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Prophylaxis and Treatment of Anthrax in Pregnant Women: A Systematic Review of Antibiotics

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Abstract

Objective—To review the safety and pharmacokinetics of antibiotics recommended for anthrax post-exposure prophylaxis and treatment in pregnant women.

Data Sources—Articles were identified in the PUBMED database from inception through December 2012 by searching the keywords ([“pregnancy]” and [generic antibiotic name]). Additionally, hand searches of references from REPROTOX, TERIS, review articles and Briggs' Drugs in Pregnancy and Lactation were performed.

Methods of Study Selection—Articles included in the review contain primary data related to the safety and pharmacokinetics among pregnant women of five antibiotics recommended for anthrax post-exposure prophylaxis and treatment (ciprofloxacin, levofloxacin, moxifloxacin, doxycycline, amoxicillin), and of nine additional antibiotics recommended as part of the treatment regimen (penicillin, ampicillin, linezolid, clindamycin, meropenem, doripenem, rifampin, chloramphenicol, or vancomycin).

Tabulation, Integration and Results—The PUBMED search identified 3850 articles for review. Reference hand searching yielded nine additional articles. In total, 112 articles met the inclusion criteria.

Conclusions—Overall, safety and pharmacokinetic information is limited for these antibiotics. Although small increases in risks for certain anomalies have been observed with some antibiotics recommended for prophylaxis and treatment of anthrax, the absolute risk of these antibiotics appears low. Given the high morbidity and mortality associated with anthrax, antibiotics should be dosed appropriately to ensure that antibiotic levels can be achieved and sustained. Dosing adjustments may be necessary for the beta lactam antibiotics and the fluoroquinolones to achieve therapeutic levels in pregnant women. Data indicate that the beta lactam antibiotics, the fluoroquinolones, and, to a lesser extent, clindamycin enter the fetal compartment, an important consideration in the treatment of anthrax, as these antibiotics may provide additional fetal benefit

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in the 2nd and 3rd trimesters of pregnancy. Additional well designed safety and pharmacokinetic studies are needed.

Introduction

During the 2001 anthrax attacks, approximately 10,000 people were offered antibiotic prophylaxis after potential exposure to *B. anthracis* spores in contaminated mail, including many pregnant women.[1] Following this intentional release of anthrax, the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG) issued clinical guidance for anthrax post-exposure prophylaxis and treatment during pregnancy.[2, 3] Anthrax remains a national concern[4–6] and was recently described as "one of the most serious threats to national security and the health of the nation".[5] As such, the CDC is updating antibiotic post-exposure prophylaxis (PEP) and treatment guidance for anthrax, including recommendations specific to pregnant women, and review of safety and pharmacokinetic data provides an evidence-base for these recommendations.

B. anthracis manifests in three main forms of infection, cutaneous, gastrointestinal and inhalation,[7] and is a highly lethal infection with historical mortality rates as high as 88% for the inhalational form.[8] In the bioterrorist event in 2001, exposure to spores resulted in cutaneous and inhalational forms, and despite aggressive treatment, non-pregnant adults with inhalation anthrax experienced a 45% mortality rate.[9] A historical analysis of published anthrax cases in pregnant women confirmed that this infection can result in maternal death and fetal deaths.[10] Taken together, these data suggest pregnant women are at-risk for morbidity and mortality if infected with *B. anthracis* and highlight the importance of post-exposure prophylaxis and treatment of anthrax in pregnant women.

Post-exposure prophylaxis for non-pregnant adults potentially exposed to *B. anthracis* spores involves antibiotic therapy for sixty days in combination with 3 doses of the U.S.-licensed anthrax vaccine given at 0, 2, and 4 weeks. This PEP regimen is intended to prevent inhalation anthrax by killing bacteria as they germinate from the spore form to the active vegetative bacteria.[11, 12] Oral ciprofloxacin, levofloxacin, moxifloxacin, doxycycline or amoxicillin (assuming a susceptible strain) are recommended for PEP in the general population;[12] however, their long-term use during pregnancy raises questions about fetal safety. Among the antibiotics recommended for PEP, fluoroquinolones and doxycycline are typically avoided during pregnancy due to fetal safety concerns; avoidance of fluoroquinolones is based on studies demonstrating cartilage damage in young beagle dogs receiving postnatal treatment,[13, 14] and doxycycline avoidance is based on concerns of dental staining seen with the tetracyclines use during pregnancy, and of fetal bone growth delays and skeletal anomalies, which have been reported in animal studies.[15–18]

Intravenous multidrug therapy with three antibiotics is recommended for the treatment of inhalation or severe anthrax, and nine additional antibiotics (penicillin, ampicillin, linezolid, clindamycin, meropenem, doripenem, rifampin, chloramphenicol or vancomycin) have been suggested as part of the treatment regimen.[12, 19] Among these recommended antibiotics, fetal safety concerns have been raised with rifampin and chloramphenicol.[20, 21] Rifampin

has been associated with growth retardation, spina bifida and cleft palate in pregnant animal studies.[20] In addition, rifampin induces the p450 enzymatic pathway and can accelerate the degradation of Vitamin K, which raises concerns about neonatal bleeding with prenatal exposure.[20] Chloramphenicol has been associated with fetal anomalies, delayed fetal growth and fetal death in animal studies,[21] and "Grey Baby Syndrome", cardiovascular collapse due to chloramphenicol toxicity, has been reported in neonates, including in one neonate with both in utero and post-natal exposure.[21, 22]

Safety concerns are not the only consideration when recommending antimicrobial prophylaxis and treatment for anthrax in pregnant women. The pharmacokinetics of these antibiotics may differ during pregnancy.[23–26] To ensure appropriate dosing, physiologic changes that influence drug absorption and clearance need to be taken into account when selecting antibiotics for prenatal use.

In accordance with MOOSE guidelines, we conducted a systematic review of the safety and pharmacokinetic data of the 14 antibiotics most recently recommended by CDC for anthrax prophylaxis and treatment.[11,12, 19] The goals of this systematic review are to address the following questions:

1. What are the risks of congenital anomalies and neonatal complications with pregnancy-related exposure to these antimicrobials?
2. What is known about the pharmacokinetics of these antibiotics in pregnant women and how does this influence dosing recommendations?

Sources

A search strategy was developed in conjunction with an expert CDC librarian. Articles were identified through the PUBMED database from inception until December 2012 by searching the keywords ("pregnancy" and [generic antibiotic name]), and limited to articles published in English in humans. We also hand searched REPRORISK and TERIS, electronic resources that summarize the safety of medications during pregnancy, and references from antibiotic review articles.[14, 27, 28] We reviewed the Food and Drug Administration Pregnancy Category ratings for each antibiotic; a description of these ratings is available at http;// accessdata.fda.gov/scripts/cder/drugsatfda. Lastly, we hand searched the references included in the specific antibiotic sections of the textbook, Briggs' Drugs in Pregnancy and Lactation, a commonly cited practical reference obstetricians use when evaluating medication risks in pregnancy.[29]

Study Selection

For inclusion, articles needed to: 1) contain peer-reviewed primary data related to the use of antibiotics recommended by CDC (ciprofloxacin, levofloxacin, moxifloxacin, doxycycline, amoxicillin, penicillin, ampicillin, linezolid, clindamycin, meropenem, doripenem, rifampin, chloramphenicol, vancomycin) for anthrax prophylaxis and treatment, and 2) describe safety during pregnancy (restricted to articles with 5 or more cases) or contain pharmacokinetic data during pregnancy (no restriction on the number of cases). Unpublished reports, abstracts, duplicate reports, policy guidelines and review articles were excluded from the

review because they did not contain primary data. However, these articles were used to identify additional primary references. No restriction was placed on the timing in gestation of antibiotic administration for article inclusion; early pregnancy exposure was reported with respect to anomalies. Articles describing treatment of preterm labor, preterm premature rupture of membranes, and premature rupture of membranes were excluded due to the late antibiotic exposure and the confounding factors contributed by these conditions. Similarly, studies related to the treatment of syphilis were excluded because syphilis-related adverse neonatal outcomes would complicate study interpretation.

