



The relationship between weight gain during pregnancy and allopregnanolone levels: a longitudinal study

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Abstract

Objective: Large weight gain during pregnancy is a risk factor for complications for mother and fetus. Hunger and satiety are regulated in the hypothalamus, where the gamma-amino-butyric acid system (GABA) has an important role. Allopregnanolone, a progesterone metabolite, increases during pregnancy and is a potent GABA-A receptor modulating steroid. Allopregnanolone has been shown to induce overeating in rodents. The aim was to investigate whether there is a relationship between weight gain and allopregnanolone concentrations during pregnancy in humans.

Design: A longitudinal, cohort study.

Methods: Pregnant women ($n=56$) were recruited in primary care in northern Sweden. Allopregnanolone concentrations in plasma were measured using radioimmunoassay and weight was measured in gestational weeks 12 and 35.

Results: Weight increase correlated significantly to allopregnanolone in late pregnancy increase ($r_s=0.320$; $P=0.016$), indicating a positive relationship between weight increase and allopregnanolone increase. A positive relationship was also noted between allopregnanolone in the 35th gestational week and weight increase. Women who gained ≥ 11 kg during pregnancy showed higher allopregnanolone concentrations in week 35 and higher increase compared to women who increased <11 kg ($P=0.006$ and $P=0.009$ resp.). There was no difference in weight or allopregnanolone concentrations at the onset of pregnancy.

Conclusions: The results show a relationship between weight gain during pregnancy and increase in allopregnanolone concentrations.

Key words

- ▶ allopregnanolone
- ▶ pregnancy
- ▶ weight increase
- ▶ longitudinal

Introduction

Maternal obesity and excessive weight gain during pregnancy is a condition that increases the risk of several complications for both the mother and the growing fetus, with a risk that the fetus will suffer from a suboptimal environment in the uterus (1). Examples are metabolic and delivery complications, higher fetal weight and fetal adiposity, birth defects and also long-term risk in adulthood

(2, 3, 4). Recommendations given in Sweden about weight gain during pregnancy are related to pre-pregnancy BMI as recommended by US Institute of Medicine (5). Lan-Pidhainy and coworkers (6) reported that the risk for postpartum weight retention rose steeply with increasing gestational weight gain among both primiparous and multiparous women. In Sweden, the proportion of

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women who are overweight or obese (BMI 25 or more) at enrolment in antenatal care has increased from 25% in 1992 to nearly 38% in 2012. In 2013, 25% of all pregnant women in maternal care were overweight and 13% were obese (39). Weight gain during pregnancy is a normal physiological response caused by the growing fetus and tissue growth in the mother and increased maternal fat stores. The energy requirements increase with pregnancy progression. The increased energy requirements in well-nourished pregnant women are about an extra 321 MJ (1 megajoule=239 kilocalorie=1000 kilojoules), distributed over pregnancy to provide adequate nutrition and energy supply for both mother and fetus (7).

Progesterone and its metabolite allopregnanolone, in non-pregnant women are produced in the adrenal and the ovary, and in the brain of the mother (8, 9). During pregnancy allopregnanolone is also synthesized in the placenta (10) and in the fetus, causing maternal and fetal levels to rise considerably, and during late pregnancy, serum concentrations of allopregnanolone peaks, up to 100 nmol/L. After birth, levels fall rapidly to basal levels (11, 12).

The hypothalamus and the brainstem regulate the energy homeostasis to modulate appetite in response to signals by blood-borne hormones and peptides from adipose tissue and gastrointestinal organs in a complicated process (13, 40). Allopregnanolone is not a classical steroid hormone and does not bind to the progesterone receptor but binds to and acts as a potent positive modulator of the GABA-A receptor (14, 15). GABA-A receptors that are related to food intake regulation are found in the hypothalamus, around the arcuate nucleus, the key node for energy regulation (16). Depending on the concentrations of allopregnanolone, it prolongs the opening time of the GABA-A receptor and the GABA inhibitory effect is enhanced (17, 18), which in turn inhibits satiation and thus increases the appetite (16).

