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Impact of maternal central adiposity on infant anthropometry and perinatal morbidity: A systematic review

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ABSTRACT

Overweight and obesity during pregnancy are risk factors for a large number of perinatal complications, both for the mother and the infant. Risk stratification and early interventions are therefore highly clinically important to minimize future complications. Currently, body mass index (BMI) in early pregnancy is used for risk stratification of pregnant women, but a disadvantage of BMI is that it does not distinguish muscle from fat tissue and central from peripheral adiposity. Maternal fat distribution is suggested to be a better predictor than BMI of obesity-related adverse pregnancy outcomes, with central adiposity posing a greater risk than peripheral subcutaneous fat. With this study, we aimed to systematically review the evidence of what impact maternal central adiposity in early to mid-pregnancy or at most 365 days prior to conception has on infant anthropometry and perinatal morbidity.

The databases PubMed/MEDLINE, Web of Science Core Collection, CINAHL, SCOPUS, Clinical Trials, and Open Grey were searched from inception until November 2019. Eligible studies assessed the association between maternal central adiposity, in early to mid-pregnancy or at most 365 days prior to conception, and any of the following infant outcomes: preterm delivery (< 37 weeks of gestation), birthweight, macrosomia, large for gestational age, congenital malformations, hypoglycemia, hyperbilirubinemia, care at neonatal intensive care unit, and death. Two authors independently screened titles and abstracts, read the included full-text studies, and extracted data. The Newcastle-Ottawa Quality Assessment Scale for cohort studies was used to evaluate the quality of and risk of bias in the studies.

A total of 720 records were identified, 20 full-text studies assessed for eligibility, and 10 cohort studies included in the review. The results suggest that central adiposity in early to mid-pregnancy or at most 365 days prior to conception may contribute to increased birthweight and increased likelihood of delivery by cesarean section. There is also some evidence of associations between central adiposity and preterm delivery (< 37 weeks of gestation), and admission to neonatal intensive care unit. A meta-analysis was not possible to perform due to substantial heterogeneity among the included studies regarding the exposure, outcome, and statistical methods used.

Hence, central adiposity in early to mid-pregnancy or at most 365 days prior to conception could be a possible risk marker in addition to BMI for risk stratification of pregnant women. However, since the topic is only scarcely researched, and the results not unanimous, more studies are needed to further clarify the associations between maternal central adiposity and adverse neonatal complications, before any altered recommendations of guidelines could be made. To enable a future meta-analysis, studies using similar methods for central adiposity assessment,and similar outcome measures, are required.

Contents

Abbreviations: BMI, body mass index kg/m^2; LGA, large for gestational age; WC, waist circumference; WHR, waist-to-hip ratio; NICU, neonatal intensive care unit; SFT, subcutaneous fat thickness; VAT, visceral adipose tissue; CT, computed tomography; MRI, magnetic resonance imaging.

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1. Introduction

The worldwide epidemic of obesity continues unabated [1]. The number of overweight and obese individuals in 2016 was estimated to be 1.9 billion according to the World Health Organization [2]. Excessive body fat is also a common issue among women of childbearing age, with one third of pregnant women globally being overweight and one in ten obese [3].

Overweight and obesity during pregnancy are risk factors for a large number of perinatal complications, both for the mother and the infant [4,5]. Infants of mothers with obesity are at increased risk of injuries in the peripheral nervous system, skeletal injuries, respiratory distress syndrome, sepsis, seizures, and hypoglycemia compared with infants of normal-weight mothers [6]. Mothers with early pregnancy body mass index (BMI) $\geq$ 35 kg/m^2 have threefold greater odds of shoulder dystocia, and twofold greater odds of antepartum stillbirth compared with mothers with normal BMI [7]. Furthermore, the odds of giving birth to a large for gestational age (LGA) infant is three times greater among mothers with early pregnancy BMI $\geq$ 35 kg/m^2, than among normal-weight mothers [7].

