

PEER REVIEW HISTORY

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ARTICLE DETAILS

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| TITLE (PROVISIONAL) | GESTATIONAL WEIGHT GAIN AND RATE OF LATE-ONSET PREECLAMPSIA: A RETROSPECTIVE ANALYSIS ON 57,000 SINGLETON PREGNANCIES IN REUNION ISLAND |
| AUTHORS | Robillard, Pierre-Yves; Dekker, Gustaaf; Boukerrou, Malik; boumahni, brahim; Hulseay, Thomas; Scioscia, Marco |

VERSION 1 - REVIEW

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| REVIEWER | L. Hirsch University of Toronto, ON, Canada |
| REVIEW RETURNED | 07-Jan-2020 |

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| GENERAL COMMENTS | <p>Thank you for the opportunity to review the manuscript by Robillard et al. The study aimed to assess the influence of GWG on the risk for late-onset preeclampsia (LOP). Overall, I believe that the manuscript needs major editing by a native English speaker.</p> <p>These are my comments:</p> <ol style="list-style-type: none">1. Was GWG calculated at the time of delivery? Before delivery? After delivery? The timing of weighing the patient can have major impact on the total GWG – please elaborate.2. Patients with preeclampsia, especially severe one, tend to have a rapid weight gain over the last days-weeks prior to diagnosis due to edema. Perhaps preeclampsia was causing the increased GWG and not the other way around?3. The overall rate of preeclampsia (1.9%) is relatively low as compared to the literature – can the author elaborate on this matter?4. Figure 1 – the objective of the study is to test the hypothesis that GWG can modify the rate of LOP – the data presented in this figure is irrelevant to the study and can be discarded.5. The term “NORMALLY SHAPED WOMEN” to describe women with BMI <25kg/m² is inappropriate mainly since it implies that women with BMI > 25 are not normally shaped.6. Please define better the terms insufficient or excessive GWG – is +4kg GWG adequate or insufficient? Very hard to understand from the Methods section.7. The analysis is very complex and not easy to follow. I would suggest the following:<ol style="list-style-type: none">a. Figure 1 – selection of the study cohort.b. Analysis 1 – Main exposure – GWG (adequate vs. excessive). Main outcome: LOP.c. Subanalysis – according to prepregnancy BMI groups.8. The discussion deals with SGA and LGA and GWG categories – this is not the aim of this study according to the Objective section of |
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| | the abstract and Introduction. |
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| REVIEWER | Olof Stephansson Karolinska Institutet, Sweden |
| REVIEW RETURNED | 14-Jan-2020 |

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| GENERAL COMMENTS | <p>Review of manuscript bmjopen-2019-036549</p> <p>Thank you for the opportunity to review this study. This is a retrospective study on the association between gestational weight gain (GWG) and incidence of late onset preeclampsia (LOP) based on a cohort of 66,373 births in the South Reunion Island. In general, this manuscript is difficult to follow and there is scarce information about the methods used. The conclusion appears to overstate the findings of the study given its observational design.</p> <p>General comments</p> <ol style="list-style-type: none"> 1. The manuscript would improve with language editing for English grammar and style. 2. How were the OR calculated? Was it a crude or adjusted analysis? If adjusted, please present variables adjusted for and the rationale for the confounder selection. Were there any missing data in the cohort? If yes, how was this handled? 3. If the scope of the article was to study the association between GWG and late onset preeclampsia why have the authors included the section and Figure 1 on SGA, LGA and caesarean section? Please remove this from the manuscript and instead provide the reader with a Table 1 describing the characteristics of the study population. 4. How was the adequate GWG versus Global Observed Rates calculated? Is this a simulation? In what way should this information be interpreted? <p>Specific comments</p> <ol style="list-style-type: none"> 1. The article summary needs revision as it is not describing the strengths and limitations of the study in an appropriate way. 2. In the Introduction, please explain the NHS and IOM abbreviations to the reader. 3. In the methods section, what was the rationale for selecting the 2 sub categories for insufficient or excessive GWG? Were these selected a priori? 4. As for the study cohort, non-preeclamptic pregnancies is a better description than healthy pregnancies given that they could have other disorders and diseases besides preeclampsia. 5. It would be advisable to provide the manuscript with a flow chart. 6. The authors should put more emphasis on the limitations of the study and discuss them in the limitations section of the Discussion. 7. The conclusion of the Discussion needs editing and should focus on the findings and interpretations of the present study on GWG and late onset preeclampsia. 8. Unfortunately Figure 1 could not be properly visualized for the review of the manuscript. |
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| REVIEWER | Melania M Amorim Instituto de Medicina Integral de Pernambuco (IMIP), Recife, Pernambuco, Brazil |
| REVIEW RETURNED | 27-Jan-2020 |

