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ORIGINAL ARTICLE

Progesterone therapy increases free thyroxine levels—data from a randomized placebo-controlled 12-week hot flush trial

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Summary

Objective Thyroid hormones and progesterone both influence core temperature, metabolism and are crucial during pregnancy. Our objective was to discover whether progesterone therapy caused changes in thyroid physiology compared with placebo.

Design *Post hoc* analysis from a randomized (1:1) placebo-controlled 12-week trial of oral micronized progesterone (Progesterone, 300 mg/d at bedtime) for hot flushes (vasomotor symptoms, VMS) conducted in an academic medical centre.

Patients Postmenopausal euthyroid, healthy (without cardiovascular diseases or risks) women, 1–11 years since last flow on no thyroid or ovarian hormone therapy with VMS participated.

Measurements Primary outcomes were final and 12-week changes in TSH, FreeT3 and FreeT4 on progesterone *vs* placebo.

Results Women with thyroid data (69 of 133 in original trial) were randomized to progesterone ($n = 39$) or placebo ($n = 30$)—baseline thyroid values were normal. There were no VMS-thyroid interactions—VMS Score (number × intensity) did not correlate with TSH, FreeT3 or FreeT4 (Spearman's rank correlations: −0.03 to −0.19, respectively; all $P > 0.15$). At 12 weeks on progesterone, TSH levels tended to be lower (1.7 mU) than on placebo (2.2), $P = 0.06$; FreeT4 levels were higher (16.4 pmol/l) than on placebo (15.3), $P = 0.02$. FreeT3 was unchanged throughout. Analysis of covariance showed a significant increase in FreeT4 on progesterone (+2.5 pmol/l; 1.9–3.0) *vs* on placebo (+1.7; 1.1–2.4) with 95% CI of difference = 0.8 pmol/l [0.0, 1.6], $P = 0.04$.

Conclusions Progesterone caused a significant FreeT4 increase that was discovered during this randomized controlled VMS trial. The clinical importance of this increased FreeT4 level remains to be documented. Registered at ClinialTrials.gov#NCT00152438.

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Introduction

Women are more likely than men ($P < 0.0001$) to experience clinical thyroid problems.[1,2] The prevalence of TSH abnormalities increases with increasing age[2,3] and with lower socioeconomic status[2]; increasing age and lower socioeconomic status are also related to decreased progesterone production.[4] The increased prevalence of thyroid disturbances in women is likely related to women's more frequent autoimmune dysfunctions[3] and to interactions of thyroid hormones with estrogen.[5]

Normal thyroid function is important for reproductive health.[6] During pregnancy in women with treated hypothyroidism, the increase in TSH and decrease in Free thyroxine (FreeT4) levels have been attributed to estradiol-induced increased levels of circulating thyroid binding globulin (TBG), as well as to the effects of chorionic gonadotrophins.[7] Recent cross-sectional data suggest that lower mid-trimester FreeT4 levels are detrimental to the metabolic health of the mothers and also are inversely related to placental weight.[8]

Although understanding of estrogen's influences on thyroid function is extensive, especially during pregnancy,[6,7] little is known about thyroid function and progesterone. Several potential mechanisms link thyroid and progesterone actions: (1) common effects to increase core temperature and stimulate intermediary metabolism, (2) that TSH, chorionic and pituitary gonadotrophins include an identical alpha subunit, and (3) awareness that, when estradiol sits on its receptors, progesterone usually has complementary or opposing actions.[9,10] An additional potential mechanism for a progesterone–thyroid relationship is through cross-talk between the receptors for these steroids and mediators of gene transcription as both progesterone and thyroid are members of the steroid hormone superfamily.[11] Despite these

plausible hypothetical relationships between the physiologies of the thyroid axis and progesterone, there are few studies of thyroid function in relationship to endogenous or exogenous progesterone.

