Specific role of maternal weight change in the first trimester of pregnancy on birth size

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Introduction

Maternal prepregnancy body mass index (BMI) is strongly and positively associated with birthweight after accounting for gestational age (Kramer et al., 2002). When BMI before pregnancy is taken into account, maternal weight gain during pregnancy has an independent positive effect on birthweight (Heude et al., Kari, 2007, Kinnunen et al., 2003). High maternal prepregnancy BMI is associated with lower weight gain during pregnancy, which may in part be due to medical advice but may also indicate a regulation of gestational weight gain based on maternal fat stores at the start of pregnancy (Heude et al.). Maternal weight gain in early pregnancy is explained mainly by both an expansion of plasma volume and of fat stores to sustain fetal perfusion and nutrition throughout pregnancy (Bernstein et al., 2001, Naeye and Tafari, 1985). Maternal weight gain later in pregnancy is more influenced by fetal and placental weight increase and fluid retention. Therefore, maternal weight gain in the first trimester of pregnancy may have a specific effect on fetal growth. Few studies have focused on the pattern of weight gain during pregnancy, in relation with pregnancy outcomes. Abrahams et al. reported that each kilogram of maternal weight gain during the first and second trimesters was associated with an increase in birthweight (Abrams and Selvin, 1995). Neufeld et al. showed that maternal weight change from the first to the second trimester (between the 3rd and 6th month) was strongly associated with birth length, but not weight change between the 6th and 9th month, and concluded that mid-gestation may be a sensitive period for linear fetal growth (Neufeld et al., 2004).

Maternal weight change early in pregnancy may influence fetal growth through various mechanisms: quantitative and qualitative difference in energy intake and therefore an availability of nutrients for fetal and placental growth (Rosso, 1980, Abrams and Selvin, 1995); plasma volume expansion and fat storage in early pregnancy (Naeye and Tafari, 1985). On the other hand, obesity and vomiting in early pregnancy appear to be specifically related to maternal weight change in early pregnancy.

The aim of this study was to investigate the specific relationship between maternal weight change in the first trimester of pregnancy and fetal growth and birth size and to test whether this association could be mediated by placental placental growth.

Methods

Participants

Data were collected for mother-child pairs enrolled in the ongoing EDEN mother-child cohort (study of pre- and early postnatal determinants of child development and health), from University Hospitals in Nancy and Poitiers, France (Drouillet et al., 2008). Women attending their first prenatal visit before 24 weeks of gestation at these two maternity departments were invited to participate in this study. Enrolment in the study started in February and September 2003 in Poitiers and Nancy respectively, and lasted 27 months in each centre. Exclusion criteria were: multiple pregnancies, known pregestational diabetes, plans to move outside the region in the next three years, lack of ability to speak and read French. Among eligible women 55% (2002 women) accepted to participate (1 034 women in Nancy and 968 in Poitiers). The women and their offspring are being followed over five years.

Written consent was obtained for the mother and for her offspring after delivery. The EDEN study has been approved by the ethics committee (*Comité Consultatif pour la Protection des personnes dans la Recherche Biomédicale*) of Kremlin Bicêtre Hospital, and by the *Commission Nationale de l'Informatique et des Libertés* (*CNIL*).

Data collection

The mothers' prepregnancy weight and educational level were obtained by interview at inclusion. At 24-28 weeks of gestation, they answered a self-administered questionnaire and a clinical examination was performed by midwife research assistants. Maternal height was measured with a wall Seca 2006 stadiometer (Hamburg, Germany) to the nearest 0.2cm. Also during this clinical examination women's were weighed with an electronic scales Terraillon SL 351 (Hanson Ltd, United Kindom). Measures of fetal anthropometry (head circumference (HC), abdominal circumference (AC), biparietal diameter (BD), femoral length (FL)) were obtained from routine ultrasound of pregnancy monitoring at about 22 weeks, and 32 weeks of amenorrhea.

The same research assistants performed a second clinical examination, on average two days after delivery. The mother's weight was measured with the same protocol as above. The newborn were weighed using an electronic Seca scales (Hamburg, Germany: Seca 737 in

Nancy and Seca 335 in Poitiers) and birth length was measured with a wooden somatometer (Testut, Béthune, France).

Additional data were extracted from the maternity records: mother's weight measured and reported by clinicians at each prenatal visit (eight measures on average), parity and placental weight at birth. Placental weight was systematically recorded in Poitiers centre whereas in Nancy it tended to be more recorded in case of caesarean. Data on frequent vomiting in early pregnancy were obtained by questionnaire at recruitment. Data on cigarette use before pregnancy was obtained by questionnaire at 24-28 weeks of gestation and those for cigarette use during the third trimester of gestation were obtained by questionnaire in the post partum period.