The presence of obesity-associated health issues varies among individuals with obesity. In general, the risk increases with increasing BMI [8]. It is known that central adiposity with visceral fat accumulation is a stronger predictor of obesity-related complications, such as type 2 diabetes mellitus and cardiovascular disease, than is general adiposity [9].

Currently, BMI in early pregnancy is used for risk stratification of pregnant women [10]. However, this method is not optimal since BMI does not describe fat distribution. A physically fit woman with high muscle mass might have the same BMI as a woman with excessive visceral fat accumulation, when in reality the latter would have an increased risk of obesity-related complications. Maternal fat distribution is therefore suggested to be a better predictor of obesity-related adverse pregnancy outcomes than BMI [11,12].

To our knowledge, the evidence of what impact maternal central adiposity has on infant anthropometry and perinatal morbidity has not previously been systematically reviewed. Maternal central adiposity could easily be assessed in early pregnancy, and used in the model for risk stratification of pregnant women. However, it is unclear if central adiposity adds any predictive value in addition to maternal BMI. This review aimed to evaluate whether maternal central adiposity, measured in early to mid-pregnancy or at most 365 days prior to conception, is a predictor of infant anthropometry and perinatal morbidity. The possible contribution of this review is of high clinical value since excessive body weight is a major public health issue and one of the most important risk factors for pregnancy related complications.

2. Material and methods

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 guidelines [13], (Table A.3).

2.1. Data sources

The databases PubMed/MEDLINE, Web of Science Core Collection, CINAHL, SCOPUS, Clinical Trials, and Open Grey were searched from inception until November 2019. Search algorithms were created with input by a trained librarian at the Medical Library at Uppsala University (Appendix A). The reference lists of the retrieved studies were manually screened for additional relevant studies that were not captured by the electronic searches. Authors were contacted when additional information was necessary. Only studies in English were included.

2.2. Eligibility criteria

Eligible studies assessed the association between maternal central adiposity measured in early to mid-pregnancy or at most 365 days prior to conception and any of the following infant outcomes: preterm delivery (< 37 weeks of gestation), birthweight, macrosomia (birthweight $\geq$4000 g or $\geq$4500 g), LGA, congenital malformations, hypoglycemia, hyperbilirubinemia, care at neonatal intensive care unit (NICU), and death. The neonatal outcomes were chosen because they are parameters with great importance for neonatal health, or because they are common or adverse medical conditions in the neonatal period. A detailed description of the search terms used for the outcomes is presented in Appendix A. We only included studies that provided adequate data to extract likelihood estimates. When the same cohort was presented in more than one publication (eg conference abstract and peer-reviewed article), we included the publication which provided the most information. We excluded studies with poor quality according to the Newcastle-Ottawa Quality Assessment Scale for cohort studies (< 2 stars in selection domain OR < 1 star in comparability domain OR < 2 stars in outcome domain) [14].

The Newcastle-Ottawa Quality Assessment Scale for cohort studies [14] was used to evaluate the quality of and risk of bias in the studies reviewed in full-text. The scale consists of three categories (Selection, Comparability, and Outcome) and the total

score ranges from 0 to 9 stars. The quality of the studies was rated as good, fair or poor by the number of stars awarded in each domain following the guidelines of the Newcastle-Ottawa Quality Assessment Scale for cohort studies [14]:

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain.

Quality assessments were carried out independently by E.L. and F.A., with any discrepancies resolved by consensus.

2.3. Data collection and analysis

Two authors (E.L. and F.A.) independently screened titles and abstracts. In addition, E.L. and F.A. independently read the included full-text studies and extracted their data using a standardized extraction form (Appendix B). Extracted data consisted of first author, publication year, location (country), study design, study period, population size, mean maternal age (years), measures of exposure, time of measurement, and infant outcomes.