Increased appetite and lack of satiety are mechanisms that result in overeating and development of obesity over time (19). Allopregnanolone dose dependently induces increased food intake in rodents (20) and makes the rodents prefer more energy-rich food over more palatable food (21), which increased their weight after a short exposure time (22). Allopregnanolone also relates to uncontrolled eating in women with polycystic ovarian syndrome (23) – a condition with high frequency of obesity, high levels of GABA-A receptor modulating steroids and changed to allopregnanolone (24). There is no study that relates allopregnanolone to weight increase during pregnancy.

The aim of this longitudinal study was to examine whether allopregnanolone levels relate to weight gain during pregnancy in a group of pregnant women.

Subjects and methods

Participants

Sixty women were recruited among women in a larger study ($n=226$), previously described by Lundqvist and coworkers (41), to give a representative sample of weight increases during pregnancy. The 60 recruited women were the women who had the largest and smallest weight increase among the women in the larger study and were above or below the median weight increase (11 kg) in the larger population ($n=226$). The aim in the recruitment was to have a spread in the weight increase during pregnancy and to cover a large weight gain range (Fig. 1 and Table 1). The method of median split was used to divide the high weight gainers from low weight gainers. The pregnant women who attended antenatal clinics were invited to join the study by midwives at the

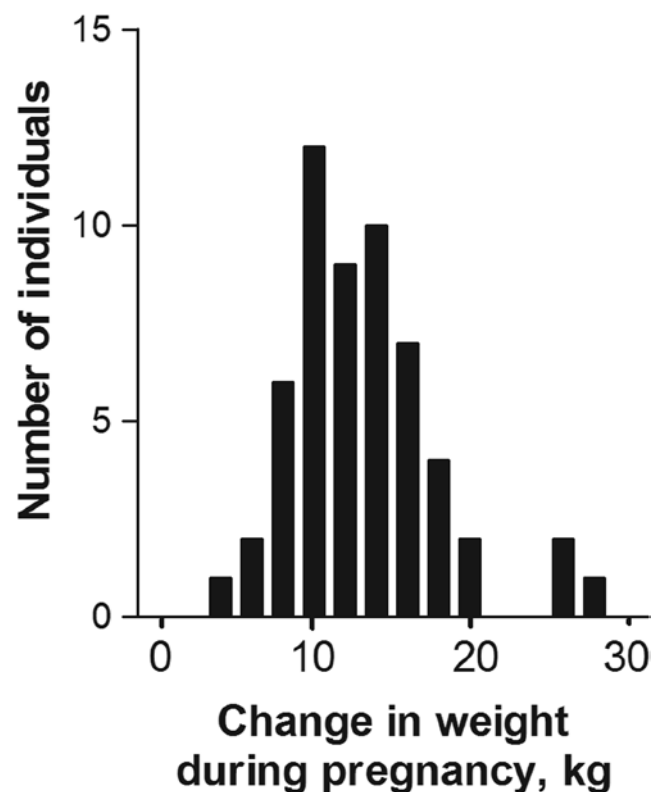


Figure 1 Distributions of weight changes during pregnancy (weeks 12–35) in the study group.

Table 1 Baseline characteristics of the participants ($n=56$).

Characteristics ($n=56$)	Median (min–max)
Age (years) ^a	32.5 (21–39)
Married/cohabitant (%) ^a	98.2
Born in Sweden (%) ^a	91.5
University education (%) ^a	66.1
Birth weight (g)	3560 (2445–4640)
Placenta weight (g)	580 (340–890)
Weight total (kg)	
Gestational week 12	66.0 (47–120)
Gestational week 35	78.5 (56–127)
BMI total (kg/m ²)	
Gestational week 12	23.7 (18–41)
Gestational week 35	28.0 (22–43)

^aAt time of inclusion.

first visit at gestational week 12. Women who agreed to participate were given verbal and written information. Signed consent was obtained from each participant during the first visit to the antenatal clinic and also on each blood sampling occasion. Three exclusion criteria were used: major medical conditions, unable to attend the ordinary antenatal welfare program and insufficient competence in the Swedish language. Blood sampling for allopregnanolone analysis was conducted in gestational weeks 12 and 35, referred to in the tables as sampling occasions 1 and 2. The internal loss was that one woman provided no blood sample, and three participants did not provide blood sample in week 35, which means a study group of 56 individuals. Body weight (light clothing) and height (no shoes) were measured and body mass index was calculated and expressed as kg/m² on each sampling occasion.