One reviewer (DMD) screened all titles and relevant abstracts identified through PUBMED and the hand searches, and selected articles for full-text review that contained primary clinical data involving each of the specific antibiotics used during pregnancy. Case series, case-control studies and prospective and retrospective cohort studies were included. A second reviewer (DJJ) independently extracted data from 20% of the articles, with 100% concordance between the two reviewers. Experts in obstetrics, anthrax, emerging infectious diseases, emergency preparedness, birth defects, and pediatrics reviewed the manuscript and the cited references to ensure accuracy and completeness.

Results

The PUBMED database search identified 3850 articles and the additional hand searches of review articles, REPRORISK and TERIS databases (periodically updated online database maintained by Thomson Reuters Micromedex Solutions) and relevant references in the textbook Briggs' Drugs in Pregnancy and Lactation revealed 9 articles. Overall, 112 papers were included in this review (Tables I and II).

Ciprofloxacin

Nine studies (1100 exposed women) described ciprofloxacin use in pregnancy.[30–39] In the largest prospective study of 549 quinolone-exposed pregnancies, no increased risk for adverse obstetrical outcomes was observed, and the malformation rate among 390 live-born infants exposed to fluoroquinolones during the first trimester of pregnancy (4.9%) was similar to previously reported malformation rates. Among these were 70 ciprofloxacin-exposed infants, of which 2 (4%) were reported as malformed.[32] Additionally, this report included prospective and retrospective data reported to the manufacturer's registry and other databases. Although no unexposed comparison group was included, six live-born infants with major or minor malformations were reported among 116 pregnancies with prenatal fluoroquinolone exposure, well within the expected rate of major and minor malformations.[4032] Also included in this report were 25 retrospective cases of malformed children with prenatal fluoroquinolone exposure, eight of whom were exposed to ciprofloxacin.[32] Given the lack of an unexposed comparison group and the inclusion of minor malformations, the interpretation of these results is difficult.[32] Nevertheless, when combined, the reported data from these 690 pregnancies did not detect a specific pattern of anomalies with ciprofloxacin or with any prenatal fluoroquinolone exposure.[32] In seven additional studies, no specific pattern of birth defects was reported in association with ciprofloxacin use.[31, 33–39, 41] Among a small database cohort of 130 women who filled a

fluoroquinolone prescription during the first trimester of pregnancy or 30 days before conception, 4 children with anomalies (2 with exposure to ciprofloxacin) were reported; however, rates of congenital malformations among infants born to exposed (3.1%) and unexposed (4.2%) women were similar (Prevalence Rate=0.7, 95% Confidence Interval (CI) 0.3–2.0).[38] No increased risk of stillbirth, perinatal death, preterm delivery or low birth weight was observed in that study.[38] Cooper et al., in their largest retrospective cohort study of 24,521 infants with fetal antibiotic exposure compared to 3400 infants without exposure, included 588 infants exposed to ciprofloxacin during pregnancy. Ciprofloxacin exposure anytime during pregnancy was not associated with malformations (Relative Risk (RR)=0.97, 95% (CI) 0.58–1.36), nor was exposure in early pregnancy (n=439, RR=0.64, 95% CI 0.31–1.3).[31] Three studies of prenatal exposure to ciprofloxacin did not observe an association with developmental delays, musculoskeletal dysfunction.[33, 37, 41]

Few investigations have directly assessed the pharmacokinetics of quinolones during pregnancy. (Table III) Serum drug levels of ciprofloxacin among 40 pregnant women were lower than among non-pregnant women (0.18 μg/ml vs. 1.06 μg//ml 4 hours post administration; 0.09 μg//ml vs. 0.54 μg//ml 6 hours post administration).[42] Ciprofloxacin crosses the placenta, with amniotic fluid concentrations increasing over time.[42] Consistent with this, an ex-vivo experimental system using human placental tissue demonstrated placental perfusion and detectable ciprofloxacin drug levels in the fetal compartment.[43]

Levofloxacin

No studies evaluating the safety of levofloxacin in pregnancy were identified. Two investigations of the in-vivo maternal pharmacokinetics of levofloxacin found that levofloxacin crossed the placenta and produced fetal levels approximately 66% of maternal levels <1 hour after dosing (5.44 μg/ml vs. 8.18 μg/ml).[44, 45] Similar to ciprofloxacin, ex-vivo placental perfusion models demonstrated transplacental transfer of levofloxacin but at lower rates than in vivo studies.[43]

Moxifloxacin

No studies evaluating the safety of moxifloxacin in pregnancy were identified. Moxifloxacin has been demonstrated in umbilical cord blood and amniotic fluid after maternal administration.[44, 46] Maternal pharmacokinetics of moxifloxacin found that moxifloxacin crossed the placenta and produced fetal levels approximately 90% of maternal levels <1 hour after dosing (3.57 μg/ml vs. 4.96 μg/ml). Additionally, comparison of moxifloxacin plasma levels between postpartum and non-pregnant women after a single intravenous dose demonstrated lower peak serum concentrations and higher volume of distribution among the postpartum women (1.96 μg/ml vs 4.95 μg/ml.)[47]

Doxycycline

We identified five articles (2164 exposed pregnant women) on the safety of doxycycline in pregnancy.[31, 48–50] The largest of these, the retrospective cohort by Cooper et al., included 1843 exposures during pregnancy, and reported similar rates of congenital anomalies among infants born to doxycycline-exposed and unexposed women, in the first 4 months of pregnancy (n=1691, RR=0.85, 95% CI 0.59–1.23) or anytime during the pregnancy

(RR=0.84, 95% CI 0.59–1.19)[31] An elevated relative risk of 2.96 (95% CI 0.75–11.67) was reported for orofacial clefts with doxycycline use in the 1st four lunar months, but this increase was not statistically significant. In a case-control study, 56 (0.30%) of 18,515 infants with congenital anomalies were exposed to doxycycline compared to 63 (0.19%) of 32,804 control infants (p=0.01). Using case-matched control paired analysis, a marginally statistically significant association (Odd Ratio [OR] =1.6, 95% CI 1.0–2.4) was reported with doxycycline exposure during pregnancy and congenital abnormalities. However, exposure in the 2nd and 3rd gestational month, the period of embryogenesis, was not significantly associated with anomalies (OR =1.8, 95% CI 0.7–5.0).[48] In a cohort study of maternal antibiotics and orofacial clefts, 2 cases of doxycycline/tetracycline exposure in the 2nd month of gestation, suggested an increased risk of cleft lip with/without cleft palate (CL +/−CP), (POR=7.30, 95% CI 1.81–29.46); however the risk estimate was no longer statistically significant when the exposure interval was extended to 3 cases exposed in the 1st trimester.[51] In the National Birth Defects Prevention Study, the adjusted odds ratio (AOR) for all oral clefts associated with periconceptional and early pregnancy exposure to tetracyclines was not significant (AOR=2.0,95% CI 0.6–6.7).[52] In a small prospective cohort study (n=34), no anomalies were reported in association with doxycycline exposure at one year of follow up.[50] Regarding pharmacokinetics, the only study that we identified demonstrated that systemic drug concentrations among women during the second trimester were similar to those in non-pregnant subjects.[53]

