

## **Pre-pregnancy body mass index and weight gain during pregnancy: relations with gestational diabetes and hypertension, and birth outcomes.**

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► **To cite this version:**

Barbara Heude, Olivier Thiébauges, Valérie Goua, Anne Forhan, Monique Kaminski, et al.. Pre-pregnancy body mass index and weight gain during pregnancy: relations with gestational diabetes and hypertension, and birth outcomes.: Maternal anthropometry and pregnancy outcomes. Maternal and Child Health Journal, Springer Verlag, 2012, 16 (2), pp.355-63. <10.1007/s10995-011-0741-9>. <inserm-00560914>

**HAL Id: inserm-00560914**

**<http://www.hal.inserm.fr/inserm-00560914>**

Submitted on 31 Jan 2011

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## **Abstract**

**OBJECTIVE:** To study the relationship between pre-pregnancy body mass index (BMI) and weight gain during pregnancy with pregnancy and birth outcomes, with a focus on gestational diabetes and hypertension and their role in the association with fetal growth.

**METHODS:** We studied 1884 mothers and offspring from the Eden mother-child cohort. Weight before pregnancy (W1) and weight after delivery (W2) were collected and we calculated BMI and net gestational weight gain ( $\text{netGWG}=(W2-W1)/(\text{weeks of gestation})$ ). Gestational diabetes, hypertension gestational age and birth weight were collected. We used multivariate linear or logistic models to study the association between BMI, netGWG and pregnancy and birth outcomes, adjusting for center, maternal age and height, parity and average number of cigarettes smoked per day during pregnancy.

**RESULTS:** High BMI was more strongly related to the risk of giving birth to a large-for-gestational-age (LGA) baby than high netGWG (odds ratio OR [95% CI] of 3.23 [1.86-5.60] and 1.61 [0.91-2.85] respectively). However, after excluding mothers with gestational diabetes or hypertension the ORs for LGA respectively weakened (OR 2.57 [1.29-5.13]) for obese women and strengthened for high netGWG (OR 2.08 [1.14-3.80]). Low in comparison to normal netGWG had an OR of 2.18 [1.20-3.99] for pre-term birth, which became stronger after accounting for blood pressure and glucose disorders (OR 2.70 [1.37-5.34]).

**CONCLUSION:** Higher net gestational weight gain was significantly associated with an increased risk of LGA only after accounting for blood pressure and glucose disorders. High gestational weight gain should not be neglected in regard to risk of LGA in women without apparent risk factors.

**Key words:** *obesity, pregnancy, gestational diabetes, hypertension, birth weight*

## **Introduction**

The prevalence of obesity has been increasing worldwide, especially among young women susceptible to become pregnant. In France, although the prevalence is lower than in the United States, the frequency of obesity has nearly doubled between 1997 and 2006 (1). In 20-39 year old women, it increased from 5.2% to 11.0% over this period. Obesity and associated cardio-metabolic complications deserve particular attention in the context of pregnancy. Indeed, it is now well recognized that maternal obesity at conception increases the risk of complications in pregnancy, labor, and birth for both the mother and the neonate (2-5). In particular, gestational diabetes mellitus and hypertensive disorders are more prevalent in obese pregnant women (6; 7). These complications themselves confer higher risks of adverse fetal and neonatal outcome, such as large-for-gestational-age (LGA) neonates in mothers with gestational diabetes, or intra-uterine growth restriction in mothers with gestational hypertension (8-11).

Another important factor influencing pregnancy and birth outcomes is weight gain during pregnancy (12; 13). Most studies show that the higher the pre-pregnancy BMI, the lower the pregnancy weight gain (14-20). It has been shown that the risks of gestational diabetes and gestational hypertension could be different according to the amount of weight gain, independent of pre-pregnancy BMI (13). Most of the studies interested in weight gain during pregnancy analyzed total weight gain thus including the weight of the fetus and the annexes; this obviously overestimates the link between weight gain and birth weight, but also between weight gain and length of gestation. This is why some studies, but very few, analyzed “net” weight gain, defined by subtracting birth weight from total weight gained during pregnancy (21; 22).

In the present study, we aimed to investigate the role of pre-pregnancy BMI and net gestational weight gain on risks of gestational diabetes and hypertension, preterm delivery, small for gestational age and large for gestational age neonates.

