Obstetric Outcomes of an Afro-Caribbean Cohort Following Universal Screening and Treatment of Subclinical Hypothyroidism

N Johnson[1], A-K Taylor-Christmas[1], V Chatrani[1], E Choo-Kang[2], M Smikle[3], R Wright-Pascoe[4], K Phillips[4], M Reid[5]

ABSTRACT

Objective: *Restoration of euthyroidism with l-thyroxine reportedly reduces obstetric complications associated with subclinical hypothyroidism (SCH). The objective was to determine if obstetric outcomes of treated subjects were equivalent to euthyroid subjects.*

Methods: *This was a prospective cohort study. Subjects were considered euthyroid if serum thyroid-stimulating hormone (TSH) was 0.4–3 mIU/L and free thyroxine (FT4) 10.29–17.05 pmol/L with negative thyroid peroxidase antibodies (TPOAb). Subclinical hypothyroidism was diagnosed if FT4 was 10.29–24.45 pmol/L and TSH 2.5–3 mU/L with positive TPOAb, or TSH > 3.0 mU/L regardless of antibody status. Subclinical hypothyroidism subjects were treated with l-thyroxine until TSH < 2.5 mIU/L. Data were analysed with Stata (StataCorp, USA).*

Results: *Seven hundred and sixty-nine singleton pregnancies were screened; 96% at 14 weeks gestation. Five hundred and eleven (66%) were euthyroid by study definition. Prevalence of SCH was 1.9% (15/769); 26% (4/15) were TPOAb positive. Eighty-one per cent were treated according to protocol; compliance was 54%. Mean gestational age (GA) at first endocrinologist visit was 22.7 ± 2.7 weeks. Normal TSH was documented in 36% at GA 33 ± 2.94 weeks. Subjects with SCH had significantly greater pre-existing history of preterm premature rupture of membranes (PPROM) and preterm labour, Caesarean sections for non-reassuring fetal heart rate and neonatal necrotizing enterocolitis.*

Conclusion: *L-thyroxine appeared to reduce obstetric complications. However, prevalence of SCH was low and compliance was < 50%.*

Keywords: Hypothyroidism, obstetric outcomes, subclinical

Resultados Obstétricos de una Cohorte Afro-Caribeña Luego del Tamizaje Universal y el Tratamiento del Hipotiroidismo Subclínico

N Johnson[1], A-K Taylor-Christmas[1], V Chatrani[1], E Choo-Kang[2], M Smikle[3], R Wright-Pascoe[4], K Phillips[4], M Reid[5]

RESUMEN

Objetivo: *Según los reportes, la restauración del eutiroidismo con l-tiroxina reduce las complicaciones obstétricas asociadas con el hipotiroidismo subclínico (SCH). El objetivo de este trabajo fue determinar si los resultados obstétricos de los sujetos tratados eran equivalentes a los de los sujetos eutiroideos.*

Métodos: *Se trató de un estudio de cohorte prospectivo. Los sujetos eran considerados eutiroideos si la hormona estimulante de la tiroide (HET) en suero era 0.4–3 mIU/L, y la tiroxina libre (FT4) 10.29–17.05 pmol/L con anticuerpos antiperoxidasa tiroidea (TPO-Ab) negativos. El hipotiroidismo subclínico era diagnosticado si FT4 era 10.29–24.45 pmol/L y TSH 2.5–3 mU/L con TPOAb positivo, ó TSH > 3.0 mU/L, independientemente del estado del anticuerpo. Los sujetos con SCH fueron tratados con l-tiroxina hasta que TSH < 2.5 mIU/L. Los datos fueron analizados con Stata (StataCorp, USA).*

Resultados: *Se tamizaron setecientos sesenta y nueve embarazos simples; 96% en 14 semanas de gestación. Quinientos once (66%) fueron eutiroides por definición de estudio. La prevalencia de SCH fue 1.9% (15/769); 26% (4/15) fueron TPOAb positivos. El 81 por ciento fueron tratados de acuerdo con el protocolo; el cumplimiento fue del 54%. La media de edad gestacional (EG) en la primera visita del en-*

From: [1]Department of Obstetrics and Gynaecology, [2]Department of Chemical Pathology, [3]Department of Microbiology, [4]Department of Medicine and [5]Tropical Medicine Research Institute, The University of the West Indies, Kingston 7, Jamaica.

