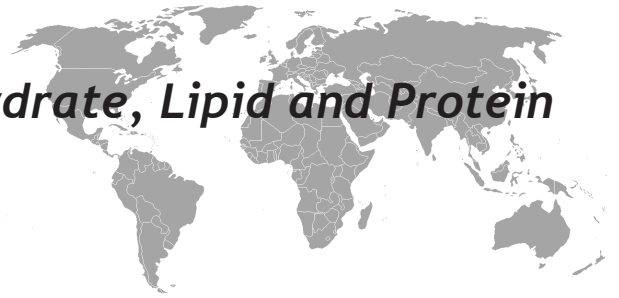
Eur J Gen Med 2014; 11(4):299-304
DOI : 10.15197/sabad.1.11.93

Review Article



Maternal and Fetal Carbohydrate, Lipid and Protein Metabolisms

Özlem Şengül[1], Suat Dede[2]

ABSTRACT

Fetal period is characterized by the rapid growth and maturation of tissues and organs. There are various alterations in carbohydrate, lipid and protein metabolisms in mother to provide nutrition to fetus. If something is wrong about these metabolisms in mother, this will indirectly affect fetus. So it is essential to elucidate the maternal and fetal carbohydrate, lipid and protein metabolisms in the management of a pregnant woman. Mild fasting hypoglycemia, postprandial hyperglycemia, hyperinsulinemia and increased peripheral insulin resistance are the characteristics of pregnancy. The fetus primarily depends on glucose as the energy source but can also use other substrates such as lactate, keto acids, amino acids, fatty acids and glycogen as energy sources. Proteins are needed as structural components. Alterations in lipid metabolism cause accumulation of maternal fat stores in the early pregnancy in order to enhance lipolysis in the late pregnancy providing glucose and amino acids for fetus while promoting usage of lipids as maternal energy source. Maternal energy metabolism affects fetal energy metabolism both in short and long terms. By the clarification of maternal and fetal energy metabolisms, it may be possible to predict and prevent some diseases of a newborn in the future.

Key words: *Fetus, carbohydrate, lipid, protein.*

Maternal ve Fetal Karbonhidrat, Lipid ve Protein Metabolizmaları

ÖZET

Fetal dönem, doku ve organların hızlı büyüme ve gelişmesi ile karakterizedir. Anneden fetüse yeterli besin sağlanması için karbonhidrat, lipid ve protein metabolizmalarında birçok değişiklikler görülür. Bunlardaki herhangi bir eksiklik veya yanlışlık fetüsü etkileyecektir. Bu nedenle maternal ve fetal karbonhidrat, lipid ve protein metabolizmalarının açıklanması önemlidir. Gebelikte açlık hipoglisemisi, postprandial hiperglisemi, hiperinsülinemi ve artmış periferal insülin direnci mevcuttur. Fetüs esas enerji kaynağı olarak glukozu kullanır, ama laktat, keto asitler, amino asidler, yağ asidleri ve glikojen de enerji kaynağı olarak kullanılabilir. Fetüs proteinleri de yapıtaşı olarak kullanır. Maternal lipid metabolizmasındaki değişiklikler; gebeliğin erken dönemlerinde maternal yağ depolarını artırırken, geç gebelik dönemlerinde lipolizi artırarak glukoz ve amino asitlerin fetüs için kullanımını sağlar, maternal enerji kaynağı olarak da yağ asitlerinin kullanımını destekler. Maternal enerji metabolizması fetal enerji metabolizmasını kısa ve uzun dönemde etkiler. Bu mekanizmaların aydınlatılması ile gelecekte yenidoğandaki bazı hastalıkların öngörülmesi veya engellenmesi mümkün olabilecektir.

