

ANTIBIOTICS EFFECTS ON PREGNANCY

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Abstract-

Background: Limited evidence is available on the safety and efficacy of antimicrobials during pregnancy, with even less according to the trimester of their use. **Objective:** This study aimed to evaluate the association between exposure to antibiotics therapy (AT) during pregnancy and short-term neonatal outcomes. **Methods:** We considered 773,237 deliveries that occurred between 2007–2017 in the Lombardy region of Italy. We evaluated the risk of neonatal outcomes among infants that were born to mothers who underwent AT during pregnancy. The odds ratios and the hazard ratios, with the 95% confidence intervals, were estimated respectively for early (first/second trimester) and late (third trimester) exposure. The propensity score was used to account for potential confounders. We also performed subgroup analysis for the class of AT. **Results:** We identified 132,024 and 76,921 singletons that were exposed to AT during early and late pregnancy, respectively. Infants born to mothers with early exposure had 17, 11, and 16% increased risk of preterm birth, low birth weight, and low Apgar score, respectively.

Keywords: Antibiotics use in pragency, aminoglycosides, penicillin, tetracyclin, Oxazolidiones, onobactums.

INDRODUCTION:

The most common infections that are encountered during pregnancy are those of the urinary tract and upper respiratory tract infections. Untreated infections are associated with an increased risk of several neonatal outcomes, such as prematurity and low birth weight. This explains why antibiotics are among the most used drugs during pregnancy, accounting for 39% of all dispensed medications during this period[1].

Several antibiotics are known to cross the placenta and changes in antibiotics pharmacokinetics are expected during pregnancy. Moreover, changes in the maternal microbiome resulting from antibiotic use may affect the maternal immune system and convey modified bacterial flora to the fetus. When taken together, these reasons explain the concerns about the implications of antibiotics use during pregnancy on adverse neonatal outcomes[2]. However, since pregnancy is often an exclusion criterion in clinical trials, and as few epidemiologic studies have been performed on this issue, limited evidence is available nowadays on the safety and efficacy of antimicrobials during pregnancy, with even less according to the trimester of their use.

We conducted a population-based cohort study in the Lombardy region of Italy to assess the potential association between the use of antibiotics during pregnancy and several short-term neonatal outcomes³.

ANTIBIOTICS USE IN PREGNANCY:

Perhaps the most clinically relevant aspect of the pregnancy microbiome is antibiotic treatment during pregnancy. Antibiotics account for 80% of all prescribed medication in pregnancy, yet surprisingly, few published human studies have carefully evaluated the direct effects of antibiotics during pregnancy on either the maternal or fetal microbiome, or evaluated long-term sequelae of such antibiotic use⁴. Thus, there may be a reason for caution in prescribing antibiotics during pregnancy.

In pregnant NOD mice, antibiotic treatment caused alteration of gut microbiota and immunological changes in the intestine of the offspring. In pregnant women, it was demonstrated that antibiotic administration during pregnancy leads to alterations in the vaginal microbiome prior to birth, with long-term effects on the early microbial colonization of the newborn and an association with childhood obesity.

There are several components to this issue. Antibiotic treatment of infectious diseases is one of the greatest advances of modern medicine. Accordingly, antibiotics are widely prescribed during pregnancy as the most important modality for treating and preventing infections. It is estimated that one in five pregnant women in Europe is prescribed at least one antibiotic during pregnancy; in the United States, the rate is double. Nevertheless, prescription of antibiotics should be carefully considered on an individual basis, weighing its benefits versus drawbacks for both the fetus and the mother. It has been shown that administration of certain antibiotics is linked to a significantly higher rate of neonatal necrotizing enterocolitis, although antibiotic treatment is also associated with a reduced rate of lung

complications and major cerebral abnormalities, relative to non-antibiotic treated controls . A more recent study published in 2008 demonstrated that the prescription of antibiotics for women in spontaneous preterm labor with intact membranes was associated with an increased risk of cerebral palsy and functional impairment among their children at 7 years of age.

