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Influence of Maternal Prepregnancy Obesity and Excessive Gestational Weight Gain on Maternal and Child Gastrointestinal Microbiome Composition: A Systematic Review

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Abstract

Background: Maternal obesity is a well-known risk factor for significant obstetric and neonatal complications. The influence of the gastrointestinal microbiome in the setting of maternal obesity during pregnancy is less understood. The purpose of this systematic review is to synthesize the literature on the relationships between maternal obesity and excessive gestational weight gain (EGWG) and the composition of maternal and child gastrointestinal microbiomes. **Method:** We searched CINHAL, OVID Medline, Web of Science, and PubMed for relevant literature using medical subject heading terms related to obesity, pregnancy, and the gastrointestinal microbiome. We assessed 249 articles for potential inclusion using the preferred reporting items for systematic review and meta-analyses framework and deemed 11 articles as relevant for this review. **Results:** Maternal obesity was associated with significant microbial changes in both maternal and infant fecal microbiome biospecimens including increases in *Bacteroidetes*, *Firmicutes*, and the *Actinobacteria* phyla and decreases in *Bifidobacteria*. However, inconsistencies in uniform taxonomic results across all studies mean that evidence of specific microbial associations with obesity and EGWG is inconclusive. **Conclusion:** Our findings suggest that both maternal and child gastrointestinal microbiome composition is altered in the setting of maternal obesity and EGWG during pregnancy. Future microbiome studies should concentrate on the investigation of metagenomic sequencing to elucidate microbial function rather than solely taxonomic composition. More diverse populations of mothers should be sampled to address health disparities and adverse outcomes of underrepresented populations. Finally, analytic pipelines should be standardized across studies to aid in reproducibility.

Keywords

microbiome, obesity, pregnancy, maternal–child health, gestational weight gain

In 2007, the National Institutes of Health (NIH) allocated over US$150 million to pursue research on the role of the microbiota in healthy and pathophysiological states (Proctor, 2016; Stulberg et al., 2016). *Microbiota* refers to all the microorganisms living on or within the human body. The human gastrointestinal tract is largely inhabited by microbes, including viruses, fungi, and bacteria, that are integral to daily functioning (Human Microbiome Project Consortium, 2012). Microbes present in the gastrointestinal tract and other body tissues such as the skin, vagina, and oral mucosa facilitate important biological processes embedded within our metabolic, endocrine, immune, and nervous systems (D'Argenio & Salvatore, 2015; Heintz-Buschart & Wilmes, 2018). Research on the microbiome has proliferated to include a wide range of health disorders including cancer (Goodman & Gardner, 2018), cardiovascular disease (Tang & Hazen, 2017), inflammatory bowel disease (Lane, Zisman, & Suskind, 2017), and mental health conditions such as anxiety and depression (Foster, Rinaman, & Cryan, 2017).

Considering the rising prevalence of obesity in the United States (Hales, Carroll, Fryar, & Ogden, 2017), research in

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humans has focused on how the stress of obesity influences the gastrointestinal microbiota. Obesity in adult, nonpregnant populations decreases microbial α diversity, the species diversity in an individual's gastrointestinal tract, leading to low-grade inflammation, which can further exacerbate microbial dysregulation (Mosca, Leclerc, & Hugot, 2016). In addition, obesity is associated with increases in β diversity, the diversity of species between individuals. A recently published systematic review on nonpregnant women reported a significant increase in bacterial species from the *Firmicutes* phylum in obese individuals compared to a larger proportion of bacteria in the *Bacteroidetes* phylum in lean individuals, illustrating specific differences in gastrointestinal microbiota between obese and lean phenotypes (Castaner et al., 2018). In contrast, Koliada et al. (2017) found inverse relationships between both *Firmicutes* and *Bacteroidetes* and increasing body mass index (BMI), illustrating the divergent results of taxonomy-based studies.

Maternal obesity is a well-documented risk factor for obstetric complications and increased risk of subsequent chronic disease in offspring (Monasta et al., 2010; Patel et al., 2012; Ruager-Martin, Hyde, & Modi, 2010; Van Lieshout, Taylor, & Boyle, 2011). The American College of Obstetricians and Gynecologists (2013) defines obesity during pregnancy as a BMI at the first prenatal appointment equal to or above 30 kg/m^2. Recommendations from the Institute of Medicine in 2009 state that women with a BMI $\geq$ 30 kg/m^2 should gain between 11 and 20 pounds between the time of conception and the onset of labor (Gilmore & Redman, 2015). Excessive gestational weight gain (EGWG) is defined as gaining more than recommended by health standards during pregnancy (Rasmussen et al., 2010). Given the rising prevalence of maternal obesity and growing evidence implicating the role of the microbiome in obesity in nonpregnant adults, a review of the currently published literature investigating maternal obesity and the gastrointestinal microbiome throughout pregnancy and the postpartum period is necessary.

