Adiponectin and Leptin during Pregnancy: A Systematic Review of Their Association with Pregnancy Disorders, Fetal Growth and Placental Function

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Systematic Review

Adiponectin and Leptin during Pregnancy: A Systematic Review of Their Association with Pregnancy Disorders, Fetal Growth and Placental Function

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Abstract: During pregnancy, the adipokines leptin and adiponectin can affect placental nutrient transport and inflammatory pathways, potentially leading to altered fetal growth and pregnancy complications including gestational diabetes mellitus (GDM) and preeclampsia (PE). The aim of this systematic review is to gather and analyze research on maternal circulating leptin and adiponectin levels and their relationship to adverse pregnancy and birth outcomes. Additionally, it seeks to determine whether these hormones are linked to alterations in placental transporters and cell signaling pathways. PubMed and MEDLINE were systematically searched to include studies published between 2012 and 2022. All primary data studies reporting serum adiponectin and/or leptin, placental mRNA and protein levels of related transporters, and adverse birth outcomes were eligible. The current systematic review encompasses a total of 14 articles. Abnormal serum maternal leptin and adiponectin levels were associated with changes in fetal growth and placental cellular signaling and nutrient transporters. A majority of studies associated elevated maternal leptin and reduced adiponectin with fetal overgrowth, although this relationship was not consistent and may be complicated when other pathologies are present. The effects of maternal leptin and adiponectin on fetal growth may be driven by placental adaptation in nutrient transporters and mitochondria. Future studies should determine if the placental effects of leptin and adiponectin that have been found in models have mechanistic roles in human pregnancy.

Keywords: leptin; adiponectin; pregnancy; birth outcomes; placenta; transporters; signaling

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1. Introduction

Maternal adaptations during pregnancy enable adequate energy to be provided for the growing fetus, which is important for normal development [1]. Several maternal adaptations are required to sustain and support a pregnancy, which include hormonal, metabolic, and immunological changes [2]. In addition, maternal genetics and the maternal environment contribute to offspring birthweight, as well as uteroplacental function [3]. Thus, fetal growth is highly dependent upon an adequate intrauterine environment, leading to an optimal birthweight due to established placentation, appropriate nutrient transfer and blood flow [4,5]. When maternal and placental adaptations to pregnancy are compromised, changes to fetal growth (either under- or over-growth) and adverse obstetric and neonatal outcomes may be a result [5,6].

Adipokines are hormones mainly released by adipose tissue, which play a significant role in mediating a number of systems associated with metabolism, appetite, inflammation, angiogenesis, insulin sensitivity, and immune response [4]. The adipokines leptin [7] and adiponectin [1] play critical roles in maintaining normal energy metabolism and expenditure, immune response, and food intake [8]. Emerging research has demonstrated that they are also critical for fetal development during pregnancy, with these maternal hormones contributing to placental insulin sensitivity, nutrient supply, vascular function, and inflammatory response [9].

In recent years, the incidence of obesity has increased, and in 2015 63.5% of Australian women were obese or overweight [10]. The prevalence of obesity in women of childbearing age is a global health concern [11]. Increased adiposity, independent of pregnancy, is associated with increased circulating leptin and decreased adiponectin [9]. In pregnancy, altered maternal leptin and adiponectin levels have been associated with fetal growth abnormalities including fetal growth restriction (FGR) and macrosomia [12]. Notably, an increase in adiposity and abnormal serum/plasma leptin and adiponectin are associated with pregnancy complications including gestational diabetes mellitus (GDM) [9], preeclampsia (PE), and stillbirth [12]. GDM is associated with increased maternal risk of developing postpartum type 2 diabetes mellitus, and cardiovascular, retinal, kidney, and liver diseases after the pregnancy [13]. Neonates born to obese mothers are more likely to be born prematurely, require a Cesarean section delivery, have obesity, and are at higher risk of developing insulin resistance and metabolic disease [14]. Leptin and adiponectin have been identified as potential biomarkers in predicting the development of GDM, PE, and adverse fetal growth [3], but the underlying mechanism linking maternal adiponectin and leptin and the increased risk of poor perinatal outcomes in pregnancy remains unclear.

