The use of antibiotics in pregnancy

Several studies have shown the number and variety of drugs taken by women during their pregnancy. Antibiotics are taken by between 17 and 41% of pregnant women. It can be assumed that urinary tract infections account for the largest portion of this antibiotic consumption. However, other foci of infections such as for example ear infections, sinusitis, tonsillitis, gonorrhoea, dental infections, and pneumonia during pregnancy will call for treatment with antibiotics. At the end of pregnancy, premature rupture of the membranes poses particular problems including the threat of ascending infections. Because of the wide variety of types of infections that may occur during pregnancy not only obstetricians but also general practitioners, internists, otolaryngologists, dentists, and other specialists may get involved in their treatment.

For treatment with antiepileptic drugs, such as phenytoin, the aim is to minimize the number of seizures as far as possible. The dosage required for this purpose has been shown to increase during pregnancy and this has been linked with lower plasma levels (Lander et al., 1977) and higher plasma clearance (Nygind, Dam & Christiansen, 1976) in pregnancy. The antihypertensive drug metoprolol has recently been shown to produce substantially lower plasma levels and to have a shorter plasma half-life in five women during the last trimester as compared to 12–23 weeks after delivery (Högstedt, Lindberg & Rane, 1983). Increased capacity of the liver to metabolize these drugs was the suggested explanation for the lower plasma levels. Serum levels of digoxin following a daily 0.25 mg maintenance dose have been shown to be significantly lower in pregnant women at term than in the same women one month after delivery (Rogers et al., 1972).

Controlled studies of ampicillin (Philipson, 1977), cephadine (Philipson & Stiernstedt, 1980), and cefuroxime (Philipson & Stiernstedt, 1982) have shown 30–50% lower plasma levels and significantly shorter plasma half-lives in women when they were pregnant as compared to in the same women after delivery and when breast feeding had ceased. These differences were already present during the first half of pregnancy and were by no means matched by the decrease in dose per kg body weight, which was marginal. Renal excretion and urine levels were unaltered by pregnancy. The data presented in those studies strongly suggest that to a great extent the lower plasma levels and the shorter half-lives are caused by increased renal function in pregnancy. As these antibiotics have a low degree of protein binding it is unlikely that an alteration in the quality or quantity of the protein binding would result in changes of such a magnitude. Controlled studies of antibiotics that are not renally eliminated are lacking. In several uncontrolled studies additional antibiotics have been associated with lower levels in the pregnant than in the nonpregnant patient. Lower plasma levels are definitely associated with lower tissue levels. Lower tissue levels are likely to result in diminished antibacterial effect, possibly insufficient if the minimum inhibitory concentration for the infecting organism is not achieved. There is no good reason why lower plasma and tissue levels in pregnant patients should be accepted as being satisfactory. In serious infections, insufficient levels of antibiotic may fail to influence the course of the disease, and the health of the pregnant woman as well as of the fetus may be jeopardized. In serious and in moderately severe infections the suffering of the pregnant woman may be unduly prolonged. Insufficient treatment of mild infections will probably result only in increased discomfort which could perhaps be avoided by proper dosage. However, in many therapeutic situations the doses of antibiotics normally used are likely to produce serum and tissue levels even during pregnancy in excess of what is required for sensitive organisms.

On the basis of available data increased dosage of antibiotics with minimal toxicity can be advocated during pregnancy. However, in cases of lower urinary tract infections...
the dosage need not be increased because the enhanced renal function will produce urinary levels of the same magnitude as in nonpregnant patients provided such antibiotics are excreted unmetabolized mainly by the kidneys. In serious infections and in cases where antibiotics such as the aminoglycosides are used, or when high antibiotic levels are crucial, close monitoring of the resulting plasma levels to ensure adequate dosing is mandatory.

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References

Management of infection in granulocytopenic patients
Fever occurs in a substantial proportion of the patients receiving cytotoxic chemotherapy: a 40–70% incidence of febrile episodes has been reported. Once fever develops, a specific microbiological diagnosis can usually be made, a posteriori, in 40–50% of the patients (EORTC, 1982; Pizzo et al., 1982) about half of whom will present with bacteraemia.

Since infection in granulocytopenic patients is difficult to diagnose early and may frequently follow a fulminant course, it has been proposed that febrile neutropenic patients should be treated empirically with antimicrobial agents, without waiting for the microbiological proof (Schimpff et al., 1971). Infection caused by Gram-negative bacilli still represents the major risk in febrile granulocytopenic patients; therefore, the regimens to be recommended must be active against these pathogens. Until recently, adequate coverage of most Gram-negative pathogens could be obtained only by combinations of antibiotics. Most studies, so far, have been conducted with combinations of β-lactam antibiotics or combinations of β-lactam drugs with aminoglycosides. Recent investigations (EORTC, 1982; Gurwith et al., 1978) showed an advantage for the β-lactam plus aminoglycoside combinations. Although aminoglycosides are not very effective as single drug therapy in granulocytopenic patients, their use in empirical therapy may 'buy time', allowing the patient to survive until definitive therapy can be devised. Whether the introduction of the new penicillins or cephalosporins will change this approach remains to be seen.

Empirical therapy in granulocytopenic patients should be undertaken with two active drugs according to recently presented evidence (Klastersky & Zinner, 1982).

The clinical significance of therapy with synergistic combinations in granulocytopenic patients has recently been reviewed (Klastersky & Zinner, 1982). There is an obvious advantage for the synergistic combinations as compared with nonsynergistic ones, the respective rates of response in Gram-negative bacillary infections being 79% and 45% respectively. At present it appears that an adequate serum bactericidal titre is also necessary for a favourable outcome in severe Gram-negative bacillary infections in nongranulocytopenic patients; it has been found that a titre ≥ 1 : 8 is associated with a better outcome (Klastersky et al., 1974; Platt et al., 1981). Granulocytopenics may require higher serum bactericidal titres.

A definite increase in the proportion of Gram-positive pathogens in granulocytopenic patients has recently been reported (Wade et al., 1982). These infections have been less aggressive than Gram-negative bacillary infections in granulocytopenic patients, leading to few cases of endocarditis and to a comparatively lower mortality rate. Earlier studies in which an antistaphylo-