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

Ibrahima Diouf, Jérémie Botton, Marie Aline Charles, Olivier Morel, Anne Forhan, Monique Kaminski, Barbara Heude

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

3 Ibrahima Diouf,<sup>1,2</sup> Jérémie Botton,<sup>1</sup> Marie Aline Charles,<sup>1,2</sup> Olivier Morel,<sup>3</sup> Anne Forhan,<sup>1,2</sup>  
4 Monique Kaminski,<sup>4,5</sup> Barbara Heude,<sup>1,2</sup> and the EDEN Study Group

5 **Authors' affiliations**

6 <sup>1</sup>INSERM, CESP Centre for Research in Epidemiology and Populations Health, U1018 Team 10  
7 "Lifelong epidemiology of obesity, diabetes and chronic renal disease", F-94807, Villejuif,  
8 France; <sup>2</sup>Univ Paris-Sud 11, UMRS 1018, F-94807, Villejuif, France; <sup>3</sup>Regional Maternity,  
9 University of Nancy; <sup>4</sup>INSERM, UMRS 953, Epidemiological research on perinatal health and  
10 women's and children's health, F-94807 Villejuif, France; <sup>5</sup>UPMC Univ Paris 06, F-75005,  
11 Paris, France.

12 Constitution of the EDEN Mother-child cohort study group : MA Charles, M de Agostini, A  
13 Forhan, B Heude, P Ducimetière, M Kaminski, MJ Saurel-Cubizolles, P Dargent, X Fritel, B  
14 Larroque, N Lelong, L Marchand, C Nabet, I Annesi-Maesano, R Slama, V Goua, G Magnin, R  
15 Hankard, O Thiebaugeorges, M Schweitzer, B Foliguet, N Job-Spira

16 *Corresponding author*

17 Ibrahima Diouf

18 INSERM U1018 16 Avenue Paul Vaillant Couturier

19 94807 Villejuif cedex, FRANCE

20 Tel: +33 1 45 59 51 01 Fax: +33 1 47 26 94 54

21 [ibrahima.diouf@inserm.fr](mailto:ibrahima.diouf@inserm.fr)

22 **Running head** : Weight change in the first trimester and birth size

23

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29 Anne Forhan: conducted research

30 Barbara Heude: had primary responsibility for final content

31

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35

## 36 **Introduction**

37 Maternal prepregnancy body mass index (BMI) is strongly and positively associated with

38 birthweight after accounting for gestational age (Kramer et al., 2002). When BMI before

39 pregnancy is taken into account, maternal weight gain during pregnancy has an independent

40 positive effect on birthweight (Heude et al., Kari, 2007, Kinnunen et al., 2003). High maternal

41 prepregnancy BMI is associated with lower weight gain during pregnancy, which may in part

42 be due to medical advice but may also indicate a regulation of gestational weight gain based

43 on maternal fat stores at the start of pregnancy (Heude et al.). Maternal weight gain in early

44 pregnancy is explained mainly by both an expansion of plasma volume and of fat stores to

45 sustain fetal perfusion and nutrition throughout pregnancy (Bernstein et al., 2001, Naeye

46 and Tafari, 1985). Maternal weight gain later in pregnancy is more influenced by fetal and

47 placental weight increase and fluid retention. Therefore, maternal weight gain in the first  
48 trimester of pregnancy may have a specific effect on fetal growth. Few studies have focused  
49 on the pattern of weight gain during pregnancy, in relation with pregnancy outcomes.  
50 Abrahams et al. reported that each kilogram of maternal weight gain during the first and  
51 second trimesters was associated with an increase in birthweight (Abrams and Selvin,  
52 1995). Neufeld et al. showed that maternal weight change from the first to the second  
53 trimester (between the 3<sup>rd</sup> and 6<sup>th</sup> month) was strongly associated with birth length, but not  
54 weight change between the 6<sup>th</sup> and 9<sup>th</sup> month, and concluded that mid-gestation may be a  
55 sensitive period for linear fetal growth (Neufeld et al., 2004).

