PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Role of Iodine-containing-multivitamins during Pregnancy for Children's Brain Function: Protocol of an On-going Randomized Controlled Trial- the SWIDDICH study
AUTHORS	Manousou, Sofia; Johansson, Birgitta; Chmielewska, Anna; Eriksson, Janna; Gutefeldt, Kerstin; Tornhage, Carl-Johan; Eggertsen, Robert; Malmgren, Helge; Hulthen, Lena; Domellöf, Magnus; Nystrom Filipsson, Helena

VERSION 1 – REVIEW

REVIEWER	John H Lazarus Prof Clinical Endocrinology Cardiff University UK
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	This is a proposal for a randomised placebo controlled double blind study of the effect of iodine supplementation on child IQ measured at different ages. Although the methodology is adequate I have some concerns: 1. Recruitment - the aim is for women <12 weeks gestation recruited at the first scheduled pregnancy visit. When is that visit usually? The problem here is that brain development in the first 12 weeks is dependent on maternal T4 levels so a substantial part of it will be missed. Ideally iodine supplementation should be started 3 months before conception but admittedly that is difficult because only around 50% of women plan their pregnancies. Could the study be limited to those women? 2. Iodine status in Sweden. Although this has probably been decreasing there is minimal iodine deficiency in the non pregnant population. This means that thyroidal iodine stores are probably adequate to sustain 1 pregnancy without ill effects on the neurodevelopment of the child. Have the authors any data on iodine stores? Perhaps the inclusion should be women who have had at least 1 child in the past ?2 years. 3. p6 'the first 200 women..... presumably there will be 100 in each group? 4.Table 1 The intervention tablet does not contain folic acid whereas the placebo does. If the intervention group takes folic acid this means they take 2 tablets per day. Will the placebo group also take 2 tablets per day otherwise the blinding will not be satisfactory. 5. A positive cost effective outcome in relation to iodine supplementation has been published (Monahan et al Lancet 2015)

	which would strengthen the advocacy for this study. 6.Because of my concerns I am unsure as to whether the study will answer the question, especially as criticisms of rcts of T4 administration relating to recruitment time have been repeatedly made.

REVIEWER	Margaret Rayman University of Surrey, UK
REVIEW RETURNED	03-Nov-2017

GENERAL COMMENTS	(The same text is in the attachment). It is greatly to the authors' credit that they have managed to get funding for such a much-needed trial and particularly with that very long follow-up. However, I have one major criticism and a few that are less important. 1. My major criticism is that the intervention iodine-containing supplement and the placebo supplement are not appropriately matched. The placebo and intervention should differ only in the amount of iodine in the supplement. Table 1 tells a very different story. The placebo contains a number of nutrients that are absent from the Intervention supplement, most notably folic acid (200 mcg), vitamin A, vitamin B6, 15 mcg vs 3 mcg B12, vitamin E, niacin, vitamin C and vitamin D. If there should be no difference in outcomes between the groups, it could potentially be because of those additional nutrients given only to the placebo group. Furthermore, the Intervention supplement contains other active ingredients that are not in the placebo, i.e. iron 12 mg, zinc 12 mg, selenium 50 mcg and calcium 50 mg. Selenium and iron are required for thyroid function so if the outcome is better in the iodine intervention group, how can we be sure that it is not at least partly down to the inclusion of these nutrients? I think this major limitation needs at least to be acknowledged in the manuscript. In fact, if the trial is not too far advanced, it would be preferable if the supplements could be properly matched for the remainder of the intervention, which should be extended to recruit a further 1263 women. As the trial stands, it cannot give the definitive answer on whether iodine supplementation is beneficial for offspring psychological development; that is an immense pity. 2. In the section entitled "Considerations on Possible Adverse Effects of Iodine or placebo", a few studies have been left out that should be included. These include two studies that are already referenced, i.e. Rebagliato et al. (52) and Abel et al. (22). The third is Murcia et al. Am J Epidemiol. 2011; 173:804-12. The adverse effects of iodine supplementation in these studies should be described. 3. Lines 35-41 mention the MITCH study. This was published in the Lancet Diabetes and Endocrinology on 10 October 2017, so that section needs to be up-dated. 4. There is no comment on whether the study is powered for the additional outcomes in the 200-strong sub-group that will have post-partum day 1-5 measurements. I suspect it is not.