Generated variables

Maternal education was categorised in three levels: "Before admission at university", "Admission at university" and "≥2 years after admission at university". We defined three categories of cigarette smoking: "never" for women who did not smoke both before and during pregnancy; "before pregnancy only" for women who smoked before but not during pregnancy; and "in pregnancy" for women who declared smoking during pregnancy. We estimated fetal weight (EFW) during the second and third trimester of gestation using the Hadlock formula based on four measures: head circumference, abdominal circumference, biparietal diameter, femoral length (Hadlock et al., 1985). Fetal growth between the second and the third trimester of pregnancy was estimated by calculating the EFW in the third trimester minus EFW in the second trimester. Also fetal growth between 6 months and delivery was calculated as birthweight minus EFW at 6 months. Large for gestational age (LGA) and small for gestational age (SGA) were defined as birthweights over the 90th percentile and below the 10th percentile, respectively, of French gestational age and gender specific reference curves (Mamelle et al., 1996). The newborn's ponderal index was computed as birthweight (kg) divided by birth length (m) cubed. Prepregnancy BMI was calculated as reported weight before pregnancy divided by height (m) squared. BMI categories were defined by: thin (BMI <18.5 kg/m^2), normal (BMI between 18.5 and 25 kg/ m^2), overweight (BMI between 25 and 30 kg/ m^2) and obese (BMI ≥30 kg/ m^2).

Population selection

From the 2002 mothers included in the EDEN study, we excluded 142 mother-child pairs with fewer than five measures of maternal weight during pregnancy. Among the mothers with at least five measures of weight during pregnancy we excluded 14 whose weight before pregnancy was missing. From the remaining mothers, we excluded from this analysis the 102 with preterm births, as weight change in the first trimester was not related to prematurity and preterm babies may have experienced specific situations which would have affected their growth in utero. Analyses were performed for 1744 mother-child pairs.

Estimation of weight change

In the EDEN study measures of women's weight through pregnancy were not obtained at the same gestational ages. Therefore, we would have many missing values if we studied weight change at given period during pregnancy. The important number of measures of women's weight at different times during pregnancy (8 measures on average) allowed us to have a precise estimation of women's weight at each week of gestation.

Maternal weight, at each week of gestation was estimated using a third-degree polynomial model, which included a subject random effect on the intercept, slope and curvature and based on women's weights measured during prenatal visits. When compared, the observed weight before pregnancy (mean ± standard deviation = 62.2±12.8, which was not included in the model) and the predicted weight (mean ± standard deviation = 62.3±12.7) were highly correlated (r=0.99). Thereafter we computed weight change at each trimester of pregnancy: for the first trimester (WCT1), predicted weight at 14 completed weeks minus predicted weight at start of gestation; for the second trimester (WCT2), predicted weight at 28 completed weeks minus predicted weight at 14 weeks; for the third trimester (WCT3), predicted weight at delivery (adjusted for gestational age) minus predicted weight at 28 weeks.

Statistical analysis

Characteristics of the mother and their newborns are described by means ± standard deviations and percentages (n). The evolution of the average weight of mothers during gestation was modelled within BMI strata. Associations between WCT1 and maternal characteristics (age, BMI, cigarette smoking, parity, education, frequent vomiting in early pregnancy and recruitment centre) were estimated with a linear regression model.

The associations between WCT1 and fetal growth and birth size were analysed in three steps

Firstly, the associations between WCT1 and fetal growth, birthweight, placental weight and birth length were analysed by linear models, with adjustment for recruitment centre, maternal age, education, prepregnancy BMI, maternal height, and additional adjustment for gestational age (gestational age at ultrasound for the EFW at the second and third trimester), cigarette smoking, parity and the newborn's gender. The relations between WCT1 and SGA and LGA were analysed with a logistic model with the same adjustments as before, except for gestational age and newborn gender.

In a second step, we adjusted for WCT2 and WCT3 to investigate whether the observed associations were independent of weight gain in later gestation.

In the final step, we selected the 1304 mother-child pairs for whom placental weight was available. Placental weight at delivery was considered to be a marker of placental growth and function. As used before in the EDEN study we adopted path analysis to investigate whether a causal relationship between WCT1 and birth size (birth weight and length) was mediated by the placenta (Regnault et al., 2011). **Figure 1** displays the model we postulated for birthweight. A single-headed arrow represents the direct effect of one variable on another, with a relation defined by a linear equation. We postulated that WCT1 might influence birthweight through placental function. In path models a given variable can be an explanatory variable in one equation and an outcome in another one. The assumption of normality is required for all variables that are influenced by at least one variable (Loehlin, 2004). Variables included in the model were pre-adjusted for variables that were significantly related with them, when considered in multivariable models (see legend of **Figure 1**). Path analyses allow an estimation of the indirect effects of a variable on an outcome (effects that are mediated by other variables) (Loehlin, 2004).

The conditions of validity of the path model were verified with some usual criteria: the hierarchical chi-square test (p value >0.05), the Goodness of Fit Index (GFI between 0.95 and 1), the Adjusted Goodness of Fit Index (AGFI between 0.95 and 1) and the Root Mean Square Error of Approximation (RMSEA <0.05) (Loehlin, 2004).