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| GENERAL COMMENTS | <p>This is an important paper that address an important question in public health. Excessive GWG is related with adverse pregnancy outcomes and LOP is a problem because this is the more frequent form of preeclampsia. If preventing excessive GWG could prevent LOP, however, remains to be established.</p> <p>Some points that require revision:</p> <p>Introduction should end with formulation of the general objective.</p> <p>In the Section "Definition of exposure and outcomes", exposure should be the categories of GWG and the main outcome the frequency of LOP, SGA and LGA could be secondary outcomes</p> <p>In line 7 of Results section: "The study population therefore consisted of 1,736", this is not the study population, this is the number of cases of preeclampsia in singleton pregnancies.</p> <p>I think that a table with main characteristics of the population with and without preeclampsia should be presented as Table 1</p> <p>Figure 1 is a secondary outcome and should be presented after the main results respective to frequency of LOP. This is a typo error (Figure 1 'shows' and not 'show')</p> <p>The plan of statistical analysis was well written and conducted.</p> |
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1 In red colour in the text

Reviewer Name

Liran Hiersch

Institution and Country

University of Toronto, ON, Canada

Please state any competing interests or state 'None declared':
None.

Please leave your comments for the authors below

Thank you for the opportunity to review the manuscript by Robillard et al. The study aimed to assess the influence of GWG on the risk for late-onset preeclampsia (LOP).

Overall, I believe that the manuscript needs major editing by a native English speaker.

Guus Dekker mainly worked on the English language

These are my comments:

1. Was GWG calculated at the time of delivery? Before delivery? After delivery? The timing of weighing the patient can have major impact on the total GWG – please elaborate.

In methods this sentence has been added: "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."

2. Patients with preeclampsia, especially severe one, tend to have a rapid weight gain over the last days-weeks prior to diagnosis due to edema. Perhaps preeclampsia was causing the increased GWG and not the other way around?

We have added in the discussion (in strength and weaknesses) the sentence: "One weakness of this retrospective study is that patients with preeclampsia, especially severe one, tend to have a rapid weight gain over the last days-weeks prior to diagnosis due to edema, but this bias should be the same in all categories (optimal, excessive or insufficient weight gain)".

3. The overall rate of preeclampsia (1.9%) is relatively low as compared to the literature – can the author elaborate on this matter?

The number of 96,861 births is in fact the total number of births in the Southern part of the island where there are only 2 maternities: ours, the University Hospital (level 3) where 77,906 births occurred (80.2% of South-Reunion). The remaining occurred in the single private maternity (level 1) we have in the area. The private maternity is not allowed to manage and deliver preeclampsia (being level 1). In our settings the preeclampsia rate was 2.5% overall, and 2.4% if we consider only singleton pregnancies. The incidence of 1.9% includes all births of South-Reunion, and we have no special explanation of this relatively low rate.

We have precised this with the sentence: "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%) recorded in our database. The overall cases of preeclampsia was of 1,842, of which 106 multiple pregnancies".

4. Figure 1 – the objective of the study is to test the hypothesis that GWG can modify the rate of LOP – the data presented in this figure is irrelevant to the study and can be discarded.