Most of the available data about thyroid function and progesterone are with progestogens such as medroxyprogesterone that, like progesterone,[12] increase basal temperature.[13] Sparse evidence suggests that progesterone does not alter TBG.[6,14] However, two physiological studies of thyroid function during the follicular and luteal phases have been performed—one shows an increase in sleep metabolic rate in the luteal phase without changes in total T4, T3 or Free T4.[15] A second study showed an earlier nocturnal decrease in TSH in the luteal phase without report of other thyroid hormone levels.[16] One small randomized controlled trial found significantly lower TSH levels during progesterone therapy in postmenopausal women[17]; FreeT4 levels, however, were unchanged.[17]

In summary, progesterone appears not to stimulate TBG[6,14] as does oral estrogen[5] may play an undocumented additional role to estradiol in the pregnancy-related thyroid-function changes[18] and potentially may suppress TSH levels.[16,17] To better understand whether progesterone causes thyroid function changes, we performed analysis of the thyroid hormone axis during a 12-week placebo-controlled trial of oral micronized progesterone for treatment of vasomotor symptoms (VMS, hot flushes and night sweats).[19] Our purposes were to: first, identify whether there were any associations between thyroid hormone levels and VMS; if this thyroid–VMS association testing were negative, then secondly to assess whether thyroid function was altered by 12 weeks of progesterone or placebo therapy.

Methods and Participants

Design

This is a secondary, *post hoc* analysis of serum from a randomized controlled progesterone treatment trial. The primary study took place within a single academic medical centre during a double-blind randomized placebo-controlled trial of 300-mg oral micronized progesterone (progesterone) *vs* identical placebo (given at bedtime) for treatment of VMS in healthy early postmenopausal women between 2003 and 2009.[19] A dose of 300 mg of progesterone at bedtime keeps the serum progesterone level at or above the luteal phase threshold for 24 h.[20] Randomization to the two therapies involved a simple, equal randomization protocol (1:1, without blocking). This trial's design involved 4 weeks of baseline data collection and 12 weeks on randomized experimental therapy.

Given that hot flushes are associated with an increase in core temperature and with narrowing of the thermoneutral zone,[21,22] and that progesterone,[12] and to a lesser extent thyroid hormones, are documented to increase core temperature; and given that there are no data to our knowledge on a relationship between VMS and thyroid physiology—investigation of VMS–thyroid relationships was necessary before it would be possible to explore progesterone–thyroid interactions. VMS data during both day (hot flushes) and during sleep (night sweats) were collected using the Daily Menopause Diary.[23] Each day women rated the absolute number (frequency, #) and intensity (on a 0–4 scale) of their daytime and night VMS. These data were summarized as a VMS Score,[24] an integrated single daily outcome: VMS Score = day VMS# times intensity plus night VMS# times intensity.

Participants

Postmenopausal women were recruited into this trial, as previously described[19] using posters, the Centre for Menstrual Cycle and Ovulation Research webpage (http://cemcor.ubc.ca), public lectures, media coverage and messages on local health authority e-mail lists. Healthy postmenopausal women 1–11 years since their last menstrual flow were eligible provided they had troublesome VMS and had no historical (high blood pressure, diabetes, heart disease, cigarette use), clinical (elevated body mass index, waist circumference or blood pressure) or laboratory (normal fasting glucose, lipids and electrocardiogram) evidence for existing cardiovascular disease or elevated cardiovascular system risks. These cardiovascular exclusions were to allow investigation of a second primary trial outcome: progesterone effects in healthy postmenopausal women on endothelial and cardiac-related function.

As previously described, women were excluded from this analysis if they had taken menopausal ovarian hormone therapy within the previous 6 months.[19] Additional exclusions for this analysis included use of thyroid hormone therapy ($n = 3$) or having abnormal baseline thyroid function tests ($n = 1$). All participants provided written informed consent. The University of British Columbia Clinical Research Ethics Board approved the primary study as well as this *post hoc* analysis of thyroid hormones in stored sera. This trial was conducted according to the principles of Helsinki.

Thyroid hormone measurements

All available fasting sera from women after a 4-week baseline and also at the end of the blinded 12-week therapy were analysed, without disclosure of treatment arm, for TSH, FreeT4 and FreeT3 by the clinical laboratory at Vancouver General Hospital. FreeT3, FreeT4 and progesterone assays were measured by the Bayer Centaur analyser (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) using a chemilumincent immune-assay; TSH was measured using a sandwich enzyme immunoassay (Siemens Dimension MXL Chemistry analyser (Siemens Healthcare Diagnostics Inc). All the hormone assays were performed in duplicate—between-assay coefficients of variation for all assays are 1.8–3.0%. Reference ranges for these three thyroid hormones for adult women in this laboratory are TSH: 0.34–4.82 mU/l; FreeT3: 3.5–6.4 pmol/l; FreeT4: 11.0–22.0 pmol/l.

