15 Use of Antibiotics in Pregnant Patients in the Intensive Care Unit

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15.1 Infections and Critical Care in Obstetric Patients

The critically sick pregnant patient is a challenge for the intensive-care physician. Several features, such as physiological changes associated with pregnancy, specific obstetric diseases and the presence of the fetus greatly complicate the assessment and treatment of these patients. The prescription must treat the mother’s disease without affecting the fetus [1].

Observational studies have reported that pregnant women take a variety of drugs during pregnancy, including prescription, over-the-counter (OTC) and herbal preparations. Results show that women, in a range of 44–96%, were exposed during pregnancy to at least one drug. An American study, which was carried out between 1996 and 2000 and included 152,531 women, showed that amoxicillin was dispensed to 34,304 women and, in all, more than 90,000 prescriptions were antibiotics [2, 3].

Women can develop an acute illness or pregnancy-induced complications that need intensive drug therapy. Several studies have analyzed obstetric admissions to the ICU [1, 4–12]. They conclude that less than 1% of deliveries are referred to the ICU, mainly for pre-eclampsia, and that maternal mortality may be highly variable, from 0% in the study of Lapinsky et al. [1] to 20% in Collop and Sahn’s study [8]. Bacterial infections were a significant, although not highly prevalent, cause of admission to the ICU.

Despite infectious diseases not being uncommon during pregnancy and the postpartum period [13, 14], severe infections that need the ICU setting are much less prevalent in this population. Although pneumonia, pyelonephritis and abortion-related infections may be life-threatening, many patients may be treated in regular wards and only severe infections in high-risk patients require critical care. However, it has been shown that infections may account for 24% of all referral diagnoses [7]. The main causes were sepsis and pneumonia [7, 15, 16].

The characteristics of septic shock in pregnant women have been described in detail by several authors [15–17]. The main causes that predispose one to septic shock include pyelonephritis, chorioamnionitis, Stevens-Johnson syndrome, premature rupture of membranes, necrotizing fasciitis, septic abortion and endometritis.

Although the microorganisms that may cause septic shock are mainly Gram-negative bacteria (usually *E. coli*), anaerobes, such as *B. fragilis*, Gram-positive microorganisms, can also be seen [16]. In addition, sexually transmitted infections are particularly relevant for their frequency and significance in pregnancy outcome [18]. Some reviews have examined the relevance of antibiotic treatment to prevent sexually transmitted infections, in order to reduce preterm birth and low birth weight [19]. Both the WHO and CDC have elaborated reference guidelines that recommend drug treatment for sexually transmitted infections in pregnancy [20].

15.2 General Considerations on Antibiotics Use During Pregnancy

Pregnancy always complicates drug treatment. Any drug may be harmful to the mother and also to the fetus so, accordingly, no pharmacological therapy must be initiated unless a clear benefit is expected. Nonetheless, the benefit-risk index recommends active treatment in ICU patients. From the pharmacological point of view, antibiotics are relatively safe drugs when used in pregnant patients with severe infections. Many current antibiotics have been used for at least 30 years and most of them seem to be free of significant teratogenic effects, at least in animals. They are given in short courses, so their adverse effects are rather predictable, but some appreciation of the balance of risks in more serious cases is also needed. However, the understandable reluctance of physicians and pharmaceutical companies to study drugs in pregnant women greatly limits the scientific evidence of the effectiveness and safety of all drugs, including antibiotics, in pregnancy. Three aspects deserve special attention when antibiotic use in pregnant women is considered: the first relates to pharmacokinetic changes induced by pregnancy; the second stresses the potential toxicity to mother and fetus,
and the third refers to the effectiveness of antibiotic regimes in obstetric infections.