2.4. Statistical analysis

We aimed to perform a meta-analysis on the included studies. Unfortunately, the studies used different measures for central adiposity and evaluated different outcomes. Further, the statistical analyses that were conducted in the studies varied. We investigated the possibility to perform a meta-analysis on a subgroup of studies that used the same proxy for central adiposity, but the studies were still too heterogeneous regarding outcomes and the statistical methods used. Therefore, it was not possible to perform a meta-analysis.

2.5. Ethical approval

No ethics approval was necessary to prepare this review.

3. Results

3.1. General characteristics of the studies

The systematic electronic database search resulted in 713 studies. After removal of 161 duplicates, 552 titles and abstracts were screened. Thereafter, 539 studies were considered irrelevant for the review and therefore excluded, leaving 13 studies for full-text reviewing. Another seven studies considered relevant for the review were found after contact with authors, by the authors of this review prior to performing the database search or amongst the references in the reviewed full-text studies. In total, 20 studies were read in full-text. A PRISMA flow diagram describing the process of searching, screening and selecting studies is presented in Fig. 1. In total, 10 cohort studies published from 1996 to 2019

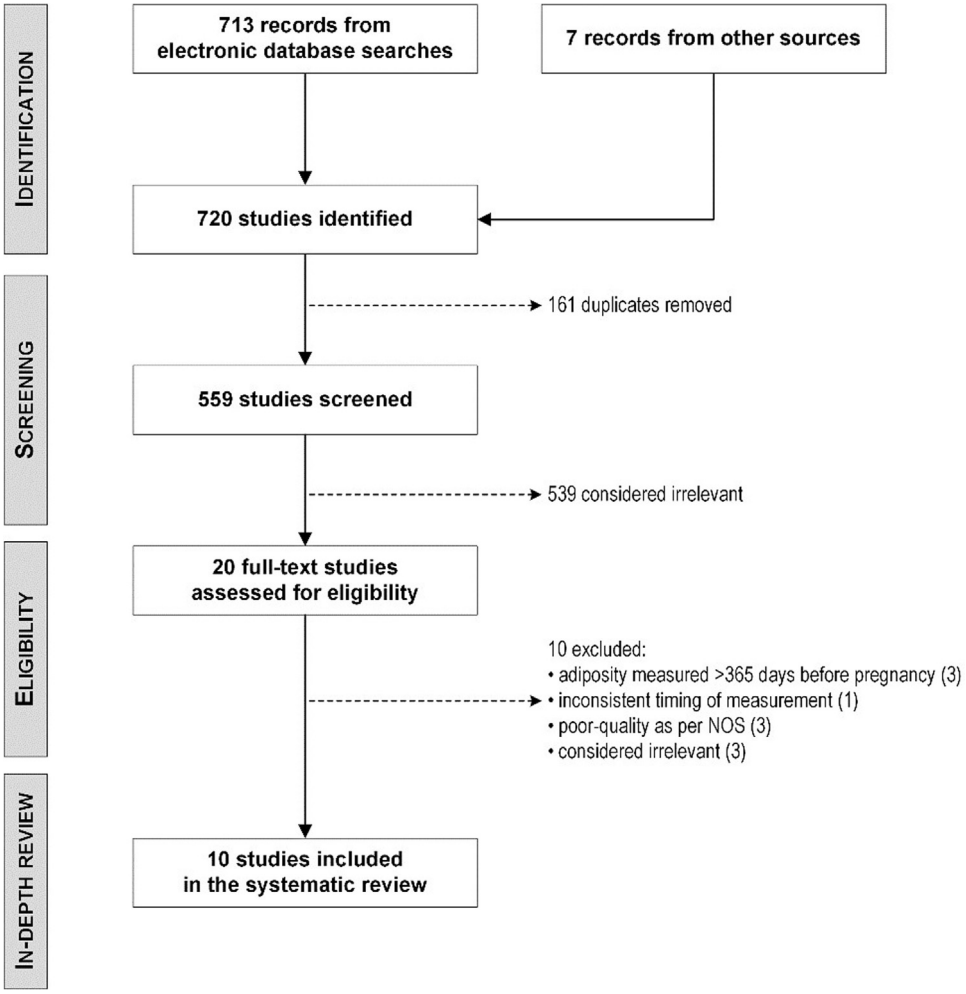

Fig. 1. Flow diagram for study selection.

