WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 3, 114-128. Review Article ISSN 2277– 7105

A REVIEW ON THERAPEUTICAL AND TOXICOLOGICAL EVENTS OF ANTIBIOTIC IN PREGNANCY

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Article Received on
28 Dec 2015,

Revised on 17 Jan 2016,
Accepted on 07 Feb 2016

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ABSTRACT

Even though pregnancy is regarded as a physiological state. At the time of pregnancy, there are some untreated sexually transmitted or urinary tract infections that associated with important morbidity, such as low birth weight, preterm birth and spontaneous abortion. It is estimated that one in four women will be prescribed an antibiotic at the time of pregnancy, analyzing almost 80% of pregnant women that prescribed the medication. In addition World Health Assembly expressed serious concern regarding antibiotic resistance due to antibiotic overuse and misuse and urged immediate action to combat antibiotic resistance on a global scale. Some of Antibiotic that have been related to pregnancy are associated with both short-term e.g., congenital abnormalities and long-term effect e.g., changes in gut micro biome, asthma, atopic dermatitis in the newborn. In addition, it is approximately that only 10% of medications have enough related data to safe and effective use in pregnancy. Antibiotics such as beta-lactams, vancomycin, nitrofurantoin, metronidazole, clindamycin and fosfomycin are mostly regarded as safe and effective in pregnancy. Fluoroquinolones and tetracyclines are generally shunned out in pregnancy. Physiologic changes in pregnancy lead to an increase in glomerulars filtration rate, increase in total body volume and enhanced cardiac output. These changes may lead to pharmacokinetic alterations in antibiotics that require dose adjustment or careful monitoring and assessment.

INTRODUCTION

Pregnant women are least-studied populations. Mainly human subject review boards refuse to accept the use of pregnant women out of alarm for the unknown fetal risks. In pregnancy the safety and pharmacokinetics of antibiotics are poorly studied and poorly implicated. Because efficacy of most of the antibiotic regimens is alike, the selection of antibiotics depends on the pharmacokinetics, safety and cost considerations.[1]

Granting organizations, especially pharmaceutical organizations, do not support research on pregnant women because of the accountability risk. The clinician repeatedly relies on commendations based on studies in laboratory animals, neonatal practice and studies carried out at the instant of abortion, cordocentesis, delivery, or cesarean section.[2]

Nearly all pregnant women are exposed to various type of medication at some stage in pregnancy. Drugs prescribed for the period of pregnancy can exercise a teratogenic consequence on fetuses and those advised during breastfeeding can furthermore impact on infant health. Antibiotics are amid the more frequently prescribed category of medication during pregnancy and lactation.[3] Contemporary approximations suggest that >40% of pregnant women are taking certain type of antibiotic immediately proceeding to delivery,[4] Either for deterrence of neonatal Group B *Streptococcus* sepsis or cesarean prophylaxis.[5]

If additional antibiotic indications for the period of pregnancy are in use into account, such as the screening and management of asymptomatic bacteriuria or bacterial vaginosis (BV) and irrational use of antibiotics to treat respiratory and genital infections, it is manifest that the huge majority of fetuses nowadays have been exposed to antibiotics before delivery. While some of these therapeutic strategies have been revealed to be beneficial to diminish short-term maternal and neonatal problems, their long-term consequences are by far less well known. We assess here a number of the most common indications for recommending antibiotics during pregnancy and confer the possible associated risks, including strategies designed at tumbling these risks. When advising antibiotics to a pregnant woman, we should question ourselves: are they truly indicated and are we practicing more injurious than wellbeing?.[6]

Clinical Pharmacology of Antibiotics

The major pregnancy-associated physiologic changes and their prospective influence on antimicrobial pharmacokinetic parameters are highlighted in table 1.[7]

The net influence of these physiologic changes facilitate maternal antibiotic concentrations tend to be 10% to 50% less than in the non pregnant status, oral absorption is less certain, and the late-gestation fetus is exposed to advanced stages of antimicrobials.

TABLE 1. Pregnancy-Associated Physiologic Changes and Their Potential Influence on Antimicrobial Pharmacokinetics.