The different paths in the model (representing the relations between the different variables) can be associated with standardized partial correlation coefficients that are interpreted as coefficients of correlation between two variables when all the other variables are held constant.

The same approach was used to assess the potential mediation of the placenta in the association between WCT1 and birth length. We assessed whether the relations were different by recruitment centre, newborn gender, parity, BMI and cigarette smoking, and vomiting in early pregnancy. Also we investigated whether or not taking into account gestational diabetes and gestational hypertension modified or results.

For sensitivity analyses we have done the same investigations in subjects from Poitiers centre only where placental weight was systematically recorded.

All analyses used SAS software (version 9.2). In particular, the TCALIS procedure was used for path analyses.

Results

In a first step of our analysis we excluded women with less than five measures of weight during pregnancy. When we compared women who were included versus those who were excluded in term-births, those who were included declared less tabacco use before and during pregnancy (p=0.006) and had a higher study level (p=0.02).

In a second step, we excluded mother-child paires whose placental weight at delivery was not available. About 94% of women from Poitiers centre had a measure of placental weight versus 43% for those from Nancy centre. In term-births, women without a measure placental weight were more frequently diagnosed for gestational hypertension and had a higher study level. Whereas birth weight and birth length were higher in those whose placental weight was measured (**table 1 in** supplementary on-line information). These differences were due to differences in these characteristics between study centres. Women from Nancy were more frequently diagnosed for gestational hypertension (5.6% versus 2.8%, p=0.005) and had a higher educational level (p<0.0001). Whereas offspring's mean birth weight and height were higher in Poitiers centre (p=0.007).

The mean weight gain of mothers in the first trimester was 3.3kg and they gained 13.6kg on average during pregnancy (**Table 1**). The proportion of women with frequent vomiting in early pregnancy was 23.6%. **Figure 2** illustrates a sigmoid curve for weight during pregnancy. Thin and normal weight women gained more weight during pregnancy. WCT1 was positively associated with maternal age whereas there was a negative association with maternal prepregnancy BMI (**Table 2**). Women from the Poitiers centre gained more weight in the first trimester than those from Nancy. Women who smoked before pregnancy only and those who were still smoking during pregnancy gained more weight in the first trimester. Educational level was negatively associated with WCT1. Frequent vomiting in early pregnancy was associated with a lower WCT1 (**Table 2**).

When adjusted for maternal and pregnancy characteristics (recruitment centre, maternal age, educational, prepregnancy BMI, maternal height, gestational age, cigarette smoking, parity, the newborn's gender), WCT1 was positively associated with fetal growth (EFW at second and third trimester, and change in EFW from second to third trimester, change in EFW between third trimester and delivery and placental weight) (**Table 3**). Further, WCT1 was positively associated with birthweight, birth length and risk of LGA, with a negative relation with risk of SGA. These associations remained significant when further adjusted for WCT2 and WCT3 (**Table 3**).

Figure 1 displays the path diagram depicting the direct associations between prepregnancy BMI, WCT1, WCT2, WCT3 and placental weight and their direct association with birthweight. The total, direct and indirect associations are reported in **Table 4**.

Results of path analysis showed that prepregnancy BMI was negatively associated with WCT1 ($r = -0.30$) and WCT2 ($r = -0.20$) while it was positively associated with WCT3 ($r = 0.13$, $p < 0.0001$). According to the postulated path diagram, prepregnancy BMI was also independently associated with placental weight (r= 0.18) and birthweight (r= 0.11, p <0.0001).

WCT1 was not independently associated with birthweight, but a significant indirect association was found (r= 0.10, p <0.0001) (**Table 4**). WCT1 was directly associated with placental weight (r= 0.10, p=0.002), which in turn was independently associated with birthweight (r= 0.52). There was a direct association between WCT1 and WCT2 (r= 0.28), which was independently associated with birthweight (r= 0.13, p <0.0001) and had a small direct association with placental weight (r= 0.07, p = 0.03).

There was only a weak association between WCT3 and birthweight (r= 0.06, p =0.03). As there was no direct association between WCT3 and placental weight, this path was removed from the model.

The associations with birth length in place of birthweight were similar to that observed for birthweight (**Figure 1 and table 2 in** supplementary on-line information). However a small independent association between WCT1 and birth length was observed (r= 0.07, p =0.01).

In summary WCT1 influenced birthweight and birth length mainly through its effects on placental weight and WCT2.

Further adjustment for gestational diabetes and gestational hypertension did not change the association between WCT1 and newborn anthropometry. When the same analyses were restricted to Poitiers centre where placental weight was systematically measured for sensitivity analyses, the same results were observed.

Discussion

Weight change in the first trimester was associated with fetal growth and birth size even when weight changes in later gestation were taken into account. Results of path analysis showed that the relation between weight change in the first trimester and birth size was in part mediated by placental weight at birth, which we used as a proxy of placental growth and function. As women in our study centres appeared to be quite different and that placental weight was systematically recorded in Poitiers centre but not in Nancy, we restricted our analysis to women in Poitiers centre and observed similar results. No difference in weight gain during the first trimester was observed between women who had a measure of placental weight (3.3g) and those without a measure of placental weight (3.2kg, p=0.7).

