CLINICAL STUDY

Pregnancy outcomes in women with severe hypothyroidism

Dania Hirsch^{1,2,3}, Sigal Levy^{4,5}, Varda Nadler⁶, Vered Kopel⁶, Bracha Shainberg⁶ and Yoel Toledano^{3,7}

¹Institute of Endocrinology, Rabin Medical Center, Beilinson Hospital, Petach Tikva 49100, Israel, ²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, ³Maccabi Health Care Services, Tel Aviv, Israel, ⁴Academic College of Tel Aviv-Yaffo, Tel Aviv, Israel, ⁵Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv, Israel, ⁶Maccabi Health Care Services-Central Laboratory, Tel Aviv, Israel and ⁷Maternal Fetal Medicine Division, Rabin Medical Center, Helen Schneider Hospital for Women, Petach Tikva, Israel

(Correspondence should be addressed to D Hirsch at Institute of Endocrinology, Rabin Medical Center, Beilinson Hospital; Email: daniaron@netvision.net.il)

Abstract

Objective: Hypothyroidism during pregnancy has been associated with adverse obstetrical outcomes. Most studies have focused on subjects with a mild or subclinical disorder. The aims of the present study were to determine the relative rate of severe thyroid dysfunction among pregnant women with hypothyroidism, identify related factors and analyse the impact on pregnancy outcomes.

Design: A retrospective case series design was employed.

Methods: The study group included 101 pregnant women (103 pregnancies) with an antenatal serum TSH level >20.0 mIU/l identified from the 2009–2010 computerised database of a health maintenance organisation. Data were collected from the medical records. Pregnancy outcomes were compared with those of a control group of 205 euthyroid pregnant women during the same period.

Results: The study group accounted for 1.04% of all insured pregnant women with recorded hypothyroidism during the study period. Most cases had an autoimmune aetiology. All women were treated with levothyroxine (L-T₄) during pregnancy. Maximum serum TSH level measured was 20.11–150 mIU/l (median 32.95 mIU/l) and median serum TSH level 0.36–75.17 mIU/l (median 7.44 mIU/l). The mean duration of hypothyroidism during pregnancy was 21.2 ± 13.2 weeks (median 18.5 weeks); in 36 cases (34.9%), all TSH levels during pregnancy were elevated. Adverse pregnancy outcomes included abortions in 7.8% of the cases, premature deliveries in 2.9% and other complications in 14.6%, with no statistically significant differences from the control group. Median serum TSH level during pregnancy was positively correlated with the rate of abortions + premature deliveries and rate of all pregnancy-related complications ($P < 0.05$).

Conclusions: Abortions and premature deliveries occur infrequently in women with severe hypothyroidism. Intense follow-up and L-T₄ treatment may improve pregnancy outcomes even when target TSH levels are not reached.

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Introduction

Thyroid dysfunction is the second most common endocrine disorder that affects women of reproductive age (1), among whom 5–15% test positive for thyroid autoantibodies. Indeed, chronic autoimmune thyroiditis is the main cause of hypothyroidism during pregnancy (2, 3, 4, 5). The generally cited prevalence rates during gestation are 0.3–0.5% for overt hypothyroidism and 2–3% for subclinical hypothyroidism (2, 3, 4, 5). However, these estimates are based on an outdated serum TSH reference range of up to 6.0 mIU/l (2, 5). Two recent studies using updated criteria have reported much higher rates of 15.5 and 18.5% positivity for gestational hypothyroidism (6, 7). Furthermore, in women with mild hypothyroidism, the diagnosis may be missed in the first trimester. During

this period, serum TSH levels normally decrease to 0.1–2.5 mIU/l, such that a serum TSH finding within the classical reference range (0.4–4.0 mIU/l) might be falsely considered normal (8).

Maternal hypothyroidism during pregnancy has been largely associated with a wide range of adverse outcomes, most importantly, with miscarriage, preterm delivery and reduced cognitive function in offspring (9). However, several authors have noted no such relationships (10, 11). These discrepancies are probably attributable to variations in thyroid dysfunction aetiology as well as to large differences in the duration, severity and management of hypothyroidism during pregnancy.