The central objective of the present review is to synthesize the literature on the relationship between maternal obesity and EGWG and the composition of maternal and child gastrointestinal microbiota. More specifically, we extracted, assessed, and discuss below the maternal and child fecal microbiota composition associated with (1) maternal obesity and (2) EGWG during pregnancy.

Method

Eligibility Criteria

We conducted this review using the preferred reporting items for systematic reviews and meta-analyses recommendations and organized it using a web-based consensus tool called Covidence (www.covidence.org). To be eligible for inclusion, studies had to (1) be conducted with human biospecimens, (2) include analysis of maternal or child gastrointestinal microbiome biospecimens (i.e., fecal swab, stool), and (3) include maternal overweight or obesity as a primary variable of interest. Studies were limited to those written in English and published in peer-reviewed journals. Because the microbiome is an emerging topic, we did not limit the search criteria to a specific date range.

Literature Search Strategy

We used several strategies for the literature search including electronic searches, ancestral searches, and hand searches of journals known to focus on content related to maternal–child health. For the electronic search, we used the online databases CINHAL, OVID Medline, Web of Science, and PubMed using keywords and medical subject heading (MeSH) terms in three main topic areas: microbiome, obesity, and pregnancy. MeSH terms used in the advanced search included ("microbiota" OR "microbiome") AND ("obesity" OR "obese") AND ("pregnancy"). The first author (C.D.) implemented the database search and pulled the relevant citations, abstracts, and full texts into Covidence. After the removal of duplicates between databases, two authors (C.D. and S.P.) assessed abstracts for inclusion criteria. The same two authors conducted a full-text article review for final consensus regarding inclusion.

Data Extraction and Quality Assessment

The two authors (C.D. and S.P.) extracted data from each article and reviewed them through the Covidence system. Because the included articles were not intervention studies, protocols were not available for extraction. Data extracted included PICO statements (population, intervention, comparison/control, outcome), number of participants, biospecimen source and time point of collection, operational definitions for prepregnancy obesity and GWG, and significant microbiota associated with maternal obesity and EGWG. We assessed all of the full-text articles included in this review for customized quality metrics to aid in the interpretation of quasi-experimental and observational studies. These quality assessment criteria focused on study design (i.e., Level I = randomized controlled trial or experimental study, Level II = quasi-experimental, Level III = nonexperimental, Level IV = qualitative) and three categories of quality assessment (A = high, B = good, or C = low quality; Keim-Malpass, Letzkus, & Kennedy, 2015). The risk assessment considers generalizability, sufficiency of the sample size, adequacy of the control group, and consistency with current scientific recommendations for sequencing and analysis. The same two authors (C.D. and S.P.) who evaluated the articles for inclusion also completed the quality assessment.

Results

We initially identified 249 records for this systematic review on the interaction between maternal obesity and EGWG and the gastrointestinal microbiome. After removing duplicates and reviewing abstracts and full-text articles for inclusion criteria, we had a final selection of 11 articles to review (see Figure 1).

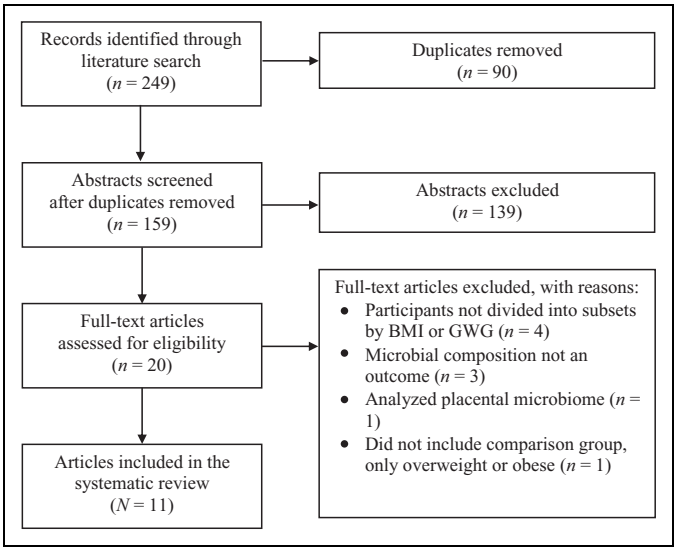

Figure 1. Preferred reporting items for systematic reviews and meta-analyses diagram of literature search and inclusion process. BMI = body mass index; GWG = gestational weight gain.