## **Population and Methods**

### Population studied

The EDEN study (Pre- and post-natal determinants of children's growth and development) is an on-going mother-child cohort, with a follow-up of the child until their fifth birthday. The primary aim of the EDEN cohort is the study of pre-natal and early post-natal nutritional, environmental, and social determinants of children's development and health. The study was proposed to all women presenting before the 24<sup>th</sup> week of gestation (week of amenorrhea) at the prenatal clinics of the University hospitals in Nancy and Poitiers, two middle-sized cities of semi rural areas in France. Enrolment started in February 2003 in Poitiers and September 2003 in Nancy, lasted 27 months in each center and 2002 women were included. Criteria of exclusion were twin pregnancies, known diabetes before pregnancy, moving outside the region planned in the next three years and not being able to speak and read French. Among all eligible women, 55% agreed to participate. Written consent was obtained from the mother for herself at inclusion and for the newborn after delivery. The study was approved by the ethics committee (CCPPRB) of Kremlin Bicêtre and by the Data Protection Authority "Comission Nationale de l'Informatique et des Libertés" (CNIL).

Among the 2002 eligible women who accepted to participate, 1884 were included in the present analysis as they had information on BMI before pregnancy and at least one pregnancy, delivery or birth outcome available. Of the other women, 18 had moved away or been lost to follow-up, 19 had a miscarriage or a termination of pregnancy, and 44 withdrew for personal reasons. For the remaining 37 women, information on weight before pregnancy was not available.

### Measurements

At 24-28 weeks, the mother had a clinical examination performed by midwife research assistants and she completed a self-administered questionnaire. Maternal height was measured

with a wall Seca 206 stadiometer (Hamburg, Germany), to the nearest 0.2 cm. A second research examination was performed by the same research assistants, on average, 2.3 days ( $\pm$  sd: 1.5) after delivery. The mother's weight was measured using electronic Terrillon SL 351 scales (Hanson Ltd, UK) to the nearest 0.1 kg. At birth, neonates were weighed using an electronic Seca scales (Hamburg, Germany: Seca 737 in Nancy and Seca 335 in Poitiers).

At 24-28 weeks, maternal plasma glucose concentrations were measured 1 h after a 50-g glucose challenge. Women with 1-h glucose concentrations over 130 mg/dL in Nancy and 140 mg/dL in Poitiers were scheduled for a 3-h 100-g oral-glucose tolerance test. Gestational diabetes was diagnosed by using the oral-glucose-tolerance test according to the Carpenter and Coustan criteria (11) when there were  $>2$  plasma glucose concentrations greater than the following cutpoints: fasting = 95 mg/dL, at 1 h = 180 mg/dL, at 2 h = 155 mg/dL, and at 3 h = 140 mg/dL. Some additional cases of gestational diabetes were diagnosed by clinicians either before or after the 24–28-week examination, and extracted from medical records of the maternity.

Weight before pregnancy, educational level and smoking habits were obtained by interview at inclusion. Some additional data were extracted from clinical records: weight at first maternity visit, clinical diagnosis of gestational hypertension, treatment for hypertension, gestational age at delivery and number of previous pregnancies. In this study, only women treated for hypertension were considered as hypertensive. Existing hypertension before pregnancy was also collected from clinical records, and permitted to confirm cases of hypertension appearing during pregnancy only (pregnancy-induced hypertension).

#### Generated variables

Large- and small-for-gestational-age (LGA and SGA) births were defined when birth weights were over the 90<sup>th</sup> and below the 10<sup>th</sup> percentiles, respectively, using French gestational age- and gender-specific reference curves (23). Pre-term delivery was defined as gestational age  $<37$  weeks.

Pre-pregnancy body mass index (BMI) was computed as reported weight (kg) divided by square of measured height (m) and categorized into four groups as underweight ( $<18.5$  kg/m<sup>2</sup>), normal ( $\geq 18.5$  and  $<25$  kg/m<sup>2</sup>), overweight ( $\geq 25$  and  $<30$  kg/m<sup>2</sup>) and obese ( $\geq 30$  kg/m<sup>2</sup>). Net gestational weight gain per week (netGWG) was computed as the difference between weight measured after delivery and reported weight before pregnancy, divided by the number of weeks of gestation and expressed in g/week. This variable was also categorized into four groups. Since one objective of this paper was to compare the strength of the association of BMI with pregnancy and birth outcome, to the strength of the association of gestational weight gain with the same outcomes, the categorization was performed so that the distribution of the number of women in each group was similar to that of the corresponding groups of the pre-pregnancy BMI categorization. Thus, pregnancy weight gain was considered as *low* under 74g per week, *normal* between 74 and 282g per week, *medium high* between 282 and 389g per week and *high* over 389g per week. The equivalence in net weight gain during a full-term pregnancy (41 weeks) was  $<3$ , 3 to 12, 12 to 16 and over 16kg respectively for low, normal, medium high and high net gestational weight gain.