Physiologic Changes	Kinetic Influences	Possible Clinical Effects
Expanded intravascular/extravascular volume (about 50%)	Increased volume or distribution	Need for larger loading dose
Reduced plasma protein concentration	Underestimation of free drug levels	
Increased (about 50%) renal blood flow and glomerular filtration rate	Increased drug clearance	Subtherapeutic drug concentrations
Need to increase dose or decrease dosing interval		
Increased progesterone-activated hepatic metabolism	Increased rate of biotransformation	Need to increase dose or decrease dosing interval
Decreased gastric motility	Reduced rate of absorption from small bowel	Unpredictable absorption of orally administered drugs
Increased rate of absorption from large bowel		
Decreased gastric acid production	Absorption of weak basic compounds	Unpredictable absorption of orally administered drugs
Thinning of fetomaternal barrier with advancing gestation	Increased transplacental diffusion	Increased fetal concentration Decreased maternal concentration Need to increase dose or decrease dosing interval

Mechanisms of Antimicrobial agents are that they cross the maternal-fetal interface primarily by simple diffusion, Even though some active and facilitated transport can occur. The rate of diffusion across the placental fence is relative to the maternal-fetal concentration gradient and the surface area of the placenta but is not relative to the thickness of the placental fence. And drugs which have a molecular weight of less than **500 kd**, increase lipid solubility, low extent of ionization, and low protein binding, they can cross to fetus more rapidly.

Nearly all antibiotics follow a similar pattern of transplacental route after intravenous infusion into the mother. Peak umbilical blood levels arise within 30 to 60 minutes subsequent to the time they peak in maternal serum.[8]

Fetal-to-maternal peak serum level ratios vary from 0.3 to 0.9 for penicillin, ampicillin, cefotaxime, cefuroxime, ticarcillin, clindamycin, and metronidazole and are less than or else equal to 1 for erythromycin and dicloxacillin. Maternal protein binding decreases fetal drug

levels. Ampicillin is merely 20% protein bound, where dicloxacillin is 96% bound. Protein binding hold a profound effect on selection of antibiotic in pregnancy.[9]

The pregnant woman is at high risk for adverse reactions owing to antimicrobial therapy than non pregnant woman. But overall incidence or severity of drug reactions is same in pregnant and non pregnant women: 5% to 10% of women need cessation of antibiotic therapy because of antibiotic effects.[10]

Prophylactic antibiotics usually are used in one of four situations: avoidance of subacute bacterial endocarditis, deterrence of GBS sepsis in the neonate, preclusion of endometritis after a cesarean section and prevention of persistent pyelonephritis.

Rational antibiotic therapy/regimen inside pregnancy

1. Impediment of premature labor

According to World Health Organization defines preterm delivery or birth that normally happened at the range of 20 weeks' gestation, but not more than 37 weeks. (11) Preterm birth is became the most devastating issues to low level income people in the prenatal period. Most of developed countries, the occurrence of preterm delivery ranges between 7% to 11%.[12] In spite in advances in obstetrical care, the negative outcome of prematurity has not increase over the last 40 years.[13] Prematurity also offer a great of neonatal morbidity and mortality in developed countries, ranges between 60%–80% of deaths, of mostly infants without congenital abnormalities. Even though births at less than 32 weeks' gestation occur only in 1%–2% of all births, which lead to 60% of prenatal mortality and 50% of long-term neurological morbidity.[14]

The Socio economic condition are very important factor as one-third of disbursing due to neonatal care and one-tenth of disbursing due to general pediatric care are caused by premature births. In neonatal care costs of an infant with a birth weight of 500–700 g in the USA is estimated at approximately USD $225,000. For the past 20 years, increasing research has focused on identifying causative etiologies of preterm birth. A high number of associated risk factors have been identified.[15]

The causative agent of maternal infection origin is the almost often found. The most causative infection and preterm birth is consistent with models suggesting that preterm labor is triggered by an inflammatory response mediated by pro-inflammatory cytokines such as

interleukin (IL)-1beta, IL-6, IL-8 and tumor necrosis factor (TNF)-alpha.[16] Laboratory and clinical report analysis have indicate that spontaneous preterm labor and delivery they are systemic ascending genital tract infections.[17]

