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A REVIEW ON CONTRAINDICATIONS OF TETRACYCLINE IN PREGNANCY

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ABSTRACT
A common class of broad-spectrum antibiotics used to treat a variety of bacterial illnesses are tetracyclines. However, due to possible negative effects on the mother and developing baby, their usage during pregnancy is linked with considerable contraindications. In addition to examining the fundamental processes of teratogenicity, the dangers of dental and bone abnormalities, and the effects on fetal development, this study critically explores the contraindications of using tetracycline during pregnancy. The study also covers the data from clinical trials and the recommendations from medical authorities that drive modern medical practice. This study attempts to offer a thorough overview of the dangers associated with tetracycline usage in pregnant women by synthesizing available evidence and emphasizes the significance of alternate antibiotic therapy during this crucial period.

KEYWORDS: Tetracycline, pregnancy, contraindications, teratogenic effects, fetal abnormalities, antibiotic safety, maternal health.

INTRODUTION

Tetracyclines are a class of broad-spectrum antibiotics that come from Streptomyces, a kind of soil-dwelling bacterium. The word "tetracycline" can be used to describe either one particular antibiotic or the entire class. These antibiotics are used to treat a wide range of bacterial illnesses and are distinguished by their four-ring molecular structure.[1,2]

Discovery

Tetracycline's history begins in the 1940s and 1950s. Benjamin Minge Duggar identified chlortetracycline, the first tetracycline antibiotic, from Streptomyces aureofaciens in 1945. With this discovery, the tetracycline class of antibiotics was established.

Development and Use

- 1950s: Tetracycline, doxycycline, and minocycline were created as tetracycline antibiotics after chlortetracycline was discovered. Because they could be taken orally and were efficient against a variety of bacterial illnesses, these antibiotics gained popularity very rapidly.
- In the 1960s and 1970s, tetracyclines were widely used to treat a wide range of illnesses, such as skin, urinary, and respiratory infections. They were also applied in agriculture to help cattle thrive and stay healthy.
- Late 20th century: As newer antibiotics were developed and antibiotic resistance emerged, the usage of tetracyclines started to wane. They are still useful, nevertheless, for some infections and ailments.[3,4]

Medical Uses

Tetracyclines are used to treat a variety of bacterial infections, including:

- **Respiratory Infections**: Such as pneumonia, bronchitis, and sinusitis.
- **Skin Infections**: Including acne, rosacea, and bacterial skin infections.
- **Sexually Transmitted Infections**: Like chlamydia and syphilis.
- **Urinary Tract Infections**: Including cystitis and pyelonephritis.
- **Gastrointestinal Infections**: Such as Helicobacter pylori infections, which can cause peptic ulcers.
- **Rickettsial Infections**: Including Rocky Mountain spotted fever and typhus.

Non-Medical Uses

- **Veterinary Medicine**: Animal illnesses caused by bacteria are treated with tetracyclines. They are also used to stimulate animal development, however the use of them for this purpose is becoming more and

more controlled because of worries about antibiotic resistance.

- **Agriculture**: Tetracyclines were once added to livestock feed to encourage development and stave against illness. Many nations have stopped this practice in an effort to lower the danger of antibiotic resistance.[5,6]

IMPORTANCE OF UNDERSTANDING CONTRAINDICATIONS

It's important to know when to avoid using tetracycline while pregnant for a number of reasons.