Amoxicillin

We identified fourteen studies (15,917 exposed pregnant women) on the safety of amoxicillin during pregnancy.[30, 31, 36, 54–62] The large retrospective cohort by Cooper et al, included 14,534 amoxicillin-exposures, which showed no increased risk of major congenital anomalies, with exposure during the 1st four lunar months (RR=1.09, 95% CI 0.86–1.37) or any time during pregnancy (RR=0.99, 95% CI 0.80–1.23). A non-statistically significant increased risk of orofacial clefts (RR=1.67, 95% CI 0.56–5.04) was observed with amoxicillin exposure in the 1st 4 lunar months of pregnancy.[31] Findings from six smaller studies did not confirm an increased risk of defects.[36, 56, 57, 59–61] A recent case-control study of 877 case infants with CL+/−CP found a higher rate of first trimester amoxicillin-exposure among mothers of case-infants (n=28) than among mothers of control-infants (OR=2.0, 95% CI 1.0–4.1).[54] A similar finding was seen in an earlier case-control study (n=1374 cases); a statistically significant association between amoxicillin exposure and CL +/−CP (n=7) was observed. The prevalence odds ratios were 15.9 (95% CI 4.9–51.2) when compared to population controls and 5.4 (95% CI 1.9–15.4) when compared to malformed controls.[55] However, a recent large cohort study (n=806,011) found that maternal antibiotic exposure early in pregnancy was not associated with an increased risk of CL+/−CP (POR=1.08; 95% CI 0.89–1.30).[51] In that study, only 9 cases were exposed to amoxicillin in the 1st trimester of pregnancy and overall none of the penicillins were associated with an increased risk.[51] No evidence of an increased risk of congenital anomalies was seen in four other studies of amoxicillin plus clavulanate use during critical time periods.[30, 58, 61, 63]

In a study in which a single oral dose of amoxicillin was given to pregnant women,[23] renal clearance and secretion were significantly higher during pregnancy than during the

postpartum period. Amoxicillin had a shorter half-life (by ~25%) during pregnancy when compared to postpartum controls. Moreover, area under the concentration time curves and peak concentration were significantly lower during pregnancy.[23] An investigation of oral absorption and subsequent systemic amoxicillin levels found similar results.[64] In contrast, studies of intravenous amoxicillin during pregnancy and/or labor found similar systemic levels as seen in non-pregnant subjects.[65, 66] Regarding transplacental passage, intravenous maternal amoxicillin used to prevent neonatal group B streptococcus (GBS) infection crossed the placenta at levels presumed to be adequate to prevent the infection.[66]

Penicillin

We identified eight studies (a total of 1685 exposed pregnancies) of the association between prenatal penicillin exposure and congenital anomalies among infants.[52, 55, 63, 67–71] Overall, no specific pattern of anomalies was detected. Some small studies reported increases in isolated birth defects, but no specific defects were consistently reported.[52, 55, 67–71]

We reviewed seven pharmacokinetic studies of penicillin use in pregnancy[72–78] which demonstrated rapid transplacental penicillin passage as early as 10 weeks gestation.[74] Amniotic fluid concentrations were comparable to maternal serum levels[78] and were considered sufficient to inhibit penicillin-sensitive bacteria.[72, 73, 75, 78] Based on renal elimination rates of penicillin in the 3rd trimester, a four-hour dosing interval is considered optimal to achieve adequate amniotic fluid levels that will inhibit penicillin-sensitive bacteria.[72]

Ampicillin

We identified 11 studies (with data on 7658 exposed pregnancies) on the association between prenatal ampicillin exposure and congenital anomalies.[36, 55, 69, 79–84] A case-control study involving 390 infants with congenital heart disease demonstrated an association between prenatal ampicillin use and congenital heart disease with a prevalence ratio estimate of 3.3 (90% CI 1.3–8.1), however, it was based on only 14 cases and controls (7 in each group) that were exposed during pregnancy.[81] In contrast, a subsequent case-control study of 298 children with congenital heart disease did not identify this association with ampicillin exposure during the 1st trimester (prevalence OR=1.2, 95% CI 0.58–2.3).[84] Similarly, a large population-based case-control study of 1644 women prenatally exposed to ampicillin found the rate of malformed newborns exposed to ampicillin (7.2%) was comparable to controls (6.9%), and no increased risk of cardiovascular anomalies was reported.[79, 82] Instead, cleft palate (CP) (OR=2.5, 95% CI 1.1–5.4), syndactyly (OR=2.4, 95% CI 1.2–4.8), and abdominal wall defects (OR=15.2, 95% CI 1.1–127.8) were seen more frequently among infants whose mothers had 1st trimester ampicillin exposure.[79, 82] When the time period for exposure to ampicillin was restricted to the critical period of organogenesis for each of these defects, the risk for abdominal defects was no longer statistically significant (OR=13.0, 95% CI=0.7–230.8).[82] In contrast, a large cohort study (n=806,011) evaluated maternal antibiotic exposure early in pregnancy and reported no increased risk of CP (POR=1.14;95% CI 0.86–1.51).[51] First trimester ampicillin or pivampicillin (an ester of ampicillin used to increase oral bioavailability) was observed in

only three cases of CP.[51] Although isolated minor defects were observed in smaller studies, no specific pattern was seen.[36, 55, 63, 69, 80, 81, 83, 84]

Increased elimination, shortened serum half-life and increased total body clearance of ampicillin has been seen in pregnant women, compared to non-pregnant women.[85] The mean peripheral volume of distribution was twice as large as that of non-pregnant adults, and mean plasma levels of ampicillin were ~50% lower during pregnancy.[25, 86–88] We identified 19 studies[73, 87–103] all of which confirmed transplacental ampicillin passage, resulting in levels in the fetal circulation deemed adequate to prevent and treat susceptible infections[73, 89–105]

Linezolid

We identified no articles on the safety or pharmacokinetics of linezolid during pregnancy.

Clindamycin

We identified one randomized controlled study of 276 women given prenatal clindamycin for six weeks in the 2nd and 3rd trimester, as treatment for genital mycoplasma to prevent low birth weight. Similar rates of malformations were reported among exposed (3.9%) and unexposed infants (4.4%), and no differences in birth weight were detected.[106] Maternal administration of clindamycin, based on non-pregnant doses resulted in serum concentrations similar to previously reported levels in male subjects[107] and in non-pregnant women.[108] Pharmacokinetic studies demonstrated transplacental passage of clindamycin,[107, 109–112] and when multiple doses were used, clindamycin and its bioactive metabolites were demonstrated in the amniotic fluid and in fetal tissues.[111] However, the distribution of clindamycin into the fetal compartment appears decreased by increased protein binding, which may be increased during pregnancies complicated by infection.[109]

Meropenem

We identified no articles on the safety of meropenem during pregnancy. Pharmacokinetic data were limited to a single ex-vivo human placenta perfusion model that demonstrated transplacental passage, with dose-dependent levels in the fetus that were lower than maternal serum levels. Based on these limited data, these levels were considered subtherapeutic to treat many fetal infections.[113]

Doripenem

We identified no articles on the safety or pharmacokinetics of doripenem during pregnancy.