In pregnancy, maternal obesity is associated with metabolic inflammation, which in turn is associated with proinflammatory cytokines and adipose tissue macrophage accumulation, in addition to increased placental inflammation [15]. This proinflammatory state extending to the placenta [10] suggests that maternal obesity exposes the placental/fetal unit to an inflammatory environment during in utero development and that placental pathophysiology may be a key mediator of adverse outcomes [11]. Leptin increases the secretion of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNFα) from human term trophoblast cells in vitro [16], and both leptin and adiponectin are proinflammatory in human placental explants [17]. Adiponectin and leptin have been shown to alter the placental nutrient transporter expression and subsequent fetal growth in mouse models [18]. This suggests that there may be a correlation between adipokine-dependent adverse maternal and offspring outcome, and placental dysfunction.

This systematic review aims to evaluate the potential link between maternal leptin and adiponectin and fetal growth. A secondary objective is to explore whether these hormone concentrations can help predict adverse pregnancy complications and identify potential indicators of altered placental function.

2. Methods

2.1. Data Sources

The following review was conducted in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The search was undertaken on PubMed and Ovid Medline, between January 2012 and December 2022 by TD and repeated by OJH and DHH. Articles were restricted to those in English. The databases were searched independently by the aforementioned authors. Once shortlisted, full texts were ordered and read. The bibliographies of articles selected for the review were also screened for suitable additional articles to be included in this review. Inclusion in the review was selected by consensus between the screening authors.

2.2. Search Strategy

Search terms from PubMed/MEDLINE were "adiponectin" OR "leptin" AND "pregnancy" AND "placenta", with searches performed from December 2012 to December 2022. Studies were then filtered manually as per the inclusion criteria. The inclusion criteria were human in vivo studies with primary data published in English. The exclusion criteria were animal models or in vitro studies, reviews, case series, or case reports, and publication in a language other than English.

2.3. Data Collection Process

The relevant experimental results were extracted from each of the included records using a data extraction sheet on Excel (Microsoft). Data were extracted manually for analysis by TD, OJH, and DHH in tabular form. Due to the heterogeneity of the studied populations, variations in methods utilized, and in the endpoints of the studies, pooling of data for meta-analysis was not considered appropriate.

The data extraction sheet included broad topics of study design, hormones measured in the study, and whether hormone levels were increased or decreased compared to control groups (the definition of "increased" and "decreased" compared to the control was taken from each publication and represents a statistically significant difference). The effects of both adiponectin and leptin on mRNA expression and protein of placental receptors and nutrient transporters were recorded in the data extraction sheet. The activation and inhibition of inflammatory signaling pathways were also included in the full text data extraction sheet. Birthweight category (i.e., macrosomia, appropriate weight, fetal growth restriction (FGR), small for gestational age (SGA), or large for gestational age (LGA)), maternal weight category (i.e., obese, overweight, or non-obese), and any relevant pathology (i.e., GDM or PE) were also noted on the extraction sheet. Birthweight categories were taken from each publication, and variation in the definition of these categories may vary between publications. Macrosomia is defined by a growth beyond an absolute birth weight, usually 4000 g or 4500 g, regardless of gestational age, and LGA is usually classified a birthweight equal to or more than the 90th centile for a given gestational age [19]. SGA is usually defined as fetuses whose estimated weight and/or abdominal circumference is below the 10th percentile of a given growth curve, with further distinctions at the 5th or 3rd percentile for data analysis [3,20]. FGR usually refers to fetuses that do not reach their growth potential [3,20].

2.4. Data Items

Duplicates were removed, then the titles and abstracts of all retrieved records were reviewed. Title and abstract screening were performed using Covidence. The relevant experimental results were extracted from each of the included records, namely concentration of leptin and adiponectin, and association between adipokines and (i) placental receptors and nutrient transporters, (ii) inflammatory signaling pathways, (iii) birthweight, and (iv) adverse pregnancy complications of GDM or PE.

2.5. Assessment of Risk of Bias

The US National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) Rating Tool for Human and Animal Studies is recommended to ensure accurate conclusions in completing systematic reviews [21]. The OHAT tool was used in this review to assess the risk of bias. The answer format for each question domain was labelled as either "definitely low", "probably low", "probably high", or "definitely high" for each study. No studies were excluded based upon the risk of bias assessment.

