**Placental Estriol Synthesis**

The estrogen products released from the placenta are dependent on the substrate available from the developing fetus. Estradiol is the primary placental estrogen secretory product at term. In addition, significant levels of estriol and estetrol are found in the maternal circulation, and they increase, particularly late in gestation (see Fig. 5-22). These hydroxylated forms of estrogen are produced in the placenta using substrates formed by the combined efforts of the fetal adrenal gland and liver.

There are important fetal-maternal interactions through the fetal liver (see Fig. 5-23). High levels of fetal hepatic 16α-hydroxylase act on adrenal-derived steroids. Ryan (1959b) and MacDonald and Siiteri (1965b) found that 16α-hydroxylated C₁₉-steroids, particularly 16α-hydroxydehydroepiandrosterone (16-OHDHEA), were converted to estriol by placental tissue. Thus, the disproportionate increase in estriol formation during pregnancy is accounted for by placental synthesis of estriol principally from plasma-borne 16-OHDHEA-sulfate. Near term, the fetus is the source of 90 percent of placental estriol and estetrol precursor in normal human pregnancy. Thus, the placenta secretes several estrogens, including estradiol, estrone, estriol, and estetrol. Because of its hemorrhoidal nature, most placental estrogens are released into the maternal circulation. Maternal estriol and estetrol are produced almost solely by fetal steroid precursors. Thus, levels of these steroids were in the past as an indicator of fetal well-being. However, low sensitivity and specificity of such tests have caused them to be discarded.

**Enzymatic Considerations**

There is very low expression of the microsomal enzyme 3α-hydroxysteroid dehydrogenase, Δ⁵-4-isomerase (3βHSD) in adrenal fetal zone cells (Doody, 1990; Rainey, 2001). This limits the conversion of pregnenolone to progesterone and of 17α-hydroxyprogrenolone to 17α-hydroxyprogesterone, an obligatory step in cortisol biosynthesis. There is, however, very active steroid sulfotransferase activity in the fetal adrenal glands. As a consequence, the principal secretory products of the fetal adrenal glands are pregnenolone sulfate and DHEA-S. Comparatively, cortisol, which likely arises primarily in the neonate and transitional zone of the fetal adrenal glands and not in the fetal zone, is a minor secretory product until late in gestation.

**Fetal Adrenal Steroid Precursor**

The precursor for fetal adrenal steroidogenesis is cholesterol. The steroid biosynthesis rate in the fetal gland is so great that its steroidogenesis alone is equivalent to a fourth of the total daily LDL cholesterol turnover in adults. Fetal adrenal glands synthesize cholesterol from acetate. All enzymes involved in cholesterol biosynthesis are elevated compared with that of the adult adrenal gland (Rainey, 2001). Thus, the de novo cholesterol synthesis rate by fetal adrenal tissue is extremely high. Even so, it is insufficient to account for the steroids produced by these glands. Therefore, cholesterol must be assimilated from the fetal circulation. Plasma cholesterol and its esters are present in the form of very-low-density lipoprotein (VLDL), LDL, and HDL.

Simpson and colleagues (1979) found that fetal glands take up lipoproteins as a source of cholesterol for steroidogenesis. LDL was most effective, HDL was much less, and VLDL was devoid of stimulatory activity. They also evaluated relative contributions of cholesterol synthesized de novo and that of cholesterol derived from LDL uptake. These authors confirmed that fetal adrenal glands are highly dependent on circulating LDL as a source of cholesterol for optimum steroidogenesis (Carr, 1980, 1981b, 1982).

Most fetal plasma cholesterol arises by de novo synthesis in the fetal liver (Carr, 1984). The low LDL cholesterol level in fetal plasma is not the consequence of impaired fetal LDL synthesis, but instead, results from the rapid use of LDL by the fetal adrenal glands for steroidogenesis (Parker, 1980, 1983). As expected, in the anencephalic newborn with atrophic adrenal glands, the LDL cholesterol levels in umbilical cord plasma are high.

**Fetal Conditions That Affect Estrogen Production**

Several fetal disorders alter the availability of substrate for placental steroid synthesis and thus highlight the interdependence of fetal development and placental function.

**Fetal Demise**

Fetal death is followed by a striking reduction in urinary estrogen levels. Similarly, after ligation of the umbilical cord with the fetus and placenta left in situ, placental estrogens production decline markedly (Cassmer, 1959). However, placental progesterone production was maintained. It was concluded that an important source of precursors of placental estrogen—but not progesterone—biosynthesis was eliminated upon fetal death.

**Fetal Anencephaly**

With absence of the adrenal cortex fetal zone, as seen with anencephaly, the placental estrogen formation rate—especially estriol—is severely limited because of diminished availability of C₁₉-steroid precursors. Therefore, almost all estrogens produced in women pregnant with an anencephalic fetus arise from placental use of maternal plasma DHEA-S. Furthermore, in such pregnancies, estrogen production can be increased by maternal administration of ACTH, which stimulates the DHEA-S secretion rate by the maternal adrenal gland. Because ACTH does not cross the placenta, there is no fetal adrenal stimulation. Finally, placental estrogen production is decreased in women pregnant with an anencephalic fetus when a potent glucocorticoid is given to the mother. This suppresses ACTH secretion and thus decreases the DHEA-S secretion rate from the maternal adrenal cortex (MacDonald, 1965a).

**Fetal Adrenal Hypoplasia**

Congenital adrenal cortical hypoplasia occurs in perhaps 1 in 12,500 births (McCabe, 2001). Estrogen production in these pregnancies is limited, which suggests the absence of C₁₉-precursors.