Maternal Obesity and Fetal Macrosomia: An Integrative Review of the Literature Regarding Interventions

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Abstract

Research suggests pre-pregnancy obesity is associated with an increased risk of macrosomia in the newborn. Since women are expected to gain weight during pregnancy, the standard recommendation of weight loss for obesity is not ideal for this population. In this systematic review of the literature regarding interventions for maternal obesity to reduce fetal macrosomia, 149 articles were screened using three different databases to identify recent randomized controlled trials related to this topic. A total of 11 full text articles were analyzed and included in the review. The articles addressed nutritional, lifestyle, and pharmacological interventions. The results indicated there is currently insufficient evidence to support specific treatment options for women with obesity during pregnancy to reduce the risk of fetal macrosomia.

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Among the *Healthy People 2020* objectives, in the section "Maternal, Infant and Child Health," objective number 16.5 is to "Increase the proportion of women delivering a live birth who had a healthy weight prior to pregnancy" (HealthyPeople.gov Staff, 2017, MICH-16.5). Recently, obesity is becoming a crucial topic among healthcare providers, due to its increasing prevalence and an increasing awareness of the negative health conditions with which it can be associated. Obesity in the pregnant mother requires specialized care based on the most current evidence, to best understand the many possible effects it could have on this unique state of health for the mother, as well as on the developing child. One important topic of researcher interest is the association between maternal pre-pregnancy obesity and macrosomia of the newborn.

The World Health Organization [WHO] (2016) defined obesity as a body mass index of greater than or equal to 30 kg/m^2. Bray (2018), in a literature review, identified numerous risk factors associated with obesity. He noted the development of weight gain tends to occur in relation to certain life circumstances, such as pregnancy and menopause in women and, in men, the transition from an active lifestyle in younger men to the more sedentary lifestyle typically seen in the 30s and older. He also indicated the mother's nutritional status during pregnancy can affect the later metabolic profile of her offspring. He posited activity as a protective factor against obesity, and, in contrast, he maintained sitting and watching television for a long time is associated with an increased risk of obesity. Other behaviors which may lead to weight gain include not getting enough sleep,

quitting smoking, eating a lot of fat and sugar, binge-eating, and overeating, according to Bray. Weight gain can also be associated with taking certain medications, such as antidepressants and certain drugs for diabetes, Bray affirmed. He indicated obesity can also occur with certain diseases, such as Cushing's syndrome or polycystic ovary syndrome, and other factors, such as genetics, environment, and psychological conditions.

Obesity places a person at risk for many negative health conditions. Perreault (2018), in a literature review, indicated many studies have shown an increased risk of mortality in the obese population. Those with obesity are more likely to develop a chronic disease, such as diabetes, cancer, coronary heart disease, or depression, Perreault expressed. She noted there is evidence at least 11 different types of cancers may have links with obesity. She also mentioned obese men and women may face discrimination and stigma in society, and the financial cost of obesity is high, related to such factors as increased medical expenses and less productivity.

Commonly used criteria for defining macrosomia include a fetal mass no less than 4000 g or, alternatively, 4500 g (Gaudet, Ferraro, Wen, & Walker, 2014). Abramowicz and Anh (2018), in a literature review, identified risks macrosomia carries for both the mother and the fetus. Adverse maternal outcomes can include such things as postpartum hemorrhage, surgical delivery, or rupture of the uterus, they reported. They indicated the offspring may experience shoulder dystocia, low blood glucose levels at birth, obesity later in life, and more. If the infant's birthweight is 5000 g or more, he is at increased risk of death, they warned. The issue is of special concern in certain impoverished nations,

since, according to Abramowicz and Ahn, mothers in these places may be at risk of pregnancy prior to full development of the pelvis or of having a small pelvis due to undernutrition. They may or may not have access to operative delivery if needed (Abramowicz & Ahn, 2018).

Current literature provides evidence for the association between maternal obesity and macrosomia of the newborn. Abramowicz and Ahn (2018) declared obesity to be a significant risk factor for macrosomia, probably contributing to its development more often than diabetes. Similarly, in their systematic review and meta-analysis, Gaudet et al. (2014) identified strong support for the link between obesity and macrosomia in the research up to that time. Along the same lines, in a large study which included 276, 436 births in 23 countries, Koyanagi et al. (2013) noted a significant connection between a high body mass index and macrosomia. Finally, Lutsiv, Mah, Beyene, and McDonald (2015) in a systematic review and meta-analysis found data to support the idea the risk of a large-for-gestational-age infant may be able to be stratified by increasing body mass index. If the evidence leans in support of an association between maternal body mass index and macrosomia, the next question is: What options do obese mothers have available to reduce their risk? While it is best for women to lose weight prior to becoming pregnant, due to safety concerns if weight is lost during gestation (Abramowicz & Ahn, 2018), for some women, this weight loss is not accomplished. They enter pregnancy obese, and it is too late for prevention. A systematic review of literature regarding interventions to reduce the risk of fetal macrosomia in the offspring of obese pregnant

women may help to shed light on options available to these women for whom prevention is no longer a possibility.

