

The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility

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The Journal of Clinical Endocrinology & Metabolism

The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility

--Manuscript Draft--

Manuscript Number:	jc.2019-40787R2
Article Type:	Clinical Research Article
Full Title:	The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility
Short Title:	Preconception prevalence of thyroid disease
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Keywords:	thyroid disease; thyroid autoimmunity; prevalence; preconception; miscarriage; subfertility		
Abstract:	<p>Objective To describe the prevalence of, and factors associated with different thyroid dysfunction phenotypes, in asymptomatic preconception women.</p> <p>Design Observational cohort study.</p> <p>Setting 49 hospitals across the UK between 2011-2016.</p> <p>Participants Women aged 16-41years with history of miscarriage or subfertility trying for a pregnancy.</p> <p>Methods Prevalences and 95%CI's were estimated using the binomial exact method. Multivariate logistic regression analyses were conducted to identify risk factors for thyroid disease.</p> <p>Intervention None.</p> <p>Main outcome measure Rates of thyroid dysfunction.</p> <p>Results Thyroid function and thyroid peroxidase antibody (TPOAb) data were available for 19,213 and 19,237 women respectively. The prevalence of abnormal thyroid function was 4.8% (95%CI 4.5-5.1); euthyroidism defined as thyroid stimulating hormone (TSH) 0.44-4.50mIU/L and free-thyroxine (fT4) 10-21pmol/L. Overt hypothyroidism (TSH>4.50mIU/L, fT4<10pmol/L) was present in 0.2% (95%CI 0.1-0.3) and overt hyperthyroidism (TSH<0.44mIU/L, fT4>21pmol/L) in 0.3% (95%CI 0.2-0.3). The prevalence of subclinical hypothyroidism (SCH) using an upper TSH concentration of 4.50mIU/L was 2.4% (95%CI 2.1-2.6). Lowering the upper TSH to 2.50mIU/L resulted in higher rates of SCH, 19.9% (95%CI 19.3-20.5). Multiple regression analyses showed increased odds of SCH (TSH>4.50mIU/L) with BMI \geq35.0kg/m² (aOR1.71 95%CI 1.13-2.57;p=0.01) and Asian ethnicity (aOR1.76 95%CI 1.31-2.37;p<0.001), and increased odds of SCH (TSH\geq2.50mIU/L) with subfertility (aOR1.16 1.04-1.29;p=0.008). TPOAb positivity was prevalent in 9.5% (95%CI 9.1-9.9).</p> <p>Conclusions The prevalence of undiagnosed overt thyroid disease is low. Subclinical hypothyroidism and TPOAb are common, particularly in women with higher BMI or Asian ethnicity. A TSH cut-off of 2.50mIU/L to define SCH results in a significant proportion of women potentially requiring levothyroxine treatment.</p>		
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Efficacy and Mechanism Evaluation Programme	Arri Coomarasamy		

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Question	Response	
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<p>Please select the statement below that describes the availability of the data generated or analyzed in your manuscript.</p>	
<p>SPECIAL REQUESTS:</p> <p>In place of a cover letter, enter specific comments or requests to the editors here</p>	<p>We would like to thank you for the continued opportunity to publish our paper in your journal. We very much wish for our study to be published in JCEM as we believe this is the best platform through which to publish this work.</p> <p>We wanted to write to you directly to address the ongoing concerns raised by reviewer 2. We would be most grateful if you could consider our response within your editorial team without sending on for reviewer comments, as we believe there is a misunderstanding of the nature and conduct of this study. We have uploaded our formal letter to yourselves in place of the point-by-point rebuttal. We have addressed the concerns raised by reviewer 2 in this letter.</p> <p>Should you decide a formal separate response to reviewer 2 is still required we will provide one.</p> <p>Many thanks.</p>



UNIVERSITY OF BIRMINGHAM

Institute of Metabolism and
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Tommys National Miscarriage
Centre

Centre for Women's and Newborn
Health, Birmingham Women's and
Children's Foundation Trust

11th May 2020

Dear JCEM editorial team,

We would like to thank you for the continued opportunity to publish our paper "***The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility***" in your journal. We very much wish for our study to be published in JCEM as we believe this is the best platform through which to publish this work. We wanted to write to you directly to address the ongoing concerns raised by reviewer 2. We would be most grateful if you could consider our response within your editorial team without sending on for reviewer comments as we believe there is a misunderstanding of the nature and conduct of this study. However, should you decide a formal separate response to reviewer 2 is still required we will provide one.

Reviewer 1:

My initial comments have been thoughtfully addressed and I have no additional concerns.

Reviewer 2:

The authors performed a survey which demonstrated that none of the 49 sites had a local policy to perform thyroid function tests in women who had one miscarriage. Nevertheless, the international guidelines are quite clear on this. The lack of a local policy does not mean that the practitioners did not follow evidence based international guidelines. In regards to the population of subfertile women, the authors note in their response that, "The principal investigators at each site, where women were recruited with subfertility, have confirmed that where possible all new patients were offered thyroid function and TPO testing... ". Furthermore, women who presented to their local practitioners with symptoms of either overt hypothyroidism or overt hyperthyroidism, would have been tested and if found to have thyroid disease, would not have been referred for inclusion in the TABLET study. For all of this reason, the study cannot be construed as a true prevalence study. As the study is not a true prevalence study it is not accurate to state that "our study approach has adopted the most pragmatic method..." and then present the data as true prevalence data. What can be stated is that within the population of women referred to participate in the TABLET study, the prevalence of thyroid disease was found to be the following. These data cannot be construed as a true prevalence study as it is unknown what percentage of women were tested for thyroid disease, found to have thyroid disease and therefore never referred for participation in the TABLET trial.

