pounds, 3 ounces.

(29–30 weeks following the final menstrual cycle)

It is now possible for the fetal brain to regulate body temperature and breathing patterns. The fetus has a feeble grasping ability. It becomes apparent that different fetuses grow at different rates. Some people grow faster than others.

• Eyes that open widely.
• The forming of toenails.
• Bone marrow produces red blood cells.
• The length from crown to rump is about 270 mm, or almost 11 inches.
• The fetus is 1300 grams nearly three pounds in weight.

(31-32 weeks subsequent to the final menstrual cycle)

There's an increase in fat under the skin. Skin becomes thicker. The fetus begins to resemble a newborn baby more and more.

The facial lanugo hairs disappear.

The eyes' pupils respond to light.

Now, the fetus might hiccup.

Just over 11 inches, or about 280 mm, is the length from crown to rump.

The fetus weighs approximately three pounds, or 1700 grams.

(33–34 weeks subsequent to the last menstrual cycle)

Under the skin, fat continues to accumulate as the fetus develops. The lungs continue to expand and produce more surfactant.

Here, if the fetus is delivered, surfactant helps the lungs stay open.

There is an increase in fetal muscle tone. The ear maintains its shape when moved.

A little under one foot, or about 300 mm, is the length from crown to rump.

The fetus weighs more than 4½ pounds, or about 2100 grams.

(35–36 weeks following the final menstrual cycle)

The nervous system and lungs both continue to expand. Moreover, extra fat accumulates beneath the skin. The fetus starts to appear plump. The head's hair starts to look normal.

In male fetuses, the testes begin to migrate from the abdomen into the scrotum.

- The clitoris in female fetuses starts to be covered by the labia, or vaginal lips.
- The fetus turns over to face downward in preparation for birth.
- The length from crown to rump is typically more than a foot.
- The fetus weighs more than five pounds, or about 2500 grams.

(37–38 weeks following the final menstrual cycle)

Fetal lungs are nearly always developed at this stage. Lower in the mother's pelvis, the fetus descends. The mother might experience a rise in bladder pressure. All lanugo hairs have vanished, with the exception of those on the upper arms and shoulders. The fetus may remain in the womb until additional fat accumulates beneath the skin, or it may be born now.

(39–40 weeks following the final menstrual cycle) This pregnancy is full term. This is the time when most babies are born. 360 is the average length from crown to rump (more than 14 inches). About 20 inches is the total length when the legs are counted. A full-term baby weighs 3400 grams, or 7½ pounds, on average.

Cause of birth defect.

Between 65 and 70 percent of all birth defects are categorized as having an unidentified cause. Twenty percent of congenital malformations are genetic in nature, and three to five percent are caused by chromosomal, or cytogenetic, defects. These comprise issues like trisomy, which is the inheritance of an entire extra chromosome, and 4p-syndrome, which is the modification of a small portion of the chromosomal complement. Maternal infection with viruses like HIV, cytomegalovirus, or rubella accounts for two to three percent of developmental abnormalities. A tiny proportion of birth defects are brought on by abnormalities in the mother's metabolism, such as those brought on by diabetes. Teratogen induced malformations account for 2% to 3% of defects. These are thought to be the outcome of exposures to the environment or iatrogenic factors.[7]

Sr no	Cause of birth defect	Percentage%
1.	Teratogen-induced malfomation	2-3%
2.	Maternal infection with viral agents	2-3%
3.	Chromosomal defects	3-5%
4.	Genetic factors	20%
5.	Unknown	65-70%

Teratogenic exposure time.

Teratogen exposure is risky during any phase of pregnancy. However, the risk is slightly higher during the first eight weeks of pregnancy. This is because the growing fetus has numerous organs and systems that make it more vulnerable to the harmful effects of teratogens. Studies show that teratogens can start to have an impact on the developing embryo as soon as the sperm fertilizes the egg, which can happen as soon as two weeks after conception.