Study Characteristics and Sampling

Table 1 lists data extracted from each study, including author, PICO statement, number of participants and biospecimens, time point of microbiome collection, and the data source (i.e., primary data collection in a cohort study or collection from a specimen biobank or repository). We have categorized studies in the table by population from which biospecimens were collected: five studies collected biospecimens from mothers only (Collado, Isolauri, Laitinen, & Salminen, 2008; Gomez-Arango et al., 2016a; Houttu, Mokkala, & Laitinen, 2017; Santacruz et al., 2010; Smid et al., 2018), four sequenced biospecimens from children only (Collado, Isolauri, Laitinen, & Salminen, 2010; Galley, Bailey, Kamp Dush, Schoppe-Sullivan, & Christian, 2014; Mueller et al., 2016; Robinson et al., 2017), and two included biospecimens from both mothers and their infants (Chu, Antony, et al., 2016; Stanislawski et al., 2017). The average time point for collection of maternal gastrointestinal microbiome biospecimens was 17.2 weeks' gestation (range = 10−24 weeks' gestation), while two studies conducted follow-up microbiome collection at 30−39 weeks' gestation (range = 30−39 weeks; Collado et al., 2008; Smid et al., 2018). Only two of the studies used biospecimens from a common biobank or biorepository (Robinson et al., 2017; Stanislawski et al., 2017). Table 1 further provides operationalization of key variables across each of the included studies. Of the 11 studies, 5 reported how they defined prepregnancy BMI (Collado et al., 2008, 2010; Houttu et al., 2017; Smid et al., 2018; Stanislawski et al., 2017), 4 of which used maternal self-report of weight and height prior to conception as the definition (Collado et al., 2008, 2010; Houttu et al., 2017; Stanislawski et al., 2017).

Objective 1: Microbiota Alterations Associated With Maternal Prepregnancy Obesity

Table 2 presents the phyla, families, genera, and species (when reported) of the microbiota the reviewed studies found to be significantly impacted by maternal prepregnancy weight status. The nine studies that categorized maternal participants by overweight or obesity status are arranged by populations from which they drew the biospecimens (i.e., maternal, child, or both) to illustrate potential trends across the sampling source. There was little agreement among studies regarding which specific microbes, at any level of taxonomy including phylum, are significantly altered in the setting of maternal obesity.

Of the nine studies, three found decreases in *Clostridium coccoides* in the setting of maternal obesity (Collado et al., 2008; Santacruz et al., 2010; Stanislawski et al., 2017), two found increases in *Staphylococcus aureus* in obese women prior to pregnancy (Collado et al., 2008; Santacruz et al., 2010), and one found increased *S. aureus* in the feces of infants at 6 months of life (Collado et al., 2010) in the setting of maternal prepregnancy obesity. Collado, Isolauri, Laitinen, and Salminen (2008) and Stanislawski et al. (2017) found that maternal prepregnancy overweight and obesity reduced α diversity of the maternal gastrointestinal microbiota, while three other studies found no difference in α diversity by maternal prepregnancy weight category (Gomez-Arango et al., 2016b; Houttu et al., 2017; Smid et al., 2018).

Assessing differences in the microbiota that are independently associated with maternal prepregnancy obesity is difficult due to confounding variables such as mode of delivery, antibiotic use, diet, and socioeconomic status, which are known to influence gastrointestinal microbiota composition (Mueller, Bakacs, Combellick, Grigoryan, & Dominguez-Bello, 2015). For example, Mueller et al. (2016) reported that bacteria in the *Bacteroidetes* phylum were enriched after vaginal delivery and decreased after cesarean delivery in infants whose mothers were overweight or obese. Galley, Bailey, Kamp Dush, Schoppe-Sullivan, and Christian (2014) found that levels of organisms in Bacteroidetes, including those in the genera *Prevotella* and *Parabacteroides,* were increased in the infants of high-income obese women and decreased, at the phylum level, in low-income women. Prepregnancy obesity may also confound analysis of the composition of microbiota associated with obesity acquired during gestation, as two studies found that mothers with prepregnancy obesity had increased abundance of organisms from the *Prevotella* genus and no difference in α diversity compared to women with prepregnancy overweight (Collado et al., 2008; Houttu et al., 2017).

Objective 2: Microbiota Alterations Associated With EGWG

Of the five studies that assessed the impact of EGWG on the gastrointestinal microbiome (Table 3), three characterized maternal biospecimens (Collado et al., 2008; Santacruz et al., 2010; Smid et al., 2018), one characterized child biospecimens

Table 1. Study Characteristics.