After direct request of reviewer 1 and 2, and critics from reviewer 3, we have removed totally the figure from the paper. As a matter of fact, the reviewers are right: SGA, LGA and cesarean-section rates are absolutely not the purpose of the present paper

5. The term "NORMALLY SHAPED WOMEN" to describe women with BMI <25kg/m² is inappropriate mainly since it implies that women with BMI > 25 are not normally shaped. The term has been replaced by NON OVERWEIGHT women

6. Please define better the terms insufficient or excessive GWG – is +4kg GWG adequate or insufficient? Very hard to understand from the Methods section.

We have precised this point in methods:

We arbitrarily created 5 categories of GWG using the published formula $(-1.2 \text{ ppBMI (kg/m}^2) \pm 2 \text{ kg)}$ [4] defined in our population of Reunion island:

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

7. The analysis is very complex and not easy to follow. I would suggest the following:

- a. Figure 1 – selection of the study cohort.
- b. Analysis 1 – Main exposure – GWG (adequate vs. excessive). Main outcome: LOP.
- c. Subanalysis – according to prepregnancy BMI groups.

Instead of ONE Table, there are now 4 Tables. Table 1 maternal characteristics (required by reviewer 1 and 3), Table 2 crude OR between optimal GWG and the cohort

Table 3 (ex Table 1), crude OR with insufficient and excessive GWG.

Table 4: LOGISTIC REGRESSION MODEL

8. The discussion deals with SGA and LGA and GWG categories – this is not the aim of this study according to the Objective section of the abstract and Introduction.

a) After direct request of reviewer 1 and 2, and critics from reviewer 3, we have removed totally the figure from the paper. As a matter of fact, the reviewers are right: SGA, LGA and cesarean-section rates are absolutely not the purpose of the present paper

b) We have removed from the discussion the sentence: “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”

Reviewer: 2 in dark blue in the text

Reviewer Name

Olof Stephansson

Institution and Country

Karolinska Institutet, Sweden

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below

→→→Review of manuscript bmjopen-2019-036549

Thank you for the opportunity to review this study. This is a retrospective study on the association between gestational weight gain (GWG) and incidence of late onset preeclampsia (LOP) based on a cohort of 66,373 births in the South Reunion Island. In general, this manuscript is difficult to follow and there is scarce information about the methods used. The conclusion appears to overstate the findings of the study given its observational design.

General comments

1. The manuscript would improve with language editing for English grammar and style.
DONE
2. How were the OR calculated? Was it a crude or adjusted analysis? If adjusted, please present variables adjusted for and the rationale for the confounder selection. Were there any missing data in the cohort? If yes, how was this handled?

In our 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.(already precised in the pre-exisiting results).

Instead of only ONE table in the original manuscript, there are now 4 tables: Table 1, main characteristics of the population (asked by reviewer 1 and 3), Table 2, at your request: simulation 2 by 2 between optimal GWG and what actually happened in our population (crude odds-ratios), Table 3, crude odds ratios (ex Table 1)to show the effect of insufficient or excessive GWG in our simulation. And, TABLE 4 logistic regression model with adjusted odds ratios. The 15% missing values for optimal GWG have been excluded, but only used these patients to be in the analysis when calculating overall PE rates.

3. If the scope of the article was to study the association between GWG and late onset preeclampsia why have the authors included the section and Figure 1 on SGA, LGA and caesarean section? Please remove this from the manuscript and instead provide the reader with a Table 1 describing the characteristics of the study population.

After direct request of reviewer 1 and 2, and critics from reviewer 3, we have removed totally the figure from the paper. As a matter of fact, the reviewers are right: SGA, LGA and cesarean-section rates are absolutely not the purpose of the present paper

4. How was the adequate GWG versus Global Observed Rates calculated? Is this a simulation? In what way should this information be interpreted?
Specific comments

Yes, it is a simulation, and it was clearly stated in the abstract in the first submitted version: "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."

5. The article summary needs revision as it is not describing the strengths and limitations of the study in an appropriate way.

