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Adipokine-myokine-hepatokine compartment-system in mothers and children: An explorative study

Clara Deibert [a, *], Nina Ferrari [b], Anne Flöck [c], Waltraut M. Merz [c], Ulrich Gembruch [c], Walter Lehmacher [a], Christina Ehrhardt [d], Christine Graf [b, d]

[a] University of Cologne Medical School, Joseph-Stelzmann-Straße 20, 50931 Cologne, Germany
[b] University Hospital of Cologne, Cologne Centre for Prevention in Childhood and Youth/ Heart Centre Cologne, Kerpener Str. 62, 50937 Cologne, Germany
[c] University Bonn Medical School, Department of Obstetrics and Prenatal, Sigmund-Freud-Straße 25, 53127 Bonn, Germany
[d] German Sport University Cologne, Institute of Movement and Neuroscience, Am Sportpark Müngersdorf 6, 50933 Cologne, Germany

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ABSTRACT

Objective: Maternal lifestyle during pregnancy has an effect of gestational development and neonatal outcome. Overweight gravidas and gravidas with excessive weight gain have an increased risk of gestational complications and neonatal metabolic disorder. The underlying mechanisms are still under discussion, but the hormonally active fat mass and its biomarkers, adipocytokines, may play a key role by potentially having a direct impact on the metabolic homeostasis of the system in concert with other biomarkers like hepatokines and myokines. Up to now little is known in terms of lifestyle habits and their effect on this complex model on maternal and fetal outcome. Therefore, we aim to investigate the influence of maternal lifestyle clusters during pregnancy on the maternal and fetal biomarkers of compartments, specifically those implying maternal fat and muscle mass, maternal liver and the placenta and who are associated with maternal body composition and birth weight.

Methods: In this exploratory pilot study at least 100 singleton pregnancies and their newborns will be included. The women will undergo assessments of anthropometric measurements, venous blood samples will be drawn and physical activity and nutritional status will be collected through questionnaires. Newborns will undergo assessments of anthropometric measurements, umbilical cord samples will be drawn and birth outcomes will be evaluated. We will measure adipokines, myokines and hepatokines and relate them to maternal lifestyle clusters and fetal outcome.

Conclusion: Our study will be the first to examine the relationship between maternal body composition, birth weight and potential biomarkers based on an innovative compartment model.

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1. Introduction

Incidences of overweight and metabolic syndrome in children increase worldwide, thereby increasing the risk for developing chronic diseases in later life. This is negatively influenced by prematurity, fetopathia diabetic, maternal obesity and gestational diabetes (GDM) [1]. Maternal obesity is an important factor of excessive birth weight and increasing risk for later obesity and metabolic disorder [2]. The additional cause next to genetic predisposition is assumed to be perinatal programming. This process describes the reaction of the developing embryonic organs, such as the hypothalamus, to the intrauterine environment influenced by the mother. One of the influences that is prominently known to affect the embryonic organs is the mother's nutrition. The perinatal programming may have lifelong consequences to metabolism as a result from faulty materno-placental nutrient supply [3]. Therefore, children's long–term reaction to carbohydrates and amino acids are programmed during sensitive fetal phases by the maternal "offer" [4]. Our compartment model describes the individual metabolically active organs and their known endocrinological functions. The effect of those organ systems upon each other and onto the mother's entire metabolism and that impact on the fetus is the basis of our examinations. Particular endocrinological factors such as insulin and leptin, but also other biomarkers such as adiponectin, resistin and TNF-alpha (TNF-α) play a key role in the development of GDM [5,6]. Examples show that these cytokines originate from different compartments like maternal liver, muscle,

* Corresponding author.
E-mail addresses: clara_deibert@web.de (C. Deibert), C.Graf@dshs-koeln.de (C. Graf).

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and adipose tissue, but also in the placenta [7–12] (Table 1), corresponding with each other and more or less with the fetus (Fig. 1). Of the biomarkers to be researched, the following is known about their function and mechanisms of action: Leptin is secreted in adipose tissue with serum levels proportional to the adipose mass. It has been demonstrated that obese subjects have higher levels than subjects with healthy body weight [11–13]. Another operant regulator of glucose homeostasis is resistin from adipose tissue, muscle cells, endothelial cells, placental villi and throphoblasts [11,14,15]. Some studies found a positive correlation between resistin levels and body fat mass, others do not confirm this link [14]. Serum levels first increase during the third trimester and then at term. The effect of the maternal metabolism is an increase in insulin resistance. Higher umbilical resistin levels at term increase neonatal hepatic glucose production and may protect neonatal hypoglycemia [15]. Adiponectin is expressed contrary to leptin, in that it enhances insulin sensitivity by increasing insulin activity and reducing glucose production. In obese mothers adiponectin levels are reduced. Presumably adiponectin is produced in the human placenta [16,17]. The present adipokines may affect pregnancy outcome and fetal growth. Leptin and resistin levels in GDM are controversial, while data relating to adiponectin levels show a decrease in GDM.

