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HALVING THE RATE OF LATE-ONSET PREECLAMPSIA IS POTENTIALLY POSSIBLE IMMEDIATELY: OPTIMIZING GESTATIONAL WEIGHT GAIN. A RETROSPECTIVE ANALYSIS ON 57,000 SINGLETON PREGNANCIES

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HALVING THE RATE OF LATE-ONSET PREECLAMPSIA IS POTENTIALLY POSSIBLE IMMEDIATELY: OPTIMIZING GESTATIONAL WEIGHT GAIN. A RETROSPECTIVE ANALYSIS ON 57,000 SINGLETON PREGNANCIES

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ABSTRACT :

Objectives: High BMI is a well-known risk factor for preeclampsia, especially for late-onset preeclampsia (LOP). We sought to investigate in singleton term pregnancies (≥37 weeks gestation) if applying adequate gestational weight gains (GWG) on our population could have an effect on the incidence of LOP rates.

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 follow and deliver all preeclamptic cases in an area with approximately 360,000 inhabitants.

Main outcomes and measures: We have made a simulation of what would have been our rate of LOP cases if all women had performed adequate GWG.

Results: Among 66,373 singleton livebirths term pregnancies, and 716 LOP (≥ 37 weeks, LOP37) we could determine the GWG in 87% of cases. Observed LOP 37 rates versus rates in patients with using adequate GWG rates were respectively: non-overweight (< 25 kg/m²): 0.77% vs 0.88%, NS; overweight (25-29.9 Kg/m²) 1.07% vs 0.57% (OR 0.53, p=0.003); class I obese (30-34.9 kg/m²), 1.56% vs 0.70% (OR 0.44, p= 0.01); severe obesity (>35 kg/m²) 2.55% vs 0.86% (OR 0.33, p= 0.06). Testing all together our overweight/obese patients, with an adequate GWG would lead to a 58% decrease (OR 0.42, p < 0.0001).

Conclusions. Targeted and strictly monitored interventions on adequate GWG might represent an effective method to reduce the rate of LOP and have the potential to at least halve its incidence in overweight women. In most Western countries, LOP represents 80-90% of all PE cases. Our results confirm that being overweight or obese at the beginning of any pregnancy is a risk factor for LOP but this is not an unchangeable risk. In fact, pregnant women have a potential pathway to actively counterbalance the morbid effects of high BMIs.

Fundings: No specific fundings were used for this study

Keywords : *Preeclampsia, late-onset preeclampsia, epidemiology, pre-pregnancy body mass index*

ARTICLE SUMMARY

Strengths and limitations:

Strengths : .

* Exhautive 18 year population-based preeclamptic cases (island population).

- Our maternity (university, level 3) is the only one providing services to follow and deliver all preeclamptic cases in the south of Reunion island (the other maternity is a private clinic, level 1 only).
- Observational study of a large cohort of women (66,373 singleton term births and 716 term pregnancies).
- In Reunion island, French overseas department, women have good prenatal care (average 9 prenatal visits and 4 ultrasonographies/pregnancy) and the hospitals European standards of care
- In Reunion, especially during the 18-year observational period, overweight and obesity has been constantly a rising problem.

Limitations: The obvious weakness is the retrospective nature of this study, but we hope that our observations will trigger proper prospective trials

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INTRODUCTION

Worldwide obesity among adults has nearly tripled since 1975 according to the Global Health Observatory of the

Worldwide obesity among adults has nearly tripled since 1975 according to the Global Health Observatory of the

World Health Organization [1], with 39% of women ≥ 18 yrs. overweight or obese. Overweight and obesity represent a definite risk for pregnancy complications like hypertensive disorders, gestational diabetes mellitus, (iatrogenic) preterm birth, delivery complications, and poor neonatal outcome. The NHS does not recommend losing weight during pregnancy as there is no evidence that losing weight during pregnancy may reduce the risk of complications [2], in line with official IOM 2009 recommendations [3], but there is a lack of consensus on optimal gestational weight gain during pregnancy.

In a previous study [4], we showed a linear association between pre-pregnancy maternal body mass index (ppBMI), neonatal weight (considering also small and large for gestational age categories), and gestational weight gain (GWG). According with those neonatal outcomes, we suggested a formula to identify an ideal "optimal GWG" for each pregnant woman (allowing a window of 4 Kg). Recently [5], we have also shown that high ppBMI (overweight and obesity class I to III) was specifically associated with late-onset preeclampsia (≥ 34 weeks of gestation, LOP, N=1,096 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 in 70% in medium-low income countries [6,7]), we therefore sought to investigate in our epidemiological perinatal database if women with an optimal GWG as calculated by our formula [4] presented an advantage or not when compared with an "inadequate GWG". As the formula that 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.

From January 1st, 2001, to June 30th, 2019, the hospital records of all women who gave birth at the maternity of the University South Reunion Island were abstracted in a standardized 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 the time of delivery and at the infant hospital discharge and regularly audited by appropriately trained staff. These epidemiological 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 have been used anonymously. All pregnant women in Reunion Island as part of the French National Health Care System have their prenatal visits, biological and ultasonographic examinations, 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 (ISSHP) relatively to the guidelines in force at the year of pregnancy. Early onset preeclampsia is defined as preeclampsia resulting in birth before 34 weeks of gestation, late onset preeclampsia at 34 weeks and onward [8]. In the present study, because optimal weight gain has been described for term pregnancies -37-42 weeks [4], we have selected only women who went to develop LOP and delivered at term (LOP37).

Design and study population

The maternity department of Saint Pierre hospital is a tertiary care centre that performs about 4,300 deliveries per year, thus representing about 80% of deliveries of the Southern area of Reunion Island, and it is the only level-3 maternity (the other maternity is a private clinic, level 1 which is not allowed to follow/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, which combines freedom of medical practice with nationwide social security. Prenatal system is based on scheduled appointments (9 prenatal visits and 4 ultrasonographies on average) starting from 6 to 8 (see below) weeks of gestation

Definition of exposure and outcomes

Infants were considered small or large for gestational age (SGA or LGA) when the age-adjusted birth weight was respectively below or over the tenth percentile according to normal tables for our specific population [9].

Pre-pregnancy BMI (ppBMI),was calculated on the recalled pre-pregnancy weight by patients themselves in the majority of cases, controlled by the booking weight at first visit (average 6-8 weeks), always written down in the maternity booklet.

We created categories of GWG using the published formula (-1.2 ppBMI (kg/m²) + 42 ± 2 kg) [4], therefore a specific and individualized window of 4 kilograms for each woman. Insufficient or excessive GWG were defined as 2 subcategories, namely (1) ± 3-9 kg and (2) ± over 10 kg (≥ 10 Kg).

Statistical analysis

Data are presented as numbers and proportions (%) for categorical variables and as mean and standard deviation (SD) for continuous ones, as appropriate. Comparisons between groups were performed using χ^2-test and odds ratio (OR) with 95% confidence interval (CI) was also calculated. 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 have been recorded and analysed with the software EPI-INFO 7.1.5 (2008, CDC Atlanta, OMS), EPIDATA 3.0 and EPIDATA Analysis V2.2.2.183. Denmark

No additional data available.

Competing interest statement. There are no competing interests for any author

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- CPP) is not required for this non-interventional study based on retrospective, anonymized data of authorized collections and written patient consent is not needed. Nevertheless, the study was registered on UMIN Clinical Trials Registry (identification number is UMIN000037012).