The clinical and subclinical chorioamnionitis are much more common in preterm than deliveries and may fall between 50% of preterm births less than 30 weeks' gestation. Hence the pattern of using antibiotics might yield a very good result in the treatment of preterm labor. Nevertheless, antibiotic treatment in the context of preterm labor with defiles membranes has been shown ineffective in preventing either preterm birth or neonatal morbi-mortality.[18]

A recent Cochrane review including 14 studies randomizing a total of 7837 women with preterm labor and intact membranes showed no significant difference in prenatal or infant mortality, in preterm birth, or in any other clinically important short-term outcomes for the infant. Maternal infection was decrease with the use of some prophylactic antibiotics compared with placebo (average risk ratio (RR): 0.74; 95% confidence interval (CI) = 0.63–0.86; number needed to treat to benefit (NNTB): 34; 95% CI = 24–63) and with any beta-lactam antibiotic compared with non-beta-lactams (RR: 0.80; 95% CI = 0.69–0.92; NNTB: 47; 95% CI = 31–119), Hence, compared with non-beta-lactam antibiotics, any beta-lactam was associated with an increase in maternal adverse drug reaction (RR 1.61, 95% CI = 1.02–2.54; number needed to treat to harm (NNTH): 17; 95% CI = 7–526). (19) Although antibiotics have been shown to be beneficial in preventing maternal and short-term neonatal complications in the in the circumstances of premature rupture of membranes (PROM) before term.[20] A review including 22 trials, involving 6872 women and babies, indicated that the use of antibiotics following PROM was associated with data significant reductions in chorioamnionitis (RR: 0.66; 95% CI = 0.46–0.96) and a reduction in the numbers of babies born within 48 h (average RR: 0.71; 95% CI = 0.58–0.87) and 7 days of randomization (average RR: 0.79; 95% CI = 0.71–0.89). The current data of neonatal morbidity were reduced: neonatal infection (RR: 0.67; 95% CI = 0.52–0.85); use of surfactant (RR: 0.83; 95% CI = 0.72–0.96); oxygen therapy (RR: 0.88; 95% CI = 0.81–0.96); and abnormal cerebral ultrasound scan prior to discharge from hospital (RR: 0.81; 95% CI = 0.68–0.98). Antibiotics had very little impact on infants' health at 7 years of age. Though a lack of evidence of longer-term benefit in childhood, the significant related to short-term morbidities are such that antibiotics are recommended to be prescribed in the context of PROM before

term. The diagnosis and treatment of asymptomatic bacteriuria, BV and gonorrhea appeared to reduce the risk of preterm birth. Nevertheless, current research likely indicate that the possible outcome and important may be lower—if any at all.[21] The research analysized the important confirmation of BV and furthermore, medication with the aims of reducing preterm birth have didn't achieved.[22]

Most of the scholars showed that due to improper medication on time being initiated and with bad prescription of antibiotic (metronidazole instead of clindamycin).[23] Even though, a very current French study indicating women in early pregnancy medication with clindamycin during 4 days and repeated 1 week later did not show any benefit either thorough studies are needed before recommending screening and medication of BV during pregnancy and these should include long-term infant outcomes. In relation to other genital infections, hence an increased rate of preterm delivery has been prescribed in women with GBS, Chlamydia, *Trichomonas vaginalis* and syphilis, treatment of these diseases is primarily objectives at preventing prenatal transmission or maternal infection.[24] There is no doubt that infection and inflammation are clearly related to the risk of preterm birth, but it has not been established whether antibiotic therapy can prevent it. Moreover, antibiotic treatment in the context of prevention of preterm birth might be harmful.[25]

2. Prevention of Group B Streptococcus Neonatal infection

GBS is one of the causing of neonatal (e.g., early and late sepsis, meningitis) and maternal infectious complications (chorioamnionitis, sepsis, endometritis).[26] GBS early onset infections (EOD) is defined as occurring within the first week after birth and late onset infections, as GBS neonatal complications happening after one week of birth. Maternal intrapartum GBS infections are the primary risk factor for EOD in infants and approximately 10%–30% of pregnant women are infected with GBS in the vagina or rectum. It has been shown that intrapartum antibiotic prophylaxis (IAP) for colonized women reduces the risk of vertical transmission of GBS, as well as the risk of EOD.[27] The reference standard for the detection of GBS colonization is considered to be culture in broth-enriched vaginal-rectal swabs. As culture takes at least 48–72 h, it cannot be used for detection of GBS colonization during labor. Although recommended to perform GBS culture from a recto-vaginal swab taken at 35–37 weeks' gestation. Different International organizations, such as the United States Centers for Disease Control and Prevention (CDC) and the Swiss Society of Obstetrics and Gynecology, recent study recommended that antenatal screening with vaginal-rectal