Rifampin

We identified nine articles on the safety of prenatal exposure to rifampin (332 women on rifampin alone or in combination with other antimicrobial agents).[114–122] No specific pattern of congenital anomalies was observed, and most outcomes were healthy pregnancies. In the largest case series of rifampin use among 226 pregnant women, nine children were noted to have major or minor congenital anomalies, but no specific pattern was reported.[123] Ten rifampin-exposed newborns were reported to have “hemorrhagic tendencies” but no further clinical information was provided.[123] Based on one case report, rifampin crossed the

placenta and was measurable in the amniotic fluid and in fetal tissue[124]; no additional pharmacokinetic data are available.

Chloramphenicol

We found five studies (totaling 290 pregnant women) with prenatal chloramphenicol exposure.[67, 125–128] Data from these five observational studies, did not suggest an increased risk of birth defects with maternal chloramphenicol use.[67, 125–127] Chloramphenicol crosses the placenta producing cord blood levels 30–106% of maternal levels.[129, 130]

Vancomycin

We identified two studies of the safety of vancomycin during the 2nd and 3rd trimester of pregnancy (with data on 23 pregnancies).[131, 132] Data are not available on the incidence of birth defects with maternal use of vancomycin, but other neonatal toxicities were evaluated in these studies. Because renal and ototoxicity are a concern with the vancomycin use, ten neonates exposed in utero were evaluated post-delivery; no defects were demonstrated.[132] Apgar scores were normal in neonates exposed to vancomycin at the time of cesearean delivery.[131] Vancomycin readily crosses the placenta[131–136] and enters the amniotic fluid and cord blood. In two studies, increased vancomycin doses were needed during pregnancy to achieve therapeutic serum levels[132, 134] but another study found that despite increased volume of distribution and plasma clearance, vancomycin levels remained in the therapeutic range during pregnancy without dosage adjustment.[135]

Discussion

This review summarizes safety and pharmacokinetic data during pregnancy for 14 antibiotics recommended for prophylaxis and treatment of anthrax. Pre-event analysis of the safety and pharmacokinetics of these antibiotics informs national guidelines and provides women and their health care providers with needed information, possibly resulting in improved adherence to public health recommendations during an anthrax event.

Ciprofloxacin and doxycycline are first-line antibiotics for anthrax post-exposure prophylaxis for adults. Levofloxacin and moxifloxacin are alternative fluoroquinolones if ciprofloxacin is not tolerated or unavailable. Amoxicillin may also be used as prophylaxis against susceptible strains of anthrax. Fluoroquinolones are generally avoided during pregnancy due to concerns about potential effects on developing cartilage, based on animal studies.[13, 14, 137, 138] Our review identified no human studies that validated these concerns; instead, available data suggest it is unlikely that ciprofloxacin poses substantial fetal safety risks. Appropriate dosing of fluoroquinolones in pregnant women is not clear; limited pharmacokinetic data suggest that these renally-excreted drugs may require higher or more frequent dosing.[42, 47]

Doxycycline is also generally avoided during pregnancy due to concerns about dental staining, fetal growth delays and maternal hepatic toxicity,[15, 16, 18, 27, 139–141] concerns based on experience with prenatal tetracycline use and animal studies. In studies of prenatal doxycycline use, no neonates demonstrated dental staining or growth delays and no maternal hepatic toxicity was reported among mothers, suggesting that these risks are likely to be

low. Although not consistently demonstrated, this review does raise the question of the potential risk for orofacial clefts with the use of doxycycline. However, it is difficult to disentangle the effects of antibiotic treatment from the effects of the underlying infection; maternal febrile illness has been associated with orofacial clefts CL+/−CP as well as with other congenital abnormalities.[142143, 144] Infections, such as influenza-like illness, have also been reported in association with congenital anomalies.[145] Based on the low birth prevalence of orofacial clefts (11/10,000 livebirths), and the potential confounder of maternal febrile illness, the absolute risk oforofacial clefting with doxycycline exposure is likely to be low.

More data are needed to guide dosing for pregnant women, but the very limited data available suggest that dosing adjustments may not be necessary during pregnancy.[53] Doxycycline undergoes both hepatic and renal excretion; while these excretion mechanisms might impact doxycycline levels during pregnancy, the effects are likely to be less than for the fluoroquinolones.

Although recent reports indicate a possible association of amoxicillin with facial clefts,[54, 55] some of these results reach only borderline statistical significance.[54] In addition, if we assume a doubling of the risk[54] in the context of the estimated birth prevalence for CL+/−CP[146], the absolute risk of orofacial clefts with exposure to amoxicillin would still be considered low. A large case-control study, the National Birth Defects Prevention Study, did not demonstrated an increased risk of orofacial clefts with exposure to the penicillin drug class, which although not specified, likely included exposures to amoxicillin.[52] In addition, two large retrospective cohort studies support the notion that the risk of orofacial clefts and amoxicillin exposure is likely low.[31, 51] In terms of dosing, amoxicillin for the non-pregnant population may be insufficient to prevent anthrax in pregnant women,[23] thus, placing these women at risk of sub-therapeutic drug levels and possibly the development of antibiotic resistance.[147]

The fluoroquinolones, doxycycline and amoxicillin are not only recommended for post-exposure prophylaxis for anthrax, but, along with nine additional antimicrobials, are among those recommended as a component of the combination antibiotic treatment. Decisions regarding the administration of antibiotics for treatment of pregnant women involves assessing antibiotic safety and fetal risks, but also must take into account disease-related risks and maternal survival benefit. For the additional nine antibiotics recommended as possible treatment, no definitive evidence of an association of prenatal antibiotic use and congenital anomalies exist.

Although ampicillin was associated with isolated cleft palate in one case-control study, this association was not uniformly demonstrated.[51, 52] Based on the estimated national birth prevalence for isolated cleft palate (6/10,000 births), doubling or even tripling the risk would still lead to a low absolute risk for this anomaly to occur after ampicillin exposure. Both amoxicillin and ampicillin demonstrate associations with orofacial facial anomalies, we believe these findings are unrelated, given the phenotypes – cleft lip with and without cleft palate and isolated cleft palate -are etiologically distinct.[148]. Although meropenem and doripenem have structural similarities to the ampicillin and the penicillins, we could not

identify any safety data for these antibiotics. We were also unable to find any published reports of linezolid safety or pharmacokinetics.

Theoretical concerns of "Grey Baby Syndrome" resulting from chloramphenicol use during pregnancy were not substantiated in this review. Given that data are available for only 290 pregnancies, the potential for this syndrome to occur with prenatal exposure to chloramphenicol has not been excluded; chloramphenicol would not be a preferred antibiotic if other antibiotics are readily available. However, as a life-saving measure for a pregnant woman, particularly when meningeal involvement with anthrax is confirmed or suspected, chloramphenicol would not be contraindicated, given that this antimicrobial enters the central nervous system readily.