56 Maternal weight change early in pregnancy may influence fetal growth through various  
57 mechanisms: quantitative and qualitative difference in energy intake and therefore an  
58 availability of nutrients for fetal and placental growth (Rosso, 1980, Abrams and Selvin,  
59 1995); plasma volume expansion and fat storage in early pregnancy (Naeye and Tafari,  
60 1985). On the other hand, obesity and vomiting in early pregnancy appear to be specifically  
61 related to maternal weight change in early pregnancy.

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

## 65 **Methods**

### 66 **Participants**

67 Data were collected for mother-child pairs enrolled in the ongoing EDEN mother-child  
68 cohort (study of pre- and early postnatal determinants of child development and health),  
69 from University Hospitals in Nancy and Poitiers, France (Drouillet et al., 2008). Women  
70 attending their first prenatal visit before 24 weeks of gestation at these two maternity

71 departments were invited to participate in this study. Enrolment in the study started in  
72 February and September 2003 in Poitiers and Nancy respectively, and lasted 27 months in  
73 each centre. Exclusion criteria were: multiple pregnancies, known pregestational diabetes,  
74 plans to move outside the region in the next three years, lack of ability to speak and read  
75 French. Among eligible women 55% (2002 women) accepted to participate (1 034 women in  
76 Nancy and 968 in Poitiers). The women and their offspring are being followed over five  
77 years.

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

## 82 **Data collection**

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

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

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

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

#### 105 **Generated variables**

106 Maternal education was categorised in three levels: "Before admission at university",  
107 "Admission at university" and "≥2 years after admission at university". We defined three  
108 categories of cigarette smoking: "never" for women who did not smoke both before and  
109 during pregnancy; "before pregnancy only" for women who smoked before but not during  
110 pregnancy; and "in pregnancy" for women who declared smoking during pregnancy. We  
111 estimated fetal weight (EFW) during the second and third trimester of gestation using the  
112 Hadlock formula based on four measures: head circumference, abdominal circumference,  
113 biparietal diameter, femoral length (Hadlock et al., 1985). Fetal growth between the second  
114 and the third trimester of pregnancy was estimated by calculating the EFW in the third  
115 trimester minus EFW in the second trimester. Also fetal growth between 6 months and  
116 delivery was calculated as birthweight minus EFW at 6 months. Large for gestational age  
117 (LGA) and small for gestational age (SGA) were defined as birthweights over the 90th  
118 percentile and below the 10th percentile, respectively, of French gestational age and gender

119 specific reference curves (Mamelle et al., 1996). The newborn's ponderal index was  
120 computed as birthweight (kg) divided by birth length (m) cubed. Prepregnancy BMI was  
121 calculated as reported weight before pregnancy divided by height (m) squared. BMI  
122 categories were defined by: thin (BMI <18.5 kg/m<sup>2</sup>), normal (BMI between 18.5 and 25 kg/  
123 m<sup>2</sup>), overweight (BMI between 25 and 30 kg/ m<sup>2</sup>) and obese (BMI ≥30 kg/ m<sup>2</sup>).

#### 124 ***Population selection***

125 From the 2002 mothers included in the EDEN study, we excluded 142 mother-child pairs  
126 with fewer than five measures of maternal weight during pregnancy. Among the mothers  
127 with at least five measures of weight during pregnancy we excluded 14 whose weight before  
128 pregnancy was missing. From the remaining mothers, we excluded from this analysis the  
129 102 with preterm births, as weight change in the first trimester was not related to  
130 prematurity and preterm babies may have experienced specific situations which would have  
131 affected their growth in utero. Analyses were performed for 1744 mother-child pairs.

#### 132 ***Estimation of weight change***

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

138 Maternal weight, at each week of gestation was estimated using a third-degree polynomial  
139 model, which included a subject random effect on the intercept, slope and curvature and  
140 based on women's weights measured during prenatal visits. When compared, the observed  
141 weight before pregnancy (mean ± standard deviation = 62.2±12.8, which was not included in  
142 the model) and the predicted weight (mean ± standard deviation = 62.3±12.7) were highly

143 correlated ( $r=0.99$ ). Thereafter we computed weight change at each trimester of pregnancy:  
144 for the first trimester (WCT1), predicted weight at 14 completed weeks minus predicted  
145 weight at start of gestation; for the second trimester (WCT2), predicted weight at 28  
146 completed weeks minus predicted weight at 14 weeks; for the third trimester (WCT3),  
147 predicted weight at delivery (adjusted for gestational age) minus predicted weight at 28  
148 weeks.