3. Results

3.1. Search Results

After removing duplicates, a total of 154 records were retrieved from PubMed/MEDLINE. The titles and abstracts of all 154 records were reviewed (Figure 1). There was a total of

129 articles excluded as they did not contain primary data (24), the full text was not available (6), they were animal studies (41), or they did not report findings on the pathophysiology of adiponectin and leptin on the placental–fetal unit (58). Lastly, 25 articles were read, and 11 studies were excluded as outcomes were not relevant (7), the studies were out of scope (3), or they included the wrong study population (1). All experimental data were extracted from 14 of the relevant studies.

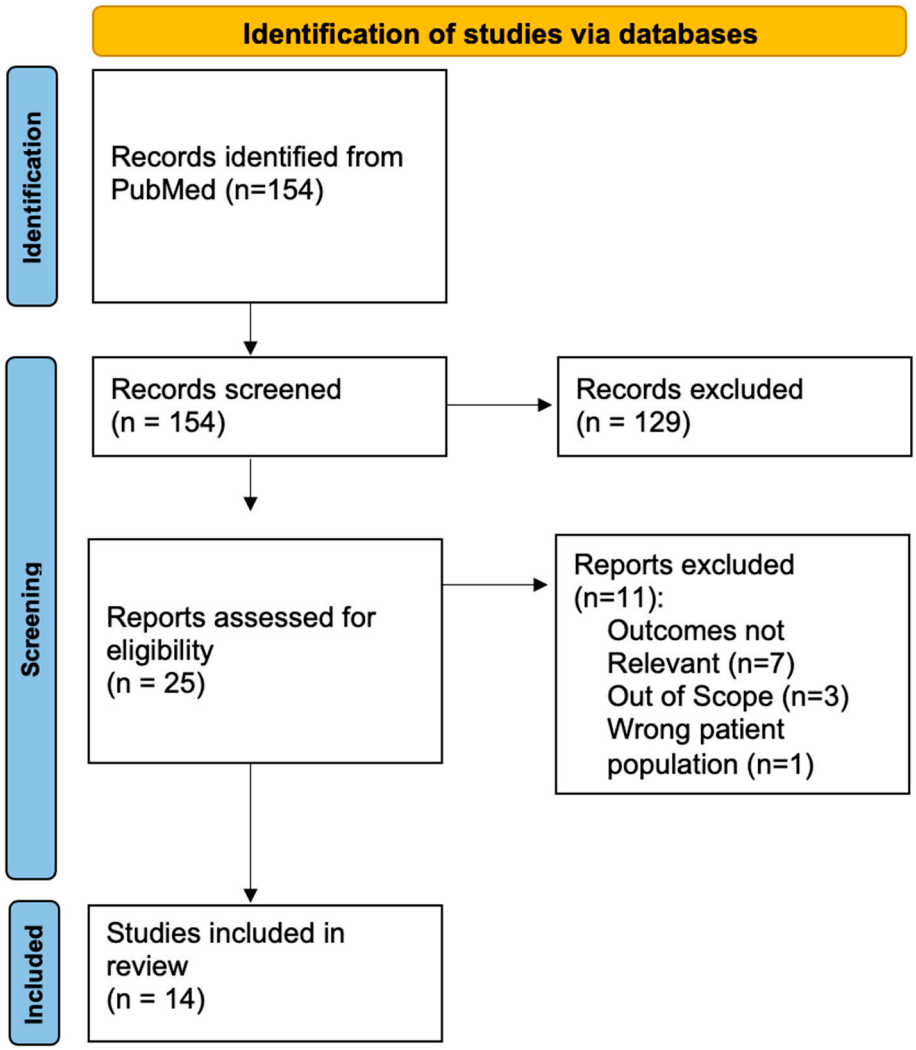

Figure 1. PRISMA diagram of search strategy for this study. A total of 154 studies were retrieved and titles and abstracts were screened. After title and abstract screening, 25 studies were assessed for eligibility. Fourteen studies were included in this systematic review.