### Statistical analysis

We described the characteristics of the mothers and of the neonates during pregnancy and birth outcomes using mean  $\pm$  standard deviation or percentages (number). As weight gain is strongly and inversely related with pre-pregnancy BMI, the associations between maternal weight gain and pregnancy outcomes were investigated in multivariable models including *both* variables together. We modeled the risks of gestational diabetes, treated hypertension, pre-term delivery, SGA and LGA, according to categories of pre-pregnancy BMI and netGWG, using logistic regression models adjusted for center, maternal age and height, parity and average number of cigarettes smoked per day during pregnancy. Reference categories for ORs were normal pre-pregnancy BMI and normal pregnancy weight gain as defined above.

We considered the interactions between the categorical variables for pre-pregnancy BMI and netGWG, but we also tested for interactions between the two variables considered as continuous traits, introducing a multiplicative term in the model, as this is a more powerful method.

For each of the three birth outcomes (pre-term delivery, SGA and LGA) we analyzed the impact of excluding women with gestational diabetes or/and hypertension. As sensitivity analyses, we performed the same analyses using weight measured at booking instead of recalled weight for the calculation of pre-pregnancy BMI, in the 1351 mothers who booked before 15 weeks.

## RESULTS

### Description of study population (Table 1)

Among the 2002 women enrolled in the cohort, the 118 women excluded from the present analysis (see Methods) were on average 2 years younger at inclusion (27 vs. 29 years). Birth weight was available for 1855 neonates. Gestational diabetes and pregnancy-induced hypertension were diagnosed in about respectively 6% and 4% of the mothers. Six percent of the births were pre-term. Small-for-gestational age (SGA) and large-for-gestational age (LGA) each accounted for 8% of the newborns.

Maternal weight gain during pregnancy decreased with increasing pre-pregnancy BMI, and obese women differed from their peers with a mean of 4 kg gained vs. about 9 kg for the other women (results not shown).

### Pre-pregnancy BMI, gestational weight gain and associations with gestational hypertension and gestational diabetes (Table 2)

Gestational diabetes and gestational hypertension were diagnosed in respectively 19% and 11% of obese women vs. only 4% and 2% in women with a normal pre-pregnancy BMI ( $P < 0.0001$ ). In the multivariate analysis, a J-shaped relationship was observed for the association between the risk of gestational hypertension and categories of increasing netGWG, but only the highest weight gain was significantly associated with more hypertension (OR [95% CI] = 3.02 [1.39;6.58] compared to normal category).

The risk of gestational diabetes increased steadily with pre-pregnancy BMI even after adjustment for weight gain ( $P$ -trend < 0.001). The risk was significantly increased in both overweight and obese mothers. There was a trend, at the limit of significance ( $P = 0.06$ ), for a decreasing risk of gestational diabetes with increasing categories of netGWG. The interaction between pre-pregnancy BMI and maternal gestational weight gain considered as continuous traits was positive and significant ( $P = 0.011$ , results not shown): the association between pre-



pregnancy BMI and gestational diabetes increased with higher netGWG, or reciprocally, the association between netGWG and gestational diabetes, which was marginally negative, tends to be positive for higher pre-pregnancy BMI.

*Pre-pregnancy BMI, gestational weight gain and associations with birth outcomes (Table 3)*

The rates of LGA increased with categories of pre-pregnancy BMI. Even if not significant, pre-term delivery tended to be more frequent in obese women. In contrast, the rate of SGA was highest in underweight women (13% vs. 5% in obese women). Before adjustment none of the birth outcome was significantly associated with maternal net gestational weight gain.

