

## PEER REVIEW HISTORY

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## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The impact of Bariatric surgery on EmbrYONic, foetal and placental Development (BEYOND): Protocol for a prospective cohort study embedded in the Rotterdam periconception cohort
<b>AUTHORS</b>	Snoek, Katinka; Klaassen, René; Laven, J; Schoenmakers, Sam; Steegers-Theunissen, Régine

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Maslin, Kate University of Plymouth
<b>REVIEW RETURNED</b>	07-Jun-2021

<b>GENERAL COMMENTS</b>	<p>The impact of Bariatric surgery on EmbrYONic, foetal and placental Development (BEYOND): A prospective cohort study embedded in the Rotterdam periconception cohort This is an interesting and important study, especially as it recruit women preconceptually, as most data on this topic is from retrospective studies.</p> <ul style="list-style-type: none"><li>• Introduction, lines 62-64: Suggest also mention pharmaceutical/medical management of obesity (increasingly used in combination with lifestyle interventions).</li><li>• Lines 67-68: Eligibility for bariatric surgery: NICE has been referenced (reference number 6). This is for the UK, however the study is not based in the UK. Suggest clarify this and add national and international criteria and references.</li><li>• Recommend the addition of some references that provide evidence of the effectiveness of bariatric surgery in weight loss (e.g. Colquitt et al, 2014, Cochrane review)</li><li>• References 7-19: these are mostly single centre studies examining the outcomes of bariatric surgery on pregnancy outcomes. There are a number of published systematic reviews on this topic, suggest it would be better to reference these instead and to explore some of the factors/variables which may lead to equivocal results (e.g. type of surgery, length of time between surgery and conception, parity, comparison group used, study design etc).</li><li>• Questionnaires: Please provide some more details about the food intake questionnaire and the format this takes: is it a food frequency questionnaire/food diary and does it quantify portion size? Does it also ask about dietary supplements? Assessment of folic acid is specified, but no other nutrients- please elaborate.</li><li>• How will the information collected from this food questionnaire be used in the results? The section titled “research implications” discusses the role of vitamin supplementation and possible over supplementation, but does not refer to nutrient intake from food – please clarify.</li></ul>
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<b>REVIEWER</b>	Akhter, Zainab Newcastle University
<b>REVIEW RETURNED</b>	15-Jul-2021

<b>GENERAL COMMENTS</b>	<p>This is a nicely written study protocol, and an important topic of research. As history of bariatric surgery is relatively rare in the obstetric population, creating a specific cohort will allow this high-risk subpopulation to be investigated further, and I look forward to reading future studies reporting on the acquired data. I only have a few comments:</p> <ul style="list-style-type: none"> <li>- Line 68+ - it is a simplistic view that bariatric surgery works based on malabsorption and restriction of nutrients alone, there are more complex processes involved such as in the endocrine system. Ensure that you state that you are defining the surgeries based on their impact on nutrient absorption (and relevance to pregnancy) rather than weight loss mechanisms.</li> <li>- Line 77 - references 8-11 are good, however there have been multiple systematic reviews and meta-analyses published on pregnancy after bariatric surgery in the past few years which are higher quality sources of evidence.</li> <li>- This is a minor comment but throughout - instead of 'contemplating pregnancy' perhaps consider 'planning pregnancy'.</li> <li>- Line 142 - some women have their gastric bands deflated due to excess vomiting and other unpleasant symptoms in pregnancy, please clarify if these would be excluded or if only women with deflated bands prior to pregnancy would be excluded.</li> <li>- If nutritional deficiencies are found during pregnancy - will the women be provided with nutritional support?</li> <li>- Although questionnaires are appropriate for collecting data on lifestyle factors, demographics, and food intake, some of the questionnaire data I feel would be more reliable if collected directly from medical history - such as results of fetal anomaly scan/congenital anomalies at birth</li> </ul>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer Reports:

Reviewer: 1  
Prof. Kate Maslin, University of Plymouth

Comments to the Author:

The impact of Bariatric surgery on EmbrYONic, foetal and placental Development (BEYOND): A prospective cohort study embedded in the Rotterdam periconception cohort This is an interesting and important study, especially as it recruit women preconceptually, as most data on this topic is from retrospective studies.