Pregnancy may change the way in which women handle antimicrobial agents; therefore, some quantitative changes on treatment effects may appear. Most pregnancy-induced effects are of a pharmacokinetic nature. In general, low maternal concentrations have been found after administration of antimicrobials, such as penicillins, cephalosporins, aminoglycosides and erythromycin [21]. The main implications of these findings refer to dosage. For instance, a moderate increase in the dosage of penicillins has been recommended [22, 23]. As a rule, full doses should be used to treat infections in pregnancy and, therefore, treatment regimes should assure that the patient is receiving her right dose. Thus, measurement of blood levels may be needed in some cases when drug pharmacokinetics is influenced by pregnancy. The reason is twofold: first, in order to assure the correct dosage according to the patient and, second, to avoid unnecessary, high blood levels that may be toxic both in the mother and the fetus [13, 24]. Also, the length of treatment should be established by the specific disease and not by the consideration that the patient is pregnant.

In spite of the assertions made in previous paragraphs, a troublesome aspect of antibiotic treatment is its theoretical ability to harm the maternal-fetal unit. Major studies which indicate an association of antibiotic exposure in pregnancy and congenital malformations are lacking [25]. Certain drugs should be avoided, since toxicity may be expected in pregnant women themselves, the fetus, or the neonate. Aminoglycosides, tetracyclines, chloramphenicol and fluoroquinolones must be used with special care in pregnancy [13, 26]. Most authors recognize that tetracyclines and aminoglycosides may have some teratogenic effects [18, 27–29]. Moreover, tetracyclines may have an increased risk of toxicity in the pregnant woman herself [27]. In turn, neonates may be damaged by sulfonamides and chloramphenicol [30]. The withdrawal of these antibiotic drugs is mandatory when the treatment of minor infections by otherwise drug-sensitive bacteria is considered. Nonetheless, these principles may be questioned when severe infection by resistant microorganisms appears.

Obstetric patients admitted to the ICU can be classified into two categories: first, patients with specific obstetric disorders (with approximately 50–80% of prevalence) and, second, pregnant patients with primarily medical disorders [31]. The most common pregnancy-related infections were chorioamnionitis and puerperal sepsis [32]. The most common unrelated infections, but complicating pregnancy, are respiratory and urinary tract infections [13]. In all, morbidity rates of severe obstetric complications range from 0.8% to 8.2%, and mortality rates from 0.02% to 37%. The great variability is explained by its different case definition, methodology and especially because of differences in health quality control among countries [33].

Clinical trials showing efficacy of antibiotics in pregnant women are scarce if compared with other areas of drug therapy. This paucity of studies is so important that some textbooks rely on the experience or the personal opinion of the authors [14]. Hence, this chapter will avoid any reference to the specific therapeutics of infections seen in the ICU and will only consider the first two topics described earlier, i.e., the pharmacokinetic changes induced by pregnancy and the safety of antibiotic drugs in the mother and the fetus.

In conclusion, the treatment of maternal infections should follow the general principles of pharmacological therapy in pregnant women. Moreover, drug efficacy ranks first in ICU patients, although the safety of the embryo or fetus should always be considered. Antibiotics must be chosen by susceptibility studies or, more often, by empirical evaluation of the most likely group of microorganisms and their most probable antibiotic susceptibility. Only when this aspect has been considered should embryonic or fetal safety concerns arise [18, 22, 34].

15.3 Pregnancy-Related Pharmacokinetic Changes of Clinical Relevance

Drug pharmacokinetics is mainly affected by pregnancy in two ways. The first concerns the progressive changes in the maternal physiology during pregnancy, which are most evident during the third trimester and the immediate postpartum. These changes affect the absorption, distribution, metabolism and elimination of some drugs. The second way is related to the placental-fetal unit compartment and modifies the amount of drug crossing the placenta, the fraction metabolized by the placenta and the distribution and elimination of the drug by the fetus [35]. The most relevant changes are observed in drug distribution and in substances predominantly eliminated, unchanged, in urine.

15.3.1 Absorption

Digestive physiology is altered by pregnancy, as shown by a delay in both gastric and intestinal motilities. The increase of plasma progesterone levels during pregnancy accounts for a 30–50% increase in the gastric and intestinal emptying time. Decreased gastric acid secretion (40% less than in non-pregnant women) and peptic activity, as well as an increase in mucus secretion, convey an increase in gastric pH. This could influence the ionization of weak acids and bases and may result in