3.2. The Relationship between Maternal Leptin and Adiponectin on Fetal Growth

3.2.1. Association between of Maternal Leptin and Fetal Growth

There was no pattern between maternal leptin and birthweight category (Table 1). Three studies showed statistical association between an increase in maternal leptin in pregnancies and LGA infants compared to those women with adequate for gestational age (AGA) infants [22–24], whereas three other studies found increased maternal leptin in pregnancies complicated by FGR compared to non-FGR pregnancies [25,26]. There was also a decrease in maternal leptin among pregnant women with SGA newborns compared to AGA infants [24]. Macrosomia was not associated with altered maternal leptin [27].

Table 1. Association between maternal leptin and fetal growth.

Reference	Maternal Serum Concentration Compared to Control	Offspring Birthweight	*p*-Value
Lazo-de-la-Vega-Monroy et al. [22]	Increased	LGA	0.028
Lekva et al. [23]	Increased	LGA	0.047
Shroff et al. [24]	Increased	LGA	<0.01
Shroff et al. [24]	Decreased	SGA	<0.05
Schoots et al. [25]	Increased	FGR	<0.01
Stefaniak et al. [26]	Increased	FGR	0.01
Shang et al. [27]	Increased	Macrosomia	ns
Kyriakakou et al. [28]	Increased	FGR	<0.05

LGA, large for gestational age; SGA, small for gestational age; FGR, fetal growth restriction. ns = not significant.

3.2.2. Association between Maternal Adiponectin and Fetal Growth

There was no pattern between adiponectin levels and birthweight category (Table 2). In one study, decreased adiponectin level was associated with LGA infants compared to AGA infants [23]. In contrast, another study found decreased adiponectin was associated with FGR compared to non-FGR pregnancies [28], whereas this relationship was not statistically significant in another study [29]. There was also an association between decreased maternal adiponectin in macrocosmic infants compared to appropriately weighted infants in one study [27], and increased adiponectin in SGA infants compared to AGA infants in another study [22].

Table 2. Relationship between maternal adiponectin and fetal growth.

Reference	Maternal Serum Concentration Compared to Control	Offspring Birthweight	*p*-Value
Lazo-de-la-Vega-Monroy et al. [22]	Increased	SGA	<0.05
Lekva et al. [23]	Decreased	LGA	0.007
Shang et al. [27]	Decreased	Macrosomia	<0.05
Kyriakakou et al. [28]	Decreased	FGR	<0.05
Zamarian et al. [29]	Decreased	FGR	ns

LGA, large for gestational age; SGA, small for gestational age; FGR, fetal growth restriction. ns = not significant.

3.3. Association between Maternal Obesity or Leptin and Placental Receptors and Nutrient Transporters

3.3.1. Association between Maternal Obesity or Leptin and Placental Expression of Receptors and Nutrient Transporters

In pregnancy, maternal obesity is associated with increased circulating leptin and changes in placental function [30], but consistent changes in placental glucose, amino acid, or leptin transporter/receptor gene expression was not found in pregnant women with obesity only (no measurement of leptin) compared to pregnancies with high maternal leptin levels (Table 3). Nogues et al. reported a decrease in placental mRNA expression of glucose transporter 1 (*Glut1*) and system A sodium-dependent amino acid transporter (*Snat*) 1 and *Snat2* in obese pregnant women [31], whereas there was an increase in mRNA expression of *Glut1* in placentas from pregnant women with GDM who also had high serum leptin, compared to non-GDM low leptin pregnancies [32]. There was no association between leptin and the placental mRNA expression of leptin receptor (*LepR*) in obese pregnant women [33].

Table 3. Association between maternal leptin/obesity and placental mRNA expression of receptors and nutrient transporters.

Reference	Participant Characteristics	mRNA	*p*-Value
Nogues et al. [31]	obese	*Glut1* ↓	0.0273
Nogues et al. [31]	obese	*Snat1* ↓	0.0273
Nogues et al. [31]	obese	*Snat2* ↓	0.0039
Balachandiran et al. [32]	↑ leptin; GDM	*Glut1* ↓	<0.05
Nogues et al. [33]	↑ leptin; obese	*LepR*	ns

Glut1, glucose transporter 1; *Snat1*, System A sodium dependent amino acid transporter 1; *Snat2*—System A sodium dependent amino acid transporter 2; *LepR*, placental leptin receptor; ↑ increased; ↓ decreased.