*Thank you for reviewing our study protocol.*

- Introduction, lines 62-64: Suggest also mention pharmaceutical/medical management of obesity (increasingly used in combination with lifestyle interventions).

*These lines have been changed from “Weight loss in obesity can be accomplished by life style and nutritional changes, bariatric surgery or a combination of both.” into (line 70-73): “Weight loss in obesity can be accomplished by lifestyle and nutritional changes, pharmaceutical therapies or medical weight loss interventions programs, bariatric surgery or a combination of these interventions.”*

- Lines 67-68: Eligibility for bariatric surgery: NICE has been referenced (reference number 6). This is for the UK, however the study is not based in the UK. Suggest clarify this and add national and international criteria and references.

*Thank you for your comment. The NICE guidelines were referenced as these are also referred to internationally, however, we have replaced the reference to the NICE guidelines by the Dutch guidelines and we have other added international criteria and references:*

11. Heelkunde NVv. Chirurgische behandeling van obesitas: Federatie Medisch Specialisten; 2020 [updated 28/10/2020. Available from: [https://richtlijnendatabase.nl/richtlijn/chirurgische\\_behandeling\\_van\\_obesitas/startpagina\\_-\\_chirurgische\\_behandeling\\_van\\_obesitas.html](https://richtlijnendatabase.nl/richtlijn/chirurgische_behandeling_van_obesitas/startpagina_-_chirurgische_behandeling_van_obesitas.html).
12. Fried M, Hainer V, Basdevant A, et al. Interdisciplinary European guidelines on surgery of severe obesity. *Obesity Facts* 2008;1(1):52-59.
13. Mechanick JI, Youdim A, Jones DB. AACE/TOS/ASSMBS Guidelines: Clinical practice guideline for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient-2013 update: cosponsored by American Association of Clinical Endocrinologists, the obesity society, and American society for metabolic & bariatric surgery. *Endocrine Practice* 2013;19(2).
14. Ridley N. Expert panel on weight loss surgery-executive report. *Obes Res* 2005;13:206-26.
15. Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery. *Obesity Surgery* 2014;24(1):42-55.

- Recommend the addition of some references that provide evidence of the effectiveness of bariatric surgery in weight loss (e.g. Colquitt et al, 2014, Cochrane review)

*The suggested reference and others have been added (line 75-76): "Bariatric surgery is an effective surgical solution to quickly lose excess weight and reach a healthier long-term weight."<sup>6-10</sup>*

6. Colquitt JL, Pickett K, Loveman E, et al. Surgery for weight loss in adults. *Cochrane Database of Systematic Reviews* 2014(8).
7. Chang S-H, Stoll CRT, Song J, et al. The Effectiveness and Risks of Bariatric Surgery: An Updated Systematic Review and Meta-analysis, 2003-2012. *Jama Surgery* 2014;149(3):275-87.
8. Maciejewski ML, Arterburn DE, Van Scoyoc L, et al. Bariatric Surgery and Long-term Durability of Weight Loss. *Jama Surgery* 2016;151(11):1046-55.
9. Wolfe BM, Kvach E, Eckel RH. Treatment of obesity: weight loss and bariatric surgery. *Circulation research* 2016;118(11):1844-55.
10. Dumon KR, Murayama KM. Bariatric surgery outcomes. *Surgical Clinics* 2011;91(6):1313-38.

- References 7-19: these are mostly single centre studies examining the outcomes of bariatric surgery on pregnancy outcomes. There are a number of published systematic reviews on this topic, suggest it would be better to reference these instead and to explore some of the factors/variables which may lead to equivocal results (e.g. type of surgery, length of time between surgery and conception, parity, comparison group used, study design etc).

*We have changed the references from single centre studies into systematic reviews and meta-analyses and have commented on some underlying mechanisms or physiology explaining the different results between the studies (line 87-92): "Unfortunately, due to fast and excessive weight loss resulting from gastro-intestinal anatomical changes of preconceptional bariatric surgery, iatrogenic malnutrition can also increase the incidence of adverse pregnancy and perinatal outcomes, such as intra-uterine growth restriction and congenital vitamin deficiencies in neonates.<sup>22-25</sup> Growth restriction seems to be mainly present after malabsorptive surgery, as nutritional deficiencies occur more often after this type of bariatric procedure."<sup>18,19</sup>*

18. Kwong W, Tomlinson G, Feig DS. Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks? *American Journal of Obstetrics and Gynecology* 2018;218(6):573-80.
19. Akhter Z, Rankin J, Ceulemans D, et al. Pregnancy after bariatric surgery and adverse perinatal outcomes: A systematic review and meta-analysis. *Plos Medicine* 2019;16(8):e1002866.

