Effects of Placental Long Non-coding RNA MALAT1 on Maternal and Fetal Metabolism in Women with Pre-pregnancy Overweight or Obesity: A Postprint Study

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Date: 2023-12-20T00:00:00+00:00

Abstract

Background: Pre-pregnancy obesity can have a series of effects on both mother and fetus, and its mechanism may be related to abnormal maternal-fetal metabolism. Therefore, exploring its mechanism is crucial for improving fetal prognosis. Objective: To investigate changes in obesity- and glucose metabolism-related factors in placentas of pregnant women with different pre-pregnancy BMI. Methods: A total of 100 singleton pregnant women who delivered at Beijing Shijitan Hospital, Capital Medical University in 2019 were selected as study subjects. Clinical data were collected through the electronic medical record system. The pregnant women were divided into pre-pregnancy underweight/normal weight group (57 cases) and pre-pregnancy overweight/obese group (43 cases) according to body weight. Reverse transcription-polymerase chain reaction was used to detect the mRNA expression of long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (LncRNA MALAT1), serum amyloid A3 (SAA3), and interleukin-6 (IL-6) in placental tissues. Results: The age of study subjects ranged from 22 to 43 years, with an average age of (32.7$±$4.2) years; among them, there were 61 primiparas, 21 patients with gestational diabetes mellitus (GDM), 14 underweight cases, 43 normal weight cases, 26 overweight cases, and 17 obese cases. The proportion of GDM and neonatal weight in the pre-pregnancy overweight/obese group were higher than those in the pre-pregnancy underweight/normal weight group, while gestational weight gain was lower than that in the pre-pregnancy underweight/normal weight group, with statistically significant differences ($P<0.05$). The expression level of LncRNA MALAT1 mRNA in placental tissues of pregnant women in the pre-pregnancy overweight/obese group was higher than that in the pre-pregnancy underweight/normal weight group, with a statistically significant difference

(P<0.05). The mRNA expression levels of LncRNA MALAT1, SAA3, and IL-6 in placental tissues of pre-pregnancy obese pregnant women were higher than those of pre-pregnancy normal weight pregnant women, with statistically significant differences (P<0.05). Conclusion: Excessive pre-pregnancy BMI has a greater impact on mother and infant during pregnancy, masking the effect of controlled gestational weight gain. In obese pregnant women, LncRNA MALAT1 may regulate glucose and lipid homeostasis through SAA3 and IL-6, involving inflammatory changes and oxidative stress, thereby affecting fetal metabolism, which warrants further in-depth exploration.

Full Text

Impact of LncRNA MALAT1 in the Placentas of Pre-Pregnancy Overweight/Obese Women on Maternal and Infant Metabolism

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Abstract

Background: Pre-pregnancy obesity can have a range of effects on both the mother and the fetus, possibly due to abnormalities in maternal-fetal metabolism. Therefore, exploring the underlying mechanisms is essential to improve fetal prognosis.

Objective: To investigate alterations in obesity- and glucose metabolism-related factors in the placentas of pregnant women with different pre-pregnancy BMI levels.

Methods: A total of 100 singleton pregnant women who delivered at Beijing Shijitan Hospital, Capital Medical University in 2019 were selected as study subjects. Clinical data were collected from the electronic medical record system. Subjects were divided into a low/normal pre-pregnancy body mass group (n=57) and an overweight/obese group (n=43) based on their pre-pregnancy body mass. Expression of long non-coding RNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (LncRNA MALAT1), Serum Amyloid A3 (SAA3), and Interleukin 6 (IL-6) mRNA in placental tissue was measured using reverse transcription-polymerase chain reaction.

Results: Subjects ranged in age from 22 to 43 years, with a mean age of (32.7$±$4.2) years; 61 were primiparas, 21 had gestational diabetes mellitus (GDM), 14 had low body mass, 43 had normal body mass, 26 were overweight,

and 17 were obese. The overweight/obese group had a higher proportion of GDM and higher neonatal body mass compared to the low/normal body mass group, but lower gestational weight gain, with statistically significant differences ($P<0.05$). LncRNA MALAT1 mRNA expression in placental tissue was significantly higher in the overweight/obese group than in the low/normal body mass group ($P<0.05$). Furthermore, LncRNA MALAT1, SAA3, and IL-6 mRNA expression levels in placental tissue were all significantly higher in obese pregnant women compared to those with normal pre-pregnancy body mass ($P<0.05$).