Our response

We understand the reviewers concern regarding our study not representing a true prevalence study, however we have detailed our reasons below to contest this notion.

With regards to the issue of testing and prior diagnosis of thyroid disease in women seen in primary care, this would relate only to women who were symptomatic of thyroid disease. Primary care practitioners in the UK would not be offering thyroid function testing to asymptomatic women. The key important point of note in our prevalence study is that all women approached for screening were asymptomatic. We completely agree that symptomatic women are likely to have already been tested and treated prior to any secondary care contact. We are not making any objection to this statement. Our study presents the rates of thyroid disease in the asymptomatic, ordinarily unscreened, population.

As the reviewer correctly states, international guidance (in particular the Endocrine Society Clinical Practice guideline (ESCPG) by De Groot et al in 2012) does state that women with a prior history of miscarriage should be offered thyroid function testing. However, this is not currently, and never has been, standard practice in the UK amongst primary or secondary care providers. We have confirmed through our principal investigator survey that no woman with a history of 1 or 2 miscarriages would have been offered routine thyroid function testing outside of our study at any of the recruiting hospitals. This UK practice is also verified by Professor Boelaert, who led the UK NICE guidance on management of thyroid diseases and is a member of the Society for Endocrinology Clinical Committee. Therefore, our reported disease prevalence in asymptomatic women with history of 1 or 2 miscarriages is as accurate as possible.

Regarding the prevalence of disease in the population of women with history of recurrent miscarriages, we believe this is also accurate. UK guidance recommends all women with recurrent pregnancy losses are cared for by professionals with the necessary expertise and should be seen in specifically designated recurrent miscarriage clinics. Through our principal investigator survey, we confirmed that all new referrals to the recurrent miscarriage clinics (defined as women with 3 or more pregnancy losses) were offered thyroid function testing within the scope of our study. This, therefore, represents as close to a true prevalence as possible in this population.

The only population where we accept there may be an underestimate of the true prevalence is the subfertility population. This is due to the inconsistent practice across the recruiting sites. Some hospitals had a local policy to offer routine thyroid function testing to all women presenting with subfertility. As not all women were screened at their first fertility appointment, we accept that a proportion of women may have been already diagnosed and treated for thyroid dysfunction. This is reflected in the conclusion of our manuscript.

Overall, we strongly believe that our study has adopted the most pragmatic approach to determine an accurate measurement of thyroid disease prevalence in asymptomatic women with history of miscarriage or subfertility. Consequently, we are anxious to not lose the overall message in our study, which would be the case if we were to make the changes as requested by reviewer 2. We also note that reviewer 1 has not raised the issue of inaccurate prevalence.

We hope that you and your editorial team can review our response independently and we look forward to hearing from you.

Yours sincerely,

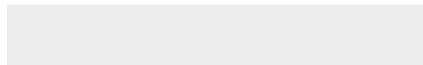
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Revised Manuscript - Changes Highlighted
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1 **The prevalence of thyroid dysfunction and autoimmunity in women with history**
2 **of miscarriage or subfertility**

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91 **Abstract**

92 **Objective**

93 To describe the prevalence of, and factors associated with different thyroid dysfunction
94 phenotypes, in asymptomatic preconception women.

95

96 **Design**

97 Observational cohort study.

98

99 **Setting**

100 49 hospitals across the UK between 2011-2016.

101

102 **Participants**

103 Women aged 16-41years with history of miscarriage or subfertility trying for a pregnancy.

104

105 **Methods**

106 Prevalences and 95%CI's were estimated using the binomial exact method. Multivariate
107 logistic regression analyses were conducted to identify risk factors for thyroid disease.

108

109 **Intervention**

110 None.

111

112 **Main outcome measure**

113 Rates of thyroid dysfunction.

114

115 **Results**

116 Thyroid function and thyroid peroxidase antibody (TPOAb) data were available for 19,213
117 and 19,237 women respectively. The prevalence of abnormal thyroid function was 4.8%
118 (95%CI 4.5-5.1); euthyroidism defined as thyroid stimulating hormone (TSH) 0.44-
119 4.50mIU/L and free-thyroxine (fT4) 10-21pmol/L. Overt hypothyroidism (TSH>4.50mIU/L,
120 fT4<10pmol/L) was present in 0.2% (95%CI 0.1-0.3) and overt hyperthyroidism
121 (TSH<0.44mIU/L, fT4>21pmol/L) in 0.3% (95%CI 0.2-0.3). The prevalence of subclinical
122 hypothyroidism (SCH) using an upper TSH concentration of 4.50mIU/L was 2.4% (95%CI
123 2.1-2.6). Lowering the upper TSH to 2.50mIU/L resulted in higher rates of SCH, 19.9%
124 (95%CI 19.3-20.5). Multiple regression analyses showed increased odds of SCH
125 (TSH>4.50mIU/L) with BMI \geq 35.0kg/m² (aOR1.71 95%CI 1.13-2.57;p=0.01) and Asian
126 ethnicity (aOR1.76 95%CI 1.31-2.37;p<0.001), and increased odds of SCH
127 (TSH \geq 2.50mIU/L) with subfertility (aOR1.16 1.04-1.29;p=0.008). TPOAb positivity was
128 prevalent in 9.5% (95%CI 9.1-9.9).

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Conclusions

The prevalence of undiagnosed overt thyroid disease is low. Subclinical hypothyroidism and TPOAb are common, particularly in women with higher BMI or Asian ethnicity. A TSH cut-off of 2.50mIU/L to define SCH results in a significant proportion of women potentially requiring levothyroxine treatment.

Keywords

Thyroid disease, thyroid autoimmunity, prevalence, preconception, miscarriage, subfertility

Precis

This study of over 19,000 women with history of miscarriage or subfertility found undiagnosed overt thyroid disease in preconception women is low. Subclinical hypothyroidism is common, particularly in higher BMI or Asian women.