The study was approved by the Regional Ethical Review Board at Umeå University, Sweden (Dno 04-171M). The study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants after full explanation of the purpose and nature of all procedures used.

Biochemical analyses

Blood samples were provided in gestational weeks 12 and 35 for analysis of allopregnanolone concentrations in plasma. Allopregnanolone analyses were made at Umeå Neurosteroid Research Center, Umeå University, using radioimmunoassay (RIA); the method has been described in detail by Timby and coworkers (25). A brief

description of the analyses is as follows: the samples (0.4 mL) were extracted with diethyl ether (Merck KGaA, Darmstadt, Germany). Allopregnanolone was separated from cross-reacting steroids with celite chromatography. The chromatography separates allopregnanolone from the major cross-reacting steroids (25). Allopregnanolone was measured by RIA using a polyclonal rabbit antiserum raised against 3- α -hydroxy-20-oxo-5 α -pregnan-11-yl-carboxymethyl ether coupled to bovine serum albumin, provided by RH Purdy (The Scripps Research Institute, La Jolla, CA, USA) (26). The largest cross-reactivity was against pregnanedione and delta-4-pregnene-20-one steroids. All these are well separated from allopregnanolone with the preceding chromatography (25). The sensitivity of the assay was 25 pg. The intra-assay coefficient of variation was 6.5%, and the inter-assay coefficient of variation was 8.5%. Our values are consistent with the literature (11). The concentrations obtained at 12 and 35 weeks correspond well to the concentrations obtained with GC-MS (27).

Statistical analysis

Data were analyzed using descriptive and nonparametric statistics, and the central tendency was expressed as median and range, but when more suitable, as mean and SEM. The distribution of weight increases during pregnancy in the group shows a normal distribution however with slight skewness and kurtosis. Therefore, we have chosen to use nonparametric statistics in the calculations. Spearman's correlations coefficient (r_s) was used for testing relationship between allopregnanolone levels and weight groups. To further elucidate the relation between weight increase and the allopregnanolone concentrations, the participants were divided into two weight groups based on the median weight increase in the study group at 11 kg: participants with <11 kg ($n=27$) or ≥ 11 kg ($n=29$). Differences between weight groups and different factors were tested with Mann–Whitney U test. $P < 0.05$ was considered statistically significant. A logistic regression with the factors allopregnanolone concentration, ethnicity, age and baseline weight in kg was made. Weight increase in kg was the outcome measure. IBM SPSS Statistics, version 22 (IBM Corporation, New York, NY, USA) was used for data analyses.

Results

Table 1 shows the baseline characteristics of the participants. The distribution of weight increase among the participants is illustrated in Fig. 1. Fig. 2, top, shows that weight increase during pregnancy is significantly correlated to allopregnanolone concentrations in late pregnancy ($r_s=0.320$; $P=0.016$). Fig. 2, bottom, shows that weight increase during pregnancy between gestational weeks 12 and 35 is significantly correlated to increased allopregnanolone concentrations during the same period ($r_s=0.310$; $P=0.020$). Table 2 shows the differences in distribution within and between the two sampling occasions in weight increase group low (<11 kg) and high (≥ 11 kg). Allopregnanolone level was significantly higher in the high weight increase group compared to the low weight increase group ($P<0.01$, Table 2), although

both weight groups had the same starting weight and concentration. No significance between weight groups low and high increase was obtained in placenta weight (median, range: 598, 340–800 vs 562, 450–890, resp.) or the fetal birth weight (median, range 3505, 2830–4475 vs 3615, 2445–4640, resp.). In Fig. 3, no differences are seen in the starting allopregnanolone levels, which rise from the same starting levels in early pregnancy to late pregnancy. When comparing the differences in the distribution on sampling occasion 2, i.e. gestational week 35, a significantly higher level was found in the group with high weight increase ($P<0.01$) compared to women with low weight increase.

A logistic regression was made using allopregnanolone concentration, age, baseline weight and ethnicity as coefficients and weight gain in kg as outcome. The results show that only allopregnanolone concentration is significant (coefficient 0.03557) giving an odds ratio of 1.036 with 2.5–97.5% CI=1.0019 to 1.0717 and $P=0.0385$, the R^2 value is 0.267 according to the Nagelkerke's method.