cultures and selective IAP administration to GBS-positive women and it has been reported that adherence to these recommendations has decreased the incidence of GBS EOD (from 1.7 cases per 1000 live births in the early 1990s to 0.34–0.37 cases per 1000 live births in recent years).[28,29]

However, several problems exist with these recommendations. In the absence of systematic screening or widespread IAP, the incidence of EOD in some countries (e.g., the United Kingdom (UK)) is much lower (0.5/1000 births) and in relation to what was observed in the USA after universal screening and IAP, despite comparable vaginal carriage rates.[30]

Research indicated that low sensitivity (33%–50%) of antenatal GBS culture to detect colonization during labor.[45–48] Most Cases of EOD in in new born at term has happened among mothers with negative antenatal GBS analysis results and it has been reported that at least 10% of this group of women turned positive at labor.[31]

In recent guidelines, most of the women do not receive IAP and their neonates are at risk of EOD,[32] In neonates born preterm are at highest risk of EOD (risk of 1 in 3.5–4.5 depending on gestational age at delivery). As recto-vaginal culture is identified only at 35–37 weeks, the maternal colonization status is not usually known at labor and also, IAP is given systematically—irrespective of colonization status. The idea to carry out systematic GBS antenatal screening is not universally accepted. Some of the developed countries, such as the UK, apply mostly a risk factor policy.[33] Therefore, studies indicated that a very low percentage of newborns with EOD had risk factors (53%).[34] In the reverse relation, since colonization with GBS almost has 20% of pregnant women, it might cause a risk factor of over treatment used. The possible way of stopping the occurrence of GBS neonatal sepsis, experts and International organizations intended upon the number of women and fetuses they are willing to treat in order to avoid the occurrence of the cases of GBS EOD. Indifferent approaches of systematic antenatal screening and IAP to colonized women, between 700 and 1000 women and their fetuses are treated to prevent one case of GBS EOD. With the risk-based strategy, high number of them without being at risk as the mother is not colonized. Consequently, it is of extreme significant to choose a right attempting to expose the highest at-risk factor in relation to population, the antibiotic prophylaxis, which is colonized women delivering preterm.

3. Intra amniotic infection during labor

Based on Intrapartum clinical chorioamnionitis, most diagnosed on the basis of the presence of fever, uterine tenderness, maternal or fetal tachycardia, foul-smelling or purulent amniotic fluid, leucocytosis or elevated C-reactive protein (CRP), is present in 4%–10% of women in labor. Chorioamnionitis is related with a high risk of necrotizing enterocolitis (odds ratio (OR): 1.24; 95% CI = 1.01–1.52) and child cerebral palsy (OR: 2.42; 95% CI = 1.52–3.84), as well as maternal complications (e.g., endometritis and sepsis). The Broad-spectrum antibiotics, such as co-amoxiclav plus gentamicin, are occationally the standard of care as treatment allows to prevent maternal complex.[35]

Nevertheless, the important of such treatment for the prevention of infant cerebral palsy is less established as the risk persists regardless of antibiotic Prescription. Although there is no doubt that antibiotics should be prescribed in the context of chorioamnionitis, Therefore correct diagnosis should be made to avoid any error of treatment, so that the treatment will be carry out at the right time.

4. Deterrence of Maternal Infectious Morbidity after Cesarean Section

In developed countries the rate of Cesarean section Continue increases at the high rate of 30%–40%. The increased risk factor among the women delivering by cesarean ranges from 5to 30 fold of postpartum infection-related complications (including endometritis, sepsis, urinary tract infection. and surgical site infection (4.4%) compared with those delivering vaginally (0.2%–5%).[36]

Women undergoing cesarean delivery (CD) before labor or membrane rupture are at a much lower risk of infection-related complications (5.5%–17.3%) than those having a CD during labor, which the risk of postpartum infection (without antibiotic prophylaxis) is as high as 8%–30%.

