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## INTOLERANT DRUGS IN PREGNANCY

(DRUGS WHICH CROSS PLACENTAL BARRIER)

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### **ABSTRACT:**

The use of certain drugs during the pregnancy might pose a risk to the developing foetus, raising concerns about the potential adverse effects on the foetal development and maternal health. This abstract will provide an overview of the intolerant drugs during pregnancy, focusing on their pharmacological activities, mechanism of crossing the placental barrier, and associated risks. Drugs that cross the placenta can impact foetal development by affecting the organs and systems, which leads to the congenital abnormalities and many other complications. The main factors that might influence the passage of the drug to the foetus might be the size, molecular weight, ionisation, or its binding strength. Some common examples of the "Intolerant Drugs" are:

Thalidomide, ACE Inhibitors, Warfarin, Tetracyclines, Retinoids, and Ribavirin. All of these drugs have been evident to show some severe birth defects like limb abnormalities, kidney functioning issues, heart defects, or sometimes it can be fatal. It's important to note that the assessment of drug safety during pregnancy is complex, and varies under different circumstances. Healthcare workers play a crucial role in the evaluation of the risks and benefits of medication use in each case, considering factors such as the specific drug, the trimester of pregnancy, the health status of the pregnant individual, and alternative treatment options. Henceforth, this Abstract emphasises on the importance of medical guidance and reducing the risks associated with drug exposure during the pregnancy.

**keywords:** Intolerant drugs, foetal development, placental barrier, abnormalities, drug exposure, drug safety, medical guidance.

### **INTRODUCTION:**

Pregnancy represents a delicate and a transformative period of a woman's life, which is characterized by the physiological changes and the development of a new life (fetus). However, this journey of the gestation period is not without its challenges, especially when it comes to the use of medication for their existing health conditions. Some medications have the potential to cross the placental barrier. The placenta which serves as a gateway to nutrients and oxygen, may also become a gateway through which certain drugs/medicines can reach the developing fetus<sup>[1]</sup>.

This introduction looks into the classification of intolerant drugs during pregnancy, focusing on their ability to cross or travel through the placenta barrier and the related implications for the fetus. It is important to understand the mechanism by which these certain drugs cross the barrier to avoid the potential risk which can be fatal too.

This article will explore the various factors which are influencing the passage of drugs, by focusing on drugs with known adverse effects and reactions during the pregnancy, it also emphasizes women taking a piece of professional medical advice to avoid any complications. By pointing out the issue of maternal-fetal health we are also clarifying the critical aspect of the fetus as well<sup>[2]</sup>.

## **PLACENTAL BARRIER:**

The placental barrier is a vital and highly regulated organ that plays a crucial role during pregnancy. This placenta barrier serves as an important channel for the exchange of nutrients, gases, and waste products between the maternal and fetal circulations while simultaneously providing a protective barrier<sup>[3]</sup>.

The placenta barrier structurally consists of several layers, including maternal decidua, syncytiotrophoblast, cytotrophoblast, fetal capillary endothelium, and connective tissue. This complex organ arrangement acts as a filter, which selectively allows the substances to pass through based on their size, charge, and lipid solubility. Understanding the complexity of the placenta barrier is essential for healthcare professionals when advising pregnant individuals on medication use because notably, a drug that crosses the placenta has the potential to affect or impact fetal development, making it important for us to consider the safety of medications during pregnancy.<sup>[4]</sup>

## **-HOW THE DRUGS CROSS THE PLACENTA BARRIER-**

Drugs crosses the placenta barrier mainly through the process of diffusion. The placenta, a specialized organ that develops during pregnancy, facilitates the exchange of substances between the maternal and fetal circulations. The fetus's blood vessels are contained in tiny hairlike projections called the villi of the placenta that extend into the wall of the uterus. The mother's blood passes through the intervillous space. The placental membrane separates the mother's blood in the intervillous space from the fetus's blood.

The medications in the mother's blood can cross this placental membrane into the blood vessels of the villi and then pass to the umbilical cord of the fetus<sup>[5]</sup>.

There are certain factors that influence the crossing of the drug through the barrier like size and molecular weight, lipid solubility, ionization, and the protein binding of the drug.