1. **Preserving Fetal Health**: Tetracyclines have the ability to penetrate the placenta and impact the growing baby, resulting in long-term tooth discolouration, decreased bone formation, and more defects in development.
2. **Informed Clinical Decision-Making**: By selecting safer alternatives to antibiotics, medical professionals can prevent possible damage by using their knowledge of these risks to guide their prescription decisions.
3. **Preventing Long-Term Effects**: Long-term negative consequences for the kid, such dental and bone problems, can be avoided by staying away from contraindicated drugs.
4. **Improving Maternal Safety**: A mother's general health throughout pregnancy is enhanced when she understands and complies with contraindications, which helps avoid difficulties.[7,8]

RELEVANCE TO PREGNANCY AND PRENATAL CARE

Knowledge of tetracycline contraindications is important for several facets of pregnancy and prenatal care, including:

1. **Prenatal Care Protocols**: By include information on contraindications in prenatal care protocols, expecting moms are guaranteed to get safe and efficient care.
2. **Education and Counseling**: Giving expectant mothers correct information on the dangers of particular drugs encourages them to make well-informed decisions and stick to safer treatment alternatives.
3. **Preventative Health Strategies**: By minimizing the amount of hazardous drugs that pregnant women are exposed to, preventative health strategies that take contraindications into account can be developed.
4. **Policy and recommendations**: The review's findings can help shape clinical recommendations and policy that support the best practices for the use of antibiotics during pregnancy and raise the bar for prenatal care as a whole.[9]

CHEMICAL COMPOSITION AND STRUCTURAL DETAILS

- **Molecular Formula**: C22H24N2O8
- **Molecular Weight**: 444.435 g/mol
- **Core Structure**: Tetracyclines are characterized by a four-ring structure known as a hydronaphthacene nucleus. This core structure consists of:
  - **Four Hydrocarbon Rings (A, B, C, D)**: Arranged in a linear, fused configuration.
  - **Functional Groups**: Various functional groups are attached to this core, influencing the antibiotic's activity and properties.
- **Functional Groups**
  - **Amino Group**: Typically found at position 4.
  - **Hydroxyl Groups**: Often present at positions 5, 6, 10, 11, and 12.
  - **Keto Groups**: Present at positions 3 and 12a.
  - **Methyl Groups**: Often attached to the rings to modify activity and pharmacokinetics.
- **Structural Modifications**: Changes made to these functional groups result in a variety of tetracycline derivatives with unique pharmacological characteristics.

Examples of Tetracyclines

- **Tetracycline**: Effective against a wide range of gram-positive and gram-negative bacteria.
- **Doxycycline**: A second-generation tetracycline.
  - **Properties**: Improved absorption and longer half-life.
  - **Uses**: Effective for respiratory tract infections, acne, and certain sexually transmitted infections (STIs).
- **Minocycline**: A semi-synthetic derivative.
  - **Properties**: Better penetration into tissues and enhanced activity against certain bacteria.
  - **Uses**: Acne, respiratory infections, and multi-drug resistant infections.
- **Oxytetracycline**: A naturally occurring tetracycline.
  - **Properties**: Broad-spectrum antibiotic with similar uses to tetracycline.
  - **Uses**: Infections in both humans and animals, including pneumonia, skin infections, and urinary tract infections.
- **Tigecycline**: A glycylcycline, derived from minocycline.
  - **Properties**: Overcomes many tetracycline-resistant mechanisms.
  - **Uses**: Complicated skin and intra-abdominal infections, and community-acquired pneumonia.[10,11]

PHARMACOKINETICS

Absorption

- **Oral Absorption**: When tetracyclines are administered orally, they are often effectively absorbed from the digestive system. Food, particularly dairy products and other goods containing calcium, magnesium, aluminum, and iron, can dramatically limit their absorption, though, since these substances form insoluble complexes with tetracyclines in the stomach.
- **Bioavailability:** Within the class, tetracyclines have varying levels of bioavailability. As an illustration,

doxycycline and minocycline are more bioavailable than tetracycline.

- **Distribution**: Tetracyclines are extensively distributed throughout bodily fluids and tissues, reaching therapeutic concentrations in the majority of tissues, including as the kidney, liver, lungs, skin, bone, and teeth.