As discussed above, the healthy microbiome is important for maintaining a normal pregnancy and, therefore, it has been suggested that we may be using too many antibiotics during pregnancy. A large systematic review concluded that antibiotics during the second and third trimester do not reduce adverse pregnancy outcomes and morbidity . In addition, even a short course of antibiotics perturbs bacterial communities in human hosts . In one study, it was shown that, within 30 days following cessation of antibiotic treatment, fecal microbiota reached an average similarity of 88 % to baseline, with the level rising to 89 % within 60 days; however, the microbiota did not completely return to baseline over the timescale studied. Thus, antibiotics cause an immediate perturbation of the ecosystem, followed by incomplete recovery of the gut microbiome. The response to a given antibiotic is individualized, and may be influenced by prior exposure to the same drug[5]. Accordingly, even a short course of antibiotics may sometimes have a long lasting residual effect on the microbiome, with possible metabolic or immune consequences.

The use of antibiotics during pregnancy has also been associated with increased risk of asthma in early childhood, increased risk of childhood epilepsy, and increased risk of childhood obesity. Of course, the argument could be made that the primary maternal infection was the cause for the increased risk of these conditions, rather than the treatment itself. Nevertheless, we suggest that antibiotics in pregnancy may affect the bacterial ecosystem of the mother as well as that of the fetus, and therefore that their use should be carefully considered based on what is known, and what remains unknown, regarding their effects.

Recent studies have demonstrated that priming of the immune system and microbiota-driven immune changes begin in utero and are not – as traditionally believed – induced postnatally by the newborn’s microbiota . These new insights suggest that the maternal microbiota during pregnancy actually drives early postnatal innate immune development . It is becoming clearer that the maternal microbiota, in concert with maternal antibodies, are important in preparing the fetus for host-microbial symbiosis later in life. The mechanisms of this phenomenon are now being explored and involve microbial molecular transfer (without any live bacteria). In addition, maternal antibodies have a dual effect, promoting pathogen neutralization whilst simultaneously enhancing microbial molecular transfer. Gomez de Aguero et al. recently showed that pups of mothers transiently colonized during pregnancy have a greater capacity to avoid inflammation in response to bacterial molecules and penetration of intestinal microbes. Thus, the maternal microbiota plays a role in shaping the postnatal immune system and interferences with maternal microbiota during pregnancy may hinder the natural process of prenatal immune priming[6].

We believe that the issue of antibiotics during pregnancy is one of the greatest challenges of human microbiome research and certainly deserves increased focus in the form of observational and interventional studies to unravel the role of these drugs in human development.

Aminoglycosides

Amikacin, gentamicin, streptomycin, and tobramycin are the most commonly prescribed aminoglycosides. During pregnancy, the serum half-life of aminoglycosides is shorter and clearance is increased. Due to this and a larger volume of distribution in pregnant women, aminoglycosides may have a lower serum peak concentration compared to nonpregnant women. Aminoglycosides cross the placenta and may result in toxicities, especially if administered in the first trimester of pregnancy. Case reports of irreversible bilateral congenital deafness with maternal use of streptomycin in the first trimester have been described, leading to a boxed warning and FDA Pregnancy Category of D for the class in the United States. Other aminoglycosides have not commonly been associated with similar hearing loss; however, if hearing abnormalities did occur, symptoms were mild without clinical significance. Animal studies with gentamicin in rats and rabbits did not result in fetal toxicity. Traditional or extended interval dosing of aminoglycosides in pregnancy are both supported in the literature. Despite toxicity reports, short courses of aminoglycosides may be used in pregnant women with careful monitoring if the likely benefit outweighs the potential risk. Possible risks should be explained to the patient, especially in the first trimester. Due to the risks specifically associated with streptomycin use, this agent should be avoided[7].