To date, the majority of studies have focused on mild or subclinical hypothyroidism during pregnancy (3, 12, 13). Data on severe hypothyroidism remain scarce. In addition, although some studies have reported

treatment with levothyroxine (L-T₄) (14), most authors have not clearly stipulated whether the patients were receiving L-T₄ or not. Thus, correlating obstetrical morbidity to factors such as the timing of diagnosis of thyroid dysfunction (before or after conception), initiation of treatment and adequacy of the L-T₄ dose is often unfeasible.

The aims of the present study were to determine the relative rate of severe thyroid dysfunction among pregnant women with hypothyroidism, identify related factors and analyse the impact of severe hypothyroidism on pregnancy outcomes.

Subjects and methods

This retrospective study was performed at Maccabi Healthcare Services, the second largest publicly funded health maintenance organisation in Israel, and was approved by its Ethics Review Board. Using the computerised database of 2009–2010, files of all pregnant women were reviewed for serum TSH values. The presence of pregnancy was based on the woman's report and confirmed by the medical records. The diagnosis of hypothyroidism was based on a serum TSH reference range of up to 2.5 mIU/l in the first trimester and up to 3.0 mIU/l in the second and third trimesters, as recommended by the Endocrine Society and the American Thyroid Association guidelines (15, 16). Severe hypothyroidism was defined as a serum TSH level >20.0 mIU/l measured during pregnancy. Its rate was calculated as the number of pregnant women with severe hypothyroidism divided by the number of pregnant women with hypothyroidism.

The women with a serum TSH level >20.0 mIU/l during a singleton pregnancy were identified, and their files were reviewed for demographic and clinical parameters as follows: age at the onset of pregnancy, number of previous pregnancies, aetiology of hypothyroidism, duration from the diagnosis of hypothyroidism to the onset of the studied pregnancy and presence of anti-thyroid autoantibodies. The following laboratory parameters, related specifically to each pregnancy period, were retrieved: number of serum TSH tests undergone, serum TSH levels, gestational age during serum TSH measurements, serum free T₄ (FT₄) levels at the time of maximum serum TSH measurement and L-T₄ doses. Serum TSH and FT₄ levels were quantified with the respective immunoassay kits using the Advia Centaur automated analyser (Siemens Health Care Diagnostics, Tarrytown, NY, USA). The assay for anti-thyroid peroxidase antibody (anti-TPO) was performed using the Immulite-2000 automated analyser (Siemens Health Care Diagnostics).

All documented pregnancy complications were recorded, including fetal loss (defined as miscarriage before 20 weeks and stillbirth after 20 weeks), preterm delivery (20–37 weeks), pre-eclampsia, polyhydramnios

or oligohydramnios, intrauterine growth retardation, caesarean section, vacuum delivery, *post partum* haemorrhage, and small or large for gestational age. The duration of hypothyroidism in pregnancy was calculated as the time from the detection of an elevated serum TSH level to the detection of a within-range serum TSH level. For women with two pregnancies during the study period, each pregnancy was analysed separately. The rate of obstetrical complications was compared with those of an age-matched control group of women with singleton pregnancies insured by the same health maintenance organisation during the same period who were found to have a serum TSH level of 0.1–2.5 mIU/l in the first trimester. All women included in the control group were healthy, with no known thyroid disorders. All had undergone one serum TSH test during pregnancy. None had any evidence of thyroid dysfunction up to the time of data collection for the present study (2013).