Maternal rifampin exposure during pregnancy was associated with newborn "hemorrhagic tendencies"[123] in one study, yet the clinical significance of this finding is unknown. A case series report of 3 neonates prenatally-exposed to rifampin was not included in our review because it contained less than 5 cases; however, in this series three neonates demonstrated substantial hemorrhagic complications and consequently, two died from blood-loss related hypovolemic shock.[118] Additionally, given that rifampin induces p450 hepatic enzymes, which can result in increased degradation of Vitamin K[14], and is capable of crossing the placenta, there is biologic plausibility for an association with neonatal bleeding. Bleeding concerns would not be a contraindication for rifampin anthrax treatment, but it would be important to ensure that all infants born to mothers receiving rifampin during pregnancy receive prophylactic Vitamin K and be monitored closely for signs of bleeding.

Pharmacokinetic data are generally lacking to inform the dosing of many of the antibiotics recommended for treatment. Fluoroquinolones may require alternative dosing for pregnant women, but more data are needed. For doxycycline, no substantial data exist to recommend differential dosing. Beta-lactam antibiotics are nearly exclusively cleared by the renal system and renal filtration is increased during pregnancy; thus, treatment of anthrax with higher doses of amoxicillin, penicillin, ampicillin, and meropenem may be necessary during pregnancy. Data are mixed regarding vancomycin dosing during pregnancy, but monitoring vancomycin levels in pregnant women treated for anthrax may ensure adequate serum levels.

This systematic review has several limitations. The body of evidence reporting safety and pharmacokinetics of antibiotic use in pregnancy is substantially limited, as is the case with 91% of drugs that are FDA licensed.[149] Given the limited data, we chose to set our inclusion criteria broadly, as to provide as comprehensive an assessment as possible of the available data within the confines of our search. However, this means that often the data are from uncontrolled studies with mostly observational data, which may actually overestimate the risks due to publication bias. In addition, we also did not restrict the antibiotics regimen by dose or timing of exposure, which may lead to less accuracy when looking at specific neonatal outcomes. Because each antibiotic has unique chemical, pharmacokinetic, and potentially safety characteristics, we did not conduct the systematic search by antibiotic class; this limits the generalizability of our results to other antibiotics in the same class. Lastly, we limited our study to searches of PUBMED and to articles published in English,

which means there may be additional data that could be included in the safety and pharmacokinetic analysis of these drugs in pregnancy.

Despite these limitations, our review is strengthened by its congruence with a similar review article by Nahum et al[27] as well as its agreement with the conclusions reached by the electronic resources REPROTOX and TERIS.[14, 18, 20, 21] Similar to these resources, this review highlights the limited exposure and adverse event data available. Although new data suggests a closer evaluation of the risk of orofacial clefts and antibiotic exposure may be warranted, we have reached similar conclusions to previous authors- all of the antibiotics suggested for prophylaxis and treatment of anthrax - have evidence of low risks during pregnancy.[27]

The limited data demonstrate the urgent need for additional safety and pharmacokinetic research in pregnant women. Given the rarity of anthrax as a naturally-occurring infection, ex-vivo models and animal research studies may be required to study the safety and pharmacokinetics of antibiotics recommended for post-exposure prophylaxis and treatment during pregnancy. Use of these antibiotics for treatment of other infections may provide opportunities to capture additional safety and pharmacokinetic data, but is limited by the lack of an ongoing national system to capture these data effectively. In an anthrax bioterrorism event, women and their fetuses will be at risk for morbidity and mortality and might even be at higher risk for maternal and fetal death[10], emphasizing the importance of substantial pre-event planning. To best inform clinical guidance, ongoing evaluation of new and existing evidence of the risks and benefits of proposed mitigating strategies or medical countermeasures are needed. Our review suggests that the 14 antibiotics recommended as part of anthrax post-exposure prophylaxis and treatment regimens for pregnant women likely pose low risk. However, dosing adjustments for pregnant women need to be considered, and future efforts to refine dosing are needed. We recommend that additional safety and pharmacokinetic studies involving this at-risk population be strongly considered to ensure adequate preparedness in the event of bioterrorism involving anthrax.

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Table 1

Summary of Antibiotic Studie

Antibiotic (# of articles) *b*	**Safety**	**Pharmacokinetics**	**REPROTOX**	**TERIS Risk/Data**	**FDA** *a*	**Briggs'**
Amoxicillin (18 articles)	2 case-control studies suggest increased risk of cleft lip with or without cleft palate, based on small numbers of exposed cases, but most studies suggest no increased risk	Limited data: Dosing adjustments are likely necessary to maintain adequate levels	2011: Acceptable for use during pregnancy	2008: Therapeutic doses are unlikely to pose a substantial risk. Data are insufficient to state there is no risk	B	Pregnancy: compatible
Ampicillin (34 articles)	1 Case-control study suggested increased risk of isolated cleft palate, based on small numbers of exposed cases, but most studies suggest no increased risk	Limited data: Dosing adjustments may be necessary	2012: Not believed to increase adverse outcomes	2010: Therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk. Data are insufficient to say there is no risk	B	Pregnancy: compatible
Chloramphenicol (7 articles)	No increased risk of congenital anomalies Inadequate data to determine risk of "Grey Baby Syndrome"	No data	2012: Avoided during pregnancy due to bone marrow toxicity and the possibility of a neonatal syndrome that includes circulatory collapse and death	2003: Teratogenic risk is unlikely based on limited to fair data. Data are insufficient to say there is no risk. Maternal treatment in late pregnancy may be associated with vascular collapse in the newborn infant	C	Pregnancy: compatible
Ciprofloxacin (11 articles)	No clear association with congenital anomalies	Limited data: Dosing adjustments may be necessary	2012: Avoided during pregnancy because fluoroquinolones are toxic to developing cartilage in experimental animal studies. No adverse effects in human pregnancy have been documented	2010: Therapeutic doses are unlikely to pose a substantial risk Data are insufficient data to state there is no risk	C	Pregnancy: Human data suggest low risk
Clindamycin (7 articles)	Data too limited to draw a conclusion	Limited data: Dosing adjustments appear unnecessary	2012: Based on experimental animal studies, not expected to increase the risk of congenital anomalies	2007: Although a small risk cannot be excluded, a high risk of congenital anomalies in the children of women treated with clindamycin is unlikely	B	Pregnancy: compatible

Antibiotic (# of articles)[b]	Safety	Pharmacokinetics	REPROTOX	TERIS Risk/Data	FDA [a]	Briggs'
Doripenem (0 articles)	Data unavailable	No data	No summary	2011: Teratogenic risk is undetermined	B	
Doxycycline (6 articles)	No clear association with specific congenital anomalies Data too limited to determine risk of fetal tooth staining, bone growth delays but unlikely	Limited data: Dosing adjustments do not appear necessary	2011: Avoided in pregnancy because other tetracyclines caused transient suppression of bone growth and with staining of developing teeth. Based on experimental animal studies and human reports, doxycycline is not anticipated to increase the risk of congenital anomalies.	2010: Therapeutic doses are unlikely to pose a substantial risk of fetal malformations Data are insufficient to state there is no risk. Risk of dental staining is undetermined, but may be substantial because other tetracyclines cause staining of primary dentition in fetuses exposed during the second and third trimester of pregnancy	D	Pregnancy: Contraindicated in 2nd and 3rd trimesters
Levofloxacin (3 articles)	No data	Limited data: Dosing adjustments may be necessary	2011: Avoided during pregnancy due to cartilage toxicity in juvenile animals. Adverse effects in human pregnancy have not been demonstrated	No summary	C	Pregnancy: Human data suggest low risk
Linezolid (0 articles)	Data unavailable	No data	2012: Linezolid does not cause congenital malformations in mice and rats at doses causing maternal toxicity, decreased embryo viability and decreased fetal weight. There are no human data.	2011: Teratogenic risk is undetermined	C	
Meropenem (1 article)	No data	No data	No summary	No summary	B	Pregnancy: Limited human data- animal studies suggest low risk
Moxifloxacin (3 articles)	No data	Limited data: Dosing adjustments may be necessary	2011: Avoided during pregnancy due to concern about cartilage toxicity shown in juvenile laboratory animals	No summary	C	