Anahtar kelimeler: *Fetüs, karbonhidrat, lipid, protein.*

INTRODUCTION

Fetal period is the intrauterine period between 12th gestational week and birth and it is characterized by the rapid growth and maturation of tissues and organs. Carbohydrate and lipid metabolisms in pregnancy provide us continuous supply of nutrients to the fetus in spite of maternal intermittant food intake (1). The fetus primarily depends on glucose as the energy source and obtains glucose from the mother through the placenta. There are various alterations in carbohydrate, lipid and protein

[1]*Atatürk Teaching and Research Hospital, Obstetrics and Gynecology Department Ankara,* [2]*Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Ankara*

Correspondence: *Özlem Şengül*
Atatürk Eğitim ve Araştırma Hastanesi, Bilkent/Ankara/Turkey
Telefon:05056342770
E-mail:ozlem.sengul@yahoo.com

Received: 04.10.2013, Accepted: 23.10.2013

metabolisms in mother to provide nutrition to fetus. If something is wrong about these metabolisms in mother, this will indirectly affect fetus. For example maternal diabetes mellitus and hyperglycemia may cause hyperinsulinemia and macrosomia in fetus (2) or the newborn with intrauterine growth retardation may have decreased amount of hepatic glycogen and adipose tissue due to decreased supply of maternal glucose. This may affect the newborn after delivery if hypothermia and hypoxia may deplete energy reserves (3). So it is essential to elucidate the maternal and fetal carbohydrate, lipid and protein metabolisms in the management of a pregnant woman.

Maternal carbohydrate metabolism

In early pregnancy, glucose tolerance is normal or slightly improved (4) and basal glucose and insulin concentrations are not different from the prepregnancy period (5). A progressive increase in basal and postprandial insulin concentrations is seen with advancing pregnancy (6). Pregnancy is characterized by a progressive increase in nutrient-stimulated insulin responses in spite of minor deterioration in glucose tolerance, resulting in progressive insulin resistance (7). It is suggested that insulin action in late normal pregnancy is 50–70% lower than in non-pregnant women by the hyperinsulinemic-euglycemic glucose clamp technique and intravenous glucose tolerance test (4,5,8-10). The alterations in the levels of human chorionic somotomammotrophin, progesteron, cortisol and prolactin all have a role in these changes (1). Glucose production from the glycogen depots in the liver also contributes hyperglycemia (11). In pregnancy basal hepatic glucose production has been shown to increase by 16–30% to meet the increasing needs of fetus (5,12). In spite of progressive decrease in insulin sensitivity with advancing pregnancy, endogenous hepatic glucose production was shown to remain sensitive to increased insulin concentration in normal pregnancy (1). Mild fasting hypoglycemia, postprandial hyperglycemia and hyperinsulinemia (13) and increased peripheral insulin resistance (4) may also be observed in pregnancy.

Fetal carbohydrate metabolism

The placenta and fetal liver function to supply nutrients to the fetus for fetal metabolism and growth (14). Carbohydrate is suplied to the fetus mostly in the form of glucose and lactate (15). Lactate is supplied to the fetus by the uteroplacental tissues and fetus gets glucose mostly from mother through placenta and also by gluconeogenesis (15,16). Fetus uses nutrients for the continuation of fetal oxidative metabolism, growth and maturation of tissues and organs. Fetal oxidative metabolism can be determined by oxygen usage and production of carbondioxide (14). It is difficult to estimate production of carbondioxide because of the huge difference between carbon usage and expulsion of rapidly growing fetus (14). Methodological advances in kinetic studies by using stable isotopic tracers and mass spectrometric quantification provide us better understanding of fetal energy metabolism (17).

Fluctuations in maternal blood glucose are reflected to fetal glucose concentrations. Glucose passes through the placenta without using energy by facilitated diffusion (18,19) and fetal glucose concentration is the 70-80% of maternal glucose concentration (20). The facilitated glucose diffusion is mediated by glucose transporters (GLUT) and GLUT 1, the dominant isoform in most fetal tissues and the placenta, is the rate limiting step of glucose transport (21). GLUT 1 in the placenta are saturated at glucose levels of 198-235 mg/dl (22), which may be a protective mechanism for the fetus (23). Although uterine, placental and fetal glucose uptakes are related to maternal glucose concentrations, the distribution of uterine glucose uptake to fetal and uteroplacental glucose uptakes is regulated by fetal glucose concentrations independent of the maternal glucose levels (20). The rates of umblical uptake and utilization of glocose did not change with gestational age when they were evaluated on a weight specific basis in piglets (24). A fetus uses 55 kcal/kg/day based on calculation of fetal oxygen consumption (25). Fetus gets 80% of energy consumption from carbohydrates and fetal glucose utilization rate is higher in fetus than in adults (5-7 mg/kg/min vs 2-3 mg/kg/min) (23). Endogenous insulin has an essential role in the regulation of glucose metabolism in late gestation (26). Leptin has a role in the formation of neural pathways that are needed for the control of gluconeogenesis and tissue maturation in the late pregnancy (27).

