

Endocrine Regulation of Human Fetal Growth: The Role of the Mother, Placenta, and Fetus

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The environment in which the fetus develops is critical for its survival and long-term health. The regulation of normal human fetal growth involves many multidirectional interactions between the mother, placenta, and fetus. The mother supplies nutrients and oxygen to the fetus via the placenta. The fetus influences the provision of maternal nutrients via the placental production of hormones that regulate maternal metabolism. The placenta is the site of exchange between mother and fetus and regulates fetal growth via the production and metabolism of growth-regulating hormones such as IGFs and glucocorticoids. Adequate trophoblast invasion in early pregnancy and increased uteroplacental blood flow ensure suffi-

cient growth of the uterus, placenta, and fetus. The placenta may respond to fetal endocrine signals to increase transport of maternal nutrients by growth of the placenta, by activation of transport systems, and by production of placental hormones to influence maternal physiology and even behavior. There are consequences of poor fetal growth both in the short term and long term, in the form of increased mortality and morbidity. Endocrine regulation of fetal growth involves interactions between the mother, placenta, and fetus, and these effects may program long-term physiology. (*Endocrine Reviews* 27: 141–169, 2006)

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effects of poor fetal growth. This review will focus on available evidence from human studies and will discuss the role of the mother, placenta, and fetus in the endocrine regulation of fetal growth.

II. The Physiology of Human Fetal Growth and Development

A. The role of the mother in fetal growth regulation

1. *The maternal genome and the maternal environment.* Normal fetal growth involves an increase in cell number during embryonic and fetal development, followed by an increase in cell size, which becomes dominant after 32 wk gestation (1). Fetal growth and development are influenced by genetic as well as environmental factors. Maternal genes have an important specific influence over fetal growth (2). In particular, maternal height, which represents uterine capacity and the potential for growth, is a major determinant of fetal size (3). Although birth weights are similar and correlate among siblings, it is known that environmental influences are also important in determining growth. This is demonstrated by the fact that birth weights are more closely related in half-siblings with the same mother than in those with the same father (4). In a study of pregnancies involving ovum donation, Brooks *et al.* (5) found that the only factors contributing to birth weight were gestational age and the recipient mother's weight, whereas the weight of the donor mother was not related to birth weight. These studies indicate that the uterine environment is a key determinant of fetal growth.

A variety of maternal and uteroplacental factors limit the growth of the fetus. Maternal constraint refers to the limited capacity of the uterus to support fetal growth and is important to limit fetal overgrowth and the subsequent dystocia, to ensure the mother's capacity for future successful preg-

I. Introduction

THE HUMAN FETUS develops along a narrow growth trajectory that must balance the demands of the fetus with the capabilities of the mother. If the fetus grows to be too large, a difficult delivery is likely, putting the mother at risk, whereas being too small has its own risks for the fetus. Understanding the endocrine factors regulating these processes may assist in future clinical care of small neonates, which has the potential to improve the health of the population as a whole. A large body of human data has been collected regarding the physiology of human fetal growth and development as well as the short-term and long-term

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Abbreviations: AME, Apparent mineralocorticoid excess; FEV₁, forced expiratory volume at 1 sec; GR, glucocorticoid receptor; hCG, human chorionic gonadotropin; HPA, hypothalamic-pituitary-adrenal; 11 β -HSD, hydroxysteroid dehydrogenase; 11 β -HSD1, 11 β -HSD type 1; 11 β -HSD2, 11 β -HSD type 2; IGFBP, IGF-binding protein; IUGR, intra-uterine growth restriction; MMP, matrix metalloprotease; MR, mineralocorticoid receptor; PAPP-A, pregnancy-associated plasma protein-A; PG, prostaglandin; SGA, small for gestational age.

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nancies (6). Maternal constraint may be supply limited, by maternal size or nutrient availability, or may be demand driven, as in the case of multiple pregnancies (6).

2. Maternal nutrient intake. The mother is the supplier of oxygen and essential nutrients to the fetus via the placenta. Maternal diet, caloric intake, and metabolic function each have an important role to play in supplying nutrients to the fetus. In addition, alterations in maternal metabolism in response to hormonal signals ensure a redirection of required nutrients to the placenta and mammary gland (7). Increased caloric intake is necessary during the second and third trimesters to cope with most fetal and placental growth (7). Protein intake may be particularly important, and whereas some studies found a relationship between low protein intake in late pregnancy and reduced birth weight (8), others found no effect of protein supplementation on fetal growth in undernourished mothers (9). Nonetheless, supplementation of calories or specific vitamins to undernourished women does increase birth weight in situations of acute and/or chronic starvation (10). For example, folic acid, iron, and vitamin A supplementation to pregnant women in Nepal resulted in an increase in mean birth weight of 37 g and a 16% reduction in the rate of low birth weight compared with pregnant women given vitamin A alone (11). However, multiple micronutrient supplementation with folic acid, zinc, iron, vitamin A, and 10 other micronutrients was not of additional benefit compared with folic acid and iron, suggesting that iron deficiency may be an important cause of reduced fetal growth (11). A Cochrane systematic review of six randomized controlled trials found that balanced protein-energy supplementation was able to reduce the risk of small for gestational age (SGA) neonates by approximately 30% (12). The majority of the evidence comes from trials conducted in developing countries and/or in poor communities, and the relevance for women in developed countries is less clear.

Glucose is an important nutrient in the control of fetal growth. Studies of diabetic women have shown that low blood glucose levels during pregnancy as a result of excessively tight glycemic control lead to a greater incidence of SGA neonates, whereas having high blood glucose levels contributes to a high incidence of macrosomia (13, 14).

Low nutrient intake is associated with poor fetal growth. Compulsory food rationing during the Dutch famine (1944–1945) was as low as 400–800 calories/d at the height of the famine, and when exposure occurred during the second and third trimester, maternal weight gain and fetal growth were significantly reduced (15). Mitchell *et al.* (16) conducted a case-control study to determine the role of maternal diet on the risk of SGA infants. They found that women with babies of normal birth weight consumed more fish, carbohydrate-rich foods, and folate supplements at the time of conception compared with those with SGA babies. In late pregnancy, the only dietary influence on birth weight was the consumption of iron supplements, which correlated with higher birth weights. This study suggested that nutritional effects are most likely to have an influence in early pregnancy.

A recent prospective cohort study of more than 500 preg-

nant women in South Australia investigated the importance of macronutrient intake in early and late pregnancy on placental and fetal growth (17). Maternal dietary intake (total energy, protein, and carbohydrate) was examined using food frequency questionnaires in early pregnancy (16 wk gestation, reflecting diet since conception) and late pregnancy (30–34 wk gestation). A positive correlation was found between the proportion of total energy intake contributed by protein in early pregnancy and birth weight, placental weight, and ponderal index. In addition, there was an inverse relationship between carbohydrate intake in early pregnancy and ponderal index at birth. These relationships were independent of total energy intake, maternal prepregnancy weight, and gestational weight gain. Nutritional requirements for fetal development vary with gestational age, and data from this study suggest that macronutrient intake in early pregnancy had the greatest effects on size at birth (17). Different protein sources may also have specific influences on fetal growth due to their amino acid or micronutrient composition. There is a correlation between dairy protein intake and placental weight (8) and femur growth (18). These studies emphasize the importance of maternal nutritional intake and nutrient availability in contributing to maternal weight gain and adequate fetal growth.

The fetus likely exerts its own influences on maternal nutritional intake. Fetal sex is known to affect fetal growth, with male fetuses being larger, on average, than female fetuses (19). Tamimi *et al.* (20) studied maternal dietary intake during the second trimester of pregnancy and suggested that the fetus may be able to modulate its mother's nutritional input, because women pregnant with a male fetus had a higher energy intake compared with women pregnant with a female fetus. After adjustment for confounding factors, this related to an extra 796 kJ/d contributed by 8% higher protein, 9.2% higher carbohydrates, and more than 10% higher lipid intakes in women pregnant with a male fetus compared with women pregnant with a female fetus (20). Fetal sex-specific signals may have an important influence on fetal growth regulation; however, the nature of these signals is not understood.

3. Maternal uterine artery blood flow. Increased uterine blood flow is essential to meet metabolic demand from the growing uterus as well as the placenta and fetus (21). Total maternal blood volume (22) and cardiac output increase by approximately 40% during pregnancy (23), and the total uteroplacental blood flow represents 25% of cardiac output (21). Thaler *et al.* (24) found that uterine artery volume flow rate increased by more than 3-fold during pregnancy, partly influenced by an increased artery diameter and reduced resistance to flow. In addition to increased uterine blood flow during normal pregnancy, the development of new blood vessels also occurs in the uterus, possibly promoted by the placental hormones human chorionic gonadotropin (hCG) (25) and IGF-II (26). Using Doppler assessment of the uterine arteries at 23 wk gestation, Albaiges *et al.* (27) identified that uterine artery blood flow resistance was associated with an increased risk of subsequent SGA.

4. Influences on maternal development during pregnancy

a. Maternal smoking and drug use. Maternal cigarette smoking is associated with reduced birth weight, and early reports suggested a doubling of the rate of low birth weight in smokers compared with nonsmokers and a dose-dependent effect with increasing number of cigarettes smoked (28–30). More recent studies demonstrate a 3.5-fold increased risk of SGA infants in women who smoke during pregnancy (31), with a greater effect on low birth weight with increasing maternal age (32, 33). Maternal smoking affects the entire range of birth weights, shifting the birth weight distribution curve to the left (34). In 1965, MacMahon *et al.* (34) established that women who smoked before pregnancy but not during pregnancy had babies of similar size to nonsmoking mothers and that paternal smoking also had no influence on birth weight. Smoking reduces birth weight by approximately 150–200 g (35), representing one of the largest preventable effects on intrauterine growth restriction (IUGR) (3). Growth restriction is usually symmetrical with reduced weight, head circumference, and abdominal circumference (1). The mechanism of the effect of maternal smoking relates to both the higher levels of carbon monoxide in maternal blood that cross the placenta to the fetus, leading to fetal tissue hypoxemia (36), and the vasoconstrictive effects of nicotine (37). In addition, there may be an interaction between maternal smoking and nutritional intake, which adversely affects fetal growth. Women who smoke have different diets from nonsmokers, due to the suppression of appetite by smoking (38). Studies have suggested that pregnant smokers have lower circulating concentrations of vitamin C, β -carotene, vitamin B₁₂, vitamin B₆, and folate compared with pregnant nonsmokers, possibly due to lower dietary intake, increased utilization, or decreased absorption of these micronutrients (38). Randomized controlled trials of smoking cessation programs for pregnant women have been successful in improving fetal growth (39).

Components of cigarette smoke have effects on amino acid transport from the mother to fetus. *In vitro*, nicotine has been demonstrated to reduce activity of the major transporter of the microvillous membrane, sodium-dependent system A, in human placental slices, suggesting an independent effect of nicotine associated with IUGR (40). Such changes in amino acid transport are significant for the development of IUGR, due to the small difference between the placenta's capacity to transport amino acids and fetal demand (41).

The use of drugs, such as cocaine and marijuana, also has significant negative effects on fetal growth. Cocaine use contributes to an increased rate of low birth weight and a reduction in mean birth weight by at least 100 g (42, 43). The mechanisms of cocaine's effect include transient vasoconstrictive effects on the placental vasculature and specific inhibition of amino acid transport by systems A and L (41).

b. Maternal hypoxia. Maternal hypoxia influences fetal growth, and its effect is independent of socioeconomic status, prematurity, maternal smoking, pregnancy-induced hypertension, and parity (44, 45). Studies in Colorado have demonstrated a mean difference in birth weight of 241 g between residents of high altitude (2744–3350 m) and lower altitude

(915–1524 m) (45). A 3-fold increase in the rate of low birth weight was found at the highest altitudes in the United States (2500–3100 m) compared with the lowest altitudes (<500 m), with a far greater increase in the proportion of low birth weights due to IUGR than prematurity (44). Altitude is a strong predictor of IUGR through changes in third trimester fetal growth. Krampfl *et al.* (46) performed serial ultrasound measurements of fetal size from 14–42 wk gestation in several hundred women at sea level and at 4300 m in Peru and found that the reduction in fetal growth occurs from approximately 25 wk gestation. The effect of altitude was greater on abdominal circumference than on head circumference, and mean birth weight was reduced by approximately 400 g (46).