Table 1
Characteristics of the included studies.

Author, year	Country	Study design, study period	Study population size	Mean age (years)	Exposure measurement	Time for measurement	Outcomes	Adjusted likelihood estimates (95 % CI)	Quality according to NOS
Bo et al., 2003	Italy	Cohort study, 1999–2001	700	31–32	Waist-to-hip ratio	24–28 wk	LGA	OR 1.81 (1.12–2.93)[a]	7
							Cesarean section	OR 1.51 (1.02–2.24)[a]	
Brown et al., 1996	USA	Cohort study, 1989–1992	521	29.3	Waist-to-hip ratio	365 days before – 45 days after conception	Birthweight	120 g / 0.1 WHR unit (54–187)	7
Eley et al., 2019	Australia	Cohort study, 2015–2016	997	30.6	Abdominal subcutaneous fat thickness	18–23.9 wk	Cesarean section	OR 1.32 (1.18–1.48)[b]	8
							Preterm delivery < 37 wk	NS	
							Admission to special/ intensive care nursery	OR 1.14 (1.01–1.28)[b]	
							Apgar score < 7 at 5 min	OR* 1.40 (1.13–1.73)[b]	
							Neonatal hypoglycemia	OR 1.21 (1.05–1.40)[b]	
							Resuscitation	OR 1.16 (1.02–1.33)[b]	
							Birthweight z-score	B coefficient 0.08 (0.04–0.12)[b]	
Gao et al., 2017	China	Cohort study, 2015	919	29.9	Waist circumference	First prenatal care visit	LGA	OR 2.14 (1.21–3.75)[c]	6
							Cesarean section	OR 1.71 (1.11–2.63)[c]	
Kennedy et al., 2016	Australia	Cohort study, 2012–2014	1385	29.3	Abdominal subcutaneous fat thickness	11–14 wk	Preterm delivery < 37 wk	OR 1.23 (1.07–1.44)[d]	9
							Cesarean section	NS	
							Birthweight > 4000 g	NS	
							Birthweight < 2500 g	OR 1.22 (1.00–1.47)[d]	
							Low Apgar 1 min	NS	
							Neonatal hyperbilirubinemia	NS	
							Neonatal respiratory distress	NS	
							Admission to neonatal intensive care unit	OR 1.23 (1.07–1.44)[d]	
							SGA	NS	
							LGA	NS	
						18–24 wk	Preterm delivery < 37 wk	NS	
							Cesarean section	OR 1.19 (1.06–1.35)[d]	
							Birthweight > 4000 g	NS	
							Birthweight < 2500 g	NS	
							Low Apgar 1 min	NS	
							Neonatal hyperbilirubinemia	NS	
							Neonatal respiratory distress	OR 1.27 (1.05–1.55)[d]	
							Admission to neonatal intensive care unit	OR 1.28 (1.08–1.52)[d]	
							SGA	NS	
							LGA	NS	
McDonnold et al., 2016	USA	Cohort study, 2003–2008	2276	23–24	Waist-to-hip ratio	9–16 wk	LGA	NS	9
							Cesarean section	0.8–0.84: OR 1.43 (1.08–1.89)[e] ≥ 0.85: OR 1.74 (1.35–2.25)[e]	
Ray et al., 2017	Canada	Cohort study, 2012–2015	463	32.9	Visceral adiposity tissue	11–14 wk	Preterm delivery < 37 wk	RR 3.1 (1.5–6.5)[f]	9
							Combination preterm delivery < 37 wk and preeclampsia	RR 16.9 (1.2–231.1)[f]	
Retnakaran et al., 2017	China	Cohort study, 2009–2017	1484	24.6	Waist circumference	Median of 20 weeks before pregnancy	Birthweight	NS	9
							LGA	NS	
							SGA	NS	
Salem et al., 2012	England	Cohort study, 1991–1992	3083	28	Waist-to-hip ratio	First trimester	Birthweight ≥ 4000 g	WHR quartile three: OR 1.58 (1.10–2.26)[g] WHR quartile four: OR 1.57 (1.07–2.30)[g]	8
							Birthweight ≥ 4500 g	NS	
							Birthweight ≥ 95th percentile of cohort	WHR quartile three: OR 1.77 (1.09–2.89)[g]	