### 149 **Statistical analysis**

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

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

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

165 In the final step, we selected the 1304 mother-child pairs for whom placental weight was  
166 available. Placental weight at delivery was considered to be a marker of placental growth  
167 and function. As used before in the EDEN study we adopted path analysis to investigate  
168 whether a causal relationship between WCT1 and birth size (birth weight and length) was  
169 mediated by the placenta (Regnault et al., 2011). **Figure 1** displays the model we postulated  
170 for birthweight. A single-headed arrow represents the direct effect of one variable on  
171 another, with a relation defined by a linear equation. We postulated that WCT1 might  
172 influence birthweight through placental function. In path models a given variable can be an  
173 explanatory variable in one equation and an outcome in another one. The assumption of  
174 normality is required for all variables that are influenced by at least one variable (Loehlin,  
175 2004). Variables included in the model were pre-adjusted for variables that were  
176 significantly related with them, when considered in multivariable models (see legend of  
177 **Figure 1**). Path analyses allow an estimation of the indirect effects of a variable on an  
178 outcome (effects that are mediated by other variables) (Loehlin, 2004).

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

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

187 The same approach was used to assess the potential mediation of the placenta in the  
188 association between WCT1 and birth length. We assessed whether the relations were

189 different by recruitment centre, newborn gender, parity, BMI and cigarette smoking, and  
190 vomiting in early pregnancy. Also we investigated whether or not taking into account  
191 gestational diabetes and gestational hypertension modified or results.

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

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

## 196 **Results**

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

201 In a second step, we excluded mother-child pairs whose placental weight at delivery was  
202 not available. About 94% of women from Poitiers centre had a measure of placental weight  
203 versus 43% for those from Nancy centre. In term-births, women without a measure  
204 placental weight were more frequently diagnosed for gestational hypertension and had a  
205 higher study level. Whereas birth weight and birth length were higher in those whose  
206 placental weight was measured (**table 1 in** supplementary on-line information). These  
207 differences were due to differences in these characteristics between study centres. Women  
208 from Nancy were more frequently diagnosed for gestational hypertension (5.6% versus  
209 2.8%,  $p=0.005$ ) and had a higher educational level ( $p<0.0001$ ). Whereas offspring's mean  
210 birth weight and height were higher in Poitiers centre ( $p=0.007$ ).

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

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

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

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

235 independently associated with placental weight ( $r= 0.18$ ) and birthweight ( $r= 0.11$ ,  $p$   
236  $<0.0001$ ).

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

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

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

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

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

## 255 **Discussion**

256 Weight change in the first trimester was associated with fetal growth and birth size even  
257 when weight changes in later gestation were taken into account. Results of path analysis

258 showed that the relation between weight change in the first trimester and birth size was in  
259 part mediated by placental weight at birth, which we used as a proxy of placental growth  
260 and function. As women in our study centres appeared to be quite different and that  
261 placental weight was systematically recorded in Poitiers centre but not in Nancy, we  
262 restricted our analysis to women in Poitiers centre and observed similar results. No  
263 difference in weight gain during the first trimester was observed between women who had a  
264 measure of placental weight (3.3g) and those without a measure of placental weight (3.2kg,  
265  $p=0.7$ ).

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

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

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

300 The mother provides oxygen, nutrients, hormones, and antibodies to the foetus via the  
301 placenta, and the end products of fetal metabolism are removed via the placenta. Placental  
302 weight at delivery is positively correlated with the newborn's weight but the maximal  
303 growth of the placenta precedes that of the foetus. Its growth rate is initially greater than  
304 that of the fetus (Thame et al., 2004). A small placenta usually alters fetal growth (Belkacemi  
305 et al.). Maternal nutrition is associated with placental weight (Belkacemi et al., 2010) and a  
306 reduction in maternal nutrition in early pregnancy may alter placental growth and birth  
307 weight. In our study, maternal weight gain (used as a proxy of nutritional state) in the first

308 trimester influenced placental weight at delivery. Thame et al. found that placental volume  
309 at 14 weeks of gestation and the rate of placental growth between 17 weeks and 20 weeks  
310 were significantly associated with fetal measurement at 35 weeks, even when placental  
311 volume at 24 weeks was added to the model (Thame et al., 2004). The rapid growth of the  
312 placenta early in pregnancy is important to supply nutrients necessary for fetal growth. All  
313 these findings confirm the hypothesis that placental volume and placental growth are  
314 influenced by maternal nutrition in early pregnancy, and in turn, also contribute to fetal  
315 growth.