How Teratogenic Drugs effect Fetus growth

The fetus's development stages, as well as drug's strength and dosagr, determine how the drug affect the developing embryo.

The dosage of a drug that reaches the fetus affects its effectiveness as well. The mother's dosage, the drug's distribution in the mother's bloodstream, placental function, the genetic and physiological state of the mother and fetus, and exposure to other medications, chemicals, or environmental dangers all have an impact on this dosage.

- They may also change how the placenta functios, generally by causing blood vessels to expand more quickly and lowering the amount of nutrients and oxygen the fetus receives from the mother.
- They may inadvertently harm the fetus by forcing the uterine muscles to contract violently, decreasing blood flow, or inducing premature labor.

4% to 5% of congenital diseases are caused by teratogen exposure during fetal development. Research has additionally demonstrated that teratogen exposure impacts both physical and cognitive development.[2]

List of commonly prescribed dugs with there teratogenic effect.

Sr. No	Teratogenic Agent/Drugs	Class Of Drug	Common Use	Teratogenic Effect	Recommendation Advice.
1.	Thalidomide. (Introduce in 1950. Banned in Nov 1961). [8,9,10,11,12]	Immunomodulatory & Anti Inflammatory.	In 1950 it was prescribed to treat morning sickness in pregnant womon. Now used successfully to treat a rang of adult condition including multiple Myeloma, complications of leprosy, cancer as well as crohn's disease and HIV.	Phocomelia of upper and lower limbs. Pre-axial polydactly. Trifalangeal thumb . Facial hemangiomas. Esophageal and duodenal artesian. Cardiac defect. Renal angenesis. Urinary tract anomalies. Genital anomalies. Dental anomalies. Facial palsy. Opthalmoplegia. Exophthalmia. Microphthalmia.	Single 50mg tablet of Thalidomide drug during pregnancy is sufficient to cause birth defect up to 50% of Pregnancies. Avoid use of Thalidomide in pregnancy specially in first and second Trimester this period is highly sensitive /critical period.
2.	Captopril Enalapril. [2,13,14]	(ACE Inhibitors) Angiotensin Converting Enzyme Inhibitors.	It is used to treat Hypertension.	Small formation of amniotic fluid. Spontaneous abortion. Intrauterine and Neonatal death. Central nervous system and Limb defect. Calcarial hypoplasia. Renal disorder.	(ACE) inhibitors should not be used during the second or third trimester of pregnancy. However, there is no evidence linking first-trimester use to poor fetal outcomes Patients should begin taking a different medication before entering the second trimester of pregnancy, such as labet-alol or alpha-methyldopa
3.	Aspirin Ibuprofen Indomethacin Acetaminoph en Naproxen Celcoxih & other salicylate. [15,16,17,18]	NSAID (Non Steroidal Anti Inflammatory Drugs)	Use to relieve pain, reduce inflammation, And bring down a high temperature.	Increase risk of premature closure. Presistent fetal pulmonary hypertension. Congenital heart defect. Intracranial hemorrhages. Renal toxicity. Orofacial clefts.	Avoid in Second & Third Trimester.