Conclusion: Excessive pre-pregnancy BMI has a more significant impact on mother and child during pregnancy, overshadowing the benefits of controlling gestational weight gain. In obese pregnant women, LncRNA MALAT1 may regulate glucose and lipid homeostasis through SAA3 and IL-6, involving inflammatory changes and oxidative stress, thereby affecting fetal metabolism. This mechanism warrants more in-depth exploration.

Keywords: Obesity, maternal; Diabetes, gestational; LncRNA MALAT1; Retrospective studies

Introduction

The global prevalence of overweight and obesity continues to rise, making refined weight management during pregnancy increasingly important [1]. Maternal obesity during pregnancy can have numerous adverse effects on both mother and fetus. Numerous studies have shown that maternal overweight or obesity during pregnancy increases the risk of obesity and related chronic metabolic diseases in offspring [2-4]. The underlying mechanism may be related to bidirectional metabolic, circulatory, and endocrine factors between mother and fetus, with their balanced state contributing to placental microenvironment stability [5]. Therefore, we hypothesized that the series of maternal-fetal problems caused by obesity during pregnancy may be associated with certain placental factors.

Long non-coding RNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (LncRNA MALAT1) is a long non-protein-coding RNA approximately 6.5 Kb in length that has been extensively studied in diabetes. Reports have confirmed that dysregulated LncRNA MALAT1 expression participates in the pathological processes of diabetes-related microvascular disease and diabetic retinopathy [6-7]. Serum Amyloid A3 (SAA3) is a direct target of LncRNA MALAT1, and inflammatory cascade regulators Interleukin 6 (IL-6) and Tumor Necrosis Factor α (TNF-α) also play important roles. LncRNA MALAT1 has also been reported to be involved in lipid metabolism [8], with both animal experiments and studies in obese populations demonstrating that MALAT1 promotes cellular lipid accumulation by regulating the expression of lipid transcription factors [9].

Consequently, this study examined LncRNA MALAT1, SAA3, and IL-6 expres-

sion in placentas from pregnant women with different pre-pregnancy BMI levels. The objective was to screen for placental factors potentially associated with obesity and maternal-fetal metabolic abnormalities, and to explore their impact on maternal and infant metabolism and underlying mechanisms in conjunction with delivery outcomes, with the goal of enabling more precise pregnancy management for obese women.

Methods

1.1 Study Subjects

We selected 100 singleton pregnant women who delivered at Beijing Shijitan Hospital, Capital Medical University in 2019 and met the inclusion criteria. Inclusion criteria were: singleton pregnancy; full-term delivery with regular prenatal care at our hospital; no intrauterine infection; no internal or surgical comorbidities; no placenta previa; and voluntary provision of placental tissue. Exclusion criteria were: multiple pregnancy; miscarriage before 28 weeks; intrauterine infection; intrauterine fetal death; internal or surgical comorbidities; placenta previa; and irregular prenatal care. This study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University [sjtkyll-lx-2021(11)], and all participants provided informed consent.

1.2 Research Methods

Clinical data were collected through the electronic medical record system, including: general information (age, height, weight, education level, employment status, and calculated BMI); parity; history of uterine scar; uterine fibroids; gestational weight gain (defined as the difference between the last recorded maternal weight before delivery and pre-pregnancy weight); early pregnancy fasting insulin; early pregnancy fasting glucose; maternal outcomes (including cesarean section, dystocia [vaginal assisted delivery and shoulder dystocia], gestational diabetes mellitus [GDM], and postpartum hemorrhage); and neonatal outcomes (neonatal birth weight, macrosomia [birth weight $\geq$ 4,000 g], small-for-gestational-age [birth weight $<$ 10th percentile for gestational age], and fetal distress).

1.3 Grouping

According to the 2009 Institute of Medicine (IOM) definitions [10], pre-pregnancy underweight was defined as BMI $<$ 18.5 kg/m^2, normal weight as 18.5 $\leq$ BMI $<$ 25.0 kg/m^2, overweight as 25.0 $\leq$ BMI $<$ 30.0 kg/m^2, and obesity as BMI $\geq$ 30.0 kg/m^2. Pregnant women were divided into a low/normal pre-pregnancy body mass group (57 cases) and an overweight/obese group (43 cases).

1.4 Reverse Transcription-Polymerase Chain Reaction (RT-PCR) Detection of LncRNA MALAT1, SAA3, and IL-6 mRNA Expression in Placental Tissue

Following the manufacturer' s instructions, the reverse transcription reaction system was prepared [0.5 g RNA + 2 L 5×TransScript All-in-One First-Strand cDNA Synthesis SuperMix for qPCR (Beijing TransGen Biotech Co., Ltd.) + 0.5 L gDNA remover]. The reaction was performed in a GeneAmp® PCR System 9700 (Applied Biosystems, USA) at 42°C for 15 minutes and 85°C for 5 seconds. The reaction system was then diluted 10-fold in nuclease-free water, and cDNA was stored at -20°C.