Method

The researcher established certain criteria for studies to be included in this review. Sources had to be academic, randomized controlled trials, and published within the last five years (2013-2017), to promote the trustworthiness and relevance of the results. For simplification, the researcher assumed articles from PubMed were academic. She made one exception to the date range, identified later in the discussion of the search process. She defined the population as pregnant mothers with obesity, considered a body mass index of no less than 30 kg/m^2 per the WHO guidelines (2016). Since the purpose of this review was to give a broad overview of interventions, she did not define characteristics of the mother such as ethnicity, age, comorbidities, and others. She researched the following outcome: reduction of risk of macrosomia of the infant. She included studies which used either 4000 g or 4500 g as the threshold of macrosomia (Gaudet et al., 2014). She only included articles in which interventions occurred after the woman was pregnant; she excluded trials with preventive measures as interventions. Studies had to compare the risk of macrosomia with the intervention to the risk with having no intervention, other than standard care.

She discovered and obtained the majority of sources through searching three databases: CINAHL Plus with Full Text, Cochrane Library, and MEDLINE w/ Full-Text (EBSCO). She last searched these on February 2, 2018. In all three databases, she searched the terms “maternal obesity and macrosomia.” For CINAHL, she maintained the

default advanced search settings, with two alterations. (The default settings were as follows: “Search modes Boolean/Phrase;” no additional boxes checked or date range selected, and all drop-down list options set to “all.”) She set the “Published Date” to January 2013 to December 2017, and she checked the box to select only “Peer Reviewed” articles. For Cochrane, she used the default advanced search settings, except she limited the dates to 2013-2018. (The default settings were to search all years and Cochrane databases, with no other boxes checked.) After results were populated, she selected “Trials” instead of “Cochrane Reviews.” For MEDLINE, she kept all of the default advanced search settings, except changing the dates in the same manner as for CINAHL. (The default settings were as follows: “Search modes Boolean/Phrase;” no additional boxes checked or date range selected, and all drop-down list options set to “all.”) These databases provided the bulk of the sources for the review.

She chose two other articles through using the Google search engine, on February 6, 2018, using the search terms “maternal obesity and macrosomia interventions.” These appear in the reference list under Buschur and Kim (2012), which she accepted though slightly out of the date range, since it was still one of the first articles to be displayed on Google’s results, as well as Muktabhant, Lawrie, Lumbiganon, and Laopaiboon (2015). By using the “Similar Articles” feature of PubMed, where the former article was located, she identified one more article on the same date, Tanvig (2014). Also on February 6, she identified one other article; it was the original article (McCarthy, 2016) referenced in a response article (Ryu, Kim, Park, & Enkhbold, 2017) which had been populated in the

original search. It seemed more fitting to use the original document. After these articles were added, the searches were complete.

She screened all of the articles identified through searching for eligibility (n=202). She first removed all duplicates (n=53). If an article was clearly not relevant to the research question, based on the title, she removed it. If there was uncertainty, she screened the abstract for more information about the population and studied outcome, along with other inclusion criteria; if she found it to be unrelated, she removed it. This process eliminated many articles (n=120). The remaining articles either seemed likely to offer information which would help answer the research question, or they seemed unlikely to but were closely enough related they warranted further reading. Full text articles, if available, she screened for the remaining articles (n=29). Articles which did not meet the specified inclusion criteria she removed (n=18). There were a few articles which did not exactly meet the criteria but were closely related and had important information related to the research question. These she included in the review, to contribute to the overall perspective and increase the number of studies finally included in the review (n=11). The article screening process is depicted in Figure 2.

Results

The researcher screened articles using the process described in the Prisma Flowchart (Moher, Liberati, Tezlaff, & Altman, 2009), seen in Figure 2. She included a total of 11 articles in the review after screening. She documented reasons for excluding records which made it to the full text screening. Sixteen she excluded for not being randomized