VERSION 1 – AUTHOR RESPONSE

REBUTTALS

We are very pleased to have such highly renowned reviewers for our study. Thank you for your valuable comments. The changes are highlighted in the revised manuscript. Attention, we present unpublished data in the reply to the reviewers (highlighted in yellow below) that is not aimed to be published in a supplement to this article, but is only for the eyes of the reviewers.

Editor

Comment 1. Please check your title and make sure that it reads clearly.

Answer 1: Thank you for this comment. Looking at the title from another view we have changed it to "The Role of Iodine Containing Multivitamins during Pregnancy for Children's Brain Function: Protocol of an On-going Randomized Controlled Trial- the SWIDDICH study"

Comment 2. Please complete and include a SPIRIT checklist, ensuring that all points are included and state the page numbers where each item can be found.

Answer 2: The Spirit check-list has been completed and corresponding missing items have been added to the manuscript. Page numbers have been stated.

Reviewer 1

Comment 1 Recruitment - the aim is for women <12 weeks gestation recruited at the first scheduled pregnancy visit. When is that visit usually? The problem here is that brain development in the first 12 weeks is dependent on maternal T4 levels so a substantial part of it will be missed. Ideally iodine supplementation should be started 3 months before conception but admittedly that is difficult because only around 50% of women plan their pregnancies. Could the study be limited to those women?

Answer 1: We agree that iodine supplements may ideally be initiated before conception. Practically, preconceptional recruitment of women is not possible in our setting. The women will not be known by health care before pregnancy. The only way would be an advertisement in the newspaper, directed to those planning a pregnancy, which would be very ineffective and would also create a strong selection bias. We include women at the earliest possible stage, apart from what the reviewer suggests, in gestational week 7-12 (see correction, page 5) and this is far much better that the recent publication by Casey et al in New England Journal of Medicine [1] with negative results, where pregnant women were included in mean gestational week 16.6-18.0. Our recruitment time is similar to the MITCH study, where women were included in gestational week 10-11 [2]. To address these concerns, we have added this important consideration on page 7-8.

Comment 2: Iodine status in Sweden. Although this has probably been decreasing there is minimal iodine deficiency in the non- pregnant population. This means that thyroidal iodine stores are probably adequate to sustain 1 pregnancy without ill effects on the neurodevelopment of the child. Have the authors any data on iodine stores?
Perhaps the inclusion should be women who have had at least 1 child in the past ?2 years.

Answer 2: We are sorry that we were not able to present our results, from the pilot study on the first 200 women (100 in each group) in the manuscript. They were presented as an oral presentation at European Thyroid Association 2016. This data will be included in a separate publication together with selenium and iron data and it shows inadequate iodine status in pregnant women during the 1st

trimester. For your information, we give you the iodine results below: ATTENTION NOT TO BE PUBLISHED

	1st trimester	p	2nd trimester	p	3rd trimester	p	Mother postpartum	p	Baby	p
UIC-iodine	111		140		136		41		93	
UIC-placebo	110	0.528	90	**<0.001**	65	**<0.001**	23	**0.001**	47	**0.002**
FT4-iodine	15		13		12					
FT4-placebo	15	0.434	12	0.557	12	0.065				
TSH-iodine	1.20		1.65		1.90					
TSH-placebo	1.20	0.566	1.60	0.940	2.05	0.524				
Tg-iodine	21				22					
Tg-placebo	18	0.280			30	**0.002**				

In fact, our study has as an exclusion criterion, those with a very recent pregnancy and lactating period (during the previous 6 months), as we judged it unethical to risk "placebo" treatment in those that may be worse off. We also exclude vegans for the same reason.
At the ATA conference 2017, we also presented national data from a cross-sectional investigation of pregnant women, where the hypothesis of iodine deficiency during pregnancy in all trimesters was confirmed. They did not differ by trimester and mean UIC was 101 µg/L. UIC was 83 µg/L if they had lower intake than 75 µg iodine/ day in a supplement and 141 µg/L if iodine intake from supplements was ≥ 75 µg/ day (unpublished).