Suresh et al., 2012	Australia	Cohort study, 2006–2010	1200	28.8	Abdominal subcutaneous fat thickness	18–22 wk	Cesarean section Preterm delivery < 37 wk LGA Cumulative adverse pregnancy outcomes[i]	OR 1.05 (1.03–1.07)[h] NS OR 1.21 (1.09–1.35)[h] OR 1.04 (1.01–1.06)[h]	9

(< 7), low birthweight < 2500 g, intrauterine growth restriction, hemorrhage after gestational week 20, premature preterm rupture of membranes.
* unadjusted model.
LGA, large for gestational age; NOS, Newcastle-Ottawa Quality Assessment Scale for cohort studies; NS, not significant; SGA, small for gestational age; WHR, waist-to-hip ratio; wk, weeks of gestation.
[a] WHR > 0.9 compared with WHR ≤ 0.9 (reference).
[b] per 5-mm increase in abdominal subcutaneous fat thickness.
[c] waist circumference ≥ 80 cm compared with < 80 cm (reference).
[d] per 5-mm increase in abdominal subcutaneous fat thickness.
[e] compared with WHR ≤ 0.8 (reference).
[f] visceral adipose tissue depth quintile five compared with quintile one through four (reference).
[g] compared with WHR quartile one (reference).
[h] per 5-mm increase in abdominal subcutaneous fat thickness.
[i] including gestational diabetes, pre-eclampsia, gestational hypertension, instrumental deliveries, cesarean deliveries, preterm birth, macrosomia > 4000 g, LGA, SGA, 5-min Apgar score < 7.

fulfilled the inclusion criteria and were included in this systematic review [11,12,15–22] (Table 1). The quality of the studies and risk of bias according to the Newcastle-Ottawa Quality Assessment Scale for cohort studies are listed in Table A.1.

3.2. Early pregnancy and mid-pregnancy maternal abdominal subcutaneous fat thickness and perinatal outcomes of the infant

Kennedy et al. [11] measured maternal abdominal subcutaneous fat thickness (SFT) by ultrasonography at two time points, at 11–14 weeks and at 18–22 weeks of gestation in 1385 women. There was no change in SFT in underweight and normal weight women between the two time-points, but in overweight and obese women, SFT decreased between the first and second measure. A wide distribution was seen for SFT among the overweight and obese women. In a logistic regression model adjusting for early pregnancy BMI, age, parity and smoking habits, every 5-mm increase in SFT at the first time point increased the odds of NICU admission by 23 %, preterm delivery (< 37 weeks of gestation) by 23 %, and low birthweight (< 2500 g) by 23 % (Table 1). In the second trimester, every 5-mm increase in SFT was associated with odds of NICU admission that were 28 % higher, of cesarean section 24 % higher, and respiratory distress of the neonate 27 % higher (Table 1). Abdominal SFT was not associated with macrosomia after adjustments.

