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Gestational weight gain and rate of late-onset preeclampsia: a retrospective analysis on 57 000 singleton pregnancies in Reunion Island

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ABSTRACT

Objectives To investigate in singleton term pregnancies (≥37 weeks gestation) if applying optimal gestational weight gains (optGWG) on our population could have an effect on the incidence of late-onset preeclampsia (LOP).

Design 18.5-year-observational cohort study (2001–2019).

Settings Centre Hospitalier Universitaire Hospitalier Sud Reunion's maternity (French overseas department, Indian Ocean), the only maternity providing services to take care of all preeclamptic cases in an area with approximately 360 000 inhabitants.

Main outcomes and measures Simulation rates of LOP between women achieving optimal versus inappropriate GWG (insufficient and excessive) in the non-overweight, overweight and class I–III obesity categories.

Results Among 66 373 singleton term pregnancies with a live birth, and 716 LOP (≥37 weeks, LOP37), the GWG could be determined in 87% of cases. In a logistic regression model validating the independent association of optGWG, maternal ages and body mass index (BMI), primiparity, smoking habit, chronic hypertension with term preeclampsia, optGWG reduced the risk of LOP37, aOR 0.74, p=0.004. Primiparity, higher maternal BMI, chronic hypertension and higher maternal age increased the risk of LOP37. The 'protective' effect of optGWG appeared stronger in patients with overweight and obesity in a linear manner: 0.57% versus 1.07% (OR 0.53, p=0.003), overweight; class I obese (30–34.9 kg/m²), 0.70% vs 1.56% (OR 0.44, p=0.01); severe obesity (≥35 kg/m²) 0.86% vs 2.55% (OR 0.33, p=0.06). All patients with overweight/obesity together, OR 0.42, p<0.0001.

Conclusions Overweight and obesity may not result in a higher risk of developing LOP at term when a optGWG is achieved. The results of this large retrospective population cohort study suggest that targeted and strictly monitored interventions on achieving an optGWG might represent an effective method to reduce the rate of LOP and would have the potential to halve its rate in women with overweight/obesity. These findings suggest a potentially achievable pathway to actively counterbalance the morbid effects of high BMIs, so we solicit adequately powered prospective trials.

Strengths and limitations of this study

- ► 18-year population-based study of all preeclamptic cases in a vast area (island population).
- ► University, level 3 hospital is the only maternity service to care and deliver all preeclamptic cases in the South of Reunion island.
- ► Observational study of a large cohort of women (66 373 singleton term births and 716 preeclamptic term pregnancies).
- ► The cohort of pregnant women with overweight/obesity studied represented a significant part of the whole population.
- ► Retrospective population study that allowed observations based on associations.

INTRODUCTION

Worldwide obesity among adults has nearly tripled since 1975 according to the Global Health Observatory of the WHO,[1] with 39% of women≥18 years being overweight or obese. Being overweight or obesity represents a definite risk for pregnancy complications like hypertensive disorders, gestational diabetes mellitus, (iatrogenic) preterm birth, delivery complications and poor neonatal outcome. The British National Health Service does not recommend losing weight during pregnancy as there is a lack of evidence that losing weight during pregnancy may reduce the risk of complications,[2] in line with official Institute of Medicine (IOM) 2009 (US IOM) recommendations,[3] but there is no consensus on what represents optimal gestational weight gain (OptGWG) during pregnancy.

We have previously demonstrated[4] that there is a linear association between prepregnancy maternal body mass index (ppBMI), gestational weight gain (GWG) and birth weight. On the basis of this linear association, a formula was developed to identify the ideal individual 'optimal GWG' for each pregnant woman (allowing a window of ±2 kg).[4] Using the same population data set,[5] we also demonstrated that high ppBMI (overweight

and obesity class I to III) was associated with late-onset preeclampsia (≥34 weeks of gestation, LOP, n=1096 cases) in a linear progressive fashion (R^2 0.93) while early-onset preeclampsia (<34 weeks gestation, EOP, n=491 cases) was not (R^2 0.14). LOP represents the vast majority of cases of the disease (90% in high-income countries and approximately 70% in medium–low income countries).[6 7] Therefore, we sought to investigate in our comprehensive epidemiological population perinatal database if women with an OptGWG[4] (from a birth weight perspective) would also have lower rates of LOP compared with women with an 'inadequate GWG'. As the formula we proposed has been established for term pregnancies (37 weeks onward),[4] only term preeclamptic women were selected for this study ('LOP37').