Statistical analysis

The demographic characteristics of the study and control groups were compared using an independent samples *t*-test, and the rates of obstetrical complications were compared using a χ^2 test. Pearson's correlation coefficients were calculated between demographic and clinical characteristics and serum TSH levels. For further analyses, we used the median serum TSH level during pregnancy (and not the first, maximum or mean level) because of obvious inter-correlations of the various TSH parameters and the stable nature of the median. We also analysed pregnancy complications in association with the last serum TSH level, which is representative of the impact of L-T₄ treatment during pregnancy. Logistic regression was used to analyse the effect of the median and last TSH levels during pregnancy and additional demographic and clinical characteristics in univariate and multivariate models, yielding odds ratios (OR) for predicting the risk of obstetrical complications. Since TSH levels were noticeably skewed to the right, the values were log-transformed before application of the statistical tests in order to achieve a normal distribution. Clinical parameters that could be confounded by a short pregnancy duration (in cases of miscarriage or preterm delivery), namely the time span of hypothyroidism during pregnancy and number of serum TSH tests undergone during pregnancy, were excluded from the multivariate model. Abortions and preterm deliveries were analysed as a single factor owing to the small number of each. Similarly, all pregnancy-related complications were grouped and analysed as a single factor. The first and last L-T₄ doses recorded during pregnancy as well as thyroid auto-antibody status were analysed separately from the multivariate analysis to avoid a reduced sample size because of unavailable data.

Table 1 Demographic and clinical data of 101 women with severe hypothyroidism during pregnancy (103 pregnancies) and 205 healthy controls (205 pregnancies).

Variable	Study group	Control group	P value
Age at conception (years)			
Mean (s.d.)	32.8 (5.0)	32.3 (4.4)	NS
Median	33	32	
Range	22–43	21–46	
Number of current pregnancies			
Mean (s.d.)	2.9 (1.9)	3.2 (1.9)	NS
Median	2	3	
Range	1–10	1–11	
GA at first TSH test (week)			
Mean (s.d.)	9.2 (6.2)	8.7 (2.5)	NS
Median	7	8	
Range	3–32	4–14	
First TSH level (mIU/l)			
Mean (s.d.)	35.22 (33.15)	1.24 (0.7)	<0.001
Median	25.43	1.18	
Range	0–150.0	0.1–2.5	

GA, gestational age; NS, not specific.

Results

During 2009–2010, serum TSH tests were performed in 48 326 of the 106 600 pregnant women (45.3%) insured at Maccabi Healthcare Services. Maternal hypothyroidism, defined as an elevated trimester-specific serum TSH level, was detected by the central laboratory in 9872 pregnancies (20.4%), whereas serum TSH levels >6.0 and >10.0 mIU/l were found in 1511 (3.1%) and 449 (0.9%) pregnancies respectively. Of the 9872 pregnancies in women with hypothyroidism, severe hypothyroidism, defined as a serum TSH level >20.0 mIU/l, was detected in 109 (1.1%). Six pregnancies were excluded from the study because of a twin pregnancy or pregnancy that terminated in abortion performed for reasons not relevant to our analysis (cytomegalovirus infection, Down syndrome and fear of the consequences of gestational hypothyroidism). The remaining 103 pregnancies (1.04% of the cohort) in 101 women were included in the study.

The mean age of the study population was 32.8 ± 5 years. Anti-thyroid antibody test was performed in 84 pregnancies (81.6%), and data were missing in the remaining 19. In 69 (67% of all pregnancies), the test was positive, indicating a definite link to an autoimmune aetiology. Other causes of hypothyroidism were I-131 treatment for Graves' thyrotoxicosis in nine women (8.7% of the pregnancies), thyroidectomy for Graves' thyrotoxicosis in one (0.97%), multinodular goitre in five (4.9%) and papillary thyroid carcinoma in two (1.9%). Two women (1.9%) had congenital hypothyroidism and one (0.97%) had *post partum* thyroiditis. In 14 women (13.6%), specified aetiology was not recorded. The mean time from the diagnosis of hypothyroidism to the onset of the studied pregnancy was 6.4 ± 6.3 years. In 16 cases (15.5%),

hypothyroidism was first diagnosed during the studied pregnancy. The first serum TSH measurement was performed during the first trimester in 91 pregnancies (88.3%), in the second trimester in 11 (10.7%) and in the third trimester in one (0.97%).

The control group included 205 healthy women with a serum TSH level (tested once during pregnancy) within the normal trimester-specific reference range of 0.1–2.5 mIU/l. Since only a small proportion of control subjects underwent additional thyroid tests such as FT₄ and thyroid autoantibody tests, these variables were not analysed.