Weights at each week of gestation were estimated based on measures of weight during pregnancy (eight on average). Previous studies used piecewise linear regression models to estimate weight change at each trimester of pregnancy from measured weights during pregnancy (Abrams, 1995, Carmichael et al., 1997). In our study a polynomial model and three degrees was adequate, as the quadratic term was not significant. The important number of measures of women's weight (eight measures on average) at different moments of pregnancy in the EDEN study allowed a precise estimation of women's weight at each week of gestation. To verify that our model gave good estimations of women's weights during pregnancy, we compared women's reported prepregnancy weight (mean= 62.2kg ±12.8kg, which was not included in our model) to women's prepregnancy weight obtained with the model (mean=62.3kg ±12.7). These two measures were comparable and highly correlated (r=0.99). The same verification was done with women's weight measured between 24 and28 weeks (25th week on average) and women's weight at 25 weeks of gestation obtained with our model. The two measures were also comparable and highly correlated. Thereafter we added women's weight measured between 24 and 28 weeks of gestation to our model to reduce the number of women with less than 5 measures of weight in our sample.

In this study weight change in the first trimester is considered as an indicator of women’s nutritional status in early pregnancy. One may argue that, due to physiological changes in early pregnancy, weight change in the first trimester of pregnancy may not fully reflect the women’s nutritional status. However the physiological changes in early pregnancy are related to women’s nutrition status. The choice of the first trimester as a limit of the early pregnancy period may be found arbitrary. However it is more common to adopt the limits of different trimesters as different stages of pregnancy. Also, it would have been interesting to have a longitudinal model of repeated measurements of fetal biometry, but since we had only two fetal measurements during pregnancy, this was not possible in this study. The use of birthweight minus estimated fetal weight at 6th month of pregnancy as an indicator of fetal growth may be weakened by the fact that the error of measurement of brithweight may be different to the error of measurement of fetal size by ultrasound (errors related to the use of ultrasound).

The relation between WCT1 and birthweight and birth length may be explained by several mechanisms: an adequate placental development which in turn influences fetal growth; fat storage in early pregnancy and its later release for fetal growth; an availability of macronutrients and micronutrients for early fetal growth.

The mother provides oxygen, nutrients, hormones, and antibodies to the foetus via the placenta, and the end products of fetal metabolism are removed via the placenta. Placental weight at delivery is positively correlated with the newborn’s weight but the maximal growth of the placenta precedes that of the foetus. Its growth rate is initially greater than that of the fetus (Thame et al., 2004). A small placenta usually alters fetal growth (Belkacemi et al.). Maternal nutrition is associated with placental weight (Belkacemi et al., 2010) and a reduction in maternal nutrition in early pregnancy may alter placental growth and birth weight. In our study, maternal weight gain (used as a proxy of nutritional state) in the first trimester influenced placental weight at delivery. Thame et al. found that placental volume at 14 weeks of gestation and the rate of placental growth between 17 weeks and 20 weeks were significantly associated with fetal measurement at 35 weeks, even when placental volume at 24 weeks was added to the model (Thame et al., 2004). The rapid growth of the placenta early in pregnancy is important to supply nutrients necessary for fetal growth. All these findings confirm the hypothesis that placental volume and placental growth are influenced by maternal nutrition in early pregnancy, and in turn, also contribute to fetal growth.

Plasma volume expansion in early pregnancy was identified as an important factor of weight gain in early pregnancy and particularly necessary for fetal growth. Abrahams et al. suggested that a low plasma volume expansion might limit uteroplacental flow, reducing the transfer of nutrients to support fetal growth (Abrams and Selvin, 1995).

Neufeld et al. reported that weight change between the 3^{rd} and 6^{th} month of gestation had a positive effect on linear fetal growth and not weight change from 6 to 9 months of gestation (Neufeld et al., 2004). In our study we found an effect of WCT1 on birth length independently of placental weight suggesting that the influence of weight change in early pregnancy on birth length may begin early in the first three months but this independent effect of WCT1 on birth length was small. Weight change in the first trimester may reflect energy intake at this stage of pregnancy and therefore correspond to an availability of nutrients that supply fetal growth even in the earliest stage of the first trimester, before the contact between the embryo and maternal blood via the placenta (Burton et al., 2007). It has been suggested that endometrial-decidual glands are sources of nutrients for the embryo, the endometrium contains large accumulations of glycogen that are greatest close to the materno-fetal interface (Burton et al., 2007). The endometrial-decidual glands have also been identified as a source of growth factors such as the epidermal growth factor (Burton et al., 2007, Hempstock et al., 2004) which stimulates cytotrophoblast cell proliferation which represents the materno-fetal interface during early pregnancy (Hamilton and Boyd, 1960).