MATERIAL AND METHODS

The hospital records of all women giving birth at the maternity of the University Hospital South Reunion Island from 1 January 2001 to 30 June 2019 were abstracted in a standardised fashion. The study sample was drawn from the hospital perinatal database which prospectively records data of all mother–infant pairs since 2001. Information is collected at time of delivery and at infant hospital discharge and then regularly audited by appropriately trained staff. This perinatal data base contains information on obstetrical risk factors, description of delivery and maternal and neonatal outcomes. For the purpose of this study, records have been validated and used anonymously. All pregnant women in Reunion Island (as part of the French National Health Care System) have prenatal visits, periodic blood tests and ultrasound scans, and anthropological characteristics recorded in a maternity booklet.

Preeclampsia, gestational hypertension and eclampsia were diagnosed according to the definition issued by the International Society for the Study of Hypertension in Pregnancy relatively to the guidelines in force at the year of pregnancy. EOP is defined when diagnosis is made before 34 weeks of gestation while LOP manifests at ≥34 weeks.[8] Because OptGWG has been assessed for term pregnancies –37 to 42 weeks,[4] only women who went to develop LOP and delivered at term (LOP37) were selected.

Design and study population

The maternity department of Saint Pierre hospital, a tertiary care centre with about 4300 deliveries per year (about 80% of all deliveries of the Southern area of Reunion Island) is the only level-3 maternity. The other maternity unit, a level 1 private hospital, is not allowed to manage and deliver preeclamptic pregnancies. Reunion Island is a French overseas region in the Southern Indian Ocean. The entire pregnant population has access to maternity care free of charge as provided by the French healthcare system, combining freedom of medical practice with nationwide social security. Prenatal system is based on scheduled appointments (nine prenatal visits and four ultrasounds on average) starting from 6 to 8 (see below) weeks of gestation

Definition of exposure and outcomes

Booking BMI (ppBMI) was obtained at the first antenatal visit (average 6–8 weeks). Weight is measured at arrival in labour ward. In case of imminent delivery (<10% of cases), the documented weight during the last antenatal visit prior to birth was used for calculations.

Primary outcome

We arbitrarily created five categories of GWG using the published formula (−1.2 ppBMI (kg/m²)+42 ± 2 kg)[4] defined in our population of Reunion Island:

- Optimal GWG range: opt GWG±2 kg.
- Insufficient GWG
  - Moderately insufficient: OptGWG minus 3 to 9 kg.
  - Severely insufficient: OptGWG minus 10 kg and below.
- Excessive GWG
  - Moderately excessive: OptGWG plus 3 to 9 kg.
  - Severely excessive: OptGWG plus 10 kg and over.

Statistical analysis

Data are presented as numbers and proportions (%) for categorical variables and as mean and SD for continuous variables, as appropriate. Comparisons between groups were performed using χ^2 test and OR with 95% CI. Paired t-test was used for parametric and the Mann-Whitney U test for non-parametric continuous variables. P values <0.05 were considered statistically significant. Epidemiological data were recorded and analysed with the software EPI-INFO V.7.1.5 (2008, CDC Atlanta, OMS), EPIDATA V.3.0 and EPIDATA Analysis V.2.2.2.183 (Denmark).

Multiple regression was used to validate the independent association of maternal age and other confounding factors with LOP37. Variables associated with term preeclampsia in bivariate analysis known to be associated with the outcome in the literature were included in the model. A stepwise backward strategy was then applied to obtain the final model. The goodness of fit was assessed using the Hosmer-Lemeshow test. A p value below 0.05 was considered significant. All analyses were performed using MedCalc software (V.12.3.0; MedCalc Software's, Ostend, Belgium).