The combination of hypoxia and pregnancy appears to be important in alterations in maternal physiology, including changes in immune pathways (47). Coussons-Read *et al.* (47) found that maternal serum levels of the proinflammatory cytokines, TNF- α and IL-6, were increased at high altitude (3100 m) compared with moderate altitude (1600 m), and the antiinflammatory cytokine, IL-10 was decreased by the third trimester, whereas none of these parameters differed between residents of moderate and high altitude at 3 months post partum. Moore *et al.* (48) found that maternal hypoventilation and a decreased maternal arterial O₂ content in the third trimester were directly related to infant birth weight at 3100 m. In women living at high altitude in Peru, an increased ventilatory response to hypoxia during pregnancy was associated with a rise in birth weight through increases in maternal oxygenation (49).

There is an interaction between maternal hypoxia and alterations in placental and uterine blood flow, which could contribute to reduced nutrient transport to the fetus (50). At high altitude, less common iliac flow reaches the uterine artery (51). Despite an increase in uterine artery flow velocity, the uterine artery diameter is reduced, resulting in lower volumetric flow in late pregnancy (51). Studies of the placenta from high-altitude pregnancies have demonstrated that there is less remodeling of the uteroplacental arteries compared with those at moderate altitude (52). These studies suggest that physiological changes in response to high-altitude residence, which reduce blood flow to the fetoplacental unit, are detrimental for fetal growth.

c. Maternal inflammatory diseases. The presence of a maternal inflammatory disease may contribute to reduced fetal growth. We have investigated the effect of maternal asthma on fetal growth and placental function (53–59). Previous epidemiological studies have linked maternal asthma with an increased risk of low birth weight (60); however, the mechanisms are poorly understood. In a prospective cohort study, women with mild asthma were found to have female neonates of reduced mean birth weight, and the use of antiinflammatory inhaled steroid medication for asthma was protective against these changes in fetal growth (55). There were no alterations in fetal growth at 18 and 30 wk gestation as measured by ultrasound, suggesting a late gestation decline in growth, which was accompanied by a reduction in placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) activity (54, 55). We speculate that inflammatory fac-

tors may be involved in the regulation of placental 11 β -HSD2 activity in this context (54, 55). In addition, there may be a role for reduced placental blood flow in altering fetal growth in women with moderate and severe asthma (53).

Several other inflammatory diseases are also associated with reduced fetal growth, including rheumatoid arthritis (61), inflammatory bowel disease (62), systemic lupus erythematosus (63), and periodontal disease (64). In addition, elevated maternal serum or placental inflammatory cytokines have been associated with IUGR (65–67). Women with active inflammatory arthritis during pregnancy had smaller neonates at birth compared with healthy control women or women whose disease was in remission (68), suggesting that active inflammation during pregnancy may contribute to a reduction in fetal growth.

Maternal health influences the maternal state during pregnancy with implications for fetal growth. In addition to inflammatory diseases, many other maternal factors, including preeclampsia (69), anemia (70, 71), infections (1), and alcohol consumption (72), influence fetal growth via changes in placental function.

B. The role of the placenta in fetal growth regulation

The placenta receives and transmits endocrine signals between the mother and fetus and is the site of nutrient and waste exchange. The total placental surface area for exchange is 11 m² at term (73). In fetal growth restriction, both the placental villous surface area and placental volume are decreased (73, 74). Adequate placental growth is essential for adequate fetal growth. SGA neonates have significantly reduced placental weights compared with appropriately grown neonates of the same birth weight (75). Several aspects of placental function are critical for human fetal growth and development, including adequate trophoblast invasion, an increase in uteroplacental blood flow during gestation, transport of nutrients such as glucose and amino acids from mother to fetus, and the production and transfer of growth-regulating hormones.

1. Trophoblast invasion and uteroplacental blood flow. Adequate trophoblast invasion is required to sustain fetal growth. When the blastocyst adheres to the uterus, fetal trophoblast cells differentiate into villous or extravillous cells (23). Migration and invasion of extravillous cytotrophoblasts into the maternal uterine epithelium are processes that are essential for increased uteroplacental blood flow as pregnancy progresses (23). Maternal uterine spiral arteries are transformed into larger, low-resistance vessels (76), capable of transporting the increased maternal blood to the placenta (21). During the modification and remodeling of spiral arteries, the muscular and elastic walls of the arteries are replaced with a fibrinoid layer embedded with trophoblast cells, allowing low-pressure intervillous flow (21, 77). The absence of trophoblast-induced changes in decidual or myometrial segments of spiral arteries is a feature of some pregnancies complicated by fetal growth restriction (78). The syncytiotrophoblast cell layer, which is differentiated from cytotrophoblast cells, is the site where hormones such as estrogen, progesterone, hCG, placental lactogen, and placental GH are produced to maintain the pregnancy (6).

Increased blood flow during pregnancy increases the flow of nutrients from the mother to the fetus. Uteroplacental blood flow was shown to be reduced by up to 50% in women with preeclampsia (79), a group susceptible to IUGR, and uterine artery volumetric flow was also reduced by one third in late gestation in high-altitude pregnancies (51). There is a decrease in number and surface area of terminal villi in IUGR, representing a malfunction of vascularization in these pregnancies (26).

Doppler velocimetry techniques are used to detect increased vascular resistance in the uterine arteries, which occurs as a result of inadequate trophoblast invasion of the spiral arteries (31). In addition, examination of the fetal circulation, particularly umbilical artery waveforms, may reflect placental insufficiency (31). Umbilical vein blood flow, measured by Doppler ultrasound techniques (80), is decreased in IUGR fetuses in relation to fetal size (81), representing reduced perfusion of the fetal tissues (82). A study of 70 human fetuses found a strong correlation between absolute umbilical vein flow and fetal head and abdominal circumferences, with an increase in umbilical vein diameter and mean velocity throughout pregnancy (83). There was also an exponential increase in flow from 97 ml/min at midgestation to 529 ml/min in late gestation, but no corresponding increase in flow per kilogram of fetal weight, suggesting that increasing flow is driving the increase in fetal size in late gestation (83). Di Naro *et al.* (84) also demonstrated reduced umbilical vein flow in IUGR fetuses, both in absolute terms and when adjusted for abdominal circumference. In addition, they found that the cross-sectional area of the umbilical cord and of the umbilical vein itself was lower in IUGR fetuses than normally grown fetuses (84). These studies suggest the importance of trophoblast invasion and changes in uteroplacental and umbilical blood flow for maintaining appropriate fetal growth through the supply of oxygen and nutrients.

2. Nutrient transport across the placenta. The placenta is a metabolically active organ that extracts 40–60% of the total glucose and oxygen supplied by the uterine circulation (85). The remaining nutrients and metabolites are transferred across the placenta to the fetus by passive diffusion, facilitated diffusion, active transport (86), endocytosis, or exocytosis (87). Transport by passive diffusion (of oxygen, carbon dioxide, and urea) is limited by the placental exchange area and blood flow. Facilitated diffusion (of glucose and lactate) involves transfer down a concentration gradient by a carrier molecule, without a requirement for additional energy. Active transport requires both carrier proteins and the input of additional energy (85). Placental transfer increases as the fetal growth rate increases (88).

a. Amino acid transport. Amino acid transporters exist within the fetal (basal) and maternal (microvillous) facing syncytiotrophoblast plasma membranes (89). System A, a sodium-dependent active transporter, is found mostly on the microvillous membrane and transports neutral amino acids such as alanine, proline, glycine, and serine (89). System ASC, found mostly on the basal membrane, transports neutral amino acids (90). Sodium-independent system L transports phenylalanine and branched-chain amino acids (89),

whereas systems y^+ and y^+L transport cationic amino acids such as arginine across the microvillous and basal membranes, respectively (89). Amino acids may also be metabolized and processed by the placenta. For example, leucine is deaminated in the placenta, and the deaminated product and leucine itself are both transferred to the fetus (91).

In fetal growth restriction there are alterations in amino acid transport by the placenta and uptake by the fetus. Jansson *et al.* (92) found that *in vitro* uptake of lysine in the basal membrane and leucine in both the basal and microvillous membranes was decreased in placentae from IUGR pregnancies, suggesting reduced activity of amino acid transporters. Fetal plasma collected at midgestation from SGA fetuses showed a reduction in essential amino acids with lower levels of α -aminonitrogen and decreases in branched-chain amino acids such as valine, leucine, and isoleucine along with serine (93, 94) and phenylalanine (95). Economides *et al.* (86) found that the ratio of nonessential to essential amino acids was increased with fetal hypoxemia, assessed by umbilical vein PO_2 . In IUGR, the activity of system A in the microvillous membrane is reduced (96), whereas the expression and activity of glucose transporters in the syncytiotrophoblast are not changed (90). However, there have also been findings of reduced system A activity in macrosomic babies of diabetic mothers (97), and Godfrey *et al.* (98) described an inverse relationship between size at birth in the normal range and placental system A activity. This increase in activity with reduced size may represent a compensatory mechanism in smaller babies.

Taurine, although not incorporated into proteins, is an essential amino acid for the fetus, with a variety of physiological functions that are important for fetal growth and central nervous system development (99). TAUT is the human taurine transporter that is primarily expressed in the microvillous membrane (100). Norberg *et al.* (99) demonstrated that sodium-dependent transport of taurine was specifically reduced in the microvillous membrane by 34% in IUGR placenta compared with those from normal pregnancies. Roos *et al.* (100) found that the expression of TAUT protein was unaltered in IUGR, confirming that a reduction in activity may be responsible for reduced taurine transport in IUGR.

The fetus may influence the expression of placental amino acid transporters in response to a slowing of fetal growth. Studies in transgenic mice lacking the P0 transcript of the IGF-II gene found that whereas there was a decrease in passive diffusion of nutrients in association with reduced growth, there was an up-regulation of active amino acid transport, possibly as a compensatory mechanism to attempt to improve fetal growth (101). The fetus may signal to the mother, through the placenta, that more nutrients are required in the case of poor growth.

b. Glucose transport. Glucose is the main source of energy for the human fetus and placenta. The fetus produces minimal amounts of glucose, thereby requiring glucose transport from the mother, which is carried out by facilitated diffusion using transporters found on the maternal and fetal sides of the trophoblast (102). Glucose transporter 1 is found in abundance in the microvillous membrane of the syncytiotropho-

blast at levels three times higher than the basal membrane (103). Hypoglycemia in SGA fetuses may be related to reduced supply and transfer of glucose across the placenta (104). In a perfusion study, baseline glucose consumption was 2-fold higher in preterm IUGR placentae compared with normally grown preterm placentae, suggesting that placental consumption of glucose may contribute to alterations in maternal-fetal concentration differences in glucose (105). However, there was no change in glucose transfer to the fetal side of the placenta (105), confirming previous work showing no alteration in glucose transporter expression or activity in IUGR placentae (106, 107). Another study found that the maternal-fetal glucose concentration gradient was increased in relation to the clinical severity of IUGR, possibly representing an adaptation to maintain glucose uptake across the placenta (102).

c. Fatty acid transport. In the third trimester, fatty acids are required for changes in fetal tissue composition, particularly that of the brain and adipose tissue (108). The n-3 and n-6 fatty acid structures can only be acquired from the maternal diet and placental transfer (109). Free fatty acids may be transferred across the placenta via passive diffusion (110) as well as by fatty acid binding proteins and fatty acid transfer proteins in the microvillous and basal membranes (109). The essential fatty acid, linoleic acid, was found to be significantly higher in IUGR placentae compared with those from appropriately grown fetuses (111), which may have implications for fetal brain development (112). The activity of lipoprotein lipase, a triglyceride hydrolase in the microvillous membrane, was recently found to be reduced in preterm IUGR samples compared with gestational age-matched controls (113).

3. Placental hormone production. During human pregnancy, the placenta is an important endocrine organ. It produces numerous hormones, including estrogens and progesterone, hCG, human GH variant, and human placental lactogen. Some of these hormones play a role in the regulation of fetal growth. A study of mothers who were malnourished or anemic found that cord blood concentrations of human placental lactogen, GH, and IGF-I were increased compared with those of healthy pregnant women (114). Another study found a link between changes in placental lactogen measured in maternal serum and the fetal growth velocity, assessed using ultrasound measurements (115). Placental lactogen may promote early embryonic growth (116) and is thought to exert its influence on the fetus by stimulating production of other hormones such as IGF-I and insulin (117). There are little data to suggest a direct role for estrogens and progesterone in human fetal growth regulation; however, some studies have demonstrated correlations between the concentrations of these hormones and birth weight or placental weight (118, 119).