There was no significant interaction between the effects of pre-pregnancy BMI and netGWG for the different outcomes considered. The risk of pre-term delivery was not significantly associated with pre-pregnancy BMI ( $P$ -trend=0.49), although the lowest risk was observed in underweight women. In contrast, an inverse J-shaped relationship was observed with increasing gestational weight gain. Indeed, the risk was highest in low weight gain mothers (OR=2.18 [1.20;3.99]), and lowest in the medium-high weight gain group (OR=0.46 [0.23;0.91]). When mothers with gestational diabetes or hypertension were excluded, the association of low weight gain with pre-term delivery was reinforced (OR=2.70 [1.37;5.34], **Table 4**). For SGA, a significant decreasing risk was found with increasing pre-pregnancy BMI ( $P$ =0.005) and increasing maternal weight gain ( $P$ =0.008), and this was not strongly modified after selection of mothers without gestational diabetes or hypertension. Lastly, the risk of LGA increased steadily with pre-pregnancy BMI ( $P$ -trend<0.0001) and more weakly with categories of netGWG ( $P$ -trend=0.027). Obese mothers were at increased risk for LGA, and this risk was already present in overweight women (OR=1.66 [1.07;2.57] compared to normal category). Excluding women with gestational diabetes or pregnancy hypertension from the analysis had the strongest impact on the results for LGA: the association between categories of pre-pregnancy BMI and LGA was weakened, whereas the relationship with

netGWG was strengthened (**Table 4**). Even medium-high netGWG was significantly associated with higher risk of LGA in this subsample.

## DISCUSSION

Our results showed that weight gain in pregnancy was lower when pre-pregnancy BMI was higher. In particular, women who were overweight or obese before pregnancy generally gained less weight during pregnancy and very few had an excessive weight gain. Conversely, only 2 of the 161 lean women had a low weight gain. This relationship has been well established (14-20) but the reason for this is not obvious. It can be speculated that medical management and/or personal efforts for not gaining too much weight could be responsible for a part of this association. However, during pregnancy, fat is stored to secure energy supply during fetal growth and lactation. In obese women, no additional storage is necessary, which suggests that pregnancy weight gain could be restricted because of physiological mechanisms.

Our study was based on self-reported measures of weight before pregnancy whereas many studies have found that weight is more likely to be under-reported by women with a high pre-pregnancy BMI (24). Such a bias would therefore impact on the calculation of gestational weight gain and lead to an over-estimation of weight gain in overweight and obese women. We performed a sensitivity analysis and used weight measured at booking instead of recalled weight for the calculation of gestational weight gain and BMI. Gestational weight gain was divided by the number of remaining weeks of gestation, and then multiplied by 41 to obtain a full term pregnancy. The results obtained on the 1351 mothers who booked before 15 weeks were very similar, gestational weight gain was respectively of 10.9, 10.2, 8.4 and 4.3 kg in lean, normal, overweight obese mothers respectively (results not shown). We also performed all the association analyses presented in the paper with those new two variables and the results were unchanged, even if less significant because of the loss of power (results not shown).

As expected (25), gestational hypertension and gestational diabetes were more frequent in women with higher pre-pregnancy BMI. High weight gain was also associated with an increased risk of gestational hypertension, but in contrast, a tendency for an inverse relation was observed between weight gain and risk of gestational diabetes. This last result was also obtained in previous studies (26), and in particular in a recent Danish study on about 60 000 term-pregnancies (13). This could be attributable to reverse causation, since diagnosis of gestational diabetes may be accompanied with diet recommendations resulting in a decreased weight gain in late pregnancy, as Catalano et al. previously suggested (26). On the other hand, it is also possible that common factors such as weak insulin resistance present from the beginning of pregnancy favor both gestational diabetes and low weight gain during pregnancy.

Because of different habits in the two centres, the criteria for inviting mothers to a second glucose load test were different. Indeed, the number of women performing this test was higher in Nancy (290) than in Poitiers (179), but the final number of cases was not significantly higher in Nancy (6.6%) than in Poitiers (6%,  $p=0.50$ ). Therefore, those methodological differences between the centres may not have impacted on our results.

Consistent with previous studies, we found that low weight gain was significantly associated with a higher risk of pre-term delivery (13; 17; 22; 27-29). We show that this is true even if only maternal weight gain is considered. Moreover, the association was strengthened after excluding women with gestational diabetes and gestational hypertension. The lowest risk of prematurity was observed in medium-high weight gain (12 to 16 kg net maternal weight gain for a term pregnancy, 16 to 20 kg equivalent total weight gain during pregnancy). Some studies found that the magnitude of the association decreases as pre-pregnancy BMI increases (22; 27), whereas in our study, the interaction with pre-pregnancy BMI was not significant, probably because of the small number of cases in the extreme groups. Recently, Nhor et al.

found a statistically significant interaction between the effects of pre-pregnancy BMI group and weight gain on preterm birth (13; 27): the risk was potentiated at the extremes, namely among underweight women with a low weight gain and obese women with a high weight gain. However, this interaction was observed only for induced preterm deliveries, not for spontaneous preterm births, suggesting the predominant role of obstetric care in obesity related diseases.