RESULTS :

During the 18.5-year period, 96,861 births were recorded in our database with an incidence of preeclampsia of 1,842 (1.9%), of which 106 multiple pregnancies (5.8%). The study population therefore consisted of 1,736 singleton preeclamptic pregnancies, 69% of which with LOP (N=1,203). After excluding fetal deaths (in utero fetal deaths, medical terminations of pregnancies ≥22 weeks) and preterm pregnancies (< 37 weeks), the final study population was 66,373 healthy pregnancies and 716 LOP37 (41% of our preeclamptic cases, representing 60% of our LOP cases). In these 66,373 term pregnancies, we could determine in the global population the GWG (calculated as weight at delivery minus pre-pregnancy weight) in 57,703 pregnancies (86.9% of our term singleton deliveries), and in 603 (84.2%) of our LOP37 patients.

FIGURE 1 show the different incidence of SGA and LGA babies, the different rates of cesarean section (C-section), according to ppBMI and GWG. Insufficient GWG led to an excess of SGA, while an excessive GWG higher rates of LGA babies. But there is also a constant rise in C-section rates for different GWG.

TABLE1 ANALYSES MORE SPECIFICALLY THE INCIDENCE OF LOP PER CATEGORIES OF MATERNAL ppBMI AND DIFFERENT GWG.

Table 1 present the global LOP rates in the different BMI categories, and the LOP rates within these categories for pregnant women with a below optimal GWG, optimal GWG and above GWG.

NORMALLY SHAPED WOMEN AT THE BEGINNING OF PREGNANCY (< 25 kg/m²), N= 35,402 (61% OF OUR PARTURIENTS). Adequate GWG: 21.0% (7456/35,402). In these women, the natural LOP rate is of 0.77%. It is of note that the 62% of women with insufficient GWG (17,559+ 4465) presented a LOP rate of 0.4-0.5% (OR 0.50 and 0.61, p= 0.002, as compared with adequate GWG), but as previously published at the expense of a 20% rate of SGA.

OVERWEIGHT WOMEN 25-29.9 kg/m², N= 12,369 (21% OF OUR PARTURIENTS). Adequate GWG: 28.0% (3471/12,369). The observed rate in this category is 1.07% vs 0.57% adequate GWG. Adequate GWG compared with the global LOP rate gave an OR of 0.53 [0.32-0.84], p= 0.003. The 47% of women with excessive weight gain (4604+ 679) presented a high risk of LOP, incidence of .3.4% for those with a gain over 10Kg (OR 4.6, p <0.0001), 1. 3.% of LOP (OR 2.2 , p <0.0001) with those over 3-9kg as compared with adequate GWG.

OBESE WOMEN CLASS I (30-34.9 kg/m²) N= 6019 (10.4% OF OUR PARTURIENTS). Adequate GWG: 18.8% (1134/6019). The observed rate in this category is 1.56% vs 0.7% adequate GWG. Adequate GWG compared with the global LOP rate gave an OR of 0.44 [0.20-0.88], p= 0.01. The 71% of women with excessive weight gain (2799+ 1476) presented a high risk of LOP, incidence of .2.6% for those with a gain over 10Kg (OR 3.8, p <0.0001), and 1. 5.% of LOP (OR 2.2 , p= 0.02) with those over 3-9kg as compared with adequate GWG.

OBESE WOMEN CLASS II and III (≥ 35 kg/m²), N= 3913 (6.8% OF OUR PARTURIENTS). Adequate GWG: 6% (233/3913). The observed rate in this category is 2.55 % vs 0.86 % adequate GWG. Adequate GWG compared with the global LOP rate gave an OR of 0.33 [0.04-1.2], p= 0.06. The 91% of women with excessive weight gain (2314+ 1259) presented a high risk of LOP, incidence of 3.2% for those with a gain over 10Kg (OR 3.8, p = 0.02), and 1. 9.% of LOP (OR 2.2 , NS) with those over 3-9kg as compared with adequate GWG.

Not directly shown in the Tables, considering globally our LOP incidence, non-obese women (< 25 kg/m²), 60% of our population, have a LOP37 rate of 0.77%. In the 40% of our overweight/obese women, this LOP37 rate is of 1.46%. If we had 'applied' in these 40% of women an adequate GWG (in a window of 4 kg) their LOP37 rate would have been 0.62% (30/4838) instead of 1.46% (326/22,246) effectively obtained in our cohort. If we calculate this adequate GWG vs the global "obese observed rate", we obtain an OR of 0.42 [0.28-0.60], p< 0.0001 (a decrease of 58% in the LOP 37 rate).

DISCUSSION . The main findings of this study suggest that optimizing GWG might represent an effective method to reduce the LOP37 rate in overweight/obese women. Last year, we did our study on GWG [4] because we had noticed on our population that there was a kind of "fatality" just observing facts: lean women (15-19 kg/m²) had a rate of SGA babies of 15%, and a very low rate, 5%, of LGA newborns, while, conversely, very obese women (40-44.9 kg/m²) had exactly the reverse 7% SGA and 20% of LGA. What was unexpected and astonishing was to see a balanced rate of SGA-LGA (10% of each category; the very definition of SGA/LGA, tenth percentiles), occurring only among women who had a normal pre-pregnancy BMI 20-24.9 kg/m². At first glance, it seemed then that "Nature" had condemned the human species to have normally shaped newborns only with women who were themselves perfectly shaped in terms of corpulence. Deepening the observation, we noticed that, according to the gestational weight gain (or loss) we could indeed achieve this 10% crossing point of SGA/LGA newborns in **all women** if we had an optimal gestational weight gain (GWG) for each of them. What we called "Maternal Fetal Corpulence symbiosis, MFCS" [4]. That is why, in all the tables and figures reproduced in this paper, one can notice that the equilibrium points ("adequate GWG") show the closest combination to the 10% SGA/LGA crossing point. These figures also clearly demonstrate that insufficient GWG invariably leads to a high rate of SGA, while in reverse, excessive GWG give an excessive rate of LGA.

In a recent study, we have demonstrated that it is only late onset preeclampsia, LOP which is associated with overweight/obese women (defined at the beginning of pregnancy, pre-pregnancy body mass index, BMI) [5]. The present study focuses on what could be the incidence of LOP if we had achieved the MFCS point, or optimal GWG,in all our parturients. Our results (per BMI category), indicate that applying this new concept of optimal GWG (and as such also achieving the physiological 10% equilibrium of SGA/LGA) would lead to about a halving of the LOP37 rate in LOP; in overweight (25-39.9 kg/m²) OR 0.53 (p= 0.003, a 47% decrease of LOP), in obese (30-34.9 kg/m²) OR 0.44, p= 0.01, a 56% decrease), and in severely obese (35 kg/m² and over),OR of 0.33 (p= 0.06, 67% decrease). In this last category, among our 3913 severe obese, only 340 (8.6%) of them "dared" to lose weight during pregnancy (see tables) with only 2 LOP women in the adequate group; because of these few numbers, the p value is close to significance (p= 0.06).

A further, fundamental surprising, and concerning discovery: (recalling our 18 year clinical practice) only 21% (12,294/57,703) of women could be considered to have an adequate GWG during their pregnancy in the entire cohort (Table 1). Most likely, this is quite similar in other parts of the world, as our unit is a university maternity, we have always tried to follow the international recommendations, in particular the international IOM 2009 on gestational weight gain [3].

For a decade, there has been a very strong ongoing controversy on gestational weight gain in the literature, with the strongest debates on what to do with obese women (pre-pregnancy BMI): are the GWG 5-9 kg recommendations for obese (> 30 kg/m²) adequate ? Would it not be better to accept a GWG below 5 kg, or even a gestational weight loss [10-13]? Differentiating obese women in the 3 classes of obesity: class 1 (30-34.9 kg/m²), class 2 (35-39.9 kg/m²) and class 3 (40 kg/m² and over), the real debate should be whether or not super obese women need to lose weight during pregnancy?". According to Kiel et al [14], class 3 women (40 kg/m² and over) should lose between 1 and 4 kg, while according to Marguerison Zilko et al [13] or Oken et al [15] these class 3 women should lose 7 kg. In contrast, Kapadia et al in 2015, in a very comprehensive meta-analysis (only based on Odds-Ratios) , concluded [16] that "gestational weight loss should not be advocated in general for obese women".