The mean age of the control group was 32.3 ± 4.4 years. There were no differences between the study and control groups in age, number of current pregnancies or gestational age during the first TSH test (Table 1).

Figure 1 depicts the comparison of the obstetrical outcomes between the study and control groups. Ninety-two pregnancies (89.3%) in the study group ended in term delivery of an apparently healthy newborn. Abortions were recorded in eight pregnancies (7.8%) and premature deliveries in three (2.9%). Other obstetrical complications occurred in 15 pregnancies (14.6%) as follows: non-elective caesarean section in eight (7.8%), vacuum delivery in two (1.9%), gestational hypertension in one (0.97%), polyhydramnios in one (0.97%), small-for-gestational age newborn in two (1.9%) and large-for-gestational-age newborn in one (0.97%). In the control group, 183 pregnancies (89.3%) ended in term delivery. Abortions were recorded in 19 pregnancies (9.3%) and premature deliveries in three (1.5%). Additional complications

Figure 1 Obstetrical outcomes in 103 pregnancies (101 women) in the study group and 205 pregnancies in the control group.

Table 2 Thyroid function and treatment variables in 103 pregnancies (101 women) with severe maternal hypothyroidism.

Variable	Mean (S.D.)	Median	Range
GA at maximum TSH level (week)	13 (8.6)	9	3–36
Maximum TSH level (mIU/l)	43.88 (29.75)	32.95	20.11–150.0
Free T ₄ at the time of maximum TSH level (pmol/l)	10.2 (2.6)	10.3	3.3–16.4
No. of TSH tests	4.41 (2.31)	4	1–11
Mean gestational TSH level (mIU/l)	20.34 (17.24)	13.7	1.9–75.17
Median gestational TSH level (mIU/l)	15.68 (18.74)	7.44	0.36–75.17
Last gestational TSH level (mIU/l)	11.93 (21.79)	3.2	0.03–132.05
Duration of recorded antenatal hypothyroidism (weeks)	21.2 (13.2)	18.5	3–42
First L-T ₄ dose recorded during pregnancy (µg/week)	554.78 (482.4)	700	0–1850
Last L-T ₄ dose recorded during pregnancy (µg/week)	1019.49 (394)	1050	350–2100

GA, gestational age; L-T₄, levothyroxine.

occurred in 36 pregnancies (17.6%); non-elective caesarean section in 21 (10.2%), vacuum delivery in three (1.5%), gestational hypertension in four (1.9%), polyhydramnios in three (1.5%), oligohydramnios in two (0.98%), intrauterine growth retardation in one (0.5%) and *post partum* haemorrhage in two (0.98%). There were no statistically significant between-group differences in the rates of abortion, abortions+premature deliveries or all pregnancy complications. Further analysis of obstetrical complications was performed for the 91 pregnancies in the study group (88.3%) in which the first serum TSH test was performed during the first trimester. Miscarriages were documented in eight pregnancies (8.8%), premature deliveries in three (3.3%) and any pregnancy complication in 25 (27.5%). There were no significant differences for any of these outcomes compared with those of the control group.

Data on thyroid function and treatment parameters in the study group are presented in Table 2. Maximum serum TSH level ranged from 20.11 to 150.0 mIU/l (median 32.95 mIU/l); in 73 pregnancies (70.9%), the highest serum TSH level measured was also the first measured level during pregnancy. The median level ranged from 0.36 to 75.17 mIU/l (median 7.44 mIU/l). The last antenatal serum TSH level ranged from 0.03 to 132.05 mIU/l (median 3.2 mIU/l). Serum FT₄ level at the time of maximal serum TSH measurement was within the laboratory non-pregnancy-related reference range (10.3–19.7 pmol/l) in 50 pregnancies (48.5%) and below this range in 50 pregnancies. Data on the remaining three pregnancies were not found.

