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EC MICROBIOLOGY
Review Article

Antibiotic Use in the First Trimester of Pregnancy

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Received: November 29, 2019; **Published:** December 06, 2019

Abstract

Introduction: In order to prolong the life of babies and reduce neonatal and maternal mortality rates, antibiotics are being used sporadically. Pregnant patients in certain situations face life-threatening infections, warranting the use of antibiotics. Apart from an alteration in drug pharmacokinetics, risk of teratogenic potential and toxicity to developing fetus needs to be studied extensively. Some data suggests the even with antibiotics considered safe in pregnancy, long term childhood obesity and compromised immunity in children is seen. Enhanced cardiac output, increased glomerular filtration rate and an increase in total body volume are some of the common physiological changes seen in pregnancy. These changes influence the pharmacokinetics and drug interaction and require careful dose adjustment and monitoring. More research and data need to be collected to ascertain the safety of antibiotics used in pregnancy.

Aim of the Work: An overview of antibiotic use in the first trimester of pregnancy. The Classification of drugs and antibiotics generally considered safe in the first trimester.

Methodology: The review is comprehensive research of PUBMED from year 1941 to 2017.

Conclusion: A complete knowledge of the safety and side effects of the drugs used in pregnant and lactating women is absolutely necessary. The teratogenic potential and toxic risk profile of all drugs must be taken into consideration, and a risk to benefit analysis must be done before prescribing antibiotics. The first trimester is the stage of organogenesis, and with major implications on the unborn fetus is the drug crosses the placenta.

Keywords: *Antibiotics in Pregnancy; Safe Antibiotics; Teratogenicity; Drugs in Pregnancy*

Introduction

In 2006 - 2008, over 90% of women reported using at least one prescription or over-the-counter medication during pregnancy, and over 80% reported use during the first trimester, a critical period of organogenesis [1].

Infections like UTI, respiratory infections, viral infections are extremely common in pregnancy. Due to this, routinely, pregnant women have prescribed antibiotics and other drugs. It is seen in almost 2 to 7% of pregnant women that Urinary tract infections (UTI) such as cystitis, pyelonephritis, etc. are extremely common [2].

A myriad of congenital malformations is linked to the use of drugs during the first trimester and last trimester of pregnancy. A careful analysis of the risk of exposure to these drugs must be taken into account in relation to the benefit to the mother [2].

Methodology

We did a systematic search for Acute Gastroenteritis in Children using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: antibiotics in pregnancy, safe antibiotics, teratogenicity, drugs in pregnancy.

Classification of drugs in pregnancy

The Swedish system for the classification of fetal risk of drugs was the first of its kind and was implemented in 1978. Drugs for use in pregnant women are classified in 4 general categories--A to D. The US Food and Drug Administration (FDA) introduced a system in 1979 also using the letters A to D, together with an X category [3].

Category	Definition
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote.
B	Either animal studies do not indicate a risk to the fetus, and there are no controlled studies in pregnant women, or animal studies have indicated fetal risk, but controlled studies in pregnant women failed to demonstrate risk.
C	Either animal studies indicate a fetal risk, and there are no controlled studies in women, or there are no available studies in women or animals.
D	There is positive evidence of fetal risk, but there may be certain situations where the benefit might outweigh the risk (life-threatening or serious diseases where other drugs are ineffective or carry a greater risk).
X	There is definite fetal risk based on studies in animals or humans or based on human experience, and the risk clearly outweighs any benefit in pregnant women.

Table 1: *FDA classification of drugs used in pregnancy [3].*

The risk to benefit ratio

The pregnancy risk to benefit ratio is defined as the risk to the fetus compared to the benefits to the mother. This ratio is calculated by taking into account the:

1. The genotype of mother and fetus,
2. The embryonic stage at exposure,

3. The dose of the drug, and
4. Exposure to other drugs or environmental agents that may increase or decrease potential abnormalities.