We considered the following covariates as possible confounders in this analysis: maternal BMI by increment of 5 kg/m², gestational diabetes, chronic hypertension, OptGWG (Yes/No), smoking, primiparity and maternal age by increment of 5 years. We included these variables and calculated the χ^2 for trend (Mantel extension), the ORs for each exposure level compared with the first exposure level.

Patients and public involvement

Patients were not involved in the design and planning of the study.

RESULTS

During the 18.5-year period, there were 96 861 births in the South of the island of Réunion, of which 77 906 delivered at the university's maternity (80.4%). The overall number of cases of preeclampsia was 1842, of which 106 cases occurred in multiple pregnancies. The number of cases of preeclampsia in singleton pregnancies was therefore 1736 with 1203 (69%) of LOP. After excluding fetal deaths (in utero fetal deaths, medical terminations of pregnancies ≥22 weeks) and preterm pregnancies (<37 weeks), the final study population was made of 66 373 normotensive pregnancies and 716 LOP37. In these 66 373 term pregnancies, the GWG (calculated as weight at delivery minus booking weight) could be calculated in 57 703 pregnancies (86.9%), and in 603 (84.2%) of LOP37 patients.

The main population characteristics are presented in table 1. Preeclamptic mothers were in average older than controls (a difference of 0.6 year, 28.3 vs 27.7, p=0.01), more likely primiparous (OR 1.94, p<0.0001), and to be single (OR 1.16, p=0.05). Women with LOP had a higher rate of gestational diabetes mellitus (OR 1.37, p=0.004) and chronic hypertension (OR 6.6, p<0.0001), and had a significantly higher BMI (27.4 vs 24.7 kg/m²; p<0.0001)

Table 1 Population characteristics

Characteristics	Term preeclampsia (≥37 weeks) n=716 (%)	Term controls (≥37 weeks) n=66 373 (%)	OR (95% CI)	P value
Maternal age (SD)	28.3±7.0	27.7±6.5	Difference 0.6 year	0.01
Parity ±SD	1.1±1.7	1.28±1.5		0.03
Primiparity	382 (53.4)	24 437 (37.1)	1.94 (1.7 to 2.25)	<0.0001
Women living single	283 (39.6)	23 579 (36.0)	1.16 (1.0 to 1.35)	0.05
Education >10 years	408 (59.2)	36 862 (58.1)	1.06	0.21
Unemployed	479 (66.9)	45 730 (68.9)	0.92	0.12
Origin Reunion Island	590 (82.3)	54 425 (82.2)		
BMI (mean±SD, kg/m^2)	27.4±7.35 n=684	24.7±5.9 n=63 423	Difference 2.7 kg/m²	<0.0001
Obesity ≥30 kg/m²	217 (31.7)	10 908 (17.2)	2.24 (1.9 to 2.6)	<0.0001
BMI categories				<0.0001
≤19 (underweight)	82 (11.9)	13 342 (21.0)		
20–24 (normal)	233 (34.1)	25 502 (40.2)		
25–29 overweight	152 (22.2)	13 671 (21.6)		
30–34 (obesity I)	104 (15.2)	6671 (10.1)		
35–39 (obesity II)	70 (10.2)	2841 (4.5)		
>40 (obesity III)	43 (6.3)	1396 (2.2)		
Smoking	59 (8.3)	8031 (12.1)	0.65 (0.49 to 0.85)	0.001
No of prenatal visits	9.0±2.76	9.0±2.73		NS
No of ultrasonographies	4.7±1.7	4.4±1.7		0.003
Weight gain (kg)	14.3±7.3 n=622	12.1±6.2 n=58 287	Difference 2.2 kg	<0.0001
Gestational diabetes	100 (14.3)	7061 (10.8)	1.37 (1.1 to 1.69)	0.004
Chronic hypertension	56 (7.8)	829 (1.3)	6.6 (5.0 to 8.8)	<0.0001
Delivery (weeks)	38.2±1.1	38.9±1.1	Difference 0.7 week	<0.0001

Term pregnancies ≥37 weeks gestation.
BMI, body mass index.