Author(s)	PICO Statement	Participants and Comparison Groups	Definition of Prepregnancy BMI and Obesity	Time Point for Microbiome Collection	Sample Source[a]	Quality Assessment[b]
Biospecimens collected from mothers only						
Collado et al. (2008)	Do BMI and GWG alter the maternal gastrointestinal microbiota before delivery?	$N = 54$ women: • $n = 18$ OW (called OW in study but defined as OB according to post-2008 guidelines) • $n = 36$ NW Groups: OW and NW	BMI: Maternal self-report of weight at first clinic visit Overweight/obesity: BMI $\geq$ 30 kg/m^2	First (10–15 weeks' gestation) and third (30–35 weeks' gestation) trimesters of pregnancy	Study	IIB
Houttu et al. (2017)	Does the degree of overweight alter the composition of the maternal gastrointestinal microbiome during pregnancy?	$N = 99$ women • $n = 52$ OW • $n = 47$ OB Groups: OW and OB	BMI: Maternal self-report of weight at first clinic visit Obesity: BMI $\geq$ 30 kg/m^2	< 17 weeks' gestation	Study	IIB
Gomez-Arango et al. (2016a, 2016b)	Is there a difference in gut microbiome composition and circulating metabolic hormones between OW and OB pregnant women?	$N = 70$ women • $n = 29$ OW • $n = 41$ OB Groups: OW and OB	BMI: not reported Obesity: BMI $\geq$ 30 kg/m^2	16 weeks' gestation	Study	IIB
Santacruz et al. (2010)	Do body weight and GWG[c] alter the composition of the maternal gastrointestinal microbiome during pregnancy?	$N = 50$ women • $n = 34$ NW • $n = 16$ OW Groups: NW and OW/OB	BMI: not reported Obesity: BMI $\geq$ 25 kg/m^2	24 weeks' gestation	Study	IIB
Smid et al. (2018)	Does EGWG change the maternal gastrointestinal microbiome during pregnancy?	$N = 31$ women Groups: Above and below median GWG for this cohort, baseline and follow-up	BMI: Weight at first clinic visit Obesity: BMI $\geq$ 30 kg/m^2	Baseline: < 20 weeks' gestation Follow-up: 36–39 weeks' gestation	Study	IIIB
Biospecimens collected from mothers and infants						
Chu et al. (2016)	Does maternal obesity alter the neonatal and infant gut microbiome in early life?	$N = 157$ women, 157 infants Groups: High fat intake and control	Not reported	First maternal and infant stool samples at 24–48 hr after delivery and second sample at 4–6 weeks of life	Study	IIB
Stanislawski et al. (2017)	Is maternal prepregnancy overweight/obesity associated with differences in the maternal gastrointestinal microbiota at the time of delivery or in the gastrointestinal microbiota of their infants during the first 2 years of life?	$N = 169$ women, 181 infants Groups: NW and OW/OB mothers	BMI: Maternal self-report of weight at first clinic visit Overweight and obesity: BMI $\geq$ 25 kg/m^2	Maternal sample 4 days after delivery, newborn samples at 6 time points over the first 2 years of life	Biobank	IIA

(continued)

Table 1. (continued)

Author(s)	PICO Statement	Participants and Comparison Groups	Definition of Prepregnancy BMI and Obesity	Time Point for Microbiome Collection	Sample Source[a]	Quality Assessment[b]
Biospecimens collected from infants only						
Collado et al. (2010)	Do maternal BMI status and EGWG alter the microbiota of their infants?	$N = 42$ infants, 26 NW mothers, 16 OW mothers Groups: OW and NW	BMI: Maternal self-report of weight at first clinic visit Overweight: BMI ≥ 25 kg/m^2	1 and 6 months of life	Study	IIA
Galley et al. (2014)	Is maternal obesity associated with differences in the composition of the gut microbiome in children in early life?	$N = 77$ infants, 25 OB mothers, 51 non-OB mothers Groups: OW and OB	BMI: Not reported Obesity: BMI ≥ 30 kg/m^2	18–27 months of age	Study	IIB
Mueller et al. (2016)	Is maternal prepregnancy BMI associated with differences in the gastrointestinal microbiota between infants delivered vaginally and those delivered via ECS?	$N = 74$ neonates • $n = 18$ VD • $n = 56$ ECS • $n = 31$ to OW/OB mothers Groups: VD and ECS	BMI: Not reported Overweight and Obesity: ≥ 25 kg/m^2	2 days after delivery	Study	IIB
Robinson et al. (2017)	Is GWG[c] associated with changes in infant fecal microbiota composition, bacterial-community richness, and Shannon diversity index?	$N = 84$ infants Groups: GWG categories	Not reported	<1 year of age	Biobank	IIB

Note. Studies are arranged to highlight the population studied. BMI = body mass index; ECS = elective cesarean section; EGWG = excessive gestational weight gain; GWG = gestational weight gain; NW = normal weight; OB = obese; OW = overweight; PICO = population, intervention, comparison/control, outcome; VD = vaginal delivery.

[a]Samples were either sourced directly from a biobank or from a prospective cohort study. [b]The quality assessment score includes level (Level I = randomized controlled trial or experimental study, Level II = quasi-experimental, Level III = nonexperimental, Level IV = qualitative) and quality assessment (A = high, B = good, or C = low quality) which was adapted from Keim-Malpass, Letzkus, and Kennedy (2015). [c]GWG was defined by the Institute of Medicine guidelines.

Table 2. Significant Microbiota and Their Association With Maternal Obesity.

