Estimation of Rates of Production and Transfer of Hormones in Pregnancy

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Although the level of estrogens, particularly that of estriol, in the urine of the mother is a useful index of fetal viability, little can be learned from it about the secretion and metabolism of hormones made by the fetus and the placenta. Estriol is the end product of a complex array of processes involving the secretion by the fetal and maternal adrenals of neutral precursors such as dehydroisoandrosterone and its sulfate, their hydroxylation at C-16 by the liver and other organs, and, finally, aromatization by the placenta. The estrogens formed in the placenta enter partly into the maternal and partly into the fetal circulations and undergo further metabolism prior to their excretion in the urine. If we are to evaluate the role of hormones in the development of the fetus and to diagnose and treat abnormal conditions of the intrauterine patient, insight must be gained into the processes of synthesis and metabolism. Therefore, methods must be developed to measure rates of secretion and metabolism of the hormones made by the fetus and the placenta. This presentation describes some of our efforts to develop methods to measure rates of entry of steroids into the maternal and fetal circulations as well as to measure rates of exchange between these circulations.

A model schematizing the rates of transfer between maternal and fetal circulations is shown in Figure 1. \( v_{MF} \) is the rate at which a compound, A, is transferred from the maternal to the fetal circulation, \( v_{FM} \) is the rate of transfer in the opposite direction; \( Q_F \) and \( Q_M \) are the rates at which A enters into the fetal and maternal circulations.

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Fig. 1. Model illustrating the fates of a compound in fetal (F) and maternal (M) circulations.

$v_F$ and $v_M$ represent the rates at which A is irreversibly removed from the fetal and maternal blood streams. The precise meaning of each of these rates is evident from the model. For instance, $v_{FM}$ represents the total transfer of A from the fetal to the maternal circulation and includes all pathways by which such transfer may occur. If the compound under study were estradiol ($E_2$), $v_{FM}$ would indicate not only the transfer of $E_2$ directly through the "placental barrier" but also transfers occurring via other routes as, for instance, through the fetal membranes or via metabolic intermediates. An example of the latter mechanisms of transfer would be the following: fetal oxidation of $E_2$ to estrone ($E_1$) and sulfation of $E_1$ to estrone sulfate ($E_1S$), placental hydrolysis of $E_1S$ to $E_1$, release of $E_1$ into the maternal blood and maternal conversion of $E_1$ into $E_2$. It is also evident from the model that $Q_F$, for example, indicates the rate of entry of $E_2$ into the fetal circulation excluding the amount coming from the mother ($v_{MF}$) or reentering from other pools ($w_F$). $Q_F$, therefore, indicates the rate at which the compound enters de novo into the fetal circulation from sources other than the maternal circulation. It is likely that for placental hormones such as $E_2$, progesterone, HCG or chorionic growth hormone-prolactin, $Q_F$ is equal to the rate at which the hormone is released from the placenta into the fetal circulation. The rates of re-entry ($w_F, w_M$) are also well defined by the model. Thus, $w_F$ indicates the rate at which the compound leaves the fetal blood stream and returns to it without appearing in the maternal circulation. Other than these specifications, no assumptions must be made about the fate of the compound during this recirculation.

There are several experimental approaches that will yield data from which $Q_F$, $Q_M$, $v_{MF}$ and $v_{FM}$ (but not $w_F$ or $w_M$) can be calculated. In one such experimental design, tracers of a compound, A, are infused intravenously at a constant rate. For instance, A, labeled with tritium, is infused at a rate $P_F^{3H}$ through a catheter into the fetal circulation while, simultaneously, $^{14}C$-labeled A is infused at a rate $P_M^{14C}$ into a peripheral vein of the mother. If the infusions are continued for an ap-