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RESEARCH

Longitudinal trajectories of maternal TSH in healthy pregnant women in Catalonia

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Abstract

Objective: Longitudinal evaluation of thyroid function throughout pregnancy in the same subject could offer precise information about its dynamics as a physiological mechanism of adaption to the requirements. In this study, we evaluated longitudinal trajectories of maternal thyroid function during pregnancy by a latent class growth analysis and explored their association with maternal–fetal outcomes.

Methods: A prospective observational study was carried out, including 414 healthy pregnant women, from the first trimester to delivery. Thyroid function and autoimmunity were measured in the three trimesters. Clinical data during pregnancy were obtained. Longitudinal mixed model techniques were performed to explore trajectories of gestational thyroid function.

Results: Three different longitudinal trajectories were obtained from maternal thyrotropin (TSH) levels: low-increasing TSH (class 1) in 86% of cases, high-increasing TSH (class 2) in 9.7%, and decreasing TSH (class 3) in 4.3%. No statistical differences in free thyroxine levels were found among the three classes. Differences in maternal age ($P = 0.027$) and initial maternal weight ($P = 0.043$) were observed among the groups. In logistic regression analysis, maternal age correlated with longitudinal trajectories. The three longitudinal classes remain when women with thyroid autoimmunity (TAI) are excluded. Multinomial logistic regression showed maternal age correlated with longitudinal trajectories independently of TAI status.

Conclusions: Three differentiated TSH trajectories were found in healthy pregnant women living in Catalonia, as previously described. No association with obstetric outcomes was observed in these different chronological thyroid pathways, but maternal age might condition the longitudinal mechanism of thyroid function regulation throughout pregnancy.

Key Words

- thyroid function
- pregnancy
- thyroid
- trajectories
- feto–maternal outcomes

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Introduction

Thyroid hormones are involved in many processes during intrauterine life, such as somatic growth, metabolic regulation, and neurodevelopment (1). Consequently, maternal thyroid dysfunction has been related to obstetric and fetal outcomes, such as an increased risk of miscarriages, prematurity, preeclampsia, or alterations in fetal neurodevelopment (2, 3, 4). On the other hand, during pregnancy, physiological changes occur in the thyroid gland that modulate the maternal thyroid function (5), including changes in hormonal metabolism and iodine absorption, inducing a dynamic regulation of the hypothalamic–pituitary–thyroid axis throughout pregnancy. For this reason, the measurement of thyroid function in healthy pregnant women differs from non-pregnant women, and current guidelines recommend to establish local reference ranges for thyroid hormone values during specific time points of pregnancy (6). Our group has recently described trimester-specific reference ranges for thyrotropin (TSH) and free thyroxine (FT4) in a cohort of healthy pregnant women living in Catalonia (7).

It should be noted that the reference ranges of thyroid function per trimester of pregnancy used to be established through cross-sectional measurements that do not give longitudinal information throughout pregnancy in a given individual. The sequential chronological evaluation of maternal thyroid function throughout pregnancy in the same subject could give more precise information related to specific outcomes at the end stage of gestation and neonatal period. In this regard, there are only two studies from the same research group dealing with latent class growth analysis (LCGA) to describe different temporal changes in thyroid function (TSH and fFT4) throughout pregnancy (8, 9). These latent classes allow obtaining a longitudinal and dynamic knowledge of the relationship between maternal thyroid function and different feto–maternal outcomes and offspring behavioral problems related to specific latent classes. However, the influence of iodine and vitamin supplementation and iodine deficiency status on these latent classes have not been evaluated.

This study aimed to describe the pattern of longitudinal modifications of maternal TSH throughout the pregnancy by using their concentrations measured in a cohort of healthy pregnant women living in Catalonia. Thus, we performed an LCGA of TSH, and we evaluated the effect of maternal characteristics (age, parity, body mass index), including iodine status and iodine supplementation on the distribution and prevalence of these classes. The role of thyroid autoimmunity (TAI) as a potential confounder has also been analyzed.

Material and methods

Study design and subjects

We performed a prospective observational study, including 414 healthy Caucasian pregnant women attending a primary pregnancy care center (ASSIR La Riera, Badalona, Spain), recruited during the first trimester of pregnancy (before week 10 of gestational age) and followed up monthly to delivery. All women underwent a standardized institutional protocol, including clinical data collection, and an obstetric examination and fetal ultrasonography to confirm the normal progression of the pregnancy.

In all cases, iodine or multivitamin supplementation, including iodine at a dose of 200 µg/day, was prescribed either before pregnancy or at the first visit before week 10. Exclusion criteria, applied at the moment of recruitment, were as follows: twin and assisted reproductive technology pregnancies, the presence of maternal and/or fetal disorders that might represent an obstetric or perinatal risk; personal history of known thyroid dysfunction; thyroid hormone or anti-thyroid drug treatment; or recent exposure to iodinated antiseptics or other iodinated compounds. Participants were also excluded during the study if they met the criteria for thyroid hormone replacement or anti-thyroid drug treatment, according to the ATA 2017 guidelines (6). The study flowchart is included in Fig. 1.