Maternal abdominal SFT was measured during the routine antenatal ultrasound at 18–22 weeks of gestation in 1200 women by Suresh et al. [12]. The authors did not find any evidence for effect modification of early pregnancy BMI as an interaction term on the multivariate model, and therefore discarded BMI from the models. Every 5-mm increase in SFT increased the odds of having an LGA infant by 21 % and the odds of cesarean section by 5 % (Table 1). The authors combined several adverse pregnancy outcomes (gestational diabetes mellitus, pre-eclampsia, gestational hypertension, instrumental deliveries, cesarean delivery, preterm delivery (< 37 weeks of gestation), macrosomia (> 4000 g), LGA, small for gestational age, 5-min Apgar score < 7, low birthweight (< 2500 g), intrauterine growth restriction, antepartum hemorrhage, and premature rupture of membranes) into a cumulative adverse pregnancy outcome. Every 5-mm higher value in SFT increased the odds for this cumulative adverse pregnancy outcome by 4 %. A 5 kg/m^2 increase in early pregnancy BMI increased the odds of giving birth to an LGA infant by 10 %, but did not predict the likelihood of cesarean section or the cumulative adverse pregnancy outcome.

Eley et al. measured abdominal SFT by ultrasonography at 18–23.9 weeks of gestation in 997 pregnant women [22]. They found that every 5-mm increase in SFT raised the odds of admission to special care nursery or intensive care nursery by 14 %, cesarean section by 32 %, 5-min Apgar score < 7 by 40 %, hypoglycemia by 21 %, resuscitation by 16 %, and increased the birthweight z-score B coefficient by 0.08 (Table 1). No increased likelihood was seen for preterm delivery. While BMI was not adjusted for in the models, comparative analyses were performed with early pregnancy BMI as the exposure. Every 5 kg/m^2 increase in early pregnancy BMI raised the odds of cesarean section by 29 %, hypoglycemia by 16 %, and increased the birthweight z-score B coefficient by 0.16. Thus, SFT, but not early pregnancy BMI, was a predictor of admission to special care nursery, neonatal resuscitation, and 5-min Apgar score < 7.

3.3. Early pregnancy maternal visceral adipose tissue and perinatal outcomes of the infant

Only one such study was included, where Ray et al. [19] reported on the association between visceral adipose tissue (VAT)

in early pregnancy and preterm birth (< 37 weeks of gestation). Visceral adipose tissue was measured by ultrasonography at 11–14 weeks of gestation in 463 pregnant women. Women with VAT depth in the highest quintile (ie five) had a risk of preterm delivery threefold higher than women in quintiles one through four (Table 1). Further, women in quintile five had a risk almost 17-fold greater of having both preeclampsia and preterm delivery (Table 1). Models were adjusted for maternal age, parity, history of chronic hypertension, pre-pregnancy BMI, and use of acetylsalicylic acid [19].

3.4. Pre-pregnancy and early pregnancy waist circumference and perinatal outcomes of the infant

A pre-conceptional cohort consisting of 1484 newly married women was followed by Retnakaran et al. [20]. Waist circumference (WC) and BMI were assessed at a median of 20 weeks before pregnancy. Outcomes included birthweight, LGA, and small for gestational age. Adjustments were made for maternal age, years of education, pre-pregnancy BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, blood glucose, gestational length, pregnancy weight gain, gestational diabetes, and infant sex. Pre-pregnancy WC was a positive predictor of birthweight before adjustments, but not after (Table 1).

Gao et al. [21] measured maternal WC at the first prenatal care visit in 919 women. A WC $\geq$ 80 cm increased the odds of giving birth to an LGA infant by 114 %, and of cesarean section by 71 % (Table 1). Adjustments were made for street/address, maternal age, maternal education, smoking or passive smoking, alcohol consumption, family income, parity, paternal age, paternal education, paternal BMI, infant sex, and gestational age. Maternal BMI was not adjusted for in the multivariate logistic regression models.

3.5. Pre-pregnancy, early pregnancy and mid-pregnancy waist-to-hip ratio and perinatal outcomes of the infant

Brown et al. [15] measured waist-to-hip ratio (WHR) in 521 women between 365 days prior to and 45 days after conception. There was an observed association between maternal WHR and birthweight with an increase of 0.1 unit of WHR predicting an increase in birthweight of 120 g, after adjustments for gestational age, infant sex, parity, mother's height, pregnancy weight gain, mother's age, and BMI (Table 1). The authors state that the timing of the WHR measure (365 days to 45 days prior to conception, 45 days to 1 day before conception, or 1 day before to 45 days after conception) did not affect the prediction of infant size.