The beneficial in decreasing postpartum infectious morbidity both in high-risk (in labor post-membrane rupture) is associated with Antibiotic prophylaxis for women undergoing CD has being proved[37] or less-risk patients (non-laboring with intact membranes). In a series of review of over 80 studies on the trial of prophylactic antibiotics for CD, the Cochrane Collaboration specifically examined the adverse effect of prophylactic antibiotics on the rate of maternal postpartum fever, wound infection, endometritis, urinary tract infection, serious infectious morbidity/death, as well as maternal side-effects and length of hospital stay.[38]

In most of the CDs (both elective and emergency), the only outcome that increased following prophylactic antibiotics was maternal side-effects. For all other outcomes, the use of antibiotics was associated with significant ratio of reduction, with an effect size of 40%–65%. Endometritis and wound infection were decrease following both choice and emergency CD. Before then, consensus was to give antibiotic prophylaxis after umbilical cord clamping in order to avoid the newborn being exposed to any potential diseases. Irrespective of this prophylaxis, postpartum infectious morbidity is still high in some developed countries, such as the USA. Recently, research has been carrying out to evaluate whether antibiotic prophylaxis before skin incision (as for gastrointestinal surgery) could further decrease postpartum maternal complications. Many review indicated that antibiotics given before skin incision were more effective in reducing endometritis than when given after cord clamping (RR: 0.57; 95% CI = 0.36–0.90).[39] Therefore, it can be associated with so many effects. But few reviews have investigated neonatal morbidity. This indicated that the rate of short-term complications was similar if antibiotics were given before or after cord clamping (neonatal sepsis (0.82; 95% CI = 0.47–1.42); Anticipated neonatal sepsis requiring great work (RR: 0.94; 95% CI = 0.72–1.22); or neonatal intensive care admissions unit (RR: 0.90; 95% CI = 0.62–1.28).[40] Note, therefore there is no prospective study investigating the mid- or long-term effect on the infant.[41] The results are not universal with some studies indicating no difference in maternal complications irrespective of whether antibiotics are given before skin incision or after cord clamping].[42] The USA has the much higher rate in postoperative morbidity than other developed countries—probably due to high rates of obesity and diabetes. Therefore, antibiotic prophylaxis reduces the risk of postpartum infectious maternal morbidity after cesarean section, in addition more research are require before changing the current standard of health care, which is to prescribe them after cord clamping.[43] There are also related hazards with the guidelines of transmission and treatment of genital toxins, such as *T. vaginalis*or BV, for the inhibition of preterm birth. In the case of *T. vaginalis*, it has been presented that treatment with metronidazole increased the hazard of preterm delivery (19% in the metronidazole group *vs.* 10.7% in the placebo group (RR: 1.8; 95% CI = 1.2–2.7; $p = 0.004$).[44]

It has been conjectured that the antibiotic encourages the deliverance of humiliation particles, which enriches the inflammatory cascade and hence preterm labor and delivery. Additional problem when diagnosing BV or vaginitis is the use of culture from vaginal secretions. It is well known that cultures should not be used for diagnosing BV and unsophisticated vaginitis.

Unfortunately, the use of wet stand microscopy is diminishing and gynecologists habitually trust on vaginal culture.[45]

In this case, the possibility to have a positive vaginal culture is very high (20% for GBS, 10% for *E. coli*, 30%–50% for *Gardenerellavaginalis*, *etc.*), which does not certainly mean the existence of a pathogenic infection. The end point is that a large number of women accept antibiotics in order to treat their normal vaginal flora.

As through genital toxicities, another difficult in obstetrics is the identification of urinary area infection.[46] It is typical of precaution to accomplish urinary branches at each pregnancy visit to examine for proteinuria. This permits also to notice the attendance/nonattendance of leucocytes in the urine. Almost 60% of pregnant women have leucocytes in the urinary branches in the lack of any infectious barrier and their attendance should not be rummage-sale for the transmission or judgment of asymptomatic urinary area infection. Inappropriately, several clinicians prescribe antibiotics for a suspicion of urinary area infection or accomplish urinary culture. Once considering the women with antibiotics due to the presence of leucocytes in the branches, they are generous them aimed at no effective purpose and sensational the woman and fetus to potential side-effects. When performance culture, they are accumulative healthcare expenses as further most outcomes will originate back as ―mixed flora‖ or contamination.

