ARTICLE DETAILS

TITLE (PROVISIONAL)	Interpregnancy weight changes and impact on pregnancy outcome in a cohort of women with a macrosomic first delivery: A Prospective Longitudinal Study.
AUTHORS	Crosby, David; Walsh, Jennifer; Segurado, Ricardo; McAuliffe, Fionnuala

VERSION 1 - REVIEW

REVIEWER	Mette Bliddal OPEN - Odense Patient data Explorative Network, Odense University Hospital and Department of Clinical Research, University of Southern Denmark, Denmark
REVIEW RETURNED	16-Dec-2016

GENERAL COMMENTS	To the editor
	This study uses data from a smaller hospital-based cohort of mothers giving birth to a first child with a birth weight > 4000 kg (the ROLO study) to examine the association between interpregnancy weight changes between first and second childbirth and second and third childbirth and risk of adverse pregnancy outcomes (N=280). The subject is highly relevant as it is well known that maternal prepregnancy weight and gestational weight gain affect child health. The impact of interpregnancy weight change is less studied, yet, as also reported by the authors, it has been studied in larger populations. I find the subject relevant and the data suitable for this study, however, the method and the results are inadequately reported and due to lack of reporting (numbers and tables) I find the paper difficult to follow, and transparency is lacking.
	To the authors
	You examine the association between interpregnancy weight changes between first and second childbirth and second and third childbirth and risk of adverse pregnancy outcomes (not clearly specified) in a hospital-based cohort of mothers who had a macrosomic first child. The topic is highly relevant and your data are suitable for conducting such a study. I applaud you for having measured weights and heights of your study population. There are, however, some limitations that make the paper difficult to evaluate. To exemplify:
	• Nowhere in the method section is mentioned when the exposure is measured, this is only mentioned as a note to Table 1
	• The outcomes are not specified: neither in the method section, nor in the result section
	• I recommend you to give more data on results in tables. I miss numbers in the different categories for instance to calculate unadjusted OR myself. Further, a table with numbers and statistics from results reported from line 190 to 199 would make the results more transparent. Also results not statistically significant are

appropriate to report in details.
• I wonder why you report medians and standard error of mean (SEM) for descriptive variables. The first indicate non-parametric distributions of data, the second imply normal distribution. I suggest you report median and interquartile range, especially for weight: the percentage of women changing BMI categories is high (difference from first pregnancy to third is 10.7%) indicating that some women gained fairly much as it takes some weight gain (for most) to actually change BMI categories (one BMI unit corresponds to approximately 3 kilo for a woman of 1.68 meters) (1).
• In the adjusted model (Table 2) you adjust for maternal age in second pregnancy and BMI in third pregnancy. I'm a bit puzzled why you do not choose baseline characteristics instead? At least adjusting for BMI at third pregnancy in the analysis on the impact of weight gain between first and second pregnancy is conditioning on the future. Further, please be more specific on when the covariate is defined (both in the method and notes below the Table 2).
• In Table 2 the results of the conjoint time periods could profitably be presented.
• You include only few confounders in the analyses. Smoking may be a confounder, I wonder why you have not included this as a covariate?
In the discussion (l. 246-256) results from earlier studies are presented but not related to results from this study.

1. Bliddal M, Pottegård A, Kirkegaard H, Olsen J, Sørensen TIA, Nohr EA. Depressive symptoms in women's midlife in relation to their body weight before, during and after childbearing years: Weight changes and depressive symptoms. Obes Sci Pract [Internet]. 2016 [cited 2016 Dec 13]; Available from: http://doi.wiley.com/10.1002/osp4.75

REVIEWER	Aaron Caughey OHSU, USA
REVIEW RETURNED	05-Jan-2017

GENERAL COMMENTS	1. Abstract: Probably worth while including the negative findings between first and second pregnancy. 2. Introduction: Indeed, this is an important issue. Is it about the proportion of women who end up overweight or obese or is it even that a small amount of IP weight gain will make a difference? This should be further discussed in the Introduction. 3. Introduction: While there is always a need for more research, in the Discussion, the authors bring up several very large studies of this question, but they propose to study the question in a small cohort. What does this cohort bring to the literature that is missed by prior studies? 4. Methods: While birthweight and GDM are interesting, why not look at other outcomes as well? Preterm birth, preeclampsia, mode of delivery, etc. 5. Methods: Perhaps examining quartiles of quintiles of weight gain and outcomes would be interesting. 6. Results: Were the women who obtained a third pregnancy different from the women who didn't? 7. Results: The results are a bit thin, this is one reason why I would suggest examining more outcomes. 8. Discussion: Could another reason why less of an impact was seen on the second pregnancy than the third pregnancy was that the