Studies suggested that weight change in the first trimester may influence fetal growth through fat storage in early pregnancy. There is a specific pattern of fat deposition during pregnancy (Taggart et al., 1967). Starting from early pregnancy fat appears to be deposited preferentially over the hips, back, and upper thighs. Fat stored in early pregnancy is released for fetal growth as pregnancy advances (Naeye and Tafari, 1985).

Studies reported that total pregnancy weight gain is negatively associated with prepregnancy BMI (Diouf et al., 2011). To our knowledge the pattern of weight gain (through the trimesters of pregnancy) in association with prepregnancy BMI has not been reported before. We found that prepregnancy BMI was negatively associated with weight gain in the first and second trimesters of pregnancy, but it was positively associated with weight gain in the third trimester. Weight change in the first trimester seemed to be a result of physiologic adptations to the mothers' periconceptional fat. The lower weight gain during the first trimester in mothers with higher BMI did not impact on fetal growth. Women's with higher BMI have sufficient nutrient availability to support fetal and placental growth. BMI before pregnancy had significant independent effects on the newborn and placental weights (Kramer et al., 2002).

An excessive weight gain during pregnancy is associated with adverse pregnanacy outcomes (caesarean sections, gestational hypertension, macrosomia) (Crane et al., 2009). Conversely women who gained less than the recommended weight gain have higher risks of preeclampsia, caesarean sections, macrosomia, and low birth weight (Langford et al., 2009). In this study we found that weight change in the first trimester of pregnancy was associated with fetal growth and risk of large for gestational age. We did not found any association between weight change in the first trimester of pregnancy and adverse pregnancy outcomes like gestational diabetes, gestational hypertension or risk of caesarean sections. If these results are confirmed, the monitoring of weight change in early pregnancy may be considered by clinicians as an important factor in the management of fetal growth without threatened effect on women's health.

In this study we found that frequent vomiting in early pregnancy was associated with poor weight gain in the first trimester. Other studies also reported that vomiting in early pregnancy is associated with weight loss in early pregnancy (Heude et al., Kari, 2007, Kinnunen et al., 2003). When compared to infants of mothers who gained weight in early pregnancy, infants of mothers who lost weight in early pregnancy were found to more often have poor fetal growth and to be SGA (Niebyl, 2010). In our study, we did not find a statistically significant relationship between weight loss in the first three months of gestation and risk of SGA.

Conclusion

Weight change during the first weeks of pregnancy seems to impact on fetal growth, independently of later weight changes during pregnancy. Weight change in early pregnancy and placental growth appeared as two related indicators of adequate adaptation to pregnancy to support fetal growth. Weight change in early pregnancy may participate in fetal growth and placental function.

References

Abrams, B, Carmichael S., Selvin S. (1995) Factors associated with the pattern of Maternal Weight gain during Pregnancy *Obstetrics & Gynecology*, 170-176.

Abrams, B & Selvin, S (1995) Maternal weight gain pattern and birth weight. *Obstet Gynecol* **86,** 163-169.

Belkacemi, L, Nelson, DM, Desai, M & Ross, MG (2010) Maternal undernutrition influences placental-fetal development. *Biology of Reproduction* **83,** 325-331.

Bernstein, IM, Ziegler, W & Badger, GJ (2001) Plasma volume expansion in early pregnancy. *Obstet Gynecol* **97,** 669-672.

Burton, GJ, Jauniaux, E & Charnock-Jones, DS (2007) Human early placental development: potential roles of the endometrial glands. *Placenta* **28 Suppl A,** S64-69.

Carmichael, S, Abrams, B & Selvin, S (1997) The pattern of maternal weight gain in women with good pregnancy outcomes. *Am J Public Health* **87,** 1984-1988.

Crane JM, White J, Murphy P, Burrage L, Hutchens D (2009) The effect of gestational weight gain by body mass index on maternal and neonatal outcomes. *J Obstet Gynaecol Can* **31***,* 28-35.

Diouf, I, Charles, MA, Blondel, B, Heude, B & Kaminski, M (2011) Discordant time trends in maternal body size and offspring birthweight of term deliveries in France between 1972 and 2003: data from the French National Perinatal Surveys. *Paediatr Perinat Epidemiol* **25,** 210-217.

Drouillet, P, Forhan, A, De Lauzon-Guillain, B, Thiebaugeorges, O, Goua, V, Magnin, G, et al. (2008) Maternal fatty acid intake and fetal growth: evidence for an association in overweight women. The 'EDEN mother-child' cohort (study of pre- and early postnatal determinants of the child's development and health). *Br J Nutr*, 1-9.

Hadlock, FP, Harrist, RB, Sharman, RS, Deter, RL & Park, SK (1985) Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol* **151,** 333-337.

Hamilton, WJ & Boyd, JD (1960) Development of the human placenta in the first three months of gestation. *Journal of Anatomy* **94,** 297-328.

Hempstock, J, Cindrova-Davies, T, Jauniaux, E & Burton, GJ (2004) Endometrial glands as a source of nutrients, growth factors and cytokines during the first trimester of human pregnancy: a morphological and immunohistochemical study. *Reprod Biol Endocrinol* **2,** 58.