Low maternal weight gain may indicate deficiencies in nutrients, a lack of expansion of plasma volume, infection, or other unidentified problems. Further understanding of these associations is needed, because it remains unclear whether they are causal and therefore amenable to nutritional interventions.

We acknowledge that the relationship between maternal health conditions and birth outcome is complex since especially maternal anthropometry is the consequence of many other genetic or environmental factors such as eating habits, exercise and social economic conditions (30) that themselves can impact on pregnancy outcome. Additional adjustment for educational level did not change the result, but this is a very crude estimation of socioeconomic condition and the presence of residual confounding cannot be excluded.

Another limitation of this study is that the EDEN cohort was conducted in two regional maternity centers and is not representative of the general French population. We adjusted for center in order to take into account regional specificities of way of life and obstetrical practices. Moreover, a comparison with a representative survey carried out on about 15 000 pregnant French women in 2003 (31) indicates that women in the EDEN study were more educated and more often employed, showed healthier life-styles and were more likely to exclusively breast-feed when in the maternity hospital, than the general French population. We acknowledge that this limits the possibility to generalize our results to the whole French pregnant women.

Our results show clearly that both prepregnancy BMI and gestational weight gain are independently and negatively associated with SGA at birth, and the lowest risk of SGA will concern obese women who gain more weight, as shown by Ay et al. in the Generation R Study in the Netherlands (32). For many years, clinical recommendations have focused mainly on the limitation of low birth weight (23). However, the nutritional and clinical context has changed since then: more and more mothers start their pregnancy being overweight or obese, and the risk of LGA has to also be put in the balance.

It has been explicitly recognized since at least 1990, that both pre-pregnancy BMI and gestational weight gain are positively associated with birth weight (14; 15; 33-35). Few studies have considered the impact of taking into account both blood pressure and glucose tolerance disorders, on the quantification of the association between prepregnancy BMI and gestational weight gain on extreme birth weight. Indeed, as seen earlier, gestational diabetes and gestational hypertension are seen more frequently in obese women and can be important confounders for the association with birth weight. Some studies have excluded women with overt gestational diabetes, and showed that even milder degrees of gestational glucose intolerance increases the risk of LGA (36; 37). In our study, we examined the relationship after excluding women with gestational diabetes, and could observe that the association weakened but the risk of LGA remained doubled in obese women. We also performed further adjustments for blood glucose and blood pressure measured during pregnancy, and the conclusions remained unchanged (results not shown in order to simplify the presentation). This suggests that mechanisms other than maternal glucose concentration may be involved in the risk of macrosomia. This also confirms the major role of BMI before the start of pregnancy and that peculiar attention should be driven to preconception counseling for patients with obesity.

Moreover, after excluding cases of gestational diabetes, a stronger association between maternal weight gain and LGA appeared. This is the first time this result has been reported,

and it suggests that the known relationship between maternal glucose and birth weight obscures, in part, the association between maternal weight gain and birth weight, and this must be taken into account. It is possible that the large weight gain in women without glucose or blood pressure disorders may receive less attention from clinicians and it is therefore associated with a stronger risk of LGA than in other women.

In conclusion, our analysis using net maternal weight gain and taking into account glucose and blood pressure disorders reinforces the association between low maternal weight gain with premature birth and between high weight gain with LGA compared to that with pre-pregnancy BMI. Regarding the risk of LGA, our results suggest that monitoring weight gain in obese women may reduce but not alleviate the increased risk of LGA amongst these women. Moreover, high weight gain in women without gestational diabetes and/or gestational hypertension increases the risk of LGA, suggesting that more attention should be paid to mothers without apparent risk factors. However, weight gain has to be monitored tightly as low weight gain is also associated with the risk of pre-term delivery.

### **Details of ethics approval**

The study was approved by the ethics committee (CCPPRB) of Kremlin Bicêtre and by the Data Protection Authority “Comission Nationale de l’Informatique et des Libertés” (CNIL). Written consents were obtained from the mother for herself at inclusion and for her newborn child after delivery.

Authors have no conflict of interest to declare.

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**Table3: Odds Ratios [95% CI] for birth outcomes according to pre-pregnancy maternal BMI and net maternal gestational weight gain. The EDEN Mother-child cohort**

**Table 4: Odds Ratios (95% CI) for birth outcomes according to maternal pre-pregnancy BMI and gestational weight gain, after excluding cases of gestational diabetes and gestational hypertension. The EDEN Mother-child cohort**