The fetus can also use other substrates such as lactate, keto acids, amino acids, fatty acids and glycogen as energy sources (28). But gluconeogenesis and ketogenesis are not seen in the fetus when substrate supply is adequate (23). Normally fetus can not perform hepatic gluconeogenesis, and hepatic gluconeogenesis begins in the newborn period by the effects of thyroid, cortisol, and catecholamines (29). But gluconeogenesis can be seen in fetus by maternal starvation, prolonged hyperglycemia in mother and by cAMP infusion in fetus (29).

Maternal lipid metabolism

Carbohydrate and lipid metabolism are in close relationship with each other. Increased estrogen, progesteron and plasental lactogen increase levels of triglycerides, lipid, lipoproteins and apolipoproteins (30). Low density lipoprotein reaches its peak value by the 36th gestational week but decreases before birth. The level of high density lipoprotein is the maximum at the 25th gestational week and has a tendency to decrease by insulin resistance to the 32th gestational week (31). Cholesterol is used by the placenta for steroid hormone synthesis and fatty acids are used for placental oxidation and membrane formation (1). High density lipoprotein stimulates human placental lactogen through its receptors on the placenta (32). Lipids, lipoproteins and apolipoproteins decrease at various rates in the postpartum period also by the contribution of lactation (32). Alterations in lipid metabolism cause accumulation of maternal fat stores in the early pregnancy in order to enhance lipolysis in the late pregnancy by human chorionic somotomammotrophin. This provides glucose and amino acids for fetus while promoting usage of lipids as maternal energy source (1).

Fetal lipid metabolism

Glucose is the primary substrate for energy production in fetus but fetus can use other energy sources like lactate, keto acids, amino acids, fatty acids and glycogen under special conditions (23). Glycerol and certain free fatty acids pass through the placenta but triglycerides can not (23,33). Placental lipid transport to the fetus also involves lipid uptake from lipoproteins, metabolic alteration in the placenta, and release into the fetal plasma (16). Placental lactogen increases levels of free fatty acids by its lipolytic effects (31). Fetal fat accumulation occurs especially in the last trimester of pregnancy by the placental transfer of glucose and by its use as a lipogenic substrate and also by the placental transfer of fatty acids (33). Fatty acids are necessary not only as structural components but also for energy and metabolism. Amino acids are especially preferred for growth and essential fatty acids are especially used for development of brain and retina (23). Maternal glycerol is preferred to be used for gluconeogenesis instead of amino acids (23,33). Maternal ketone bodies can pass through the placenta and can be used by fetus as an energy source (33). Linoleic and linolenic acids are essential in the growth and maturation of fetal brain (34). It is suggested that matenal supplementation of a polyunsaturated fatty acid, docosahexaenoic acid may improve fetal neurodevelopment (35). In early pregnancy, fetal lipids are derived from maternal free fatty acids and in advanced pregnancy there is also synthesis in the fetal tissue (23,36). Lipogenesis is very active in the fetus and the increased maternal nutrition in late gestation uniquely enhances brown fat development which is important in conservation of heat and energy (37).

Maternal protein metabolism

Fetus gets amino acids mostly from the mother through the placenta and the passage of amino acids is critical since amino acids are the structural components of the fetus. There is a total of 1000 gram protein increase throughout the pregnancy and half of this belongs to the fetus and the fetoplacental tissues (32). Maternal serum albumin decreases and globulin increases in pregnancy. Placental lactogen and human chorionic gonodotrophin suppress deamination in the liver to prevent loss of amino acids to preserve amino acids for fetus (32). If mother gets insufficient carbohydrates and lipids, proteins are used as the energy source which is an undesirable condition. Insufficient maternal protein intake may also affect the disease susceptibility of the newborn in the future (38). In rats on a low protein diet, there was a significant decrease in the protein concentration and a significant increase in the glycogen concentration in the livers of their offsprings indicating the maternal insufficient protein intake not only reduced fetal growth but also altered the structure of the liver (38).