Heude, B, Thiebaugeorges, O, Goua, V, Forhan, A, Kaminski, M, Foliguet, B, et al. Pre-Pregnancy Body Mass Index and Weight Gain During Pregnancy: Relations with Gestational Diabetes and Hypertension, and Birth Outcomes. *Matern Child Health J.*

Kari, YL, Stephan Rössner, Martin Neovius (2007) Maternal predictors of birthweight : the importance of weight gain during pregnancy. *Obesity Research & Clinical Practice* **1,** 243-252.

Kinnunen, TI, Luoto, R, Gissler, M & Hemminki, E (2003) Pregnancy weight gain from 1960s to 2000 in Finland. *Int J Obes Relat Metab Disord* **27,** 1572-1577.

Kramer, MS, Morin, I, Yang, H, Platt, RW, Usher, R, McNamara, H, et al. (2002) Why are babies getting bigger? Temporal trends in fetal growth and its determinants. *J Pediatr* **141,** 538-542.

Langford A, Joshu C, Chang JJ, Myles T, Leet T (2011) Does gestational weight gain affect the risk of adverse maternal and infant outcomes in overweight women? *Matern Child Health J.* **7**, 860-865.

Loehlin, JC (2004) *Latent variable models: An introduction to factor, path, and structural equation analysis.* Laurence Erlbaum Associates, Inc., Mahwah, New Jersey.

Mamelle, N, Munoz, F & Grandjean, H (1996) [Fetal growth from the AUDIPOG study. I. Establishment of reference curves]. *J Gynecol Obstet Biol Reprod (Paris)* **25,** 61-70.

Naeye, RL & Tafari, N (1985) Biologic bases for international fetal growth curves. *Acta Paediatrica Scandinavica. Supplement* **319,** 164-169.

Neufeld, LM, Haas, JD, Grajeda, R & Martorell, R (2004) Changes in maternal weight from the first to second trimester of pregnancy are associated with fetal growth and infant length at birth. *Am J Clin Nutr* **79,** 646-652.

Niebyl, JR (2010) Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med* **363,** 1544-1550.

Regnault, N, Botton, J, Heude, B, Forhan, A, Hankard, R, Foliguet, B, et al. (2011) Higher Cord C-Peptide Concentrations Are Associated With Slower Growth Rate in the 1st Year of Life in Girls but Not in Boys. *Diabetes* **60,** 2152-2159.

Rosso, P (1980) Placental growth, development, and function in relation to maternal nutrition. *Federation Proceedings* **39,** 250-254.

Taggart, NR, Holliday, RM, Billewicz, WZ, Hytten, FE & Thomson, AM (1967) Changes in skinfolds during pregnancy. *Br J Nutr* **21,** 439-451.

Thame, M, Osmond, C, Bennett, F, Wilks, R & Forrester, T (2004) Fetal growth is directly related to maternal anthropometry and placental volume. *Eur J Clin Nutr* **58,** 894-900.

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Conflict of interest

The authors declare that they have no conflicts of interest

Figure legends

Figure 1: Path diagram depicting the relations between prepregnancy body mass index, weight changes in pregnancy, placental weight and birthweight.

P value codes: *** <0.0001, ** 0.0001-0.001, * 0.001-0.05

BMI= body mass index; WCT1, WCT2 and WCT3= weight changes in the first, the second and the third trimesters.

Variables in the model were pre-adjusted for characteristics which remained significantly associated with them when included in multivariate linear model among: recruitment centre, maternal age, education, maternal height, gestational age, cigarette smoking, parity, newborn gender.

Figure 2: The average weight of mothers during gestation, within body mass index strata.

Table 1: Characteristics, mean ± Standard deviation or % (frequency); of mothers and newborn.

	n	**Mean ± SD***
Age (years)	1744	29.0 ± 4.9
Height (cm)	1726	163.5 ± 6.1
Prepregnancy weight (kg)	1744	62.2 ± 12.8
Body mass index (kg/m^2)	1726	23.2 ± 4.6
Pregnancy weight gain (kg)	1717	13.6 ± 4.7
Weight gain in the first trimester (kg)	1744	3.30 ±2.48
Weight gain in the second trimester (kg)	1744	6.8 ± 2.1
Weight gain in the third trimester (kg)	1744	4.5 ± 2.3
Frequent vomiting in early pregnancy (% (n))	1724	23.6 (406)
Educational level (% (n))	1720	
1 (Before admission at university)		28.2 (485)
2 (Admission at university)		17.9 (308)
3 (≥2 years after admission at university)		53.9 (927)
Cigarette smoking (% (n))	1725	
Never		62.8 (1084)
Before pregnancy only		20.8 (358)
During pregnancy		16.4 (283)
Recruitment centre (%(n))	1744	
Poitiers		48.5 (846)
Nancy		51.5 (898)
Parity (%(n))	1744	
0		32.2 (562)
1		33.8 (590)
≥2		33.9 (592)
Gestational age (weeks)	1744	39.5 ± 1.2
Birthweight (g)	1740	3340 ± 438
Birth length (cm)	1715	49.8 ± 2.1
Small for gestational age (%(n))	1740	7.9 (139)
Large for gestational age (%(n))	1740	8.6 (149)

*standard deviation

Table 2: Mothers weight gain (kg) during the first trimester of pregnancy according to her characteristics, estimated by linear regression models.

