It is not a new idea that lipid metabolism is altered during pregnancy. Virchow and Becquerel and Rodier observed lipemia during pregnancy in the nineteenth century and concluded that it represented an elevation in plasma lipids. It is known that certain fatty acids are essential in the diet, and it follows that the mother must supply these fatty acids to the fetus.

What is new is a virtual explosion in the study of lipid metabolism. This revolution has been spurred by the growth in cardiovascular disease during the twentieth century, expansion of our understanding of lipoprotein physiology, and the awareness that lipoprotein lipid lowering can prevent coronary artery disease. As techniques and knowledge have grown, investigators with an interest in reproductive biology have performed studies of lipid metabolism as they have been feasible in human and animal models of pregnancy. To date, there has been no concerted effort to understand the relations between the alterations in lipid and lipoprotein metabolism in the pregnant woman and the growth and development of the fetus. It is the purpose of this chapter to describe what is known about alterations in lipid and lipoprotein metabolism in pregnancy and offer hypotheses on ways in which altered lipid metabolism in pregnancy affects fetal growth and development.

Basic Principles of Lipid and Lipoprotein Physiology

The body's fat store is derived from exogenous or dietary sources as well as endogenous synthesis. Fat with an obligatory dietary requirement defines the essential fatty acids (the polyunsaturated 18:2 or 18:3 fatty acids, which are elongated in the body to become precursors for prostaglandin and leukotriene metabolism). This essentiality extends to the 18:2 omega-6 series, where arachidonic acid (20:4) is the elongation product, and the omega-3 fatty acid series, where 18:3 linolenic acid is elongated to eicosapentenoic acid (20:5) and docosahexanoic acid (22:6). These 20- and 22-carbon fatty acids are converted to prostaglandins, which have competitive or alternative effects on a variety of biological processes. The omega-3 series has been reported to be essential for photoreceptor development in animals studied by Connor et al., who showed that omega-3 fatty-acid-deficient subhuman primates give birth to offspring with diminished visual capacity owing to a deficiency of 22:6 fatty acids in the photoreceptor membranes of the retina. Transfer of fatty acids across the placenta is discussed in a later section.

Apart from the requirement for essential fatty acids from the diet by both fetus and mother, all other fats, including cholesterol and fatty acids of varied lengths and saturation, that are required for normal physiological functions are synthesized by the body. Approximately 1.0–1.2 g of cholesterol enters and leaves the body's metabolism per day in nonpregnant persons, and the situation seems to be similar during pregnancy. About 300–500 mg of cholesterol is ingested per day but only about one-half of the cholesterol ingested in the diet is absorbed. Studies of Kesaniemi et al. showed that the fraction of cholesterol absorbed is subject to some autoregulation depending on the low density lipoprotein (LDL) cholesterol levels and the apoprotein (apo) E phenotype present at two alleles in combinations of three isoforms: E2, E3, and E4.

Even with these effects and possibly others on cholesterol absorption, the percentage of cholesterol absorbed from the diet varies only between 40% and 50%. Nothing is known about the effect of pregnancy on this process. Most cholesterol entry into the body pool in nonpregnant individuals and probably pregnant women is derived from endogenous synthesis. This process occurs largely in the liver, to a lesser extent in the intestine, and in certain instances of high metabolic demand in the adrenal, ovary, and testes.

Cholesterol is made available to body tissues that require it for new cell growth or cellular renewal largely by the lipoprotein cascade. By this process,
dietary cholesterol, hepatic cholesterol, and cholesterol stored in various tissues of the body, either normally or abnormally, are continually recycled so as to deliver cholesterol to sites that are in need. One site that is predominantly in need of cholesterol is the growing placenta during normal pregnancy, which synthesizes approximately 400–500 mg of steroid hormones daily, or nearly one-half the estimated daily net cholesterol input and output of the body in a nonpregnant individual. Whether this proportionality applies to pregnancy is uncertain, as cholesterol synthesis has never been measured in human pregnancy. Apart from cholesterol losses in the form of steroid hormones, the single metabolic pathway for sterol excretion in the body is via cholesterol and bile acid secretion in the bile. A schema for lipoprotein metabolism that describes the entry of cholesterol and fat via the diet, its cycling to and from the liver, and its excretion in the bile is shown in Figure 10.1.