Within the huge constraints of an abstract (300 words), we have rephrased the conclusion: "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. "

6. In the Introduction, please explain the NHS and IOM abbreviations to the reader.

We have precised in the introduction: The British National Health Service and US Institute of Medicine

3. In the methods section, what was the rationale for selecting the 2 sub categories for insufficient or excessive GWG? Were these selected a priori?

This was completely arbitrary indeed to choose 5 categories. We have put now in methods:

We created categories of GWG using the published formula $(-1.2 \text{ ppBMI (kg/m}^2) + 42 \pm 2 \text{ kg})$ [4] defined in our population of Reunion island. We have created then 5 categories:

- Adequate GWG: result PLUS or MINUS 2 kg (the formula). Therefore a window of 4kg for each woman
- Insufficient GWG
 - o Moderately insufficient: adequate GWG minus 3 to 9 kg
 - o Severely insufficient: adequate GWG minus 10 kg and below
- excessive GWG
 - o Moderately excessive: adequate GWG PLUS 3 to 9 kg
 - o Severely excessive: adequate GWG PLUS 10 kg and over

BUT, we had previously tested 9 subcategories: adequate, $\pm 3\text{-}5\text{kg}$, $\pm 6\text{-}9$, $\pm 10\text{-}14$, minus or over 15 kg, and we felt that simplifying the current presentation was easier to understand.

4. As for the study cohort, non-preeclamptic pregnancies is a better description than healthy pregnancies given that they could have other disorders and diseases besides preeclampsia.

We have include ALL our singleton term pregnancies (≥ 37 weeks) in our test calculations

5. It would be advisable to provide the manuscript with a flow chart.
DONE, FIGURE 1

6. The authors should put more emphasis on the limitations of the study and discuss them in the limitations section of the Discussion.
Discussion has been completely re-written

7. The conclusion of the Discussion needs editing and should focus on the findings and interpretations of the present study on GWG and late onset preeclampsia.

8. Unfortunately Figure 1 could not be properly visualized for the review of the manuscript.

After direct request of reviewer 1 and 2, and critics from reviewer 3, we have removed totally the figure from the paper. As a matter of fact, the reviewers are right: SGA, LGA and cesarean-section rates are absolutely not the purpose of the present paper

Reviewer: 3 in dark purple in the text

Reviewer Name

Melania M Amorim

Institution and Country

Instituto de Medicina Integral de Pernambuco (IMIP), Recife, Pernambuco, Brazil

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below

This is an important paper that address an important question in public health. Excessive GWG is related with adverse pregnancy outcomes and LOP is a problem because this is the more frequent form of preeclampsia. If preventing excessive GWG could prevent LOP, however, remains to be established.

Some points that require revision:

Introduction should end with formulation of the general objective.

In the Section "Definition of exposure and outcomes", exposure should be the categories of GWG and the main outcome the frequency of LOP, SGA and LGA could be secondary outcomes

We have put in this section the categories of GW as primary outcome, and, as we have removed the figure (showing SGA, LGA, C-section) from the manuscript, at the request of reviewer 1 and 2, we have deleted the following sentence:

"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."

In line 7 of Results section: "The study population therefore consisted of 1,736", this is not the study population, this is the number of cases of preeclampsia in singleton pregnancies.

Corrected: The number of cases of preeclampsia in singleton pregnancies was therefore of 1,736, 69% of which with LOP (N=1,203).

I think that a table with main characteristics of the population with and without preeclampsia should be presented as Table 1

We have created a Table 1 with main characteristics of the population

Figure 1 is a secondary outcome and should be presented after the main results respective to frequency of LOP. This is a typo error (Figure 1 'shows' and not 'show') we have removed the figure (showing SGA, LGA, C-section) from the manuscript, at the request of reviewer 1 and 2,

The plan of statistical analysis was well written and conducted.