The PCR reaction system was prepared [1 L cDNA + 5 L 2×perfectStart™ Green qPCR SuperMix (Beijing TransGen Biotech Co., Ltd.) + 0.2 L forward primer + 0.2 L reverse primer + 3.6 L nuclease-free water]. Reactions were performed in 384-well optical plates (Roche, Switzerland) with incubation at 94°C for 30 seconds, followed by 94°C for 5 seconds and 60°C for 30 seconds. β-actin was used as the internal reference protein, and mRNA relative expression levels were calculated using the $2^{(-\Delta Ct)}$ method. Primer sequences are shown in Table 1 .

1.5 Statistical Methods

Data analysis was performed using SPSS 22.0 statistical software. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-test. Categorical data were expressed as relative frequencies and compared using ^{2} test. $P<0.05$ was considered statistically significant.

Results

2.1 Clinical Data of Study Subjects

Subjects ranged in age from 22 to 43 years, with a mean age of (32.7$±$4.2) years. The cohort included 61 primiparas, 21 patients with GDM, 14 with low body mass, 43 with normal body mass, 26 who were overweight, and 17 who were obese. The overweight/obese group had a higher GDM proportion and higher neonatal body mass compared to the low/normal body mass group, but lower gestational weight gain, with statistically significant differences ($P<0.05$). There were no statistically significant differences between the two groups in age, early pregnancy fasting insulin, early pregnancy fasting glucose, parity, proportion of uterine scar, proportion of uterine fibroids, education level (undergraduate and above), employment status, postpartum hemorrhage, dystocia, cesarean section rate, or fetal outcomes ($P>0.05$), as shown in Table 2 .

2.2 Expression of LncRNA MALAT1, SAA3, and IL-6 mRNA in Placental Tissue

LncRNA MALAT1 mRNA expression in placental tissue was significantly higher in the overweight/obese group compared to the low/normal body mass group ($P<0.05$). There were no statistically significant differences in SAA3 and IL-6 mRNA expression between the two groups ($P>0.05$), as shown in Table 3 .

Further analysis of LncRNA MALAT1, SAA3, and IL-6 mRNA expression in placental tissue from women with normal pre-pregnancy weight versus obese women revealed that obese pregnant women had significantly higher expression of LncRNA MALAT1 (4.28199 vs. 2.53154, t=-5.963, $P<0.001$), SAA3 (0.00044 vs. 0.00027, t=-2.111, $P=0.039$), and IL-6 (0.00234 vs. 0.00181, t=-2.336, $P=0.023$) compared to normal weight pregnant women.

Discussion

Previous studies have shown that children of obese mothers have significantly higher rates of obesity, with not only increased neonatal birth weight but also elevated obesity rates during childhood and adolescence, and are more likely to develop metabolic diseases such as hyperlipidemia and hyperglycemia [11-13]. Additionally, obese pregnant women have higher probabilities of dystocia and operative delivery due to larger fetuses and increased soft tissue thickness, which can lead to uterine atony, slow labor progression, and abnormal fetal position [14-15].

During pregnancy, maternal hormonal fluctuations may activate certain inflammatory signaling pathways, exacerbating placental inflammatory responses. Obese pregnant women experience more pronounced hormonal changes, which may lead to oxidative stress and even affect placental function [16-17]. This study found that LncRNA MALAT1 expression was significantly higher in placentas of overweight/obese pregnant women compared to those with low/normal pre-pregnancy weight, and expression of inflammatory cascade regulators SAA3 and IL-6 was also significantly elevated. LncRNA MALAT1 expression was significantly increased in GDM placentas.

Previous research has indicated that LncRNA MALAT1 and systemic inflammatory status affect GDM disease progression [18], and LncRNA MALAT1 is associated with oxidative stress induction and inflammatory factor production [19-20], potentially providing new targets for early prediction, gestational intervention, and precision treatment of GDM [21]. Puthanveetil et al. [6] reported that hyperglycemia could stimulate SAA3 protein expression in human umbilical vein endothelial cells via MALAT1, accompanied by increased expression of inflammatory mediators such as IL-6 and TNF-α. Our results are consistent with these findings.