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

320 Neufeld et al. reported that weight change between the 3<sup>rd</sup> and 6<sup>th</sup> month of gestation had a  
321 positive effect on linear fetal growth and not weight change from 6 to 9 months of gestation  
322 (Neufeld et al., 2004). In our study we found an effect of WCT1 on birth length  
323 independently of placental weight suggesting that the influence of weight change in early  
324 pregnancy on birth length may begin early in the first three months but this independent  
325 effect of WCT1 on birth length was small. Weight change in the first trimester may reflect  
326 energy intake at this stage of pregnancy and therefore correspond to an availability of  
327 nutrients that supply fetal growth even in the earliest stage of the first trimester, before the  
328 contact between the embryo and maternal blood via the placenta (Burton et al., 2007). It has  
329 been suggested that endometrial-decidual glands are sources of nutrients for the embryo,  
330 the endometrium contains large accumulations of glycogen that are greatest close to the  
331 materno-fetal interface (Burton et al., 2007). The endometrial-decidual glands have also  
332 been identified as a source of growth factors such as the epidermal growth factor (Burton et

333 al., 2007, Hempstock et al., 2004) which stimulates cytotrophoblast cell proliferation which  
334 represents the materno-fetal interface during early pregnancy (Hamilton and Boyd, 1960).

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

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

351 An excessive weight gain during pregnancy is associated with adverse pregnancy outcomes  
352 (caesarean sections, gestational hypertension, macrosomia) (Crane et al., 2009). Conversely  
353 women who gained less than the recommended weight gain have higher risks of  
354 preeclampsia, caesarean sections, macrosomia, and low birth weight (Langford et al., 2009).

355 In this study we found that weight change in the first trimester of pregnancy was associated  
356 with fetal growth and risk of large for gestational age. We did not found any association

357 between weight change in the first trimester of pregnancy and adverse pregnancy outcomes  
358 like gestational diabetes, gestational hypertension or risk of caesarean sections. If these  
359 results are confirmed, the monitoring of weight change in early pregnancy may be  
360 considered by clinicians as an important factor in the management of fetal growth without  
361 threatened effect on women's health.

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

### 370 **Conclusion**

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

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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  $\pm$  Standard deviation or % (frequency); of mothers and newborn.

	<b>n</b>	<b>Mean <math>\pm</math> SD*</b>
Age (years)	1744	29.0 $\pm$ 4.9
Height (cm)	1726	163.5 $\pm$ 6.1
Prepregnancy weight (kg)	1744	62.2 $\pm$ 12.8
Body mass index (kg/m <sup>2</sup> )	1726	23.2 $\pm$ 4.6
Pregnancy weight gain (kg)	1717	13.6 $\pm$ 4.7
Weight gain in the first trimester (kg)	1744	3.30 $\pm$ 2.48
Weight gain in the second trimester (kg)	1744	6.8 $\pm$ 2.1
Weight gain in the third trimester (kg)	1744	4.5 $\pm$ 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 ( $\geq$ 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)
$\geq$ 2		33.9 (592)
Gestational age (weeks)	1744	39.5 $\pm$ 1.2
Birthweight (g)	1740	3340 $\pm$ 438
Birth length (cm)	1715	49.8 $\pm$ 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.

<b>Parameter</b>	<b>Beta±SE*</b>	<b>P value</b>
Age (years)	0.04 ± 0.01	0.005
Body mass index (kg/m <sup>2</sup> )	-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	
Recruitment 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 <sup>3</sup> )	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)]<sup>3</sup>)

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
	<i>P</i> -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
	<i>P</i> -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
	<i>P</i> -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
	<i>P</i> -value	0.03	0.03	
Placental weight	Standardized beta	0.52	0.52	
	Standard Error	0.02	0.02	0
	<i>P</i> -value	<0.0001	<0.0001	

\*Standardized betas are interpretable as correlation coefficients