Microbe				Biospecimen Sampling and Study								
				Infant			Maternal				Both	
Phylum	Family	Genus	Species	Mueller et al. (2016)[a]	Collado et al. (2010)	Galley et al. (2014)	Gomez-Arango et al. (2016)	Houttu et al. (2017)	Collado et al. (2008)	Santacruz et al. (2010)	Stanislawski et al. (2017)	Chu et al. (2016)
Actinobacteria	—	—	—	−			+	+				
	Bifidobacteriaceae	*Bifidobacteria*	—		−					−	−	
	Coriobacteriaceae	*Collinsella*	—				+					
Bacteroidetes	—	—	—	+, −[a]		−[b], +[c]	+	−[d]	+			
	Bacteroidaceae	*Bacteroides*	*bacteroides*		+					−		−
	Prevotellaceae	*Provotella*	—		−	+[c]		+	+			
	Porphyromonadaceae	*Parabacteroides*	*paracteroides sp.*			+[c]					−	
	Rikenellaceae	—	—				+[d]	+				
Firmicutes	*Lachnospiraceae*	*Blautia*	*blautia sp.*			−[b]					+	
		—	—				+[d]				+	
		Sporobacteria	*WAL 1855D*								+	
	Clostridiaceae	*Faecalibacteria*	—			+						
		—	—								−	
		Clostridium	*C. histolytica*		+				+			
			C. leptum		+							
			C. perfringens		−							
			C. coccoides					+	−	−	−	
	Christensenellaceae	—	—								−	
	Enterobacteriaceae	*Enterococcus*	—	−								+
	Eubacteriaceae	*Eubacteria*	—			−						
	Peptoniphilaceae	*Finegoldia*	*finegoldia sp.*								−	
	—	—	—	+								
	Oscillospiraceae	*Oscillibacter*	—			+[c]						
	Ruminococcaceae	—	—								−	
		Ruminoccocus	*ruminoccocus sp.*								−	
	Staphylococcaceae	*Staphylococcus*	*S. aureus*		+				+	+		
Proteobacteria	*Enterobacteriaceae*	*Escherichia*	*E. coli*							+		
		Enterobactor	—							+		
	Hydrogenophilaceae	*Hydrogenophilus*	—	−								
	—	—	—	+[a]								
	Pseudomonadaceae	*Psuedomonas*	—	−								
	Xanthomonadace	—	—	−								
Tenericutes	—	—	—				+[e]					
Verrucomicrobia	*Verrucomicrobiaceae*	*Akkermansia*	*akkermansia sp.*		+							
			A. muciniphila		+				+			
Microbial diversity												
α						+[c]	−				−	
β						+[c]						+

Note. The table visualizes associations between microbe populations and maternal prepregnancy obesity as reported in the reviewed studies that used prepregnancy overweight or obesity as an independent variable. Dashes in the family, genus, or species columns indicate the studies did not report the lower taxonomic categories for that microbe. + indicates a positive association between obesity/overweight and changes to the microbe population. – indicates a negative association between obesity/overweight and changes to the microbe population. A blank cell indicates that the study did not report any significant changes to that microbe population.

[a]Mueller et al. (2016) also grouped infants by type of delivery. Findings associated with cesarean delivery are indicated with superscript alphabet "a." All others associated with vaginal delivery. [b]Associated with low income. [c]Associated with high income. [d]Association with maternal overweight and obesity. [e]Association with overweight group only.

Table 3. Significant Microbiota and Their Association With Excessive Gestational Weight Gain.

Microbe				Biospecimen Sampling and Study				
				Maternal			Both	Infant
Phylum	Family	Genus	Species	Collado et al. (2008)	Santacruz et al. (2010)	Smid et al. (2018)	Collado et al. (2010)	Robinson et al. (2017)
Bacteroidetes	*Prevotellaceae*	*Provotella*	—	+			−	
	Bacteroidaceae	*Bacteroides*	*bacteroides*					−
	—	—	—	+		+		
Actinobacteria	*Bifidobacteriaceae*	*Bifidobacteria*	—	−	−			+
Firmicutes	*Clostridiaceae*	*Clostridium*	*C. histolyticum*	+			+	
Proteobacteria	*Enterobacteriaceae*	*Enterobactor*	—		+			+
		Escherichia	*E. coli*		+			
			escherichia sp.					+
Verrucomicrobia	*Verrucomicrobiaceae*	*Akkermansia*	*A. muciniphila*		−			
Microbial diversity								
α						+		−
β								

Note. The table visualizes associations between microbe populations and excessive gestational weight gain (EGWG) as reported in the reviewed studies that used EGWG as an independent variable. Dashes in the family, genus, and species columns indicate the studies did not report the lower taxonomic categories for that microbe. + indicates a positive association between obesity/overweight and changes to the microbe population. – indicates a negative association between obesity/overweight and changes to the microbe population. A blank cell indicates that the study did not report any significant changes to that microbe population.