Distribution

- **Tissue Penetration**: Tetracyclines are effective in treating infections in tissues and bodily fluids that are permeable, such as bone tissue and cerebrospinal fluid (CSF).
- **Placental Transfer**: Tetracyclines are capable of passing through the placenta and exposing the fetus to the medication.
- **Distribution in Breast Milk**: Tetracyclines can have an impact on nursing newborns since they are excreted into breast milk in different degrees

Metabolism

- **Limited Metabolism**: The liver only slightly breaks down tetracyclines. Urine contains the majority of the drug's unaltered excretion.

Excretion

- **Renal Excretion**: The kidneys use glomerular filtration and active tubular secretion to remove tetracyclines mostly undisturbed.
- **Biliary Excretion**: A tiny percentage of tetracyclines may be eliminated through the biliary system and then enter the enterohepatic circulation.

Pharmacokinetic Considerations

- **Half-Life**: Tetracyclines have a half-life that ranges from around 6 to 18 hours, depending on the agent. This affects the length and frequency of dose.
- **Dosage Adjustments**: Because tetracyclines are excreted less readily by the kidneys in individuals with renal impairment, dosage modifications may be required.

Factors Affecting Pharmacokinetics

- **Food and Antacids**: As previously indicated, tetracycline absorption can be hindered by the simultaneous use of dairy products, antacids containing calcium, magnesium, aluminum, and iron supplements.
- **Drug Interactions**: Tetracyclines may have an adverse effect on the pharmacokinetics of other drugs by competing with them for renal tubular secretion or affecting the pH of the stomach.
- **Age and Pregnancy**: Due to variations in renal function and distribution, tetracycline pharmacokinetics might fluctuate between age groups and during pregnancy.[12,13]

MECHANISM OF ACTION

The following is a thorough overview of the bacteriostatic actions of tetracyclines:

Mechanism of Action

1. **Binding to the Ribosome**
   - The 30S ribosomal subunit of bacterial ribosomes is reversibly bound by tetracyclines. They specifically attach to the ribosome's A site, which is where incoming aminoacyl-tRNA typically attaches while protein synthesis is taking place.

2. **Inhibition of Protein Synthesis**
   - Tetracyclines stop aminoacyl-tRNA from attaching to the mRNA-ribosome complex by attaching to the 30S ribosomal subunit. This process disrupts the protein synthesis's elongation stage.
   - As a result, the creation of peptide bonds is blocked, which stops additional amino acids from joining the expanding polypeptide chain.

3. **Effect on Translation**
   - Tetracyclines prevent aminoacyl-tRNA from entering the A site, which stops translation. Since protein synthesis is necessary for bacterial survival and replication, this essentially halts bacterial growth and reproduction.

4. **Broad-Spectrum Activity**
   - Tetracyclines are effective against both gram-positive and gram-negative bacteria, demonstrating broad-spectrum action. They work well against a variety of pathogens, such as many bacteria that cause skin infections, lung infections, STIs, urinary tract infections, and more.[14,15]

5. **Bacterial Resistance**
   - Tetracycline resistance can develop via a number of mechanisms:
     - **Efflux Pumps**: Tetracyclines may be actively pumped out of cells by bacteria using efflux pumps, which lowers intracellular concentrations.
     - **Ribosomal Protection Proteins**: Bacteria that generate ribosomal protection proteins bind to the ribosome and prevent tetracycline from binding, therefore inhibiting its inhibitory activity.
     - **Enzymatic Inactivation**: Tetracyclines can be chemically changed by certain bacterial enzymes to make them inactive.[16]

SAFETY PROFILE OF TETRACYCLINE

Despite being powerful antibiotics, tetracyclines have unique safety concerns that affect how they are used in medicine. This is a thorough synopsis of their safety profile:

General Safety Concerns

1. **Photosensitivity**: Tetracyclines can make a person more susceptible to sunlight, which increases their risk of becoming sunburned or developing skin rashes. By using sunscreen and limiting extended sun exposure, this impact can be reduced.
2. **Gastrointestinal Effects**: Nausea, vomiting, diarrhea, and pain in the abdomen are typical

adverse effects. Tetracyclines might lessen gastrointestinal discomfort when taken with meals.