Based on our findings in this large population study, things now need to change: for example, for a patients with BMI 35 kg/m² a nil gain of 0 kg, for BMI 37 kg/m² a weight loss of 2.4 kg, and for BMI for 40 kg/m², a weight loss of 6 kg. We have put an online calculator consultable on smart phone at REPERE.RE (REseau PErinatal REunion), in three languages (French, Spanish and English) [17], and any reader 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]. Late onset preeclampsia (34 weeks onward) being by far the main pattern of the disease (90% in high-income countries, of which 2/3 are term preeclampsia (37 weeks onward [18]), and approximately in 70% in medium-low income countries [6,7]), immediate and strong interventions on adequate gestational weight gain (GWG) in future pregnancies could immediately, according to our experience, lower the epidemic rate of LOP 37 by some 58%. There is a strong current ongoing consensus on obesity, GWG and consequences for maternal-fetal health, especially concerning preeclampsia [18-22]. But, up to recently, we don't know how to provide proper counselling on the optimal GWG; so in our face-to-face contact with patients , we had no real 'leverage'. What is new is the individually optimized GWG that we propose [4], resulting in both a dramatic decrease in the LOP37 rate but also in a physiologic distribution of birthweights.

The strength of our study is the capturing of all perinatal outcomes in a population of the area (ap. 360,000 inhabitants, and 5,100 births per year, all receiving 'level 3, European standard of care. With 4,300 births per year, the university maternity represents 82% of all births in the south of the island. But, as a level 3 (the other maternity is a private clinic, level 1), we are sure all the preeclampsia cases were referred to our hospital during the 18.5 year period. This is therefore a real population-based study. The data in this large cohort are homogeneous as they were

collected in a single center (no intercenter variability) and not based on national birth registers but directly from medical records (avoiding inadequate codes). The obvious weakness is the retrospective nature of this study, but we sincerely hope that our observations will trigger proper prospective trials

CONCLUSION: Our results demonstrate that being overweight or obese (Class I to III) at the beginning of any pregnancy is not by defaults associated with increased maternal and perinatal risks: we can help actively to counter balance the morbid effects of high BMIs by individualized counselling women on their GWG.

Authors' contributions. Pierre-Yves Robillard participated at all the stages of the study (data collection, analysis, writings et..). Brahim Boumahni participated at the data collection. Thomas Hulsey verified all the epidemiological calculations and participated deeply to the data analysis. Gustaaf Dekker and Thomas Hulsey expertised the analysis, the text and the final writings (and the English Language). Malik Boukerrou, 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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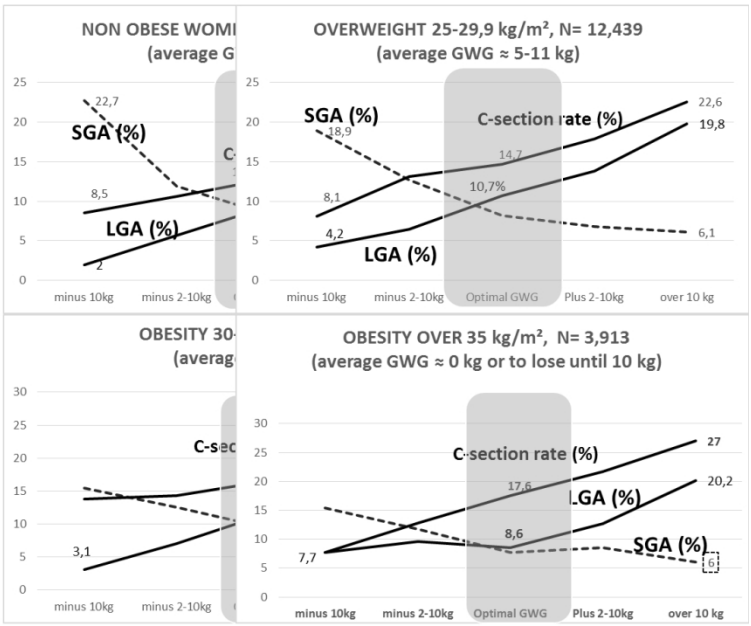
Table 1. Incidence of late onset pregnancy (%) per category of pre-pregnancy maternal BMI. All women 57,703. Observed incidence of LOP: 1.04%: 603/57,703. LOP incidence in all adequate GWG 0.78% (96/12,294).

Differences with optimal Weight gain	**Non obese <25kg/m² (%) N= 35,402**	**OR 95% CI**	**P value**	**Overweight 25-29.9kg/m² (%) N= 12,369**	**OR 95% CI**	**P value**
-10 kg and lower	20/ 4465 (0.4)	0.50 [0.3-0.82]	0.003	0/259 (0.0)	-	-
-3-9kg	97/17759 (0.5)	0.61 [0.45-0.86]	0.002	23/2807 (0.8)	**1.4**	0.12
ADEQUATE GWG ± 2kg	**66/7456 (0.88)**	**Reference**	-	**20/3471 (0.57)**	**Reference**	-
+3-9kg	70/5063 (1.4)	1.57 [1.1-2.2]	0.004	58/4604 (1.3)	**2.2 [1.3-3.7]**	<0.0001
10kg+	23/679 (3.4)	3.9 [2.4-6.3]	<0.0001	23/679 (3.4)	**4.6 [2.6-8.2]**	<0.0001
Odds Ratios: ADEQUATE GWG vs GLOBAL OBSERVED RATES	276/35402 (0.77%)	**0.88**	0.17	133/12369 (1.07%)	**0.53 [0.32-0.84]**	**0.003**
Differences with optimal Weight gain	**Obese 30-34.9kg/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)	-	-
-3-9kg	4/545 (0.7)	**1.04**	0.47	1/94 (1.1)	**1.2**	0.43
ADEQUATE GWG ± 2kg	**8/1134 (0.7)**	**Reference**	-	**2/233 (0.86)**	**Reference**	-
+3-9kg	43/2799 (1.5)	2.2 [1.07-5]	0.02	24/1259 (1.9)	2.2	0.13
10kg+	39/1476 (2.6)	3.8 [1.8-8.8]	<0.0001	73/2314 (3.2)	3.76 [1.1-23]	0.02
Odds Ratios: ADEQUATE GWG vs GLOBAL OBSERVED RATES	94/6019 (1.56%)	**0.44 [0.20-0.88]**	**0.01**	100/3913 (2.55%)	**0.33 [0.04-1.2]**	**0.06**

Adequate GWG being taken as reference, the bottom odds-ratios represent what would occur in women following the recommendations vs reality.

Fig 1: Testing outcomes (in percentages) in different maternal pre-pregnancy BMI (non-obeses, overweight, moderate obese, severe obese), with our proposed calculations [4]. SGA (small for gestational age), LGA (Large for gestational age, rate of caesarean section, pots-partum haemorrhage. GWG: gestational weight gain.



