

**Answering Reviewers**

Sunday, April 15, 2018

Dear Editors,

Please find enclosed the edited manuscript using the "Track changes" function in Word format (file name: 38349-Revised Manuscript). The manuscript has been improved according to the suggestions of Reviewer Code: 02624173

**Manuscript Title:** Hypothyroidism during pregnancy: The Controversy over Screening and Intervention

**Manuscript ID:** 38349

**Journal:** *World Journal of Obstetrics and Gynecology*

**Authorship:** AbdelHameed Mirghani Dirar, Atul Kalhan

**KEY**

|                                 |                             |
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| <i>Reviewer Comment: italic</i> | <b>Author Response: red</b> |
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**Reviewer Code: 02624173:**

*Good write up though needs few points to be reconsidered. In introduction, Liothyronine is the synthetic T3, not the natural one, mention the correct one. Being a review article, the mechanism of implication of hypothyroidism in maternal & fetal consequences should also be included. Some typos need to corrected as under: Page 10, line 4, 'women with....were received...' should be 'women with....received...'. 17 line, 'it's' should be 'its'. Table 1, please reframe the sentence mentioning risk factor1. Page 15, give full form of TGAb. Page 18, use the same units of TSH as used elsewhere. Page 19, 2nd paragraph, the sentence beginning with 'A significant...' needs to be reframed. Page 21, 1st paragraph, 'ATA guidelines does...' should be 'ATA guidelines do...' . Page 28, 1st paragraph, 5th line, 'Therefore, In...' should be 'Therefore, in...'. Use '...weeks gestation' in place of '...weeks' gestation'. Give details of the role played by selenium in thyroid hormone metabolism and how will it be beneficial if included in the treatment. Iron deficiency anemia is rampant in pregnant females especially in developing countries, will it have any bearing on the thyroid status of these women? If yes, it needs to be included in the article. If second hypothesis i.e. effectiveness of intervention is not justifiable, then what is the use of universal screening (hypothesis1)?*

**Response:** We would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We hope that our edits adequately address each of his valued comments below:

1. *(In introduction, Liothyronine is the synthetic T<sub>3</sub>, not the natural one, mention the correct one)*

**Response:** We have mentioned the correct term for the natural T<sub>3</sub> (Triiodothyronine) rather than the synthetic one (Liothyronine) in the introduction section of the manuscript (Page 5, line 3).

2. *(Being a review article, the mechanism of implication of hypothyroidism in maternal & fetal consequences should also be included)*

As suggested by the reviewer, we have included a subsection dealing with the mechanism of implication of hypothyroidism in maternal & fetal consequences (Page 7, line 20).

3. *(Some typos need to corrected as under:)*

1. *(Page 10, line 4, 'women with....were received...' should be 'women with....received...')*  
**Response:** The correction has been made (Page 13, line 5).

2. *(17 line, 'it's' should be 'its'.)* **Response:** The correction has been made (Page 13, line 17).

3. *(Table 1, please reframe the sentence mentioning risk factor1.)* **Response:** We have reframed this sentence. The sentence now reads: Women over the age of 30 (Page 14, Table 1, risk factor1).

4. *(Page 15, give full form of TGAb.)* **Response:** The full form of TGAb has been given (Page 18, line 11).

5. *(Page 18, use the same units of TSH as used elsewhere.)* **Response:** The same unit of TSH expressed in mIU/L has been corrected as used elsewhere (Page 13, line 5/ Page 15, line 27/ Page 17, line 12 and 13/ Page 21, line 26).

6. *(Page 19, 2nd paragraph, the sentence beginning with 'A significant...' needs to be reframed.)*  
**Response:** We have reframed this sentence. The sentence now reads: A significant reduction in TSH level below 0.5 mIU/L has been shown in 32% of women who received lower supplementary doses compared with 65% of women who received higher doses of LT<sub>4</sub> therapy (*p* value <0.01) (Page 22, line 23).

7. *(Page 21, 1st paragraph, 'ATA guidelines does...' should be 'ATA guidelines do...')*  
**Response:** The correction has been made (Page 24, line 19).