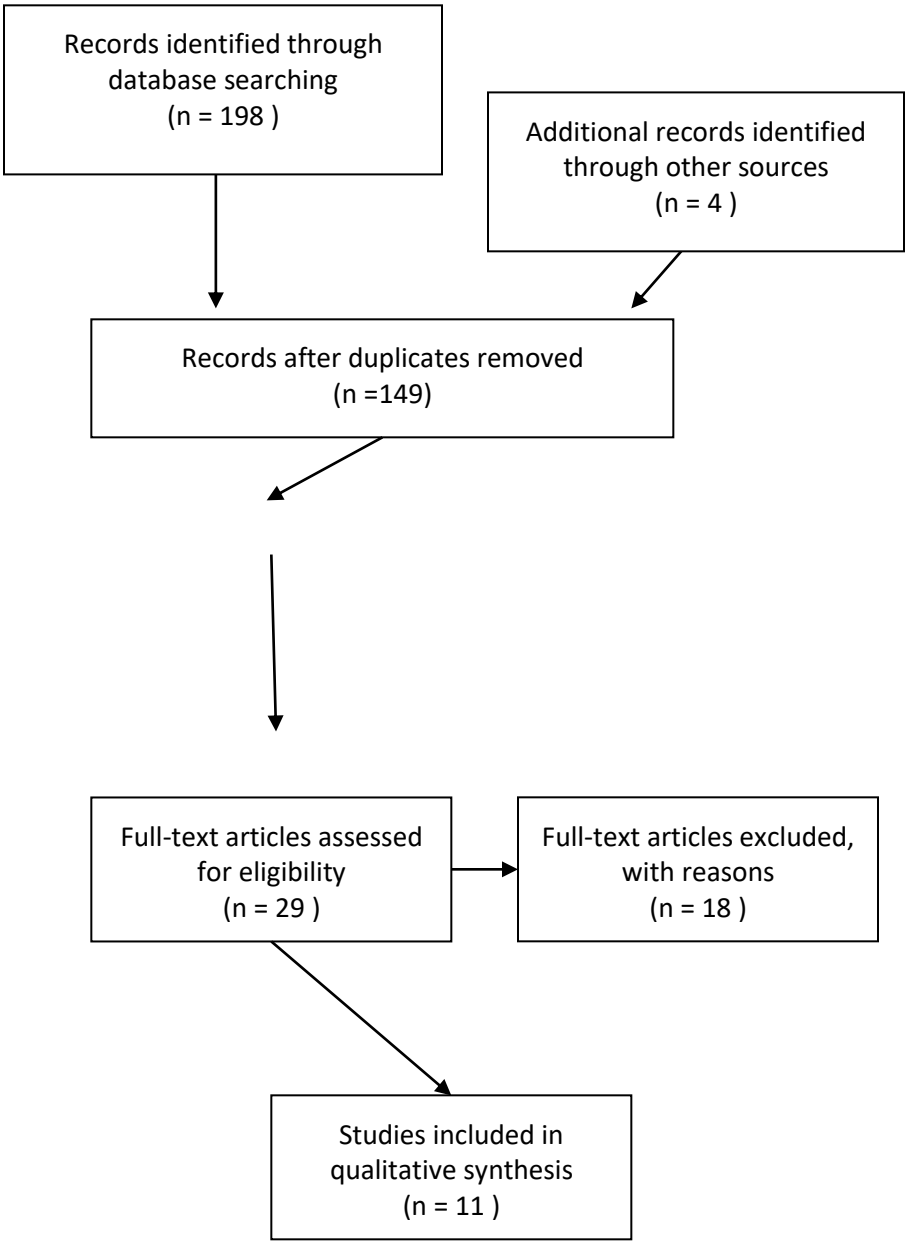

Figure 2

Figure 2. PRISMA 2009 Flow Diagram. Adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement., by D. Moher, A. Liberati, J. Tezlaff, The PRISMA Group (2009). Retrieved March 6, 2018 from http://prismastatement.org/documents/PRISMA%202009%20flow%20diagram.pdf Copyright 2009 by PRISMA. Adapted with permission.

controlled trials (Ainscough, Lindsay, Gibney, & McAuliffe, 2016; Buschur & Kim, 2012; Catalano & deMouzon, 2015; Johansson et al., 2015; Lee, et al., 2016; Muktabhant et al., 2015; Opie, Neff, & Tierney, 2016; Poston & Patel, 2014; Robertson & Ladlow, 2017; Ryu et al., 2017; Sabau et al., 2014; Schuster, Madueke-Laveaux, Mackeen, Feng, & Paglia, 2016; Sukumar et al., 2016; Szostak-Wegierek, 2014; Tanvig, 2014; Willis, Lieberman, & Sheiner, 2015). One article she excluded because it was the study design for a randomized controlled trial which had not yet been completed (Nagle et al., 2013). Another article she excluded because it was unable to be accessed using interlibrary loan (Bohiltea, Bodean, & Cîrstoiu, 2017). She attributed the large number of excluded articles, even prior to screening full texts, to the broad search terms used, compared to the specificity of the research question. Once the final articles had been selected, she reviewed them more thoroughly and assessed them for risk of bias.

Reviews of Articles and Assessments of Risk of Bias

Barakat and colleagues (2016) documented a randomized controlled trial which recruited pregnant women with uncomplicated pregnancies, who were Caucasian and spoke Spanish. After screening, randomization and attrition, their final analysis included 382 women in the intervention group and 383 in the control group. The intervention consisted of tri-weekly, supervised, moderately difficult exercise sessions in a local hospital, during the time between the ninth to 11th week of pregnancy and the third trimester's finish. In contrast, the control group women received advice to exercise and standard appointments but no extra interventions, besides calls to check on their

exercising status. Barakat and colleagues (2016) found the risk of macrosomia was 2.5 times less in the intervention group for women of all body mass indexes [BMIs].

Data Collection Form

Article Name_____
Study design_____
Level of evidence_____
_____
Description of participants_____
_____
Definition of Maternal Obesity_____
Definition of fetal macrosomia_____
_____
Intervention_____
_____
General outcome concerning the research question:_____
_____
_____

Summary of significant limitations_____
_____
_____
Risk of bias_____
_____
Miscellaneous points of interest:_____
_____
_____

Figure Two

Figure 1. Data collection form. By C. Stalcup. Copyright 2018 by Charity Stalcup. Printed with permission.

To contextualize the results of this study, the researcher assessed the risk of bias and found it to be average, on a subjective scale of low, average, and high. Barakat et al. (2016) specified a random numbers table was used to assign participants and conceal assignments, and three people accomplished the randomization. Barakat et al. indicated blinding of those performing the assessments but did not specify the methods of blinding. Since the intervention required participants to attend an exercise program, researchers could not blind the participants. The risk of attrition bias was unlikely as the researchers were unable to follow up with a similar number of women from the control group (37/420) and the intervention group (38/420), for similar reasons. Only two reasons were different between the groups. One was some of the intervention group were lost due to quitting the program and ruptured membranes. Another was some of the control group were lost due to persistent bleeding. Significantly, the researchers did not exclude anyone with a successful follow-up from the analysis, and the number lost to follow-up was within the expected percentage planned by Barakat and colleagues. Since Barakat et al. indicated they obtained secondary outcomes from the medical record, but did not specify what these outcomes were, selective outcome reporting may be a possibility. It is uncertain whether the researchers included all of the outcomes assessed in the report. Though there are strengths to this study, the uncertain aspects lend to a risk of bias rating of average.