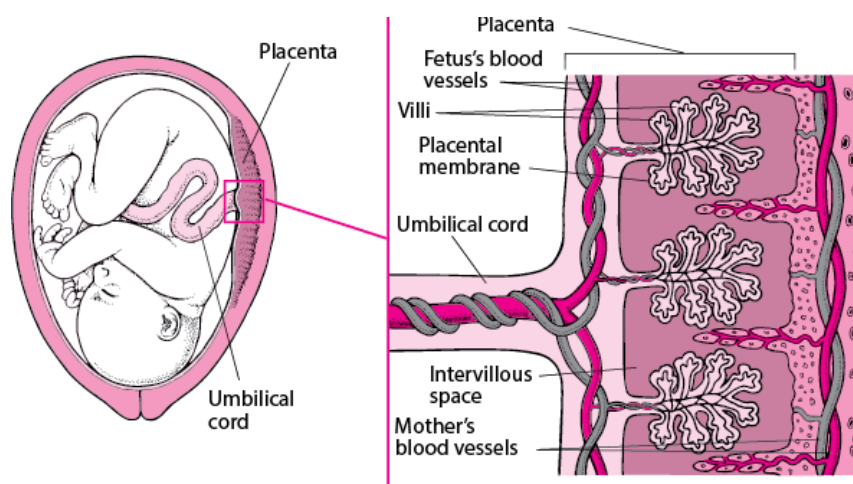


figure.1

In the pregnancy, the increased size of uterus decreased renal blood flow in supine position. This results in decreased excretion and prolonged effects of renally excreted drug.

The drug effect can be mainly changed or influenced by the pharmacokinetic changes in pregnancy, it is shown that hydrophilic drugs are more diluted and distributed in non pregnant women than in the pregnant women, whereas the hydrophobic drugs are more soluble in pregnant women. These drugs have therapeutic or

adverse effects on the mother and for placental transfer to the fetus, excretion of drugs increased by kidneys, mainly which are excreted primarily unchanged in the urine<sup>[6]</sup>.

### **Drugs and the stages of pregnancy**

Some drugs can be harmful when they are used at any stage of pregnancy; however, other drugs can be particularly damaging at some stages (table.1). The various stages during the fetal development and the effect of drugs during these stages are mentioned below:

**The stage of conception:** if the fetus is exposed at the time of conception and implantation, the embryo may be aborted. As the fetus progresses through the first 12-15 days the cells are still totipotential.

**The stage of organ formation:** most of the body organs and systems of the developing fetus, are formed within the first ten weeks of pregnancy. During this stage some drugs and alcohols may cause malformations of different parts of the developing fetus such as the heart, the limbs, and the facial features.

**The stage of prenatal growth:** after the tenth week, the fetus grows rapidly in terms of weight and size. At this stage, certain drugs may damage organs that are still developing, such as the eyes, nervous system etc. continuous drug use may also pose the risk of miscarriage and premature delivery. But the greatest danger drugs pose is their potential with the interference with growth. During the first 3 months the chances of physical malformations is increased because this is the critical stage of physical development.

**The stage of birth:** some drugs can be harmful especially at the end of pregnancy. They may make delivery more difficult or dangerous, or it might create problems or pose a danger for the newborn baby.

(TABLE.1) VARIOUS DRUGS AND THEIR INDICATIONS/CONTRAINDICATIONS DURING PREGNANCY<sup>[7]</sup>.

<b>DRUGS</b>	<b>I TRIMESTER</b>	<b>II &amp; III TRIMESTER</b>
Antihistamines	contraindicated	Fenistil can be used
Antacids	Can be used	Can be used
Digestants	Digestine, serpostine can be used	As 1st trimester
Antiflatulents	Disflatyl, flatidyl can be used	As 1st trimester
Peptic ulcer	Sucralfate can be used	As 1st trimester
Antiemetics	Cortagen B6 can be used	As 1st trimester
Laxatives	Absolute contraindication	contraindicated
Anthelmentics	Absolute contraindication	Contraindicated
Antispasmodics	Buscopan compsitium can be used	As 1st trimester
Urinary tract infection	Amoxicillin can be used	As 1st trimester
Antibiotics	Penicillin, ampicillin can be used	As 1st trimester

## **DRUGS THAT CROSS PLACENTAL BARRIER:**

Certain drugs cross the placental membrane and directly affect the fetus. Some of the intolerant drugs will be discussed below:

- **ISOTRETINOIN**

The isotretinoin drug is commonly known by the brand name ACCUTANE, is a potential oral medication that is used to treat acne.