22. Belogolovkin V, Salihu HM, Weldeselasse H, et al. Impact of prior bariatric surgery on maternal and fetal outcomes among obese and non-obese mothers. *Archives of Gynecology and Obstetrics* 2012;**285**(5):1211-18.
23. Cools M, Duval ELIM, Jespers A. Adverse neonatal outcome after maternal biliopancreatic diversion operation: report of nine cases. *European Journal of Pediatrics* 2006;**165**(3):199-202.
24. Josefsson A, Blomberg M, Bladh M, et al. Bariatric surgery in a national cohort of women: sociodemographics and obstetric outcomes. *American Journal of Obstetrics and Gynecology* 2011;**205**(3):206. e1-06. e8.
25. Lesko J, Peaceman A. Pregnancy outcomes in women after bariatric surgery compared with obese and morbidly obese controls. *Obstetrics & Gynecology* 2012;**119**(3):547-54.

- Questionnaires: Please provide some more details about the food intake questionnaire and the format this takes: is it a food frequency questionnaire/food diary and does it quantify portion size? Does it also ask about dietary supplements? Assessment of folic acid is specified, but no other nutrients- please elaborate.

*We have added more details regarding the food intake questionnaire (line 186-188): "Women and their male partners will fill out a self-administered, validated food frequency questionnaire regarding food intake of the previous four weeks. <sup>1-3</sup> Portion sizes are quantified by this questionnaire."*

*Dietary supplementation use is evaluated by the general questionnaire. Therefore we have changed this sentence from "Moreover, preconceptionally and during the first trimester a general questionnaire will be filled out including geographical background, education and lifestyle. At 24 weeks GA a questionnaire is filled out regarding information about folic acid intake, lifestyle, prenatal screening, results of the foetal anomaly scan (around 20 weeks of gestation) and previous pregnancy outcome. "*

*into*

*(line 189-193) "Moreover, preconceptionally and during the first trimester a general questionnaire will be filled out including geographical background, education and lifestyle. At 24 weeks GA a questionnaire is filled out regarding information about folic acid intake, any vitamin supplementation, lifestyle behaviour, prenatal screening, results of the foetal anomaly scan (around 20 weeks of gestation) and previous pregnancy outcome."*

- How will the information collected from this food questionnaire be used in the results? The section titled "research implications" discusses the role of vitamin supplementation and possible over supplementation, but does not refer to nutrient intake from food – please clarify.

*We are also planning on evaluating nutrient intake and have added nutrient intake from food in the "research implications" section (line 305-308): "Besides, quantitative and qualitative information about dietary intake will be retrieved from the food frequency questionnaires and will provide insight into possible dietary issues in these patients. This can contribute to health care improvement delivered by dietitians and other health care professionals for postbariatric pregnant patients."*

Reviewer: 2

Dr. Zainab Akhter, Newcastle University

Comments to the Author:

This is a nicely written study protocol, and an important topic of research. As history of bariatric surgery is relatively rare in the obstetric population, creating a specific cohort will allow this high-risk subpopulation to be investigated further, and I look forward to reading future studies reporting on the acquired data. I only have a few comments:

*- Line 68+ - it is a simplistic view that bariatric surgery works based on malabsorption and restriction of nutrients alone, there are more complex processes involved such as in the endocrine system.*

Ensure that you state that you are defining the surgeries based on their impact on nutrient absorption (and relevance to pregnancy) rather than weight loss mechanisms.

We agree that the consequences of bariatric surgery are more complex than only mechanical postsurgical alterations. This is why we have changed the sentence “There are three types of bariatric surgery: 1. malabsorptive surgery, in which the small intestines are partially bypassed, 2. restrictive surgery, in which the stomach size is decreased, and 3. a combination between malabsorptive and restrictive surgery.”

into

(line 80-84) “There are different types of bariatric surgery, based on their endocrine, metabolic and (patho)physiological consequences. Malabsorptive procedures lead to impaired uptake of nutrients, whereas restrictive procedures mainly decrease food intake. However, a sleeve gastrectomy, which is often considered a restrictive procedure, also has endocrine and metabolic effects.<sup>16</sup>”

16. Benaiges D, Más-Lorenzo A, Goday A, et al. Laparoscopic sleeve gastrectomy: more than a restrictive bariatric surgery procedure? *World Journal of Gastroenterology* 2015;21(41):11804.