3.3.2. Association between Maternal Obesity or Leptin and Protein Expression of Placental Receptors and Nutrient Transporters

The association between maternal obesity or elevated leptin and the protein levels of placental receptors and nutrient transporters was summarized in Table 4. In pregnant women with an increase in serum leptin and LGA infants, placental protein levels of SNAT2 were decreased [22]. In addition, SNAT1 in placentas from pregnant women with obesity was decreased [32]. Despite no change in mRNA expression (Table 3), there was a decrease in placental LEPR from obese pregnant women compared to non-obese pregnant women [33]. Placental GLUT1 was increased in women with increased leptin levels and GDM [32]. In contrast, there was a decrease in GLUT1 transporters in placentae from obese women compare to non-obese women [31].

Table 4. Association between maternal leptin and placental protein expression of receptors and nutrient transporters.

Reference	Participant Characteristics	Protein	*p*-Value
Nogues et al. [31]	obese	GLUT1 ↓	0.0221
Nogues et al. [31]	obese	SNAT1 ↓	0.0283
Lekva et al. [22]	↑ leptin; LGA	SNAT2 ↓	0.01
Balachandiran et al. [32]	↑ leptin; GDM	GLUT1 ↑	<0.05
Nogues et al. [33]	↑ leptin; obese	LEPR ↓	<0.01

GLUT1, glucose transporter 1; SNAT1, system A sodium-dependent amino acid transporter 1; SNAT2, system A sodium-dependent amino acid transporter 2; LEPR, leptin receptor; ↑ increased; ↓ decreased.

3.3.3. Association between Maternal Adiponectin and Placental Expression of Receptors and Nutrient Transporters

Analysis of the association between adiponectin and expression of placental receptors and nutrient transporters was summarized in Table 5. Reduced adiponectin was associated with decreased *Snat2* mRNA [23] and decreased *AdipoR2* and *AdipoR1* mRNA [23,33]. Moreover, there was a significant association between increased placental expression of *Glut1* mRNA among pregnant women with low levels of adiponectin [33].

Table 5. Association between maternal adiponectin and placental mRNA expression of receptors and nutrient transporters.

Reference	Participant Characteristics	mRNA	*p*-Value
Lekva et al. [23]	↓ adiponectin; LGA	*Snat2* ↓	0.01
Lekva et al. [23]	↓ adiponectin; LGA	*AdipoR1* ↓	ns
Lekva et al. [23]	↓ adiponectin; LGA	*AdipoR2* ↓	0.001
Balachandiran et al. [32]	↓ adiponectin; GDM	*Glut1* ↑	<0.05
Nogues et al. [33]	↓ adiponectin; obese	*AdipoR1* ↓	<0.05
Nogues et al. [33]	↓ adiponectin; obese	*AdipoR2* ↓	<0.05

Glut1, glucose transporter 1; *Snat1*, System A sodium dependent amino acid transporter 1; *Snat2*—System A sodium dependent amino acid transporter 2; *AdipoR1*; placental adiponectin receptor 1; *AdipoR2*, placental adiponectin receptor 2; ↑ increased; ↓ decreased.

3.3.4. Correlation between Maternal Adiponectin and Placental Receptors and Nutrient Transporters

Low serum adiponectin was associated with altered placental receptors and nutrient transporters (Table 6). Low adiponectin was associated with an increase in GLUT1 transporter placental protein levels in GDM patients compared to non-GDM patients [32]. Nogues et al. (2019) reported a decrease in both ADIPOR1 and ADIPOR2 protein in placentas from obese patients [33].

Table 6. Correlation between maternal adiponectin and placental protein for receptors and nutrient transporter.

Reference	Participant Characteristics	Protein	*p*-Value
Balachandiran et al. [32]	↓ adiponectin; GDM	GLUT1 ↑	<0.05
Nogues et al. [33]	↓ adiponectin; obese	ADIPOR1 ↓	<0.05
Nogues et al. [33]	↓ adiponectin; obese	ADIPOR2 ↓	<0.05

GLUT1, glucose transporter 1; ADIPOR1; placental adiponectin receptor 1; ADIPOR2, placental adiponectin receptor 2; ↑ increased; ↓ decreased.