INTRODUCTION

169
170
171 Thyroid disorders are amongst the most prevalent medical conditions in women of
172 reproductive age. The prevalence of thyroid disorders in pregnancy are well documented
173 in those with known disease, however, there is little known of the unscreened
174 asymptomatic preconception population.

175
176 Detection of thyroid disorders preconception is essential due to the adverse effects
177 thyroid abnormalities have on conception and pregnancy. It is well established that both
178 uncontrolled thyrotoxicosis and overt hypothyroidism are associated with adverse
179 pregnancy outcomes such as reduced fertility, miscarriage, pre-eclampsia and pre-term
180 birth¹⁻³. Subclinical hyperthyroidism and subclinical hypothyroidism (SCH) are
181 biochemical diagnoses defined by an abnormal serum thyroid stimulating hormone (TSH)
182 with normal concentrations of free thyroxine. They may represent the earliest stages of
183 thyroid dysfunction and can progress to overt disease⁴. SCH has been linked to
184 subfertility, miscarriage, pre-term birth, pre-eclampsia, and perinatal mortality⁵. Thyroid
185 peroxidase antibodies (TPOAb) have also been associated with adverse pregnancy
186 outcomes such as subfertility, recurrent miscarriages and pre-term birth^{6,7}. The presence
187 of TPOAb increases the risk of progression to subclinical and overt thyroid disease in
188 pregnancy^{8,9}.

189
190 There is international agreement on the treatment of overt thyroid disease. However, the
191 treatment strategies for SCH or TPOAb pre-conception and antenatally are debated. The
192 European Thyroid Association (ETA) and American Thyroid Association (ATA)
193 recommend levothyroxine (LT4) replacement in pregnant women with SCH^{10,11}. The ATA
194 guideline specifically refers to using internal or transferable pregnancy-specific TSH
195 reference ranges and if these are not available, an upper reference limit of 4.0mIU/L may
196 be used¹¹. The same guideline recommends a lower threshold for treatment in TPOAb
197 positive women, using a cut off TSH of >2.5mIU/L¹¹. These recommendations are based
198 on the notion that any possible benefits of treatment with LT4 are thought to outweigh
199 any potential risks. However, a retrospective cohort study of 5405 women with SCH in
200 pregnancy contests this notion¹². This study found that women who received LT4
201 treatment had lower adjusted odds of pregnancy loss (OR 0.62, 95% CI 0.48 to 0.82) but
202 higher odds of preterm delivery (1.60, 1.14 to 2.24), gestational diabetes (1.37, 1.05 to
203 1.79), and pre-eclampsia (1.61, 1.10 to 2.37) compared to untreated women. The cohort
204 was subgrouped into women with pre-treatment TSH values of 2.5-4.0mIU/L and those
205 with TSH values 4.1-10mIU/L. The adjusted odds of pregnancy loss were lower in treated
206 women than in untreated women if their pre-treatment TSH concentration was 4.1-
207 10mIU/L (OR 0.45, 0.30 to 0.65) but not if it was 2.5-4.0mIU/L (0.91, 0.65 to 1.23)

208 (p<0.01). This study not only shows no benefit from treating the mildly elevated TSH
209 subgroup but also suggests harm in doing so¹².

210 The definition of SCH and recommendations of when to initiate LT4 treatment differs
211 between population subgroups. The Endocrine Society Clinical Practice Guideline
212 (ESCPG) recommends a preconception TSH of <2.5mIU/L for all subfertile women and
213 women with history of miscarriage or pre-term birth¹³. The 2017 ATA guideline
214 recommends “*subclinically hypothyroid women undergoing IVF should be treated with*
215 *LT4...to achieve a TSH concentration <2.5mU/L*”¹¹. The American Society for
216 Reproductive Medicine (ASRM) guideline on subclinical hypothyroidism in the infertile
217 female adopts a similar guidance which is that TSH concentrations over the non-pregnant
218 lab reference range (typically >4.0mIU/L) should be treated with levothyroxine to maintain
219 levels below 2.5mIU/L. It also maintains that there is insufficient evidence that LT4
220 therapy in women with TSH levels between 2.5 and 4.0mIU/L is associated with
221 improvement in pregnancy and miscarriage rates. In spite of this, they recommend that it
222 is advisable to treat when the TSH is >2.5mIU/L in the first trimester of pregnancy¹⁴.

223 Regarding screening for thyroid disease, the ATA and ASRM recommends TSH testing
224 for all women seeking care for infertility^{11,14}, this is supported by the ESCPG who also
225 recommend screening women with any history of miscarriage¹³. However, National
226 Institute of Health and Care Excellence (NICE) does not recommend routine screening
227 for women with subfertility¹⁵. The ESHRE guideline recommends TSH and TPOAb testing
228 for all women with recurrent pregnancy losses¹⁶.

229
230 In order to determine if screening programmes are cost-effective and to understand the
231 impact of varying cut-off levels for diagnosing subclinical thyroid disease, the prevalence
232 of the disease must first be established. To our knowledge, the prevalence of varying
233 degrees of thyroid dysfunction and associated risk factors has not been assessed
234 systematically in women with history of miscarriage or subfertility.

235
236 Our study objective was to describe the prevalence of, and factors associated with,
237 different thyroid dysfunction phenotypes, in preconception asymptomatic women with
238 history of miscarriage or subfertility.

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245

METHODS

246
247
248 This was a multi-centre prospective observational cohort study conducted across 49
249 hospitals in the UK between November 2011 and January 2016. This study directly linked
250 to a large multi-centre randomised controlled trial (The TABLET trial; ISRCTN15948785).