It belongs to a class of drugs called retinoids and is also a derivative of vitamin A. Isotretinoin is mainly known for its effectiveness, but it also comes with significant risks and potential side effects. One of the major concerns with Isotretinoin is its teratogenic (**Able to disturb the growth and development of an embryo or fetus**) side effects, meaning it can cause severe birth defects if taken during pregnancy. In recent times, many regulatory authorities have established strict pregnancy prevention programs for those using isotretinoin. Hence, to minimize the fatal exposure. The isotretinoin drug should only be used under medical supervision, and all individuals must be aware of its potential risks and side effects<sup>[8]</sup>. Pregnant individuals or those planning pregnancy should avoid isotretinoin, and alternative acne treatments may be recommended like; **topical retinoids-tazarotene(Tazorac), antibiotic azithromycin(Zithromax), and Benzoyl peroxide.**

- **TETRACYCLINES**

The tetracyclines belong to a class of antibiotics, during pregnancy is generally discouraged, especially during the second and third trimesters. The tetracyclines, which include drugs like doxycycline, minocycline, and tetracycline itself, can cross the placenta and may affect fetal development.

These antibiotics can potentially interfere with the development of fetal bones and teeth, leading to discoloration and deficient mineralization. Hence, the pregnant woman should avoid tetracycline use unless it is deemed essential or is prescribed by a healthcare professional who is aware of its potential risks and benefits.

In some cases antibiotic treatment is necessary during pregnancy, alternative antibiotics that are considered safe can be recommended<sup>[9]</sup> like, **amoxicillin, ampicillin, and Cephalosporins**, including cefactor and cephalixin.

- **ACE INHIBITORS and ARBs**

ACE inhibitors (Angiotensin-Converting Enzyme inhibitors) and ARBs ( Angiotensin II Receptor Blocker) are the classes of medications that are used to manage conditions like hypertension, and heart failure. However, their use during pregnancy is not recommended, particularly during the second and third trimesters as these medications can potentially interfere with the fetal development, particularly affecting the development of the kidneys. Their use has been evidence of increased complications during pregnancy, including renal dysfunction and many other serious conditions like Oligohydramnios (when the person has low levels of amniotic fluid).

Pregnant women are advised to discuss alternative medicines with their doctor to manage their healthcare conditions while avoiding the potential risks and complications<sup>[10]</sup>.

Some alternatives can be Methyldopa (Aldomet), Labetalol, and Calcium Channel Blockers (Nifedipine).

- **RIBAVIRIN**

Ribavirin drug is an antiviral medication that has been associated with potential risks during pregnancy. It is used to treat some viral infections, including Hepatitis C and respiratory syncytial virus (RSV). However, the use of ribavirin during pregnancy is not recommended because of its potential teratogenic effects and it also may cause harm to the developing fetus.

According to the studies, it is recommended for individuals who are pregnant, or planning to , or breastfeeding to not take the ribavirin medications as it may pose a risk and may cause complications.

We can consider alternative treatment if it is necessary for the person with closely monitoring the patient and under the medical guidance<sup>[11]</sup>.



Some alternatives can be, **Respiratory Syncytial Virus(RSV) treatment, Direct-acting antivirals(DAAs), and Interferon-Free Direct-Acting Antivirals(DAAs).**

- **PETHIDINE**

The pethidine drug which is also known as ‘meperidine’, during pregnancy is a concerned topic for the prescription of these drugs. Pethidine is an opioid analgesic which is usually taken for managing the pain, including during labour period. However, its use in pregnancy is associated with potential risks.

Pethidine can cross the placenta and affect the fetus, potentially causing respiratory depression and other complications. Also, the opioid use during pregnancy is linked to the risk of neonatal withdrawal symptoms in the newborn<sup>[12]</sup>.

Many alternatives of this pethidine drug can be epidural anaesthesia or other non-opioid pain management options, intravenous opioid analgesics (like:fentanyl), nitrous oxide, acetaminophen and NSAIDs.

- **WARFARIN**

Warfarin is an anticoagulant drug which is commonly used to prevent blood clotting.

However, its use during pregnancy is associated with potential risks, particularly during the first trimester. Warfarin drug can cross placental barrier and may affect the fetal development.