Comment 3: p6 'the first 200 women..... presumably there will be 100 in each group?

Answer 3: Yes, this is correct. We have now excluded the section about post-partum analyses 1-5 days, after the comment 4 from reviewer 2 (page 6).

Comment 4: Table 1 The intervention tablet does not contain folic acid whereas the placebo does. If the intervention group takes folic acid this means they take 2 tablets per day. Will the placebo group also take 2 tablets per day otherwise the blinding will not be satisfactory.

Answer 4: All Swedish women are recommended to take extra folic acid and many of them even extra iron, depending on the hemoglobulin status. This administration does not interfere with the study medications. They are not, however, allowed to take another multivitamin besides the study medication, so that they do not exceed appropriate levels of certain compounds. This is clarified on page 6.

Comment 5: A positive cost effective outcome in relation to iodine supplementation has been published (Monahan et al Lancet 2015) which would strengthen the advocacy for this study.

Answer 5: We thank the reviewer for this information and have added it on page 10.

Comment 6: Because of my concerns I am unsure as to whether the study will answer the question, especially as criticisms of rcts of T4 administration relating to recruitment time have been repeatedly made.

Answer 6: We share some of the reviewer's concerns but due to lack of resources, it is not possible for us to change the study design of this ongoing study. The most relevant concern is the different composition of the multivitamin/mineral supplements used in the intervention and placebo groups. It is

possible that selenium will have an effect, besides the iodine effect, if the study population is selenium deficient. However, this would actually increase the chances that the study will detect a significant difference between groups, since selenium deficiency entails cognitive impairment [3]. Furthermore, this will represent reality: Iodine supplementation is recommended in several countries, but multivitamins are used, as pure iodine supplements are not available in most countries. To elucidate any additional effect of the selenium compound in the supplement, we will evaluate plasma selenium concentrations in the women. The results need to be carefully interpreted together with experienced statisticians to sort out selenium and iodine effects on thyroid metabolism (see reviewer 2, answer 1).

We have a window right now in Sweden when this study is possible, because the authorities do not recommend general iodine supplementation to pregnant women – as there are no data on an iodine problem in pregnant women in the country. In the lack of RTC proving a beneficial effect on children, country authorities may also judge the scientific reason to implement an iodine supplement strategy as weak, but not necessarily. When we present our national data, they may change their opinion. Even though we have a continuous discussion with the National Food Agency and they will promote this study as a stakeholder, we do not have the time to disrupt the inclusion and wait for a better supplement. We may not be able to do this study at all, due to ethical reasons, in 1 or 2 years' time, if authorities decide on a general recommendation. A way to address this issue – that is very much on our minds – if inclusion rate is good and we get a stable financial situation, is to add a third arm that can be either pure iodine or pure selenium.

Reviwer 2

Comment 1: My major criticism is that the intervention iodine-containing supplement and the placebo supplement are not appropriately matched. The placebo and intervention should differ only in the amount of iodine in the supplement. Table 1 tells a very different story. The placebo contains a number of nutrients that are absent from the Intervention supplement, most notably folic acid (200 mcg), vitamin A, vitamin B6, 15 mcg vs 3 mcg B12, vitamin E, niacin, vitamin C and vitamin D. If there should be no difference in outcomes between the groups, it could potentially be because of those additional nutrients given only to the placebo group. Furthermore, the Intervention supplement contains other active ingredients that are not in the placebo, i.e. iron 12 mg, zinc 12 mg, selenium 50 mcg and calcium 50 mg. Selenium and iron are required for thyroid function so if the outcome is better in the iodine intervention group, how can we be sure that it is not at least partly down to the inclusion of these nutrients? I think this major limitation needs at least to be acknowledged in the manuscript. In fact, if the trial is not too far advanced, it would be preferable if the supplements could be properly matched for the remainder of the intervention, which should be extended to recruit a further 1263 women. As the trial stands, it cannot give the definitive answer on whether iodine supplementation is beneficial for offspring psychological development; that is an immense pity.