As stated here to fore, intrapartum choriamnionitis would be preserved prompt through antibiotics to avoid at smallest motherly difficulties. Fever is one of the signs that may be existing with choriamnionitis.[47]

Conversely, the best repeated purpose for fever through labor and delivery is not choriamnionitis, but persistent labor (per each additional hour: OR: 1.15; 95% CI = 1.08–1.22) or epidural painlessness (11.8% of women).[48]

Hence, a comprehensive check-up, containing motherly and fetal emblems and signs, as sound as a blood investigation containing white cell counts and CRP, must be accomplished previously initial circulatory antibiotics. Discussion with obstetric sources to conclude whether chorioamnionitis is supposed is significant for supervisory new born supervision. If antibiotics have been suggested, their period should be as petite as potential in instruction to reduce introduction to the newborn over breast milk.[49] Numerous studies require exposed

that the supervision of just one dose of antibiotics after distribution is correspondingly in effect than extended period of treatment.[50,51]

CONCLUSION

The recent targets are to find a better way to prevent microbial attack to fetal/neonatal as well as in mother. The emergent anxiety related to the short- and long-term significances of antibiotic administration involves recovering investigatation approaches, as well as novel approaches to the hazard stratification of pregnant females. For every pregnant female, we should be more conscious about the hazards and safeties of antibiotics for both mother and her fetus/newborn/infant and inspire patients to be part of a common supervisory process. Accumulation, recommendations should be argued and approved inside the native environment. As the example, GBS prophylaxis or antibiotics earlier to the cesarean segment may be considered in particular countries, such as the USA, but may not be so considerable in particular European countries with minor infection rates. The current determination in 2014 World Health Assembly has evidently declared the alarm by distinguishing that antibiotic-fighting through the misuse and misapplication of these drugs is a main public health matter and wishes associate conditions to support drug organization structures. and to maintain the progress of novel diagnostics and treatment options. We may expect that this message has been sound assumed by persons in the area of obstetrics.

REFERENCES

1. Newton ER, Piper JM, Shain ST, Peairs W: Predictors of vaginal microflora. Am J Obstet Gynecol, 2001; 184: 845.
2. Wilkin SS: Immunology of the vagina. Clin Obstet Gynecol, 1983; 36: 122.
3. Nahum, G.G.; Uhl, K.; Kennedy, D.L. Antibiotic use in pregnancy and lactation: What is and is not known about teratogenic and toxic risks. Obstet. Gynecol., 2006; 107: 1120–1138.
4. Ledger, W.J.; Blaser, M.J. Are we using too many antibiotics during pregnancy? BJOG, 2013; 120: 1450–1452.
5. Verani, J.R.; McGee, L.; Schrag, S.J. Prevention of perinatal group B streptococcal disease—Revised guidelines from CDC, 2010. MMWR Recomm. Rep., 2010; 59: 1–36.
6. Macones, G.A.; Cleary, K.L.; Parry, S.; Stamilio, D.M.; Cahill, A.G.; Odibo, A.O.; Rampersad, R. The timing of antibiotics at cesarean: A randomized controlled trial. Amer. J. Perinatol., 2012; 29: 273–276.