Penicillins

Penicillins and their newer derivatives are the most widely prescribed antimicrobial class during pregnancy. Intravenous penicillin from the time of rupture of the placental membranes until delivery remains first-line prophylaxis if the patient is colonized with Group B *Streptococcus*, while ampicillin is recommended as a suitable alternative. Penicillins generally cross the placenta in high concentrations. Penicillins with increased protein binding such as the anti-staphylococcal penicillins (except methicillin) produce lower fetal tissue concentrations compared with penicillins such as penicillin G or ampicillin that have low protein binding. Due to increased plasma volume and

creatinine clearance in pregnant women, serum penicillin concentrations may be decreased by as much as 50%, which may require increased doses and/or frequency.

Penicillins have a long track record of safety, with the parent compound penicillin and the aminopenicillins (ampicillin and amoxicillin) having the most robust safety data. All penicillins and their derivatives, as well as penicillin combinations with beta-lactamase inhibitors such as clavulanate or sulbactam, have been assigned a Pregnancy Category B rating. Pregnant patients with a penicillin allergy diagnosed with syphilis should undergo desensitization followed by penicillin therapy.

Cephalosporins and Cephameycins

Cephalosporins have a long history of documented use in pregnancy. Cephalosporins remain a first-line option for many infections in pregnancy with general use reserved for patients allergic or intolerant to penicillin therapy. Cephalosporins have decreased plasma concentrations in pregnant patients because of increased renal elimination; therefore, potential dosage and frequency increases are required.

All cephalosporins-cephameycins are classified as Pregnancy Category B. Findings from a Michigan Medicaid database suggested a potential association between ceftriaxone and cardiac malformation. Ceftriaxone remains the drug of choice for the treatment of gonorrhea during pregnancy. Ceftriaxone should be used cautiously at term due to the potential risk of kernicterus in neonates. Newly approved agents such as ceftaroline, ceftolozane-tazobactam, and ceftazidime-avibactam are also Pregnancy Category B agents; however, they should be used with caution as there is a lack of published data during pregnancy.

Carbapenems

There is a paucity of data regarding the use of carbapenems during pregnancy. Ertapenem, meropenem, and doripenem are Pregnancy Category B, while imipenem-cilastatin is Pregnancy Category C. Pharmacokinetic changes associated with pregnancy have shown decreased imipenem concentrations. Carbapenem therapy should be reserved for pregnant women with infections that are resistant to penicillin and cephalosporin therapy with limited alternatives[8].

Monobactams

While its lack of cross-reactivity with penicillins and cephalosporins makes aztreonam an appealing choice, there are inconclusive data regarding its safety in pregnancy. Most safety data are in the perinatal period, which supports its Pregnancy Category B rating. Aztreonam should be used with caution during the first trimester as data are limited. Due to a lack of data at this time, aztreonam use should be restricted to patients with severe penicillin allergy for whom beta-lactam therapy is contraindicated.

Fluoroquinolones

Although fluoroquinolones are classified as Pregnancy Category C, they are generally contraindicated in pregnancy. They are widely distributed in the body and routes of elimination differ among the agents. Protein binding ranges from 20% to 50%. Fluoroquinolones may be safe during the first trimester but are not recommended, as they were associated with fetal harm in previous animal studies. There is a suggested association with fluoroquinolones and renal toxicity, cardiac defects, and central nervous system toxicity in the fetus. Animal data have demonstrated bone and cartilage damage in the fetus. Data are inconsistent and more studies are needed to confirm these associations. Authors of a recent literature review concluded that fluoroquinolones may not pose the same risks to humans as they do to animals because of weak study designs, small sample sizes, and confounding variables in the published human studies; however, the data are still not adequate to support their routine use in pregnancy. Because of the current evidence, fluoroquinolone use in pregnancy is only recommended if there is no alternative[9].

