response to the

RCOG Scientific Impact Paper

on

"Subclinical Hypothyroidism and Antithyroid Autoantibodies in Women with Subfertility or Recurrent Pregnancy Loss"

March 2021

The BFS would like to congratulate the authors on addressing this important topic in reproductive medicine. We would be grateful if the authors could consider the following suggestions to improve the scientific soundness of the paper:

1. Please propose clear definitions for sub-clinical hypothyroidism (SCH) and auto-immune thyroid disease (ATD)
2. We note that the opinion paper proposes testing for serum TSH for all sub fertile women and women with RPL. This is a major change from NICE guidance.
3. There is no recommendation about when TPOAb should be measured. It is left to clinician's discretion - please clarify.
4. There is no mention of starting doses of treatment. There is however guidance on monitoring. Please clarify
5. Line 164 – reference 17 – the study included women with TSH 2.5 to 5.0 - the study population included a mixture of mild and moderate SCH and therefore, it is incorrect to state that it was only 'mild' SCH.
6. Line 254 – reference 9: Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence (nih.gov): please review the graph in figure 2 and the table in the supplementary file. The studies where the line is to one side of midline have a flaw in the study design – for instance De Carolis et al., (2004) includes APLA and TPO Ab; Pratt et al., (1993) defines normal TSH as 0.35 to **7.0.** If you eliminate all those ones with TSH levels that frankly we would be treating without the TPOAb level – you will find the remaining studies all have lines crossing over unity – so it is possible that the numbers will actually be normal at the end.
7. Line 255…. Reference 21 – In the study by Liu et al., (2014), the authors define isolated ATD (*n*=227) as positive TPOAb and/or TgAb with normal TSH and fT4. The normal TSH was defined in this study was up to 5.22 mIU/L. So, some of the included women were not exactly isolated ATD, but ATD + SCH as per the SIP. Please consider amending the information provided.
8. Line 255…. Reference 33: Inaccurate information provided in this SIP, as the results from Bhattacharya et al., (2015) clearly suggest that the difference in miscarriage was not statistically different (p=0.153).
9. Lines 431 to 435 - We have some concerns that due to the incorrect information provided in relation to this reference (Maraka et al., 2017), it may scare women off unnecessarily of levothyroxine treatment if their TSH is > 4.0 & < 10. Please refer to Table 4 of the study. The results clearly suggest that initiating thyroxine

for women with TSH 2.5 to 4.0 does not alter the risk of miscarriage, but increases the risk of preterm birth, gestational hypertension and pre-eclampsia, however, starting thyroxine for women with TSH between 4.1 and 10.00 reduces the risk of miscarriage, but does not increase the risk for any adverse obstetric outcome.

10. Section 5.2 says use trimester specific ranges to commence LT4 if they are not already on treatment: In other words, a patient with TSH 3.0 at 8 weeks of pregnancy and was not previously on LT4 will be asked to start the treatment. Is there any data to support such a strategy? The evidence suggests (reference 44) that such a strategy is of no benefit and might in fact be harmful. Therefore, the authors should consider changing the statement to something like “due to the possible risk of harm in pregnancy, thyroxine supplementation should only be started if TSH is over 4” (which is consistent with NICE guideline).