All women in the study group were treated with L-T₄ during pregnancy. The first recorded dose was ascertained in 68 pregnancies (66%) and the last recorded dose in 59 pregnancies (57.2%). The mean duration of maternal hypothyroidism during pregnancy was 21.2 weeks (median 18.5 weeks). In 36 cases (34.9%), all recorded serum TSH levels throughout pregnancy were elevated. The women who had elevated TSH levels throughout pregnancy were significantly younger than the women who reached their target TSH level (31.2 ± 4.7 vs 33.5 ± 4.9 years, $P < 0.05$). They had also undergone fewer serum TSH tests during gestation (3 ± 1.9 vs 5.3 ± 2.1 , $P < 0.01$) and were treated with lower weekly doses of L-T₄ at the end of pregnancy (826 ± 397 vs 1090 ± 401 µg, $P < 0.05$). Persistently elevated TSH levels were marginally significantly correlated with the rates of miscarriage and premature delivery ($P = 0.053$), but not with overall pregnancy-related complications.

Table 3 presents the correlations between the clinical parameters and serum TSH levels. There was a negative correlation of both the median and last serum TSH levels with the number of serum TSH tests performed during pregnancy, as well as with the L-T₄ dose increment during pregnancy. Conversely, the median and last serum TSH levels were positively correlated with an elevated serum TSH level throughout pregnancy. The analysis of serum TSH variables against obstetrical outcomes yielded no statistically significant correlation between the first or maximal serum TSH levels and the rates of abortions+premature deliveries or all pregnancy complications.

The associations between clinical variables and pregnancy complications are summarised in Table 4.

Table 3 Bivariate correlations between clinical variables of pregnant women with severe hypothyroidism and serum TSH measurements.

Variable	Maximum TSH	Median TSH	First TSH	Last TSH
Age at conception	-0.187	-0.143	-0.177	-0.199*
Number of pregnancies	-0.159	0.112	-0.084	0.011
Hypothyroidism diagnosis before pregnancy	-0.146	0.159	-0.219*	0.117
GA at the first serum TSH measurement	-0.047	0.277 [†]	0.147	0.183
GA at maximum serum TSH measurement	-0.092	0.129	-0.441 [†]	0.064
Number of serum TSH tests during pregnancy	0.013	-0.601 [†]	-0.115	-0.504 [†]
Elevated serum TSH level throughout pregnancy ^a	-0.090	0.570 [†]	0.258 [†]	0.631 [†]
Free T ₄ at maximum serum TSH measurement	-0.536 [†]	-0.151	-0.222*	-0.041
First L-T ₄ dose recorded during pregnancy ($n=68$)	-0.034	0.040	-0.466 [†]	0.077
Last L-T ₄ dose recorded during pregnancy ($n=59$)	0.070	-0.224	-0.330*	-0.165
L-T ₄ dose change during pregnancy ($n=59$)	0.210	-0.279*	0.326*	-0.351 [†]

* $P < 0.05$; [†] $P < 0.01$. GA, gestational age; L-T₄, levothyroxine.^aAccording to trimester-specific ranges.

No correlation was found between duration of hypothyroidism before pregnancy and adverse pregnancy outcomes. The correlation remained non-significant when the duration of hypothyroidism was dichotomised to hypothyroidism first diagnosed during gestation or before conception. Similarly, serum FT₄ levels did not correlate with pregnancy outcomes when evaluated either as a continuous variable or categorically as within or below the normal reference range. On univariate analysis, there was a positive and marginally significant correlation of median serum TSH level with the rate of abortions+premature deliveries ($P=0.057$) and a significant correlation of median serum TSH level with all pregnancy-related complications ($P<0.05$). On multivariate analysis, the only variable that predicted abortions+premature deliveries and all pregnancy-related complications with statistical significance was median serum TSH level. Repeating the logistic regression analysis using the last serum TSH level during pregnancy instead of the median level yielded significant effects on the rate of abortions+premature deliveries ($P<0.05$) and on the rate of all complications ($P<0.01$) in both the univariate and multivariate models.