Statistical analysis

Characteristics of women in the two randomized therapy groups were summarized as mean (SD) and as number, percentage (%)

or, if the variable of interest was not normally distributed (as in VMS Score or age at menopause), using median and interquartile range. In the first step of the analysis, baseline thyroid hormone values were compared with VMS Scores using Spearman's rank correlation (because VMS Scores were not normally distributed). In the second step, we first cross-sectionally compared (using unpaired *t*-tests) final thyroid hormone levels between women in the progesterone ($n = 39$) and the placebo ($n = 29$) groups. In women for whom we had paired baseline and therapy values (progesterone 32, placebo 23), we performed analysis of covariance (ANCOVA) with woman and therapy as factors, taking the baseline values into account. Statistical software was Stata (version 9.2, StataCorp, College Station, TX, USA).

Results

Thyroid hormone axis data were available from 69 of 133 women randomized to progesterone ($n = 39$ of 75) or placebo ($n = 30$ of 58) (Fig. 1). Participants in this trial were healthy postmenopausal women; their mean age was 55 years (y), the majority were white or Caucasian (consistent with demographics of those with symptomatic VMS in this region), they averaged 3–5 years since their last menstruation and the majority had experienced a natural menopause (Table 1). Based on exclusion criteria, all participants had normal baseline thyroid functions; these values were not different by randomization to progesterone or placebo. No other characteristics were different by therapy assignment (Table 1).

Thyroid hormone levels were unrelated to VMS Score at baseline (Spearman's rank correlation: −0.03, −0.07 and −0.19 for TSH, Free T3 and Free T4, respectively, $P > 0.15$ in all cases). Figure 2 shows the 24-h VMS Score during the 4-week baseline run-in compared with baseline FreeT4 levels ($R^2 = 0.0135$; $P = 0.393$).

Comparisons of available final (while on randomized, blinded therapy) thyroid data between progesterone ($n = 39$) and placebo ($n = 29$) (top of Table 2) found that all values remained within normal reference ranges, but that there was a tendency towards lower TSH levels during progesterone treatment ($P = 0.06$). There was no difference in final Free T3 values by progesterone or placebo therapy ($P = 0.81$). However, there were significantly higher Free T4 levels on progesterone therapy than on placebo treatment [16.4 *vs* 15.3 with a 1.1 pmol/l difference (95% CI: 2.0–0.2); $t = -2.32$, df = 66, $P = 0.02$].

Covariate analysis of changes in thyroid function across 12 weeks of treatment with progesterone or placebo considered a smaller sample size of 32 women on progesterone and 23 women on placebo (bottom of Table 2). Progesterone treatment was associated with a small but non-significant decrease in TSH, no change in Free T3, but caused a significant increase in Free T4 levels *vs* placebo-treated women (adjusted mean difference: 0.8 pmol/l, 95% CI: 0.0–1.8; $P = 0.04$).

To further understand whether changes in TSH were related to the increased Free T4 during progesterone therapy, we assessed in the 32 women on progesterone therapy whether the within-woman change in TSH related to the within-woman change in Free T4 levels. As shown in Fig. 3, the change in TSH did not correlate with the change in Free T4 (95% CI = −0.095–0.127 pmol/l); $R^2 = 0.003$, $P = 0.767$.

Discussion

These are the first randomized controlled trial data to show that treatment with luteal phase equivalent doses of oral micronized progesterone is associated with a significant increase in Free T4 values. This 12-week randomized controlled progesterone trial documented that Free T4 levels were significantly elevated in progesterone-treated compared with placebo-treated women. There also was a trend, as previously documented,[15,16] towards lower TSH levels although there was no TSH-Free T4 interaction. The absolute increase in Free T4 on progesterone therapy (+2.5 pmol/l; 95% CI: 1.9–3.0) is greater than the longitudinal 13-year, population-based normal within-person change of 0.04 pmol/l (95% CI: −0.16, 0.24).[24] Likewise, although small,