The increase of fat mass in pregnancy is associated with an exacerbated inflammatory state. Higher circulation concentrations of inflammatory cytokines like C-reactive protein (CRP), Interleukin-6 (IL-6) and TNF-α are detected [18–20]. Also identified are myokines, a subspecies of cytokines which have a role in exercise associated metabolic adaption [21]. Myokines probably have a beneficial effect regarding chronic disease. Little is known about their impact during pregnancy. Brain-derived neurotrophic factor (BDNF) is identified as a regulator of controlling body fat mass and energy balance [21,22]. Low serum levels are associated with obesity and diabetes mellitus type 2 [23]. In contrast, physical activity may increase serum levels [22,24]. Irisin levels are inversely correlated with obesity, diabetes mellitus and GDM. Irisin precursors are expressed by the placenta. Mothers with GDM have significantly lower irisin levels than those without GDM [25]. FetuinA is a hepatokine associated with insulin resistance during pregnancy and is detected as an acute phase protein [26].

As shown in Table 1, the relevance of individual biomarkers has been established. However, the intricate interactions amongst and between biomarkers and compartments remain largely unknown. This pilot study intends to detect these interactions between the different lifestyle factors (nutrition and physical exercise) and relevant biomarkers. In order to do so, blood from the mother and the baby at the time of birth will be sampled from a vein and the umbilical cord respectively. Also, both their anthropometric data will be registered as well as the mother's lifestyle factors determined by means of retrospective questionnaire. The aim of the study is to examine the influence of maternal lifestyle clusters on maternal weight gain, birth weight and the underlying biomarkers.

2. Material and methods

2.1. Ethical consideration

We will conduct a pilot study in a cross-sectional cohort over a 5 month period at the German Sport University Cologne and the University Bonn Medical School, Germany. The protocol was submitted to the University Bonn Medical School Ethics Committee and approved under the number 269/13. Also, the following procedures will be followed: Participation in the study will only occur after reading the consent form and giving written consent. All women will be guaranteed the right to not participate in the study. The study will be carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). We will ensure confidentially of the collected data and document numbers (identifications).

2.2. Subjects and sample size

This study will include women who are admitted for delivery at the labor ward, Department of Obstetrics and Gynecology, University Bonn, with a singleton pregnancy and gestational age between 36 and 42 weeks who have given written consent. Women with multiple pregnancy, gestational age <36 weeks, the inability to speak German, mental illness and a high-risk pregnancy will be excluded from the study. The target sample size is 100 mothers and their newborns. Nearly all quantitative studies can be subjected to a sample size calculation. However, they may be of little value in early exploratory studies where scarce data are available on which to base the calculations (though this may be addressed by performing a pilot study first and using the data from that) [27].

2.3. Anthropometric and clinical data

Clinical data such as height or pregnancy related diseases are retrieved from the patients' antenatal and inpatient files. We will also consider aspects during pregnancy and relating to birth which may be important variables including: maternal age, parity, ethnicity, level of education, smoking and GDM during pregnancy,

Table 1
Selected cytokines during pregnancy (modified to D'Ippolito et al., 2012 [28]).

Cytokines	Leptin	Adiponectin	Resistin	IL-6	TNF-α	Irisin	BDNF	FetuinA
Maternal								
Circulating levels	↑	↓	↑ (3.Trim)	↑	↑ (3.Trim)	↑/↓	↑/↓	↑ (2.Trim)
Metaboliceffects	growth of adipose tissue	increases insulin activity and sensitivity; reduces glucose production	increases insulin resistance	?	reduces insulin sensitivity	negatively correlated with GDM	positively correlated with exercises	increases insulin resistance; acute phase protein; fat accumulation in liver
Fetal								
Umbilical level at term	↑	↑	↑	?	?	?	?	?
Function	increases: throphoblast-proliferation; IL-expression; VEGF-secretion; placental lipolysis (?)	decreases of transplacental insulin-mediated amino acid transport; enhancement fetal insulin sensitivity	increases hepatic glucose production; protect of neonatal hypoglycemia	Regulates hepatic immune response	increases placenta inflammation	?	?	negative regulation of neonatal bone development (?)

↑ = upregulation, ↓ = downregulation, ↑/↓ = upregulation as wall as downregulation possible, ? = currently no data available.

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