

The Gut Microbiota Regulates Metabolism and Blood Pressure in Pregnancy

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Pregnancy is a state of large changes in the metabolic and cardiovascular systems of the mother. The placenta releases many hormones and growth factors, which not only affect the infant but also the mother. Placental release of human placental lactogen and growth hormone induces insulin resistance in the mother, which ensures adequate glucose supply to the developing fetus. Women with higher pre-pregnancy levels of insulin resistance, which includes women with high pre-pregnancy body mass index (BMI) and those who are genetically predisposed, are at higher risk of developing gestational diabetes mellitus (GDM). GDM is associated with adverse outcomes for mother and infant, both perinatally and later in life.¹

For the mother, these include a higher risk in the short term for developing pre-eclampsia and delivery by Cesarean section, and in the future, type 2 diabetes and cardiovascular disease. The infant of a mother with GDM has an increased risk of being born large for gestational age and admittance to the neonatal intensive care unit for hypoglycemia. In later life, the infants of mothers with GDM face an increased risk of obesity and metabolic disease.

Prevention of GDM is therefore of key importance and reducing pre-pregnancy obesity would be ideal. However, up to half of all pregnancies are unplanned and strategies including altering diet and physical activity have not been proven to be consistently successful.² Furthermore, the substantial barriers to pregnant women engaging in these high intensity interventions, and the costs associated with implementing them in the general population, have been well described.³ Alternative strategies are needed to prevent GDM and its complications.

The gut microbiota, metabolism and immune function

Short-chain fatty acids (SCFA). In recent years, the gut microbiota—the composite of all bacteria in the gut—has been identified as a key regulator of metabolism. The gut microbiota not only synthesizes vitamins but also ferments indigestible carbohydrates into SCFA.⁴ Intestinal cells can use SCFA, such as butyrate, as an energy supply or facilitate transport of SCFA into the general circulation where they serve as signaling molecules to the liver, the kidney, adipose tissue, and endothelial cells.⁵

Cholesterol. The gut microbiota can also regulate cholesterol metabolism. Some of the bacteria in the gut microbiota can bind cholesterol to their outer membranes. Other bacteria express enzymes that convert cholesterol to coprostanolol, which cannot be absorbed by the body. Lastly, some bacteria metabolize bile acids to form secondary bile acids. All three of these mechanisms lead to lower cholesterol uptake from the gut.⁶

Immune function. The gut microbiota also regulates the immune system through altering the release of cytokines from the cells lining the intestinal wall.⁵ Finally, the gut microbiota can alter the permeability of the intestinal wall, thereby enabling leakage of bacterial products across the intestinal wall, which can lead to inflammation.

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Changes to the gut microbiota in pregnancy

The composition of the gut microbiota is determined by host and environmental factors including genetic make-up, age, diet, obesity, disease states, and medications. In pregnancy, the composition of the gut microbiota changes over gestation: the gut microbiota of women in the third trimester of pregnancy has a higher proportion of bacteria belonging to the phylum Proteobacteria. This phylum is associated with a pro-inflammatory state. In elegant experiments where germ-free mice were transplanted with the gut microbiota of women in late pregnancy, an increase in body weight and insulin resistance were observed.⁷ These changes mirror the changes seen in pregnant women and provide tantalizing indications that the gut microbiota may actually contribute to the physiological changes observed in pregnancy.

The gut microbiota regulates metabolism in pregnancy

Only a limited number of studies have addressed the role of the gut microbiota in regulating metabolism in pregnancy in humans. We recently published a study that showed that a higher abundance of the genus *Collinsella* is positively correlated with higher levels of fasting insulin, C-peptide, and triglycerides in overweight and obese pregnant women at 16 weeks gestation.⁸ The anorexigenic hormone leptin, which is secreted from adipose tissue and the placenta, is positively correlated with the abundance of the family *Lachnospiraceae*. *Lachnospiraceae* abundance increases with a higher intake of animal protein and lowers SCFA production.⁹ Furthermore, levels of the incretin hormone gastric inhibitory polypeptide (GIP) are positively correlated with the abundance of the SCFA-producing genus *Coprococcus*. These results indicate that the composition of the gut microbiome may contribute to the regulation of glucose and lipid metabolism through affecting the levels of metabolic hormones.

The gut microbiota regulates blood pressure in pregnancy

Outside of pregnancy, there has been some evidence that the composition of the gut microbiota is altered in people with hypertension.¹⁰ In early pregnancy, we have reported a negative correlation between the abundance of the SCFA-producer *Odoribacter* in the gut microbiota and blood pressure.¹¹ A potential mechanism by which higher SCFA levels can lower blood pressure is by lowering the release of inflammatory markers such as plasminogen activator inhibitor-1 (PAI-1).¹¹ However, whether the gut microbiota regulates blood pressure later in pregnancy and is altered in women who develop hypertensive disorders of pregnancy needs to be determined.

Altering the composition of the gut microbiota—a new strategy to improve pregnancy outcomes?

These early studies indicate that the gut microbiota is indeed a regulator of metabolic and cardiovascular health in pregnancy. Manipulation of the composition of the gut microbiota could therefore be a new target for the prevention of complications of pregnancy. Strategies for altering gut microbiota composition include altering dietary intake, especially dietary fiber (Fig 1), as well as probiotic and prebiotic supplementation to increase the abundance of SCFA producers. These approaches may prove to be successful. However, only if we get a deeper understanding of the complex interactions between the bacteria within the gut microbiota

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and their human host, can we hope to design successful strategies to improve pregnancy outcomes for mother and infant.

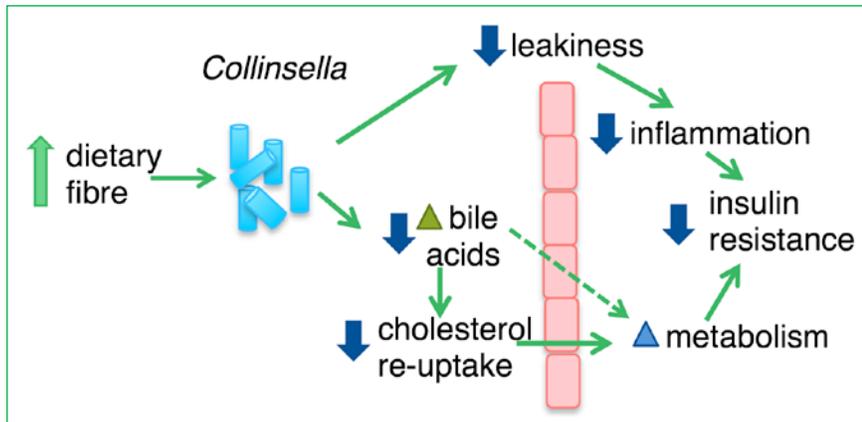


Fig 1. Model for how dietary fiber affects *Collinsella* abundance and metabolism.

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