251 252 *Eligibility criteria and recruitment setting*

253 The eligibility criteria were as follows: history of miscarriage or subfertility, aged between
254 16-41 years, actively trying for a pregnancy in the subsequent 12 months, not known to
255 have current thyroid illness, not known to have cardiac problems, and not taking
256 amiodarone or lithium.

257
258 History of miscarriage was defined as any pregnancy which was confirmed by a positive
259 pregnancy test (both biochemical and clinical pregnancies included). For women with
260 subfertility, this was defined as any woman seen in a secondary care setting for
261 subfertility.

262
263 Participants were recruited from the following clinical settings: early pregnancy units
264 (EPU) screening women with recent miscarriage; recurrent miscarriage clinics; infertility
265 clinics or women who had contacted the trial team as self-referrals via the trial website or
266 via social media. All new referrals to recurrent miscarriage services and infertility clinics
267 were approached to participate. Participants who had consented for screening, but for
268 whom no result was available (either due to insufficient sample taken or laboratory
269 processing errors), were contacted and offered a repeat blood test.

270 *Thyroid function tests*

271 Serum samples were analysed for TSH and Free T4 using any one of the study-approved
272 analysers. These were: Roche Modular E170, Roche Elecsys® 1010 or 2010, Roche
273 Cobas®, Abbott architect and Siemens Advia Centaur. All laboratories participated in the
274 UK national external quality assurance scheme (NEQAS) to ensure consistency in testing
275 and these analysers specifically were deemed to produce comparable results.

276
277 Rather than applying specific reference ranges dependent on the laboratory assay used,
278 we adopted a pragmatic approach when defining euthyroidism and used a commonly
279 accepted reference range in the UK of 0.44-4.50mIU/L for TSH and 10-21pmol/L for fT4.
280 Values below and above these ranges were considered abnormal. The euthyroid group
281 was further sub-divided into TSH 0.44-2.49mIU/L and 2.50-4.50mIU/L, as the latter is
282 commonly regarded as subclinical hypothyroidism by many fertility and early pregnancy
283 specialists. Subclinical hypothyroidism was also analysed in two further groups;
284 moderate (TSH 4.51-10mIU/L) and severe (>10mIU/L). Most guidelines adopt different

285 management approaches depending on the degree of TSH abnormality based on these
286 different cut-offs both in the preconception period^{10,11} and outside pregnancy¹⁷⁻¹⁹.

287

288 *TPO antibody evaluation*

289 A range of anti-TPO antibody assays were utilised each with different detection limits and
290 thresholds for test positivity pre-determined by the manufacturer (supplementary table
291 S1²⁰). These variations are an accepted part of normal UK practice. Quality assurance
292 for assays in the laboratories of all participating centres was provided by UK Immunology,
293 Immunochemistry and Allergy National External Quality Assurance Service (NEQAS
294 IIA),²¹ which showed over 99% concordance in the classification of samples as either
295 positive or negative for TPO antibodies across all assays. Therefore, we did not define a
296 threshold for TPO positivity but instead accepted the categorical classification provided
297 by the laboratories servicing the participating centres (supplementary table S1²⁰).

298

299 *Participant characteristics*

300 The following participant characteristics were recorded and categorised for each
301 screened patient: age, body-mass index (BMI), ethnicity and originating clinical
302 population.

303

304 Age (in years) was grouped into 5 year blocks: 17-21; 22-26; 27-31; 32-36; 37-41. BMI
305 (kg/m²) was categorised according to WHO recommendations: underweight <18.5;
306 normal weight 18.5-24.9; overweight 25.0-29.9; obese class I 30.0-34.9; obese class II
307 and III ≥ 35.0 ²². Ethnicity was selected from a list of 17 options, as per the NHS ethnic
308 category codes and grouped as: "White"; "Asian" (Indian/Pakistani/Bangladeshi/Other
309 South Asian); "Black" (African/Caribbean/Other Black); "Mixed" (mixed White/Asian,
310 mixed White/Black African, mixed White/Black Caribbean, other mixed background);
311 "Chinese" and "Other" ethnic group. Originating clinical population referred to the clinical
312 setting where patients were screened: women with history of one or two miscarriages
313 (i.e. EPU setting), women with history of recurrent miscarriage, women seen in the fertility
314 setting or other.

315

316 *Screening process*

317 Every eligible participant was approached in the relevant clinical areas and all women
318 were required to give written consent to have their blood taken for thyroid function and
319 TPOAb. For each participant screened, they were assigned an individual screening
320 number. Their baseline characteristics and corresponding thyroid function and thyroid
321 antibody results were all inputted onto an electronic data collection page. Participants
322 with normal thyroid function and positive for TPOAb were then offered to enter the full
323 trial.

324 *Statistical analyses*

325 An overall description of the study population was presented using the patient
326 characteristic subgroups as categorical variables. Prevalences, with their 95%
327 confidence intervals, were estimated for each thyroid dysfunction group and for TPOAb
328 using the binomial exact method. TPOAb positivity was further explored in thyroid
329 dysfunction subgroups.

330

331 Five clinically important thyroid dysfunction groups, which are not mutually exclusive,
332 were explored: overt hypothyroidism, overt hyperthyroidism, SCH with TSH >4.50mIU/L
333 (combining moderate and severe SCH), SCH with TSH \geq 2.50mIU/L, and SCH with TSH
334 \geq 2.50mIU/L and TPOAb positive. Multiple logistic regression analyses were performed to
335 assess the relationship between the relevant thyroid function group and the following
336 variables: age, BMI, ethnicity, population and TPOAb positivity. The reference group for
337 each patient characteristic variable was selected on the basis of which was deemed the
338 “lowest risk” or the largest group. Finally, an analysis was performed to determine the
339 relationship between TPOAb positivity and TSH concentrations.