In a medication-intervention study, Chiswick et al. (2015) documented a randomized controlled trial which recruited Caucasian, pregnant women with a BMI of at least 30 kg/m^2 in their 12^{th} to 16^{th} gestational week, who had a minimum age of 16 years.

They excluded women with complicated pregnancies, including diabetes or a history of gestational diabetes. The intervention was the administration of 500-2500mg of metformin per day, while the control group received a placebo. Chiswick et al. (2015) concluded metformin administration did not impact the baby's birthweight.

With this study, there is an average risk of bias. Chiswick et al. (2015) reported the use of an electronic block randomization procedure to assign participants; however, they did not detail the procedure, other than how the data were stratified. They did not report any process of allocation concealment. While Chiswick et al. affirmed the blinding of all involved in the study, they did not elucidate, with the exception of the Data Monitoring Committee, whom the researchers did blind and instructed not to connect with participants. However, Chiswick et al. did not describe the process of ensuring members of the committee did not meet participants or share information with other members of the study. They described attrition thoroughly, including causes, such as withdrawal from the study, miscarriages, pregnancy terminations, inability to follow up, and stillbirths. Out of the original participants, they analyzed a total of 220/223 people for the control group and 214/226 for the intervention. Many who were analyzed did not continue in the study to the end of follow up (92 control, 82 intervention). For certain outcomes, Chiswick et al. only analyzed live births, and they used statistical methods to bring data to a normal distribution. Though the number of women analyzed was more than what the researchers expected to give 85% power to the study, the number who made it all the way through was lower. Selective outcome reporting seems unlikely due to the many outcomes Chiswick et al. reported, including ones that were not statistically

significant. The major risks of bias in this study seem to be in performance and detection, meaning those directing the intervention or assessing the outcomes may have been biased based on their knowledge of participant assignment (Cochrane Methods Bias Staff, 2018), due to questions about blinding.

Dodd et al. (2014) detailed a randomized controlled trial which recruited women from city hospitals in Australia who were pregnant with only one fetus in their 10^{th} to 20^{th} gestational week, were not type 1 or 2 diabetic, and had a BMI of at least 25 kg/m^2. The intervention was nutrition, exercise, and lifestyle advice, along with accountability. In contrast, the control group received standard care, which was not likely to include this type of advice, based on the time and location of the study. Dodd et al. reported the intervention was associated with a decreased risk of fetal macrosomia but not the incidence of fetal large-for-gestational-age.

Based on the strengths of this study by Dodd et al. (2014), the risk of bias is low. They accomplished the randomization by 1:1 ratio balanced variable blocks, and the researcher tasked with running the program was not involved in client interaction. Dodd et al. eluded to but did not detail the blinding of assessors. Dodd et al. did not blind participants or those involved in their care. They thoroughly documented attrition, and reasons for not completing the trial were similar and of similar numbers in both groups. The total number they analyzed were 1080 mothers and 1075 babies in the intervention group and 1072 mothers and 1067 babies in the control group, which met the sampling goals of the researchers. Selective outcome reporting is unlikely, as Dodd et al. reported many outcomes, including some which showed no statistical significance.

In another article, Donnelly, Walsh, Byrne, Molloy, & McAuliffe (2013) described a randomized controlled trial which was based on the recruitment of women who had one macrosomic baby, were pregnant again at less than 18 weeks gestation, were at least 18 years old, and had no comorbidities, including a history of gestational diabetes. A session of nutrition counseling about consuming a low-glycemic diet was the intervention. Donnelly et al. reported the intervention was associated with smaller infant thigh circumference, which may be linked to birthweight. Some other anthropometric measures were not significantly different between the groups, such as abdominal circumference and skin-fold thickness (Donnelly et al.).

. The risk of bias in this study is difficult to judge based on this article alone, as the methods of the trial are outlined in the original trial, so information from that trial is included in this assessment. The midwife researcher had the task of randomizing the mothers' assignments, allocating them with a 1:1 ratio using a computer system and dark envelopes (Donnelly et al., 2013; Walsh, McGowan, Mahoney, Foley, & McAuliffe, 2012). Donnelly et al. reported an adequate sample size of 265 infants. The original study thoroughly documented attrition and noted that it occurred similarly between the intervention and control groups (Walsh et al., 2012). Blinding of participants was not possible with the intervention, but the authors indicated at least the sonographers were blinded. It is unclear if anyone else was blinded (Walsh et al., 2012). Selective outcome reporting seems unlikely, since they reported several aspects of neonatal anthropometry, including some which did not show any significant difference between the two groups (Donnelly et al.). The overall risk of bias seems low.

Hayes, Bell, Robson, & Poston (2014) reported a randomized controlled trial which involved pregnant women with a BMI of at least 30 kg/m^2. In this trial, the intervention addressed physical activity and nutrition. Hayes et al. reported an association between physical activity and a decreased risk of macrosomia of the infant.