Fetal insulin promotes growth of the fetus, acting as a signal of nutrient availability (120). Insulin deficiency results in a reduction in fetal growth, as the fetal tissues decrease their uptake and utilization of nutrients (121). A recent study demonstrated that venous cord blood concentrations of insulin were significantly lower in SGA neonates and correlated, overall, with birth weight, birth length, and placental

weight (122). On the other hand, the levels of insulin in maternal serum or amniotic fluid were not correlated with birth weight (122). Verhaeghe *et al.* (123) also found a reduced concentration of insulin in the cord blood from SGA neonates compared with appropriately grown neonates and, interestingly, that maternal corticosteroid administration transiently increased the insulin concentration. There is also a relationship between increased insulin production and increased fetal growth. It has been proposed that, in response to maternal hyperglycemia, the fetus increases its production of insulin, and this increase in fetal insulin is responsible for the increased growth and macrosomia observed in diabetic pregnancies (124).

During pregnancy, human GH variant is released into the maternal circulation suppressing production of pituitary GH (85). In IUGR, circulating human GH variant is reduced in maternal serum, and mRNA is reduced in the placenta (85); however, GH is not thought to be the major regulator of fetal growth prenatally, with the IGFs having a more dominant role.

a. The IGF axis. IGF-I and IGF-II are polypeptides with a sequence similar to that of insulin (125). They have mitogenic properties, inducing somatic cell growth and proliferation (126, 127), and they have the ability to influence the transport of glucose and amino acids across the placenta (128). Alterations in the IGF axis are associated with fetal growth restriction in both animal models and human studies.

b. Knockout mice studies. Using knockout and transgenic mice, it has been demonstrated that IGF-I and IGF-II are required for optimal fetal and placental growth (101, 129–131). IGF-I knockouts are 60% smaller than their wild-type littermates with no alteration in placental size (130, 131). IGF-II knockouts are also 60% smaller but, in addition, reduced placental growth is evident from embryonic d 13.5 (129, 130). In IGF-I/IGF-II knockouts, birth weight was further reduced to 30% of normal size (131). Knocking out the IGF-I receptor, either alone or in combination with IGF-I or IGF-II, resulted in postnatal death due to respiratory failure and a 50% reduction in fetal size (131). In recent work, selective mutation of the placental promoter of the IGF-II gene (P0 in mice) resulted in a proportionate reduction in size of all parts of the placenta by embryonic d 12 and in fetal size by d 16, despite the fact that this transcript constitutes only 10% of all placental IGF-II mRNA (101, 132). No further reductions in placental growth were observed when all IGF-II was absent, suggesting that the P0 transcript is essential for determining the action of IGF-II on the placenta (101). Overexpression of the IGF-binding protein (IGFBP)-1, in transgenic mice results in a transient decrease in mid-gestation fetal growth (133).

c. IGF Receptors. The type 1 IGF receptor is a transmembrane heterotetrameric ($\alpha_2\beta_2$) glycoprotein similar in structure to the insulin receptor (134). It binds both IGF-I and IGF-II through an extracellular α -subunit and has 15–20 times greater affinity for IGF-I than for IGF-II (135). In the syncytiotrophoblast, type 1 IGF receptors are found mainly on the microvillous membrane, facing the maternal side (136). The type 2 IGF receptor (mannose-6-phosphate recep-

tor) is a single-chain polypeptide with a high affinity for IGF-II, which is unable to bind IGF-I or insulin (131). Knockout of the IGF-II receptor results in placental and fetal overgrowth (137, 138), whereas recent studies in humans demonstrated that a mutation in the IGF type 1 receptor gene, which results in reduced functioning of the receptor, is associated with poor prenatal and postnatal growth (139).

d. Circulating maternal and fetal IGFs. Serum concentrations of IGF-I and IGF-II are higher in pregnant women than nonpregnant women (140) with concentrations increasing even further by the third trimester (141). These data suggest that the IGFs have a role in fetal growth regulation in addition to their well-characterized effects on postnatal growth (142). Maternal IGF production is stimulated by hormonal signals derived from the placenta. Placental GH and human placental lactogen are synthesized by the syncytiotrophoblast and released into the maternal circulation where they stimulate IGF-I production (143). Placental lactogen is also released into the fetal circulation where it stimulates the IGF axis (143). Hill *et al.* (144) demonstrated that placental lactogen was unable to promote the growth of human fetal fibroblasts and myoblasts in the presence of an antibody against IGF-I. Fetal serum concentrations of IGF-I, IGF-II, and IGFBP-3 increase significantly with advancing gestation, with the greatest rise in IGF-I (145). These circulating fetal IGFs are likely to be derived predominantly from the fetal tissues and may be modulated by the placenta (146).

e. IGFBPs. The actions of IGF-I and IGF-II are modified by the six IGFBPs, IGFBP-1–6 (147). IGFBP-1 is dynamically regulated in human plasma, and its levels can vary more than 10-fold in response to changes in insulin (147). IGFBP-1 binds IGF-I and II with greater affinity than either of the IGF receptors and thus prevents the IGFs from exerting their mitogenic actions (147). IGFBP-2, -4, -5, and -6 are present in low concentrations in plasma (147). IGFBP-3 complexes with IGF-I or II and an acid-labile subunit, acting as a reservoir for IGFs in the circulation (147, 148), and increases in maternal plasma during pregnancy (149).

IGFBP-1 is the major regulator of IGF-I action during pregnancy. It is the main product of the decidua (146, 150), the major IGFBP found in the amniotic fluid (151), and binds IGFs in fetal plasma (152, 153). IGFBP-1 can exist in one of several phosphorylated forms. In the amniotic fluid, there are up to five phosphorylated forms in addition to a nonphosphorylated form of IGFBP-1. Fetal serum contains large amounts of the nonphosphorylated form, whereas decidual cells contain only the phosphorylated forms (154). Jones *et al.* (154) found that the mix of phosphorylated forms of IGFBP-1 had 6-fold higher affinity for IGF-I than the nonphosphorylated form. Subsequently, Westwood *et al.* (153, 155) found that plasma from nonpregnant adults only contained the highly phosphorylated species, whereas pregnant plasma also contained a nonphosphorylated and three less phosphorylated variants, with concentrations at least double that of nonpregnant individuals and higher in multifetal pregnancies (156). These data demonstrate the importance of posttranslational phosphorylation of IGFBP-1 in pregnancy. The highly phosphorylated isoform has the highest affinity

for IGF-I, which is greater than that of the IGF type 1 receptor, resulting in an inhibition of IGF activity, whereas the non-phosphorylated form has a similar affinity for IGF-I as its receptor (153, 157). Dephosphorylation of IGFBP-1 may represent a mechanism by which IGF-I is released and its bioactivity increased in pregnant women. Maternal serum concentrations of IGFBP-1 increase in the first trimester, peak at midgestation and remain constant until delivery, and then fall after birth (158).

Proteolysis of IGFBPs may be an additional mechanism for altering the bioavailability of IGFs during pregnancy. Pregnancy-associated plasma protein-A (PAPP-A) is secreted by the decidua and placenta into the maternal circulation during pregnancy (159), and cleaves IGFBP-4, a potent inhibitor of IGF action, thereby increasing the activity of local IGFs (160). Low circulating levels of PAPP-A in early pregnancy have been associated with an increased risk for IUGR (161). Transgenic mice studies have shown that disruption of the PAPP-A gene results in a 40% reduction in fetal growth (162). A similar proteolytic mechanism operates for IGFBP-1. In first trimester decidualized endometrial cells, proteolysis of IGFBP-1 by matrix metalloproteinase (MMP)-3 or MMP-9 produced fragments that could not bind IGF-I (163). This mechanism was disrupted by tissue inhibitors of metalloproteinases, suggesting that MMPs specifically regulate placental development by increasing the bioavailability of IGFs (163).

f. Placental IGFs. IGF-I and IGF-II are produced by the placenta and may act as local growth regulators (164). The mRNA abundance of placental IGF-II is greater than that of IGF-I at all gestational ages and is found throughout the chorionic villi, chorionic plate, basal plate, and fetal membranes (146, 150). The decidua produces all the binding proteins, with IGFBP-1 in greatest abundance. IGFBP-1 produced by the maternal decidua may be involved in cell to cell communication with IGF-II produced by fetal trophoblast cells (146). The autocrine or paracrine actions of IGF-II and IGFBP-1 may be especially important during implantation and trophoblast invasion (165, 166). IGFBP-3 has been localized to both the microvillous and basal membranes, and IGFBP-1 is predominantly found on the basal surface, facing the fetal side (167).

Immunohistochemistry and *in situ* hybridization studies have shown that placental expression of IGF-I is increased in some cases of IUGR, possibly as a compensatory mechanism for reduced fetal growth (168). However, another study showed that IGF-I secretion from decidual explants was reduced in cases of IUGR, and a correlation with birth weight was observed (169). However, across the birth weight spectrum, no correlation between decidual secretion of either IGF-I or IGFBP-1 and birth weight was noted by the same group, suggesting that reduced IGF-I in IUGR represents a hormonal profile specific to this condition (170). Abnormal production of IGF-I from the placenta has been proposed to play a role in some cases of IUGR (171). Across a group of normal and diabetic pregnancies, placental IGF-II mRNA was positively correlated with placental weight (172).

g. The fetal IGF axis. Most IGFs in the fetal circulation originate from fetal tissues that express IGFs and their bind-

ing proteins, which allow the fetus to adjust local levels of growth factors, thereby modulating cellular growth and differentiation in an autocrine or paracrine manner. Receptors for IGFs have been identified in the human fetus from as early as the first trimester (173), which allow IGF-I and IGF-II to exert growth-promoting effects on fetal cells (174), including fetal fibroblasts, fetal myoblasts (175), and fetal adrenal cortical cells (176). IGF-I itself has been localized to many human fetal tissues, with high expression in the lung and intestine (175, 177). In addition, IGF-II has been found in the fetal kidney, liver, adrenal, and muscle (175) and may be present in larger quantities than IGF-I (178). IGF-II is thought to be the dominant regulator of fetal adrenal growth, due to high expression in midgestation and regulation by ACTH (176). With the exception of the cerebral cortex, IGF-I and IGF-II mRNA expression was also found in all fetal tissues examined by Han *et al.* (179).

In the fetal tissues, IGFBP-1 has been localized to the liver, lung, muscle, kidney, pancreas, adrenal, and intestine (180), and *de novo* synthesis of IGFBP-1 to IGFBP-4 has been observed in fetal liver and kidney explants (181). IGFBP-1 mRNA is predominantly found in the fetal liver, whereas the other IGFBPs are located in most tissues of the fetus (182). IGFs may be complexed to IGFBP-1 on the surface of fetal cells as the pattern of immunostaining for fetal IGFs and IGFBP-1 was found to be similar in most sites (180). The presence of IGF-I and IGF-II mRNA and protein in most fetal tissues suggests a local role for them in modulating growth.

There are fetal sex differences in the IGF axis. IGF-II concentrations in umbilical cord serum from male neonates were significantly higher than those in female neonates (183), and cord plasma IGF-I and IGFBP-3 were higher in female neonates than in males (184). Vatten *et al.* (184) also found that IGFBP-1 in the umbilical cord plasma was lower among females compared with males. A recent study of 987 healthy singletons found that both IGF-I and IGFBP-3 concentrations in cord blood were higher in females than males (185). In this study, there was no difference in IGF-II between male and female neonates, whereas GH concentrations were higher in males than in females (185). These findings suggest that there are sexually dimorphic patterns of fetal growth regulation.

h. The IGF axis and fetal growth. The role of the IGF axis in fetal growth has been studied in monozygotic twins who are genetically identical in addition to sharing a common uterine environment. Twin to twin transfusion syndrome causes the growth of one twin to be compromised as it donates blood to the other, and this condition accounts for a high rate of perinatal mortality (186). It is thought that fetal serum IGF-I concentrations are primarily determined by genetic influences, whereas IGF-II and IGFBP-1 concentrations are determined both by maternal environment and genetic factors (187). Donor twins with twin to twin transfusion syndrome had significantly lower levels of IGF-II and significantly higher levels of IGFBP-1, particularly the inhibitory phosphorylated isoform, compared with their recipient twin (186). In addition, there was a positive correlation between birth weight and IGF-II and a negative correlation with IGFBP-1 (186). Similarly, another study of monozygotic twins with discordant growth found lower IGF-II, similar

IGF-I, and increased total IGFBP-1 in the growth-restricted twin compared with the normally grown co-twin (188). Given that the IGF-I levels in cord blood were similar and are thought to be genetically determined, altered placental production or placental regulation was proposed to contribute to changes in IGF-II and IGFBP-1 in growth-restricted twins (186). Inadequate placental dephosphorylation of IGFBP-1 may lead to alterations in the mitogenic activity of IGF-I and of placenta nutrient transfer stimulated by IGF-I (186).