340

341 All analyses were done using Stata statistical software, release 14 (Stata Corp, College
342 Station, TX, 2015).

343

344

345

RESULTS

346

347 A total of 19,350 women gave written consent to have testing for thyroid function and
348 TPOAb. Thyroid function results were available for 19,213 women and TPOAb results
349 for 19,237 women. The list of the 49 recruitment centres and the numbers of women
350 recruited at each site is presented in supplementary table S2²⁰.

351

352 The pre-screening logs did not show any obvious disparities in age, BMI or ethnicity
353 between those who gave consent and those who did not. The most common reason for
354 declining consent was that women preferred not to know their thyroid status; this
355 contributed to less than 0.5% of all women approached; thus, the cohort was deemed
356 representative of women with no known thyroid dysfunction seen in the miscarriage care
357 and subfertility clinical settings.

358

Prevalence of thyroid dysfunction

360 The overall prevalence of thyroid dysfunction is shown in Figure 1. The overall prevalence
361 of thyroid dysfunction (euthyroidism defined as TSH 0.44-4.5mIU/L, free T4 10-21pmol/L)
362 is 4.8% (95% CI 4.5-5.1). Overt hypothyroidism (defined as TSH >4.50mIU/L and fT4

363 <10pmol/L) was present in 0.2% (95% CI 0.1-0.3) and overt hyperthyroidism (defined as
364 TSH <0.44mIU/L and fT4 >21pmol/L) in 0.3% (95% CI 0.2-0.3). The prevalence of
365 subclinical hypothyroidism (SCH) using an upper TSH concentration of 4.50mIU/L was
366 2.4% (95% CI 2.1-2.6). Lowering the upper TSH limit to 2.50mIU/L resulted in a higher
367 rate of SCH of 19.9% (95% CI 19.3-20.5).

368
369 Applying an upper limit of TSH to 2.50mIU/L to only those with subfertility or ≥ 3
370 miscarriages i.e. the “highest risk populations” showed the prevalence to be 20.1% and
371 16.1% respectively (supplementary table S3²⁰). The prevalence of thyroid dysfunction in
372 various patient characteristic subgroups is shown in supplementary table S3²⁰.

373 374 ***Risk factors for thyroid dysfunction***

375 TPOAb positivity was the factor associated most significantly with any degree of thyroid
376 dysfunction, after adjustment for confounders (Table 1). The relationship between patient
377 characteristics and thyroid function are presented in Table 1. Multiple regression
378 analyses found increased odds of SCH (TSH >4.50mIU/L) with body-mass index (BMI)
379 $\geq 35.0\text{kg/m}^2$ (aOR 1.71 (95% CI 1.13-2.57, $p=0.01$) and Asian ethnicity (aOR 1.76 (95%
380 CI 1.31-2.37) $p<0.001$), as well as increased odds of SCH (TSH $\geq 2.50\text{mIU/L}$) with
381 subfertility (aOR 1.16 (1.04-1.29) $p=0.008$).

382 383 384 ***Prevalence of and risk factors for TPO antibody positivity***

385 The overall prevalence of TPOAb was 9.5% (9.1-9.9%) (Table 2). The prevalence of
386 TPOAb positivity by patient characteristic subgroups is shown in supplementary table
387 S3²⁰. The association of patient characteristic subgroups with TPOAb positivity, following
388 adjustment for confounders, is shown in Table 3. There was a dose-response relationship
389 observed between TPOAb positivity and BMI, Class III obese women (BMI $\geq 35.0\text{ kg/m}^2$)
390 were statistically significantly more likely to be TPOAb positive compared with women of
391 normal weight. Black women were less likely to be TPOAb positive than White women.
392 There were no significant differences in TPOAb positivity between the originating
393 population groups.

394 395 ***Association between TPOAb positivity and thyroid dysfunction***

396 The prevalence of TPOAb by individual thyroid dysfunction group is shown in Table 3.
397 Women with overt thyroid dysfunction had higher prevalences of TPOAb positivity and
398 this was most pronounced in those with overt hypothyroidism. In those with subclinical
399 hypothyroidism, higher rates of TPOAb positivity were observed in the categories with
400 higher serum TSH concentrations. Of those with isolated hypothyroxinaemia (IH), 87%
401 were TPOAb positive, however on closer inspection of the free T4 data the mean was

8.9pmol/L and median 9.6pmol/L. Therefore, this group was unlikely to represent the true IH population and instead were categorised as IH due to the strict reference range used. Using a lower free T4 cut off of 8.0pmol/L resulted in only 4 cases of IH with a mean value of 2.1pmol/L and none of these were TPOAb positive.

Finally, we determined the relationship between categories of TSH concentration and the prevalence of TPOAb positivity as shown in Figure 2. The probability of TPOAb positivity was lowest in women with TSH 0.44-2.5mIU/L and increased gradually with increasing TSH concentrations. TPOAb positivity was associated with both raised and suppressed TSH concentrations, and more pronounced effects were seen with higher concentrations.

DISCUSSION

Main findings

To our knowledge, this is the first systematic evaluation, adopting the most pragmatic approach, to assess thyroid function and TPOAb status in asymptomatic preconception women with history of miscarriage or subfertility. Using current accepted reference ranges, we classified 95.2% of women as euthyroid, with undiagnosed disorders of overt hypothyroidism in 0.2%, overt hyperthyroidism in 0.3%, severe subclinical hypothyroidism (TSH >10mIU/L) in 0.2% and SCH (TSH>4.50mIU/L) in 2.4%. Lowering the upper limit of TSH to 2.50mIU/L, as is the recommendation by international societies for “high risk” women (i.e. those with history of RPL or undergoing ART), would class 16-20% of women as subclinically hypothyroid.