Yan et al. [9] found that LncRNA MALAT1 expression was increased in high-fat diet-induced mouse hepatocytes and in the livers of obese mice. LncRNA

MALAT1 binds to Sterol Regulatory Element-Binding Protein (SREBP)-1c protein in the cell nucleus, inhibiting its ubiquitination. This protein is activated by insulin and highly expressed in hepatocytes, serving as a key transcription factor regulating hepatic fat generation, thereby increasing cellular lipid accumulation. Knockdown of LncRNA MALAT1 significantly downregulated SREBP-1c expression and reversed hepatic lipid accumulation and insulin resistance in obese mice. Other studies have shown that in pancreatic islet cells of diabetic mice, increased LncRNA MALAT1 expression inhibits insulin secretion and induces β-cell dysfunction [22], while LncRNA MALAT1-deficient mice show improved insulin sensitivity [23]. LncRNA MALAT1 expression is significantly increased in the muscle of high-fat diet mice, associated with insulin resistance and glucose homeostasis pathways [24].

However, some reports suggest that LncRNA MALAT1 is decreased in white adipose tissue of obese mice, and its loss does not affect diet-induced adipose tissue accumulation or lipid homeostasis in obese mice [25]. Similar studies in obese populations have found that compared to normal-weight subjects, adipose-derived stem cells from obese subjects show differential expression of multiple LncRNAs in exosomes, with LncRNA MALAT1 expression significantly elevated [26]. Ebrahimi et al. [27] detected LncRNA MALAT1 expression in adipose tissue of obese women and found that LncRNA MALAT1 expression was positively correlated with major adipogenic genes such as SREBP-1c and PPARγ, thereby playing a role in lipid regulation.

There are reports on the mechanism by which LncRNA MALAT1 regulates lipid metabolism, suggesting it modulates interactions between the hypothalamus and adipose tissue. For example, adipocytes from obese mice secrete extracellular vesicles containing LncRNA MALAT1 that can modulate hypothalamic anorexigenic pro-opiomelanocortin neurons through mTOR signaling, thereby affecting energy intake, which has been confirmed both in vivo and in vitro [28]. Studies in malignant tumor patients have also found that LncRNA MALAT1 can regulate Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) transcription; knockdown of LncRNA MALAT1 significantly downregulates PPAR-γ, thereby inhibiting adipogenesis and causing fat loss [29].

Our study analyzed gestational weight gain and delivery outcomes in pregnant women with different pre-pregnancy BMI levels. We found that even with reduced gestational weight gain, excessive pre-pregnancy BMI still increased neonatal body mass and GDM incidence, suggesting that pre-pregnancy obesity has a greater impact on maternal and fetal outcomes during pregnancy and may diminish the benefits of gestational weight control. In obese pregnant women, LncRNA MALAT1 may regulate inflammatory changes through SAA3 and IL-6, modulating maternal glucose and lipid homeostasis and thereby affecting fetal metabolism. Combined with literature review, we hypothesize that LncRNA MALAT1 may regulate signaling pathways in the fetal hypothalamus, modulating energy intake in offspring and thus exerting long-term effects, which warrants further in-depth exploration and research.

This study has several limitations: (1) The sample was derived from pregnant women who delivered at our hospital, and differences among prenatal care providers and subtle variations in prenatal education and weight management models may have influenced maternal and neonatal outcomes; (2) The mechanisms by which obesity affects metabolism are complex, involving multiple pathways, routes, and factors that require more comprehensive analysis and discussion; (3) This study only detected differences in SAA3 and IL-6 expression between pre-pregnancy normal weight and obese pregnant women, likely due to sample size limitations.

In summary, compared with gestational weight management, pre-pregnancy obesity has a greater impact on maternal and fetal outcomes during pregnancy, potentially diminishing the benefits of gestational weight control. The underlying mechanism may involve LncRNA MALAT1 regulating inflammatory changes through SAA3 and IL-6, thereby affecting fetal metabolism.

Author Contributions: ZHANG Jin proposed the main research objectives, designed the study, analyzed data, and wrote the manuscript; ZHANG Rui and CHI Jingjing collected clinical data and performed statistical analysis; LI Ya conducted the experiments; BAI Wenpei was responsible for quality control and review of the article, overall responsibility for the article, and supervision of the research.

Funding: This study was supported by the Beijing Natural Science Foundation (7202075), the China Railway Group Medical and Health Special Project (J2021Z604), the National Menopause Care Specialty Program (2019), and the Beijing Hospital Management Center Clinical Medicine Development Special Fund (ZYLX202112).

Conflict of Interest: The authors declare no conflict of interest.

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Received: 2023-04-11; Revised: 2023-11-23

Note: Figure translations are in progress. See original paper for figures.