Answer 1: Yes, as we wrote to reviewer 1 in comment 6, we are aware of the problem and have different strategies to partly overcome it, by including analysis of selenium, B12 and iron – substances known to affect cognition in both groups (see data below) and by including another arm to sort out confounding. This study uses commercially available multivitamins at the pharmacy and data can very quickly be implemented into clinical practice, as pure iodine is not available in most countries. If we show a cognitive difference between those on multivitamins with iodine compared to multivitamins without iodine (but other compounds) it is still a very valuable knowledge as multivitamins with iodine can be advocated.
Regarding the possible effects of other compounds in multivitamins, we will direct that issue for selenium, iron and B12 and compare levels in both group in our pilot of 200 women. Iron did not differ and in fact the amount of iron in the multivitamin is far smaller than the amount that women usually take as iron supplements during pregnancy (see answer on comment 4, reviewer 1).
Even though other compounds, apart from selenium, B12 and iron, may be regarded as a systematic bias, it is important to be aware of that the amounts are low, in relation to contributions from different food intake. To that, adds how the foods are eaten together in the meals, which influences the bioavailability.

Comment 2: In the section entitled "Considerations on Possible Adverse Effects of Iodine or placebo", a few studies have been left out that should be included. These include two studies that are already referenced, i.e. Rebagliato et al. (52) and Abel et al. (22). The third is Murcia et al. Am J Epidemiol. 2011; 173:804-12. The adverse effects of iodine supplementation in these studies should be described.

Answer 2: We are pleased to include this valuable contribution into the manuscript, see page 10.

Comment 3: Lines 35-41 mention the MITCH study. This was published in the Lancet Diabetes and Endocrinology on 10 October 2017, so that section needs to be up-dated.

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Answer 4: No, these measures were only done in the pilot study (n=200) and we realised that the drop-out was so large that the results would be unreliable. Therefore, we decided to exclude the postpartum measurements directly after delivery. They were, moreover, not necessary for the total study when we had decided on the children follow-up. As this information may confuse the reader and will not give reliable results, we exclude the section about post-partum analyses 1-5 days, see page 6.

1. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med. 2017;376(9):815-25.
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3. Skroder HM, Hamadani JD, Tofail F, Persson LA, Vahter ME, Kippler MJ. Selenium status in pregnancy influences children's cognitive function at 1.5 years of age. Clin Nutr. 2015;34(5):923-30.

VERSION 2 – REVIEW

REVIEWER	John H Lazarus Cardiff University Uk
REVIEW RETURNED	28-Dec-2017

GENERAL COMMENTS	Thank you for the additions and alterations to this ms which is now much improved. You quote some guidelines but not the most up to date eg Alexander et al THYROID 2017 and De Groot et al Endo Soc guidelines JCEM 2012. These should be referred to.

REVIEWER	Margaret Rayman University of Surrey UK
REVIEW RETURNED	30-Dec-2017

GENERAL COMMENTS	Unfortunately, I still find much to comment on in this revised manuscript. I have annotated the Word document (attached) to

	indicate where changes still need to be made. I shall leave it to the Editor to review a further revision and decide whether it has sufficiently addressed the comments I have made on the manuscript. There is also considerable work for a copy editor to bring the standard of English up to an appropriate level. - The reviewer provide a marked copy with additional comments. Please contact the publisher for full details

VERSION 2 – AUTHOR RESPONSE

REBUTTALS

We are very pleased to have such highly renowned reviewers for our study. Thank you for your valuable comments. The changes are highlighted in the revised manuscript. Attention, we present unpublished data in the reply to the reviewers (highlighted in yellow below) that is not aimed to be published in a supplement to this article, but is only for the eyes of the reviewers.

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