In addition, all women provided blood samples at the three trimesters of gestation. Urinary iodine collection was made from spot urine samples at each trimester of pregnancy, coinciding with blood tests. All serum and urine samples were stored at −80°C until analyzed.

The Ethics Committee of the University Hospital Germans Trias i Pujol (HUGTiP) approved the study (number code PI-14-104), and written consent was obtained from all the participants.

Laboratory procedures

Biochemical parameters were measured using an AU58222 analyzer (Beckman Coulter, Fullerton, CA, USA). Architect® Ref.7K78 (Abbott Diagnostic Division)

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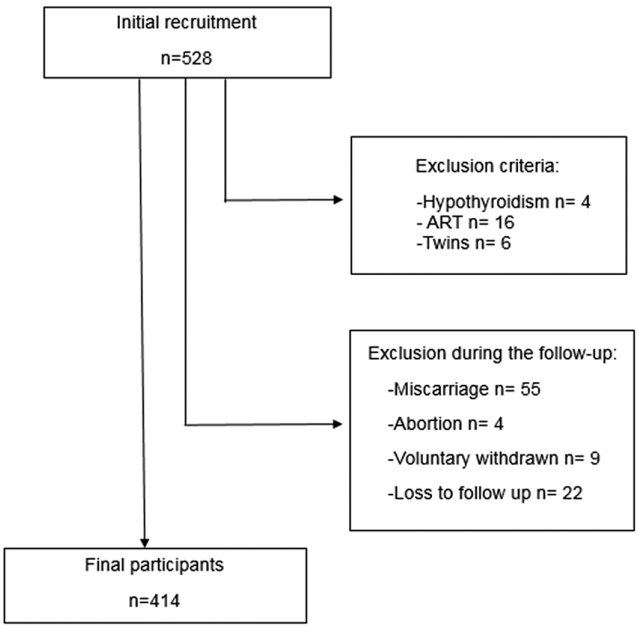

Figure 1
Study flowchart. ART, assisted reproductive technology.

was used to measure total beta-human chorionic gonadotropin (β-hCG); its limit of quantitation (LoQ) was <1.02 IU/L, and coefficients of variability (CVs) ranged between 1.6 and 4.9% for a concentration range between 24 and 5060 IU/L. The expected total hCG values for pregnant women at different gestational ages are (P 2.5-P 97.5): 1–10 weeks: 202–231,000 IU/L; 11–15 weeks: 22,536–234,990; 16–22 weeks: 8007–50,064; and 23–40 weeks: 1600–49,413 IU/L.

The Abbott Architect automated chemiluminescence immunoassay (CLIA) analyzer was used to measure serum TSH (Architect TSH® Ref. 7K62, Abbott Diagnostic Division). The LoQ for TSH was <0.0038 mIU/L. Intra-analysis CVs ranged between 1.7 and 5.3% for a concentration between 0.09 and 16.3 mIU/L. Trimestral TSH reference ranges for our pregnant population are 0.03–3.78 mIU/mL for the first trimester, 0.51–3.53 mIU/mL for the second trimester, and 0.50–4.32 mIU/mL for the third trimester of pregnancy (7). FT4 was measured in the three trimesters using the Architect® CLIA (FT4 Ref.7K65, Abbott Diagnostic Division). For Architect® CLIA, LoQ < 5.15 pmol/L, with intra-analysis CVs between 3.6 and 7.8% for a concentration range between 8.9 and 38.7 pmol/L, and the RR for the general population was 9.0–19.0 pmol/L.

For anti-thyroid peroxidase antibodies (aTPOAb) (Architect Ref.2K47, Abbott Diagnostic Division), the sensitivity of the assay was 0.16 IU/mL, LoQ was <0.50 IU/mL, and total CVs were <5%. An aTPOAb concentration <5.61 IU/mL, corresponding to the 97.5th percentile of the reference interval for the euthyroid population, was regarded as TPO-negative. For anti-thyroglobulin antibodies (aTgAb) (Architect Ref. 2K46, Abbott Diagnostic Division), the sensitivity of the assay was 0.16 IU/mL, LoQ was <1.0 IU/mL, and intra-analysis CVs were <5.9%. The reference range for the general population is <4.11 IU/mL. Urine fluid iodine concentrations were measured following the Benotti technique (10).