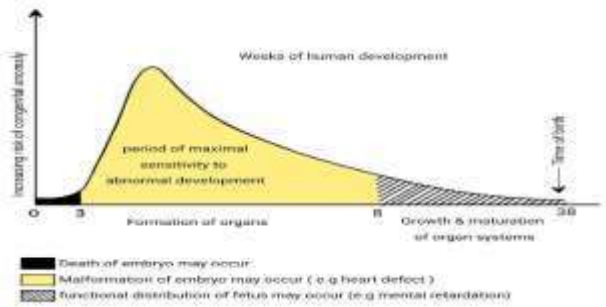
4.	Tetracycline, Nitrofurantoin, Streptomycin, Kanamycin. [19,20]	Antibiotic.	Used to treat or prevent some type of bacterial infection. It work by precluding(preventing) growth and spread of bacteria.	Impaired teeth. Yellow Brown discoloration of teeth. Impaired bone development. Hemolytic effect [red blood cell destroy faster].	Antibiotic pharmacokinetics are predicted to alter during pregnancy, as numerous antibiotics are known to cross the placenta Avoid in pregnancy mostly in Second & Third Trimester.
5.	Lithium. [21,22,23]	Antidepressant.	Use to treat clinical depression. Lithium is effective treatment in pregnancy & postpartum for prevention of relapse in bipolar disorder.	premature birth, decreased body weight of the child. Cardiac malformation. intrauterine growth retardation. neonatal adaptive syndrome & persistent pulmonary. Neonatal hypoglycaemia.	Avoid use of lithium in Pregnancy.
6.	Fuconazole, Ketoconazole, Itraconazole, Terbinafne, Griseofulvin [24,25]	Antifungal.	Use to treat fungal infections.	Cause birth defects as well as spontaneous abortion. premature rupture of membranes, preterm labor and neonatal candidiasis. congenital abnormalities in the fetus.	Topical medications, such as topical azoles, can be prescribed for superficial infections at any point during pregnancy. Treatment for superficial fungal infections that need to be administered systemically, such as mycetoma, chromomycosis, and dermatophytic onychomycosis, should be started after delivery.
7.	Statins.[26]	Lipid Lowering.	Statins are a group of medicines that can help lower the level of low-density lipoprotein (LDL) cholesterol in the blood.	Congenital anomalies, cardiac malformation, Spontaneous abortion/still birth.	Additionally, it was discovered that taking statins was linked to an increased incidence of first-trimester

					spontaneous abortions.
8.	Isotretinoin [27]	Vitamin A.	Use to treat multiple dermatological condition such as skin problems like pimples & acne, rosacea, scarring alopecia, ichthyosis/non melanoma skin cancer prophylaxis.	numerous congenital defects including craniofacial defects, cardiovascular and neurological malformations, or thymic disorders.	Avoid in Pregnancy.
9.	Warfarin. [28]	Anticoagulant.	Its Help to prevent blood clots.	Robotic revocations; can beget the fetal warfarin pattern. Nasal hypoplasia, Narrow nasal ground, Scoliosis, Spinal calcifications, Femur and heel bone calcification, Low birth weight, Experimental disabilities.	Avoid during all Trimester.
10.	Promethazine. [29]	Antiemetic.	Use to treat Nausea and vomiting which is a common problem occurring in up to 70–85% of all pregnancies.	Effect on growth.	The majority of exposure occurred in the first and second Trimester. Avoid in 1&2 Trimester.
11.	Trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbital, and primidone. [30,31,32,33]	Folic Antagonist.	Folic acid antagonists, often called antifols, are cytotoxic drugs used as antineoplastic, antimicrobial, antiinflammatory, and immune-suppressive agents.	Neural-tube defects, but also of cardiovascular defects, oral clefts, and urinary tract defects. The folic acid component of multivitamins may reduce the risks of these defects.	First-trimester exposure to folic acid antagonists is associated with increased risk of congenital malformations. Avoid in first trimester.

Some pregnancies are unplanned /unintended in such cases women do not realize they are pregnant and addicted to illicit [illegal] drugs / Substance which are only used to change one's mood or state of consciousness and are not intended for therapeutic purpose. E.g. Alcohol, Tobacco, Cocaine etc. using such types of drugs may interfare with the development of fetus and cause Teratogenic effect on fetus.