7. Chow AW, Jewesson PJ: Pharmacokinetics and safety of antimicrobial agents during pregnancy. Rev Infect Dis, 1985; 7: 287.
8. Walmer D, Walmer ER, Gibbs RS: Enterococci in post-cesarean endometritis. Obstet Gynecol, 1988; 71: 159.
9. Chow AW, Jewesson PJ: Pharmacokinetics and safety of antimicrobial agents during pregnancy. Rev Infect Dis., 1985; 7: 287.
10. Chow AW, Jewesson PJ: Pharmacokinetics and safety of antimicrobial agents during pregnancy. Rev Infect Dis., 1985; 7: 287.
11. Goldenberg, R.L.; Culhane, J.F.; Iams, J.D.; Romero, R. Epidemiology and causes of preterm birth. Lancet, 2008; 371: 75–84.
12. Marcos, Z. Arriving too early. Lancet Neurol., 2013; 12: 332–333.
13. Chang, H.H.; Larson, J.; Blencowe, H.; Spong, C.Y.; Howson, C.P.; Cairns-Smith, S.; Lackritz, E.M.; Lee, S.K.; Mason, E.; Serazin, A.C.; et al.
14. Mercer, B.M. Preterm premature rupture of the membranes. Obstet. Gynecol., 2003; 101: 178–193.
15. Takayama, J.I.; Matsuo, N. The enigma of spontaneous preterm birth. N. Engl. J. Med., 2010; 362: 2032–2033.
16. Farina, L.; Winkelman, C. A review of the role of proinflammatory cytokines in labor and noninfectious preterm labor. Biol. Res. Nurs., 2005; 6: 230–238.
17. Wei, S.Q.; Fraser, W.; Luo, Z.C. Inflammatory cytokines and spontaneous preterm birth in asymptomatic women: A systematic review. Obstet. Gynecol., 2010; 116: 393–401.
18. Lyon, D.; Cheng, C.Y.; Howland, L.; Rattican, D.; Jallo, N.; Pickler, R.; Brown, L.; McGrath, J. Integrated review of cytokines in maternal, cord and newborn blood.
19. Kenyon, S.L.; Taylor, D.J.; Tarnow-Mordi, W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: The ORACLE I randomised trial. Lancet, 2001; 357: 979–988.
20. Kenyon, S.; Boulvain, M.; Neilson, J.P. Antibiotics for preterm rupture of membranes. Cochrane Database Syst. Rev., 2013; 12, doi:10.1002/14651858.CD001058.
21. Uncu, Y.; Uncu, G.; Esmer, A.; Bilgel, N. Should asymptomatic bacteriuria be screened in pregnancy? Clin. Exp. Obstet. Gynecol., 2002; 29: 281–285.
22. Brocklehurst, P.; Gordon, A.; Heatley, E.; Milan, S.J. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst. Rev., 2013; 1: doi:10.1002/14651858.CD000262.pub4.

23. Okun, N.; Gronau, K.A.; Hannah, M.E. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: A systematic review. Obstet. Gynecol., 2005; 105: 857–868.
24. Cunnington, M.; Kortsalioudaki, C.; Heath, P. Genitourinary pathogens and preterm birth.
25. Mercer, B.M.; Goldenberg, R.L.; Das, A.F.; Thurnau, G.R.; Bendon, R.W.; Miodovnik, M.; Ramsey, R.D.; Rabello, Y.A.; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.
26. Allardice, J.G.; Baskett, T.F.; Seshia, M.M.; Bowman, N.; Malazdrewicz, R. Perinatal group B streptococcal colonization and infection. Amer. J. Obstet. Gynecol., 1982; 142: 617–620.
27. Baltimore, R.S.; Huie, S.M.; Meek, J.I.; Schuchat, A.; O'Brien, K.L. Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics, 2001; 108: 1094–1098.
28. Van Dyke, M.K.; Phares, C.R.; Lynfield, R.; Thomas, A.R.; Arnold, K.E.; Craig, A.S.; Mohle-Boetani, J.; Gershman, K.; Schaffner, W.; Petit, S.; et al. Evaluation of universal antenatal screening for group B streptococcus. N. Engl. J. Med., 2009; 360: 2626–2636.
29. Lukacs, S.L.; Schrag, S.J. Clinical sepsis in neonates and young infants, United States, 1988–2006. J. Pediatr., 2012; 160: 960–965.
30. Heath, P.T.; Balfour, G.; Weisner, A.M.; Efstratiou, A.; Lamagni, T.L.; Tighe, H.; O'Connell, L.A.; Cafferkey, M.; Verlander, N.Q.; Nicoll, A.; et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet, 2004; 363: 292–294.
31. Puopolo, K.M.; Madoff, L.C.; Eichenwald, E.C. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics, 2005; 115: 1240–1246.
32. Towers, C.V.; Rumney, P.J.; Asrat, T.; Preslicka, C.; Ghamsary, M.G.; Nageotte, M.P.
33. Royal College of Obstetricians and Gynaecologists. The prevention of early-onset neonatal group b streptococcal disease. Green-top Guidel., 2012; 36: 1–13.
34. Lyytikainen, O.; Nuorti, J.P.; Halmesmaki, E.; Carlson, P.; Uotila, J.; Vuento, R.; Ranta, T.; Sarkkinen, H.; Ammala, M.; Kostiala, A.; et al. Invasive group B streptococcal infections in Finland: A population-based study. Emerg. Infect. Dis., 2003; 9: 469–473.
35. Gibbs, R.S.; Dinsmoor, M.J.; Newton, E.R.; Ramamurthy, R.S. A randomized trial of intrapartum vs. immediate postpartum treatment of women with intra-amniotic infection. Obstet. Gynecol., 1988; 72: 823–828.
36. Lamont, R.F.; Sobel, J.D.; Kusanovic, J.P.; Vaisbuch, E.; Mazaki-Tovi, S.; Kim, S.K.; Uldbjerg, N.; Romero, R. Current debate on the use of antibiotic prophylaxis for caesarean section. BJOG, 2011; 118: 193–201.