(Robinson et al., 2017), and one included both maternal and child biospecimens (Collado et al., 2010). Studies reported positive associations between EGWG and abundance of *Clostridium histolyticum*, *Bacteroidetes* (phylum), *Enterobacter* (genus), *E. coli*, and *Escherichia sp.* and negative associations between EGWG and abundance of *Akkermansia muciniphila* and *Bacteroides bacteroides*. However, there are inconsistencies in the directionality of association across studies for organisms in the *Prevotella* genus, with Collado et al. (2008) finding a positive association with EGWG and Collado, Isolauri, Laitinen, and Salminen (2010) reporting a negative association. Likewise, Collado et al. (2008) and Santacruz et al. (2010) found a negative association between EGWG and abundance of organisms in the *Bifidobacteria* genus in maternal biospecimens during pregnancy, while Robinson et al. (2017) reported a positive association in infants younger than 1 year of life, demonstrating a potential divergent relationship between the maternal and infant microbiomes.

Discussion

Research on the association between the composition and diversity of gastrointestinal microbiota and obesity in humans has been conducted largely outside of pregnancy. In the present systematic review, we examine the state of the science exploring the effects of maternal obesity and EGWG on maternal and infant microbiota during this unique time period. Overall, the studies found that the compositional diversity of the microbiota and relative abundances of specific microbes are significantly altered in maternal prepregnancy obesity and EGWG compared to normal weight and adequate GWG. However, results may be confounded by variables such as antibiotic use and delivery method, which are known to influence microbiota composition and could result in inconsistencies in the directionality of the association between maternal obesity and/or EGWG and compositional changes in the microbiota.

Our synthesis of these articles indicates that, despite the lack of differences in macronutrient consumption among weight groups (i.e., obese, overweight, normal weight; Gomez-Arango et al., 2016a, 2016b; Houttu et al., 2017; Santacruz et al., 2010), there are differences in reported maternal and child microbiomes. Although the differences in microbiome composition among these weight groups remain unclear, patterns in both maternal and child microbiome composition suggest that the relationships among GWG, composition of the microbiome, and host metabolism during pregnancy may have significant functional impacts. For example, two of the reviewed studies demonstrated that the microbiota may be influencing insulin resistance and glucose homeostasis in mothers (Gomez-Arango et al., 2016b; Houttu et al., 2017), suggesting that bacterial functional differences may contribute to obesogenic changes in maternal metabolism. Thus, bacterial taxonomy may be less important than functional genetic components common to several bacterial species that may be driving changes in maternal metabolism during gestation.

Modulation of Maternal Obesity by the Microbiome

While the articles included in this review examined the influence of maternal obesity and GWG on microbiota composition, conversely, some researchers have argued that the microbiome could be a key mechanism in the development of maternal and child obesity risk (Ley et al., 2005; Mohammadkhah, Simpson, Patterson, & Ferguson, 2018; Suez, Shapiro, & Elinav, 2016). Experimental evidence for the influence of the gastrointestinal microbiome on the development of obesity comes from animal

studies comparing germ-free mice to conventional mice reared in a pathogen-free environment (Bäckhed, Manchester, Semenkovich, & Gordon, 2007). In a landmark study by Bäckhed et al. (2004), the distal gut microbiota from pathogen-free mice were transplanted into germ-free mice, resulting in a 60% increase in body fat within 2 weeks. More importantly, there was no increase in calorie consumption or changes in energy expenditure, suggesting that the gastrointestinal microbiota affects phenotypic characteristics related to obesity of the host (Bäckhed et al., 2004). In addition, several studies in both human and animal models have implicated microbial composition as an important modulator for obesity, noting, for instance, reduced microbial diversity in obese, nonpregnant women (Ley et al., 2005; Suez et al., 2016).

Inflammation and Metabolic Syndrome

Gastrointestinal microbiota contribute to the regulation of energy homeostasis; thus, disruption in these microbiota can cause metabolic diseases (Smith et al., 2011). First, increased intestinal permeability (called leaky gut syndrome) and dysbiosis of the microbiota drive chronic and widespread inflammation in the tissue (Turner, Nedjai, Hurst, & Pennington, 2014). This inflammatory process stimulates the activation of macrophages, which are essential components of protective immunity (Ang & Ding, 2016; Turner et al., 2014). The largest population of macrophages is located in the intestines (Ang & Ding, 2016). In noninflamed intestinal tissue, macrophages kill predatory microbes without any inflammatory response (den Besten et al., 2013). However, in the presence of dysbiosis of the microbiota, the macrophages attract inflammatory immune cells (typically monocytes derived from the innate immune system) that secrete interleukin-8 and transforming growth factor-β (den Besten et al., 2013; Turner et al., 2014). Secreted chemokines and cytokines perpetuate the inflammatory process, resulting in immune cell infiltration of adipose tissue and immune exhaustion leading to lower resistance to infection (Sze & Schloss, 2016). Future research should address the role of the gastrointestinal microbiota and the immune system in the progression of obesity as well as insulin resistance, impaired glucose tolerance, and the resulting cardiovascular disease risk.

