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Excess pregnancy weight gain leads to early indications of metabolic syndrome in a swine model of fetal programming☆

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ARTICLE INFO

Article history:
Received 15 March 2013
Revised 24 December 2013
Accepted 7 January 2014

Keywords:
Maternal weight gain
Metabolic syndrome
Insulin resistance
Pig
Programming

ABSTRACT

Few data exist on the impact of maternal weight gain on offspring despite evidence demonstrating that early-life environment precipitates risks for metabolic syndrome. We hypothesized that excessive weight gain during pregnancy results in programming that predisposes offspring to obesity and metabolic syndrome. We further hypothesized that early postweaning nutrition alters the effects of maternal weight gain on indications of metabolic syndrome in offspring. Pregnant sows and their offspring were used for these experiments due to similarities with human digestive physiology, metabolism, and neonatal development. First parity sows fed a high-energy (maternal nutrition high energy [MatHE]) diet gained 12.4 kg (42%) more weight during pregnancy than sows fed a normal energy (maternal nutrition normal energy) diet. Birth weight and litter characteristics did not differ, but offspring MatHE gilts weighed more ($P < .05$) at age of 3 weeks (4.35 vs 5.24 ± 0.35 kg). At age of 12 weeks, offspring from MatHE mothers that were weaned onto a high-energy diet had elevated ($P < .05$) blood glucose (102 vs 64 mg/dL, confidence interval [CI]: 67-91), insulin (0.21 vs 0.10 ng/mL, CI: 0.011-0.019), and lower nonesterified fatty acid (0.31 vs 0.62 mmol/L, CI: 0.34-0.56) than offspring from the same MatHE sows weaned to the normal energy diet. These effects were not observed for offspring from sows fed a normal energy diet during pregnancy. These data indicate that excessive gestational weight gain during pregnancy in a pig model promotes early indications of metabolic syndrome in offspring that are further promoted by a high-energy postweaning diet.

Abbreviations: MatNE, maternal nutrition normal energy; MatHE, maternal nutrition high energy; GWG, gestation weight gain; IOM, Health Institute of Medicine; BMI, body mass index; NEFA, nonesterified fatty acid; PWnNE, postweaning normal energy; PWnHE, postweaning high energy; MatNE→PWnNE, maternal nutrition normal energy to postweaning normal energy; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; Pck1, phosphoenolpyruvate carboxykinase, cytosolic form; PGC1a, peroxisome proliferator-activated receptor γ coactivator 1a.

☆ This work was supported by funds from the Showalter Trust Foundation, Purdue University.

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http://dx.doi.org/10.1016/j.nutres.2014.01.001

1. Introduction

Weight gain during pregnancy, known as gestational weight gain (GWG), comprises growth of the developing conceptus and expansion of maternal adipose tissue. The Institute of Medicine (IOM) of the National Academy of Sciences advises an inverse relationship between prepregnancy body mass index (BMI) and pregnancy weight gain [1]. Women considered to be "overweight" or "obese" based on a BMI greater than 25 kg/m^2 for overweight and 30 kg/m^2 for obese are encouraged to gain less weight during pregnancy than those considered to be "normal" or "underweight" based on a BMI of 18.5 kg/m^2 to 25 kg/m^{2}and less than 18.5 kg/m^2, respectively. These GWG guidelines were established by the IOM to promote healthy pregnancy outcomes for the mother and offspring. However, recent estimates indicate that less than half of pregnancies in the United States meet the IOM guidelines for weight gain, with 65% to 85% of the pregnancies that do not meet the recommendations gaining more than the recommended amount of weight [1]. Furthermore, over 40% of women with a normal prepregnancy BMI exceed IOM guidelines for recommended weight gain during pregnancy [2]. Excess weight gain during pregnancy is associated with increased neonatal adiposity [3]. Dynamic mathematical modeling of energy balance during pregnancy links excessive gestational weight gain with increased energy intake [4], but the relation of energy-generating nutrients with weight gain and offspring health has not been adequately investigated. Consequently, gestational weight gain may represent a modifiable lifestyle factor to reduce incidence of childhood overweight and obesity.