Fetal protein metabolism

Fetus needs 10 essential amino acids and cysteine, histidine and taurine. Ammonia produced by placenta is used by the liver for protein synthesis. Placenta can also produce some aminoacids like glutamate and aspartate (23). Fetal amino acid concentration is usually higher than maternal levels (39). Amino acids pass through the placenta by active transport by Na+ /K+ - ATPase and H+ dependent transport. Protein molecules like albumin and gamma globulin pass to the fetus by pinocytosis (28). Active transport of amino acids may be either via accumulative transporters or exchangers. The accumulative transporters increase intracellular amino acid concentrations against concentration gradient, usually by cotransporting extracellular sodium (40) and exchangers change the intracellular amino acid composition by exchanging amino acids between the intracellular and extracellular compartments (40,41).

Fetus needs proteins as structural components and glucose as an energy source. Glucose and amino acid metabolisms interact with each other. Fetus tries to keep energy metabolism stable and in conditions with insufficient energy supplies, fetus may drop growth (20). In only prolonged energy and protein restriction, protein synthesis is affected to an important extend (42,43). The interaction of maternal and fetal energy metabolism. Maternal energy metabolism closely affects fetus in several ways. Maternal undernutrition causes low birthweight fetuses with increased risk of energy balance disorders (44). Maternal nutrition during pregnancy may also affect intrauterine development of body composition. Fetal abdominal fat was highest with low protein maternal diet; and fetal midthigh fat was highest at intermediate protein, high fat, and low carbohydrate diets (45). Maternal hypothyroidism may cause glucose intolerance and may contribute to the increased risk of type 2 diabetes in the offspring in rats (46). Gestational diabetes mellitus alters neonatal plasma lipids metabolism and causes hypercholesterolemia in the newborn period (47). Alterations in fetal development and growth have been associated with lifelong adverse health problems (48). Intrauterine growth restriction increases low-density lipoprotein cholesterol in rats and the fructose diet which is used as an enhancer of metabolic syndrome causes hypertriglyceridemia and hyperinsulinemia and decreased fasting glucose levels in rats (49). In rats maternal fructose intake during pregnancy causes maternal hyperglycemia and up-regulates hepatic sterol regulatory element-binding protein-1c expression in fetuses and in dams; leading to defects in carbohydrate and lipid metabolism in the adult offspring (50). Pregnant rats exposed to hypoxia demonstrated decreased fetal body and liver weight and it is suggested that prenatal hypoxia has a role in metabolic changes that enhances fetal vulnerability for nonalcoholic fatty liver disease, probably via insulin signaling pathway and glucose transporters (51).

Hormones are also critical in the regelation of energy metabolism. Insulin, insulin-like growth factor and thyroid hormones have anabolic effects on cellular nutrient uptake and production of energy; and leptin has a role in development of specific fetal tissues and glucocorticoids inhibit growth in utero (52). The fetus exposed to sustained hypoglycemia may have maintained hepatic insulin action in contrast to fetuses being exposed to placental insufficiency (53). Fetal sheep with intrauterine growth restriction have increased hepatic glucose production that is not suppressed by insulin; and cortisol and norepinephrine concentrations were positively correlated with glucose production rates (54). Maternal energy metabolism affects fetal energy metabolism both in short and long terms. By the clarification of maternal and fetal energy metabolisms, it may be possible to predict and prevent some diseases of a newborn in the future.