Rather than the article by Hayes et al. (2014), the risk of bias was assessed based on the original study (Poston et al., 2013) which Hayes et al. secondarily analyzed. Poston et al. accomplished randomization using an online program, but whether allocations were concealed from assessors was not specified. Poston et al. did not discuss blinding, and it would not have been possible given the nature of the intervention. The researchers depicted attrition clearly in a figure, with similarities between the control and intervention group and a final sample size of 75 and 84 mothers and babies, respectively, in the control group and 79 and 85 mothers and babies, respectively in the intervention group, all of whom were analyzed. The risk of selective outcome reporting seems low, since Poston et al. gave detailed reports of the outcomes and their significance and included the primary outcomes, even though they were not significant. With questions concerning blinding and concealment and a relatively small sample size but otherwise well documented methodology, the study by Poston et al. seems to have an average risk of bias.

In a secondary analysis, Horan, McGowan, Gibney, Donnelly, & McAuliffe (2014) reported outcomes of a randomized controlled trial which involved women pregnant with their second baby, whose first baby had been macrosomic. The intervention was advice about following a low-glycemic index diet, while the control

group did not receive dietary advice. Horan et al. reported the intervention did not lead to a significant effect on infant birthweight. Horan et al. specified that the statistical analysis was performed in two ways, one excluding and one including those who did not adequately report what they ate, but the difference was not significant. Most of the rest of the information related to risk of bias would be in the original study, which is the same one (Walsh et al., 2012) secondarily analyzed by Donnelly et al. (2014), therefore, this study can also be given a rating of low risk of bias.

Kizirian et al. (2016) described a randomized controlled trial which recruited women in Australia in their 12^{th} – 20^{th} gestational week with " … the following risk factors: pregnancy BMI (in kg/m^2) ≥ 30age ≥35 y, polycystic ovary syndrome, previous history of GDM or glucose intolerance, history of a previous newborn weighing >4000 g, family history of type 2 diabetes (first-degree relative), or belonging to an ethnic group with a high prevalence of GDM … " and who did not have dietary restrictions or diabetes prior to pregnancy (Kizirian et al., 2016, p. 1074). The intervention was a low-glycemic diet, while the control group had a traditionally recommended high fiber diet. When factors such as weight the mother gained during pregnancy, BMI, and gestational diabetes were not accounted for, Kizirian et al. found an association between the low-glycemic index diet and a decreased risk of macrosomia. When these factors were accounted for Kizirian et al. still found weight for age was higher in the control group.

Due to several shortcomings, the risk of bias in this study by Kizirian et al. (2016) is high. Kizirian et al. did not describe the process of randomization of participants and allocation concealment. There was no indication of blinding of those who analyzed the

data. The researchers and participants were not blinded. They documented attrition substantially. Forty-six of the participants of the original study were not willing to be a part of this follow up. Of those who were willing, some dropped out due to unstated personal factors or going out of the country. By the end of the 12-month study, the sample sizes were small at 15 infants in the intervention group and 14 in the control. Kizirian et al. also noted, due to the voluntary nature of participant selection from a previous study, many of the participants were well-educated women who may have had somewhat positive dietary practices in the first place. Since Kizirian et al. included several outcomes, including those which were not statistically significant or supportive of their hypothesis, selective outcome bias seems unlikely. The risk of bias in this study is somewhat high, but it is valuable as a pilot study and starting point for future randomized controlled trials.

Syngelaki et al. (2016) reported a randomized controlled trial which recruited ethnically diverse, nondiabetic, singleton pregnant women, in their 12th to 18th gestational week, with a BMI greater than 35 and otherwise uncomplicated pregnancies, including no history of gestational diabetes. 1-3 g of metformin daily was the intervention, while control groups received a placebo medication. They provided exercise and nutritional advice to both groups. Syngelaki et al. indicated the intervention did not affect birthweight or size for age of the baby.

With its strengths and weaknesses, the risk of bias in this study by Syngelaki et al. (2016) is average. They accomplished randomization with numbers randomized by a computer, without restrictions, but did not specify the process of allocation concealment.

The pills of both the intervention and control group were the same in appearance, taste, and size, but Syngelaki et al. provided no other information about how they blinded participants, clinicians, and researchers. They provided attrition numbers, but not reasons for women declining to continue. They randomized 450 women, 202 in the intervention group and 198 in the control group. Selective outcome reporting seems unlikely, since Syngelaki et al. reported many outcomes, including non-significant findings.

Along with these articles, McCarthy et al. reported another randomized controlled trial (2016). This trial recruited pregnant women who had not yet reached 20 weeks of gestation, spoke English, were not pregnant with multiples, did not have diabetes prior to pregnancy, had nothing known to be abnormal with the baby, and had a BMI of at least 25 kg/m2. The intervention was "… serial self-weighing and simple dietary advice … " (McCarthy et al., 2016, p. 966). McCarthy et al. did not find the intervention to be associated with a decrease in gestational weight gain or adverse outcomes such as shoulder dystocia or heavy perineal tearing.

An average risk of bias seems appropriate for this trial completed by McCarthy et al. (2016). They accomplished randomization with a computerized random number table. They stratified by BMI and used a 1:1 ratio for allocation. With dark envelopes which were not opened until BMI was factored and informed consent to participate received, concealment was accomplished. Researchers did not blind participants and clinicians, but McCarthy et al. affirmed but did not detail blinding of assessors. They documented attrition well, with similar reasons for dropping out among both groups, such as giving birth elsewhere or miscarriage. They analyzed 184 women in the control group

and 187 in the intervention group. McCarthy et al. performed the analysis in two different ways, one including only those with all primary outcome data and one including those with some absent. The results were not significantly different. Selective reporting of outcomes may be present, as most of the outcomes focused on the mother. McCarthy et al. did not say much about fetal outcomes. Since most women in the control group also weighed themselves several times, McCarthy et al. noted more cross-over than expected between the groups.