Research has not yet fully deconvoluted the complex interplay among obesity, weight gain, and metabolic syndrome during childbearing years and pregnancy. Rather than obesity alone, it is a combination of the effects of maternal behaviors (e.g., diet, exercise), biological factors (e.g., microbiota composition and function, epigenetics), and the environment (e.g., food security, structural inequality) that likely influence metabolic outcomes.

Fetal Programming and Transgenerational Obesity

The investigation into the gastrointestinal microbiota's influence on maternal obesity is important due to the known effects of obesity on fetal programming (Neri & Edlow, 2015). Research examining fetal programming provides compelling evidence about how early in utero development may predispose a child to chronic metabolic concerns later in life (Kwon & Kim, 2017; Rinaudo & Wang, 2012). The critical period in fetal development coincides with rapid cell differentiation and proliferation (Widdowson & McCance, 1975). The maternal microbial milieu has the potential to influence maternal obesity, thereby increasing birth weight, which could lead to chronic cardiometabolic health concerns such as childhood obesity, hypertension, renal disease, and diabetes (Rinaudo & Wang, 2012). Research suggests that one of the impacts of maternal obesity and EGWG is an increase in facultative anaerobes, such as *Proteobacteria*, *Actinobacteria,* in the child's gastrointestinal microbiome that delay maturation of the microbiota (Chong, Bloomfield, & O'Sullivan, 2018). Facultative anaerobes, normal early colonizers in the neonatal gut, consume oxygen and facilitate the establishment of ubiquitous microbiota such as *Bifidobacteria* and *Bacteroides* (Chong et al., 2018). Initiation of the colonization of *Bifidobacteria* and *Bacteroides* shows the adaptive colonization that occurs as the immune system and microbiota mature (Chong et al., 2018). In the setting of maternal obesity, maturation of microbiota, which normally occurs over the first 2 years of childhood, may be prevented or delayed as facultative anaerobes fail to give way to the strict anaerobes normally inhabiting the gastrointestinal compartment of adults and older children (Rodríguez et al., 2015).

Various studies have shown a difference in gastrointestinal microbiota composition between obese and normal-weight children (Bervoets et al., 2013; Ignacio et al., 2016; White et al., 2013). Ignacio et al. (2016) found significantly higher abundances of *Bifidobacteria* in lean compared to overweight children. Research has shown that *Bifidobacteria* have immune system benefits including host protection against pathogens (O'Callaghan & van Sinderen, 2016). Using a novel type of time-series analysis, White et al. (2013) detected significant associations between specific gastrointestinal microbiota and child growth trajectory measured by child weight-for-age *Z*-scores. However, the microbiome is only one potential determinant of childhood obesity. Other factors, both modifiable and unmodifiable, include genotype and environmental factors (Siega-Riz, Siega-Riz, & Laraia, 2006).

16S Ribosomal RNA (16S rRNA) Gene Sequencing and Bioinformatics Analysis

Studying the microbiome composition requires the extraction of DNA from the biospecimen, often from a fecal sample or swabbing of the area of interest. The most common method for classifying microbial taxonomy and phylogeny is 16S rRNA gene sequencing (Janda & Abbott, 2007), which uses short strands of DNA called primers that are designed to target specific variable regions of the 16s rRNA gene. The 16s rRNA gene is highly conserved, or passed through generations, and acts as a microbe-specific genetic signature. These signatures allow researchers to characterize the abundance of specific microbes and the overall phylogenetic diversity of the

microbiota present in a biospecimen. In eight of the reviewed studies (Chu, Meyer, Prince, & Aagaard, 2016; Galley et al., 2014; Gomez-Arango et al., 2016b; Houttu et al., 2017; Mueller et al., 2016; Robinson et al., 2017; Smid et al., 2018; Stanislawski et al., 2017), investigators used 16S rRNA gene sequencing across two different platforms (i.e., Illumnia and Ion Torrent) to characterize the microbiota. Limitations of 16S rRNA sequencing include low resolution and sensitivity of taxonomic identity compared to shotgun metagenomic sequencing, which comprehensively samples genes from the entire microbial genome, resulting in information about which microorganisms are present and their functional role in the community (Poretsky, Rodriguez-R, Luo, Tsementzi, & Konstantinidis, 2014). For studies focused on complex phenotypes, such as obesity, information about both microbial composition and function is needed to enhance scientific understanding.