3.4. Association between Maternal Adiponectin and Leptin and Placental Inflammatory Signaling Pathways

3.4.1. Association between Elevated Maternal Leptin and Placental Inflammatory Signaling Pathways

In placentas from pregnancies affected by SGA, increased maternal serum leptin was associated with an increased phosphorylation of AMP-activated protein kinase (AMPK) and reduced phosphorylation of mammalian target of rapamycin (mTOR) (Table 7) [22].

Table 7. Correlation between maternal leptin and adiponectin and inflammatory signaling pathways.

Reference	Participant Characteristics	Protein	*p*-Value
Lazo-de-la-Vega-Monroy, et al. [22]	↑ leptin; SGA	pAMPK ↑	<0.05
Lazo-de-la-Vega-Monroy, et al. [22]	↑ leptin; SGA	p-mTOR ↓	<0.02
Lazo-de-la-Vega-Monroy, et al. [22]	↓ adiponectin; SGA	pAMPK ↑	<0.05
Lazo-de-la-Vega-Monroy, et al. [22]	↓ adiponectin; SGA	p-mTOR ↓	0.02

AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin, ↑ increased; ↓ decreased.

3.4.2. Association between Reduced Adiponectin and Placental Inflammatory Signaling Pathways

There was an association between reduced adiponectin and placental inflammatory signaling pathways (Table 8). Despite no significant changes to phosphorylation of p38-mitogen-activated kinase (MAPK) [34,35], there was an increased phosphorylation of AMPK and reduced phosphorylation of mTOR [22].

Table 8. Association between maternal leptin and adiponectin and GDM and PE.

Reference	Maternal Serum Concentration	Pathology	*p*-Value
Shroff et al. [24]	↑ leptin	PE	<0.05
Hogg et al. [36]	↑ leptin	PE	<0.05
Hogg et al. [36]	↑ leptin	GDM	<0.0001
Schoots et al. [25]	↑ leptin	PE	<0.05
Shang et al. [27]	↓ adiponectin	GDM	<0.05
Balachandiran et al. [32]	↓ adiponectin	GDM	<0.05

GDM, gestational diabetes mellitus; PE, preeclampsia; ↑ increased; ↓ decreased.

3.5. Adiponectin and Leptin in GDM and PE

Association between Elevated Leptin and Reduced Adiponectin in GDM and PE

Maternal leptin was found to be elevated in pregnancies complicated with PE [24,25,36]. Maternal leptin was also increased in pregnant women with GDM [33]. Maternal adiponectin was reduced in pregnancies complicated with GDM [27,32] (Table 8).

4. Discussion

This systematic review analyzed the potential associations between maternal circulating adiponectin and leptin with fetal growth, placental nutrient transport, placental signaling pathways, and pregnancy complications (GDM and PE). This review found that circulating maternal adiponectin and leptin may play a role in fetal growth through changes to placental signaling pathways that affect functions related to nutrient transport and energy homeostasis, as well as contribute to the pathology associated with GDM and PE.

4.1. Maternal Leptin and Adiponectin Influences on Fetal Growth

Leptin and adiponectin have often opposing concentrations and effects, and both change during pregnancy. Maternal leptin levels increase during pregnancy and decrease postpartum, with the greatest increase in the second trimester when maternal physiological changes to glucose homeostasis occur [37,38]. During pregnancy, adiponectin levels are physiologically reduced in the third trimester, the greatest peripheral insulin resistance period, which means that levels decrease proportionately with insulin sensitivity. Conversely, compared to the pre-gravid state, serum adiponectin is increased in early gestation [1,39,40]. Both leptin and adiponectin levels are influenced by a range of factors. Although adiponectin is produced by adipocytes, it is paradoxically decreased in individuals with insulin resistance and obesity [41,42]. Leptin levels are strongly associated with BMI, but in pregnancy levels may also be influenced by factors including parity [43]. The studies included in the current review showed increases in circulating maternal leptin may be associated with LGA infants. Three separate studies with a combined sample size of 1650 pregnancies (including 199 LGA infants) found an association of increased leptin with LGA, with this sample size giving a reasonable level of confidence in this association. An additional study also reported nonsignificant elevated maternal leptin in cases of macrosomia [27]. In contrast, adiponectin was inversely correlated with fetal/infant growth and birthweight, with maternal levels decreased in cases of LGA and macrosomia in a total of 508 women from two studies [23,27]. Maternal leptin increases placental nutrient transport to the fetus by stimulating amino acid uptake, which could be the mechanism of the increased fetal growth when maternal leptin levels are increased [9].