The association of early pregnancy WHR on infant macrosomia were studied in 3083 pregnant women by Salem et al. [17]. Macrosomia was defined as birthweight $\geq$4000 g, birthweight $\geq$4500 g, or LGA ($\geq$95th percentile of birthweight adjusted for gestational age and sex). In analyses adjusted for age, pre-pregnancy BMI, ethnicity, smoking habits, and gestational age, women in WHR quartiles three and four had 58 % and 57 % greater odds of giving birth to an infant with a birthweight $\geq$4000 g, respectively, compared with women in quartile one (Table 1). For LGA, the odds were 77 % greater for women in quartile three, but not for women in quartile two or four, compared with women in quartile one (Table 1).

McDonnold et al. [18] compared the likelihood of giving birth to an LGA infant and having a cesarean section among 2276 pregnant women with WHR < 0.80, 0.80–0.84, or $\geq$ 0.85, measured at 9–16 weeks of gestation. There were no observed associations between high WHR and LGA birth (Table 1), which was only predicted by early pregnancy BMI $\geq$ 30 kg/m^2. Compared with pregnant women with WHR < 0.80, the odds were 43 % greater of having a cesarean section among mothers with WHR 0.80–0.84 and 74 % greater among mothers with WHR $\geq$ 0.85. Adjustments were made for maternal age, gestational age, years of schooling, race, smoking, and alcohol status.

Bo et al. [16] measured WHR in 700 pregnant women at 24–28 weeks of gestation and evaluated the likelihood of LGA and cesarean section. Mothers with central adiposity (ie WHR > 0.9) had odds 81 % greater of delivering an LGA baby and odds 51 % greater of having a cesarean section (Table 1). Adjustments were made for age, gestational weight gain, gestational age, gestational hyperglycemia, pre-pregnancy obesity, and smoking status.

4. Discussion

4.1. Main findings

In this review, 10 cohort studies were included that evaluated maternal central adiposity in early to mid-pregnancy or at most 365 days prior to conception and infant anthropometry or perinatal morbidity. The review showed that maternal central adiposity was associated with infant birthweight, LGA, and delivery by cesarean section. There was also some evidence of associations between maternal central adiposity and preterm delivery (< 37 weeks of gestation), and admission to NICU. A summary of the authors' subjective evaluation of the evidence for the different offspring outcomes is presented in Table A.2. The included studies used several different proxies for maternal central adiposity: ultrasonography was adopted to measure abdominal SFT in three studies [11,12,22] and VAT in one study [19], while two studies used WC [20,21] and four WHR [15–18]. There was a moderate consistency in the observed associations for the different measurement methods (Table 1).

4.2. Assessment of body fat distribution

Body fat distribution can be estimated by several techniques, for example WC, WHR, ultrasonography, bioelectrical impedance analysis, dual energy X-ray absorptiometry, computed tomography (CT), and magnetic resonance imaging (MRI) [23]. Computed tomography and MRI are the golden standard methods for measuring visceral fat (cross sectional or volumetric measurement) [23]. However, CT is not suitable for assessment of body fat distribution during pregnancy because of ionizing radiation, and MRI is both expensive and time consuming. Ultrasonography, WC, and WHR are feasible methods for assessing body fat distribution during pregnancy, although all three methods have merits and demerits.