1

209x297mm (150 x 150 DPI)

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			1-2
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	2&4
Methods			
Study design	#4	Present key elements of study design early in the paper	2& 5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	

Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	
Study size	#10	Explain how the study size was arrived at	
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			7-8
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	
Participants	#13b	Give reasons for non-participation at each stage	
Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they	

		were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	
Discussion			9-11
Key results	#18	Summarise key results with reference to study objectives	
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9-10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

BMJ Open

OPTIMIZING GESTATIONAL WEIGHT GAIN MAY HALVE THE RATE OF LATE-ONSET PREECLAMPSIA IN OVERWEIGHT/OBESE WOMEN: A RETROSPECTIVE ANALYSIS ON 57,000 SINGLETON PREGNANCIES, REUNION ISLAND

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OPTIMIZING GESTATIONAL WEIGHT GAIN MAY HALVE THE RATE OF LATE-ONSET PREECLAMPSIA IN OVERWEIGHT/OBESE WOMEN: A RETROSPECTIVE ANALYSIS ON 57,000 SINGLETON PREGNANCIES, 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 follow and deliver all preeclamptic cases in an area with approximately 360,000 inhabitants.

Main outcomes and measures: Simulation of LOP rates 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 livebirths term pregnancies, and 716 LOP (≥ 37 weeks, LOP37) we could determine the GWG in 87% of cases. In a logistic regression model validating the independent association of optGWG, maternal ages and BMI, primiparity, smoking, chronic hypertension with term preeclampsia, opt GWG has a protective effect, aOR 0.74, p= 0.004. Primiparity, maternal BMI, chronic hypertension and maternal ages increase the risk. Incidence of LOP37 and crude OR in our simulation comparing optGWG with our cohort gave in overweight (25-29.9 Kg/m²) 0.57% vs 1.07% (OR 0.53, p=0.003); 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 overweight/obese patients together, OR 0.42, p < 0.0001.

Conclusions. Being overweight/obese have not to result in a higher risk of developing LOP, the results of this large retrospective population cohort suggest that targeted and strictly monitored interventions on adequate GWG might represent an effective method to reduce the rate of LOP and would have the potential to halve its incidence in overweight/obese women. These findings suggest a potentially achievable pathway to actively counterbalance the morbid effects of high BMIs; an approach urgently requiring adequately powered prospective trials.

Fundings: No specific fundings were used for this study

Keywords : *Preeclampsia, late-onset preeclampsia, epidemiology, pre-pregnancy body mass index*

ARTICLE SUMMARY

Strengths and limitations:

Strengths : .

. Exhaustive 18 year population-based preeclamptic cases (island population).

- Our maternity (university, level 3) is the only one providing services to follow and deliver all preeclamptic cases in the south of Reunion island (the other maternity is a private clinic, level 1 only).
- Observational study of a large cohort of women (66,373 singleton term births and 716 term pregnancies).
- In Reunion, especially during the 18-year observational period, overweight and obesity rates have continuously increased.

Limitations: The retrospective nature of this study, allowing observations based on associations

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INTRODUCTION

Worldwide obesity among adults has nearly tripled since 1975 according to the Global Health Observatory of the World Health Organization [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 IOM 2009 (US Institute of Medicine) recommendations [3], but there is a lack of consensus on what represents optimal gestational weight gain (GWG) during pregnancy.

In a previous study [4], we showed a linear association between pre-pregnancy maternal body mass index (ppBMI), neonatal weight (considering also small and large for gestational age categories), and gestational weight gain (GWG). Based on these birthweight outcomes, we provided d a formula to identify the ideal individual "optimal GWG" for each pregnant woman (allowing a window of ± 2Kg). Recently [5], we have also shown that high ppBMI (overweight and obesity class I to III) was specifically associated with late-onset preeclampsia (≥ 34 weeks of gestation, LOP, N=1,096 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 in 70% in medium-low income countries [6,7]), we therefore sought to investigate in our comprehensive epidemiological population perinatal database if women with an optimal GWG [4](from a birthweight perspective) would also have lower rates of other pregnancy complications, and for this particular study lower rates of LOP compared with women with an "inadequate GWG". As the formula that 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.

From January 1st, 2001, to June 30th, 2019, the hospital records of all women who gave birth at the maternity of the University South Reunion Island were abstracted in a standardized 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 the time of delivery and at the infant hospital discharge and regularly audited by appropriately trained staff. This epidemiological 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 have been used anonymously. All pregnant women in Reunion Island as part of the French National Health Care System have their prenatal visits, biological and ultasonographic examinations, 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 (ISSHP) relatively to the guidelines in force at the year of pregnancy. Early onset preeclampsia is defined as preeclampsia resulting in birth before 34 weeks of gestation, late onset preeclampsia at 34 weeks and onward [8]. In the present study, because optimal weight gain has been described for term pregnancies -37-42 weeks [4], we have selected only women who went to develop LOP and delivered at term (LOP37).

Design and study population

The maternity department of Saint Pierre hospital is a tertiary care centre that performs about 4,300 deliveries per year, thus representing about 80% of deliveries of the Southern area of Reunion Island, and it is the only level-3 maternity (the other maternity is a private clinic, level 1 which is not allowed to follow/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, which combines freedom of medical practice with nationwide social security. Prenatal system is based on scheduled appointments (9 prenatal visits and on average 4 ultrasounds) 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). Women are systematically weighted at their arrival in labour& delivery . In rare cases of imminent delivery (< 10%) the documented weight during the last antenatal visit prior to birth was used for calculations.

Primary outcome: We arbitrarily created 5 categories of GWG using the published formula (-1.2 ppBMI (kg/m²) ± 2 kg) [4] defined in our population of Reunion island:

- Optimal GWG range: optimal GWG result PLUS or MINUS 2 kg (the formula)
- Insufficient GWG
  - Moderately insufficient: adequate GWG minus 3 to minus 9 kg
  - Severely insufficient: adequate GWG minus 10 kg and below
- excessive GWG
  - Moderately excessive: adequate GWG PLUS 3 to plus 9 kg
  - Severely excessive: adequate GWG PLUS 10 kg and over

Statistical analysis

Data are presented as numbers and proportions (%) for categorical variables and as mean and standard deviation (SD) for continuous ones, as appropriate. Comparisons between groups were performed using χ^2-test and odds ratio (OR) with 95% confidence interval (CI) was also calculated. 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 have been recorded and analysed with the software EPI-INFO 7.1.5 (2008, CDC Atlanta, OMS), EPIDATA 3.0 and EPIDATA Analysis V2.2.2.183. Denmark

To validate the independent association of maternal age and other confounding factors on term preeclampsia we realized a multiple regression logistic model. Variables associated with term preeclampsia in bivariate analysis, with a p-value below 0.1 or 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 (version 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, optimal gestational weight gain (YES/NO), smoking, primiparity and maternal ages by increment of 5 years. We included these variables and calculated the χ^2 for trend (Mantel extension), the odds ratios for each exposure level compared with the first exposure level.

Patients and Public involvement. The South-Reunion perinatal database (since 2001) includes 264 items. It is considered as a fully medical database , datasheets are electronically completed solely by midwives, obstetricians and neonatologists. All epidemiological studies are obligatorily performed on anonymized data (French law). As such, there is no direct patient or public involvement.

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%) and as such recorded in the perinatal database. The overall number of cases of preeclampsia was 1,842, of which 106 multiple pregnancies . The number of cases of preeclampsia in singleton pregnancies was therefore 1,736, 69% of which 1,203 developed LOP, Figure 1. After excluding fetal deaths (in utero fetal deaths, medical terminations of pregnancies ≥22 weeks) and preterm pregnancies (< 37 weeks) the final study population was 66,373 normotensive term pregnancies and 716 LOP37. In these 66,373 term pregnancies, we could determine the GWG (calculated as weight at delivery minus booking weight) in 57,703 pregnancies (86.9% of our term singleton deliveries), and in 603 (84.2%) of our LOP37 patients.