Tetracyclines

Labeled as Pregnancy Category D, tetracyclines have proven teratogenicity in humans.¹⁹ They are associated with congenital defects, with large doses being linked to maternal liver toxicity.¹⁹ In general, tetracyclines penetrate into tissues and body fluids with the degree of penetration correlated to lipid solubility (minocycline > doxycycline > tetracycline).²⁶ Routes of elimination differ by agent and protein binding widely ranges by agent.²⁶ Tetracyclines cross the placenta and when used beyond the second trimester, they can bind to calcium in the developing fetus and cause permanent discoloration of bones and teeth. They are contraindicated past the fifth week of pregnancy.¹⁹ Tetracyclines should be used with extreme caution, if at all, in pregnancy, and only when a clear benefit has been established. In rare cases, doxycycline may be considered in pregnant women who have life-threatening tick-borne illnesses.

Oxazolidinones

Currently, there are a lack of pharmacokinetic and controlled studies of linezolid and tedizolid in pregnant women. Linezolid distributes well into tissue and has 31% protein binding, whereas tedizolid is highly protein bound (70–90%).²⁶ Positive maternal outcomes without fetal teratogenesis were detailed in a case report of 4 weeks of linezolid use starting at 14 weeks of pregnancy.³⁹ Both agents are Pregnancy Category C and animal studies in mice, rats, and rabbits have not shown teratogenic effects.¹⁹ However, in rats, linezolid and tedizolid resulted in mild fetal toxicities, including decreased fetal body weight and reduced ossification of the sternebrae at maternally toxic doses¹⁰.²⁶ A reduction in fetal weight and increase in costal cartilage abnormalities were seen with tedizolid use in mice with the absence of maternal toxicities (4-fold increase in the estimated human exposure based on area under the concentration curve [AUC]).²⁶ Fetal weight loss and maternal toxicity were identified with tedizolid use in rabbits. However, in a prenatal and postnatal toxicity study of rats, no offspring defects were documented with tedizolid used at the highest tested dose equivalent to the plasma AUC exposure of the 200 mg/day clinical human dose.²⁶ Oxazolidinones could be considered for use during pregnancy.

Daptomycin

Daptomycin is Pregnancy Category B.¹⁹ It is highly protein bound (90–93%), has a volume of distribution of 0.1 L/kg, and is primarily excreted by the kidneys.²⁶ There are no controlled trials with daptomycin (a cyclic lipopeptide) during pregnancy. However, isolated reports suggest that daptomycin may be safe to use. In the first report, a woman in the third trimester was successfully treated with daptomycin 4 mg/kg for 14 days for vancomycin- and ampicillin-resistant *Enterococcus faecium* pyelonephritis. In another report, a 14-week pregnant patient with a history of drug abuse was successfully treated with daptomycin 6 mg/kg for 6 weeks for tricuspid valve endocarditis. No adverse effects were noted in the patient or in the neonate at birth in either report. In animal studies, daptomycin was administered to rats and rabbits at doses 2–4 times human doses with no evidence of harm to the fetus. Daptomycin should be used in pregnancy only if the benefit outweighs the risk^[11].

Metronidazole

Metronidazole is classified as Pregnancy Category B; however, it is contraindicated in the first trimester of pregnancy.¹⁹ Several trials have linked metronidazole use in asymptomatic *Trichomonas vaginalis* infection or increased fetal fibronectin concentrations with increased preterm birth (PTB) rates. Multivariate analysis showed no relationship between metronidazole exposure at any time during pregnancy with PTB, low birth weight, or congenital abnormalities.⁴⁸ Vaginal metronidazole should be used with caution during pregnancy, as a potential link with congenital hydrocephalus has been suggested.⁴⁹ Metronidazole also remains a guideline-recommended therapy for bacterial vaginosis and *Trichomonas* infections in pregnancy; however, risk of repeat exposure during pregnancy is unknown and a reduced risk of PTB has not been clearly established.