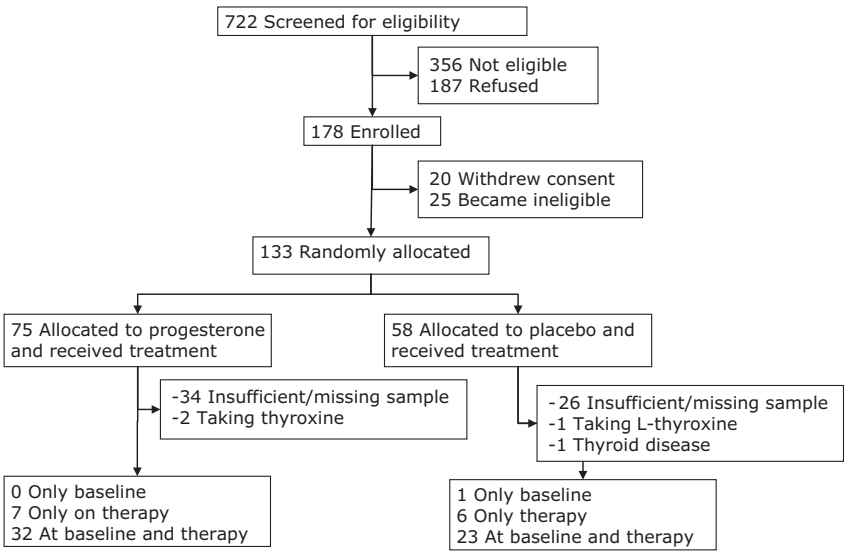

Fig. 1 This consort figure shows the flow of participants through the hot flush and night sweat (vasomotor symptoms, VMS) randomized controlled trial of oral micronized progesterone (Progesterone, 300 mg at bedtime daily) or identical placebo.[18] In addition, it illustrates those excluded from without adequate serum samples and those participating in this thyroid physiology sub-study.

Table 1. Baseline characteristics of women with thyroid function data including thyroid stimulating hormone (TSH), Free triiodothyronine (Free T3) and Free thyroxine (Free T4) data randomized to oral micronized progesterone (Progesterone, 300 mg at bedtime) ($n = 39$) or Placebo ($n = 30$). Hot flush and night sweat data are reported as Vasomotor Symptom Score (VMS Score = 24-h number times severity). Data are mean (SD), number (%) or median (interquartile range), as appropriate. The two groups are not significantly different in any measured characteristic

	Progesterone $N = 39$	Placebo $N = 30$
Age (years)	55.6 (4.1)	54.7 (4.7)
Waist circumference (cm)	79.0 (6.1)	77.2 (6.7)
Body mass index (kg/m^2)	25.0 (2.8)	24.5 (2.9)
Systolic blood pressure (mmHg)	117.5 (11.7)	115.4 (13.9)
Diastolic blood pressure (mmHg)	71.1 (7.1)	71.4 (8.4)
Heart rate (beats/min)	63.8 (6.7)	62.1 (6.4)
White/Caucasian # (%)	34 (87)	29 (97)
Education # (%)		
<Grade 9	1 (3)	–
High school graduate	4 (10)	1 (3)
Trades/professional certificate/ diploma	10 (26)	12 (40)
Some university	5 (13)	3 (10)
University with certificate/ diploma	3 (8)	2 (7)
University degree	16 (41)	12 (40)
Type of Menopause # (%)		
Natural	37 (95)	29 (97)
Hysterectomy without ovariectomy	–	1 (3)
Surgical menopause	2 (5)	–
Years since final menstrual period (median, IQR)	4.7 (2.2–7.1)	2.8 (1.6–4.6)
Employment # (%)		
Full-time	24 (65)	16 (50)
Part-time	6 (16)	6 (19)
Self-employed	–	2 (6)
Unemployed	–	1 (3)
Homemaker	2 (5)	1 (3)
Retired	5 (14)	5 (16)
Student	–	1 (3)
VMS Score (24-h # × severity)	18.8 (11.9)	16.1 (10.2)
VMS Frequency (#/24-h day)	7.3 (3.4)	6.9 (3.5)
	$N = 32$	$N = 24$
TSH mU	1.8 (0.9)	1.9 (1.0)
Free T 3 pmol/l	4.9 (0.5)	5.1 (0.6)
Free T 4 pmol/l	13.9 (1.6)	13.6 (1.5)

the adjusted mean difference in the Free T4 increase between progesterone and placebo of 0.8 pmol/l is also greater than that within-person 0.04 pmol/l longitudinal change.[25] Given that the coefficient of variation in the FreeT4 assay is three per cent and the mean Free T4 level is 13.7 pmol/l, the observed adjusted change is double the potential maximal analytical variability of 0.41 pmol/l. These data, therefore, suggest that the increase in Free T4 during oral micronized progesterone therapy compared with placebo therapy is neither likely to be due to endogenous variance nor is it likely related to lack of analytical precision.