We identified higher body-mass index, Asian ethnicity, subfertility and TPOAb positivity as independent factors associated with higher TSH concentrations. 9.5% of women expressed TPOAb. Women with a history of ≥ 3 miscarriages or subfertility were not more likely to be TPOAb positive than those with one or two previous miscarriages. Raised BMI (≥ 35.0 kg/m²) was associated with higher rates, while Black ethnicity was linked to lower rates of TPOAb positivity.

Strengths and limitations

The main strengths of this study were the large sample size and the widespread geographical representation across the UK, allowing precise determination of the prevalence of and risk factors for different forms of thyroid dysfunction.

One of the limitations is that our population belonged to a “selected population”, with miscarriage or infertility. There is no control group in our study as the eligibility criteria for screening had to match with that of the TABLET trial. Therefore, thyroid function in these

441 women may not represent that of true unselected “low risk” women with no
442 gynaecological or obstetric risk factors. On the other hand, this study includes women
443 who have engaged in the health system and therefore those who are most likely to benefit
444 from a screening programme. Many “low risk” women have no contact with health
445 professionals in the preconception period or have unplanned pregnancies, thus would
446 not have the chance to be screened.

447

448 The variables collected within our cohort study were limited for pragmatic reasons and
449 we have therefore been unable to perform detailed exploratory analyses. For example,
450 we have not been able to comment on the rates of thyroid dysfunction in women with
451 different causes of subfertility or analyse the data separately for those who underwent
452 IVF treatment and those who did not. However, we present an overall prevalence of
453 thyroid dysfunction in women within a “high risk” population.

454

455 Another limitation is that our exploration of risk factors did not adjust for multiplicity; hence
456 we cannot rule out increased chance of false positive findings.

457

458 Finally, we did not assess iodine status. Previous studies in the UK have suggested that
459 UK is a mildly iodine deficient population and this could have increased the prevalence
460 of thyroid disease²³.

461

462 ***Underestimation of true prevalence?***

463 It could be speculated that our reported prevalence’s are an underestimation of the true
464 rates. The reason for this is that it is unknown how many women with miscarriage or
465 subfertility may have been screened for thyroid dysfunction and treated by their
466 Gynaecologist or primary care provider and therefore never referred to participate in our
467 study.

468

469 For women with history of 1 or 2 miscarriages it is not routine practice in the UK to offer
470 thyroid function or TPOAb testing in primary or secondary care. The clinicians recruiting
471 at each site in our study have verified that these women would not have been tested prior
472 to or outside of our study. Therefore, these women were opportunistically screened within
473 our study and so the results reflect as close to as possible the true disease prevalence.

474

475 For women with 3 or more miscarriages, routine practice in the UK is for referral to a
476 secondary care provider with a recurrent miscarriage service for further investigations.
477 All clinicians recruiting in this setting verified that, where possible, all new patients were
478 offered TFT and TPOAb testing at initial contact within the remit of our study. Therefore,
479 the findings in this population also represent the best possible true prevalence rates.

480

481 With regards to the subfertile population, TPOAb testing was not routinely performed at
482 any of our recruiting sites outside of the study. Therefore, we can be reassured that our
483 reported TPOAb prevalence in subfertile women is as close as possible to the true
484 prevalence. However, testing for thyroid dysfunction in the subfertile population is an
485 important potential confounder which may have resulted in underestimation of the true
486 prevalence and the results should therefore be interpreted with some caution. Although
487 the UK leading clinical guidance provider, NICE, do not recommend routine thyroid
488 function testing in subfertile women this is common practice across secondary care
489 providers. Despite the fact we urged all sites to approach women on their initial contact
490 in secondary care, this was not consistent as some women were recruited from clinics in
491 the outpatient setting while others were only approached at the point of starting IVF
492 treatment. In addition, some subfertile women may have already had their thyroid
493 function tested (and treated) by their primary care provider prior to referral. This means
494 that there will be an unknown proportion of women who were offered TFT testing outside
495 of the remit of our study and may have already been diagnosed and treated and therefore
496 excluded from our prevalence figures. It would be very difficult to quantify the number of
497 women potentially missed and we believe our study approach has adopted the most
498 pragmatic method of capturing the women presenting to secondary care for subfertility.
499 However, we accept that the reported disease prevalence for thyroid dysfunction in the
500 asymptomatic subfertile population is likely to be higher than we have found.

501 502 ***Interpretation***

503 Our data are consistent with studies reporting that women with subfertility are more likely
504 to have subclinical hypothyroidism^{5,24,25}. Our observation of higher TSH concentrations
505 in Asian and lower concentrations in Black women, may reflect normal inter-ethnic
506 variation, consistent with previous documentation of lower TSH levels in people from
507 Black or Hispanic origin compared with White Caucasian populations²⁶. A large Dutch
508 study of 3944 women found significant ethnic differences in serum TSH, T4, and TPO-
509 antibody positivity and important diagnostic discrepancies were identified when
510 population and ethnicity-specific reference ranges were applied resulting in a change of
511 diagnosis for 18% of women²⁷. Further work is required to prevent misdiagnosing and
512 subsequent mistreatment for women from certain ethnic backgrounds.

513
514 Higher prevalence of TPOAb have been reported in women with subfertility (10-31%) and
515 recurrent pregnancy loss (17-33%) compared with the general population (6-20%)²⁸. Our
516 data did not identify a significant association between TPOAb positivity and a history of
517 recurrent miscarriage or infertility. The recently published TABLET (Thyroid Antibodies
518 and LEvoThyroxine) trial, to which this study was linked, found no improvement in live
519 birth or any secondary pregnancy or neonatal outcomes in euthyroid TPOAb positive
520 women taking 50mcg LT4 compared with placebo²⁹. However, around 8% of women in

521 each group did go on to develop thyroid dysfunction and detection of this would not have
522 been possible without knowing TPOAb status and performing the appropriate thyroid
523 monitoring in pregnancy. Further evidence is required to determine the need to screen
524 these specific populations.