On analysis of the association between L-T₄ treatment and pregnancy outcomes, a higher recorded L-T₄ dose at the end of pregnancy was significantly correlated with a lower risk of abortion+premature delivery (OR=0.997, 95% CI=0.995–0.999). In addition, comparison of patients who were antibody positive ($n=69$, 67%) or antibody negative ($n=15$, 14.6%) for adverse obstetrical outcomes showed a marginally significant correlation between the presence of antibodies and a higher rate of all pregnancy complications ($P=0.058$). There was no significant correlation with the rate of abortions+premature deliveries.

Discussion

Knowledge on thyroid disease during pregnancy has rapidly expanded in the last 20 years. Two management guidelines and one update on the diagnosis and treatment of thyroid dysfunction during gestation and *post partum* have recently been introduced (15, 16, 17). Using the guideline-recommended trimester-specific reference interval, we found that 20.4% of pregnant women tested for serum TSH levels have hypothyroidism. Applying the same criteria to a large cohort of women aged 18–40 years, Blatt *et al.* (6) found that 23% were evaluated for gestational hypothyroidism, either subclinical or overt, of whom 15.5% tested positive. Similarly, Granfors *et al.* (7) reported a 20% serum TSH testing rate and an 18.5% overall rate of elevated TSH levels. The somewhat higher rate found in the present study might be explained by the significantly higher frequency of serum TSH testing in our cohort (45.3%). Be that as it may, both our rates and those in other recent studies (6, 7) are considerably higher than

Table 4 Predictive values of clinical variables for pregnancy-related complications in pregnant women with severe hypothyroidism.

Variable	Combined abortions+premature deliveries, odds ratio		All pregnancy-related complications, odds ratio	
	Univariate	Multivariate	Univariate	Multivariate
Age at conception	0.983	1.052	0.925	0.922
Number of pregnancies (gravida)	1.051	1.347	0.863	0.938
Hypothyroidism duration before current pregnancy	0.935	0.891	1.007	1.033
GA at maximum serum TSH measurement	0.773	0.71	0.932	0.941
Serum free T ₄ level at maximum TSH measurement	0.854	0.967	0.970	1.033
Median serum TSH level	1.764 [†]	2.5*	1.536*	1.679*

* $P<0.05$; [†] $P=0.057$. GA, gestational age.

the traditionally accepted prevalence of 2–3% based on the outdated upper limit of 6.0 mIU/l serum TSH levels (2, 5). Accordingly, only 3.1% of the women in the present cohort had serum TSH levels above this value.

Exposure of obstetric health providers to the professional guidelines for thyroid disease in pregnancy has been found to positively impact patient care (18). Nevertheless, severe hypothyroidism during pregnancy may still be occasionally encountered in clinical practice, either in women previously undiagnosed or in women treated with L-T₄ before pregnancy. Moreover, since universal screening of pregnant women for thyroid disease is not yet recommended (15, 16), there are probably cases of significant hypothyroidism in pregnancy that go undiagnosed. In the present study, severe maternal hypothyroidism was defined as a serum TSH level >20.0 mIU/l. The American Thyroid Association defines overt hypothyroidism as a serum TSH level >2.5 mIU/l in conjunction with a decreased FT₄ level or serum TSH level >10.0 mIU/l regardless of the FT₄ level (15). To further current knowledge on the impact of significant maternal thyroid deficiency on pregnancy outcomes, we examined women with a serum TSH level >20.0 mIU/l. Using this criterion, severe hypothyroidism was found in 1.1% of all pregnancies characterised by an elevated trimester-specific TSH level. Thus, our cohort included the most extreme cases of maternal hypothyroidism in pregnancy detected during the study period. Nevertheless, most of the women carried the pregnancy to term without complications. We found no statistically significant differences in the rate of pregnancy complications between the study and control groups. Furthermore, the 7.7% abortion rate in the present study is comparable to the 6% pregnancy loss reported by

Negro *et al.* (13) in pregnant women with very mild subclinical hypothyroidism (TSH level 2.5–5.0 mIU/l) and negative thyroid autoantibodies.