Table 2 Incidence of term preeclampsia (%): simulation versus observed rates if women had an adequate gestational weight gain (GWG) in the same population, Crude ORs.

	Non-overweight <25 kg/m² n=35 402	OR 95% CI	P value	Overweight 25–29.9 kg/m² n=12 369	OR 95% CI	P value
ORs: Adequate GWG versus observed rates	66/7456 (0.88%) versus 276/35 402 (0.77%)	**0.88**	0.17	20/3471 (0.57%) versus 133/12 369 (1.07%)	**0.53 (0.32 to 0.84)**	**0.003**
	Obese 30–34.9 kg/m² n=6019	**OR 95% CI**	**P value**	**Severe obese ≥35 kg/m² n=3913**	**OR 95% CI**	**P value**
ORs: adequate GWG versus observed rates	8/1134 (0.7%) versus 94/6019 (1.56%)	**0.44 (0.20 to 0.88)**	**0.01**	2/233 (0.86%) versus 100/3913 (2.55%)	**0.33 (0.04 to 1.2)**	**0.06**

and were more represented in all categories of obesity (class I–III; p<0.0001). Level of education, rate of unemployment and geographical origin (city vs rural) showed no significant difference between LOP37 patients and controls. It is of note that in spite of a shorter average length of gestation (38.2 vs 38.9 weeks; p<0.0001), preeclamptic women had a higher GWG on average (14.3 vs 12.1 kg, p<0.0001), and lighter babies (2918 vs 3187 g; p<0.0001). The rate of low birth weight (<2500 g) and small for gestational age (SGA) neonates was significantly higher in the LOP group (respectively, OR 4.9 and 2.7; p<0.0001).

Table 2 provides an overview comparing the rate of LOP37 in women with OptGWG with women with non-OptGWG in the different BMI categories. LOP rates in the different BMI categories and calculated OptGWG subcategories were reported in table 3.

LOP37 was observed in 0.77% of all non-overweight women (<25 kg/m²; n=35 402 that represented 61% of all births). It is of note that 62% of women with insufficient GWG (17 559+4465) showed a LOP rate of 0.4%–0.5% (OR 0.50 and 0.61, p=0.002, as compared with OptGWG), but with an SGA rate of 20%, as previously published.[4]

The overall observed LOP37 rate in overweight women (25–29.9 kg/m², n=12 369, 21% of our study group) was 1.07% while in women with obesity class I (30–34.9 kg/m², n=6019, 10.4% of the study population) the overall observed LOP37 rate was 1.56%. In women with obesity class II and III (≥35 kg/m², n=3913, 6.8% of the study population), the observed LOP37 rate was 2.55%.

In the overweight/obese combined women who managed to achieve an OptGWG, the LOP37 rate was 0.62% (30/4838 compared with 326/22 246; OR=0. 42 (0.28 to 0.60), p<0.0001).

Table 4 presents the independent association of OptGWG with the other major risk factors for LOP37. Multiple logistic regression model to validate the independent association of adequate GWG and other confounding factors for term preeclampsia was used. OptGWG and smoking (negative coefficient) showed a similar protective effect of 0.74. Primiparity, maternal BMI, chronic hypertension and maternal age increase the risk. Controlling for all the other factors, ppBMI remains an independent risk factor (coefficient 0.06, on average an increase of 6% per increment of 5 kg/m²).

DISCUSSION

The main findings of this study indicate that optimising GWG might represent an effective method to reduce the LOP37 rate in women with overweight/obesity. GWG is closely linked to birth weight. In a previous study, we derived a mathematical model to calculate optimal GWG from a birth weight perspective.