525

526 ***Implications for clinical practice***

527 We have shown the prevalence of differing thyroid abnormalities when universally
528 screening otherwise healthy women with history of miscarriage or subfertility. Using this
529 strategy, 0.5% were found to have overt thyroid dysfunction. In pregnancy, severe SCH
530 would be considered overt hypothyroidism and so a further 0.2% would need definitive
531 treatment. Screening for SCH, using a TSH cut off of 2.5mIU/L as recommended for
532 women with subfertility or recurrent miscarriage, will result in up to 20% of women
533 diagnosed as having thyroid dysfunction and potentially requiring levothyroxine
534 treatment, with 4% having SCH *and* TPOAb. Not forgetting that these figures are likely to
535 represent an underestimate of the true prevalence. This could constitute a significant
536 burden to healthcare systems, and may generate unnecessary patient anxiety. In the
537 absence of evidence of benefit with LT4 treatment and possible suggestion of harm, for
538 mild SCH or TPOAb positivity we pose the question of whether screening should be
539 performed at all in asymptomatic individuals. Although knowing TPOAb status will identify
540 those women who require antenatal monitoring of thyroid function, there is no proven
541 treatment to modify pregnancy outcome. Case finding in the subfertile and recurrent
542 miscarriage populations, by identifying risk factors such as ethnicity and BMI, may be a
543 better strategy.

544

545 ***Future work***

546 Many clinicians screen for and treat subclinical hypothyroidism (TSH \geq 2.50mIU/L and
547 normal fT4) in women with subfertility or history of miscarriage, despite ongoing
548 uncertainty over the benefits and cost implications of this management strategy. Further
549 studies, including health economic analyses, are needed to determine if treating 0.7% of
550 such women, who have undiagnosed severe SCH or overt thyroid disease and are at risk
551 of pregnancy complications, outweighs the costs of universal screening. It is well
552 established that screening should not be implemented if treatment does not have any
553 effect on the natural progression of the disease. Large randomised trials are needed to
554 establish if preconception LT4 treatment of mild SCH with or without TPOAb positivity is
555 beneficial. If treatment is found to be beneficial, this study presents the prevalence of
556 thyroid disorders that can be expected and explored which factors are associated with
557 thyroid dysfunction and TPOAb positivity that could guide the development of suitable
558 cost-effective screening strategies and aid clinical decision making in primary and
559 secondary care.

560 **Ethical approval**

561 Ethical approval was obtained from Berkshire B Research Ethics Committee (REC
562 reference 13/SC/0642).

563

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567

568 **Author disclosure statement**

569 No competing financial interests exist.

570

571 **Authors contributions**

572 The study was designed by R. Dhillon-Smith (RDS), A. Coomarasamy (AC), K. Boelaert
573 (KB), A. Tobias (AT), P.P. Smith (PPS), S. Chan (SC), S. Thangaratinam (ST), J. Daniels
574 (JD) and L.J. Middleton (LJM). Data gathering was carried out by RDS, J.J. Chu (JJC),
575 K. Sunner (KS), K. Baker (KB) and S. Farrell-Carver (SFC). Data analysis was performed
576 by AT, PPS and LJM. The data and analyses are vouched for by RDS, AC, AT, and PPS.
577 RDS, AC, KB and SC wrote the paper and made the decision to publish. RDS wrote the
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581 Underwood and M.D. Kilby provided critical input in to the conduct of the trial and drafting
582 of the manuscript.

583

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691

692 **Figure Legend**

693

694

695 **Figure 1. Overall prevalence of thyroid dysfunction**

696 (Free T4 measured in pmol/L and TSH in mIU/L)

697

698 **Figure 2. Probability of TPO antibody positivity vs. TSH concentration**

Table legend

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Table 1. Risk factors for clinically important thyroid dysfunction groups

	Overt Hypothyroid (n=36)		Overt Hyperthyroid (n=49)		SCH (TSH >4.50, ft4 10-21) (n=451)		SCH (TSH ≥2.50, ft4 10-21) (n=3825)		SCH (TSH ≥2.50, ft4 10-21) and TPOAb positive (n=784)	
	aOR ¹	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
Age (years)										
17-21	1.79	(0.18, 18.11)	2.45	(0.46, 13.05)	0.94	(0.39, 2.30)	1	(0.71, 1.40)	1.2	(0.50-2.90)
22-26	Ref		Ref		Ref		Ref		Ref	
27-31	0.8	(0.20, 3.28)	0.78	(0.26, 2.36)	0.67	(0.44, 1.03)	1.04	(0.89, 1.22)	1.38	(0.92-2.07)
32-36	0.75	(0.19, 2.96)	0.57	(0.18, 1.78)	0.99	(0.7, 1.46)	1.07	(0.92, 1.25)	1.28	(0.87-1.90)
37-41	0.56	(0.11, 2.82)	0.54	(0.14, 2.05)	0.86	(0.56, 1.35)	1.01	(0.85, 1.20)	1.29	(0.84-1.99)
BMI										
<18.5	-	-	4.35*	(1.21, 15.56)	0.37	(0.09, 1.50)	0.79	(0.56, 1.12)	0.94	(0.38-2.31)
18.5-24.9	Ref		Ref		Ref		Ref		Ref	
25.0-29.9	3.92*	(1.34, 11.42)	0.74	(0.30, 1.84)	1.06	(0.78, 1.45)	1.07	(0.95, 1.20)	0.95	(0.71-1.27)
30.0-34.9	1.37	(0.26, 7.14)	0.46	(0.10, 2.01)	1.23	(0.84, 1.81)	1.06*	(1.00, 1.42)	1.51*	(1.04-2.18)
≥35.0	1.84	(0.35, 9.65)	0.33	(0.04, 2.50)	1.71*	(1.13, 2.57)	1.38**	(1.16, 1.64)	1.73**	(1.16-2.58)
Ethnicity										
White	Ref		Ref		Ref		Ref		Ref	
Black	0.88	(0.11, 6.94)	4.63*	(1.48, 14.50)	0.68	(0.34, 1.36)	0.68**	(0.55, 0.85)	0.49	(0.23-1.04)
Asian	1.29	(0.45, 3.68)	1.79	(0.72, 4.46)	1.76**	(1.31, 2.37)	1.38**	(1.22, 1.55)	1.06	(0.78-1.43)
Chinese	-	-	-	-	0.82	(0.20, 3.42)	1.17	(0.76, 1.80)	0.48	(0.13-1.79)
Mixed	-	-	-	-	0.43	(0.11, 1.77)	0.65*	(0.44, 0.96)	0.55	(0.19-1.57)
Other	-	-	4.38	(0.97, 19.64)	0.94	(0.38, 2.35)	1.08	(0.78, 1.48)	0.81	(0.38-1.73)