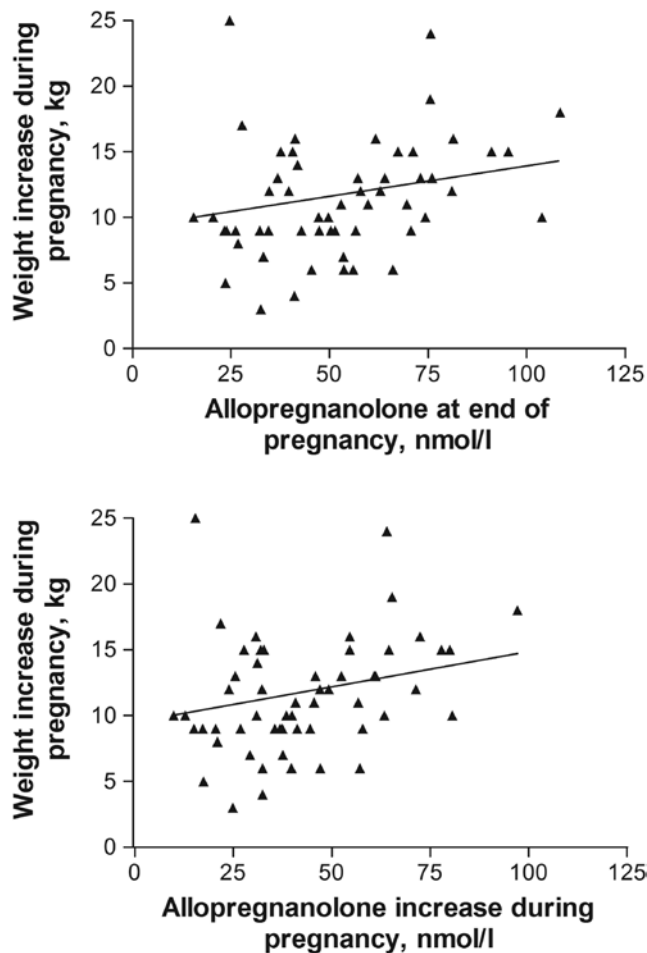


Figure 2
Weight increase during pregnancy related to allopregnanolone concentrations, top at the gestational week 35, bottom change from week 12 to 35.

Discussion

Main findings

This study reports that allopregnanolone concentrations at the end of pregnancy and increases during pregnancy relate to weight change during pregnancy. Further analysis in groups separated by degree of weight increase reveals that both groups have similar allopregnanolone levels and weight at the beginning of the pregnancy, but the group with higher allopregnanolone levels increases more in weight than the group with lower levels. The causal relation cannot be solved in this study as we only investigate relationships here. The weight gain during pregnancy is not all fat but e.g. due to fluids retention, amniotic fluid volume and the baby's weight.

However, there are indications in the literature, mainly in animal studies, of a causal relation between allopregnanolone exposure and increased energy intake and weight increase (28).

Allopregnanolone concentrations have been studied in different weight increase contexts, mostly in animal models; human studies are more limited, particularly in pregnant women. Allopregnanolone levels fluctuate during the menstrual cycle (29), and in the luteal phase, when levels are higher increased energy intake has been reported (30). Our findings of a relation between increased allopregnanolone levels and weight

Table 2 Descriptive and comparative data of the participants.

	Sampling occasion 1 week 12 (n=56)	Sampling occasion 2 week 35 (n=56)	Differences between sampling occasions 1–2
Weight group low <11 kg (kg, median, min–max) ^a	66.0 (47–120) ^c	72.0 (56–127)	6
Weight, group high ≥11 kg (kg, median, min–max) ^b	66.0 (50–86) ^c	80.0 (62–103)	14
Allopregnanolone, (nmol/L, median, min–max) weight group low	8.9 (4.0–23.2) ^c	45.4 (15.5–103.9) ^d	35.6 ^e
Allopregnanolone, (nmol/L, median, min–max) weight group high	10.8 (5.6–15.9) ^c	61.7 (24.7–108.5) ^d	49.3 ^e