REFERENCES

1. *Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr 2000;71:1256S-61S.*
2. *Cordero L, Landon MB. Infant of the diabetic mother. Clin Perinatol 1993;20:635-48.*
3. *Gabbe SG, Quilligan EJ. Fetal carbohydrate metabolism: its clinical importance. Am J Obstet Gynecol 1977;127:92-103.*
4. *Catalano PM, Tyzbir ED, Roman NM. Longitudinal changes in insulin release and insulin resistance in non-obese pregnant women. Am J Obstet Gynecol 1991;165:1667-72.*
5. *Catalano PM, Tyzbir ED, Wolfe RR, Roman NM, Amini SB, Sims EAH. Longitudinal changes in basal hepatic glucose production and suppression during insulin infusion in normal pregnant women. Am J Obstet Gynecol 1992;167:913-9.*
6. *Lesser KB, Carpenter MW. Metabolic changes associated with normal pregnancy and pregnancy complicated by diabetes mellitus. Semin Perinatol 1994;18:399-406.*
7. *Kühl C. Aetiology of gestational diabetes. Baillieres Clin Obstet Gynaecol 1991;5:279-92.*
8. *Catalano PM, Tyzbir ED, Wolfe RR, et al. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. Am J Physiol 1993;264:E60-7.*
9. *Buchanan TA, Metzger BE, Freinkel N. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or gestational diabetes. Am J Obstet Gynecol 1990;162:1008-14.*
10. *Ryan EA, O'Sullivan MJ, Skyler JS. Insulin action during pregnancy: studies with euglycemic clamp technique. Diabetes 1985;34:380-9.*
11. *Boden G. Fuel metabolism in pregnancy and in gestational diabetes mellitus. Obstet Gynecol Clin North Am 1996;23:1-10.*
12. *Assel B, Rossi K, Kalhan S. Glucose metabolism during fasting through human pregnancy: comparison of tracer method with respiratory calorimetry. Am J Physiol 1993;265:E351-6.*
13. *Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 1981;140:730-6.*
14. *Battaglia FC, Meschia G. Principal substrates of fetal metabolism. Physol Rev 1978;58:499-527.*
15. *Fowden AL, Silver M. Glucose and oxygen metabolism*

in the fetal foal during late gestation. Am J Physiol 1995;269:R1455-61.

16. Hay WW Jr. Placental transport of nutrients to the fetus. Horm Res 1994;42:215-22.

17. Cowett RM, Farrag HM. Selected principles of perinatal-neonatal glucose metabolism. Semin Neonatol 2004;9:37-47.

18. Bell GI, Burant CF, Takeda J, Gould GW. Structure and function of mammalian facilitative sugar transporters. J Biol Chem 1993;268:19161-4.

19. Widdas, W. F. Transport mechanisms in the foetus. Brit Med BUZZ1961; 17: 107-11.

20. Hay WW, Jr. Placental-fetal glucose exchange and fetal glucose metabolism. Trans Am Clin Climatol Assoc 2006;117:321-39.

21. Simmons RE. Cell glucose transport and glucose handling during fetal and neonatal development. In: Polin RA, Fox WW, editors. Fetal and Neonatal Physiology. Philadelphia: Saunders; 2011: 560-8.

22. Oakley NW, Beard RW, Turner RC. Effect of sustained maternal hyperglycemia on the fetus in normal and diabetic pregnancies. Br Med J 1972;1:466-9.

23. Rao PN, Shashidhar A, Ashok C. In utero fuel homeostasis: Lessons for a clinician. Indian J Endocrinol Metab 2013;17:60-8.

24. Fowden AL, Forhead AJ, Silver M, MacDonald AA. Glucose, lactate and oxygen metabolism in the fetal pig during late gestation. Exp Physiol 1997;82:171-82.

25. Sinclair JC. Metabolic rate and temperature control in the newborn. In: Goodwin JW, Gooden LO, Chance GW, editors. Perinatal Medicine. Baltimore: Williams and Wilkins; 1976: 558-77.

26. Fowden AL, Hay WW Jr. The effects of pancreatectomy on the rates of glucose utilization, oxidation and production in the sheep fetus. Q J Exp Physiol 1988;73:973-84.

27. Forhead AJ, Fowden AL The hungry fetus? Role of leptin as a nutritional signal before birth.J Physiol. 2009;587:1145-52.

28. Blackburn ST. Carbohydrate, fat and protein metabolism. In: Blackburn ST, editor. Maternal, fetal, and neonatal physiology. 2nd ed. St Louis: Saunders; 2003: 599-629.

29. Kalhan S, Parimi P. Gluconeogeneis in the fetus and neonate. Semin Perinatol 2000;24:94-106.

30. Salameh WA, Mastrogiannis DS. Maternal hyperlipidemia in pregnancy. Clin Obstet Gynecol 1994;37:66-77.

31. Desoye G, Schweditsch MO, Pfeiffer KP, Zechner R, Kostner GM. Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. J Clin Endocrinol Metab 1987;64:704-12.

32. Larque E, Ruiz-Palacios M, Koletzko B. Placental regulation of fetal nutrient suply. Curr Opin Clin Nutr Matab Care 2013;16(3):292-7.