Nitrofurantoin

An antibacterial specific to the urinary tract, nitrofurantoin is considered Pregnancy Category B.¹⁹ Animals exposed to doses 25 times that of normal human administration did not result in teratogenic effects. Because of limited systemic exposure and its relatively benign adverse effect profile combined with proven effectiveness, nitrofurantoin is commonly used in UTI management in pregnant women. A recent meta-analysis of eight studies did not demonstrate any association of nitrofurantoin exposure in women with major congenital malformation. The meta-analysis did include three case-controlled studies that revealed a significant increase (OR 1.22; 95% CI 1.02–1.45) in malformations, including an increased risk in hypoplastic left heart (OR 3.07).⁵⁰ Although not commonly reported, nitrofurantoin may increase the risk of hemolytic anemia in pregnant patients with severe glucose-6-phosphate dehydrogenase deficiency as indicated by one case report¹². Although there may be some concern in the recent meta-analysis requiring further investigation of possible teratogenic effects, nitrofurantoin remains an option for treatment of UTI and prevention of recurrent UTI in pregnant women

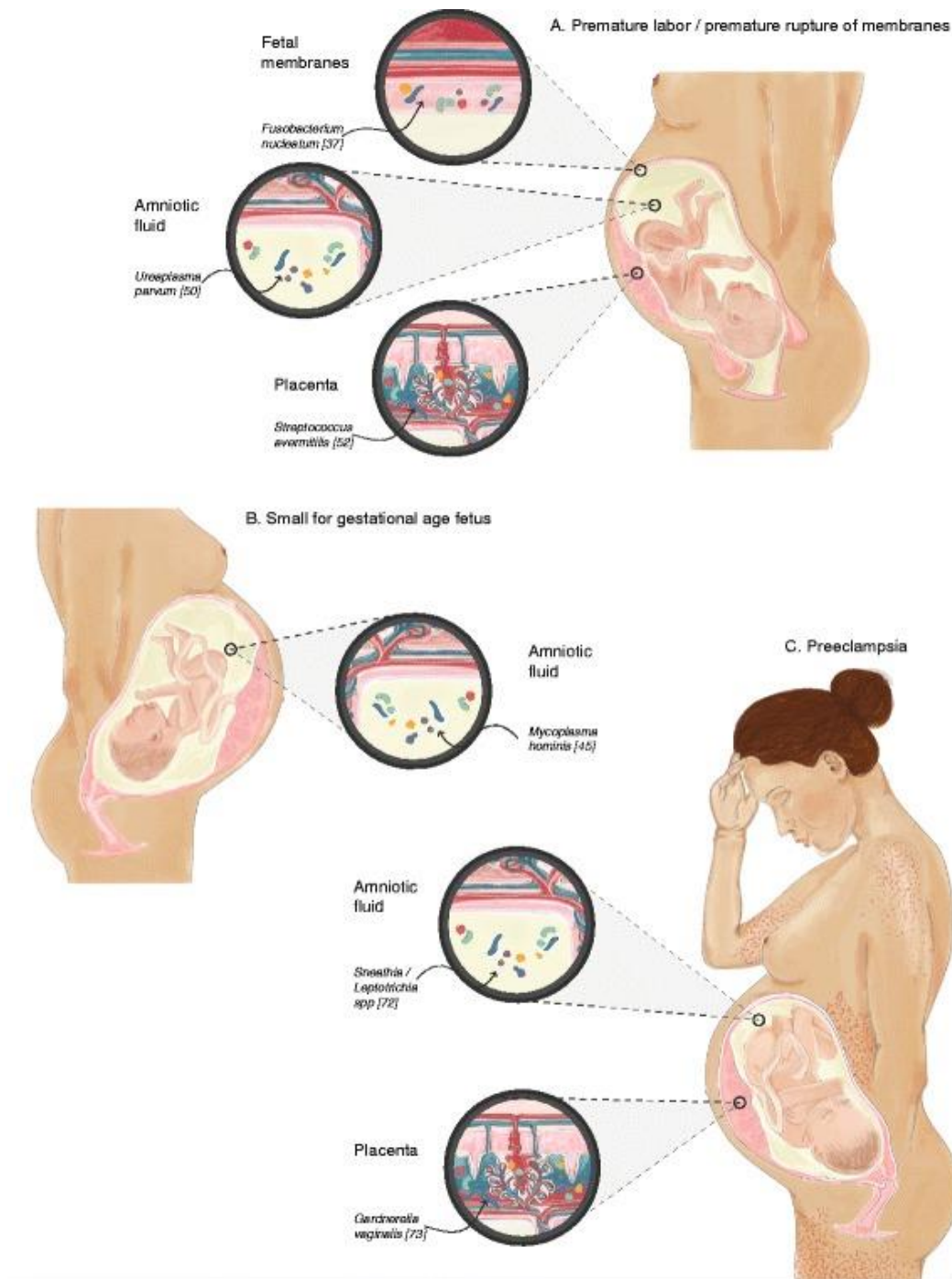


Fig:1 Antibiotics effect on pregnancy

The fetoplacental microbiome in various pregnancy complications involving the placenta. Examples of specific disease-associated species are shown. **a** Bacteria are found in the placenta (*Streptococcus avermitilis*), fetal membranes (*Fusobacterium nucleatum*), and amniotic fluid (*Ureaplasma parvum*) in cases of premature labor and premature rupture of membranes. **b** Bacteria are present in amniotic fluid (*Mycoplasma hominis*) in small-for-gestational-age (intrauterine growth restriction) fetuses. **c** Bacteria are present in the placenta (*Gardnerella vaginalis*) and amniotic fluid (*Sneathia/Leptotrichia spp*) in cases of preeclampsia. A pregnant woman is illustrated, exhibiting headache, edema, and petechia

Benefits and harms of antibiotics

Most pregnant women are prescribed to use a variety of medicines. The drugs may have teratogenic influences on the fetus during pregnancy. In addition, drugs used during breastfeeding can have severe effects on the health of the baby. During pregnancy and lactation, one of the most used drugs is antibiotics frequently prescribed by doctors [13].

Side effects of misuse of antibiotics