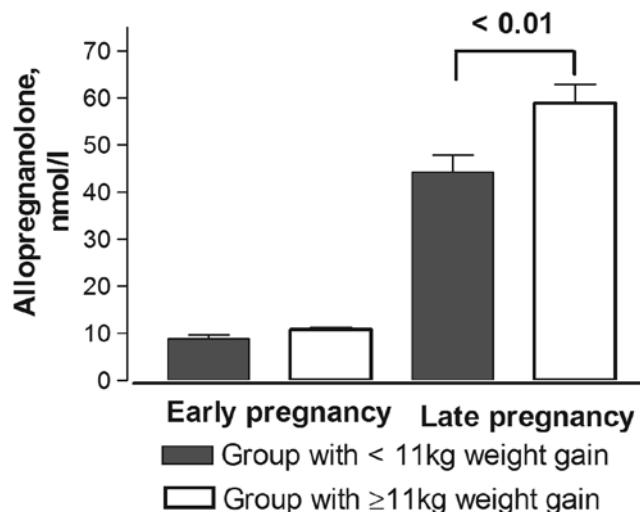
Differences in the distributions were tested with Mann–Whitney *U* test.

^aWeight gain <11 kg; ^bWeight gain ≥11 kg; ^cNon-significant between weight groups; ^dSignificant difference $P < 0.01$; ^eSignificant difference $P < 0.01$.

increase in late pregnancy are in line with other studies (11, 12). Allopregnanolone enhances activity in the GABA system, with a reduced feeling of satiety and increased feeling of hunger as a result (13, 16, 31, 32). Of the two complementary systems that regulate food intake, the homeostatic system that is based on energy needs and the pleasure system that is based on rewards (33), allopregnanolone seems to be an endogenous factor enhancing the homeostatic system. An advantage for the pregnancy and the fetus is that an increased intake of nutrients during pregnancy is needed to ensure the needs of the growing fetus. One disadvantage of reduced satiety may be eating larger portions than necessary and putting on more weight, which can be difficult to lose again after birth. According to Berg and coworkers (34), a larger meal size is a factor for overnutrition, and hence, obesity, but the choice of type of foods is also crucial for weight development. Too much energy-rich foods are not favorable dietary content (<http://www.livsmedelsverket>.

se/en/food-habits-health-and-environment/dietary-guidelines/food-for-you-who-are-pregnant, cited 150614). As mentioned before, in animal models where a choice is given between a more palatable food and a more energy-rich food, allopregnanolone will increase the intake of the more energy-rich over more palatable food (21).

Davis and coworkers found that short intervals between pregnancies and excessive weight gain in first pregnancy are risk factors for maternal obesity (35). Gaillard and coworkers and Williams and coworkers suggest that consequences of maternal obesity and excessive weight gain can affect the health of the mother and fetus for life (4, 36). A course of action is therefore important to optimize diet and reduce weight gain and to help the mother regain her former weight after birth. Forsum and coworkers found that physical activity decreased in early pregnancy (37), and by interviewing pregnant women, Goodrich and coworkers found both motivators and barriers for exercise and healthy eating and also those women lacked knowledge regarding healthy gestational weight gain recommendations (38).

**Figure 3**

The mean \pm s.d. increase of allopregnanolone between the two weight groups divided by median split at 11 kg. Median increase was 6 and 14 kg in groups low and high weight increase respectively. Differences in concentration increases between the groups were tested with Mann–Whitney *U* test, $P < 0.01$.

Limitations

Some limitations of this study should be mentioned. Information about food intake was not included in this study, which could enhance the image and possible explanatory factor for the allopregnanolone–weight relation. This is a correlation study and the causal relation cannot be drawn from the data. We should have made an estimation of the baby’s weight and the amniotic fluid volume at the time of blood sampling. This was however not done. Another limitation is the rather small study group; although significance was reached, a larger group would have been preferable.

Research implications

To make the picture more complete, it would be interesting to have registration of dietary intake during pregnancy in relation to allopregnanolone levels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. T B has stock in Umeçrine AB.

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Author contributions

Conception and design of the work: A L, T B and H S. Acquisition of data: A L, T B and H S. Analysis and interpretation of data: A L, H S and T B. Wrote the first paper: A L. Revised the article critically for important intellectual content: A L, H S and T B. All authors have read and agreed to submission.

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