Similar to the storage and metabolism of cholesterol, fatty acids are stored in the form of triacylglycerol (triglyceride) largely in adipose tissue, which comprises 15–25% of nonpregnant body weight. Although in situ synthesis of fatty acids in adipose tissue has been demonstrated in nonpregnant and pregnant animal models, little de novo fatty acid synthesis is believed to occur in human adipose tissue; and the circulating lipoprotein cascade is responsible for the delivery of fatty acids derived either from the diet or hepatic synthesis to adipose tissue stores. A recycling system exists in the body for delivering cholesterol and fatty acids, the two main fats of the body, to sites where they are required for new cell synthesis, energy provision, and a host of metabolic signaling processes involving phospholipids, inositol, diacyl glycerol, and prostaglandins and their metabolites.

Normal lipoprotein metabolism in the adult, which meets the needs described above, is depicted in Figure 10.1. Cholesterol and fatty acids, esterified to triglyceride, are absorbed from the intestine and incorporated into chylomicrons in the intestinal enterocyte. They are then slowly secreted into the lymphatic circulation, where they enter the general circulation via the lymphatic duct. These chylomicrons are 2000 Å or more in diameter, are opaque to light, and carry as their primary apoprotein apo B-48, a large hydrophobic apoprotein made entirely in the gut. In subhuman species and young infants, apo B-100 may be formed in the intestine, but this possibility appears not to be the case in mature humans. Smaller apoproteins are associated with chylomicrons during their formation in the gut. They include apo C-I, apo C-II, and apo C-III, which play a catalytic role in chylomicron triglyceride hydrolysis; apo A-I, apo A-II, and apo A-IV, which predominate in HDL; and apo E, mentioned above, which plays a role in chylomicron clearance by the liver. The enzyme responsible for chylomicron triglyceride clearance is lipoprotein lipase (LPL). Lipoprotein lipase is synthesized in a variety of cells but particularly adipose tissue and muscle. It has a protein structure that allows it to migrate to capillary endothelial cells, where it is anchored by a hydrophobic tail while its catalytic component is freely extended into the capillary lumen. This catalytic component can penetrate the polar surface coat of the chylomicron particle (consisting of free cholesterol and phospholipids and proteins) and enters the neutral lipid, triglyceride-containing core where it initiates triglyceride hydrolysis. The process requires apo C-II as a cofactor and is inhibited by apo C-III. The C-II/C-III ratio declines during hypertriglyceridemia and in pregnancy, but the significance of these minor changes regarding triglyceride lipolysis are not known. The process of LPL-mediated chylomicron triglyceride clearance is rapid (half-life of minutes) and provides an efficient mechanism for transporting fat (about 40% of daily caloric intake) quickly through the circulation.

Lipoprotein lipase is subject to regulation, increasing in adipose tissue capillary beds during feeding and with insulin exposure, declining with fasting and insulin deficiency, and reciprocally increasing in heart in muscle during caloric deprivation and declining during the fed state. In this manner, dietary fatty acids are delivered to these tissues appropriately based on metabolic demand. With repeated exposures of the neutral lipid core to LPL, the chylomicron particle progressively becomes smaller, and a relatively cholesterol ester-rich remnant particle emerges. This remnant particle contains variable amounts of apo E, a small 299-amino-acid, arginine- and lysine-rich peptide with a midprotein sequence that binds to specific apo E receptors located on hepatocyte surfaces in the liver. The nature of the receptor is not clearly delineated but is not believed.

![Figure 10.1. Lipoprotein metabolism in the normal adult.](image-url)