3. **Hepatotoxicity**: In rare instances, tetracycline usage has been linked to liver toxicity. Individuals who already have liver illness may be more vulnerable.
4. **Renal Toxicity**: Patients with compromised kidney function are more susceptible to renal damage from high dosages of tetracyclines.
5. **Dental and Skeletal Effects**: Dental discolouration and enamel hypoplasia might result from long-term usage or use in youngsters and pregnant women during the period when their teeth are developing. In youngsters, bone development suppression has been shown, particularly after extended treatment.
6. **Superinfection**: Extended tetracycline usage might cause non-susceptible organisms, including fungus or resistant bacteria, to proliferate excessively.

Common Side Effects: Light sensitivity, rash on the skin, nausea, vomiting, diarrhea, abdominal pain.

Long term Usage Effects

- **Dental Discoloration**: Teeth that are permanently discolored a yellow-gray-brown tint, particularly in younger children (under 8 years old).
- **Bone Growth Inhibition**: Long-term usage in kids can harm the development and growth of bones.
- **Hepatic and Renal Effects**: In rare cases, excessive dosages or extended usage might cause liver damage and renal impairment.[17,18]

MECHANISMS OF TERATOGENICITY OF TETRACYCLINES

Tetracyclines' teratogenicity is caused by a number of major processes that interfere with normal fetal development, including those that impact the production of teeth and bones. This is a thorough analysis of these mechanisms:

1. Interaction with Calcium

- **Calcium Chelation**: Divalent cations including calcium (Ca^2+), magnesium (Mg^2+), and iron (Fe^2+) are highly favored by tetracyclines. Tetracyclines create insoluble complexes with these ions, which decreases the amount of free calcium ions that are necessary for healthy cell operations and the mineralization of growing tissues.

2. Incorporation into Fetal Bone and Teeth

- **Accumulation in Fetal Tissues**: Tetracyclines' lipophilic properties and tiny molecular weight allow them to pass through the placenta. Once in the fetal circulation, they build up in tissues with elevated calcium levels, especially in growing teeth and bones.
- **Disruption of Osteogenesis**: Tetracyclines affect the function of osteoblasts, which are in charge of creating new bone. Fetal bone development retardation and poor mineralization may result from this disturbance.
- **Effects on Dental Development**: Tetracyclines interfere with the regular production of enamel in growing teeth. Enamel hypoplasia—a weak or deformed covering of enamel and irreversible tooth discoloration which can range from yellow to gray to brown can be the results of this.

3. Inhibition of Mitochondrial Protein Synthesis

- **Mitochondrial Effects**: Tetracyclines also prevent the synthesis of proteins in the mitochondria, which are the cellular organelles in charge of producing energy. This interference may cause metabolic problems and cellular malfunction, which might further impair embryonic growth and development.

4. Placental Transfer and Fetal Exposure

- **Placental Passage**: Tetracyclines easily pass from the mother's bloodstream to the fetal one. Tetracycline derivatives differ in how much they transmit to the fetus, although this is usually because of their lipophilicity and capacity to permeate biological membranes.
- **Timing of Exposure**: Tetracyclines have the greatest impact on fetal development when exposure takes place at crucial stages of organogenesis, especially in the second and third trimesters of pregnancy when the fetus is actively growing its bones and teeth.[19,20,21]

Pharmacokinetics in Pregnancy

- **Absorption**: Food and other factors may reduce the absorption of tetracyclines, even if they are efficiently absorbed from the gastrointestinal system.
- **Distribution**: They are found extensively in the placenta and bones of both mothers and fetuses
- **Metabolism**: The liver metabolizes tetracyclines very little.
- **Excretion**: Most of them are removed unaltered by renal excretion, however others may circulate through the enterohepatic system.

