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# Maternal progesterone levels are modulated by maternal BMI and predict birth weight sex-specifically in human pregnancies

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ABSTRACT

*Objective:* Successful pregnancy outcome is the result of a tailored adaptation of the maternal endocrine and immune system throughout gestation. We aimed to investigate if maternal endocrine, anthropometric and life style factors assessed longitudinally throughout pregnancy allow prediction of birth weight.

*Study design:* Data on maternal factors and obstetrical characteristics from 220 pregnancies from a German prospective pregnancy cohort were analyzed using univariate and multivariate regression models. The association between maternal progesterone levels at the end of the 1st (gw 12–14), the 2nd (gw 22–24) and the 3rd trimester (gw 34–36) and birth weight of children born at term was examined. Interaction terms were included to identify possible sex-specific associations. Furthermore, associations between maternal and obstetric characteristics and progesterone levels were tested.

*Results:* After controlling for possible confounders, progesterone in the 2nd trimester emerged as an independent predictor for birth weight in pregnancies with female ($p = 0.01$), but not male fetuses ($p = 0.6$). In female fetuses each increase of progesterone by 1 ng/ml in the 2nd trimester was associated with an increase of birth weight by 6.8 g (95%-CI = 1.44–12.24). Maternal 1st trimester BMI showed a significant inverse correlation to progesterone levels throughout gestation ($p < 0.0001$ in the 1st and 2nd, $p = 0.01$ in the 3rd trimester). This inverse association between maternal BMI and progesterone levels was confined to overweight women.

*Conclusion:* Our data support that maternal progesterone levels have the potential to serve as early biomarker for reduced birth weight and underpins the importance of normal weight when entering the reproductive phase.

## 1. Introduction

Reduced birth weight constitutes a major risk factor for a wealth of diseases in postnatal life, including cardiovascular disease (Braus, 2015; Curhan et al., 1996; Johnson et al., 1993; Law and Shiell, 1996; Troisi et al., 2008), type 2 diabetes (Hartwig et al., 2013; Lithell et al., 1996; Pilgaard et al., 2011) obesity (Arck et al., 2008; Co et al., 2015; Curhan et al., 1996; Kabiru and Raynor, 2004; Martin et al., 2016) and chronic immune diseases such as allergies and asthma (Chatkin and Menezes, 2005; Cohen et al., 1983; Nepomnyaschy and Reichman, 2006). Reduced birth weight has also been identified as a predictor for increased neonatal mortality (Bergant et al., 1998; Chen et al., 2011; Cnattingius et al., 1998). Recent epidemiological observations underscore a discernible trend towards a decreased average birth weights in developed countries (Donahue et al., 2010; Ferré et al., 2010; Freeman et al., 1984).

It has been proposed that environmental and life style factors may negatively impact on maternal immune and endocrine adaptation to pregnancy, hereby resulting in poor placentation and impaired fetal growth (Arck and Hecher, 2013; Dickey and Hower, 1996), substantially leading to reduced birth weight. Pivotal part of the endocrine adaptation to pregnancy is the increase in progesterone (Hartwig et al., 2013; Piccinni, 2007; Szekeres-Bartho et al., 2001). In mice, reduced levels of progesterone resulted in placental insufficiency and fetal growth restriction (Reik et al., 2003; Solano et al., 2015).

In humans, low serum levels of progesterone during the 1st trimester have been associated with adverse pregnancy outcomes, such as miscarriage (Arck et al., 2008; McCord et al., 1996; Sood et al., 2006; Spiliopoulos and Economides, 2016). Moreover, progesterone supplementation in women with threatened preterm delivery induced a skew towards immune tolerance (Goh et al., 2016; Hudić et al., 2011; Stirrat et al., 2014).

However, there is ambiguity with regard to the published evidence on the association between gestational progesterone levels in

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pregnancy and birth weight. A positive association was reported by some authors (Hartwig et al., 2013; He et al., 2015; Lassance et al., 2015; Mucci et al., 2003), whereas others failed to confirm this (Braus, 2015; Curhan et al., 1996; Johnson et al., 1993; Law and Shiell, 1996; Troisi et al., 2008). However, insights currently available from such studies are largely based on a single assessment time points of progesterone levels during pregnancy. Moreover, stratification of data based on fetal sex was largely neglected. Using data from the prospective Berlin Pregnancy Cohort, our group previously showed that low levels of maternal progesterone taken from a single assessment during the 1st trimester were significantly associated with a reduction in birth weight exclusively in pregnancies with female fetuses (Hartwig et al., 2013; Lithell et al., 1996; Pilgaard et al., 2011).

With the present study, we aimed to overcome some of the limitations of previous studies, especially the single assessment time points. Thus, using data from a longitudinal study design, we investigated the association between maternal factors (endocrine, life style/stress perception, anthropometric indices) throughout all trimesters of pregnancy and birth weight of male and female newborns.