Exposure to warfarin during pregnancy has been related to the increased risk of bleeding in the fetus, as well as result in some more complications. Additionally, there's also a potential risk of “warfarin-induced embryopathy” which may lead to some development issues in the fetus. In such situations where anticoagulation is necessary during pregnancy, health care providers may carefully consider the risks and benefits. Alternatives like low molecular weight heparin, may be considered as it does not cross the placenta to the same extent as warfarin does<sup>[13]</sup>.

Drugs are teratogenic only at specific times during embryogenesis. Teratogenicity is a condition in which when any drug of chemical substance which produces abnormalities in the development of an embryo. Therefore to avoid such problems it is very important to know which drugs should be prescribed during pregnancy. Food and Drug Administration (1979) of America enforced the rule for the categorization of the drug that is contraindicated during pregnancy so a classification has been carried out as follows.

**The FDA has categorized the potential teratogenic risk of medications by an A, B, C, D, and X system.**

**Category A:** Research in this category fails to show any risk to fetus in the first trimester and also shows no evidence of risks in the later trimesters. The fetal harm appears unlikely. Medications in this class are considered safe to be prescribed and also to be used in pregnancy. Examples of medications in this class are vitamins and levothyroxine.

**Category B:** the animal-reproduction studies have not demonstrated a fetal risk but there wasn't any controlled studies in pregnant women or, in another case animal studies have demonstrated risk to the fetus but that wasn't confirmed in the controlled studies of pregnant women in the first trimester and also there isn't any evidence of risks in later trimesters. Medications in this class or category are generally considered safe. Some examples of this class can be acetaminophen and amoxicillin.

**Category C:** research in this category shows that studies in animals have revealed some adverse effects on the fetus and there are no controlled studies in woman, or the studies in women and animals aren't available. Drugs from this class can be given to pregnant woman if the benefit to the mother outweighs the risk to the fetus. Some examples of medication in this class are diltiazem and spironolactone.

**Category D:** research shows that the Evidence of human fetal risk has been documented, but the benefits to the mother may be acceptable despite the risk to the fetus. Drugs in this class may be used in pregnancy if the benefits to the mother outweigh the risk to the fetus (i.e. a life threatening situation or a serious disease for

which safer medication cannot be used or are not efficacious. Examples of medications in this class are phenytoin and valproic acid.

**Category X:** Studies in animals or humans have demonstrated teratogenic effects. The risk to the fetus clearly outweighs any potential benefit to the mother. Drugs in this category are contraindicated in pregnancy. Examples of medications in this class are thalidomide and warfarin.

**(TABLE.2) Antibiotics, analgesics, antiepileptic drugs (AEDs), cough and cold, immunizations, and Diabetes Mellitus classes:**

Generic (brand)	Pregnancy category	Crosses placenta	Reported adverse effects to mother or baby from use in pregnancy	Place in therapy
Nitrofurantoin	B	Yes	Fetus: Haemolytic anemia	Not recommended in pregnancy.
Trimethoprim (TMP)	C	Yes	neural tube defects (NTD), oral clefts, cardiac defects, and urinary tract defects	Not recommended in pregnancy.
Metronidazole Topical- (Metrogel)	B	Yes	Fetus: Low birth weight babies, spontaneous abortions, and carcinogenic possibilities. Not mutagenic or teratogenic.	Safe for use only in 2nd and 3rd trimester Contraindicated in 1 <sup>st</sup> semester.
Clindamycin	B	Yes	Fetus: Increase in neonatal infection and low birth weight seen with vaginal preparation	For BV as oral alternative, but not the topical Group B strep. disease in patients with penicillin allergy
Tetracyclines	D	Yes	Fetus: Hypospadias (1st trimester only), inguinal hernia, limb hypoplasia, teeth discoloration (2nd, 3rd), cleft palates, spina bifida, polydactyly Maternal: liver toxicity, irreversible shock	Not recommended in pregnancy
Aminoglycosides	D	Yes	Fetus: ototoxicity/deafness (damage of 8 <sup>th</sup> CN) Neuromuscular weakness, respiratory depression with concomitant gentamicin and Mag sulfate	Do not use in pregnancy unless the benefit outweighs the risk to the fetus
Carbamazepine	D	Yes	Fetus: dysmorphic facial features, cranial defects, cardiac defects, spina bifida, fingernail hypoplasia, developmental delay, mild mental retardation, neural tube defects	Compatible – Maternal Benefit >>> Embryo/Fetal Risk If drug is required during pregnancy it should not be withheld because the