One of the first clinical studies of pregnancy outcomes in hypothyroid women was performed in 1981 by Montoro *et al.* (19) in nine women (11 pregnancies) with extremely severe hypothyroidism in pregnancy (mean serum TSH level >100.0 mIU/l). Using a case-study design, the authors demonstrated that even women with severe hypothyroidism may conceive and sustain pregnancy. There was one case of fetal loss in gestational week 29. However, information on early abortion was missing as, in most patients, the first antenatal TSH test was performed after gestational week 24 (19). In 1993, the same authors published a more extensive study of 68 women with thyroid deficiency, either overt ($n=23$) or subclinical ($n=45$) (20). They found that a significant percentage of the patients who were still hypothyroid at delivery developed gestational hypertension and, consequently, gave birth to premature infants with low birth weight. The authors concluded that the normalisation of thyroid function during pregnancy may prevent such complications.

Additional data on severe hypothyroidism during pregnancy are limited. Most recent reports have focused on the impact of subclinical hypothyroidism and thyroid autoimmunity on maternal and fetal health. Benhadi *et al.* (21) explored the relationship between serum TSH levels and miscarriage, fetal death and neonatal death in 2497 Dutch women, mostly euthyroid. The results revealed a 60% increase in these adverse outcomes for every doubling of the serum TSH concentration. The authors concluded that treatment of women with a mildly elevated serum TSH level or even a normal serum TSH level and positive thyroid antibodies may improve pregnancy outcomes (21).

The present study included a relatively large series of pregnant women with severe hypothyroidism. Additionally, our access to detailed information on thyroid function tests and hypothyroidism management throughout gestation made it possible to analyse the impact of various demographic and clinical parameters on pregnancy outcomes. Data on serum TSH measurements at an early gestational age were available for most participants, so that first-trimester abortions could be included in the analysis. Importantly, relatively low rates of abortions and premature deliveries (7.7 and 2.9% respectively) were detected in the study group. The abortion rate remained low (8.8%) when only pregnancies in which the first serum TSH measurement was performed before gestational week 14 were analysed.

Only a few investigators of either subclinical or overt hypothyroidism during pregnancy have specifically addressed the correlation between serum TSH levels and pregnancy outcomes, and most of them relied on very limited data. In a study of 9403 women with singleton pregnancies, including 37 with a TSH level >10.0 mIU/l, Allan *et al.* (2) found a positive

correlation between serum TSH level >10.0 mIU/l and increased rate of fetal death. However, their analysis was based on a single serum TSH measurement obtained during the second trimester as part of routine prenatal care. Thus, information on the early abortion rate was lacking, and data on follow-up and L-T₄ treatment were not reported. Casey *et al.* (3) performed a thyroid-screening study of 25 756 women with a singleton pregnancy. Compared with those in euthyroid women, pregnancies in women with subclinical hypothyroidism were three times more likely to be complicated by placental abruption and preterm birth. However, the authors did not provide specific data on 50 women in the cohort with serum TSH levels >10.0 mIU/l.

In the present study, all women were treated with L-T₄ during gestation, most of them prior to conception. Although there are large epidemiological studies that have analysed the correlation of a single serum TSH measurement, mostly in euthyroid women, with various gestational complications, previous reports on pregnancy outcomes in L-T₄-treated women are sparse. Vissenberg *et al.* (14) conducted a systematic review on the treatment of thyroid disorders before conception and in early pregnancy (14). Nine studies on overt or subclinical hypothyroidism were analysed, including two cohort studies and one case-control study addressing treatment adequacy. In women with overt hypothyroidism, L-T₄ was found to be effective in reducing the risk of miscarriage and preterm delivery. In women with subclinical hypothyroidism, the evidence was insufficient (14). Included in their review was the pivotal study of Abalovich *et al.* (22) evaluating 51 women with hypothyroidism, usually subclinical, at the time of conception. Within the subgroup of women who received inadequate treatment according to repeated serum TSH measurements, pregnancy ended in abortion in 60% of those with overt hypothyroidism and 71% of those with subclinical hypothyroidism; there was also an increased prevalence of preterm deliveries. Conversely, the abortion rate among women with adequately treated hypothyroidism was very low, and the majority carried the pregnancy to term without complications. In another study (23), among 63 pregnant women treated with L-T₄ substitution for hypothyroidism, 31 (49%) had serum TSH values outside the reference range. In this subgroup, fetal loss rate was 29% compared with 6% in patients whose serum TSH values were within the reference range ($P<0.05$). Fetal loss occurred in 26% (5/19) of the pregnancies associated with high serum TSH levels.