Antibiotic (# of articles)[b]	**Safety**	**Pharmacokinetics**	**REPROTOX**	**TERIS Risk/Data**	**FDA** [a]	**Briggs'**
			Moxifloxacin is not expected to increase the risk of congenital anomalies.			
Penicillin (15 articles)	No increased risk of congenital anomalies	Limited data: Dosing adjustments may be necessary to maintain adequate levels	2011: Not believed to increase adverse pregnancy outcomes	2007: No teratogenic risk based on good data	B	Pregnancy: compatible
Rifampin (11 articles)	No increased risk of congenital anomalies	No data	2011: Conflicting animal studies, human experience does not suggest increase in adverse pregnancy outcome	2007: Therapeutic disease during pregnancy are unlikely to pose a substantial teratogenic risk but data are insufficient to state there is no risk	C	Pregnancy: compatible
Vancomycin (6 articles)	No increased risk of congenital anomalies	Limited data: Dosing adjustments may be necessary but can be determined by measuring serum drug levels	2009: Based on animal studies, vancomycin is not expected to increase the risk of congenital malformations. The few human case reports are reassuring.	2006: Teratogenic risk is undetermined	B	Pregnancy: compatible

[a] The Food and Drug Administration assigns pregnancy-related drug risks to 5 categories. Category A: adequate, well-controlled studies in humans have not shown an increased risk of fetal abnormalities. Category B: animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Category C: animal studies have shown an adverse effect, and there are no adequate and well-controlled studies in pregnant women, or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus; however, the benefits of therapy may outweigh the potential risk. Category X: adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities; use is therefore contraindicated in women who are or may become pregnant.

[b] Total 121 however 9 articles with data on multiple antibiotics

Table II

Safety of Safety data for PEP antibiotics

Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
Cooper (2008)	**Ciprofloxacin** (n=588)	**Retrospective cohort** using Tennessee Medicaid data 1985–2000 Outcome: major congenital malformations ascertained by: 1) birth certificates, 2) hospital discharge data, 3) death certificates, 4) hospital records	II-2	2 categories of exposure: 1) < 4 months, 2) entire PG	Not reported	Rate of congenital malformations among exposed - 2.9%, unexposed - 3%. **Multivariable analysis:** Exposure in 1st 4 months: Relative Risk =0.64, (95% CI 0.31–1.30} Exposure any time during pregnancy: Relative Risk= 0.97 {95% CI 0.58–1.63}
Eric (2007)	**Ciprofloxacin** (n=9) Also included norfloxacin (n=1)	**Case series** in Serbia, 2001; Outcome: major and minor malformations ascertained by 1) detailed examination by pediatrician of newborns at birth, 2) pathophysiological exam of fetuses	III	1st trimester	Not reported	1 newborn had a choroid plexus cyst
Wogelius (2005)	**Ciprofloxacin** (n=130 all fluoroquinolones)	**Database** cohort in 4 Danish counties of all female residents with >20 week live birth or stillbirth; Outcome: stillbirth, perinatal death, preterm birth (PTB), low birth weight (LBW), congenital malformations	II-2	(130) 1st trimester or within 30 days before (87) during entire pregnancy	Not reported	Prevalence rate (PRR) of congenital malformations 0.7 (95% CI 0.30–2.0); 1st trimester exposed- 3.1%, unexposed 4.2%, PTB exposed 6.9%, unexposed 5 % LBW exposed 1.2% unexposed 1.9%
Loebstein (1998)	**Ciprofloxacin** (n=105) Total exposed to quinolones (n=−200) Also included: norfloxacin n=93, ofloxacin n=2, Controls exposed to other antibiotics (n= 200)	**Prospective cohort** from 4 teratogen information systems; Outcomes: congenital anomalies, developmental outcomes (based on post –delivery maternal/physician interview and Denver Developmental Scale)	II-2	(136) 1st trimester (34) 2nd trimester (30) 3rd trimester	No association between quinolone exposure and major pregnancy outcomes with the exception of lower birth rates among quinolone-exposed women (attributed to higher rates of therapeutic abortion)	No association between quinolone exposure during organogenesis and congenital malformations Relative Risk O.85 (95% CI 0.21–3.49) No difference in developmental milestones between those exposed to quinolones and those

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Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
						unexposed
Wilton (1998)	**Ciprofloxacin** (n=9)	**Meta-analysis** of cohort studies identified through Prescription Pricing Authority, United Kingdom; Outcomes: pregnancy outcome and congenital anomalies ascertained by physician questionnaire	III	(9) 1st trimester	5 live births including 1 preterm birth, 1 ectopic pregnancy, 1 spontaneous abortion, 2 elective terminations	No congenital anomalies among 5 live births with first trimester exposures.
Schaefer (1996)	**Ciprofloxacin** (n=70) Other quinolones included: Norfloxacin (n=318_, oflaxacin (n=93), pefloxacin (n=57). 2 quinolone (n=8)	**Prospective cohort** of pregnant women contacting the European Teratogen Information System, 1986–1994; Outcomes reported by mother or physician questionnaire and data from manufacturer (Bayer) registry	II-3	Ciprofloxacin only: 43 exposures during 1st trimester	Ciprofloxacin only: 42 normal births, 2 preterm births, 1 IUGR, 3 “postnatal disorder”; 15 elective terminations, 6 spontaneous abortions	Among women exposed in 1st trimester to Ciprofloxacin - 4.7% congenital anomalies among live births exposed during 1st trimester (2/43)
Koul (1995)	**Ciprofloxacin** (n=8)	**Case series** of women treated with ciprofloxacin for multi-drug resistant enteric fever, India Outcome: developmental delays and cartilage damage ascertained by clinical follow up:	III	(1) 1st trimester (6) in 2nd trimester (2) at 35 weeks	All full term pregnancies with healthy newborns and normal Apgar scores	No developmental delays or cartilage damage in 7 children followed up to 5 years. Normal growth in 6 month old exposed in 1st trimester
Berkovitch (1994)	**Ciprofloxacin** (n=10)) Norfloxacin (n=28); 38 matched women unexposed to fluoroquinolones but receiving other antibiotics	**Prospective cohort** of pregnant women who consulted Motherisk from 1989–1992, Outcome: Perinatal complications, birth weight, birth defects, and developmental milestones ascertained by follow-up interview with mother after delivery and at mean age of 27 months and confirmation with physician	II-2	(35) 1st trimester	No difference in major outcomes of pregnancy. Fetal distress and cesarean section more common in quinolone group (p=. 005). Exposed newborns had higher average birth weight (p=.05),	No malformations in exposed group 1 ventricular septal defect in unexposed group. No differences in major developmental milestones measured by Denver Developmental Scale at 11–63 months
Bomford (1993)	**Ciprofloxacin** (n=103)	**Case series** created by manufacturer (Bayer) from reports of ciprofloxacin use in during pregnancy from health professionals requesting information	III	(87) 1st trimester (2) in 1st and second trimester (4) in 2nd trimester (4) in 3rd trimester (6) unspecified	63 healthy live births; 18 therapeutic abortions, 10 SAB, 4 IUFD	8 congenital anomalies identified in association with receiving ciprofloxacin: Rubinstein-Taybi syndrome,