Variations across the reviewed studies regarding the microbiota reported to be associated with maternal obesity or EGWG could be due, at least in part, to variations in the bioinformatics pipelines (i.e., Quantitative Insights Into Microbial Ecology [QIIME], mothur, MetaGenome Rapid Annotation using Subsystem Technology), reference genomes (i.e., SILVA, GreenGenes), and software (i.e., statistical software, SPSS, R) investigators used to guide analyses of the biospecimens. Inconsistencies across studies, therefore, could be due to bioinformatic limitations with paired-end sequencing reads with reference genomes resulting in unclassified microbiota or only broad, phylum-level classification. In all of the studies except for four (Collado et al., 2008, 2010; Robinson et al., 2017; Santacruz et al., 2010), authors reported using QIIME, big data, open-source software built for microbiome analysis from raw FASTQ sequencing data on Illumina platforms (Caporaso et al., 2010). Just under half of the studies (5/11) reported the reference database they used and in all five it was GreenGenes (Galley et al., 2014; Gomez-Arango et al., 2016b; Mueller et al., 2016; Smid et al., 2018; Stanislawski et al., 2017). Authors should always report these methodological pipelines and associated code to increase the transparency of results and contribute to the larger body of knowledge in obesity and microbiome research (Kelsey, Dreisbach, Alhusen, & Grossmann, 2019). Most of the studies used either SPSS or R for their analysis, but two studies (Mueller et al., 2016; Smid et al., 2018) did not report this information. In conducting future studies, investigators should consider measures to increase reproducibility including making data available for public use, publishing in open science journals, and using processing and analysis code that is freely available.

Limitations

Importantly, there are several limitations across the studies included in this review that restrict our ability to draw conclusions about associations between maternal obesity and EGWG and maternal and infant microbiota. First, the studies were not consistent in the composition of their comparison groups. While most of the studies used the categories of both maternal overweight (25−29.9 kg/m^2) and obesity (above 30 kg/m^2), two grouped obesity and overweight together into one comparison group with a BMI above 25 kg/m^2 (Gomez-Arango et al., 2016b; Houttu et al., 2017), making comparisons across studies difficult. The literature has shown that the risk of adverse pregnancy and neonatal outcomes is higher among obese mothers compared to overweight mothers; thus, this difference in classification is an important distinction (Gilmore & Redman, 2015; Siega-Riz et al., 2009). In addition, several studies did not include a normal-weight control group (Gomez-Arango et al., 2016a, 2016b; Houttu et al., 2017). On the other hand, all of the studies that examined GWG used the recently revised IOM guidelines, making comparisons among studies easier to conduct (Collado et al., 2008, 2010; Robinson et al., 2017; Santacruz et al., 2010; Smid et al., 2018). Second, most of the reviewed studies did not fully describe the baseline demographic characteristics of participants. For the studies in which investigators did describe these characteristics, most biospecimens were from participants of Scandinavian descent. Given the reported disparities in risks associated with prepregnancy and parity-related obesity for African American and Hispanic populations and the continued ethnic and racial disparities in maternal morbidity and mortality (Harper, Dugan, Espeland, Martinez-Borges, & Mcquellon, 2007), researchers should attempt to recruit participant samples that are racially and ethnically representative of the study setting's population and should also acknowledge the racial and ethnic bias inherent in their samples.

Limitations of our systematic review process include the following: (1) we only included published data, (2) our original search criteria did not include *gestational weight gain* as a search term, (3) Covidence does not allow for further delineation of database imports, that is, the database from which we drew each study is not identified, and (4) our ability to make comparisons across studies was limited because not all collected both maternal and child biospecimens.

Nursing Implications

The impact of the gastrointestinal microbiome on health, particularly during pregnancy, is not fully understood. Nurses need to be competent in the biological underpinnings of microbiology in order to understand its relation to direct patient care. The emergence of new frontiers in personalized nutrition, obesity management, fecal transplants, and direct-to-consumer microbiome sequencing means that nurses will be at the front line of educating patients and their families. More research is required on prebiotics and probiotics before recommendations for specific therapies for influencing the maternal microbiota can be made.

Conclusion

In this systematic review, we synthesized data from 11 articles on the interaction between maternal obesity and/or EGWG and the maternal and infant microbiome. We found evidence that

the composition of both maternal and child gastrointestinal microbiomes is associated with maternal obesity, but the directionality, mechanisms, and significant microbes have yet to be fully determined. Further research using advanced methods, such as shotgun metagenomic sequencing, should be conducted to discern the functional relevance of the microbiota in association with metabolism during gestation. Current research is largely focused on the characterization and taxonomic composition of microbial communities. An important step in this area of research would be an enhanced understanding of the cardiometabolic and immune outcomes associated with dysbiosis. Future research in this area should implement standardized approaches to biospecimen collection, sequencing platforms, and analytic methods, which will more easily allow for the interpretation of findings in terms of clinical relevance.

Author Contributions

Caitlin Dreisbach contributed to conception, design, acquisition, analysis, and interpretation; drafted the article; critically revised the article; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Stephanie Prescott contributed to acquisition, analysis, and interpretation; critically revised the article; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Jeanne Alhusen contributed to conception and design; critically revised the article; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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