Correspondence: Dr N Johnson, Department of Obstetrics and Gynaecology, The University of the West Indies, Kingston 7, Jamaica. E-mail: nadinej@cwjamaica.com

DOI: 10.7727/wimj.2014.275

docrinólogo fue 22.7 ± 2.7 semanas. La TSH normal fue documentada en 36% en EG 33 ± 2.94 semanas. Los sujetos con SCH tenían una historia previa significativamente mayor de ruptura prematura de membranas pretérmino (RPMP) y trabajo de parto prematuro, cesáreas por frecuencia cardíaca fetal desalentadora y enterocolitis neonatal necrotizante.

Conclusión: *La L-tiroxina parece reducir las complicaciones obstétricas. Sin embargo, la prevalencia de SCH fue baja y el cumplimiento < 50%.*

Palabras claves: Hipotiroidismo, resultados obstétricos, subclínico

West Indian Med J 2016; 65 (1): 79

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as thyroid-stimulating hormone (TSH) above > 97.5th percentile with normal free thyroxine (FT4) with or without thyroid antibodies (1). It is associated with adverse obstetric outcomes such as miscarriage, anaemia, hypertensive disorders of pregnancy, placental abruption, premature delivery, postpartum haemorrhage, perinatal mortality and neonatal intensive care admission (2−4). While the majority of evidence suggests a link with adverse obstetric outcomes (5), other studies report conflicting data suggesting no adverse obstetric effects (3), or effect on perinatal mortality (6, 7). There are, however, limitations with study metho-dology questioning the validity of latter reports (5).

Studies suggest reduction of obstetric complications with maternal l-thyroxine therapy to restore euthyroidism (8, 9). Fewer adverse outcomes were found in a trial of women who had universal screening and treatment of thyroid disease during pregnancy, compared to those who were not treated and only identified after delivery (10). The previously reported beneficial effect from l-thyroxine therapy on fetal neurocognitive development (11) was recently questioned by results from a large trial that failed to show benefit, though the validity of these conclusions have also been questioned (12, 13).

Universal screening for SCH in pregnancy is controversial, with the Endocrine Society failing to reach a consensus recommendation in support or against (14). Therapy is also controversial. The Endocrine Society recommends l-thyroxine should be instituted if serum TSH is > 2.5 mIU/litre in the 1st or > 3.0 mIU/litre in the 2nd trimester (14). The American Thyroid Association (ATA) guidelines say there is insufficient evidence to recommend for or against therapy in thyroid peroxidase antibodies (TPOAb) negative women, but recommend therapy if antibodies are present (5). Against this background, the study objective was to determine if obstetric outcomes of subjects, diagnosed with SCH and treated with l-thyroxine, were equivalent to those of euthyroid subjects.

SUBJECTS AND METHODS

The study methodology is similar to that of our previous report on prevalence rates of SCH following universal screening of this cohort (15). A prospective cohort study was conducted at the University Hospital of the West Indies, from September 2009 to June 2012. Ethical approval was obtained from the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee (ECP 257, 2008/2009). Subjects were recruited at the booking antenatal visit. A standardized questionnaire was administered by an interviewer after informed consent. Demographic data along with reproductive history, personal and family histories of thyroid diseases were collected. Subjects with a previous history of thyroid disease were excluded. Data were anonymized to maintain confidentiality.

We attempted to obtain blood samples at 14 weeks gestation. Sera were measured for TSH, FT4 and TPOAb concentrations by the Chemical Pathology and Immunology Laboratories. Thyroid-stimulating hormone and FT4 were determined by a chemiluminescent method on an IMMULITE 1000 Analyser (Diagnostics Products Corporation). The intra-assay precision of TSH was 4.5–13.8%. The inter-assay precision was 8.0−17.5%. The functional sensitivity was 0.005 mIU/L. The intra-assay precision of FT4 was 3.5–6.8%. The inter-assay precision was 6.7–7.0%. The functional sensitivity was 0.3 ng/dL. Thyroid perioxidase was considered positive at a titre of 1:100 measured by haemagglutination kit for semiquantitative measurement (Thymune-M, Murex).