Sr.no	Teratogenic Agent	Teratogenic effect on Developing fetus	Mechanism Action	Recommendation or Advice
1.	Alcohol. [34,35,36]	Mental retardation. Foetal alcohol syndrome Hypoplasia [incomplete development]. Congenital heart disease.	Alcohol is converted to acetaldehyde by the enzyme alcohol dehydrogenases, which interferes with brain development and prevents DNA synthesis and the transfer of amino acids from the placenta to the fetus. The susceptibility is correlated with ADH levels, which vary in expression as a result of genetic variations in ADH alleles.	Do not Consume during pregnancy strictly avoid it in all stages.
2.	Tobacco. [37,38,39]	Reduce blood flow to placenta. Abnormal fetal Growth. [Prematurity]. Spontaneous abortion. Low birth weight. Perinatal mortality.	Because nicotine reduces the perfusion of fetal tissues, it interferes with intrauterine growth and raises the risk of placental abruption. Cigarette smoke contains carbon monoxide, which also crosses the placenta and raises blood levels of carboxyhemoglobin.	Do not Consume during pregnancy.
3.	Cocaine. [36,40]	Microcephaly [head of baby's is small compare to normal one.] Growth retardation. Mental retardation.	Because of its vasoconstrictor action, cocaine may cause the fetus's blood flow to stop. The amount of time it takes for someone to experience the benefits of cocaine depends on how it is ingested. Since cocaine enters the brain more quickly, ingesting it and smoking it produce the strongest quick-hit high. However, this also implies that the high brought on by ingesting or smoking cocaine wears off faster. Placental abruption, intrauterine growth retardation, branch blights, vascular disorders, tardiness, respiratory issues, ilea artesian, blights in brain growth and central nervous system (CNS), and neurobehavioral disorders are among the teratogenic effects.	Do not consume during pregnancy.

Rate of teratogenicity



Epidemiology studies

The most effective way to determine whether a gestational exposure has a negative impact on developing infant is through formal epidemiology studies. which can quantify the strength of association between a given drug exposure and abnormalities in the newborn. Additionally, while it is impossible to prove absolute safety, epidemiology studies can offer some measure of reassurance if risk is not found to be elevated, and the degree of reassurance, like evidence of risk, can be quantified. The degree of reassurance is dependent on the sample size [Powder]of study. A study may report that there is no correlation between drug and birth defect simply because the sample size was too small to detect anything other than a very small amount of abnormalities.

Formal epidemiology studied are the most effective way to assess where a gestational exposure affect the developing infant negatively. Epidemiology Studies can quantify the strength of association between a given drugs exposure and abnormalities in newborn. they can also identify associations between a given drugs exposure and abnormalities in the newbon and they can quantify the strength of such association.

Class Effects: In certain situation, knowing the pharmacological mode of action, activity relationship, structure of class of therapeutic agent can help predict the potential safety and efficacy of novel agent. However, such knowledge is generally not predicative of human teratogenesis. For example, thalidomide and glutethimide are closly related by chemical structure, but there is no evidence that glutethimide is teratogenic.

Preventing Birth defects:

Not all birth defect can be avoided, but managing health condition can help women have higher chance of giving birth to a healthy child.

I. Get 400 microgram [mcg] of folic acid every day. folic acid is a B Vitamin help in preventing major birth defect of developing spine. E.g. Anencephaly and Spina bifida.
II. Any new/regular medication of post conception should administered with doctor consult.
III. Should take appropriate vaccines regular.
IV. Avoid consuming non therapeutic substance e.g. alcohol, tobacco, cocaine.
V. Take regular antenatal check-ups & Maintain Healthy lifestyle.[41]

CONCLUSION

The physiology of pregnancy is unique, which makes it difficult to treat acute and chronic disorder with medication and to manage the symptoms of many pregnancy related complaints. All health care professional, including pharmacist have a duty to provide patient with complete, accurate and up-to date information regarding the risk and benefits of using medication while pregnancy. Effectively/Accurately identification exposure and measuring the amount of exposure are necessary when counselling women who have used drugs about their risk of teratogens. This might be simple when prescribing medication, but it can be challenging when dealing with illegal substance. Additional, even there though there may be more recent option, medication that have been in use for a long time are frequently preferred because fetal safety has been establish.

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