Alterations in the IGF axis are observed in dichorionic twins and in singletons of low birth weight. Two studies in dichorionic dizygotic twins with discordant birth weight have found that the smaller twin had lower cord blood levels of amino acids and IGF-I and higher levels of IGFBP-1 (188, 189) and that the IGFBP-1 concentration was negatively associated with total essential amino acids (189). Numerous studies, conducted with a range of sample sizes (from 20 to 585 subjects), across a range of birth weights, using either cord blood or fetal blood obtained by cordocentesis, have found a positive relationship between cord blood IGF-I and birth weight in normal term singleton infants (183, 184, 190–198). A summary of these data on the relationship between the IGF axis and fetal growth in singleton pregnancies is presented in Table 1 (183, 184, 190–207). Some have also found a relationship between cord blood IGF-I and other parameters of size such as birth length (184, 193), crown-rump length (199), ponderal index (191) or placental weight (191, 192, 199), but not head circumference (208). In pregnancies complicated by IUGR, umbilical cord blood IGF-I is reduced compared with pregnancies with normal fetal growth (209–213). These differences may be apparent earlier in gestation as measurements of fetal IGF-I and IGF-II by cordocentesis showed that fetal IGF-I and third trimester IGF-II were reduced in cases of growth restriction (211). Some studies have not been able to demonstrate any relationship between cord blood IGF-I and birth weight in normal term infants (203, 206). In addition, the relationship between IGF-II and birth weight is unclear with some groups finding a positive correlation in term singletons (190, 197) and others finding no correlation (183, 191) or no difference between normally grown and growth-restricted groups (209). A positive correlation has been demonstrated between cord blood IGF-II and placental weight (194).

The relationship between cord blood IGFBPs and fetal growth has been investigated extensively (Table 1). There is a positive correlation between IGFBP-3 and birth weight and an inverse correlation between IGFBP-1 and birth weight in preterm and term infants (191, 192, 195, 197, 198, 200, 201, 204, 207). Increased cord blood IGFBP-1 (213) and reduced IGFBP-3 have been observed in IUGR neonates (210, 211, 213). An increase in phosphorylated isoforms of IGFBP-1 and a reduced proportion of nonphosphorylated to total IGFBP-1 was observed in SGA fetuses, suggesting that the bioactivity of IGFBP-1 is increased in cases of poor fetal growth (214).

The relationship between maternal IGFs and fetal growth is less well characterized (Table 1). A positive relationship between maternal IGF-I and birth weight and an inverse relationship between maternal IGFBP-1 and birth weight was observed by Boyne *et al.* (198) in a cohort of 325 pregnant women after 35 wk gestation. Reduced maternal IGF-I (141,

215–217), IGF-II (217), and elevated IGFBP-1 (216) have been described in cases of fetal growth restriction. However, other studies could not demonstrate any association between maternal IGF-I or IGFBP-1 measured at any stage of pregnancy, with birth weight or the development of IUGR (205, 210, 218). Similarly, several studies report no correlation between maternal IGFBP-3 and fetal growth (195). These studies differ in the number of subjects and the birth weight ranges examined and the gestational age at which the samples were collected. Despite the differences in results obtained from the various studies, it is clear that the IGF axis has a crucial role to play in modulating normal fetal growth during human pregnancy, with IGF-I, IGFBP-1, and IGFBP-3 implicated as having central roles in fetal growth and IGF-II having an important role in placental growth.

4. *Effects of endogenous and exogenous glucocorticoids on fetal growth and development.* Glucocorticoids are essential for the development and maturation of fetal organs before birth. In humans and many animal species, there is a rise in cortisol concentrations during late pregnancy that parallels the increased maturity of fetal organs (219). In the sheep, infusion of ACTH, cortisol, or dexamethasone into the preterm fetus resulted in delivery of lambs within 4–7 d (220, 221). Adrenal growth and lung maturation were accelerated compared with term lambs, suggesting an effect of glucocorticoids on fetal lung development (220, 221). Glucocorticoids contribute to maturation of other organs including the thymus, gastrointestinal tract (222, 223), liver (224), and kidney (225). Incubation of human fetal lung explants with dexamethasone stimulates fatty acid synthesis and fatty acid synthetase activity, which are involved in surfactant production (226). Many of the studies on fetal organ maturation by glucocorticoids have been carried out in animals such as the sheep, which may differ significantly from the human.

Betamethasone administration to women at risk of preterm delivery has confirmed the effectiveness of glucocorticoids in maturing the fetal lungs because it lowers the incidence of neonatal respiratory distress syndrome and its associated mortality (227). Glucocorticoid treatment has been shown to result in an increase in the ratio of lecithin to sphingomyelin in amniotic fluid, an indicator of fetal lung development and surfactant synthesis (228, 229). Today, antenatal glucocorticoids are given to 7–10% of pregnant women in Europe and North America (230) during preterm labor, to mature the fetal lungs and reduce the risk of neonatal morbidity and mortality. Several observational cohort studies have suggested that high doses of exogenous glucocorticoids may have adverse effects on the fetus, such as an increased incidence of gastroesophageal reflux (231) and modifications in fetal heart rate (232, 233). *In vitro* studies suggest that effects on the fetal vascular system may be due to the vasodilatory properties of glucocorticoids (234, 235). A significant reduction in birth weight in preterm infants delivered between 30 and 32 wk gestation, by as much as 161 g, has been observed after antenatal dexamethasone treatment, in comparison with an historical cohort that did not receive dexamethasone (236). In observational studies, multiple doses of antenatal glucocorticoids have been linked to small reductions in fetal growth compared with single doses (237).

TABLE 1. Studies of the relationship between the IGF axis and fetal growth in singleton pregnancies

Study	Sample size	Sample type	Measure of fetal growth	Correlation with:			
				IGF-I	IGF-II	IGFBP-1	IGFBP-3
Gluckman <i>et al.</i> , 1983 (183)	206	Umbilical cord serum	Birth weight	+ve	None		
Bennett <i>et al.</i> , 1983 (190)	43 (11 PTD)	Umbilical cord blood	Birth length	+ve	None		
			Birth weight	+ve	+ve		
Ashton <i>et al.</i> , 1985 (199)	20	Fetal plasma (15–23 wk)	Fetal weight	+ve			
			Placental weight	+ve			
			Crown-rump length	+ve			
			Crown-heel length	+ve			
Fant <i>et al.</i> , 1993 (191)	44	Umbilical cord serum	Birth weight	+ve	None	None	+ve
			Placental weight	+ve	None	None	+ve
			Ponderal index	+ve	+ve	None	+ve
			Birth weight			-ve	
Verhaeghe <i>et al.</i> , 1993 (200)	538	Umbilical cord serum	Birth weight				-ve
Wang <i>et al.</i> , 1993 (201)	44 (PTD)	Umbilical cord serum	Birth weight				-ve
Osorio <i>et al.</i> , 1996 (202)	44	Umbilical cord serum	Maternal serum				None
			Umbilical cord serum	+ve	None		+ve
Ostlund <i>et al.</i> , 1997 (192)	27	Fetal serum from cordocentesis	Birth weight	+ve	None		+ve
			Placental weight	+ve			
			Birth weight	+ve			
Klauwer <i>et al.</i> , 1997 (193)	138	Umbilical vein serum	Placental weight	+ve	None	None	+ve
			Birth weight	+ve			
Ong <i>et al.</i> , 2000 (194)	199	Umbilical cord blood	Birth length	+ve	None	None	
			Birth weight	+ve		-ve	+ve
			Birth length	+ve		-ve	+ve
			Head circumference	+ve			
			Ponderal index	+ve	+ve	-ve	+ve
			Placental weight	+ve	+ve	-ve	+ve
Halhali <i>et al.</i> , 2000 (203)	48 (24 PE, 24 NT)	Umbilical cord serum	Birth weight	+ve (PE)			
			Birth length	+ve (PE)			
			Birth weight	+ve (PE)			
Orbak <i>et al.</i> , 2001 (195)	50	Umbilical vein blood	Maternal serum				+ve
			Umbilical vein serum	+ve			None
Christou <i>et al.</i> , 2001 (196)	142	Umbilical cord serum	Birth weight	+ve	None		+ve
Shibata <i>et al.</i> , 2002 (197)	101	Umbilical vein plasma	Birth weight	+ve	+ve		+ve
Vatten <i>et al.</i> , 2002 (184)	585	Umbilical cord plasma	Birth weight	+ve			-ve
			Birth length	+ve			-ve
			Ponderal index	+ve			
			Birth weight	None			None
Verhaeghe <i>et al.</i> , 2002 (205)	289 (24–29 wk)	Maternal serum	Birth weight	None			None
Diaz <i>et al.</i> , 2002 (206)	26 (15 PE, 11 NT)	Umbilical cord serum	Maternal serum (late gestation)	+ve (PE)			
			Maternal serum (late gestation)	+ve (PE)			
Boyne <i>et al.</i> , 2003 (198)	325	Umbilical cord serum	Birth weight	+ve			-ve
			Abdominal circumference	+ve			-ve
			Placental weight	+ve			
			Maternal serum (9, 25, 35 wk gestation)				
			Birth weight	+ve (35 wk)			-ve (35 wk)
Verhaeghe <i>et al.</i> , 2003 (207)	76 (PTD)	Umbilical vein blood	Abdominal circumference	+ve (35 wk)			
			Placental weight	+ve			
			Birth weight	+ve			-ve
			Birth length	+ve			-ve
			Placental weight	+ve			-ve
			Ponderal index	+ve			None

PE, Preeclampsia; NT, normotensive; PTD, preterm delivery.

Repeated courses of betamethasone were associated with a 4% reduction in head circumference and a 9% reduction in birth weight in preterm infants born before 33 wk gestation,

compared with single doses of betamethasone (238). However, these data should be interpreted with caution, because the studies were observational, with a lack of control groups,

potential for confounding, and, in some cases, *post hoc* analysis. In addition, the effect of multiple courses on birth weight was generally quite small [39 g decrease compared with single courses at the same gestational age in the study from Banks *et al.* (237)], and differences in other measures of fetal growth, such as head circumference, were sometimes not observed. Recent evidence from multicenter randomized controlled trials suggests that there is no additional decrease in fetal growth when repeated courses of antenatal steroids are used compared with single doses (239, 240). Moreover, long-term follow-up studies of infants treated with antenatal corticosteroids during randomized trials have also failed to show negative effects of steroid treatment on blood pressure, both in childhood (241) or young adulthood (242, 243).

Although these data from randomized controlled trials in humans are reassuring, many animal studies have demonstrated that administration of exogenous synthetic glucocorticoids can inhibit fetal growth. Synthetic glucocorticoid treatment to pregnant ewes in midgestation results in reduced fetal weight (244), with the greatest effect in animals receiving repeated doses (245). In the sheep model, there are differences in the effects of betamethasone on fetal growth, depending on whether it is administered directly to the fetus or administered to the mother (246). Moss *et al.* (246) found that repeated maternal, but not fetal, injections of betamethasone, reduced birth weight and resulted in reduced fetal calcium and lactate concentrations. Reduced body weight or organ weight at birth after glucocorticoid treatment during pregnancy has also been demonstrated in mice (247), rats (248), rabbits (249), rhesus monkeys (250), and guinea pigs (251). Other effects of glucocorticoid administration in animals included decreased brain weight, neurological damage (252–254), and placental lesions (255). Fowden *et al.* (256) examined the mitogenic effect of endogenous cortisol on sheep fetal growth. In late gestation, the crown-rump length decreased in parallel with the fetal cortisol surge, and this decrease in growth could be prevented by fetal adrenalectomy (256). This study linked the rise in cortisol in late gestation with a reduction in fetal growth in sheep. However, glucocorticoids also stimulate expression of ovine placental 17 α -hydroxylase and parturition with attendant changes in uterine metabolism (257). The effects of glucocorticoids on fetal growth may also be mediated by changes in IGF-I. In pregnant rats, treatment with betamethasone or dexamethasone decreased maternal plasma IGF-I, which was related to reduced liver-to-body weight ratio (258, 259). In human preterm infants treated with dexamethasone postnatally, there was evidence that the growth-suppressing effects of dexamethasone may be mediated by suppression of the IGF axis (260). Indirectly or directly, glucocorticoids have a beneficial effect on fetal organ maturation before birth but may also have the potential to reduce fetal growth.

a. The placental glucocorticoid barrier, 11 β -HSD. In human pregnancy, endogenous maternal cortisol concentrations are 5–10 times higher than fetal cortisol concentrations (261–263), and this difference is maintained by the presence of 11 β -HSD2 in the placenta, which acts as a barrier enzyme to control the passage of cortisol from mother to fetus. Two isoforms of 11 β -HSD, which interconvert glucocorticoids

with their inactive 11-keto metabolites, have been cloned and characterized in humans (264, 265). The reduced nicotinamide adenine dinucleotide phosphate-dependent 11 β -HSD type 1 (11 β -HSD1) catalyzes the bidirectional interconversion of cortisol and cortisone, but acts primarily as an oxidoreductase, converting cortisone to cortisol, due to its higher affinity for cortisone [Michaelis-Menten constant (K_m) in the nanomolar range] compared with cortisol (K_m in the micromolar range) (266). The nicotinamide adenine dinucleotide-dependent 11 β -HSD2 is a high-affinity unidirectional enzyme: it catalyzes only the dehydrogenase reaction, which converts active cortisol to inactive cortisone (267). 11 β -HSD1 and 11 β -HSD2 are members of the short-chain alcohol dehydrogenase superfamily (268), sharing about 21% homology (269), and the genes encoding them are found on chromosome 1 (264) and chromosome 16 (270), respectively.