For the purposes of this study, subjects were considered euthyroid if TSH was 0.4–3 mU/L and FT4 was 10.29–17.05 pmol/L with negative TPOAb. Subclinical hypothyroidism was diagnosed if the following criteria were satisfied: normal FT4 (10.29–24.45 pmol/L [laboratory non-pregnant reference value]) and serum TSH 2.5−3 mU/L with positive TPOAb or serum TSH > 3.0 mU/L regardless of antibody status. Subjects were referred to the endocrinologist for assessment and therapy. After medical evaluation, if there were no contraindications, l-thyroxine therapy was initiated at a starting dose of 25−50 μg with the goal of reducing TSH to < 2.5 mU/L as per ATA and Endocrine Society Guidelines (5, 14). Follow-up included review at six-week intervals by the endocrinologist to monitor thyroid function tests, compliance with and side effects of l-thyroxine. Obstetric outcomes, along with details of endocrinology visits and medical therapy were collected from review of patient dockets at six weeks postpartum.

Data analysis was performed using Stata Statistical Software, release 12 (StataCorp LP, College Station, TX). Values are expressed as counts (frequency) or means with standard deviation. Differences in group mean values were tested by independent *t* test. Associations between categorical variables

were tested with the Chi-squared statistic or Fisher exact test as appropriate.

RESULTS

In total, 1402 subjects were recruited at the booking antenatal visit. Samples from 769 singletons and 15 twin pregnancies were obtained due to patient default. Only singleton pregnancies were analysed. Mean gestational age (GA) at recruitment was 11 weeks (range 6–19); 96% were screened at 14 weeks gestation. Mean TSH was 1.1 mU/L (0.0–7.5) and mean FT4 was 11.58 pmol/L (3.86–52.77). Prevalence of TPOAb was 2.6%.

As per study definition of euthyroidism, 511 subjects (66%) satisfied the criteria. Prevalence of SCH was 1.9% (15/769), 26% (4/15) of whom were TPOAb positive. For patients with SCH, mean TSH and FT4 were 3.79 ± 1.29 mU/L and 11.84 ± 1.29 pmol/L, respectively.

Demographic factors are shown in Table 1 and were similar in both groups. Past medical history was also similar but for a significantly greater incidence of a history of preterm premature rupture of membranes (PPROM) and preterm labour found in SCH subjects than normal subjects. Significantly more subjects with SCH were TPOAb positive compared with normal subjects (27% (4 /15) *vs* 0% (0/511) $p < 0.05$).

For subjects diagnosed with SCH referred to the endocrine clinic, 73% (11/15) were treated according to the protocol. Mean GA at the first endocrinologist visit was 23.1 ± 2.6 weeks. Forty per cent (6/15) were treated with a thyroxine dose of 25 μg, 20% (3/15) were treated with 50 μg, 6% (1/15) had an escalating dose from 50−100 μg and 13% (2/15) received no therapy. Compliance with the protocol was 47% (7/15). Normal TSH was documented in 33% (5/15) at mean GA of 32.6 ± 2.7 weeks.

Table 2 shows obstetric outcomes which had no significant differences in miscarriage, anaemia, gestational hypertension, placental abruption, premature delivery or postpartum haemorrhage. Subclinical hypothyroidism subjects had significantly more Caesarean sections for non-reassuring fetal heart rates.

Table 2: Obstetric outcomes of euthyroid and subclinical hypothyroid subjects

	Euthyroid (n = 511)	**Subclinical hypothyroidism (n = 15)**	***p***
2nd trimester miscarriage	17 (3.3)	0	ns
Anaemia	70 (14)	3 (20)	ns
Gestational hypertension	46 (9)	2 (13)	ns
Mild pre-eclampsia	12 (2)	0	ns
Severe pre-eclampsia	11 (2)	0	ns
Placental abruption	2 (0.3)	0	ns
Gestational age at delivery (weeks)	37.2 ± 4.5	37.5 ± 2.1	ns
Preterm delivery < 37 weeks	39 (7.6)	3 (20)	ns
Induction of labour	2 (0.3)	0 (0)	ns
Vaginal delivery	352 (69)	12 (80)	ns
Caesarean section	159 (31)	3 (20)	ns
Previous Caesarean	31 (19)	0	ns
Non-reassuring fetal status	19 (12)	2 (67)	< 0.05
Failure to progress	19 (12)	1 (33)	ns
Other	38 (24)	0	ns
Postpartum haemorrhage	20 (3.9)	0	ns