Zhang (2015) described a randomized controlled trial based in China which recruited women who had previously had one baby and had been healthy pre-gestation, were aged 18 to 40 years, and had given birth to a live baby. These women were tested for pregnancy regularly as part of the trial process. The intervention was the implementation of a nutritional regimen to give dietary council tailored to each individual early in pregnancy, and control group also participated. Zhang (2015) found the intervention to be effective in significantly lessening a woman's risk of giving birth to a baby with macrosomia.

Due to some considerable limitations, there is a high risk of bias with this study. Zhang (2015) indicated participant selection for the intervention group was random, but he did not specify methods. It is unclear whether the control group was random or if the researchers selected them based on similarities to the intervention group. Zhang gave no indication of allocation concealment or blinding of anyone involved, nor did he discuss attrition. It is possible Zhang did not include some outcomes, especially other pregnancy

complications, which might have been lumped into one category, such as " … labor abnormalities … " (Zhang, 2015, p. 647).

In another article, Poston et al. (2015) reported a randomized controlled trial which involved women who were pregnant with one baby, in their 15th week to 19th week and 6th day of pregnancy, who had a BMI no less than 30 kg/m^2, and no comorbidities or use of metformin. The intervention was an 8-week course of health coaching, regarding diet and exercise, while the control group simply attended their doctors' appointments as usual. Poston et al. (2015) did not find an association between the intervention and a decreased risk of a large-for-gestational age infant.

With its many strengths, the risk of bias with this study by Poston et al. (2015) is low. Poston et al. affirmed use of a computer system to randomize allocations, but details of how it functioned are not specified, except minimization was used based on specific factors listed in the article. Researchers and participants were unblinded, apparently including those who analyzed the data. Poston et al. detailed attrition, including participants' reasons for leaving the trial, which were the same in both groups, including such things as fetal death and failure to attend appointment. Poston et al. documented the exclusion of fetal deaths in both groups. The control sample size was 651 mothers and 751 neonates; there were 629 mothers and 761 neonates in the intervention group. The risk of selective outcome reporting is low because Poston et al. included many outcomes in the text and even more in supplementary tables, including insignificant findings.

Integrated Results of All Studies Included in Review

One of the biggest areas of possible bias which the researcher noticed across the studies is not blinding participants and researchers. Donnelly and colleagues (2013) as well as Walsh et al. (2012) pointed out blinding is not an option for nutritional interventions. This point could also be applied to exercise interventions. In either case, it is necessary for the participant and at least some of the researchers to know what group they are in. Risk of bias by article is included in Table 1.

For most of the articles, exclusion criteria included those who had certain complications of pregnancy, sometimes including gestational diabetes or a history of it (Barakat et al., 2016; Chiswick et al., 2015; Dodd et al., 2014; Donnelly et al., 2013; Horan et al., 2014; Kizirian et al., 2016; McCarthy et al., 2016; Poston et al., 2015; Syngelaki, 2016; Zhang, 2015). Obviously, safety was the priority with these studies, but it does limit the generalizability of the findings. It is difficult to say whether the outcomes would be the same if women with complicated pregnancies were included in the sampling. Women with other pregnancy complications besides obesity cannot necessarily have the results applied to their situations. There is a lack of research involving treatment in this vulnerable population and what treatments may be effective and safe for them. The limited studies of complicated pregnancies form an obstacle to evidence-based care for women in this category.

Of the 11 articles screened, seven were carried out in Europe, (Barakat et al., 2016; Chiswick et al., 2015; Donnelly, 2013; Hayes, 2014; Horan et al., 2014; Poston et al., 2015; Syngelaki et al., 2016), three in Australia or New Zealand (Dodd 2014; Kizirian et al., 2016; McCarthy et al., 2016), and one in China (Zhang, 2015). Research is

lacking for the Americas, Africa, and Asia. It is uncertain whether the results of these studies are generalizable to these other continents, as socioeconomics and ethnicity are important factors in the etiology of obesity (Bray, 2018). Some of the studies required participants to have an ability to speak English (Horan et al., 2014; McCarthy, 2016). Four of the studies assessed an ethnically diverse population (Dodd, 2014; Kizirian et al., 2016; Poston et al., 2015; Syngelaki et al., 2016), but three of the studies recruited primarily Caucasians (Barakat et al., 2016; Chiswick et al., 2015; Horan et al., 2014).

Table 1

Summary of Findings

Trial (By Citation)	Intervention Type	Outcome	Risk of Bias
Chiswick et al. 2015	Medication	No impact on birthweight	Average
Donnelly et al. 2015	Nutritional	Decreased infant thigh circumference	Low
Kizirian et al. 2016	Nutritional	Decreased risk large weight for age	High
Syngelaki et al. 2016	Medication	No effect on birthweight	Average
Barakat et al. 2016	Exercise	Decreased risk of macrosomia	Average
Dodd et al. 2014	Nutritional and Exercise	Decreased risk of macrosomia	Low
Hayes et al. 2014	Exercise	Decreased risk of macrosomia	Average
Horan et al. 2014	Nutritional	No effect on birthweight	Low
Poston et al. 2015	Nutritional and Exercise	No effect on LGA	Low
Zhang 2015	Nutritional	Decreased risk macrosomia	High
McCarthy et al. 2016	Behavioral and Nutritional	Did not lead to decreased gestational weight gain, negative outcomes	Average

Whether the results of these ethnically limited studies are generalizable to other populations is questionable.