8. (Page 28, 1st paragraph, 5th line, 'Therefore, In...' should be 'Therefore, in...'.) **Response:** The correction has been made (Page 32, line 7).
9. Use '*...weeks gestation*' in place of '*...weeks' gestation*'. **Response:** The correction has been made in different parts within the manuscript (Page 6, line 6/ Page 9, line 29/ Page 10, line 19/ Page 13, line 23/ Page 14, line 4/ Page 17, line 17/).
10. Give details of the role played by selenium in thyroid hormone metabolism and how will it be beneficial if included in the treatment. **Response:** As suggested by the reviewer, we have added some details of the role played by selenium in thyroid hormone metabolism and how will it be beneficial if included in the treatment (Page 23, line 14).
11. Iron deficiency anemia is rampant in pregnant females especially in developing countries; will it have any bearing on the thyroid status of these women? If yes, it needs to be included in the article. **Response:** We fully agree with the reviewer that there is a link between iron deficiency anaemia and thyroid status as suggested in several animal and human studies. Accordingly, we have included a subsection dealing with this effect and also we found that we have to include other physiological effects of pregnancy such as the rise in renal blood flow and glomerular filtration rate, the effect of the hCG molecule, increased binding capacity of the TBG and increased placental deiodination (Page 7, line 4).
12. If second hypothesis i.e. effectiveness of intervention is not justifiable, then what is the use of universal screening (hypothesis1)? **Response:** hypothesis 1 "universal screening for asymptomatic women in early pregnancy will be effective": this incorporates both overt as well as subclinical hypothyroidism. There is level 1 evidence which suggests adverse maternal as well as foetal outcomes if overt hypothyroidism remains untreated in pregnancy; on the other hand there is lack of evidence of beneficial impact of therapeutic intervention in subclinical hypothyroidism; so universal screening if cost effective will improve obstetric as well as foetal outcomes in a subset of patients (overt hypothyroidism) even though the other subgroup (subclinical hypothyroidism) may not be benefited by this approach (Page 29, line 9).

- **Cited work for reviewer feedback is placed within the references section in the manuscript (Page 35-37, Page 41) as under:**

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2. **Hershman JM.** Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 249-265 [PMID: 15157839 DOI: 10.1016/j.beem.2004.03.010]
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5. **Abu-Ouf NM, Jan MM.** The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi Med J* 2015; **36**: 146-149 [PMID: 25719576 DOI: 10.15537/smj.2015.2.10289]
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10. **Li S, Gao X, Wei Y, Zhu G, Yang C.** The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy. *J Nutr Sci Vitaminol (Tokyo)* 2016; **62**: 397-401 [PMID: 28202844 DOI: 10.3177/jnsv.62.397]

11. Erdogan M, Kösenli A, Ganidagli S, Kulaksizoglu M. Characteristics of anemia in subclinical and overt hypothyroid patients. *Endocr J* 2012; 59: 213-220 [PMID: 22200582 DOI: 10.1507/endocrj.EJ11-0096]
12. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev* 2014; 94: 355-382 [PMID: 24692351 DOI: 10.1152/physrev.00030.2013]
13. Koibuchi N, Jingu H, Iwasaki T, Chin WW. Current perspectives on the role of thyroid hormone in growth and development of cerebellum. *Cerebellum* 2003; 2: 279-289 [PMID: 14964687 DOI: 10.1080/14734220310011920]
14. Zoeller RT. New insights into thyroid hormone action in the developing brain: the importance of T3 degradation. *Endocrinology* 2010; 151: 5089-5091 [PMID: 20962056 DOI: 10.1210/en.2010-0926]
15. Calvo R, Obregón MJ, Ruiz de Oña C, Escobar del Rey F, Morreale de Escobar G. Congenital hypothyroidism, as studied in rats. Crucial role of maternal thyroxine but not of 3,5,3'-triiodothyronine in the protection of the fetal brain. *J Clin Invest* 1990; 86: 889-899 [PMID: 2394838 DOI: 10.1172/JCI114790]
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Thank you again for publishing our manuscript in the *World Journal of Obstetrics and Gynecology*

Sincerely yours,

**AbdelHameed Mirghani Dirar**

Northern Borders Health Affairs Directorate,  
Prince Abdel Aziz Bin MUSAAD Hospital  
Endocrinology and Diabetes Center  
Arar 91421, North Zone Province  
Saudi Arabia.

E. mail: [adirar@moh.gov.sa](mailto:adirar@moh.gov.sa)

Cell phone: +966508494973

Fax: +966146612474