Degree of Placental Passage

- **High Placental Transfer**: Tetracyclines easily pass through the placenta, including tetracycline, doxycycline, and minocycline. Within the tetracycline class, various drugs have varying degrees of placental transit.
- **Fetal Exposure**: A number of factors, including the drug's unique pharmacokinetic characteristics, the mother's dosage, and the gestational age of the fetus, affect the fetus's exposure to tetracyclines.[22,23]

ADVERSE EFFECTS ON FETAL DEVELOPMENT DUE TO TETRACYCLINE EXPOSURE

Tetracycline exposure during pregnancy can have a number of negative impacts on the development of the fetus. The following is a list of possible side effects:

1. **Dental Discoloration**: Tetracyclines have the ability to attach to calcium ions and integrate into growing

teeth, resulting in a yellow, gray, or brown discoloration. If exposure takes place in the latter half of pregnancy or in early childhood, the effect is more noticeable.

2. **Enamel Hypoplasia**: Exposure to tetracycline during tooth development may result in hypoplasia, or diminished enamel production. This leaves teeth with enamel that is poorly formed and more prone to injury and decay.
3. **Skeletal Abnormalities**: Extended or high-dose tetracycline exposure might hinder the fetus's ability to develop and mineralize its bones, which may result in skeletal abnormalities such growth retardation and limb malformations:
   - Growth retardation
   - Limb deformities
   - Delayed ossification (bone formation)
4. **Inhibition of Long Bone Growth**: Tetracyclines have the ability to prevent the fetus's long bones from growing longer, which might result in shorter limbs or other skeletal deformities.
5. **Hepatotoxicity**: Although uncommon, tetracyclines have been linked to liver toxicity in expectant mothers, which may have an impact on the health of the mother and fetus.
6. **Renal Toxicity**: Excessive tetracycline dosages may cause renal toxicity, especially in developing fetal kidneys that have not reached complete maturity.
7. **Neurodevelopmental Effects**: According to the few data available, tetracycline exposure during pregnancy may have an impact on an unborn child's behavior and cognitive development.
8. **Reduced Birth Weight**: While less research has been done than the other side effects, there is evidence to imply that tetracycline usage during pregnancy may be linked to a lower birth weight.
9. **Potential Cardiovascular Effects**: Although additional study is required to validate this relationship, certain studies have revealed a possible link between tetracycline exposure and cardiovascular malformations in babies.

Tetracycline exposure has been shown to have negative effects on fetal development, which emphasizes the need of avoiding these antibiotics during pregnancy, particularly during key stages of organogenesis. To promote the best possible outcomes for mother and child, healthcare practitioners should carefully examine alternate treatment alternatives and inform patients about the possible dangers associated with using tetracycline during pregnancy.[24,25,26]

CLINICAL GUIDELINES AND RECOMMENDATIONS REGARDING TETRACYCLINE USE DURING PREGNANCY

Current Medical Guidelines

Due to their established hazards to fetal development, tetracyclines are widely advised against usage during pregnancy by medical standards. Below is a list of the most recent recommendations:

1. **American College of Obstetricians and Gynecologists (ACOG)**
   - Because tetracyclines may cause damage to the fetus, namely tooth discolouration and bone deformities, ACOG advises against using them during pregnancy.
   - Tetracyclines should be avoided after the first trimester, when fetal organogenesis takes place.
2. **Centers for Disease Control and Prevention (CDC)**
   - To avoid potential negative effects on fetal bone and tooth development, the CDC advises against using tetracyclines during pregnancy, particularly in the second and third trimesters.
3. **World Health Organization (WHO)**
   - Due to their teratogenic potential, tetracyclines should not be used during pregnancy. Instead, pregnant women should use other antibiotics to treat infections.[27,28]

Table 1: Contraindications of Tetracycline in Pregnancy.