Studies such as those reviewed here involving asking women to agree to an intervention must necessarily have informed consent; women cannot be forced to participate in a trial. Hayes et al. (2014) noted evidence for the benefit of exercise to obese pregnant women has not helped to increase their level of activity, so education is not necessarily a sufficient intervention. For some, this lack of response is due to logistical issues or discomfort with activity (Hayes et al., 2014). Poston et al. (2015) pointed out there is difficulty in recruiting obese pregnant women for behaviorally-based interventions, and effectiveness of the interventions may only be generalizable to motivated women. Kizirian et al. (2016) noted women who participated in their trial tended to be well educated and already had some beneficial dietary practices prior to the intervention. It is difficult to know if effectiveness of interventions can be generalized to those who did not make the choice to participate in the studies.

Five of the trials reviewed utilized a behavioral intervention (Barakat et al., 2016; Dodd et al., 2014; Hayes et al., 2014; Poston et al., 2015; McCarthy et al., 2016). Hayes et al. (2014) had women wear a device to objectively measure level of activity. Barakat et al. (2016) designed an in-hospital regular exercise program involving various forms of moderately difficult exercise. Poston et al. (2015) used an eight-week program of in person and over the phone sessions, essentially providing coaching for women about behaviors and how to set goals and increase activity level from what they are normally used to. McCarthy et al. (2016) used serial self-weighing as a behavioral intervention,

focusing on its low cost and low difficulty as an intervention. Dodd et al. (2014) used an intervention which focused on providing accountability and encouraging individualized goal setting to help women increase their activity levels. Hayes et al. (2014) emphasize the importance of behavioral interventions which are acceptable to the women participating in them for best outcomes. The results of these behavioral interventions varied, with three reports of reduced risk of macrosomia (Barakat et al., 2016; Dodd et al., 2014; Hayes et al., 2014) and two reports of insignificant outcomes (McCarthy et al., 2016; Poston et al., 2015). Research is still lacking in trials comparing different styles of behavioral intervention, to see which is most effective at producing change in women's lifestyles.

Eight of the trials consisted of a dietary intervention (Dodd et al., 2014; Donnelly et al., 2015; Horan et al., 2014; Kizirian et al., 2016; McCarthy et al., 2016; Poston et al., 2015; Zhang, 2015). Donnelly et al. (2013) and Kizirian et al. (2016) advised a low-glycemic index diet, while Poston et al. (2015) advised a medium-to-high-glycemic index diet. Zhang (2015) focused on general good nutrition habits, with more specific advice for those with gestational diabetes. Dodd et al. (2014) gave individualized dietary advice and addressed things like sugar and fat content of diet. As with the behavioral interventions, the results of these trials varied, with four reports of decreased risk of macrosomia or a related outcome (Dodd et al., 2014; Donnelly et al., 2015; Kizirian et al., 2016; Zhang, 2015) and three reports of no significant effect on macrosomia or an alternately chosen, similar outcome (Horan et al., 2014; McCarthy et al., 2016; Poston et

al., 2015). Randomized controlled trials are lacking about specific foods which may be beneficial or add risk to the pregnant woman and her baby.

Chiswick et al. (2015) and Syngelaki et al. (2016) studied metformin administration as an intervention. Syngelaki et al. used a maximum dose higher than the dose Chiswick et al. administered (2500 and 3000 mg, respectively). Syngelaki et al. also implemented dietary and exercise counseling, to both the intervention and the control groups. Both trials excluded women with complicated pregnancies or comorbidities (Chiswick et al.; Syngelaki et al.). Neither Chiswick et al. or Syngelaki et al. found metformin to be useful in reducing the risk of macrosomia. Research is lacking concerning whether metformin may be useful in women with high risk pregnancies. Randomized controlled trials of other drugs which may be effective in reducing risk of macrosomia are lacking.

Of the 11 studies included, four had outcomes of a decreased risk of macrosomia in the intervention. The interventions included behavioral counseling, exercise, and nutritional guidance (Barakat et al., 2016; Dodd et al., 2014; Hayes, 2014; Zhang, 2015). Poston et al. (2015) performed a well-designed study with large sample sizes and found no significant effect of a behavioral and nutritional program in reducing the risk of macrosomia. They postulated past reviews which found an association between behavioral changes and reduced risk of macrosomia were based on small or limited studies and therefore biased. Bias may indeed be an issue but is questionable. The sample sizes of the articles should be considered when assessing bias. Hayes et al. (2014) had a small sample size of only 183, while Barakat et al. (2016) had a sample size of 765.

Zhang (2015) had a relatively small sample size of 256 and a high risk of methodological bias. Dodd et al. (2014) had a large sample size of 2152 mothers and 2142 infants, which is actually more than the sample size of Poston et al. (2015), who had a sample size of 1555. It is unclear what caused the difference in outcome between the two large trials, but the sample size and design of both seem credible and the findings valid (Dodd et al., 2014; Poston et al., 2015).