Antibiotic resistance is a natural phenomenon, but it can be caused by the misuse of antibiotics. The plans to inhibit his misuse of antibiotics can have consequent worldwide results for inhibiting the expansion of antibiotic-resistant bacterial strains. There is some data that antibiotic implementation can lead to severe side effects such as gastrointestinal abnormalities, allergic reactions, and cardiac arrhythmias, and death. The expansion of resistant bacteria is recognized as a main problematic issue linked to the overuse of antibiotics. It is claimed that the use of antibiotics during fetal-neonatal life has an opposing and long-term influence on the maternal intestinal microbiota and the maternal vaginal microbiota. Furthermore, it can lead to the expansion of allergic illnesses. Antibiotics may also inhibit and delay with the beginning colonization of the baby's gut microbiota. This inhibition may restrict the development and growth of the baby's immune system, causing diseases and allergies. Overuse of antibiotics for pregnant women is linked to the presence of many antibiotic-resistant organisms, as the rate of erythromycin-resistant *Streptococcus* (Group B) -one of the selective antibiotics after premature rupture of membranes (PROM) prescribed in most British hospitals- and reaches 35%.

In conclusion, according to the results of researches, as specifically evidences published by the American Dental Association with American Obstetricians, the use of some antibiotics during pregnancy are allowed and can be used normally and safely by pregnant women [14].

Conclusions

The use of antibiotics in pregnancy requires careful assessment and a discussion of risk versus benefit to mother and fetus, both short and long term. In general, many antibiotics are considered safe in pregnancy, especially beta-lactams, macrolides, clindamycin, and fosfomycin; however, additional data are needed for the majority of antibiotic classes. Emerging antibiotic resistance will certainly play a role in future use of broad-spectrum and alternative agents in pregnancy. Pharmacists play a prominent role in risk assessment and evaluation of available evidence for optimal antibiotic selection, dosing, duration of therapy, and monitoring. Pharmacists should also be aware of the new detailed product labeling for pregnancy that was implemented in the summer of 2015.

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