11 β -HSD1 is mostly found in tissues such as the liver (271), adipose tissue (271), lung (272), and testis (273) with its main function being to increase the availability of glucocorticoids for the glucocorticoid receptor (GR), allowing prereceptor control of local glucocorticoid action (269). In the gestational tissues, 11 β -HSD1 is found in the decidua (271, 274) and chorion (275), and the endothelium of placental villous tissue (275), where it regulates the effect of cortisol on other placental pathways such as prostaglandin (PG) biosynthesis and metabolism (276, 277).

11 β -HSD2 is found in specific tissues such as the kidney (278, 279), colon (280), adrenal (271), and the placenta (279, 281). Its presence in mineralocorticoid target tissues, especially the kidney, is necessary to protect the mineralocorticoid receptor (MR) from occupation by cortisol (282). Cortisol has a much higher plasma concentration than aldosterone, the “natural” mineralocorticoid, but the two compounds have equal affinity for the MR (283). The 11-keto metabolites formed by 11 β -HSD2 are unable to bind to the MR, whereas aldosterone is not metabolized by 11 β -HSD2 and therefore remains active. Overactivation of the MR by cortisol leads to sodium retention and potassium excretion in the renal tubules, resulting in hypertension and suppression of the renin-angiotensin system (284). This can occur after excess ingestion of licorice, which contains the 11 β -HSD inhibitor, glycyrrhetic acid (285), and in a congenital disease known as apparent mineralocorticoid excess (AME), which results from mutations of the 11 β -HSD2 gene (286).

The primary function of placental 11 β -HSD2 is to maintain the glucocorticoid balance and protect the fetus from the high concentrations of endogenous maternal glucocorticoids (287). Synthetic glucocorticoids such as dexamethasone and betamethasone are not extensively metabolized by placental 11 β -HSD2, possibly due to protection from their 9-halogen group (288, 289). In addition to its barrier role, 11 β -HSD2 in the placenta may also protect the MR as in tissues such as the kidney (290, 291). Hirasawa *et al.* (290) colocalized 11 β -HSD2 and MR immunoreactivity and mRNA in the placenta and suggested a role for 11 β -HSD2 in regulation of maternal-fetal electrolyte and water transport in the placenta in addition to its barrier role. Driver *et al.* (291, 292) have also found mineralocorticoid-responsive genes and a functional MR in human cytotrophoblast cells, suggesting that 11 β -HSD2 may be involved in placental sodium transport.

The ability of the placenta to metabolize cortisol and other glucocorticoids to 11-keto products was first described by Osinski (281) in 1960. An immunohistochemical study by Krozowski *et al.* (279) found that 11 β -HSD2 was localized to syncytiotrophoblast cells lining the chorionic villi. Similarly, Hirasawa *et al.* (290) detected 11 β -HSD2 immunoreactivity in syncytiotrophoblast from 5 wk to term. In placental bed biopsies, 11 β -HSD2 immunoreactivity was found in fused syncytiotrophoblast, invasive extravillous trophoblast, and trophoblast lining the maternal spiral arteries (292). Sun *et al.* (275) found 11 β -HSD2 mRNA (but not 11 β -HSD1) in the placenta and no expression of 11 β -HSD2 in the amnion, chorion, or deciduas. Activities of both the type 1 and type 2 enzyme were demonstrated in the human perfused placenta by Sun *et al.* (293), whereas Benediktsson *et al.* (287) found that most of the maternally administered cortisol was converted to cortisone with no cortisone to cortisol conversion detected. Dodds *et al.* (294) also demonstrated cortisol to cortisone conversion in the perfused placenta, which could be eliminated by coprefusion with the 11 β -HSD inhibitor, glycyrrhetic acid.

Immunohistochemical studies have localized 11 β -HSD1 to the chorion trophoblast, amnion epithelial cells, the endothelium of placental and umbilical blood vessels, and the decidua (275). Others have confirmed the presence of 11 β -HSD1 in decidual stromal cells (271, 292). 11 β -HSD1 mRNA was found in the amnion and placenta, with the greatest abundance in the chorion (275).

Human studies on changes in the expression and activity of the 11 β -HSD isozymes in the placenta and fetal membranes throughout gestation have produced conflicting results. In 1973, Beitins *et al.* (295) demonstrated that at term, 75% of the cortisol found in the fetus was of fetal origin, whereas all the cortisone in the fetus was of maternal origin. This suggested that placental 11 β -HSD2 was acting as an effective glucocorticoid barrier at term and that fetal cortisol was mainly derived from the fetal adrenal and not from a maternal source (295). Similar work from Murphy *et al.* (296) indicated that high levels of 11 β -HSD activity were present in early gestation (13–18 wk), with 85% of infused maternal cortisol converted to cortisone by the placenta. Giannopoulos *et al.* (297) examined placental 11 β -HSD activity and found that type 2 activity predominated and that this activity decreased from early (8–12 wk) to late (38–40 wk) gestation. Similarly, Blasco *et al.* (298) described a decrease in placental 11 β -HSD2 activity from early to late gestation. Studies have shown an increase in 11 β -HSD1 conversion of cortisone to cortisol in the fetal membranes with advancing gestational age (299, 300). No labor-associated changes in 11 β -HSD2 mRNA abundance or enzyme activity have been described (275, 301, 302). These studies suggest that the barrier function of 11 β -HSD, although effective throughout pregnancy, may decrease with increasing gestation.

More recent studies have described an increase in 11 β -HSD2 activity (303, 304) and mRNA abundance (305) in the placenta from mid to late gestation. Shams *et al.* (304) compared samples collected in the first and second trimester with preterm samples (27–36 wk gestation) and term placenta (39–40 wk gestation). They did not examine any trends within the term group, but found an overall increase in

placental 11 β -HSD2 activity across the whole of pregnancy (304). Similarly, Schoof *et al.* (305) compared a preterm group with a term group, with a wide range of gestational ages from 18–41 wk, finding an overall increase in 11 β -HSD2 mRNA. In 2003, Kajantie *et al.* (306) published a report on 107 small preterm placentae (22–32 wk) and demonstrated a fall in placental 11 β -HSD2 activity rate as gestation progressed. In the guinea pig, a species with a hemomonochorial placental structure similar to that of the human, 11 β -HSD2 activity falls significantly in late gestation (307). Murphy and Clifton (302) found a decrease in 11 β -HSD2 activity in the last few weeks of human gestation and an increase in placental 11 β -HSD1 mRNA abundance with spontaneous labor. This may be a mechanism by which cortisol concentrations rise at term to regulate fetal maturation and activate pathways associated with labor (302).

b. Placental 11 β -HSD2 and fetal growth. Placental 11 β -HSD2 is important in the regulation of fetal growth, and reductions in 11 β -HSD2 activity have been associated with reduced human fetal growth, as outlined in Table 2 (54, 55, 304, 306, 308–313). Shams *et al.* (304) demonstrated that there was a significant reduction in enzyme activity in placentae from pregnancies complicated by IUGR compared with normally grown term deliveries and appropriately grown preterm deliveries. Further work demonstrated that there were also reductions in 11 β -HSD2 mRNA levels but no mutations in the gene (311). In pregnant women with asthma, we found that reduced birth weight in female neonates was specifically associated with reduced placental 11 β -HSD2 activity, but not protein or mRNA levels, which suggests posttranslational regulation (54, 55). One study found a positive correlation between placental 11 β -HSD2 activity and birth weight in 27 term placentae (308). However, a larger study from this group with 111 samples was unable to confirm this result (309). In the latter report, only one neonate was low birth weight, suggesting that the correlation between 11 β -HSD2 activity and birth weight may not be apparent within the normal weight range, but may become more significant when low birth weight infants are studied (309). Hofmann *et al.* (312) found no correlation between placental 11 β -HSD2 activity and birth weight in healthy term pregnancies or in pregnancies complicated by hypertension or IUGR. However, others have reported reduced 11 β -HSD2 activity or mRNA in placentae from patients with preeclampsia, where there was decreased fetal growth, compared with normotensive pregnancies (310, 313). Kajantie *et al.* (306) observed a positive correlation between relative birth weight and placental 11 β -HSD2 activity in small preterm infants between 22 and 32 wk gestation. In addition, lower birth weight was associated with reduced umbilical cord vein cortisone, confirming the reduction in transplacental cortisol to cortisone conversion in association with reduced fetal growth (306).

AME results from mutations of the 11 β -HSD2 gene and is associated with moderate IUGR (314, 315). Kitanaka *et al.* (314) found that 17 of 18 AME patients had a birth weight less than 2700 g. Placental 11 β -HSD2 activity was examined in a 28-wk twin stillbirth from a family with two other children with AME (315). Placental 11 β -HSD2 activity was approximately 15% of that in five gestational age-matched controls,

TABLE 2. Studies of the relationship between placental 11 β -HSD2 and human fetal growth

Study	Sample size	Sample type	Population	11 β -HSD2 assay	Findings
Stewart <i>et al.</i> , 1995 (308)	27	Placental homogenates	Term	Activity	Positive correlation between activity and birth weight, but not with placental weight
Rogerson <i>et al.</i> , 1997 (309)	111	Placental homogenates	Term	Activity, mRNA (Northern blot)	No correlation between activity and birth weight
Shams <i>et al.</i> , 1998 (304)	101	Placental homogenates (activity), fixed placenta (IHC)	First trimester (n = 16), second trimester (n = 9), PTD AGA (n = 14), term (n = 50), IUGR (n = 12)	Activity, IHC	Activity reduced in IUGR compared to term or preterm AGA groups
McCalla <i>et al.</i> , 1998 (310)	28	Placental homogenates	Normotensive (n = 17), PE (n = 11)	Activity, cord blood cortisol	Activity lower in PE and accompanied by an increase in cord blood cortisol
McTernan <i>et al.</i> , 2001 (311)	86	Placental tissue	First trimester (n = 35), second trimester (n = 6), PTD (n = 4), term (n = 22), IUGR (n = 19)	mRNA, gene mutations	Decreased mRNA in IUGR compared to gestational age matched controls. No mutations found in 11 β -HSD2 gene
Hofmann <i>et al.</i> , 2001 (312)	195		Healthy controls (n = 133), PIH (n = 26), PIH + proteinuria (n = 21), IUGR (n = 15)	Activity	No correlation between activity and birth weight in healthy, PIH, or IUGR
Schoof <i>et al.</i> , 2001 (313)	55	Placental tissue	Healthy controls (n = 20), PTD (n = 17), PE (n = 18)	mRNA (quantitative RT-PCR)	Activity 3-fold lower in PE compared to healthy controls. Correlation between mRNA and birth weight and placenta weight in term placentae
Murphy <i>et al.</i> , 2002 (54)	74	Placental microsomal homogenates (activity and protein) and placental tissue (mRNA)	Healthy controls (n = 11), asthma (n = 63)	Activity, protein (Western), mRNA (quantitative RT-PCR)	Reduced activity in women with asthma who did not use ICS associated with lower birth weight centile
Murphy <i>et al.</i> , 2003 (55)	65	Placental microsomal homogenates (activity and protein) and placental tissue (mRNA)	Healthy controls (n = 11), asthma no ICS (n = 14), asthma + ICS (n = 40)	Activity	Reduced activity in female neonates (mothers with asthma, no ICS use) in association with reduced birth weight
Kajantie <i>et al.</i> , 2003 (306)	107	Placental homogenates	Small preterm	Activity rate, total activity, cord vein cortisol and cortisone	Positive correlation between birth weight and activity rate, total activity, and cord blood cortisone