The stage of pregnancy exposure is most important with respect to risk to the fetus. Generally, as the pregnancy progresses, risk decreases. The first trimester is most crucial as it is the stage of organogenesis. Organogenesis in an important time in fetal development. This is the period of development of important organs and extends from 6 weeks to 10 weeks. This period makes the fetus most prone to any birth or developmental defects due to exposure to external factors (drugs, toxins, trauma, radiation, etc. Any medication prescribed during pregnancy must take into account the risk to the fetus versus the benefit to the mother. Untreated infections lead to significant fetal risk, sometimes leading to birth defects, spontaneous abortions, premature labor, and other fetal abnormalities. Hence a calculated approach should be taken before prescribing any medication in pregnancy and particularly during the first trimester [4].

Physiological changes in pregnancy affecting pharmacokinetics of drugs

Antibiotic drug therapy is impacted by a number of physiologic changes during pregnancy. These changes, in turn, influence the pharmacokinetics and pharmacodynamics of the drug [5].

A common effect of an increase in progesterone is the vasodilation of the afferent and efferent arterioles causing increase in the renal blood flow to up to 50% of the normal [5]. Since GFR (glomerular filtration rate) increases and serum creatinine decreases, we see an increased rate of elimination of renal excreted antibiotics. 3 weeks prior to delivery, the GFR reaches postpartum values [6].

Change in gastrointestinal motility affects the bioavailability, absorption and may ultimately lead to delayed onset of action of drugs [7].

Changes in hepatic enzymes are known to take place in pregnancy. However, whether the effect of these is clinically significant and actually requires dose adjustment, is controversial and requires further research [6,7]. Finally, there is decreased protein binding and increased concentrations of an unbound drug due to decreased albumin and alternations in maternal plasma pH [5,6].

Pregnancy and antibiotics

Urinary and respiratory tract infections are common in pregnancy and warrant use of antibiotics. Clindamycin, quinolones, macrolides, doxycycline, and phenoxymethylpenicillin exposure was linked to teratogenic effects and organ damage to the fetus. Amoxicillin, cephalosporins, and nitrofurantoin are considered safe and not associated with organ-specific damage. There is a small absolute risk of birth defects, however since controlled studies on a section of pregnant women assessing the effect of the prescribed drug is not routinely done, and data available is limited, physician should opt for safe drugs to prescribe in pregnancy [8].

Antibiotic pregnancy ratings

Antibiotic	FDA Pregnancy Category Rating	Notes
Aminoglycosides	D	Studies suggest streptomycin may cause hearing loss in newborns and should be generally avoided. Other drugs in this class should only be considered for use in case of benefit outweighing the risk.
Beta-lactams and monobactams		
1. Penicillins: Including extended-spectrum penicillins, amino-penicillins; and beta-lactam/beta-lactamase inhibitor combinations	B	Considered safe
2. Cephalosporins (all generations) and cephamycins	B	Ceftriaxone associated with kernicterus
3. Carbapenems Doripenem, ertapenem, and meropenem Imipenem-cilastatin	 B C	Take precaution, use only when penicillins or cephalosporins are not an option

4. Aztreonam	B	Use only if severe allergy to beta-lactams
5. Fluoroquinolones	C	Avoid unless benefits outweigh risks
Glycopeptides and lipoglycopeptides		
1. Vancomycin	B	Appears to be safe and effective
2. Lipoglycopeptides: Telavancin, dalbavancin, oritavancin	C	Avoid in pregnancy unless benefits outweigh risks
Macrolides and ketolides		
Macrolides		
1. Azithromycin, erythromycin	B	Azithromycin is considered safe; use erythromycin and clarithromycin with safety and when the benefit is greater than risk
2. Clarithromycin	c	Azithromycin is considered safe; use erythromycin and clarithromycin with safety and when the benefit is greater than risk
3. Telithromycin	C	May use if benefits outweigh risks
4. Oxazolidinones: Linezolid, tedizolid	C	May use if benefits outweigh risks
5. Tetracyclines: Tetracycline, minocycline, doxycycline	D	Should be avoided
Miscellaneous Antibiotics		
Clindamycin	B	Safe and effective.
Daptomycin	B	The risk to benefit ratio to be considered before prescribing.
Fidaxomicin	B	Systemic exposure is limited; hence, fetal exposure is limited. However, not prescribed routinely
Fosfomycin	B	Safe and effective generally
Metronidazole	B	Avoid topical route
Nitrofurantoin	B	Considered safe and effective
Polymyxin: Polymyxin B, polymyxin E	C	Should be used with caution. Careful monitoring of adverse events
Folate Antagonist: Sulfamethoxazole, trimethoprim	C	Trimethoprim and sulfamethoxazole are known to cause major congenital malformations and must be avoided. Sulfamethoxazole causes kernicterus and should be avoided after 32 weeks gestation
Tigecycline	D	Avoid and only prescribe when the benefit is higher than risk
Antimycobacterial agents		
Isoniazid (INH)	C	Monitor hepatic enzymes closely while on therapy
Ethambutol	B	Monitor hepatic enzymes closely while on therapy.
Pyrazinamide	c	Combine pyridoxine with INH therapy
Rifampin, rifabutin, rifapentine	C	
Bedaquiline	B	