Values are n (%), mean ± SD

Table 1: Population demographics and past medical history

	Euthyroid (n = 511)	**Subclinical hypothyroidism (n = 15)**	***p***
Age (year)	27.7 ± 5.9	25.9 ± 6.6	ns
Weight (kg)	72.8 ± 17.4	72.5 ± 15.0	ns
Parity	0 (0−7)	0 (0−4)	ns
Miscarriage	0 (0−5)	0 (0−4)	ns
History of preterm labour	27 (5.2)	3 (20)	< 0.05
PPROM	7 (1.4)	2 (13)	< 0.05
Recurrent miscarriage	2 (0.4)	0	ns
Previous Caesarean section	43 (8)	0	ns
Thyroid disease	1 (0.2)	0	ns
Goitre	2 (0.4)	0	ns
Diabetes mellitus	3 (0.6)	0	ns
Autoimmune disease	3 (0.6)	0	ns
Hyperemesis gravidarum	11 (2.1)	0	ns
Gestational trophoblastic disease	0	0	ns
Hypertension	21 (4.1)	0	ns
Family history of thyroid disease	31 (6.1)	0	ns
Family history of autoimmune disease	4 (0.78)	0	ns

Values are mean ± SD, median (range) and n (%)
PPROM: preterm premature rupture of membranes

Table 3 shows neonatal outcomes. These were similar for number of live births, birthweight, five-minute Apgar scores, admission to the neonatal intensive care unit (NICU) and length of stay, neonatal deaths and respiratory distress syndrome. However, neonates of SCH subjects had significantly greater incidence of necrotizing enterocolitis (6% *vs* 0.4%, $p < 0.05$).

Table 3: Neonatal outcomes of euthyroid and subclinical hypothyroid subjects

	Euthyroid (n = 511)	Subclinical hypothyroidism (n = 15)	*p*
Live births	440 (86)	14 (93)	ns
Birthweight (kg)	3.05 ± 0.60	3.04 ± 0.69	ns
≤ 1.0	7 (1.4)	0	ns
≤ 1.5	10 (1.9)	1 (6.7)	ns
≤ 2.5	57 (11.1)	2 (13.3)	ns
5-minute Apgar*	9, 0	9, 1	ns
NICU admissions	66 (13)	2 (13)	ns
Length of NICU stay (days)	6, 8	22, 0	ns
Respiratory distress syndrome	18 (35)	1 (7)	ns
Necrotizing enterocolitis	2 (0.4)	1 (6)	< 0.05
Intraventricular haemorrhage	0	0	ns
Neonatal deaths	2 (0.4)	0	ns

n (%), mean ± SD, *median and interquartile range
NICU = neonatal intensive care unit

DISCUSSION

This study serves to compare obstetric outcomes of treated SCH subjects with euthyroid subjects. Subclinical hypothyroidism has been associated with intrauterine growth restriction (16), preterm labour and placental abruption (17), pre-eclampsia, perinatal mortality and miscarriage (4). Treatment of thyroid hormone abnormalities during pregnancy was shown to result in a significant decrease in adverse outcomes (10). The incidence of obstetric complications in the treated group was low, with almost equivalent outcomes to euthyroid subjects. While this suggests l-thyroxine therapy had a positive effect in reducing adverse obstetric outcomes, prevalence of SCH in the cohort was low and compliance was suboptimal (< 50%). Only one-third of patients were confirmed euthyroid in the third trimester. As such, we cannot conclude with certainty that this effect was solely due to l-thyroxine therapy.

An increased Caesarean section rate was reported in women with SCH (18). The Caesarean section rate in our study was not significantly different between the groups. However, a significant difference was seen in Caesarean sections for non-reassuring fetal status. Severe maternal hypothyroidism early in gestation is associated with fetal distress in labour, suggesting that inadequate maternal replacement leads to fetal distress and that early adequate replacement therapy is prudent (19). As normal TSH was documented in only one-third of SCH subjects, a possible effect of residual hypothyroidism is suggested.