IHC, Immunohistochemistry; PTD, preterm delivery; AGA, appropriate for gestational age; PE, preeclampsia; PIH, pregnancy-induced hypertension; ICS, inhaled corticosteroid.

and immunohistochemical staining for 11 β -HSD2 was virtually absent in the AME placenta (315). Both the siblings with AME and the placenta were shown to have a point mutation in exon V of the 11 β -HSD2 gene (315). There have been other reports of stillbirth in families with 11 β -HSD2 mutations and AME (316). These studies suggest that reduced 11 β -HSD2 activity may be related to reduced fetal growth and possibly an increased risk of fetal death.

c. 11 β -HSD2 in the fetus. The midgestation human fetus (16–19 wk) contains 11 β -HSD2 mRNA and activity, but not 11 β -HSD1, in the kidney, lung (317), gonad, liver, adrenal (318), and colon (319–321). 11 β -HSD2 is colocalized with the

GR (322) or MR (323) in many tissues. The presence of placental 11 β -HSD2, high levels of 11 β -HSD2 activity in fetal tissues, and the absence of 11 β -HSD1 in the fetus all contribute to a predominance of cortisone over cortisol in the fetal circulation (324). The presence of 11 β -HSD2 enzyme in the fetal tissues may serve to locally regulate the positive and negative effects of glucocorticoids on the fetus.

d. Regulation of placental 11 β -HSD2. Placental 11 β -HSD2 is an important modulator of fetal glucocorticoid exposure, and it is regulated by many placental hormones and factors associated with pregnancy, including estradiol, progesterone, and PGs. In syncytiotrophoblast cell cultures, progesterone

reduced 11 β -HSD2 activity, in a dose-dependent manner, through a non-receptor-mediated mechanism and also reduced 11 β -HSD2 mRNA abundance, an effect that was reversed by treatment with progesterone receptor antagonists (325). In addition, Pepe and Albrecht (326) reported that 11 β -HSD2 activity in human and baboon placental homogenates was inhibited by progesterone. Estradiol was found to significantly decrease activity but not mRNA of 11 β -HSD2 in cultured placental cells (325). Nitric oxide donors inhibit 11 β -HSD2 mRNA and activity in syncytiotrophoblast cells cultured for 72 h, through a cyclic GMP-mediated pathway (327). Activators of the cAMP pathway, such as forskolin, increase 11 β -HSD2 activity and mRNA expression in JEG-3 choriocarcinoma cells (328) and syncytiotrophoblast cells (325), whereas activation of the protein kinase C pathway by phorbol 12-myristate 13-acetate had no effect on placental 11 β -HSD2 (325, 328). ATP has been shown to increase placental 11 β -HSD2 activity in microsomes via a mechanism independent of phosphorylation (329). Tremblay *et al.* (330) found that retinoic acids, the major metabolites of vitamin A, stimulated 11 β -HSD2 activity in JEG-3 cells in a dose-dependent manner via an increase in mRNA expression.

Hardy *et al.* (331) examined the effect of the PGs, PGE₂ and PGF_{2 α} and the leukotriene LTB₄ on 11 β -HSD2 activity and gene expression in JEG-3 cells. PGE₂ and PGF_{2 α} reduced 11 β -HSD2 activity to 75% of the untreated level. Blocking PG synthesis with the cyclooxygenase inhibitor indomethacin, however, did not reverse the effect but also resulted in inhibition. LTB₄ treatment resulted in a dose-dependent inhibition of 11 β -HSD2 activity. Importantly, this study showed that there were no corresponding changes in the mRNA abundance of 11 β -HSD2 by treatment with PGE₂, PGF_{2 α} or LTB₄, indicating that their effect was posttranslational (331).

Recent work from Alfaidy *et al.* (332) showed that oxygen may be an important regulator of placental 11 β -HSD2. In this study, incubation of first-trimester placental villous explants or trophoblast cell cultures from term placentae under 20% O₂ led to a significant increase in 11 β -HSD2 protein expression and activity compared with incubation under 3% O₂ (332). Similarly, Hardy and Yang (333) found that 11 β -HSD2 protein and activity more than doubled when cytotrophoblast cells differentiated into syncytiotrophoblasts under 20% O₂. However, when cells were cultured under 1% O₂, they did not differentiate and 11 β -HSD2 was not increased (333). This may be a mechanism by which maternal hypoxia influences fetal growth.

11 β -HSD2 activity is inhibited by calcium in placental microsomes and in JEG-3 cells via a posttranslational mechanism (334). Calcium, previously shown to inhibit placental 11 β -HSD2 activity, is a common second messenger for leukotrienes and PGs (331). Inhibition by calcium was reversed by the addition of a calcium chelator, and inhibition did not alter the binding capacity for cortisol and could not be overcome by the addition of extra cofactor, indicating that the effect was mediated through a change in the enzyme's catalytic efficiency (334). The catecholamines, epinephrine and norepinephrine, also inhibited placental 11 β -HSD2 through a decrease in mRNA in trophoblast cells (335). Because catecholamines are released during stress, this may be a mechanism linking prenatal stress with altered fetal development.

The regulation of 11 β -HSD2 activity has also been studied in other cell types. In the kidney, progesterone and its metabolites, such as 5 α -dihydro-progesterone, have been shown to inhibit microsomal 11 β -HSD2 (336). Hypoxia also inhibited 11 β -HSD2 activity in a renal epithelial cell line, and this study demonstrated reduced renal 11 β -HSD2 in healthy men as a result of ascending to high altitude (337). In bronchial epithelial cells, dexamethasone was found to increase 11 β -HSD2 mRNA and protein and increase activity over 72 h in a dose-dependent manner (338). Previous work in osteosarcoma cells indicated that the proinflammatory cytokines, TNF- α and IL-1 β , inhibit both activity and mRNA expression of 11 β -HSD2 in a dose-dependent manner (339). However, the effect of these and other inflammatory cytokines on placental 11 β -HSD2 has not been examined.

Glucocorticoids have an important role in the regulation of fetal development, *i.e.*, promoting maturation of organs required for extrauterine survival. An important prereceptor mechanism exists to control the actions of glucocorticoids during pregnancy in the form of placental and fetal 11 β -HSD2. Alterations in the activity of the placental 11 β -HSD2 barrier, which result in an increase in maternal glucocorticoids crossing to the fetus, may have a deleterious effect on fetal growth and postnatal development.

e. The role of 11 β -HSD2 in fetal programming. Glucocorticoids are thought to have a role in the fetal origins of adult disease. Although no human studies have investigated the relationship between changes in placental 11 β -HSD2 and health outcomes in later life, animal studies have implicated decreased 11 β -HSD2 activity in fetal programming.

In rats, Benediktsson *et al.* (248) showed a positive correlation between placental 11 β -HSD2 activity and term fetal weight and a negative correlation with placental weight. Treatment of pregnant rats with dexamethasone, a steroid not extensively metabolized by placental 11 β -HSD2, resulted in a decrease in maternal weight gain, reduced birth weight, and significantly raised blood pressure 140–150 d after birth compared with untreated rats (248). This study proposed that the relationship between low birth weight, high placental weight, and increased adult blood pressure may be mediated by glucocorticoid exposure *in utero* (248).

Levitt *et al.* (340) found that administration of dexamethasone to rats in late pregnancy resulted in an 11% reduction in birth weight and elevated blood pressure in offspring at 16 wk of age. The same group later demonstrated that inhibition of placental 11 β -HSD2 by carbenoxolone treatment throughout pregnancy gave similar results (341). They observed a 20% decrease in birth weight and elevated blood pressure in adult offspring. When mothers were adrenalectomized, this effect did not occur, highlighting the importance of exposure to maternally derived endogenous glucocorticoids (341). Similar studies by another group found that maternal carbenoxolone treatment in pregnant rats resulted in smaller offspring with glucose intolerance in later life and reduced hepatic 11 β -HSD1 and reduced renal 11 β -HSD2 gene expression (342).

Maternal protein restriction has been shown to decrease birth weight and placental 11 β -HSD2 activity in rats (343). In early adulthood, offspring also had raised systolic blood

pressure (343). The study by Langley-Evans *et al.* proposed that maternal undernutrition results in fetal glucocorticoid exposure, which leads to the programming of hypertension in later life (343). Further work demonstrated that a low protein maternal diet reduced 11 β -HSD2 gene expression in the rat placenta and in the fetal and neonatal kidney and adrenal (344). The authors suggested that altered exposure of the fetus and, in particular, the fetal kidney to glucocorticoids may lead to the observed increase in GR protein and mRNA expression in the kidney, which was a possible mechanism for raised blood pressure in later life (344).

A recent study by Bloomfield *et al.* (345) has suggested that factors other than glucocorticoids may play a role in fetal programming. In the sheep, they found that maternal undernutrition for 60 d before conception, and for the first 30 d after mating, resulted in alterations in the development of the fetal hypothalamic-pituitary-adrenal (HPA) axis. However, these changes occurred in the absence of elevated maternal cortisol concentrations. In fact, maternal cortisol and ACTH levels were greatly suppressed during undernutrition, suggesting that programming of the fetal HPA axis may occur without excess glucocorticoid exposure (345).

f. Sexually dimorphic responses to glucocorticoids in the human fetus. Studies in humans and animals indicate that there are fetal sex-specific responses to glucocorticoids. These data have implications for understanding the fetal response to stress, responses to antenatal glucocorticoid treatment, and long-term programming. We have collected information from pregnant women with and without asthma and found that the presence of asthma had sex-specific effects on fetal growth and placental function. Pregnant women with asthma, who did not use preventative inhaled steroid medication, had smaller female neonates (55). The reduction in female fetal growth was accompanied by a significant reduction in placental 11 β -HSD2 activity (55). Overall, placental 11 β -HSD2 activity was higher in samples collected from female fetuses than males (55, 56), suggesting that placental glucocorticoid metabolism differs according to the sex of the fetus. Similar results have previously been reported in the mouse placenta (346) and adult human kidney 11 β -HSD2 (347). This may contribute to altered sensitivities to the effects of glucocorticoids in male and female fetuses (56). Despite the reduction in placental 11 β -HSD2 activity with maternal asthma and female fetal sex, there was a nonsignificant alteration in cord blood cortisol, but a significant reduction in cord blood estriol was observed (55). These data suggest that alterations in glucocorticoid metabolism in the female fetus result in downstream effects on glucocorticoid-regulated pathways. In the presence of maternal asthma, placental 11 β -HSD2 activity was unaltered in males, and cord blood cortisol levels were similar to those in females, whereas there was no change in estriol. These data suggested that the male fetus was less sensitive to the effects of glucocorticoids compared with the female fetus.

These differences in fetal response to glucocorticoids may have been due to alterations in GR or MR expression. In asthmatic pregnancies, decreased placental GR α and MR mRNA was observed in female fetuses, whereas there was an increase in placental GR α and MR mRNA in male fetuses

(56). There may also be differences in receptor expression at the level of the promoter, due to regulation by sex steroids.

Several factors responsible for fetal growth regulation during human pregnancy may be altered in a fetal sex-specific manner, which could contribute to increased susceptibility to low birth weight in the male fetus, as observed with maternal smoking (348) and caffeine intake (349), or to an increased susceptibility to low birth weight in the female fetus, as observed with hypertension-associated IUGR (348).

5. Imprinted genes in placental and fetal development. Genomic imprinting may be the result of an evolutionary conflict between maternal and paternal alleles, particularly in the context of nutrient transfer from mother to fetus (350). Imprinting refers to the inheritance of some genes primarily from the maternal allele, and of others primarily from the paternal allele (351). In mammals, many imprinted genes have roles in fetal growth and development and influence placental function (352), being expressed in the placenta and fetus, where they act to control resource utilization (353). In general, paternally inherited genes increase the transfer of resources (nutrients) to the fetus, thereby promoting growth; conversely, maternally inherited genes reduce nutrient transfer to the fetus, thereby conserving maternal resources for future offspring (353).