TABLE 1 shows the main population characteristics. Preeclamptic mothers were in average older than controls (a difference of 0.6 year, 28.3 vs 27.7, p= 0.01), were more prone to be primiparas (OR 1.94, p < 0.0001), to live single OR 1.16, p= 0.05, to present gestational diabetes mellitus, OR 1.37, p= 0.004, had a much higher rate of chronic hypertension, OR 6.6, p < 0.0001, and had a much higher BMI 27.4 vs 24.7 kg/m², p < 0.0001, with higher incidences in all categories of obesity (class I to III), p < 0.0001. There was no difference between PE women and controls in terms of level of education, unemployment, geographical origin. Pregnancies beneficiated of good prenatal followup, on average 9 prenatal visits and 4 ultrasounds. It is of note that in spite of a shorter length of gestation 38.2 vs 38.9 weeks (p < 0.0001), preeclamptic women had a much higher gestational weight gain of 2.2 kg in average: 14.3 vs 12.1 kg, p < 0.0001, and lighter babies 2918 vs 3187g, p < 0.0001. They had higher rates of low birthweight < 2500g and SGA babies, respectively OR 4.9 and 2.7, p < 0.0001.

TABLE 2 summarizes our simulation between only the optimal GWG women according to our equation ± 2kg and what we had actually observed during these 18 year of clinical practice, with crude Odds-ratios. First of all, non-overweight women < 25 kg/m² represented 61% of the entire cohort (35,402/57,703) and presented a low rate of term preeclampsia (0.77%). Overweight women presented a PE rate of 1.07% (close to the global rate of all the population (1.04%), class I obesity a PE rate of 1.56%, and severe obese ≥ 35 kg/m² a PE rate of 2.55%. In overweight women, if women had gained an adequate GWG, they would have had a PE rate of 0.56% (vs

1.07%, OR 0.53, p= 0.03), class I obese a PE rate of 0.7% (vs 1.56%, OR 0.44, p= 0.01), and in severely obese women ≥ 35 kg/m² a PE rate of 0.86% (vs 2.55%, OR 0.33, p= 0.06).

TABLE 3 ANALYSES MORE SPECIFICALLY THE INCIDENCE OF LOP PER CATEGORY OF MATERNAL BOOKING BMI AND DIFFERENT GWG's.

Table 1 present the observed overall LOP rates in the different BMI categories, and the LOP rates within these categories for pregnant women with a below optimal GWG, optimal GWG and above GWG.

NON OVERWEIGHT WOMEN at time of the booking visit (< 25 kg/m²), N= 35,402 (61% of our parturients). Adequate GWG: 21.0% (7456/35,402); in these women, the LOP rate is of 0.77%. It is of note that the 62% of women with insufficient GWG (17,559+ 4465) had a LOP rate of 0.4-0.5% (OR 0.50 and 0.61, p= 0.002, as compared with adequate GWG), but as previously published at the expense of a 20% rate of SGA.

OVERWEIGHT WOMEN 25-29.9 kg/m², N= 12,369 (21% of our parturients). Adequate GWG: 28.0% (3471/12,369); the observed overall rate in this category is 1.07% vs 0.57% in women with optimal GWG (OR 0.53 [0.32-0.84], p= 0.003). The 47% of women with excessive weight gain (n=4604 and n =679) had a high risk of LOP of .3.4% for those with a gain over 10Kg excess (OR 4.6, p <0.0001), and 1. 3.% of LOP (OR 2.2 , p <0.0001) for those with an excess of 3-9kg as compared with adequate GWG.

OBESE WOMEN CLASS I (30-34.9 kg/m²) N= 6019 (10.4% of our parturients). Adequate GWG: 18.8% (1134/6019); he observed overall rate in this category is 1.56% vs 0.7% for women with an optimal GWG. Adequate GWG compared with the overall LOP rate gave an OR of 0.44 [0.20-0.88], p= 0.01. The 71% of women with excessive weight gain (n=2799 and n=1476) had a high risk of LOP, rate of .2.6% for those with a gain over excess 10Kg (OR 3.8, p <0.0001), and 1. 5.% of LOP (OR 2.2 , p= 0.02) with those with 3-9kg excess as compared with adequate GWG.

OBESE WOMEN CLASS II and III (≥ 35 kg/m²), N= 3913 (6.8% of our parturients). Adequate GWG: 6% (233/3913).; he observed rate in this category is 2.55 % vs 0.86 % in women with optimal GWG(OR 0.33 [0.04-1.2], p= 0.06). The 91% of class II/III obese women with excessive weight gain (N= 2314 and N = 1259) had an

increased risk of LOP; 3.2% for those with a gain over excess 10Kg (OR 3.8, p = 0.02), and

1. 9.% of LOP (OR 2.2 , NS) with those with excess of 3-9kg as compared with adequate GWG.

The overall LOP incidence in non-obese women , 60% of our population is 0.77% (Table 2). In overweight/obese women, representing 40% of population, the LOP37 rate is 1.46%. In the overweight/obese combined women who managed to achieve an optimal GWG the LOP37 rate was 0.62% (30/4838 compared with 326/22,246) (OR = 0. 42 [0.28-0.60], p< 0.0001) .

TABLE 4. Multiple logistic regression model to validate the independent association of adequate GWG and other confounding factors for term preeclampsia. Optimal GWG and smoking (negative coefficient of -0.30) have a similar protective effect of 0.74, p < 0.001. Primiparity, maternal BMI, chronic hypertension and maternal ages increase the risk. Controlling for all the other factors, maternal pre-pregnancy BMI is still an independent factor (coefficient 0.06, increment of 6% per increment of 5 kg/m²).

DISCUSSION .

In a recent study on the same population cohort, we demonstrated that being overweight or obese is primarily a risk factor for late onset preeclampsia, LOP (≥ 34 weeks gestation) [5]. The present study demonstrates that the actual risk of an overweight/obese women of developing LOP is strongly influenced (association) by her GWG. Maternal weight gain is closely linked to birthweight. In a previous study we also arrived at a mathematical model to calculate optimal GWG from a neonatal birthweight perspective.

In short, we previously demonstrated [4] that only women with a normal BMI give birth to neonates with birthweights following a normal Gaussian distribution, i.e with (per definition) 10% small for gestational age (SGA) and 10% large for gestational age (LGA) neonates, while lean women (15-19 kg/m²) have a high rate of 15% of SGA babies and a very low rate, of 5%, of LGA newborns. Conversely, very obese women (40-44.9 kg/m²) have exactly the reverse 7% SGA and 20% of LGA [4]. Further analysis showed that women in the low or high BMI categories could still achieve a normal (10% SGA and 10% LGA) birthweight distribution if they achieved a certain 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 BMI spectrum followed a straight line, allowing a simple equation y= ax+b to define the optimal gestational weight gain (GWG).

The data of the current study indicate that for overweight and obese women achieving an optimal GWG is associated with about a halving of the LOP37; in overweight (25-39.9 kg/m²) OR 0.53 (p= 0.003, a 47% decrease of LOP), in obese (30-34.9 kg/m²) OR 0.44, p= 0.01, (a 56% decrease), and in severely obese (35 kg/m² and over), OR of 0.33 (p= 0.06, 67% decrease). Therefore, the main findings of this study appear to indicate that optimizing GWG might represent an effective method to reduce the LOP37 rate in overweight/obese women.

A concerning further finding was that fact that over these 18 year only 21% (12,294/57,703) of women could be considered to have an optimal GWG during their pregnancy. Most likely, this is quite similar to 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 gestational weight gain [3].