33. Herrera E, Amusquivar E. Lipid metabolism in the fetus and the newborn. Diabetes Metab Res Rev 2000;16:202-10.

34. Crawford MA, Hassam AG, Williams G. Essential fatty acids and fetal brain growth. Lancet. 1976;1:452-3.

35. de Groot RH, Hornstra G, van Houwelingen AC, Rumen F. Effect of linolenic acid supplementation during pregnancy on maternal and neonatal polyunsaturated fatty acid status and pregnancy outcome. Am J Clin Nutr 2004;79:251-60

36. Hendrickse W, Stammers JP, Hull D. The transfer of free fatty acids across the human placenta. Br J Obstet Gynaecol 1985;92:945-53.

37. Symonds ME, Stephenson T. Maternal nutrient restriction and endocrine programming of fetal adipose tissue development. Biochem Soc Trans 1999;27:97-103.

38. Ramadan WS, Alshiraihi I, Al-karim S. Effect of maternal low protein diet during pregnancy on the fetal liver of rats. Ann Anat 2013;195:68-76.

39. Cetin I, Marconi AM, Corbetta C, et al. Fetal amino acids in normal pregnancies and in pregnancies complicated by intrauterine growth retardation. Early Human Development 1992;29:183-6.

40. Bröer S. Adaptation of plasma membrane amino acid transport mechanisms to physiological demands. Pflugers Arch 2002;444:457-66.

41. Verrey F. System L. hHeteromeric exchangers of large, neutral amino acids involved in directional transport. Pflugers Arch 2003;445:529-33.

42. Wilkening RB, Boyle DW, Teng C, Meschia G, Battaglia FC. Amino acid uptake by the fetal ovine hindlimb under normal and euglycemic hyperinsulinemic states. Am J Physiol 1994;266:E72-8.

43. Johnson JD, Dunham T, Skipper BJ, Loftfield RB. Protein turnover in diseases of the rat fetus following maternal starvation. Pediatr Res 1986;20:1252-7.

44. Lukaszewski MA, Eberlé D, Vieau D, Breton C. Nutritional manipulations in the perinatal period program adipose tissue in offspring. Am J Physiol Endocrinol Metab 2013 Sep 17. [Epub ahead of print]

45. Blumfield ML, Hure AJ, MacDonald-Wicks LK, et al. Dietary balance during pregnancy is associated with fetal adiposity and fat distribution. Am J Clin Nutr 2012;96:1032-41.

46. Karbalaei N, Ghasemi A, Faraji F, Zahediasl S. Comparison of the effect of maternal hypothyroidism on carbohydrate metabolism in young and aged male offspring in rats. Scand J Clin Lab Invest 2013;73:87-94.

47. Eslamian L, Akbari S, Marsoosi V, Jamal A. Association between fetal overgrowth and metabolic parameters in cord blood of newborns of women with GDM. Minerva Med 2013;104:317-24.

48. Lager S, Powell TL. Regulation of nutrient transport across the placenta. Pregnancy 2012;2012:179827.

49. Malo E, Saukko M, Santaniemi M, et al. Plasma lipid levels and body weight altered by intrauterine growth restriction and postnatal fructose diet in adult rats. Pediatr Res 2013;73:155-62.

50. Mukai Y, Kumazawa M, Sato S. Fructose intake during pregnancy up-regulates the expression of maternal and fetal hepatic sterol regulatory element-binding protein-1c in rats. Endocrine 2013;44:79-86.

51. Cao L, Mao C, Li S, et al. Hepatic insulin signaling changes: possible mechanism in prenatal hypoxia-increased susceptibility of fatty liver in adulthood. Endocrinology 2012;153:4955-65.

52. Fowden AL, Forhead AJ Endocrine interactions in the control of fetal growth. Nestle Nutr Inst Workshop Ser 2013;74:91-102.

53. Thorn SR, Sekar SM, Lavezzi JR, et al. A physiological increase in insulin suppresses gluconeogenic gene activation in fetal sheep with sustained hypoglycemia. Am J Physiol Regul Integr Comp Physiol 2012;303:R861-9.

54. Thorn SR, Brown LD, Rozance PJ, Hay WW Jr, Friedman JE. Increased hepatic glucose production in fetal sheep with intrauterine growth restriction is not suppressed by insulin. Diabetes 2013;62:65-73.