The IGF-II gene is paternally expressed, whereas the IGF-II receptor gene is maternally expressed. Mutations of these genes are associated with disorders of fetal growth, such as the fetal and postnatal overgrowth observed in Beckwith-Wiedemann syndrome, as a result of overexpression of IGF-II (354). Mouse knockout studies have also demonstrated that altered expression of imprinted genes can cause changes in the ability of the placenta to exchange nutrients by altering the thickness and surface area of exchange in placental tissues (355). It is possible that imprinted genes may also play a role in the regulation of placental blood vessel development and the control of nutrient transporter expression and, in this way, they may also indirectly control fetal growth and development (353).

Genomic imprinting is an example of the delicate balance that is human fetal growth regulation. The needs of the mother must be protected, while also allowing the fetus to grow to its genetic potential. The mother and fetus interact via endocrine signals from the placenta, which control the complex process of fetal growth. Environmental influences that alter any aspect of placental function, such as blood flow, nutrient transporter expression, glucocorticoid metabolism, or hormone production, play a significant role in reducing fetal growth, with consequences for long-term health.

6. Summary. Figure 1 summarizes the interactions between the fetus, placenta, and mother described in this section. The fetus communicates with the mother via the placenta. The maternal genome and environment interact to influence maternal development before pregnancy. Several factors, including maternal health, smoking, hypoxia, and nutritional status, influence the maternal pregnancy state. Hormones produced by the placenta influence maternal metabolism and behavior, nutrient intake, and uterine artery blood flow. These changes are necessary to promote placental develop-

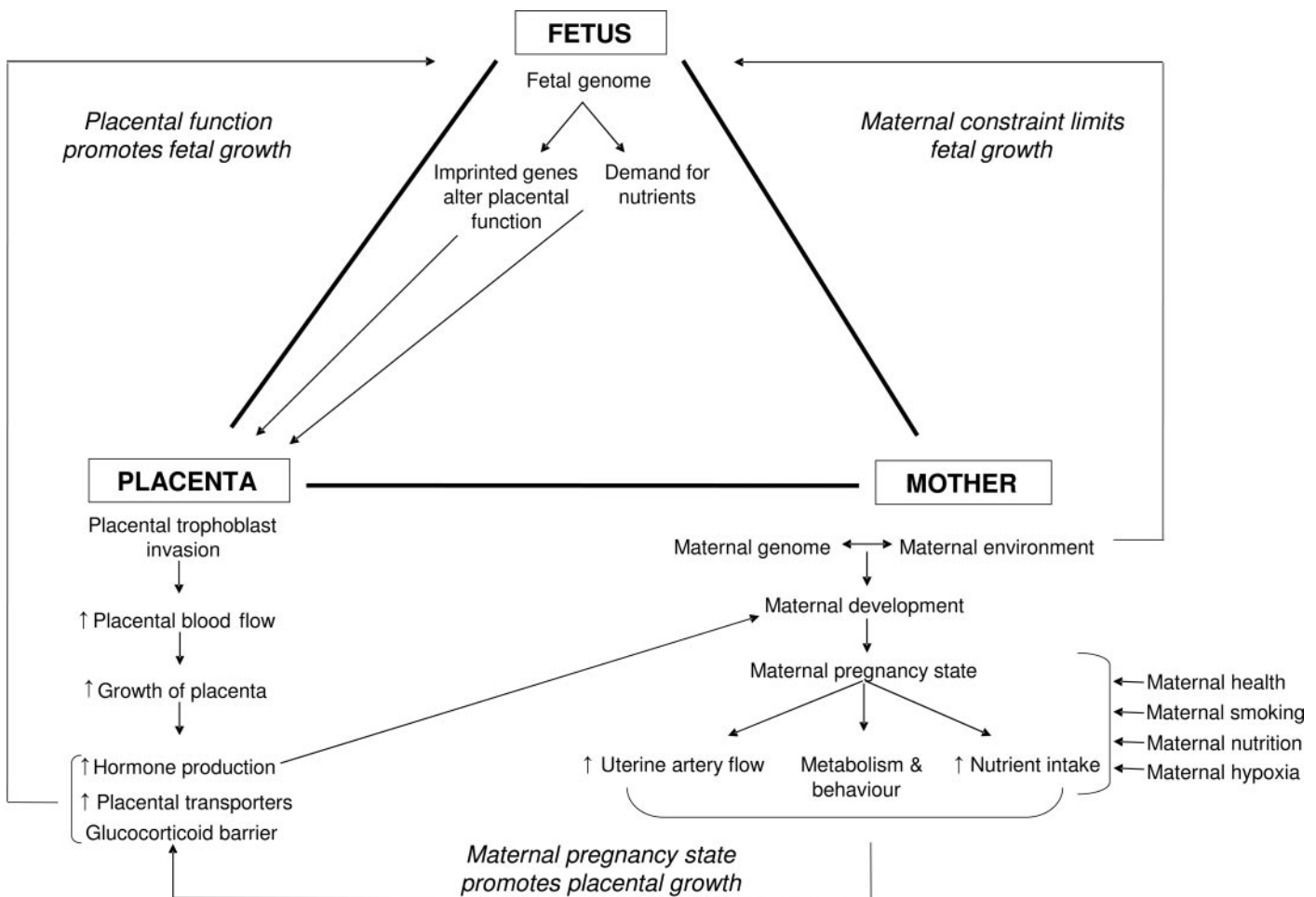


FIG. 1. Interactions between the fetus, placenta, and mother during human pregnancy. Maternal constraint limits fetal growth, whereas the maternal pregnancy state promotes placental growth, which in turn promotes fetal growth. The fetus and mother communicate via the placenta.

ment and growth. Placental trophoblast invasion and the ensuing increase in blood flow ensure the growth of the placenta, allowing it to produce hormones for signaling between the mother and fetus and transporters to transfer nutrients and waste between the mother and fetus. The placenta also maintains the glucocorticoid balance between the mother and fetus. Adequate placental function promotes fetal growth, which is influenced by the fetal genome and maternal constraint. A dysfunction in any of these pathways can lead to alterations in fetal growth, which has adverse consequences both in the short term and long term.

III. Pathological Effects of Poor Fetal Growth

A. Short-term effects of low birth weight

Low birth weight, independent of prematurity, is a significant contributor to neonatal morbidity and mortality (1) and leads to substantial health care costs (356). The World Health Organization defines low birth weight as birth weight less than 2500 g (357). SGA neonates are less than the 10th percentile for gestational age relative to the reference population (1). Some of these neonates may be healthy but are genetically destined to be born small (31). On the other hand,

IUGR refers to a pathological process, where the fetus does not reach its genetic growth potential due to an event or events that occur *in utero* (31). Clinically, it can be difficult to distinguish between these manifestations of low birth weight; however, adjusting for variables such as maternal size, ethnicity, and parity can increase the sensitivity of repeat ultrasounds in detecting and distinguishing between SGA and IUGR infants (31). In addition, abnormal Doppler velocimetry accompanied by low estimated fetal weight suggests IUGR, whereas the SGA fetus often has a slower growth trajectory but normal Doppler results (31).

Low birth weight is a significant health problem worldwide. There are more than 13 million low birth weight infants born in developing countries each year, the majority in Asia, followed by Africa and Latin America (358). In the United States, low birth weight affects approximately 5–6% of live births in Caucasians and 10–12.5% of live births in African Americans (359). Low birth weight is associated with an increased risk of morbidities including birth asphyxia, meconium aspiration, persistent fetal circulation, hypoglycemia, hypothermia, and hypocalcemia (1, 360) and an increase in mortality up to 15 yr of age, which is primarily accounted for by higher infant mortality rates (361). Neonatal mortality within a population can be reduced by 30–50% following a

100-g increase in mean birth weight due to maternal nutritional supplementation (362). In Gambia, mean birth weight was significantly increased by 136 g and mean head circumference was increased by 3.1 mm after the use of maternal dietary supplements, which were associated with a significant overall reduction in stillbirths and perinatal mortality (10). The risk of postnatal death in term infants weighing 2000–2499 g has been estimated to be increased 2-fold compared with infants weighing 2500–2999 g and increased 4-fold compared with infants weighing 3000–3499 g (363). Maximizing fetal growth will reduce a significant burden on the health care system from both neonatal mortality and morbidity.

Fetal growth restriction may be classified as symmetrical (Type I) or asymmetrical (Type II). In symmetrical growth restriction, the entire body is proportionally small (2). This accounts for 25% of IUGR cases and often results from an alteration in growth in early gestation, during the period of cellular hyperplasia, and may be the result of genetic anomalies, severe malnutrition, or maternal smoking (1). Suboptimal first-trimester growth, represented by a small crown-rump length measurement, is a good predictor of birth weight less than 2500 g at term, or birth weight below the fifth percentile (364). In 1963, Gruenwald (365) first observed that growth-restricted infants had higher brain weight (brain sparing) and lower thymus weight than premature infants of the same size. This type of growth restriction is defined as asymmetric growth restriction and may occur during the periods of cellular hypertrophy later in gestation. It is often the result of uteroplacental insufficiency secondary to other maternal complications (1). The ponderal index, $[\text{birth weight (g)}/\text{birth length (cm)}^3] \times 100$, which is unaffected by race or infant sex, is a measure of fetal growth used to assess the thinness or obesity of the neonate. Infants with symmetrical growth restriction have a normal ponderal index, whereas those with asymmetric growth restriction have a reduced ponderal index due to a normal length but low weight (1). Ponderal index has been a useful measure in studies linking changes in fetal growth with disease in adulthood.

B. Fetal origins of adult disease

Events *in utero* may determine long-term health outcomes into adulthood. This concept is known as fetal programming or the developmental (fetal) origins of adult disease. Small size at birth is a strong predictor for the development of diseases in adult life, including diabetes (366), cardiovascular disease (367), atherosclerosis (368), hypertension (369), and stroke (370). However, not all studies have supported this hypothesis. Recently, Huxley *et al.* (371) conducted an analysis of more than 100 studies that had previously reported on the relationship between birth weight and systolic blood pressure in later life. They found that the size of the effect of birth weight on subsequent blood pressure diminished with increasing sample size, such that smaller studies were more likely to report an inverse relationship, whereas larger studies, which were less likely to be subject to publication bias, reported much smaller associations. Similarly, the association between birth weight and cholesterol levels in later life

was found to be heavily influenced by studies of small sample size, and adjustment for current weight may also have exaggerated the association due to the independent relationships between birth weight and current weight, and current weight and cholesterol levels (372).

Despite this negative data, there are studies from many populations that support the concept of the fetal origins of adult disease. Several theories have been proposed that account for the fetal response to the expected environment after birth. Adaptation of the fetus to the maternal environment *in utero* is believed to lead to changes in body structure, physiology, and metabolism that persist into extrauterine life. The adaptation may be suitable for the intrauterine environment but inappropriate for extrauterine conditions. The thrifty phenotype hypothesis was proposed to explain the relationship between fetal growth and the development of type 2 diabetes. Hales and Barker (373, 374) proposed that poor nutrition in early life (either fetal or infant) leads to alterations in the development of key organ systems such as the pancreas, resulting in insulin resistance, while sparing other organs such as the brain. When individuals experience a change in their environment postnatally, these adaptations are no longer appropriate and, as a result, lead to disease. The presence of additional factors, such as obesity, can further increase the risk of disease (373, 374).

More recently, Hanson and Gluckman (375) have extended this model into the theory of the predictive adaptive response. In this model, maternal constraint is used as a strategy to ensure that the fetus is always able to survive in the case of reduced nutrition in the postnatal environment. However, the risk of disease in later life increases when there is a mismatch between the prenatal and postnatal environment, either because of increased fetal demand relative to maternal supply, reduced or increased maternal supply relative to fetal demand, or a change in the postnatal environment (375).

David Barker has been at the forefront of the epidemiological research into the fetal origins of adult disease. Studies by Barker and Osmond (376, 377) examined the geographical relationship between current death rates from heart disease or stroke and prior infant or maternal mortality rates in England and Wales. The rate of ischemic heart disease in 1968–1978 was closely correlated with neonatal and postneonatal mortality in 1921–1925 (376). Furthermore, the geographical distribution of death rates from stroke was more closely correlated with past maternal mortality than with other variables, suggesting that the health of mothers may be linked to the risk of disease in their offspring (377). Similar data have been reported recently with studies proposing that prenatal factors contribute to the geographical distribution of stroke mortality in both the United States and England and Wales, which cannot be fully explained by adult lifestyle (370).

1. *Effects on blood pressure.* Studies of almost 10,000 children at age 10, born in 1970 and more than 3,000 adults at 36 yr of age, born in 1946, were conducted by Barker *et al.* (378). There was an inverse relationship between birth weight and systolic blood pressure, independent of current weight, which was stronger in the adults. Increased systolic blood

pressure in children was unrelated to gestational age and prematurity and only associated with reduced fetal growth (378). A study from another group found a similar relationship between systolic blood pressure in children aged 5–8 yr and birth weight, but only when standardized for current weight (379).