Contraindication	Description	Impact on Fetus
Dental Abnormalities	Tetracyclines bind to calcium in developing teeth.	Permanent yellow-gray to brown discoloration; enamel hypoplasia.
Skeletal Abnormalities	Interference with bone mineralization.	Inhibited bone growth; potential skeletal deformities and delayed development.
Hepatotoxicity	Risk of fatty liver degeneration in pregnant women.	Potential liver damage in the fetus; exacerbation of maternal liver conditions like preeclampsia.
Nephrotoxicity	Risk of kidney damage.	Impaired renal function in the fetus, affecting fluid balance and waste management.
Neurodevelopmental Concerns	Potential impact on the developing nervous system.	Possible neurodevelopmental issues, though specific impacts are still under investigation.
Interaction with Calcium	Chelation of calcium, essential for fetal bone and tooth development.	Disruption of normal calcium processes, leading to abnormal bone and tooth development.

Placental Transfer	Tetracyclines cross the placenta, exposing the fetus to the drug.	Direct fetal exposure increases risk of teratogenic effects, especially during critical periods of development.
FDA Classification (Category D)	Indicates positive evidence of human fetal risk.	Strong contraindication for use during pregnancy due to proven risks.
Ethical and Legal Considerations	Prescribing tetracyclines during pregnancy can lead to legal repercussions and ethical dilemmas.	Ensures that both healthcare providers and patients are protected; emphasizes the need for informed consent.

RECOMMENDATIONS BY HEALTH ORGANIZATIONS

- **FDA (Food and Drug Administration)**: Tetracyclines provide evidence of fetal harm based on human data, which leads to their classification as Category D medications during pregnancy. It is important to carefully balance the dangers and possible advantages of tetracycline use in pregnant women.
- **European Medicines Agency (EMA)**: Just like the FDA, the EMA recommends against using tetracyclines while pregnant, especially in the second and third trimesters.

COMPARATIVE ANALYSIS WITH OTHER ANTIBIOTICS

Healthcare professionals frequently choose for antibiotics with a safer profile when treating infections during pregnancy instead of tetracyclines:

1. **Penicillins (e.g., Amoxicillin)**
   - Penicillins are efficient against a variety of bacterial illnesses and are generally regarded as safe to use during pregnancy.
2. **Cephalosporins (e.g., Cephalexin)**
   - Because of their strong efficiency against a variety of bacterial infections and minimal risk of teratogenicity, cephalosporins are also often used in pregnancy.
3. **Macrolides (e.g., Azithromycin)**
   - Macrolides are an additional choice that have a good safety record during pregnancy and are especially helpful for STIs and respiratory tract infections.

Alternatives to Tetracycline

- **Avoidance of Tetracyclines**: Penicillins, cephalosporins, and macrolides are better options for treating infections in pregnant women due to the hazards connected with tetracyclines.

Tetracyclines should not be used during pregnancy due to strong evidence of teratogenic consequences, including as bone and dental deformities, organ damage, and possible effects on neurodevelopment. It is imperative to follow clinical standards and regulatory recommendations in order to protect the developing fetus and the mother. Prioritizing alternative antibiotics that have been shown to be safe for use during pregnancy will help treat infections successfully without endangering the health of the fetus.[29,30]

CONCLUSION

In conclusion, tetracyclines are an important family of antibiotics that effectively treat a wide range of bacterial illnesses throughout a broad spectrum. But using them while pregnant has a number of serious concerns, including the possibility of organ poisoning and teratogenic consequences including tooth discolouration and stunted bone growth. The drug's capacity to chelate calcium and pass through the placental barrier, directly affecting fetal development, is the cause of these unfavorable effects. Tetracyclines are therefore categorized as Category D for pregnancy by regulatory agencies such as the FDA, citing strong evidence of fetal damage. When treating pregnant women, healthcare practitioners should give priority to safer options such cephalosporins and penicillins. To reduce risks and guarantee the health of both the mother and the fetus, adherence to clinical guidelines and knowledgeable patient counseling are crucial. This study emphasizes how important it is to carefully assess and follow contraindications in order to protect the health of expectant mothers and their developing unborn children.

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