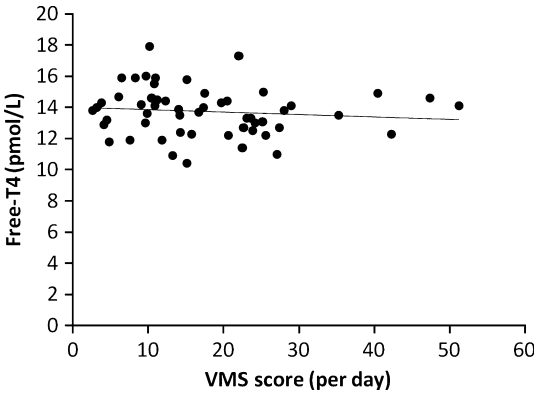

Fig. 2 This scatter plot shows the baseline 24-h day mean hot flushes and night sweats (vasomotor symptoms, VMS) as the VMS Score (incorporating both number and intensity of flushes on a 0-4 scale during the daytime and during sleep) compared with the baseline Free Thyroxine (Free T4) level. Baseline was during the 4 weeks prior to experimental treatment in this randomized controlled progesterone VMS treatment trial. FreeT4 = 14.021 − 0.016 *VMS Score. $R^2 = 0.0135$, $P = 0.393$.

The observation that there is a nonsignificant trend towards lower TSH values during progesterone therapy is consistent with results from a smaller and shorter controlled trial in which TSH was a significant 24% lower during progesterone than during placebo treatment.[17] In that study, Free T4 did not change and Free T3 was not reported.[17] It is also consistent with data showing a trend towards lower night-time TSH values during the luteal phase.[16]

This trial is also the first to quantitatively examine a potential relationship between thyroid function and hot flushes and night sweats—no important relationships were observed. In a prospective observational Norwegian study, however, in 57 initially regularly menstruating women aged 51, as women became postmenopausal, higher TSH levels were noted in those with VMS compared with those without.[26]

Our VMS–thyroid analysis ideally should have included women with minimal or no vasomotor symptoms. As ours was a treatment trial, women were required to have treatment-requiring, troublesome VMS (at least five mild, or fewer more intense, daytime hot flushes or at least one night sweat per week of sufficient intensity to awaken them).[19] Further study of potential thyroid–VMS interactions is needed.

The strengths of this study are its prospective, randomized placebo-controlled design, and that blinding was maintained throughout thyroid hormone analysis. This trial also examined all three major hormones of the thyroid axis: TSH, Free T4 and Free T3. These data are limited, however, as a *post hoc* analysis of sera from a trial designed and registered for other purposes. It is puzzling that placebo as well as progesterone caused an increase in Free T4. This increase was smaller than that shown on progesterone, so that analysis of covariance documented a significantly greater Free T4 increase on progesterone therapy. Although it is regrettable that sera from more women in the primary trial were unavailable for thyroid hormone analysis, this should not bias results.

Table 2. Thyroid hormone [thyroid stimulating hormone (TSH, mU/l), Free Triiodothyronine (Free T3, pmol/l) and Free Thyroxine (Free T4, pmol/l)] baseline values and differences between those randomized to oral micronized progesterone (Progesterone) and Placebo in a Hot Flush Treatment trial. Unadjusted comparisons are final, 12-week thyroid hormone measures during blinded therapy. Adjusted differences include those with both baseline and final measures analysed taking baseline values into account with Analysis of Covariance. Data are reported as mean [95% confidence interval (CI)]. Bolding indicates statistical significance