A two-fold higher incidence of preterm delivery ≤ 34 weeks was shown in women with untreated SCH. The mechanism is unknown but may be linked to defective placentation (17). Subclinical hypothyroidism subjects had a significantly greater incidence of a history of preterm labour and PPROM prior to pregnancy. These factors are associated with a high risk of recurrence. However, low incidence was seen in the current pregnancy during which l-thyroxine was replaced. As a reduced rate of preterm delivery has been shown with l-thyroxine therapy (9), a therapeutic effect could be postulated.

The prevalence of TPOAb in SCH subjects was 27%; significantly more than that in euthyroid subjects. Positive TPOAb have been linked with increased miscarriage and preterm labour (9). No significant differences in these outcomes were demonstrated between the groups, again suggesting possible beneficial effect from l-thyroxine therapy.

Adverse neonatal outcomes previously reported include sepsis, respiratory distress syndrome, transient tacchypnoea and apnoea (6). These are all complications of preterm birth and showed equivalent outcomes in treated and euthyroid subjects. Birthweights, gestational age at delivery and preterm births were equivalent in both groups but a higher incidence of necrotizing enterocolitis was seen in treated subjects. Necrotizing enterocolitis has been reported in a neonate with congenital hypothyroidism (20). Hypothyroidism is thought to cause peripheral neuropathy of the intestine resulting in decreased gut motility and intestinal bacterial overgrowth (20). The fetus derives some maternal thyroxine from placental transmission. Low maternal thyroxine levels in treated non-compliant subjects may possibly account for this finding. Our study was not powered to look at impaired neurological development in childhood. The gestational age at first visit to the endocrinologist was also beyond that recommended for optimal impact of maternal therapy on the fetus.

The low prevalence of SCH resulted in a limited total number of subjects (n = 15), which may limit the study power to identify differences in obstetric or neonatal outcomes. Similar to Negro *et al* (9), our findings are suggestive of a possible beneficial effect of l-thyroxine in patients with SCH. Formal screening programmes emphasizing multidisciplinary management, patient counselling, adherence to therapy, follow-up and compliance monitoring would be necessary to overcome the study limitations.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Miss Marjorie Mclean and the nursing staff of the antenatal clinic with sample collection and patient recruitment. This research was funded by the New Initiative Programme, Principal's Research Grant, University of the West Indies, Mona (UWI /NIF 16348).

REFERENCES

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004; **291:** 228−38.

2. Glinoer D. The systematic screening and management of hypothyroidism and hyperthyroidism during pregnancy. Trends Endocrinol Metab 1998; **9:** 403−11.
3. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 2008; **112:** 85–92.
4. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update 2011; **17:** 605−19.
5. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; **21:** 1081−125.
6. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab 2009; **94:** 772–9.
7. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab 2010; **95:** 1084–94.
8. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002; **12:** 63–8.
9. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006; **91:** 2587−91.
10. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 2010; **95:** 1699–707.
11. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; **341:** 549–55.
12. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012; **366:** 493–501.
13. Vila L, Velasco I, Gonzalez S, Morales F, Sanchez E, Torrejon S et al. Controversies in endocrinology: on the need for universal thyroid screening in pregnant women. Eur J Endocrinol 2014; **170:** R17–R30.
14. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; **97:** 2543−65.
15. Johnson N, Chatrani V, Taylor-Christmas A, Choo-Kang E, Smikle M, Wright-Pascoe R et al. Population reference values and prevalence rates following universal screening for subclinical hypothyroisim during pregnancy of an Afro-Caribean cohort. Eur Thyroid J 2014; **3:** 234–9. doi: 10.1159/000367654.
16. Alvarez-Pedrerol M, Guxens M, Mendez M, Canet Y, Martorell R, Espada M et al. Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. Eur J Endocrinol 2009; **160:** 423–9.
17. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005; **105:** 239–45.
18. Idris I, Srinivasan R, Simm A, Page RC. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. Clin Endocrinol (Oxf) 2005; **63:** 560–5.
19. Wasserstrum N, Anania CA. Perinatal consequences of maternal hypothyroidism in early pregnancy and inadequate replacement. Clin Endocrinol (Oxf) 1995; **42:** 353–8.
20. Amer T, David R, Oberfield SE. Necrotizing enterocolitis and hypothyroidism in a newborn infant: treatment with intravenous L-thyroxine. Am J Perinatol 1994; **11:** 30–2.