For a decade, there has been a very strong ongoing controversy on gestational weight gain in the literature, with the strongest debates on what to do with obese women, with in particular the question wehther or not the IOM advice of a GWG 5-9 kg recommendations for obese is adequate ? Would it not be better to accept a GWG below 5 kg, or even a gestational weight gain loss [9-12]? The findings in this study and our previous findings on normal birthweight distribution indicate that the IOM guidelines are incorrect. Also Kiel et al [13], Marguerison Zilko et al [12] and Oken et al [14] recommended weight loss in superobese pregnant women, concept challenged by Kapadia et al [15].

We have put an online calculator consultable on smart phone at REPERE.RE (REseau PErinatal REunion), in three languages (French, Spanish and English) [16], and any 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]. Late onset preeclampsia (34 weeks onward) being by far the main pattern of the disease (90% in high-income countries, of which 2/3 are term preeclampsia (37 weeks onward [17,18]), and approximately in 70% in medium-low income countries [6,7]). There is a strong current ongoing consensus on obesity, GWG and consequences for maternal-fetal health, especially concerning preeclampsia [17-21]. Urgent further work is required to identify ways to assist women in achieving an optimal GWG, with further RCT to confirm that such intervention would translate in a marked reduction in LOP rates.

In our logistic regression model, controlling for all the other factors, maternal pre-pregnancy BMI is still an independent factor (coefficient 0.06, increment of 6% per increment of 5 kg/m²), which is counterbalanced by the effect of optimal gestational weight gain (optGWG): adjusted OR 0.74, p= 0.007 identical to the crude OR of 0.74, p= 0.004, Table 2. It is of note that the well-known protective effect of smoking in late onset preeclampsia is confirmed [5], while, in our population, preeclamptic women were less smokers than controls 8.3 vs 12.1%, Table 1.

The strength of our study is the capturing of all perinatal outcomes in a population of the area (ap. 360,000 inhabitants, and 5,100 births per year, all receiving level 3, European standard of care. With 4,300 births per year, the university maternity represents 82% of all births in the south of the island. But, as a level 3 (the other maternity is a private clinic, level 1), we are sure all the preeclampsia cases were referred to our hospital during the 18.5 year period. This is therefore a real population-based study. The data in this large cohort are homogeneous as they were collected in a single center (no intercenter variability) and not based on national birth registers but directly from medical records (avoiding inadequate codes). One weakness of this study is that patients with preeclampsia, especially severe preeclampsia, tend to have a rapid weight gain over the last days-weeks prior to diagnosis due to edema (a high difference of 2.7 kg, Table 1), but this bias should be the same in the different BMI categories . In addition, the other obvious weakness is the retrospective nature of this study, demonstrating association and not necessarily causation but we sincerely hope that our observations will trigger proper prospective trials because the potential health care benefits are immense.

CONCLUSION: Our results suggest 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 late onset preeclampsia: we may help actively to counter balance the morbid effects of high BMIs by individualized counselling women on their GWG. This approach may urgently require adequately powered prospective trials.

Authors' contributions. Pierre-Yves Robillard participated at all the stages of the study (data collection, analysis, writings et..). Brahim Boumahni participated at the data collection. Thomas Hulsey verified all the epidemiological calculations and participated deeply to the data analysis. Gustaaf Dekker, Marco Scioscia and Thomas Hulsey expertised the analysis, the text and the final writings (and the English Language). Malik Boukerrou, 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.

No additional data available.

Competing interest statement. There are no competing interests for any author

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- CPP) is not required for this non-interventional study based on retrospective, anonymized data of authorized collections and written patient consent is not needed. Nevertheless, the study was registered on UMIN Clinical Trials Registry (identification number is UMIN000037012).

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Table 1. Population characteristics. Term pregnancies ≥ 37 weeks gestation

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 [1.7-2.25]	< 0.0001
Women living single	283 (39.6)	23,579 (36.0)	1.16 [1.0-1.35]	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)	54425 (82.2)		NS
BMI (mean ± sd,kg/m²)	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 [1.9-2.6]	< 0.0001
BMI categories • ≤19 (underweight) • 20-24 (normal) • 25-29 overweight • 30-34 (obesity I) • 35-39 (obesity II) • >40 (obesity III)	 82 (11.9) 233 (34.1) 152 (22.2) 104 (15.2) 70 (10.2) 43 (6.3)	 13,342 (21.0) 25,502 (40.2) 13,671 (21.6) 6671 (10.1) 2841 (4.5) 1396 (2.2)		< 0.0001
Smoking	59 (8.3)	8031 (12.1)	0.65 [0.49-0.85]	0.001
Nb of prenatal visits	9.0 ± 2.76	9.0 ± 2.73		NS
Number 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 [1.1-1.69]	0.004
Chronic hypertension	56 (7.8)	829 (1.3)	6.6 [5.0-8.8]	< 0.0001
Hospitalization	323 (45.1)	7416 (11.3)	6.4 [5.5-7.5]	< 0.0001
Delivery (Weeks)	38.2 ± 1.1	38.9 ± 1.1	Difference 0.7 week	< 0.0001
C-section	230 (32.1)	9472 (14.4)	2.8 [2.4-3.3]	< 0.0001
Induced delivery	523 (73.0)	14,078 (21.4)	9.9 [8.4-11.7]	< 0.0001
Birth weight (g)	2918 ± 508	3187 ± 440	Difference 269g	< 0.0001
Low BW <2500g	149 (20.8)	3357 (5.1)	4.9 [4.1-5.9]	< 0.0001
Small for gestational age	170 (23.7)	6777 (10.3)	2.71 [2.27-3.2]	< 0.0001
Large for gestational age	56 (7.8)	6231 (9.5)	0.81	0.12

Table 2. Incidence of term preeclampsia (%): Observed rates versus simulation if women had an adequate GWG in the same population, Crude Odds Ratios. In all women (N=57,703), observed incidence of LOP: 1.04%: 603/57,703. LOP incidence in all adequate GWG: 0.78% (96/12,294). OR = 0.74 [0.59-0.92], p= 0.004.

	Non overweight < 25 kg/m² N= 35,402	**OR 95% CI**	**P value**	**Overweight 25-29.9kg/m² N= 12,369**	**OR 95% CI**	**P value**
Number of observed cases	276 (0.77%)			133 (1.07%)		
Simulation: Nb of preeclampsia cases in women with adequate GWG± 2kg (%)	N= 7456 66 (0.88%)	**0.88**	0.17	N= 3471 20 (0.57%)	**0.53 [0.32-0.84]**	0.003
	Obese 30-34.9kg/m² N= 6019	**OR 95% CI**	**P value**	**Severe Obese ≥ 35 kg/m² N= 3913**	**OR 95% CI**	**P value**
Number of observed cases (%)	94 (1.56%)			100 (2.55%)		
Simulation: Nb of preeclampsia cases in women with adequate GWG± 2kg (%)	N= 1134 8 (0.7%)	**0.44 [0.20-0.88]**	**0.01**	N= 233 2 (0.86%)	**0.33 [0.04-1.2]**	**0.06**

Table 3. Incidence of term preeclampsia (%) per category of pre-pregnancy maternal BMI. All women 57,703. Observed incidence of LOP: 1.04%: 603/57,703. LOP incidence in all adequate GWG 0.78% (96/12,294).