Parameter	**Beta±SE***	***P* value**
Age (years)	0.04 ± 0.01	0.005
Body mass index (kg/m^2)	-0.16 ± 0.01	<.0001
Cigarette smoking		<0.0001
Never	-0.76 ± 0.16	
Before pregnancy only	0.12 ± 0.19	
During pregnancy	reference	
Parity		0.34
0	-0.13 ± 0.16	
1	-0.21 ± 0.14	
≥2 (reference)	reference	
Educational level		<.0001
1 (Before admission at university)	0.72 ± 0.14	
2 (Admission at university)	0.30 ± 0.16	
reference		
Vomiting in early pregnancy		0.0008
Not frequent	0.45 ± 0.13	
Frequent	reference	
Recruitement centre		0.002
Poitiers	0.36 ± 0.11	
Nancy	reference	

*standard error

Table 3: Newborn characteristics for a one kg change in weight during the first trimester of pregnancy (WCT1), before and after adjustment for weight change in the second and third trimesters of pregnancy (WCT2 and WCT3). Results are from separate linear and logistic models.

	Before adjustment for WCT2 and WCT3		**Further adjustment for WCT2 and WCT3**	
	Beta ± se*	P value	Beta ± se	P value
Estimated fetal weight at 20-24 weeks (g)	1.26 ± 0.64	0.05	1.47 ± 0.65	0.02
Change in estimated fetal weight from 20-24 to 30-34 (g)	9.53 ± 2.66	0.0003	7.86 ± 2.72	0.004
Estimated fetal weight at 30-34 weeks (g)	12.78 ± 2.57	<0.0001	11.24 ± 2.63	<0.0001
Change in Estimated fetal weight from 30-34 weeks to birth (g)	11.17 ± 4.10	0.006	6.07 ± 4.16	0.14
Birthweight (g)	24.19 ± 3.98	<0.0001	17.74 ± 4.02	<0.0001
Birth length (cm)	0.09 ± 0.02	<0.0001	0.07 ± 0.02	0.0001
Ponderal index † (kg/m^3)	0.05 ± 0.028	0.07	0.03 ± 0.03	0.31
Placental weight (g)	5.30 ± 1.40	0.0001	4.76 ± 1.45	0.001
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Small for gestational age	0.86 (0.79-0.94)	0.0004	0.90 (0.82-0.97)	0.005
Large for gestational age	1.13 (1.06 -1.21)	0.0005	1.10 (1.03 -1.19)	0.008

Adjustment for recruitment centre, maternal age, education, prepregnancy body mass index, maternal height, gestational age, cigarette smoking, parity, newborn gender

