Drugs in pregnancy

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Introduction

- The use of drugs in pregnancy is complicated by the potential for harmful effects on the growing fetus, altered maternal physiology and the paucity and difficulties of research in this field.
- There is potential for harmful effects on the growing fetus.
- Because of human variation, subtle effects to the fetus may be virtually impossible to identify.
- There is altered maternal physiology.
- There is notable paucity of and difficulties in research in this area.
- Assume all drugs are harmful until proven otherwise.

Harmful effects on the fetus

- Because experience with many drugs in pregnancy is severely limited, it should be assumed that all drugs are potentially harmful until sufficient data exist to indicate otherwise. ‘Social’ drugs (alcohol and cigarette smoking) are definitely damaging and their use must be discouraged. In the placenta, maternal blood is separated from fetal blood by a cellular membrane .
- Most drugs with a molecular weight of less than 1000 can cross the placenta. This is usually by passive diffusion down the concentration gradient, but can involve active transport. The rate of diffusion depends first on the concentration of free drug (i.e. non-protein bound) on each side of the membrane, and second on the lipid solubility of the drug, which is determined in part by the degree of ionization.
- Diffusion occurs if the drug is in the unionized state. Placental function is also modified by changes in blood flow, and drugs which reduce placental blood flow can reduce birth weight.

Harmful effects on the fetus

- This may be the mechanism which causes the small reduction in birth weight following treatment of the mother with atenolol in pregnancy. Early in embryonic development, exogenous substances accumulate in the neuroectoderm. The fetal blood–brain barrier is not developed until the second half of pregnancy, and the susceptibility of the central nervous system (CNS) to developmental toxins may be partly related to this. The human placenta possesses multiple enzymes that are primarily involved with endogenous steroid metabolism, but which may also contribute to drug metabolism and clearance.
- The stage of gestation influences the effects of drugs on the fetus. It is convenient to divide pregnancy into four stages, namely fertilization and implantation (17 days), the organogenesis/embryonic stage (17–57 days), the fetogenic stage and delivery.

Recognition of teratogenic drugs

Major malformations that interfere with normal function occur in 2–3% of newborn babies, and a small but unknown fraction of these are due to drugs. Two principal problems face those who are trying to determine whether a drug is teratogenic when it is used to treat disease in humans:

1. Many drugs produce birth defects when given experimentally in large doses to pregnant animals. This does not necessarily mean that they are teratogenic in humans at therapeutic doses. Indeed, the metabolism and kinetics of drugs at high doses in other species is so different from that in humans as to limit seriously the relevance of such studies.
2. Fetal defects are common (2–3%). Consequently, if the incidence of drug-induced abnormalities is low, a very large number of cases has to be observed to define a significant increase above this background level. Effects on the fetus may take several years to become clinically manifest.