In short, we previously demonstrated[4] that only women with a normal BMI give birth to neonates with birth weights followed a normal Gaussian distribution, that is, with (by definition) 10% SGA and 10% large for gestational age (LGA) neonates, while lean women (15–19 kg/m²) had a high rate of 15% of SGA babies and a very low rate (5%) of LGA newborns. Conversely, women with morbid obesity (BMI 40–44.9 kg/m²) had exactly the reverse, 7% SGA and 20% of LGA newborns.[4] Further analyses showed that women in the low or high BMI categories could still achieve a normal (10% SGA and 10% LGA) birth weight distribution if they managed to achieve a definite GW: we named this 10% 'crossing' point of SGA/LGA newborns the 'Maternal-Fetal Corpulence symbiosis, MFCS'.[4] Surprisingly, it turned out that the trajectory of these 'crossing' points for the whole BMI spectrum followed a straight line, allowing a simple equation y=ax+ b to define the OptGWG.

The data of the current study demonstrate that women with overweight and obesity achieving an optimal GWG almost halve their LOP37 rate. In the overweight group (BMI 25–39.9 kg/m²), the OR was 0.53 (p=0.003, a 47% decrease of LOP37); in the obese group (BMI 30–34.9 kg/m²) the OR was 0.44 (p=0.01, 56% decrease); and in patients with severe obesity (BMI 35 kg/m² and over), the OR was 0.33 (p=0.06, 67% decrease). The fact that over

Table 3 Incidence of term preeclampsia (%) per category of adequate or non-adequate gestational weight gain (GWG; adequate GWG as reference)

Differences with adequate weight gain	Non-overweight <25 kg/m² (%) n=35 402	OR 95% CI	P value	Overweight 25–29.9 kg/m² (%) n=12 369	OR 95% CI	P value
–10 kg and lower	20/4465 (0.4)	0.50 (0.3 to 0.82)	0.003	0/259 (0.0)	–	–
–3 to 9 kg	97/17 759 (0.5)	0.61 (0.45 to 0.86)	0.002	23/2807 (0.8)	**1.4**	0.12
Adequate GWG±2 kg	**66/7456 (0.88)**	**Reference**	–	**20/3471 (0.57)**	**Reference**	–
+3 to 9 kg	70/5063 (1.4)	1.57 (1.1 to 2.2)	0.004	58/4604 (1.3)	**2.2 (1.3 to 3.7)**	<0.0001
10 kg+	23/679 (3.4)	3.9 (2.4 to 6.3)	<0.0001	23/679 (3.4)	**4.6 (2.6 to 8.2)**	<0.0001
Differences with adequate weight gain	**Obese 30–34.9 kg/m² (%) n=6019**	**OR 95% CI**	**P value**	**Severe obese ≥35 kg/m² (%) n=3913**	**OR 95% CI**	**P value**
–10 kg and lower	0/65 (0.0)	–	–	0/13 (0.0)	–	–
–3 to 9 kg	4/545 (0.7)	**1.04**	0.47	1/94 (1.1)	**1.2**	0.43
Adequate GWG±2 kg	**8/1134 (0.7)**	**Reference**	–	**2/233 (0.86)**	**Reference**	–
+3 to 9 kg	43/2799 (1.5)	2.2 (1.07 to 5)	0.02	24/1259 (1.9)	2.2	0.13
10 kg+	39/1476 (2.6)	3.8 (1.8 to 8.8)	<0.0001	73/2314 (3.2)	3.76 (1.1 to 23)	0.02

All women 57 703. Observed incidence of late-onset preeclampsia (LOP): 1.04%: 603/57 703. LOP incidence in all adequate GWG 0.78% (96/12 294).

these 18 year only 21% (12,294/57,703) of women could be considered to reach an OptGWG during pregnancy is concerning. It is likely that this is quite similar to what happens in other parts of the world, since our unit, being a university maternity, always tried to follow the international recommendations, in particular the international IOM 2009 on GWG.[3]

For a decade, we have witnessed an ongoing controversy on the 'optimal' GWG in the international literature, with the strongest debates on what to do with women with obesity, in particular the question whether or not the IOM advice of a GWG of 5–9 kg for women with obesity is adequate.[9–12] The findings of this study and our previous findings on GWG and normal birth weight distribution

Table 4 Multiple logistic regression model to validate the independent association of adequate gestational weight gain (GWG) and other confounding factors for term preeclampsia)