Unadjusted differences	Progesterone $N = 39$	Placebo $N = 29$	Mean difference (CI)	*P*-value
TSH	1.7 (1.4 to 1.9)	2.2 (1.7 to 2.7)	0.5 (0.0 to 1.0)	0.06
Free T3	5.0 (4.8 to 5.1)	5.0 (4.7 to 5.3)	0.0 (−0.3 to 0.3)	0.80
Free T4	16.4 (15.7 to 17.0)	15.3 (14.6 to 16.0)	−1.1 (−2.0 to −0.2)	0.02
Adjusted differences	$N = 33$	$N = 24$	Adjusted mean difference (95% CI)	
Baseline TSH	1.8 (1.4 to 2.1)	2.0 (1.5 to 2.4)		
Therapy TSH	1.6 (1.4 to 1.9)	2.0 (1.5 to 2.5)		
TSH Change	−0.1 (−0.3 to 0.0)	0.1 (−0.3 to 0.4)	−0.2 (−0.6 to 0.1)	0.21
Baseline Free T3	5.0 (4.8 to 5.1)	5.1 (4.8 to 5.4)		
Therapy Free T3	5.0 (4.8 to 5.1)	5.0 (4.7 to 5.4)		
Free T3 Change	0.0 (−0.1 to 0.1)	0.0 (−0.2 to 0.2)	−0.1 (−0.5 to 0.3)	0.72
Baseline Free T4	13.8 (13.3 to 14.4)	13.6 (12.9 to 14.3)		
Therapy Free T4	16.3 (15.7 to 16.9)	15.3 (14.6 to 16.1)		
Free T4 Change	2.5 (1.9 to 3.0)	1.7 (1.1 to 2.4)	0.8 (0.0 to 1.8)	0.04

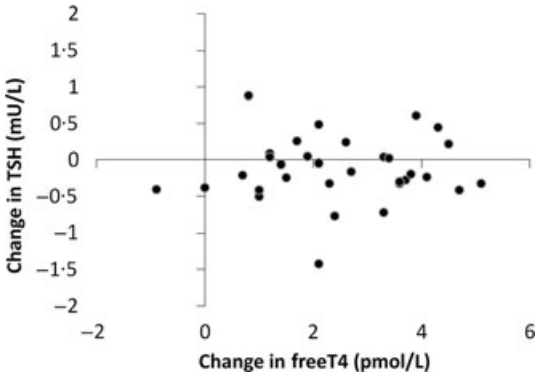

Fig. 3 This scatterplot of the 32 women randomized to progesterone therapy and having baseline and final results shows the changes from baseline in free thyroxine (Free T4) levels compared with the changes from baseline in thyroid stimulating hormone (TSH) levels. The lack of a relationship is described by Diff_TSH = −0.174 + 0.016 *Diff_FreeT4. $R^2 = 0.003$, $P = 0.767$.

That we did not measure TBG may also be perceived as detrimental, however, the literature suggested no relationship to us; also, albumen levels did not change on progesterone therapy in the cardiovascular outcome analysis from the same trial (J.C. Prior; unpub. data). It would also perhaps have been ideal to assess deiodinase enzyme activity,[27] but these analyses were not available to us.

Whether or not the observed relationship between progesterone therapy and increased Free T4 levels has physiological importance is currently unknown. It is possible that progesterone plays a role in preventing inappropriately low Free T4 levels during pregnancy.[8] It is also possible that Free T4 mediates the progesterone-associated higher basal temperature[12] and the increased luteal phase energy requirements.[28] Cigarette use and body mass index were associated with thyroid function in a recent large cohort study.[25] Given that the women participating in this trial were carefully screened to be nonsmokers without diabetes or hypertension and to have normal cardiovascular function, this study needs to be repeated in an unselected community cohort of postmenopausal women. Finally, a larger randomized controlled trial of progesterone *vs* placebo in postmenopausal women without VMS or sleep disturbances is needed to confirm the increase in Free T4 shown here.

In summary, these data from a blinded and randomized controlled 12-week progesterone treatment trial in healthy postmenopausal women with hot flushes and night sweats document for the first time that progesterone therapy appears to cause an increase in Free T4. The clinical importance of this observation remains to be determined.

Author contributions

P.S. co-ordinated the primary trial for 1 year, did the initial thyroid–progesterone literature searches and wrote the first draft; J.C.P. had the idea for the study, obtained the funding for and directed the primary trial and importantly revised the manuscript; S.K. and J.C.P. obtained funding for the thyroid hormone analyses; C.L.H. initially co-ordinated the primary trial, supervised data entry and performed all statistical analyses; M.P. provided advice on thyroid testing, supervised the hormonal assays and advised on their interpretation. All authors have reviewed, critically revised and approved the submitted document.

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