In contrast to the positive association of leptin with fetal growth discussed above, Schoots et al. [25] and Stefaniak and Dmoch-Gajzlerska (2022) [26] reported increased maternal leptin associated with fetal undergrowth (IUGR and SGA), and Kyriakakou et al. found an association of increased maternal leptin and decreased maternal adiponectin with FGR [29]. Although a 2019 meta-analysis reported no significant differences in maternal leptin concentrations between SGA and AGA neonates [44], there may be an association of elevated maternal leptin with growth restriction under certain conditions. Leptin is produced by the placenta during pregnancy (in addition to adipose tissue production) and has pleiotropic effects on placental function including promoting the proliferation and survival of trophoblast cells [30], but in vitro studies have shown that overstimulation of placental leptin receptors has negative effects related to changes in signaling pathways [45] that may lead to placental dysfunction. The placenta does not produce endogenous adiponectin, and adiponectin in the maternal circulation also does not cross the placenta; however, the placenta does express adiponectin receptors, and as a consequence placental function could impact nutrient transport and fetal growth [1]. Animal models and in vitro studies have found that low adiponectin can induce placental dysfunction, in particular influencing intracellular signaling pathways that affect mitochondrial function and nutrient transport [34], although this may not affect fetal growth [46,47]. As placental dysfunction

is a common cause of growth restriction, further research in this area should concentrate on how leptin and adiponectin can affect placental signaling pathways in vivo, and how pathway changes may relate to placental (dys)function associated with growth restriction.

The assessment of fetal growth/size used in the different studies may also have affected these results. The size of a fetus is determined through biometric evaluations using various formulae, and controversies exist in defining fetal growth/size [3]. A fetus is classified as SGA when its size falls below a predefined threshold for its gestational age, typically indicated by an estimated fetal weight or abdominal circumference below the 10th percentile of reference ranges, although alternative thresholds (e.g., 5th or 3rd percentiles) are also used, whereas FGR refers to a fetus that fails to achieve its genetically predetermined growth potential. Unlike SGA, which simply indicates a smaller size, FGR implies that the fetus is not growing as expected. A consensus-based definition for FGR including both biometric and functional parameters was published in 2016 [48], but in practice, SGA is often used as a surrogate for FGR [49]. The specific definitions of FGR or SGA were not included in all studies in this review; additionally, some studies used the older and less well-defined term IUGR. A complete picture of how maternal leptin and adiponectin affect fetal growth, especially impaired fetal growth associated with adverse outcomes, requires accurately reported definitions. Further, although impaired fetal growth is associated with an increased risk of poor outcomes [50], FGR definitions have limited success in predicting adverse neonatal outcomes [51]. The measurement of other parameters that may indicate uteroplacental function (e.g., maternal leptin and adiponectin or markers of the placental response to these factors) could improve the prediction of FGR and adverse perinatal outcomes by reporting directly on the function of fetoplacental unit.

4.2. Maternal Leptin and Adiponectin Influences Placental Nutrient Transporters

To identify the potential placental-mediated mechanisms for the association of maternal leptin and adiponectin levels with fetal growth changes, we summarized data on placental transporters involved with nutrient transfer and growth. Maternal stimuli influence placental function, and our results suggest that there is also placental adaptation to stimuli that may modulate effects on fetal growth. Nogues et al. [31] reported a decrease in the GLUT1 glucose transporter, in addition to structural and functional changes, in the placentae of obese patients (these changes may be related to the increased circulating leptin found in obesity [52]), and other workers found a decrease in both SNAT1 and SNAT2 in placentae of obese individuals with increased leptin and decreased adiponectin [23,31]. An increase of SNAT transporters can increase nutrient transport to the fetus and lead to fetal overgrowth [18], whereas decreased placental SNAT transporter levels are associated with IUGR and fetal undergrowth [53,54]. As GLUT1 and SNAT transporters transfer glucose and amino acids to the fetus, decreased levels of these transporters may be a compensatory mechanism in the placenta that helps limit fetal overgrowth [55]. However, Shang and Wen (2018) found an increase in SNAT transporters in the placentas of infants with macrosomia [56], suggesting that the specific mechanisms involved in placental response need to be further explored.