				benefits of preventing seizures outweigh potential fetal harm
Ethosuximide (Zarontin)	C	Unknown	Foetus: spontaneous haemorrhage, patent ductus arteriosus, cleft lip/palate, mongoloid facies, short neck, altered palmar crease and accessory nipple, hydrocephalus	Limited human data. Probably compatible.
Felbamate (Felbatol)	C	Unknown	Fetus: mental retardation. Maternal: aplastic anaemia, acute liver failure	Limited Human Data – Animal Data Suggest Moderate Risk. Drug crosses placenta in animals, not yet described in humans. B
Phenytoin (Dilantin)	D	Unknown	Foetus: congenital abnormalities, haemorrhage at birth, neurodevelopment abnormalities Maternal: folic acid deficiency	Compatible – Maternal Benefit >>> Embryo/Foetal Risk Maintain lowest level required to prevent seizures to lessen risk of foetal anomalies.
Primidone	D	Unknown	Newborn: neurologic manifestations (overactivity/tumor); mechanism for hemorrhagic effects is due to suppression of VitK-dependent clotting factors, recommend administration of VitK to infant immediately after birth	If benefits > risks (e.g., drug needed in life-threatening situation or serious disease with no safer drug)
Tiagabine (Gabitril)	C	Unknown	Fetus: one incidence with unspecified malformations, otherwise unknown	Safest course: Avoid in 1 <sup>st</sup> trimester; later trimesters unknown
Trimethadione	D	Unknown	Fetus: mental retardation, craniofacial defects, genitourinary defects, malformed hands, clubfoot	Contraindicated in 1 <sup>st</sup> trimester
Diphenhydramine (antihistamine)	B	Yes	1 <sup>st</sup> trimester – cleft palate, cardiovascular defects, oral clefts, spina bifida, polydactyly, limb reduction defects and hypospadias Maternal: premature labor	DOC if parenteral antihistamines are indicated Meclizine and cyclizine: viable alternatives
Cetirizine (antihistamine)	C	Unknown	1 <sup>st</sup> trimester – spontaneous abortion, ectopic kidney, undescended testes	Consider diphenhydramine or chlorpheniramine

Benzonatate (anti-tussive)	C	Unknown	There has not been sufficient clinical experience to establish the safety of benzonatate in general during pregnancy	If possible, use of benzonatate during pregnancy should be avoided
Guaifenesin (expectorant)	C	Unknown	1st trimester –increase frequency of inguinal hernias and cardiovascular defects	Use only if Benefits > Risks
Nasal Steroids Budesonide (Rhinocort) Fluticasone (Flonase) Mometasone (Nasonex) Triamcinolone (Nasacort)	C B D	Unknown	1st trimester - orofacial clefts, Cono truncal defects, neural tubal defects and limb abnormalities. Congenital malformations, premature birth, low birth weight, C- section, stillbirth multiple births. Budenoside: no increased risk of these AE. Triamcinolone: in animals' cleft palate, umbilical hernia, undescended testes, reduced ossification, growth retardation.	The benefits of treatment must be carefully weighed against the potential risks of therapy of the nasal corticosteroids, budesonide is the best choice. It is the only inhaled corticosteroid that is category B
Glyburide (Sulfonylurea)	C	Yes	Possible ear defects in 1st trimester, fetal hypoglycemia	Insulin is recommended first line by the ADA; ACOG recommends use of this agent in D2 or GDM
Sitagliptin (Januvia)	B	Unknown	No good studies in humans; animal studies show no defects/complication at high doses	Possible; No human data
Regular insulin (Humulin)	B	No	None reported	Drug of choice
Lispro insulin (Humalog)	B	No	Case reports: sudden neonatal death, growth retardation; controlled studies: as efficacious as regular insulin	Recommended
Glulisine insulin (Apidra)	C	Unknown	No available studies	Not recommended unless benefits > risks
Detemir insulin (Levemir)	C	Unknown	Visceral abnormalities were seen in animals	Not recommended
Aspirin (Bufferin, Ecotrin) <b>NSAID</b>	C	Yes	Foetal: increased perinatal mortality, teratogenic effects, pulmonary HTN, bleeding risk, premature ductus arteriosus closure Maternal: anaemia, ante/post partum haemorrhage, prolonged labour	Should not be used in pregnancy, consider acetaminophen