	Multiple logistic regression for term preeclampsia (≥37 weeks)			
	Coefficient	**OR**	**95% CI**	**P value**
Optimal GWG (Yes/no)	–0.30	0.73	0.59 to 0.92	0.007
Smoking	–0.29	0.74	0.56 to 0.98	0.04
Maternal BMI (increment of 5 kg/m²)	0.06	1.06	1.05 to 1.07	<0.0001
Gestational diabetes mellitus	–0.058	0.94	0.74 to 1.18	0.61
Chronic hypertension	1.51	4.5	3.3 to 6.2	<0.0001
Maternal age (increment of 5 years of age)	0.03	1.03	1.02 to 1.05	<0.0001
Primiparity	1.07	2.9	2.45 to 3.48	<0.0001

Optimal GWG and smoking (negative coefficient) have a similar protective effect of 0.74. Primiparity, maternal body mass index (BMI), chronic hypertension and maternal ages increase the risk. Controlling for all the other factors, maternal prepregnancy BMI is still an independent factor (coefficient 0.06, increment of 6% per increment of 5 kg/m²).

indicate that the IOM guidelines are incorrect. Also other researchers like Kiel *et al*,[13] Marguerison Zilko *et al*[12] and Oken *et al*[14] recommended weight loss in superobese pregnant women, a concept challenged by Kapadia *et al*.[15] We have put an online calculator accessible for any smart phone at REPERE.RE (REseau PErinatal REunion), in three languages (French, Spanish and English),[16] and every reader is invited to validate these findings in their own populations.

In Reunion Island, we have witnessed the LOP rate rising year after year since 2000, as we are a country where obesity is a public health problem (our obesity rate in women was of 11% in 2001 and 21% in 2018).[5] In a recent study on the same population cohort, we demonstrated that being overweight or obese is primarily a risk factor for LOP (≥34 weeks gestation)[5] being by far the main pattern of the disease (90% in high-income countries, of which 2/3 37 weeks onward,[17 18] and approximately 70% in medium–low income countries[6 7]). Optimising GWG is a hot topic in current perinatology, with a particular focus on long term maternal and child health. This study indicates that optimising GWG may represent an effective strategy to reduce the risk of LOP37.[17–21] Further research is urgently required to identify ways to assist women in achieving an optimal GWG, with randomised controlled trials to confirm that such intervention would translate our findings in a marked reduction in LOP rates.

The strength of our study is the capturing of all perinatal outcomes in a population of the area (approximately 360 000 inhabitants, and 5100 births per year) in the only level 3 maternity in the area, where we are sure that all preeclampsia cases were referred to our hospital during the 18.5-year period. A weakness of this study is that patients with preeclampsia, especially severe preeclampsia, tend to have a rapid weight gain over the last days and weeks prior to diagnosis due to oedema (a high difference of 2.7 kg, table 1), but this bias should be the same in the different BMI categories. The other obvious weakness is the retrospective nature of this study, demonstrating association and not necessarily causation.

CONCLUSION

Our findings indicate that being overweight or obese (class I to III) at the beginning of any pregnancy is not by default associated with increased maternal and perinatal risks concerning LOP: we may help actively to counterbalance the morbid effects of high BMIs by individualised counselling on their GWG. This approach urgently requires adequately powered prospective trials.

Contributors P-YR participated at all the stages of the study (data collection, analysis, writings, etc). BB participated at the data collection. TH verified all the epidemiological calculations and participated deeply to the data analysis. GD, MS and TH expertised the analysis, the text and the final writings (and the English Language). MB, as the head of the Sud-Réunion University's maternity, is the cornerstone of the existence of the perinatal data base made in its department and being worried by the obesity problem in la Reunion asked for more research on gestational weight gain.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was conducted in accordance with French legislation. As per new French law applicable to trials involving human subjects (Jardé Act), a specific approval of an ethics committee (comité de protection des personnes) is not required for this non-interventional study based on retrospective, anonymised data of authorised collections and written patient consent is not needed.

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