Anthropometry measurements (WC and WHR) are cheap, fast, and easy to perform. Waist circumference is considered to represent both visceral and subcutaneous fat, while hip circumference corresponds to subcutaneous fat [23]. Thus, high WHR would represent a relatively high amount of visceral fat tissue [23]. However, both WC and WHR provide only indirect measurements of central adiposity [23,24], and WC and WHR were poor predictors of trunk fat mass when compared with dual energy X-ray absorptiometry scans [25]. Importantly, anthropometric measures such as WC and WHR are problematic in pregnant women, especially in late pregnancy, when the growing uterus may affect the measurement [24]. One of the studies included in this review [16], measured waist and hip circumferences between 24–28 weeks of gestation. While the authors claim that the uterus at this time during pregnancy has limited influence on the minimal abdominal girth, McCarthy et al. [24] advise against the use of both WC and WHR during pregnancy as the uterus could affect the results. Another limitation concerning anthropometry measurements is where to place the measuring tape when examining the waist. For example, studies included in this review used slightly

different measuring points for WC: at the narrowest point around the waist [16,17], one inch above the navel [15], or at the midpoint between the lowest rib and the iliac crest [21]. If anthropometric measurements would be implemented as a clinical routine, the measures should preferably be taken early in pregnancy to avoid impact of the growing uterus. Further, the assessors should be trained to provide standardized measurements, and self-measuring should be avoided to minimize reporting bias.

Ultrasonography has the potential to distinguish between visceral and subcutaneous fat compartments [27], and since the method does not involve any radiation, it is a favorable method for estimating central adiposity during pregnancy [24]. Stolk et al. [26] evaluated the validity and reproducibility of ultrasonography measurements of abdominal adipose tissue in 19 non-pregnant individuals. They compared ultrasonography measurements with CT scans, and found them to be strongly correlated ($r = 0.81$; $p < 0.001$). If ultrasonography measures would be implemented as a clinical routine to determine body fat distribution, the measures could easily be obtained when the woman is attending a routine ultrasound examination.

Birthweight, macrosomia, and LGA were the infant outcomes most commonly evaluated among the studies included in this review. Only a few studies assessed perinatal morbidity, such as preterm birth, low Apgar score, acidosis (low umbilical pH), neonatal hypoglycemia, and admission to NICU. Thus, future research should preferably consider evaluation of maternal central adiposity on these outcomes, as well as infant anthropometry.

4.3. Strengths and limitations

Strengths of our systematic review include the number of databases searched, and the use of search algorithms created with input from a trained librarian, including both MeSH terms and numerous synonyms. A limitation is the breadth of the research question, regarding both the definition of central adiposity (estimated with different methods), and the multiple outcomes searched for. Nonetheless, if the research question had been narrowed, it is likely that even fewer studies would have fulfilled the inclusion criteria, so that a review might not have been possible. Further, we were not able to find data on pre-pregnancy BMI and gestational weight gain in relation to central adiposity on the women included in the different cohort studies in this review. Both pre-pregnancy BMI and gestational weight gain are associated with infant birthweight [28,29], and might have biased the results in this review. Moreover, some of the studies measured central adiposity in mid-pregnancy (> 20 weeks of gestation) [11,12,16,22], when the growing uterus could affect the measurements [24]. Lastly, we could not perform a meta-analysis, due to the substantial heterogeneity among the included studies. The studies used different proxies for central adiposity, and the measurements were taken at different time points during pregnancy. In addition, the infant outcomes assessed were diverse, as were the statistical methods used. Thus, a meta-analysis could not be conducted. We even evaluated the possibility of performing meta-analyses including subgroups of studies that used the same proxy for central adiposity, but unfortunately, the studies were still too diverse regarding the exposure, outcome, and statistical method used, to be included in a meta-analysis.

5. Conclusion

Overweight and obesity are increasing health issues among pregnant women, and it is desirable to identify high-risk pregnancies in order to allocate preventive actions. Central adiposity in early to mid-pregnancy or at most 365 days prior to conception could be a possible risk marker in addition to BMI for risk stratification of pregnant women. However, since the topic is only scarcely researched, and the results not unanimous, more studies are needed to further clarify the associations between maternal central adiposity and infant perinatal morbidity before any altered recommendations of guidelines could be made. To enable a future meta-analysis, studies using similar methods for central adiposity assessment, and similar outcome measures, are required.

Declaration of competing interest

The authors report no declarations of interest.

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Supplementary data

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