VERSION 2 – REVIEW

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| REVIEWER | Liran Hirsch University of Toronto., ON, Canada |
| REVIEW RETURNED | 19-Feb-2020 |

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| GENERAL COMMENTS | I reviewed the revised manuscript and feels that this is a markedly improved version of the manuscript. Still, there are several issues that need to be sorted: 1. Table 1: Too long with many irrelevant details: Hospitalization, C-section, Induced delivery, Birth weight (g), Low BW \leq 2500g, Small for gestational age, Large for gestational age – all of these are irrelevant to the CURRENT study and should be deleted. Having too |
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| | <p>much data is confusing and takes the edge from the main question of this study (GWG and risk for LOP).</p> <p>2. Table 2: In the title for BMI < 25 kg/m² : in table 2 it is called Non overweight, however, in table 3 it is called Non obese – please be consistent throughout the manuscript.</p> <p>3. Title of Table 2 is too long – should be shorter with not so many details.</p> <p>4. All tables should be able to stand alone – explanation of abbreviation is needed for all.</p> <p>5. What is the reference group in Table 2?</p> |
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| REVIEWER | Melania Maria Ramos de Amorim Instituto de Medicina Integral Prof. Fernando Figueira, Brazil |
| REVIEW RETURNED | 20-Feb-2020 |

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| GENERAL COMMENTS | <p>I think this is a better version of the manuscript, but now I have two doubts:</p> <p>1. Why did you decide the level of significance to include variables in the multivariable analysis is 0.1 and not 0.2?</p> <p>2. I think the results of bivariate analysis should be presented for a better understanding.</p> |
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VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1 (modifications in red in the text)

Reviewer Name: Liran Hirsch

Institution and Country: University of Toronto., ON, Canada

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

I reviewed the revised manuscript and feels that this is a markedly improved version of the manuscript.

Still, there are several issues that need to be sorted:

1. Table 1: Too long with many irrelevant details: Hospitalization, C-section, Induced delivery, Birth weight (g), Low BW \square 2500g, Small for gestational age, Large for gestational age – all of these are irrelevant to the CURRENT study and should be deleted. Having too much data is confusing and takes the edge from the main question of this study (GWG and risk for LOP).

All these items have been deleted

2. Table 2: In the title for BMI < 25 kg/m² : in table 2 it is called Non overweight, however, in table 3 it is called Non obese – please be consistent throughout the manuscript.

Corrected in Table 3

3. Title of Table 2 is too long – should be shorter with not so many details.

The details “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.” have been deleted

4. All tables should be able to stand alone – explanation of abbreviation is needed for all.

5. What is the reference group in Table 2?

The reference groups are the observed cases. This has been added in the table. On the other hand, as it is the reverse, we have precised also for Table 3: Incidence of term preeclampsia (%) per category of adequate or non-adequate GWG (adequate GWG as reference).

Reviewer: 3 (modifications in green in the text)

Reviewer Name: Melania Maria Ramos de Amorim

Institution and Country: Instituto de Medicina Integral Prof. Fernando Figueira, Brazil

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I think this is a better version of the manuscript, but now I have two doubts:

1. Why did you decide the level of significance to include variables in the multivariable analysis is 0.1 and not 0.2?

We modified the sentence: “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.”

By:

Variables associated with term preeclampsia in bivariate analysis known to be associated with the outcome in the literature were included in the model

2. I think the results of bivariate analysis should be presented for a better understanding.

We have modified all the Tables (as suggested by reviewer 1), and the bivariate analysis are mainly in Tables 1 and 2 (but also in Table 3 for sub-categories)

VERSION 3 - REVIEW

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| REVIEWER | Melania M Amorim Instituto de Medicina Integral Prof. Fernando Figueira |
| REVIEW RETURNED | 29-May-2020 |

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| GENERAL COMMENTS | Thank you for the opportunity to review the revised version of your manuscript. As I had comment before, you address an important question in the clinical practice, the possibility of preventing preeclampsia if excessive gestational weight gain is avoided. Currently it is possible we have an excess of cases of preeclampsia associated with overweight/obesity. I think that incorporating all suggestions and after editorial requirements the overall quality of the article has improved substantially and I recommend its approval for publication. |
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