In agreement with the study of Montoro *et al.* (19), but not with the two more recent reports mentioned above (22, 23), we showed that most pregnancies (89.4%) in women with severe antenatal hypothyroidism end successfully in normal term delivery. This finding is particularly noteworthy as the majority of our participants were positive for thyroid autoantibodies, a factor that has been found to be independently

associated with miscarriage, even in the presence of normal thyroid function (24). Thyroid autoantibodies were not measured in most women in the control group, probably owing to their within-range serum TSH level. Possible reasons for the relatively low rate of abortions and premature deliveries in the present study may be the normal median FT₄ level at the time of maximal serum TSH measurement, the delivery of L-T₄ treatment to all women and the consequent improvement in their thyroid status and the thorough obstetrical management provided to all insured women in Israel. It is also possible that hypothyroidism *per se* does not cause abortions, but rather serves as an indication of another, direct, cause such as autoimmunity against the fetoplacental unit. If this were true, a simple linear correlation between serum TSH levels and risk of abortion, as suggested by Benhadi *et al.* (21), would not be expected.

The rate of all pregnancy complications in both the study and control groups was relatively high (25.2 and 28.3% respectively). However, this is a composite outcome of all recorded adverse events during pregnancy, among which non-elective caesarean section was a major component: 7.7 and 10.2% of the pregnancies in the study and control groups respectively. These rates are comparable to the 10% rate of non-elective caesarean sections in the general population in Israel (Prof Yariv Yogeve, personal communication).

In accordance with the results of Abalovich *et al.* (22), we did not find a correlation between the first and maximum antenatal serum TSH levels and pregnancy outcomes. A higher rate of uneventful pregnancy was related to factors reflecting intensive follow-up and treatment, such as the number of serum TSH measurements and L-T₄ dose increment during pregnancy. These parameters were correlated with the median and last gestational TSH levels, which were found, on multivariate analysis, to be significant predictors of pregnancy complications. These results highlight, in agreement with previous observations (22), the significance of adequate L-T₄ treatment in pregnant women with gestational hypothyroidism. Higher serum TSH levels and, particularly, higher last antenatal TSH values in L-T₄-treated pregnant women may be regarded as an expression of treatment failure. Apparently, this may lead to adverse pregnancy outcomes.

The present study has several limitations. First, the absolute number of abortions and premature deliveries was low such that analysis of a larger cohort and/or a much larger control group, with increased statistical power, might have yielded more statistically significant results, including possible differences in gestational outcomes between the study and control groups. The correlation between the lower median and last gestational TSH levels and better pregnancy outcomes in the study group supports the importance of detecting and

treating hypothyroidism during pregnancy. Second, the present study did not investigate fetal cognitive development, which has been found to be impaired in pregnancies with much milder maternal hypothyroidism (25). Finally, the retrospective design of the study carries the potential risk of incomplete availability of data. Specifically, although data on gestational age at delivery or abortion were ascertained in all cases, other adverse obstetrical effects in both the study and control groups may have been underestimated because of incomplete documentation. Similarly, the information on L-T₄ replacement and titration in the study group was partial in some cases.

In conclusion, based on current criteria, severe hypothyroidism, defined as a TSH level > 20.0 mIU/L, occurs in 1.1% of the pregnancies in women with gestational hypothyroidism. According to our retrospective analysis of detailed clinical and laboratory data, severe hypothyroidism in L-T₄-treated pregnant women is typically not associated with abortions or premature deliveries. Yet, intense follow-up and treatment for hypothyroidism are valuable in improving pregnancy outcomes even in women who do not reach the recommended TSH goals.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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