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Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
		Outcome: pregnancy outcome and congenital anomalies ascertained by case reporting from health professional				deformation of the right ear causing hearing loss, ventricular hypoplasia (brain), severe cognitive impairment, spasticity, blindness, hypospadias, aplasiar femur, indentation of left ear, amelia of the forearm, hip dysplasia, femur-ulna complex
Cooper (2008)	**Doxycycline** (n=1843)	**Retrospective cohort** using Tennessee Medicaid data 1985–2000 Outcome: major congenital malformations ascertained by: 1) birth certificates, 2) hospital discharge data, 3) death certificates, 4) hospital records	II-2	2 categories of exposure: 1) < 4 months, 2) entire PG Pregnancy	Not Reported	Rate of congenital malformations Exposed - 2.5% Unexposed - 3%. **Multivariable analysis:** Exposure in 1st 4 months: Relative Risk =0.85 (95% CI 0.59–1.23} Exposure any time during pregnancy: Relative Risk= 0.84 {95% CI 0.59–1.19}
Eric (2007)	**Doxycycline** (n=41)	**Case series** in Serbia, 2001; Outcome: major and minor malformations ascertained by 1) detailed examination by pediatrician of newborns at birth, 2) pathophysiological exam of fetuses	III	1st trimester	Not reported	1 malformation: diastasis of rectus abdominal muscle
Kazy/Czeizel (2007)	**Doxycycline** (n=78)	**Retrospective cohort** from Hungarian Case Control surveillance of Congenital Anomalies 1980–1996 Outcome: fetal growth retardation ascertained through registry data	III	(27) 1st month (20) in 2nd and 3rd month (20) in 2nd trimester (11) in 3rd trimester	No significant difference in: 1) mean gestational age, p=0.08 2) mean birth weight, p=0.70 Preterm births: Exposed 3.8% Unexposed 9.2% Odds ratio =0.4 (95% CI 0.1–0.4) No difference in low birth weight: Exposed 6.4% Unexposed 5.9%	

Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
					Odds ratio 1.2 (95% CI 0.5– Odds ratio 1.2 (95% CI 0.5–1.8)	
Czeizel (1997)	**Doxycycline** (n=63)	**Retrospective cohort** from Hungarian Case Control Surveillance of Congenital Anomalies 1980–1996 Outcome: congenital abnormalities ascertained through 1) registry data 2) questionnaires to parents, 3) prenatal log books	II-2	1st trimester (31) 2nd trimester (12) 3rd trimester (4) Unknown (9)	Not reported	**All 10 anomalies:** Odds ratio= 1.6 (95% CI 1.1–2.3) **Specific anomalies** Entire Pregnancy: Cleft lip and/or palate Odds Ratio= 3.9 (95% CI 1.9–8.2) Esophageal atresia = Odds Ratio 5.8 (95% CI 1.4–24.1); 2– 3 months: Neural tube defects Odds ratio= 4.5 (95% CI 1.0–20.1)
Horne (1980)	**Doxycycline** (n=54)	**Prospective cohort** of pregnant women divided into 3 groups: **A.** Doxycycline 1st trimester and 2nd trimester if culture positive **B.** Doxycycline 1st trimester only **C.** Controls – routine care Outcome: Pregnancy outcome and abnormalities ascertained by clinical follow up and by maternal report at 1 year of age	III-3	(50) 1st trimester only (3) 1st and 2nd trimester (1) unknown	Percentage of fetal loss : 15% Group A, 25% Group B and 25% Group C. Percentage of normal, full term deliveries : 83% Group A, 75% Group B and 75% Group C	No fetal anomalies reported among 43 infants 1 year old infants (mothers exposed in the 1st and 2nd trimester)
Eric (2012	**Amoxicillin (n=128) Amoxicillin-clauvulanate (n=50)**	**Prospective cohort** of 6992 pregnant women in maternity hospitals in Croatia	II-2	1st trimester (40) 2nd trimester (30) 3rd trimester (47) Unspecified (85)	Not reported	6 fetuses with malformations: Urogenital system, short lingual frenulum (1), hypospadias, talipes valgus, micrognathia, right ear flap
Molgaard-Nielsen (2012)	**Amoxicillin (n=9 cases)**	**Prospective cohort** of 806, 011 livebirths in Denmark from 1996–2008 Outcome: orofacial clefts	II-2	1st trimester (9) 2nd month (2) 3rd month (1)	Not reported	All antibiotics: POR Cleft lip with or without palate =1.08 {95% CI 0.89–1.30}

Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
		by exposure to antibiotics				POR Cleft Lip alone=1.14 {95% CI 0.86–1.51}
Cooper (2008)	**Amoxicillin** (n=14534)	**Retrospective cohort** using Tennessee Medicaid data 1985–2000 Outcome: major congenital malformations ascertained by: 1) birth certificates, 2) hospital discharge data, 3) death certificates, 4) hospital records	II-2	2 categories of exposure: 1) < 4 months, 2) entire PG	Not reported	Rate of congenital malformations Exposed - 3% Unexposed - 3%. **Multivariable analysis**: Exposure in 1st 4 months: Relative Risk =1.09 (95% CI 0.86–1.37} Exposure any time during pregnancy: Relative Risk= 0.99 {95% CI 0.80–1.23}
Eric (2008)	**Amoxicillin** (n=81) **Amoxicillin-clauvulanate** (n=12)	**Case series** in Serbia, 2001; Outcome: major and minor malformations ascertained by 1) detailed examination by pediatrician of newborns at birth, 2) pathophysiological exam of fetuses	III	Amoxicillin: (32) 1st trimester (27) 2nd trimester, (43) 3rd trimester; 12 used Augmentin: (8) 1st trimester (3) 2nd trimester (4) 3rd trimester		Malformations: Amoxicillin (4 exposed in all trimesters): short lingual frenulum, hypospadias, talipes valgus, micrognathia Augmentin (1 exposed in 1st trimester): malformed ear flap
Puho (2007)	**Amoxicillin (n=7)**	**Retrospective cohort** Hungarian Congenital Abnormality Registry 1980–1996. Outcomes: cleft lip/ palate and posterior cleft palate associated with amoxicillin exposure ascertained by : prenatal log book, maternal questionnaires, home visits	II-2	2 categories of exposure: 1) 2nd – 3rd month 2) entire pregnancy		Cleft lip/palate Prevalence odds ratio 2nd –3rd month of exposure to controls= 15.9 (CI 4.9–51.2) Prevalence odds ratio to malformed infants =5.4 (95% CI 1.9–5,4)
Rahangdale (2006)	**Amoxicillin** (n=25)	**Retrospective cohort** of patients treated for Chlamydia at Kaiser facilities July 1999–Dec 2000 compared to other antibiotics Outcome: congenital anomalies ascertained by medical record abstraction	III	Entire pregnancy		1 infant with dysmorphic features in Amoxicillin group

Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
Berkovitch (2004)	**Amoxicillin-clauvulanate** (n=191) **Amoxicillin** (n=191)	**Prospective cohort** of women who contacted Israeli Information Service 1999–2000. Outcome: obstetrical outcomes and major anomalies ascertained by questionnaire and follow up telephone interview, medical record review	II-2	1st trimester	**Spontaneous abortion:** Amoxicillin: 7.3% Augmentin: 6.3% **Preterm delivery:** Amoxicillin: 3.8% Augmentin: 3% **Low birth weight:** Amoxicillin: 4.4% Augmentin: 3.6% **Cesearean delivery:** Amoxicillin : 21% Augmentin: 12.3%	Rate of major anomalies Augmentin - 1.9% Amoxicillin - 3% **Major anomalies** Augmentin: clubfoot, unilateral hydronephrosis, ventricular septal defect/pulmonic stenosis; Amoxicillin: ventricular septal defect, congenital hip dislocation, tracheo-esophageal fistula
Jepsen (2003)	**Amoxicillin** (n=401)	**Retrospective cohort** of pregnant women in Denmark delivering after 28 weeks from Birth Registry and linked to Pharmacy database. 1991–2000. Outcome: birth weight, preterm delivery, spontaneous abortions and congenital malformation ascertained by Birth registry and Hospital Discharge Registry	II-2	2 categories of exposure: **1** Anytime during PG **2** (147) 1st trimester	**Preterm delivery:** Exposed 1st trimester- 6.1% Exposed anytime 5% Controls 6.3% Odds Ratio =0.78 (95% CI 0.49–1.22) **Low birth weight** Exposed 1st trimester - 1.4% Exposed anytime 1.3% Controls 1.9% Adjusted odds ratio= 0.63 (95% 0.28–1.67) **Spontaneous abortions** Cases- 1.2% Controls 1.3% Adjusted odds ratio=0.92 (95% CI 0.69–1.23)	**Rate of congenital anomalies** 1st trimester - 4.8% Anytime in PG - 4.0%, Controls = 4.1% Adjusted Odds ratio= 1.16 (95% CI=.54–2.5)
Czeizel (2001)	**Amoxicillin-clauvulanate** (n=52)	**Retrospective cohort** from Hungarian Case Control Surveillance of Congenital Anomalies 1991–1996 Outcome: congenital abnormalities ascertained through 1) registry data 2) questionnaires to parents, 3) prenatal log books	II-2	1st trimester (20)) 2nd trimester (12) 3rd trimester (20) (56 controls)	**No differences in major pregnancy outcomes** Threatened abortion : 36.5% cases 19.6% controls	**Rate of congenital malformations** Entire Pregnancy Odds ratio = 2.6 (95% CI 1.1–6.0) for cardiovascular anomalies Specific Defects: Ventricular Septal Defect (7), Atrial Septal Defect (6) 2nd–3rd month Odds ratio=3.4 (95% CI 0.3–33) Entire pregnancy

Author	Antibiotic	Study Design	Quality Rating[a]	Gestational Age at Exposure	Maternal Outcome	Neonatal Outcome
						Odds Ratio for hypospadias = 4.3 (95% CI 1.2–15.4) 2nd–3rd month Odds Ratio for hypospadias =7.0 (95% CI 0.4–135.5)
Ou (2001)	**Amoxicillin** (plus erythromycin or clindamycin) (n=23)	**Case series** Taiwan 1993–1999 of women treated with threatened abortion with antibiotics Outcome: pregnancy outcome and neonatal anomalies ascertained by clinical follow up	III	1st trimester	(22) term deliveries (1) 1st trimester fetal demise	No neonatal anomalies reported
Cavenee (1993)	**Amoxicillin/Probenicid** (n=71)	**Case series** Pregnant women treated at Parkland hospital for Gonorrhea 3 treatments Groups: **1** Ceftriaxone **2** Amoxicillin **3** Spectinomycin Outcomes; infant delivery, congenital anomalies ascertained by medical records	III	2 categories of exposure: **1** Less than 14 weeks (n=14) **2** greater than 14 weeks (n=57)		**Exposed 1st trimester** - 1 major malformation: unexplained asymmetric Intrauterine growth restriction with microcephaly **Exposed < 14 weeks:** 4 minor malformations **Exposed >14 weeks:** 10 minor malformations Overall: 1% risk of major malformations, 20% risk of minor malformations
Pedler (1985)	**Augmentin** (n=39)	**Prospective randomized clinical** trial of pregnant women with bacteruria England	I	Entire pregnancy (10) in 1st trimester		No anomalies in the Augmentin group

[a] Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force and the American College of Obstetricians and Gynecologists: **I** Evidence obtained from at least one properly designed randomized controlled trial. **II-1** Evidence obtained from well-designed controlled trials without randomization **II-2** Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group. **II-3** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence. **III** Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. This grading schema was modified to include downgrading by one level for studies with major design flaws.

Table 3

Summary of Pharmacokinetics of PEP Antibiotics

Antibiotic	Maternal PK Findings	Placental Transmission	Transmission into breast milk	Potential Maternal Dosing Implications
Ciprofloxacin	Generally lower levels of all quinolone antibiotics noted during pregnancy; non-specific findings	Yes. Low-moderate level passage to fetus. Appears to concentrates in amniotic fluid; AF:MS* ratio increases over 12 hours after dosing: 0.57–10.0	Yes. Does not appear to concentrate in breast milk. Noted to have declining M:P** ratio over time after dosing.	Likely that dose adjustments in pregnancy are necessary to maintain drug levels equal to non-pregnant women. However, no specific data exists and no specific data-driven recommendations can be made. Quinolone antibiotics have approximately 50–70% excretion by kidney.
Levofloxacin /Moxifloxacin (based partially on ofloxacin data)	Generally lower levels of all quinolone antibiotics noted during pregnancy; non-specific findings	Yes. Moderate to high level passage to fetus. Concentrates in amniotic fluid; AF:MS ratio increases over 12 hours after dosing: 0.35–2.57	Yes. Noted to have declining M:P** ratio over time after dosing	Dose adjustments in pregnancy are likely necessary to maintain drug levels equal to non-pregnant women. However, no specific data exists and thus no formal recommendations can be made.
Doxycycline	Limited investigation does not suggest substantial differences during pregnancy when compared to non-pregnant subjects	Yes. No additional information available.	Yes. M:P ratio is approximately 0.25–0.33	Does not appear that changes to dosing are required. Undergoes enterohepatic recirculation, and excreted unchanged in urine and feces
Amoxicillin	Investigations of oral dosing demonstrate marked differences in PK parameters engendered by pregnancy. Investigations using intravenous dosing do not demonstrate marked differences in PK parameters when compared to non-pregnant women.	Yes. Reaches therapeutic levels without high level drug concentration	Yes. Appears to be present in small amounts. Does not appear to be clinically significant	May need to consider shorter dosing intervals and/or increased dosing when attempting to achieve levels similar to non-pregnant women. This appears to be especially true for orally administered drug. High level renal excretion noted for all β-lactams