	impact matters more over time? Did the authors look at length of time between the pregnancies as well? 9. Discussion: This is a unique cohort b/c these women all had large neonates at their first birth. Can the authors consider why this might matter and how this would differentiate from the basline population? 10. Discussion: The conclusion is about postnatal advice from Obstetricians. While I appreciate that is an important thing to do, it is unclear from this current study that this would actually make a difference. Rather, they should consider that it is important to identify ways for women to maintain a healthy weight through health habits throughout the life cycle.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

•   Nowhere in the method section is mentioned when the exposure is measured, this is only mentioned as a note to Table 1

This has been added to the methods section

•   The outcomes are not specified: neither in the method section, nor in the result section

The outcomes have now been specified in the methods and results section

•   I recommend you to give more data on results in tables. I miss numbers in the different categories for instance to calculate unadjusted OR myself. Further, a table with numbers and statistics from results reported from line 190 to 199 would make the results more transparent. Also results not statistically significant are appropriate to report in details.

A table with these results has been included and not statistically significant results are reported now.

•   I wonder why you report medians and standard error of mean (SEM) for descriptive variables. The first indicate non-parametric distributions of data, the second imply normal distribution. I suggest you report median and interquartile range, especially for weight: the percentage of women changing BMI categories is high (difference from first pregnancy to third is 10.7%) indicating that some women gained fairly much as it takes some weight gain (for most) to actually change BMI categories (one BMI unit corresponds to approximately 3 kilo for a woman of 1.68 meters) (1).

Median and interquartile ranges have now been reported in the results section and table 1

• In the adjusted model (Table 2) you adjust for maternal age in second pregnancy and BMI in third pregnancy. I'm a bit puzzled why you do not choose baseline characteristics instead? At least adjusting for BMI at third pregnancy in the analysis on the impact of weight gain between first and second pregnancy is conditioning on the future. Further, please be more specific on when the covariate is defined (both in the method and notes below the Table 2).

This has now been adjusted for maternal age and BMI in the index pregnancy and this has been specified in the text and in the table.

• In Table 2 the results of the conjoint time periods could profitably be presented.

This has now been included in table 2

• You include only few confounders in the analyses. Smoking may be a confounder, I wonder why you have not included this as a covariate?

Smoking was not accurately collected on the hospital computerised database so has not been included in the analysis.

In the discussion (l. 246-256) results from earlier studies are presented but not related to results from this study.

We have made a comment relating our study results to the previous studies presented

Reviewer: 2

1. Abstract: Probably worth while including the negative findings between first and second pregnancy.

These have now been included

2. Introduction: Indeed, this is an important issue. Is it about the proportion of women who end up overweight or obese or is it even that a small amount of IP weight gain will make a difference? This should be further discussed in the Introduction.

This has been further discussed in the introduction

3. Introduction: While there is always a need for more research, in the Discussion, the authors bring up several very large studies of this question, but they propose to study the question in a small cohort. What does this cohort bring to the literature that is missed by prior studies?

The benefits of this study that it is a prospective longitudinal study, within a cohort of women without GDM and hypertensive disorders in their index pregnancy who delivered a baby >= 4kg, and subsequently delivered 2 further babies. This has been discussed further in the discussion.

4. Methods: While birthweight and GDM are interesting, why not look at other outcomes as well? Preterm birth, preeclampsia, mode of delivery, etc.

These have now been included in methods, results and table 3.

5. Methods: Perhaps examining quartiles of quintiles of weight gain and outcomes would be interesting.

This has been addressed in methods, results and table 3.

6. Results: Were the women who obtained a third pregnancy different from the women who didn't?

There were no differences between demographics of women in their second pregnancy who obtained a third pregnancy compared with those who did not.

7. Results: The results are a bit thin, this is one reason why I would suggest examining more outcomes.

This has been addressed in methods, results and table 3.

8.   Discussion: Could another reason why less of an impact was seen on the second pregnancy than the third pregnancy was that the impact matters more over time? Did the authors look at length of time between the pregnancies as well?