The programming effects of maternal gestational weight gain on offspring are not well understood. Pregnancy weight gain exceeding IOM recommendations is associated with childhood adiposity and a risk for the offspring being overweight at ages 3 years [5], 7 years [6], and 9 years [7]. Fat mass, a more direct measure of childhood adiposity, is associated with excessive GWG [7,8] at age of 9 years [7] but not age of 6 years [8]. In addition, women who exceed the IOM GWG recommendations, especially those who had a high rate of weight gain in early pregnancy, are more likely to have children that, at age 9 years, have elevated leptin and systolic blood pressure [7]. Although several animal studies have explored the negative impacts of maternal obesity before conception [9-11], excess maternal weight gain during pregnancy, with normal prepregnancy BMI, has not been extensively characterized. We hypothesized that excessive weight gain during pregnancy would predispose offspring to early-life obesity and aspects of the metabolic syndrome and that early postweaning nutrition would modulate the effects of maternal diet.

The objectives of this study were to determine effects of excess maternal gestational weight gain on offspring during early life at the key developmental milestones of birth, weaning, and early adolescence because it is now widely accepted that developmental plasticity extends past gestation to include neonatal life [12,13]. Primigravid commercial swine were used as a model of first pregnancy weight gain due to availability, the ability to control pregnancy weight gain, abundant overlap in physiology and metabolism with human beings, and the close developmental similarities of the piglet and human neonate [14]. Because dysregulation of glucose metabolism in offspring is a hallmark of a challenging in utero environment and a well-characterized outcome for models of both maternal energy restriction [15,16] and obesity during pregnancy [17], we focused our analysis in the piglets on indicators of metabolic syndrome in blood and transcripts in liver and intestine that are sensitive to insulin and in utero programming, specifically phosphoenolpyruvate carboxykinase, cytosolic form (Pck1) and peroxisome proliferator-activated receptor γ coactivator 1a (PGC1a). Because liver and intestine account for approximately 45% of whole body oxygen consumption in pigs [18], changes in their activity in response to maternal diet are likely to have important consequences with regard to energy metabolism and predisposition to adiposity.

To evaluate the offspring response to maternal weight gain, we measured birth weight, weight gain, adiposity, glucose, insulin, nonesterified fatty acids (NEFAs), and abundance of key insulin and developmentally responsive transcripts. We evaluated the interaction of the maternal and postweaning diet energy density on offspring growth, glucose metabolism, and intestinal and hepatic gene expression. We hypothesized that material weight gain during pregnancy leads to alterations in metabolism for offspring partly through changes in expression of insulin-responsive genes in liver and intestine.

2. Methods and materials

2.1. Diets and animals

Crossbred gilts from the Purdue University Animal Sciences Research and Education Center were artificially inseminated and individually housed in 0.6 × 2.1 m gestation stalls. Upon confirmation of pregnancy, gilts were blocked at 3 weeks of gestation by weight and boar used for insemination and assigned to either a normal energy maternal diet (maternal nutrition normal energy [MatNE], n = 9) or a maternal high-energy diet (maternal nutrition high energy [MatHE], n = 5) during gestation (Table 1). All diets were formulated to meet National Research Council Requirements for Swine (1998) using commercially available ingredients. Gilts fed the normal energy diet received 2.05 kg of feed per day, and those on the high-energy diet received 3.0 kg; both groups were allowed ad libitum access to water. The gilts were fed once per day at 0630. The MatHE diet was designed to provide a 50% increase in metabolizable energy intake and pregnancy weight gain. Weight of gilts was determined at 21, 48, 63, and 77 of days gestation and at day 21 of lactation. Back fat at the 12th rib was measured in pregnant gilts using B-mode ultrasound (Aloka American Ltd, Wallington, CT) at 21, 48, 63, and 77 days of gestation and at the end of lactation on day 21. Blood samples for serum and plasma were collected, approximately 4 hours after feeding, by venipuncture from the jugular vein at 21, 48, and 77 days of gestation. Serum was allowed to clot at room temperature for 10 minutes. All plasma and serum samples were stored on ice until they were centrifuged at 2000*g* for 20 minutes. Serum and plasma were stored at –20°C pending analysis for glucose, insulin, and NEFA.