The outcomes of studies which did not find a decreased risk of macrosomia varied. The two trials which used metformin as an intervention showed no effect on macrosomia, but they did find some other possible benefits, such as a decreased risk of inflammatory biomarkers and preeclampsia and lower gestational weight gain in the mother (Chiswick, 2015; Syngelaki, 2016). Donnelly et al. (2013) found their dietary intervention to be associated with a smaller thigh circumference in the infant, but they did not find this association with other measures of infant anthropometry such as abdominal circumference or skin-folds. Kizirian et al. (2016) found a relationship between a low glycemic index diet and lower infant bodyweight, but the significance of this relationship was lost when outlying infants were included in the analysis and when adjustments were made for maternal characteristics such as BMI. Even with the adjustments and inclusion of the outliers, Kizirian et al. (2016) still found an association between the intervention and lower weight for age of the baby. Horan et al. (2014) found an association between the intervention group and lower levels of central adiposity among the neonates. McCarthy et al. (2016) did not find their intervention to effectively reduce poor maternal outcomes or gestational weight gain, but they did find self-weighing had no association

with poor quality of life in those studied. Each study offered valuable information to be used for further research.

Discussion

The results of this literature review were inconclusive to define a specific, reliable intervention for preventing macrosomia in women who are currently pregnant and obese. There is evidence exercise, nutrition, and lifestyle coaching may reduce the risk of infant macrosomia, large for gestational age, or increased thigh circumference (Barakat et al., 2016; Dodd et al., 2014; Donnelly et al., 2015; Hayes et al., 2014; Kizirian et al., 2016), but other studies, including a well-constructed study with a strong intervention and low risk of bias, found no effect on large-for-gestational age of the fetus and macrosomia (Horan et al., 2014; Poston et al., 2015). In addition, a low cost, simple intervention was not found to be helpful in improving maternal outcomes (McCarthy et al., 2016). None of the results of these studies can simply be ignored. More research with strong methodologies, large sample sizes, and varied populations is needed to identify effective, reliable interventions for these women and their offspring.

This review has many limitations. One researcher screened and reviewed articles. The researcher had to make certain simplifications in order to keep the review manageable, given the time and resources available. These simplifications included things such as only using one set of search terms, limiting to randomized controlled trials, and focusing only on main outcomes of each article which related to the research question. If an article's relevance to the review was questionable, and it was not readily available, the tendency was to screen it out. Specifically, one article which otherwise

seemed to meet the criteria to be included, she left out due to inaccessibility (Bohiltea et al., 2017). She included articles which did not directly answer the research question. She accomplished data extraction from the selected articles and synthesis of the data primarily in a non-systematic, qualitative manner. Bias assessment was subjective and the opinion of only one researcher. The researcher was a senior level, Bachelor's of Science in Nursing student and had only limited knowledge in the field of the research question.

The importance of research on the topic of maternal obesity and its relationship to macrosomia as well other negative health outcomes cannot be overstated. In Committee Opinion No. 549, the American College of Obstetricians and Gynecologists (2013), in the abstract, stated, "In the United States, more than one third of women are obese, more than one half of pregnant women are overweight or obese, and 8% of reproductive-aged women are extremely obese, putting them at a greater risk of pregnancy complications" (p. 213). Obesity is an issue that affects the sisters, daughters, mothers, and friends, of a huge percent of America's population. The ethical principles of beneficence and nonmaleficence dictate doing what is possible to give these women options for intervention.

To effectively prevent macrosomia in obese mothers, interdisciplinary collaboration is essential to ensure all aspects of the issue are addressed. This principle can be seen in that a search of this topic populated articles from many different journals and medical specialties, from obesity to endocrinology to obstetrics. Bogaerts, Van den Bergh, Witters, and Devlieger (2013) found maternal anxiety experienced early on in pregnancies of obese women may be linked to postpartum weight retention. If the woman

is anxious due to the obstetric risk factors she has due to her obesity, she may find herself locked in an unfortunate cycle, anxious in relation to obesity and obese in relation to anxiety. Pregnant women may have various reasons for not seeking medical help with weight management, such as logistics, work responsibilities, feeling less up to being out and about during pregnancy, or simply insufficient motivation (Olander & Atkinson, 2013). There are numerous factors to consider when seeking to effectively address this important issue.

In treating women with obesity, practitioners need to consider the psychological, psychosocial, and physical aspects of the woman's condition. Does she desire to lose weight? If so, what circumstances are preventing her from accomplishing this goal? Does she need more education regarding her risk or more motivation to do something about the knowledge she already has? Would she benefit from a social worker consultation, to help address life circumstances that may be involved? The fact that research regarding interventions for maternal obesity in the pregnant mother is sparse reinforces the importance of preventative care. Still, even the limited research available may be useful to provide encouragement and motivation for a pregnant mother with obesity, and some, such as the very noninvasive intervention in the McCarthy et al. (2016) study could likely be trialed safely under a doctor's supervision. It is the responsibility of both the patient and the practitioner to become informed and address this issue.

For the Christian practitioner, this issue is of special significance. Psalms 139:2-3 states:

> For you formed my inward parts; you knitted me together in my mother's womb. I praise you, for I am fearfully and wonderfully made. … Your eyes saw my unformed substance; in your book were written, every one of them, the days that were formed for me, when as yet there was none of them. (English Standard Version)

God knows and cares deeply about the life of both the mother with obesity and the life of her unborn child. Christian practitioners have a responsibility to follow God's example by caring for and valuing these mothers and their babies. By offering interventions to these women to reduce their pregnancy risks, they can offer hope. This hope is especially important in a population of women at risk of depression and public stigma related to their weight (Perreault, 2018). By researching effective treatments and applying these in practice, these practitioners can show they value both mother and child in the way God intended.

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