Differences with optimal Weight gain	**Non obese <25kg/m² (%) N= 35,402**	**OR 95% CI**	**P value**	**Overweight 25-29.9kg/m² (%) N= 12,369**	**OR 95% CI**	**P value**
-10 kg and lower	20/ 4465 (0.4)	0.50 [0.3-0.82]	0.003	0/259 (0.0)	-	-
-3-9kg	97/17759 (0.5)	0.61 [0.45-0.86]	0.002	23/2807 (0.8)	**1.4**	0.12
ADEQUATE GWG ± 2kg	**66/7456 (0.88)**	**Reference**	-	**20/3471 (0.57)**	**Reference**	-
+3-9kg	70/5063 (1.4)	1.57 [1.1-2.2]	0.004	58/4604 (1.3)	**2.2 [1.3-3.7]**	<0.0001
10kg+	23/679 (3.4)	3.9 [2.4-6.3]	<0.0001	23/679 (3.4)	**4.6 [2.6-8.2]**	<0.0001
Odds Ratios: ADEQUATE GWG vs GLOBAL OBSERVED RATES	276/35402 (0.77%)	**0.88**	0.17	133/12369 (1.07%)	**0.53 [0.32-0.84]**	**0.003**
Differences with optimal Weight gain	**Obese 30-34.9kg/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)	-	-
-3-9kg	4/545 (0.7)	**1.04**	0.47	1/94 (1.1)	**1.2**	0.43
ADEQUATE GWG ± 2kg	**8/1134 (0.7)**	**Reference**	-	**2/233 (0.86)**	**Reference**	-
+3-9kg	43/2799 (1.5)	2.2 [1.07-5]	0.02	24/1259 (1.9)	2.2	0.13
10kg+	39/1476 (2.6)	3.8 [1.8-8.8]	<0.0001	73/2314 (3.2)	3.76 [1.1-23]	0.02
Odds Ratios: ADEQUATE GWG vs GLOBAL OBSERVED RATES	94/6019 (1.56%)	**0.44 [0.20-0.88]**	**0.01**	100/3913 (2.55%)	**0.33 [0.04-1.2]**	**0.06**

Adequate GWG being taken as reference, the bottom odds-ratios represent what would occur in women following the recommendations [4] vs reality.

TABLE 4. Multiple logistic regression model to validate the independent association of adequate GWG and other confounding factors for term preeclampsia.Optimal GWG and smoking (negative coefficient) have a similar protective effect of 0.74. Primiparity, maternal BMI, chronic hypertension and maternal ages increase the risk. Controlling for all the other factors, maternal pre-pregnancy BMI is still an independent factor (coefficient 0.06, increment of 6% per increment of 5 kg/m²).

	Multiple Logistic Regression for Term preeclampsia (≥ 37 weeks)			
	coefficient	**Odds Ratio**	**95% CI**	**P**
Optimal GWG (yes/No)	-0.30	0.73	[0.59-0.92]	0.007
Smoking	-0.29	0.74	[0.56-0.98]	0.04
Maternal BMI (increment of 5 kg/m²)	0.06	1.06	[1.05-1.07]	<0.0001
Gestational diabetes mellitus	-0.058	0.94	[0.74-1.18]	0.61
Chronic hypertension	1.51	4.5	[3.3-6.2]	<0.0001
Maternal Age (increment of 5 years of age)	0.03	1.03	[1.02-1.05]	<0.0001
Primiparity	1.07	2.9	[2.45-3.48]	<0.0001

Figure Legend: Flow chart of Reunion cohort (2001-2019)

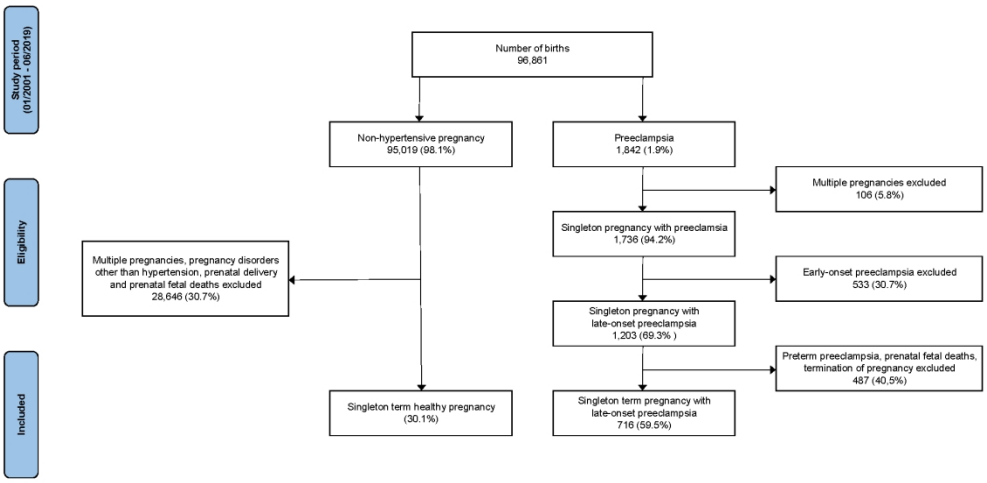

Figure Legend: Flow chart of Reunion cohort (2001-2019)

176x86mm (300 x 300 DPI)

Reporting checklist for case-control study.

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		Reporting Item	Page Number
Title and abstract			1-2
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
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Objectives	#3	State specific objectives, including any prespecified hypotheses	2&4
Methods			
Study design	#4	Present key elements of study design early in the paper	2& 5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
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Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	
Study size	#10	Explain how the study size was arrived at	
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	
Statistical methods	#12c	Explain how missing data were addressed	
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	
Statistical methods	#12e	Describe any sensitivity analyses	
Results			7-8
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	
Participants	#13b	Give reasons for non-participation at each stage	
Participants	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they	

		were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	
Discussion			9-11
Key results	#18	Summarise key results with reference to study objectives	
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9-10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

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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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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 livebirth, 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 BMI, primiparity, smoking habit, chronic hypertension with term preeclampsia, opt GWG 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 overweight and obese patients in a linear manner: 0.57% vs 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 overweight/obese patients 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 overweight/obese women. These findings suggest a potentially achievable pathway to actively counterbalance the morbid effects of high BMIs, so we solicit adequately powered prospective trials.

Fundings: No specific fundings were used for this study

Keywords : *Preeclampsia, late-onset preeclampsia, epidemiology, pre-pregnancy body mass index*

ARTICLE SUMMARY

Strengths and limitations:

Strengths : .

- . 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 term pregnancies).
- The cohort of overweight/obese pregnant women studied represented a significant part of the whole population.

Limitations: Retrospective population study that allowed observations based on associations

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INTRODUCTION

Worldwide obesity among adults has nearly tripled since 1975 according to the Global Health Observatory of the World Health Organization [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 IOM 2009 (US Institute of Medicine) recommendations [3], but there is no consensus on what represents optimal gestational weight gain (GWG) during pregnancy.

We have previously demonstrated [4] that there is a linear association between pre-pregnancy 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" (OptGWG) for each pregnant woman (allowing a window of ± 2Kg) [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=1,096 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 birthweight 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 01-01-2001, to 30-06-2019 were abstracted in a standardized 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 (ISSHP) relatively to the guidelines in force at the year of pregnancy. Early onset preeclampsia is defined when diagnosis is made before 34 weeks of gestation while late onset preeclampsia manifests at ≥ 34 weeks [8]. Because OptGWG has been assessed for term pregnancies -37-42 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 4,300 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 1private 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 (9 prenatal visits and 4 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 5 categories of GWG using the published formula (-1.2 ppBMI (kg/m^2) + 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 plus10 kg and over

Statistical analysis

Data are presented as numbers and proportions (%) for categorical variables and as mean and standard deviation (SD) for continuous variables, as appropriate. Comparisons between groups were performed using χ^2-test and odds ratio (OR) with 95% confidence interval (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 7.1.5 (2008, CDC Atlanta, OMS), EPIDATA 3.0 and EPIDATA Analysis V2.2.2.183. 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 (version 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, optimal gestational weight gain (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 odds ratios 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.

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- CPP) is not required for this non-interventional study based on retrospective, anonymized data of authorized collections and written patient consent is not needed.