Ibuprofen (Advil, Midol,)	B	Unknown	Foetal: ductus arteriosus constriction, pulmonary HTN in 3rd trimester Maternal: prolonged labour, spontaneous abortion	Should be avoided when possible and completely avoided during the 3rd trimester.
Acetaminophen (Analgesic antipyretic)	B	Yes	Foetal: overdose can lead to liver toxicity Maternal: overdose can lead to liver toxicity	Drug of choice for analgesia and fever during pregnancy
Morphine (Narcotic analgesic)	C	Yes	Foetal: addiction, possible relation to inguinal hernia and respiratory depression Maternal: addiction	Should only be used when analgesia or anaesthetic is clearly indicated
Fentanyl (Narcotic analgesic)	C & D	Yes	Foetal: respiratory depression, dependence and loss of foetal heart rate variability without hypoxia	Only use when benefits > risks
Tramadol (central analgesic)	C	Yes	Foetal: dose related foetal toxicity in animals, respiratory depression and addiction	Should be avoided until further evidence concerning the dose related foetal toxicity is available
Ergotamine (Sympatholytic)	X	Yes	Foetal: increase uterine tone leading to foetal hypoxia, teratogenic and foetal toxicity	Do not use in pregnancy

**Social drugs:** In addition to counsel the pregnant women regarding use of various prescribed and non-prescribed medications during pregnancy. They should be informed about risk of using following substances during pregnancy:

**Cigarette smoking:** Maternal smoking is one of the few known preventable cause's of prenatal morbidity and mortality. The most common and known effect of smoking on the fetus during pregnancy is reduction in birth weight. Birth defects of heart, brain and face are also more common among the pregnant woman who smoke. Risk of sudden infant death syndrome (SIDS), Mis-located placenta (placenta previa), premature detachment of placenta, premature rupture of the membranes, preterm labor, uterine infections, miscarriages, stillbirths, premature births therefore are increased<sup>[14]</sup>. Changes in uterine and placental oxygenation may be the causes of infant death, pre-maturity or spontaneous abortions. Therefore all women's should be informed of the risk of smoking on the fetus and encouraged to quit smoking during pregnancy.

**Alcohol:** Fetal alcohol syndrome is one of the most serious consequences of drinking during pregnancy . Risk of miscarriage almost doubles for women who drink alcohol in any form during pregnancy and birth weight of babies is substantially below normal. This syndrome includes inadequate growth of the fetus before or after birth, facial defects, a small head, mental retardation and abnormal behavioral development changes can be seen<sup>[15]</sup>.

**Caffeine:** Caffeine is found in various quantities in many beverages, analgesics, diet aids and stimulants; hence it is the most commonly ingested drug during pregnancy Evidence suggests that consuming caffeine during pregnancy possess little or no risk to the fetus. Caffeine contained in coffee, tea, and some sodas and some drugs is a stimulant that readily crosses the placenta to the fetus. If taken in high dose it may stimulate the fetus increasing heart and breathing rate. Caffeine also may decrease blood flow across placenta and decreases the absorption of iron, increasing risk of anaemia<sup>[16]</sup>.

**CONCLUSION:**

The use of intolerant drugs during the pregnancy pose a complex challenge, requiring a delicate balance between the maternal health needs and safe-guarding the fetal well being. Medications that cross the placental barrier, such as isotretinoin, ribavirin, thalidomide, tetracyclines, and many others may pose significant risks to fetal development. This review summarizes the safe and unsafe list of drugs during pregnancy. It is the responsibility of all clinicians including pharmacists to counsel patients with complete, accurate and current information on the risks and benefits of using medications during pregnancy. The first safe methods to refrain from such interaction during pregnancy are always consulting the medical practitioners and prescribing the drugs especially during the pregnancy as there are so many complications in it. Drugs may also become less effective during the pregnancy because of pharmacokinetic changes such as increased metabolism. Doses of these drugs may need to be adjusted during pregnancy. There are many alternatives for these intolerant drugs which can be prescribed under a professional's medical guidance and in the monitoring of the fetus. All these precautions and considerations can minimise the risk and complications during pregnancy and will result in a safe and healthy outcome for both mother and the child.

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Fig.1 By **Ravindu Gunatilake**, MD, Valley Perinatal Services; **Avinash S. Patil**, MD, University of Arizona College of Medicine