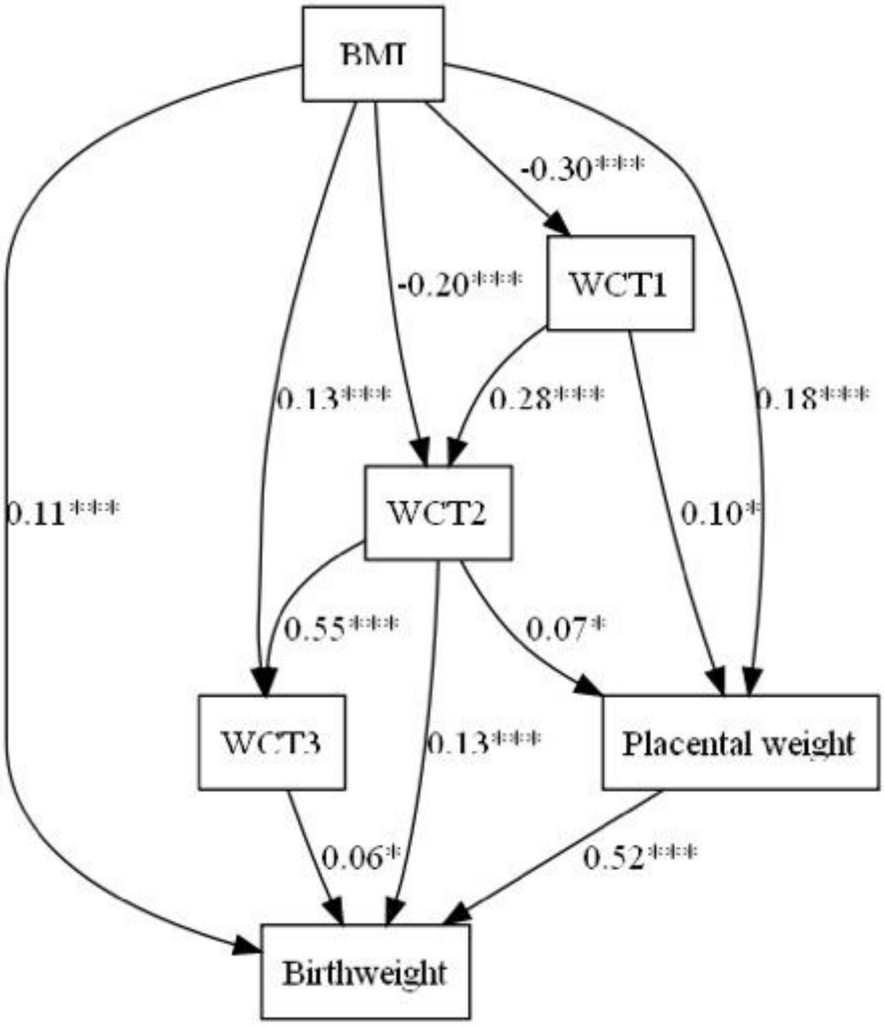
*se= standard error

†Ponderal index= [(birthweight (kg)] / [birth length (cm)]^3)

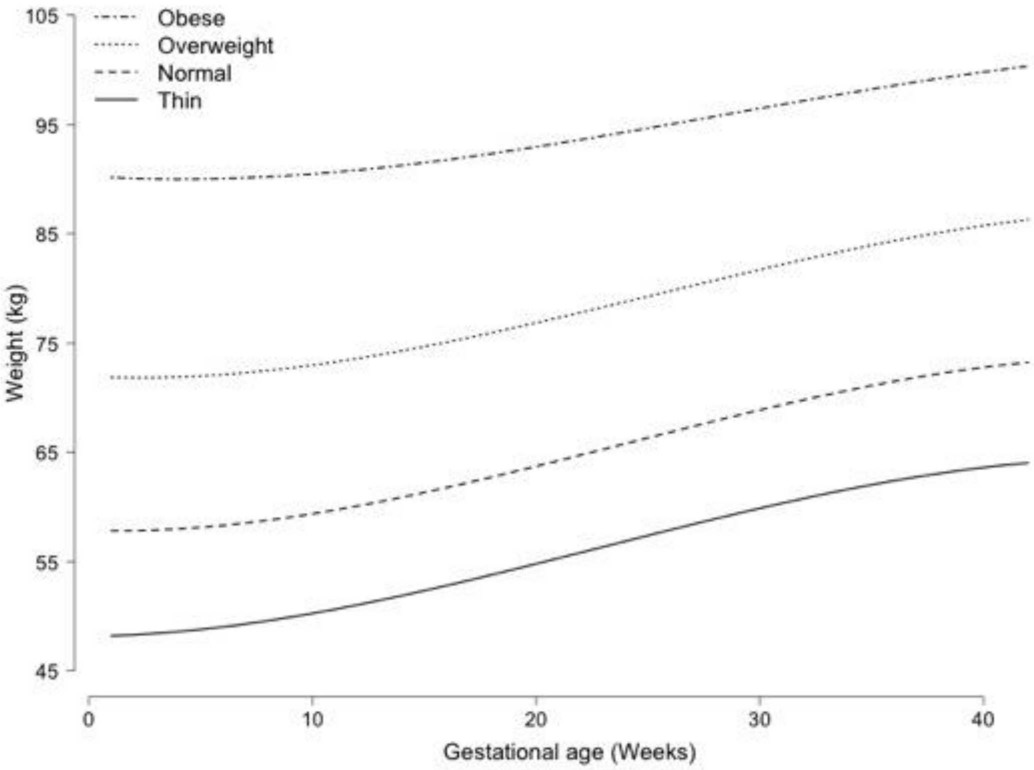
Table 4: Total, direct and indirect associations of maternal anthropometry and placental weight on birthweight.

		Total	Direct	Indirect
Prepregnancy Body mass index	Standardized beta	0.14	0.11	0.03
	Standard Error	0.03	0.02	0.02
	P-value	<0.0001	<0.0001	0.11
Weight change in the first trimester	Standardized beta	0.10		0.10
	Standard Error	0.02	0	0.02
	P-value	<0.0001		<0.0001
Weight change in the second trimester	Standardized beta	0.20	0.13	0.08
	Standard Error	0.03	0.03	0.02
	P-value	<0.0001	0	0.002
Weight change in the third trimester	Standardized beta	0.06	0.06	
	Standard Error	0.03	0.03	0
	P-value	0.03	0.03	
Placental weight	Standardized beta	0.52	0.52	
	Standard Error	0.02	0.02	0
	P-value	<0.0001	<0.0001	

*Standardized betas are interpretable as correlation coefficients



BMI
-0.30***
WCT1
-0.20***
0.13***
0.28***
0.18***
WCT2
0.11***
0.10*
0.55***
0.07*
WCT3
0.13***
Placental weight
0.06*
0.52***
Birthweight



105
95
85
75
65
55
45
Weight (kg)
Obese
Overweight
Normal
Thin
0
10
20
30
40
Gestational age (Weeks)