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 1,842, of which 106 cases occurred in multiple pregnancies. The number of cases of preeclampsia in singleton pregnancies was therefore 1,736 with 1,203 (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) and were more represented in all categories of obesity (class I to III; p < 0.0001). Level of education, rate of unemployment, and geographical origin (city versus 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 (2,918 vs 3,187g; p < 0.0001). The rate of low birthweight (<2,500g) and 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-Opt GWG 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 + 4,465) 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 obese women Class I (30-34.9 kg/m², N= 6019, 10.4% of the study population) the overall observed

LOP37 rate was 1.56%. In obese women class II and III (≥ 35 kg/m², N= 3,913, 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% (30/4,838 compared with 326/22,246) (OR = 0. 42 [0.28-0.60], 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, maternal pre-pregnancy BMI 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 optimizing GWG might represent an effective method to reduce the LOP37 rate in overweight/obese women. GWG is closely linked to birthweight. In a previous study we derived a mathematical model to calculate optimal GWG from a birthweight perspective.

In short, we previously demonstrated [4] that only women with a normal BMI give birth to neonates with birthweights followed a normal Gaussian distribution, i.e. with (by definition) 10% small for gestational age (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, morbidly obese women (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) birthweight 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 optimal gestational weight gain (OptGWG).

The data of the current study demonstrate that overweight and obese women 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 severely obese patients (BMI 35 kg/m² and over), the OR was 0.33 (p= 0.06, 67% decrease). The fact that over 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 obese women, in particular the question whether or not the IOM advice of a GWG of 5-9 kg for obese women is adequate [9-12]. The findings of this study and our previous findings on GWG and normal birthweight distribution 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 3 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 late onset preeclampsia, 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]). Optimizing GWG is a hot topic in current perinatology, with a particular focus on long term maternal and child health. This study indicates that optimizing 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 randomized 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 (ap. 360,000 inhabitants, and 5,100 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 edema (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 late onset preeclampsia: we may help actively to counterbalance the morbid effects of high BMIs by individualized counselling on their GWG. This approach urgently requires adequately powered prospective trials.

Authors' contributions. Pierre-Yves Robillard participated at all the stages of the study (data collection, analysis, writings et..). Brahim Boumahni participated at the data collection. Thomas Hulsey verified all the epidemiological calculations and participated deeply to the data analysis. Gustaaf Dekker, Marco Scioscia and Thomas Hulsey expertised the analysis, the text and the final writings (and the English Language). Malik Boukerrou, 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.

Data availability. No additional data available.

Competing interest statement. There are no competing interests for any author

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Table 1. Population characteristics. Term pregnancies ≥ 37 weeks gestation

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 [1.7-2.25]	< 0.0001
Women living single	283 (39.6)	23,579 (36.0)	1.16 [1.0-1.35]	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)	54425 (82.2)		NS
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 [1.9-2.6]	< 0.0001
BMI categories • ≤19 (underweight) • 20-24 (normal) • 25-29 overweight • 30-34 (obesity I) • 35-39 (obesity II) • >40 (obesity III)	 82 (11.9) 233 (34.1) 152 (22.2) 104 (15.2) 70 (10.2) 43 (6.3)	 13,342 (21.0) 25,502 (40.2) 13,671 (21.6) 6671 (10.1) 2841 (4.5) 1396 (2.2)		< 0.0001
Smoking	59 (8.3)	8031 (12.1)	0.65 [0.49-0.85]	0.001
Nb of prenatal visits	9.0 ± 2.76	9.0 ± 2.73		NS
Number 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 [1.1-1.69]	0.004
Chronic hypertension	56 (7.8)	829 (1.3)	6.6 [5.0-8.8]	< 0.0001
Delivery (Weeks)	38.2 ± 1.1	38.9 ± 1.1	Difference 0.7 week	< 0.0001

Table 2. Incidence of term preeclampsia (%): Simulation versus Observed rates if women had an adequate GWG in the same population, Crude Odds Ratios.

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

Table 3. Incidence of term preeclampsia (%) per category of adequate or non-adequate GWG (adequate GWG as reference). All women 57,703. Observed incidence of LOP: 1.04%: 603/57,703. LOP incidence in all adequate GWG 0.78% (96/12,294).

Differences with Adequate Weight gain	**Non overweight <25kg/m² (%) N= 35,402**	**OR 95% CI**	**P value**	**Overweight 25-29.9kg/m² (%) N= 12,369**	**OR 95% CI**	**P value**
-10 kg and lower	20/ 4465 (0.4)	0.50 [0.3-0.82]	0.003	0/259 (0.0)	-	-
-3-9kg	97/17759 (0.5)	0.61 [0.45-0.86]	0.002	23/2807 (0.8)	**1.4**	0.12
ADEQUATE GWG ± 2kg	**66/7456 (0.88)**	**Reference**	-	**20/3471 (0.57)**	**Reference**	-
+3-9kg	70/5063 (1.4)	1.57 [1.1-2.2]	0.004	58/4604 (1.3)	**2.2 [1.3-3.7]**	<0.0001
10kg+	23/679 (3.4)	3.9 [2.4-6.3]	<0.0001	23/679 (3.4)	**4.6 [2.6-8.2]**	<0.0001
Differences with Adequate Weight gain	**Obese 30-34.9kg/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)	-	-
-3-9kg	4/545 (0.7)	**1.04**	0.47	1/94 (1.1)	**1.2**	0.43
ADEQUATE GWG ± 2kg	**8/1134 (0.7)**	**Reference**	-	**2/233 (0.86)**	**Reference**	-
+3-9kg	43/2799 (1.5)	2.2 [1.07-5]	0.02	24/1259 (1.9)	2.2	0.13
10kg+	39/1476 (2.6)	3.8 [1.8-8.8]	<0.0001	73/2314 (3.2)	3.76 [1.1-23]	0.02

TABLE 4. Multiple logistic regression model to validate the independent association of adequate GWG and other confounding factors for term preeclampsia. Optimal GWG and smoking (negative coefficient) have a similar protective effect of 0.74. Primiparity, maternal BMI, chronic hypertension and maternal ages increase the risk. Controlling for all the other factors, maternal pre-pregnancy BMI is still an independent factor (coefficient 0.06, increment of 6% per increment of 5 kg/m²).

	Multiple Logistic Regression for Term preeclampsia (≥ 37 weeks)			
	coefficient	**Odds Ratio**	**95% CI**	**P**
Optimal GWG (Yes/No)	-0.30	0.73	[0.59-0.92]	0.007
Smoking	-0.29	0.74	[0.56-0.98]	0.04
Maternal BMI (increment of 5 kg/m²)	0.06	1.06	[1.05-1.07]	<0.0001
Gestational diabetes mellitus	-0.058	0.94	[0.74-1.18]	0.61
Chronic hypertension	1.51	4.5	[3.3-6.2]	<0.0001
Maternal Age (increment of 5 years of age)	0.03	1.03	[1.02-1.05]	<0.0001
Primiparity	1.07	2.9	[2.45-3.48]	<0.0001

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE case-controlreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			1-2
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	2&4
Methods			
Study design	#4	Present key elements of study design early in the paper	2& 5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	5
Eligibility criteria	N/A	For matched studies, give matching criteria and the number of controls per case	
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	5-6

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	11
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6
Statistical methods	N/A	Describe any methods used to examine subgroups and interactions	
Statistical methods	N/A	Explain how missing data were addressed	
Statistical methods	N/A	If applicable, explain how matching of cases and controls was addressed	
Statistical methods	N/A	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	8
Participants	N/A	Give reasons for non-participation at each stage	

Participants	N/A	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	16
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	N/A	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17-19
Main results	N/A	Report category boundaries when continuous variables were categorized	5-6
Main results	N/A	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	N/A	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10-11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2