Table 2: *Antibiotic pregnancy rating [9,10].*

Antibiotics and their teratogenic effects

A human teratogen is defined as an agent that causes birth defects by altering the growth or structure of the developing embryo or fetus. Maternal rubella was the first teratogen to be identified in 1941 by Norman Gregg, an ophthalmologist. During pregnancy it was found that exposure to rubella causes a triad of defects, namely, cataracts, heart malformations, and deafness in the infants [11].

Following the identification of thalidomide, an antinauseant, as a major human teratogen causing severe birth defects in 1961, research in teratology began to expand, and there was increased awareness of the possible teratogenic impact of maternal exposures during pregnancy [12].

the main adverse reaction pattern in adults of aminoglycosides consists of ototoxicity and kidney damage. The aminoglycosides cross the placenta [13] and their concentration in the amniotic fluid ranges from 30% to 60% of the average maternal concentration in blood. Severe intrauterine otological damage has been reported after the administration of aminoglycosides to mothers. Moreover, there is also a risk of nephrotoxicity in the fetus, although no proven cases have been published. Tumor-inducing effects due to aminoglycosides are unknown [14].

The 5-nitroimidazoles are usually considered safe. However, the warning issued is due the effects of mutation seen in some bacteria after exposure to the drug [15]. In some animal experiments tumor-inducing effects (liver carcinoma, malignant lymphoma, lung tumors, and mammary tumors) could be demonstrated. Evidence of fetal malformations in animals or in humans has not been reported. The nature of the side-effects of the aminoglycoside group and polymyxins is similar, i.e. nephrotoxicity to acute renal failure and neurotoxicity, e.g. convulsions, neuromuscular blockade, ataxia, dizziness, and circumoral paresthesia. Hence usually polymyxins are avoided in pregnancy [16,17].

Tetracyclines are deposited as a calcium-complex when given during the period of calcification of the teeth in the mineralization zones and cause a greyish-brown or yellow discoloration of the teeth as well as hypoplasia and enamel defects. Similarly, tetracyclines demonstrate a deposition in growing bones with possible disturbances of longitudinal growth. In tissue culture studies an inhibition of osteogenesis has been observed in the presence of tetracyclines [18].

Aminoglycosides and vancomycin have similar side effects. Nephrotoxicity, ototoxicity, which is dose-dependent, permanent, or transient deafness, are seen. Although vancomycin transfer across the placenta has not been studied in detail, pregnant women, as a precaution, should not take vancomycin [19].

Chloramphenicol is known to cause “gray baby syndrome” [20]. This is seen when the drug is not only administered during pregnancy but also in premature babies or full-term babies. Chloramphenicol levels in fetal blood reach 30% to 80% of maternal blood. Another side-effect of sulfonamides is caused by the competition of sulfonamides with bilirubin at common serum binding sites. Sulfonamides administered in the third trimester to mother or new-born babies have been known to displace the unconjugated bilirubin from plasma albumin. This bilirubin is free to enter the bloodstream and tissues and crosses the blood-brain barrier and produces kernicterus [21,22].

Conclusion

A complete knowledge of the safety and side effects of the drugs used in pregnant and lactating women is absolutely necessary. The teratogenic potential and toxic risk profile of all drugs must be taken into consideration, and a risk to benefit analysis must be done before prescribing antibiotics. The first trimester is the stage of organogenesis, and with major implications on the unborn fetus is the drug crosses the placenta.

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Volume 16 Issue 1 January 2020