Further studies from Barker *et al.* (380) examined more than 5000 men born in Hertfordshire between 1911 and 1930 and found that mortality from ischemic heart disease was more common in men with low weights at birth and 1 yr of age. A similar trend was noted for death from chronic obstructive lung disease, but not death from lung cancer (380). The relationship between higher systolic blood pressure and low birth weight has been found to be consistent in children aged 0–10 yr, and in adults at 36 yr, 46–54 yr, and 59–71 yr, but the relationship becomes more pronounced with age (381).

Placental size is an important determinant of fetal size and, not surprisingly, associations between placental size and the fetal to placental weight ratio and blood pressure in adult life have also been described (382). Systolic and diastolic blood pressures at age 50 were strongly related to both placental weight and birth weight independent of gestational age, current alcohol consumption, and current body mass index, in a cohort of 449 men and women born in Lancashire between 1935 and 1946 (382). The highest blood pressures were found in those with a low birth weight and high placental weight (382). Similar relationships were observed within each social class (382). An inverse correlation between placental weight and the length to head circumference ratio suggested the possibility that changes in the fetal circulation, such as diversion of blood flow to the brain at the expense of other parts of the body, may lead to permanent alterations in blood vessel development and particularly arterial structure (366, 382).

Maternal diet during pregnancy may influence fetal growth with consequences for adult blood pressure. A particularly high or low protein diet during pregnancy has adverse effects on blood pressure in offspring (383). During the Dutch famine, neonates exposed during mid or late gestation had reduced birth weights compared with neonates born before the famine or conceived after the famine (15, 384). Exposure to the famine in late gestation has been associated with impaired glucose tolerance and type 2 diabetes in the offspring at 50 yr of age (15). Offspring exposed during early gestation had an increased prevalence of coronary heart disease, respiratory disease, hypertension, diabetes, and cancer at 50 yr of age (384).

2. Effects on the development of Syndrome X. Small size at birth has been linked to Syndrome X, or the combination of non-insulin-dependent diabetes mellitus, hypertension, and hyperlipidemia (366). In Hertfordshire, 64-yr-old men with Syndrome X had lower weights at birth and 1 yr of age, whereas higher birth weights were associated with lower 2-h plasma glucose and insulin concentrations and lower blood pressures (385). In Lancashire, men and women at age 50 with Syndrome X had lower birth weights as well as a small head circumference and low ponderal index at birth. The association between fetal growth and diabetes may be due to

alterations in fetal pancreatic development and a reduction in insulin-secreting capacity (366).

Other studies have found higher plasma glucose in children who were thin at birth with a low ponderal index (386) and in adults of reduced birth weight (387). Alterations in β -cell development and function during undernutrition in fetal life may result in permanent changes such as a reduced capacity for insulin production, which becomes a disadvantage when nutrition is abundant (385). Alternatively, a genetic predisposition to low insulin production may result in both reduced fetal growth and glucose intolerance later in life (385).

The effects of small size at birth on adult diseases is compounded by rapid rates of childhood growth (388). Barker *et al.* (388) found that adults from Helsinki who had been born small and had the largest body mass index in childhood were at greatest risk for type 2 diabetes, hypertension, and death or hospitalization due to coronary heart disease. It is thought that developmental plasticity allows an appropriate phenotype for the current environment *in utero*; however, when nutrition improves after birth, compensatory growth occurs. The combination of these events results in physical and physiological changes that contribute to the increased risk of developing metabolic and cardiovascular diseases later in life (388). Evidence for a mechanism connecting small size at birth to obesity later in life comes from a study of “thin-fat” Indian babies, in which low birth weight was associated with low ponderal index (thinness) and reduced abdominal and midarm circumference, but marked sparing of subscapular skin fold thickness, a representative depot of central fat (389). Neonates in India and the United Kingdom with birth weights less than the 10th percentile exhibited both brain-sparing and fat-sparing characteristics, possibly putting them at risk of insulin resistance and cardiovascular disease in adulthood (389).

3. Effects on respiratory disease. Reduced fetal growth may have an effect on the development of respiratory diseases in children and adults. However, the available data are contradictory, with some studies showing an increased risk of developing asthma or having reduced lung function in smaller neonates (390, 391) and others showing an increased risk of asthma or atopy in larger neonates (392, 393). A study from Barker *et al.* (394) demonstrated that lower birth weight was associated with reduced adult forced expiratory volume at 1 sec (FEV_1) at 59–70 yr of age, and death from chronic obstructive airways disease was also related to lower birth weight. In an Indian study, adult lung function (FEV_1), was reduced with decreasing birth weight in men and women, whereas a small head circumference at birth was associated with reduced FEV_1 to forced vital capacity ratio in men but not women (395). These changes in adult lung function may be related to permanent effects of maternal undernutrition on lung development and structure, and differences between men and women may relate to sex-specific differences in lung growth *in utero* (394, 395). Lopuhaa *et al.* (396) found that men and women who had been exposed to famine in mid-gestation had a higher rate of obstructive airways disease, suggesting that fetal nutrition affects lung development, although they found no evidence of changes in serum IgE or

lung function in adulthood. Potential mechanisms linking low birth weight to poor lung function later in life have been studied in the sheep model of IUGR induced by chronic placental insufficiency or maternal anemia (397). In these studies, fetal growth restriction resulted in alterations of lung structure and function, including a thickened air-blood barrier, enhanced surfactant gene expression (397), and a reduction in total lung capacity (398).

4. Other effects on disease and behavior in later life. Numerous other adult consequences of small size at birth have been described in humans, including an increased risk of renal failure (399), depression in men but not women (400), atherosclerosis (401), and the development of preeclampsia while pregnant (402). Women of low birth weight were found to be 2.3 times more likely to develop preeclampsia than those who weighed 2500–2999 g at birth, with the risk further decreasing with increasing birth size (402). However, there was also an important effect when adult weight was considered, with lean women of low birth weight having no increased risk and overweight women of low birth weight having a 16-fold increase in risk for preeclampsia (402). Reduced birth weight in combination with high adult weight may produce the greatest risk for disease in adult life.

Low birth weight has also been linked to behavioral problems at school such as lack of motivation, aggression, and concentration difficulty at age 10 (403) and low IQ at 6 yr of age in children with no neurological impairment (404). Breslau *et al.* (404) examined outcomes for children across a range of birth weights, in an inner city area and suburban area of Michigan. In both populations, low birth weight was associated with an average IQ score five points lower than normal birth weight children, resulting in 10% of low birth weight children having an IQ more than 1 SD below the mean. In addition, a gradient effect was observed, with the largest reduction in the very low birth weight group who were less than 1500 g (403).

Developmental plasticity allows the fetus to develop along a growth trajectory that is appropriate for its intrauterine environment. However, in the case where the environment postnatally is different from that *in utero*, physiological adaptations made by the fetus may be inappropriate. The influence of fetal growth on susceptibility to disease in childhood and adulthood may be related to this mismatch. An understanding of the mechanisms that cause low birth weight is important for the development of future interventions, which may give small infants a better chance of a healthy life, both in their immediate future and in the long term.

5. Glucocorticoids and fetal programming. Studies in humans and animals have related low birth weight and prenatal stress to altered HPA axis activity in later life (405). Glucocorticoids are released into the circulation after maternal exposure to stressors, which may include physical illness (406), death of or separation from a partner (407), or a national event such as war (408). Low birth weight has been associated with elevated cortisol levels at birth (409) and elevated plasma cortisol concentrations or HPA activity in adult life in several populations (410, 411). Another group

has found that the effect of birth weight on adult plasma cortisol is dependent on gestational age at birth (412, 413). In those born before 39 wk gestation, lower birth weight was associated with higher total and free plasma cortisol, whereas in those born after 40 wk gestation, lower birth weight was associated with lower plasma cortisol (412). In children, increased urinary excretion of glucocorticoids was found in those who had the lowest or highest birth weights (414). Maternal first-trimester exposure to the stress of war has been associated with an increased risk of the offspring developing schizophrenia in adult life (408). In this epidemiological study, women were pregnant during the time of the German invasion of The Netherlands, which lasted 5 d and resulted in the death of 2200 men (408). The level of exposure to the stress would have varied widely between individuals, possibly accounting for the small increased risk of schizophrenia in the offspring (408). Lou *et al.* (406) found that maternal stress, ascertained by questionnaire as an experience of moderate-severe stressful life events (such as marital separation, job loss, death of spouse, or diagnosis of severe physical illness) during midgestation affected birth weight and was associated with small head circumference, suggesting a specific effect on the brain, thus linking prenatal stress, reduced growth, and altered brain development. Approximately 10% of maternal cortisol does cross to the fetus, and increases in maternal cortisol levels may therefore contribute to increased fetal cortisol levels during pregnancy (263). Therefore, despite the presence of the placental 11 β -HSD2 enzyme barrier, an increase in maternal glucocorticoids as a result of stress could contribute to a significant change in fetal glucocorticoid exposure (263), which would be compounded by reduced placental 11 β -HSD2 activity. Murphy *et al.* (55) found that cord blood estriol, a derivative of fetal adrenal dehydroepiandrosterone, was significantly reduced in the cord blood of females of asthmatic mothers, in conjunction with reduced 11 β -HSD2 activity and birth weight, suggesting that changes in placental function in response to asthma may lead to altered HPA development in the neonate.

Although exposure of animals to prenatal glucocorticoids has been associated with changes in blood pressure later in life, investigations of the long-term effects of antenatal glucocorticoid exposure on human neonates generally indicate no adverse effects of this treatment on subsequent blood pressure. A recent follow-up study of a cohort of subjects who participated in a randomized controlled trial of betamethasone treatment during preterm labor found that there was no significant effect of antenatal betamethasone exposure on systolic or diastolic blood pressure at 6 yr of age (241) or at 30 yr of age (243). However, in the 30-yr follow-up, it was found that subjects exposed to betamethasone *in utero* had some alterations in insulin resistance, consisting of higher plasma insulin concentrations at 30 min and lower glucose concentrations at 120 min after an oral glucose tolerance test (243). Previous studies examining blood pressure had been contradictory, with one demonstrating increased blood pressure at age 14 in those exposed to glucocorticoids (415) and another demonstrating decreased blood pressure at age 20 among those exposed to prenatal glucocorticoids (242). Further research is needed in human subjects to de-

termine the effects of antenatal glucocorticoids on long-term health.

C. Clinical interventions to improve fetal growth

There has been very little change in the rate of low birth weight and IUGR during human pregnancy, despite decreased infant mortality in recent years (359). More interventional studies are needed to improve fetal growth outcomes. There have been several randomized controlled trials of comprehensive prenatal care programs that aim to reduce specific risk factors to reduce the rate of low birth weight (416). Few of these trials have been successful, possibly because they have targeted whole populations of women who come from socioeconomically disadvantaged areas, thus including a large proportion of individuals who do not have a need for the intervention (416). It may be more appropriate to trial these strategies among specific subpopulations of women to reduce the impact of particular known and modifiable risk factors, such as smoking, undernutrition, pregnancy-related anxiety, and infection, on low birth weight (416).

Although trials that result in improved fetal growth are lacking, there has been some success with nutritional supplementation in undernourished women and in smoking cessation programs in developed countries (417). Prevention of infection, particularly with malaria and HIV, as well as improvements in maternal nutrition, are likely to be important strategies for women in developing countries (417). Understanding the endocrine interactions that influence human fetal growth and development will help address the clinical problem of low birth weight.

IV. Conclusions

Together the mother, placenta, and fetus interact during pregnancy to modulate fetal growth. Maternal nutrients are essential for growth and development of the fetus, and transport of these nutrients occurs via the placental blood supply. The placenta is also important in the production and transport of growth-promoting hormones. A barrier function for the placenta, through the activity of 11 β -HSD2, is of importance in preventing the high concentrations of glucocorticoids found in the mother from reaching the fetus in an active form. The effects of glucocorticoids may be fetal sex specific, with implications for fetal programming. Disturbances in fetal growth regulation can result in adverse outcomes for the neonate, and these adverse outcomes may persist into adult life. It is therefore important to understand the mechanisms regulating human fetal growth, and particularly the role of mother, placenta, and fetus in complicated pregnancies. As a result, a better outcome for the fetus may be achieved, which may have long-term health benefits into adulthood.

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