Since an increased BMI or high stress perception at the beginning of pregnancy is associated with an increased risk for pregnancy complications (Arck et al., 2008; Co et al., 2015; Curhan et al., 1996; Kabiru and Raynor, 2004; Martin et al., 2016), we also sought to evaluate whether maternal BMI or stress perception affect endocrine levels throughout pregnancy, primarily focusing on progesterone levels.

## 2. Materials and methods

### 2.1. Subjects and study design

A prospective pregnancy cohort was initiated the Department of Obstetrics and Fetal Medicine, University Medical Center in Hamburg in 2011. Inclusion criteria were maternal age of 18 years or higher and a viable pregnancy – confirmed by ultrasound – at gw 13–15. Women with chronic infections (HIV, hepatitis B/C), known drug or alcohol abuse, multiple pregnancies or pregnancies conceived after assisted reproductive technologies (ART), as well as pregnancies with fetal malformations were excluded. Three study visits were carried out at our Department, scheduled once per trimester (gw 12 + 0 to 14 + 6, 22 + 0 to 24 + 6 and 34 + 0 to 36 + 6).

### 2.2. Ethical approval

All study subjects signed informed consent forms and the study protocol was approved by the ethics committee of the Hamburg Chamber of Physicians and was conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects.

### 2.3. Assessment of pregnancy progression and maternal factors

During each study visit, data documentation included maternal anthropometry and psychometric assessments using standardized questionnaires. Stress perception was measured using a German version of the 14-item version of the Perceived Stress Scale (PSS) (Chatkin and Menezes, 2005; Cohen et al., 1983; Nepomnyaschy and Reichman, 2006). Symptoms of depression during pregnancy were evaluated with the validated German version of the 'Edinburgh Postnatal Depression Scale' (EPDS) (Bergant et al., 1998; Chen et al., 2011; Cnattingius et al., 1998). Both scales yield a sum score, which was subsequently used for analyses.

### 2.4. Assessment of pregnancy outcome

Information on pregnancy outcome (gw at delivery, delivery mode, child's sex and birth weight, cord-pH, APGAR-score) were obtained from a pre-stamped postcard, which was given to the pregnant women at the 2nd study visit. On this postcard, the occurrence of pregnancy complications (pregnancy-related hypertension, preeclampsia, HELLP-syndrome, gestational diabetes, preterm labor, miscarriage, preterm birth, infection during pregnancy, and others) could also be marked.

### 2.5. Progesterone and estradiol analyses

Blood was taken by venous puncture once per trimester at each study visit. Serum was harvested within 2–3 h via centrifugation (1100*g*/20 min), samples were stored at −80 °C until further use. Serum progesterone and estradiol concentrations were assayed by routine immunoassay on the ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostic Ltd, Germany) using direct chemiluminescence, according to the manufacturer's instructions at the institutional Center for Diagnostics, Department of Clinical Chemistry/Central Laboratories.

### 2.6. Statistical analyses

For descriptive data presentation, mean and standard deviations (SD) were calculated for continuous variables. Total numbers (n) and percentages were presented for categorical variables. Linear regression analyses was carried out as progesterone and birthweight are metric and the association was supposed to be linear. After exploring crude univariate associations, multivariate analyses for all three time points were tested and compared with regard to change in $R^2_{adj}$. The hypothesis was tested using a standard linear multiple regression model with progesterone as the independent and birth weight as the dependent variable under simultaneous consideration of the most important confounding variables according to our own data and the literature. These were: maternal age at birth, maternal 1st trimester BMI, smoking during pregnancy, gestational week at delivery, previous successful pregnancies, child's sex, and estradiol levels at the respective trimester. To test for sex-specific effects, an additional term for the child's sex and its' interaction with progesterone was included in the multivariate models. If a sex-specific effect was indicated, the analyses for the respective trimester were performed stratified by sex. With a second set of univariate and multivariate models potential associations between maternal and obstetric characteristics and progesterone at the different time points were explored. For this analysis, in addition to the above mentioned covariables, PSS- and EPDS-sum scores were considered. Finally, the stability of results was investigated. The evaluation of assumptions led to a transformation of progesterone values due to some outliers on the right (winzorising). Furthermore, progesterone values were centered when including the interaction with sex to avoid multicollinearity. Missing data were imputed by the Expectation-Maximation-Algorithm.

All tests were performed with a local two-tailed significance level of 0.05. All analyses were performed using the SPSS 22.0 regression and explore module.

## 3. Results

### 3.1. Characteristics of the study population

Characteristics of the study population, the psychometric assessments and the pregnancy outcome are shown in Table 1. As expected from published evidence (Donahue et al., 2010; Ferré et al., 2010; Freeman et al., 1984), our results show an increase in progesterone levels from 40.7 to 189.2 ng/ml throughout gestation (Table 1). Of interest, progesterone levels did not differ between groups of women with and without pregnancy complications ($p > 0.4$; Table 2).

### 3.2. Prediction of birth weight

Univariate prediction models for birth weight revealed no