Population										
1 or 2 miscarriages	Ref		Ref		Ref		Ref		Ref	
Recurrent miscarriage	1.46	(0.48, 4.43)	0.87	(0.26, 2.84)	0.96	(0.66, 1.39)	0.89	(0.77, 1.02)	1.01	(0.72-1.42)
Infertility	0.76	(0.26, 2.20)	1.27	(0.54, 2.99)	1.04	(0.77, 1.39)	1.16*	(1.04, 1.29)	1.09	(0.82-1.44)
Other	-	-	2.89	(0.35, 23.53)	0.69	(0.21, 2.25)	0.95	(0.65, 1.39)	0.7	(0.25-1.91)
TPO positive										
No	Ref		Ref		Ref		Ref			
Yes	21.97**	(8.36, 57.72)	8.09**	(3.75, 17.42)	8.43**	(6.50, 10.92)	3.55**	(3.12, 4.04)		

*p value <0.05

**p value <0.001

¹Adjusted odds ratios were produced for each thyroid dysfunction subgroup using the demographic variables age, BMI, ethnicity, originating clinical population and TPOAb positivity.

Table 2. Prevalence of TPOAb across different thyroid dysfunction groups

Thyroid function	TPOAb +ve n = 1827 (9.5%) 95% CI 9.1-9.9	TPOAb -ve n = 17410 (90.5%) 95% CI 91-99
	<i>% (95% CI)</i>	<i>Number; % (95% CI)</i>
Euthyroid:		
Euthyroid (TSH 0.44-4.50)	8.5% (8.1-8.9)	91.5% (91.1-92.0)
Euthyroid (TSH 0.44-2.49)	6.5% (6.1-6.9)	93.5% (93.1-93.9)
Euthyroid (TSH 2.50-4.50)	17.0% (15.8-18.3)	83.0% (81.7-84.2)
Overt thyroid disease		
Hypothyroid	53.0% (41.8-63.9)	47.0% (36.1-58.2)
Hyperthyroid	69.4% (51.9-83.7)	30.6% (16.4-48.1)
Hyperthyroid	40.8% (27.0-55.8)	59.2% (44.2-73.0)
Subclinical hypothyroid:		
Severe SCH (TSH >10.0)	80.0% (61.4-92.2)	20.0% (7.7-38.6)
Mod. SCH (TSH 4.51-10.0)	40.3% (35.6-45.2)	59.7% (54.8-64.4)
TSH >4.50	43.0% (38.4-47.7)	57.0% (52.3-61.7)
TSH ≥2.50	20.5% (19.2-21.8)	79.5% (78.1-80.8)
Subclinical hyperthyroid		
	12.9% (8.9-17.8)	87.1% (82.2-91.1)
Isolated hypothyroxinaemia		
	87.0% (73.7-95.1)	13% (4.9-26.2)

Table 3. Risk factors for TPOAb positivity

	Adjusted odds ratio (95% CI)	P value
Age (years)^a		
17-21	0.89 (0.57, 1.38)	0.599
22-26	Reference group	
27-31	0.97 (0.79, 1.19)	0.788
32-36	1.10 (0.90, 1.34)	0.368
37-41	1.12 (0.90, 1.40)	0.299
BMI (kg/m²)^b		
<18.5	0.77 (0.49, 1.22)	0.272
18.5-24.9	Reference group	
25.0-29.9	0.99 (0.85, 1.14)	0.846
30.0-34.9	1.09 (0.90, 1.32)	0.391
≥35.0	1.54 (1.25, 1.91)	<0.001
Ethnicity^c		
White	Reference group	
Black	0.43 (0.30, 0.60)	<0.001
Asian	1.13 (0.96, 1.32)	0.136
Chinese	0.91 (0.50, 1.66)	0.761
Mixed	0.69 (0.43, 1.11)	0.127
Other	1.19 (0.80, 1.75)	0.390
Population^d		
1 or 2 miscarriages	Reference group	
Recurrent miscarriage	0.84 (0.51, 1.38)	0.496
Infertility	0.95 (0.83, 1.10)	0.502
Other	1.04 (0.88, 1.24)	0.638

^a Adjusted for BMI, ethnicity and population

^b Adjusted for age, ethnicity and population

^c Adjusted for age, BMI and population

^d Adjusted for age, BMI and ethnicity