Yes this is included in the results section

9.   Discussion: This is a unique cohort b/c these women all had large neonates at their first birth. Can the authors consider why this might matter and how this would differentiate from the baseline population?

Yes, this is important, as these women are at risk of recurrent macrosomia. This has been addressed in the discussion.

10.   Discussion: The conclusion is about postnatal advice from Obstetricians. While I appreciate that is an important thing to do, it is unclear from this current study that this would actually make a difference. Rather, they should consider that it is important to identify ways for women to maintain a healthy weight through health habits throughout the life cycle.

This point has been addressed in the conclusion.

VERSION 2 – REVIEW

REVIEWER	Mette Bliddal Department of Clinical Research, University of Southern Denmark, Odense, Denmark, and OPEN - Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript again. The manuscript has improved and easier to follow, and matters addressed in the earlier review have been addressed. I have only a few comments: I'm still a bit puzzled about the percentage of women changing to the obese category between pregnancy 1 and 2 (10.7%). I recognize that you now report interquartile range as the difference between the 75th and the 25th quartile. I do, however, believe that writing the 25th and the 75th quartile would help be beneficial. As you present results from Table 3 before results from Table 2, I would recommend you to switch the two. When reading, I was puzzled about Table 2 as Table 3 was mentioned first. Further, please refer to Table 2 (now 3) after the section 207-214. You could with advantage discuss your findings in Table 2 (Now 3) which all indicate that for each increase in inter-pregnancy weight gain the odds for giving birth to a child of 4 kg or more increase. As you well comment in line 235, the impact of weight gain may be

	cumulative. Similarly, weight gain may also interact with pre-pregnancy BMI. Have you tested for interaction? In extension to comment 3 by reviewer 2 and line 262-263: the larger mentioned studies conducted by others including Bogaerts et (2013) and Villamor et al (2006) may well be historical cohort studies but data is all collected prospectively as with your data. Line 279: This sentence may be deleted.

VERSION 2 – AUTHOR RESPONSE

Many thanks for your response. Please find attached comments addressing the reviewers latest comments.

1) I recognize that you now report interquartile range as the difference between the 75th and the 25th quartile. I do, however, believe that writing the 25th and the 75th quartile would help be beneficial.

25th and 75th quartiles are now reported in the text and table.

2) As you present results from Table 3 before results from Table 2, I would recommend you to switch the two. When reading, I was puzzled about Table 2 as Table 3 was mentioned first. Further, please refer to Table 2 (now 3) after the section 207-214.

Tables 2 and 3 have been switched and the new table 2 is referred to after the section 207-214

3) You could with advantage discuss your findings in Table 2 (Now 3) which all indicate that for each increase in inter-pregnancy weight gain the odds for giving birth to a child of 4 kg or more increase.

These findings have now been discussed.

4) As you well comment in line 235, the impact of weight gain may be cumulative. Similarly, weight gain may also interact with pre-pregnancy BMI. Have you tested for interaction?

On the reviewer's suggestion we examined the interaction between baseline (pregnancy 1) BMI categories, and gain in weight between pregnancy 2 and 3 - our two statistically significant findings. Interestingly we found that despite non-significant results (possibly due to low power), the odds ratio for a baby born in the 3rd pregnancy to be over 4kg was 1.76 overall, but that this was 1.05 in Normal BMI range mothers, 3.14 in Overweight mothers, and 2.93 in Obese mothers. This finding is interesting and deserves follow-up in larger samples, powered to examine interaction effects.

5) In extension to comment 3 by reviewer 2 and line 262-263: the larger mentioned studies conducted by others including Bogaerts et (2013) and Villamor et al (2006) may well be historical cohort studies but data is all collected prospectively as with your data.

We have addressed this point in the manuscript

6) Line 279: This sentence may be deleted.

This sentence has been deleted.

REVIEWER	Bliddal, Mette OPEN - Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark and Department of Clinical Research, University of Southern Denmark, Odense, Denmark
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	Thank you for letting me review the manuscript "Interpregnancy weight changes and impact on pregnancy outcome in a cohort of women with a macrosomic first delivery: A prospective Longitudinal Study" once more. I find the manuscript to be informative and well-written, and I have no further comments. I would however support the idea of exploring further the conjoint impact of interpregnancy weight gain and pre-pregnancy BMI in a future study.