- Line 77 - references 8-11 are good, however there have been multiple systematic reviews and meta-analyses published on pregnancy after bariatric surgery in the past few years which are higher quality sources of evidence.

We have changed the references into higher impact references (line 84-86): “Since bariatric surgery leads to fast, excessive and - most importantly - long-term weight loss, preconceptional bariatric surgery in women of reproductive age can diminish the prevalence of obesity-related adverse maternal and foetal outcomes.<sup>17-21</sup>”

17. Maggard MA, Yermilov I, Li Z, et al. Pregnancy and fertility following bariatric surgery: A systematic review. *J Am Med Assoc* 2008;**300**(19):2286-96.
18. Kwong W, Tomlinson G, Feig DS. Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks? *American Journal of Obstetrics and Gynecology* 2018;**218**(6):573-80.
19. Akhter Z, Rankin J, Ceulemans D, et al. Pregnancy after bariatric surgery and adverse perinatal outcomes: A systematic review and meta-analysis. *Plos Medicine* 2019;**16**(8):e1002866.
20. Shawe J, Ceulemans D, Akhter Z, et al. Pregnancy after bariatric surgery: Consensus recommendations for periconception, antenatal and postnatal care. *Obesity Reviews* 2019;**20**(11):1507-22.
21. Al-Nimr RI, Hakeem R, Moreschi JM, et al. Effects of bariatric surgery on maternal and infant outcomes of pregnancy—an evidence analysis center systematic review. *Journal of the Academy of Nutrition and Dietetics* 2019;**119**(11):1921-43.

- This is a minor comment but throughout - instead of 'contemplating pregnancy' perhaps consider 'planning pregnancy'.

“Contemplating pregnancy” has been changed into “planning pregnancy” throughout the document.

- Line 142 - some women have their gastric bands deflated due to excess vomiting and other unpleasant symptoms in pregnancy, please clarify if these would be excluded or if only women with deflated bands prior to pregnancy would be excluded.

We have changed this sentence into (line 157-158) “Cases must have had bariatric surgery, excluding a gastric banding procedure that has been deflated or removed prior to pregnancy.” as we only aim to exclude patients with a deflated or removed gastric band before pregnancy.

- If nutritional deficiencies are found during pregnancy - will the women be provided with nutritional support?

If deficient nutritional serum values are found, the patient and her general practitioner will be notified, and she will have a consultation with the treating bariatric surgeon and/or internist in order to properly

supplement the patient. The patient will also be offered a consultation at the outpatient clinic “Healthy pregnancy” in the Erasmus MC if the homocysteine serum level is too high and she will receive advice and follow-up.<sup>1</sup> The same applies to her partner if his homocysteine serum levels turn out to be too high.

1 VAN DER WINDT M, VAN DER KLEIJ RM, SNOEK KM, et al. Impact of a blended periconception lifestyle care approach on lifestyle behaviors: Before-and-after study. *Journal of Medical Internet Research* 2020;22:e19378.

- Although questionnaires are appropriate for collecting data on lifestyle factors, demographics, and food intake, some of the questionnaire data I feel would be more reliable if collected directly from medical history - such as results of fetal anomaly scan/congenital anomalies at birth

*As not all study patients are primarily treated or followed up at the Erasmus MC, not all mentioned data can be accessed directly. However, we do request the reports of the fetal anomaly scan, medical history and gestational follow-up by the treating gynaecologist, while we also ask patients if they agree to provide written consent to request reports from the Municipal Health Services regarding growth and development of the offspring from the first years of life. In the Netherlands, children are routinely monitored by the child health clinic during the first years of life. We could add this information to the method section of this paper if necessary.*

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Maslin, Kate University of Plymouth
<b>REVIEW RETURNED</b>	02-Aug-2021
<b>GENERAL COMMENTS</b>	Thank you for this revised version and addressing the comments I made.