14 Glucose Metabolism in the Fetal-Placental Unit

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All glucose supplied to the placenta and fetus comes from the maternal glucose pool, produced by maternal glucogenesis or ingested in the pregnant woman's diet. The control of this glucose supply is the maternal arterial glucose concentration. Regulation of maternal glucose concentration is considered elsewhere (see Chapter 8). Regulation of glucose supply to the placenta and fetus, which is far more complex than a simple direct relation with maternal glucose concentration, has been the subject of considerable research for several decades. This interest is appropriate because glucose appears to be the major substrate for placental and fetal energy metabolism, accounting directly for about 85% of placental oxygen consumption and indirectly as glucose plus lactate for about 65% of fetal oxygen consumption in the lamb. Glucose contributes to the production of placental and fetal glycogen and can exchange with other carbon-containing compounds at the three-carbon level of glycolysis.

Although maternal glucose concentration is the driving force for glucose supply to the placenta, glucose transfer to the fetus is driven by the maternal-fetal arterial glucose concentration gradient. This gradient is produced by net placental glucose consumption as well as by glucose utilization in the fetus. Despite net transfer of glucose from the pregnant woman to fetus, tracer experiments have demonstrated that fetal glucose can enter the placenta via specific transporters and can enter the maternal circulation from the placenta. These observations indicate that placental and fetal glucose supply and exchange are intimately related. To the extent that fetal glucose metabolism is independent of supply, it can regulate placental-fetal glucose exchange.

Methods for Determining and Quantifying Placental-Fetal Glucose Exchange*

Net Flux Measurements: Fick Principle

Early studies of placental-fetal glucose exchange relied on measurement of plasma glucose concentration in the maternal (uterine) and fetal (umbilical) circulations. Based on variations in the fetal versus maternal concentration, early investigators such as Widdas proposed placental glucose transport schemes. More recently, measurement of transplacental glucose transport has been accomplished by application of the Fick principle [i.e., computing the product of blood flow times the whole blood glucose concentration difference across the uterine circulation (to quantify net uterine glucose uptake) and the umbilical circulation (to quantify net umbilical glucose uptake)]. Net umbilical glucose uptake represents the net transfer of glucose to the fetus by the placenta. The difference between uterine and umbilical net uptake rates represents the net rate of glucose consumption by the uteroplacental tissues. Equations are presented in Appendix 14.1, and Figure 14.1 which demonstrate this scheme and provide numerical examples. Such tissues include the maternal and fetal vasculature, uterine tissues (e.g., myometrium, endometrium), and the trophoblast itself, as well as other intervening cell layers that are unique to each species. Although the portion of net uteroplacental glucose uptake that is strictly placental (trophoblast) has not been determined, blood flow, Fick principle, and tracer estimates indicate that most net uteroplacental glucose uptake is placental.

The Fick principle method requires much more accurate measurements of glucose concentration (at least to 0.1 mg/dl, preferably 0.01 mg/dl), sampling catheters in the uterine (or other maternal) artery and vein and the umbilical vein and umbilical (or other fetal) artery, and an accurate simultaneous measurement of uterine and umbilical blood flow.

*Editor's note: Major difficulties in measurement of fetal-placental-maternal exchange have necessitated this thorough discussion of methodology.
Application of the Fick principle to quantify placental-fetal glucose exchange provides estimates of flux that represent net rates; that is, they are rates of consumption and indicative of metabolism. Under certain natural conditions (e.g., fetal gluconeogenesis producing net hepatic glucose release into the fetal circulation) or under certain experimental situations (e.g., infusion of glucose into the fetal circulation), Fick principle measurements of placental or fetal glucose metabolism are inadequate to measure total glucose utilization. Under these circumstances, tracer methodology has been applied to quantify glucose utilization rates and turnover rates in the various pools of the maternal-placental-fetal system.

**Tracer Methodology**

Application of tracer methodology to the measurement of maternal-placental-fetal glucose exchange is a complex field of investigation because of the multiple pathways for parallel and divergent fluxes of glucose and tracer glucose and because of different methods of trace administration, sampling, chemical analysis, and modeling. Such issues have been dealt with in extensive reviews.\(^6\)\(^\text{7}\) (See Chapter 1.) The following synopsis is designed to present general principles only. Symbols and equations are presented in Appendix 14.2.\(^6\)\(^\text{8}\)

### Net Utilization Versus Turnover

The term *glucose turnover* has been equated with "glucose utilization" or "glucose consumption," terms that imply metabolism when a whole animal under study functions as one compartment.\(^9\) In such a simple, one-compartment system, glucose turnover rate is the steady-state entry rate or exit rate of glucose into or out of the sampled pool within the "compartment" studied. It is calculated as:

\[
\text{Glucose turnover rate (GTR)} = \frac{r}{SA}
\]

where \(r\) = the rate of tracer glucose infusion (e.g., dpm/min), and \(SA\) = the measured glucose specific activity (e.g., dpm/mg). This equation is derived from the following relations that occur at steady state:

- Glucose turnover rate = glucose entry rate = glucose disappearance (utilization) rate
- Glucose entry rate = \(\frac{\text{pool glucose conc.}}{\text{tracer glucose conc.}}\)
- Tracer entry rate = \(\frac{\text{glucose disappearance rate}}{\text{tracer disappearance rate}}\)

Application of this technique and these equations to the study of fetal metabolism is complicated by the anatomy of the fetal circulation and the permeability...