HORMONALLY ACTIVE DRUGS AND THE FETUS

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INTRODUCTION

The concept that the placenta acts as a barrier blocking transfer of drugs from mother to fetus can no longer be supported and it now must be accepted that most drugs taken by the pregnant woman reach her unborn child (1). The extent to which the fetus is exposed to a maternally derived drug and the results of this exposure depend on many factors. These include maternal issues such as dosing regimen, bioavailability and clearance, the physicochemical properties of the drug, the structure and blood supply of the placenta and clearance of the drug from the feto-placental unit. The effect of maternally derived drugs on the fetus depends, in turn, on the stage of gestation, the ontogeny of drug receptors and metabolic systems and fetal physiology. Many of the drugs used to manage pituitary disease have widespread effects on neurotransmission and possibly on brain development and may also adversely affect development and function of the adrenal, gonads and external genitalia. For many of the drugs there is little information about possible detrimental fetal effects and what information is available is often limited to rather crude estimates of fetal well being such as the absence of malformations and survival.

This chapter reviews general aspects of pharmacokinetics in the materno-fetal unit, the pharmacology of replacement hormones and drugs used to manage pituitary tumors and their influence on the placenta and fetus.
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DRUG HANDLING BY THE MATERNO-FETAL UNIT

Maternal Pharmacokinetics

Before an orally administered drug can be pharmacologically active it must be dissolved in the stomach or small intestine and be absorbed. Intestinal blood travels first to the liver where so-called ‘first pass metabolism’ may significantly reduce the amount of drug that reaches the systemic circulation. Most drugs are small and lipophilic and circulate bound to a lesser or greater extent by proteins. Drugs that are acidic typically bind to albumin and basic drugs are often bound to α₁ acid glycoprotein and lipoproteins. With repeated doses drug plasma and tissue levels progressively rise to eventually reach a plateau. This steady state concentration reflects a balance between the rate of administration and the rate of elimination and the rate at which steady state concentrations are achieved depends on the clearance of the drug. Clearance is often expressed as ‘half-life’ or the time it takes for drug concentrations to fall to half. Drugs are cleared from the body by metabolism or renal excretion. Lipid soluble drugs are often metabolised in the liver to water soluble compounds whereas water-soluble drugs can be excreted unchanged by the kidney.

In pregnancy a series of complex physiological changes alter drug absorption and disposition. Acid secretion by the stomach falls and ionisation of weakly acidic or basic drugs may change, with alterations in absorption. Gastric emptying and gut motility slows as pregnancy progresses and this can reduce the speed of drug absorption. There are also major changes in body water in pregnancy. Maternal plasma and extracellular

Fig 1. Diagrammatic cross section of a terminal chorionic villus. The villus is bathed in maternal blood. The maternal surface of the villus is coated with a highly specialised cell, the trophoblast, and contains fetal capillaries.