37. Wallace, R.L.; Yonekura, M.L. The use of prophylactic antibiotics in patients undergoing emergency primary cesarean section. Amer. J. Obstet. Gynecol., 1983; 147: 533–536.
38. Smaill, F.M.; Gyte, G.M. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst. Rev. 2010, doi:10.1002/14651858.CD007482.pub2.
39. Rosenberg, K. Preprocedure antibiotics reduce infection after cesarean delivery. Amer. J. Nurs., 2012; 112, doi:10.1097/01.NAJ.0000422237.25309.8b.
40. Sun, J.; Ding, M.; Liu, J.; Li, Y.; Sun, X.; Liu, T.; Chen, Y.; Liu, J. Prophylactic administration of cefazolin prior to skin incision vs. antibiotics at cord clamping in preventing postcesarean infectious morbidity: A systematic review and meta-analysis of randomized controlled trials. Gynecol. Obstet. Investig., 2013; 75: 175–178.
41. Ledger, W.J.; Blaser, M.J. Are we using too many antibiotics during pregnancy? BJOG, 2013; 120: 1450–1452.
42. Yildirim, G.; Gungorduk, K.; Guven, H.Z.; Aslan, H.; Celikkol, O.; Sudolmus, S.; Ceylan, Y. When should we perform prophylactic antibiotics in elective cesarean cases? Arch. Gynecol. Obstet., 2009; 280: 13–18.
43. Capitulo, K.L.; Klein, V.R.; Wright, M. Should prophylactic antibiotics be routinely given to a mother before a cesarean birth? Amer. J. Matern. Child. Nurs., 2013; 38: 266–267.
44. Klebanoff, M.A.; Carey, J.C.; Hauth, J.C.; Hillier, S.L.; Nugent, R.P.; Thom, E.A.; Ernest, J.M.; Heine, R.P.; Wapner, R.J.; Trout, W.; et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. N. Engl. J. Med., 2001; 345: 487–493.
45. ACOG Practice Bulletin. Vaginitis. Obstet. Gynecol., 2006; 107: 1195–1206.
46. Latini Keller, V.; Junod Perron, N.; Graf, J.D.; Stoermann Chopard, C. Urinalysis: What a primary care physician needs to know. Rev. Med. Suisse, 2009; 5: 1870–1875.
47. Tita, A.T.; Andrews, W.W. Diagnosis and management of clinical chorioamnionitis. Clin. Perinatol., 2010; 37: 339–354.
48. Lieberman, E.; Lang, J.M.; Frigoletto, F., Jr.; Richardson, D.K.; Ringer, S.A.; Cohen, A. Epidural analgesia, intrapartum fever and neonatal sepsis evaluation. Pediatrics, 1997; 99: 415–419.
49. Cabbad, M.; Sijin, O.; Minkoff, H. Short course of antibiotics for post-cesarean section endometritis. Amer. J. Obstet. Gynecol., 1987; 157: 908–909.

50. Edwards, R.K.; Duff, P. Single additional dose postpartum therapy for women with chorioamnionitis. Obstet. Gynecol., 2003; 102: 957–961.
51. Chapman, S.J.; Owen, J. Randomized trial of single-dose vs. multiple-dose cefotetan for the postpartum treatment of intrapartum chorioamnionitis. Amer. J. Obstet. Gynecol., 1997; 177: 831–834.