A potential mechanistic role regulated by adipokines may be played by altered intracellular signaling. AMPK plays a role in embryonic and placental development [57]. AMPK signaling contributes to cell growth, differentiation, and nutrient transport in the placenta and fetus [57]. Additionally, mTOR is responsible for regulation of the transport of nutrients, oxygen, and growth factors [58]. The current study reported AMPK enzyme activation and mTOR protein inhibition with increased leptin and decreased adiponectin in SGA placentas [22]. An association between increased maternal adiponectin with increased placental AMPK enzyme activation has been proposed [34]. Adiponectin increases activation of placental AMPK, which regulates glucose metabolism, insulin sensitivity, and fetal growth [59], although the mechanisms differentiating each type of activator and timing are not fully understood [60].

4.3. Maternal Leptin and Adiponectin in Gestational Diabetes and Preeclampsia

GDM is a metabolic disorder of pregnancy commonly associated with fetal overgrowth. The link between maternal leptin and adiponectin levels with disease pathologies in the current study corresponds with a previous systematic literature analysis that reported significant increase in leptin in GDM patients independent of BMI [61]. Additionally, Balachandiran et al. reported an increase in GLUT1 levels in the placentae of GDM patients with increased maternal leptin [33], and Stanirowski et al. reported increased placental GLUT1 levels in GDM patients but did not report on maternal leptin directly [62]. This suggests that GDM may impact the placental adaptive response that can help limit fetal overgrowth, with the increase of placental GLUT1 transporters in GDM patients playing a potential role in the three-fold increased incidence of macrosomic infants from GDM pregnancies [63]. It has also been proposed that the increase in GLUT1 placental transporters could be due to insulin therapy in GDM patients [64], suggesting that this therapy may have underappreciated side effects on fetal growth.

PE pathogenesis is not fully understood, but likely involves placental dysfunction and is commonly associated with fetal undergrowth. All three of the studies that investigated PE found that increased maternal leptin levels were also associated with PE. It has been hypothesized that maternal leptin's role in angiogenesis and control immune function during implantation could affect the establishment of maternal–placental–fetal circulation [65]. Therefore, the elevated maternal leptin could potentially modulate trophoblast activity leading to alterations in maternal–placental–fetal circulation system and subsequent PE development.

5. Limitations

This review did not assess the amount of the changes in leptin and adiponectin or directly compare these across studies with a meta-analysis, which is a limitation as these features may relate to some of the variability in associated effects. Another limitation is the potential for terms such as LGA and FGR to be defined differently in different studies, as there is inconsistency in the definitions of these terms [3] and we have accepted the authors' definitions. This study is also limited through not assessing additional placental features that may relate to function, such as placental efficacy (placental weight compared to neonate weight) and in not investigating how pre-existing features such as maternal BMI and epigenetic changes such as cell-free methylation profiles [66] may have roles in metabolic changes that affect fetal growth. The focus of the review on two specific pregnancy complications (GDM and PE) is also a limitation, as diabetes in pregnancy and hypertensive disorders of pregnancy have variable pathophysiologies that are likely to be differentially affected by leptin and adiponectin.

Future work should compare absolute and relative leptin and adiponectin levels and use consistent definitions across studies, as well as include additional measures of placental function, pre-existing maternal features, and a wider range of pregnancy complications that may influence the effects and function of leptin and adiponectin in pregnancy.

6. Conclusions

A majority of reported studies associated elevated maternal leptin and reduced adiponectin with fetal overgrowth, although this relationship was not consistently found and may be complicated when other pathologies such as GDM are present. The effects of maternal leptin and adiponectin on fetal growth may be driven by placental adaptation that modifies features including nutrient transporters and the function of placental mitochondria. Future studies should use consistent definitions of fetal growth and determine if the effects of leptin and adiponectin on placental signaling pathways that have been found in in vitro and animal models have mechanistic roles in human pregnancy.

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