Statistical analyses

Multiple imputation algorithms were used to deal with 105 women with one of their TSH values missing. We performed longitudinal mixed model techniques to explore trajectories of gestational thyroid function. LCGA without random coefficients, with random intercept and random slope, and random intercept and slope were fitted to find the most adequate model describing the data (11). The optimal number of latent class trajectories was obtained based on the lowest Consistent Akaike Information Criterion and the adjusted Bayesian Information Criterion, Entropy, clinical significance, and interpretability (Supplementary Table 1, see section on supplementary materials given at the end of this article). LCGA was computed in R version 4.0.3, package lcmm.

Data were tested for normal distribution using the Kolmogorov–Smirnov and Shapiro–Wilk tests to apply the appropriate analysis. Quantitative data are expressed as the mean (S.D.) for normal distributed variables or as median (25th–75th percentiles) when the distribution was not normal. The non-parametric Kruskal–Wallis test or parametric ANOVA test was used to compare the continuous variables among the three trajectories groups. The chi-squared test was applied to compare categorical variables. Correlations between variables were tested using the univariate Spearman's correlation test. Multinomial logistic regression was performed to elucidate potential factors that influence the development of latent classes.

Statistical analyses were made using the software SPSS version 17.0.

Results

Baseline clinical characteristics of the 414 pregnant women at the first visit (before week 10 of gestational age) are described in Table 1.

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Table 1 Baseline clinical and biochemical characteristics of the women cohort.

Number	414
Age (years, mean ± S.D.)	32.1 ± 5.01
Weight (kg, mean ± S.D.)	64.31 ± 13.04
BMI (kg/m^2, mean ± S.D.)	24.63 ± 4.73
Parity (*n* (%))	
First gestation	143 (34.5)
Second gestation	133 (32.1)
Third or more gestation	138 (33.4)
Previous miscarriages (*n* (%))	155 (37.4)
Previous GHT (*n* (%))	6 (1.4)
Previous GDM (*n* (%))	8 (1.9)
Previous prematurity (*n* (%))	11 (2.7)
Level of education (*n* (%))	
None/primary	108 (26.1)
Secondary	192 (46.4)
Higher education	114 (27.5)
Smoking habit (*n* (%))	78 (18.8)
Current spontaneous pregnancy (*n* (%))	387 (96.8)
Consumption of iodized salt (*n* (%))	
Yes	229 (55.3)
Non	108 (26.1)
Don't know/no answer	77 (18.6)
Use of supplements	
None	133 (32.1)
Potassium iodide	124 (30.0)
Multivitamins	157 (37.9)
Biochemical data	
1T TSH (µUI/mL, mean ± S.D.)	1.41 ± 0.88
2T TSH (µUI/mL, mean ± S.D.)	1.67 ± 0.82
3T TSH (µUI/mL, mean ± S.D.)	1.99 ± 0.94
1T FT4 (ng/dL, mean ± S.D.)	0.98 ± 0.12
2T FT4 (ng/dL, mean ± S.D.)	0.81 ± 0.07
3T FT4 (ng/dL, mean ± S.D.)	0.79 ± 0.08
1T Positive aTPOAb (*n* (%))	37 (8.9)
2T Positive aTPOAb (*n* (%))	30 (7.2)
3T Positive aTPOAb (*n* (%))	18 (4.3)
1T Positive aTgAb (*n* (%))	49 (11.8)
2T Positive aTgAb (*n* (%))	38 (9.2)
3T Positive aTgAb (*n* (%))	38 (6.8)
1T hCG (mUI/mL, mean ± S.D.)	142,112.45 ± 82,483.92
1T Urinary iodine (µg/L, mean ± S.D.)	148.86 ± 92.96
2T Urinary iodine (µg/L, mean ± S.D.)	205.66 ± 123.43
3T Urinary iodine (µg/L, mean ± S.D.)	195.03 ± 120.14

1T, first trimester of gestation; 2T, second trimester of gestation; 3T, third trimester of gestation; aTgAb, anti-thyroglobulin antibodies; aTPOAb, anti-thyroid peroxidase antibodies; BMI, body mass index; FT4, free thyroxine; GDM, gestational diabetes mellitus; GHT, gestational hypertension/preeclampsia; hCG, human chorionic gonadotropin hormone; S.D., standard deviation; TSH, thyrotropin.

Concerning TAI, 37 women (8.9%) presented aTPOAb in the first trimester (1T), 30 (7.2%) in the second trimester (2T), and 18 (4.3%) in the third trimester (3T). Additionally, 49 pregnant women (11.8%) had positive aTgAb in the 1T, 38 (9.2%) in the 2T, and 38 (9.2%) in the 3T.

Latent classes of gestational thyroid function

Three different latent classes were obtained for TSH in these pregnant women using multiple imputation algorithms. The three longitudinal TSH trajectories that formed each latent class are shown in Fig. 2, and their functional descriptive characteristics are the following: (i) Low-increasing TSH trajectory (class 1 (C1)) was the more prevalent. It was detected in 356 pregnant women (86%). TSH in the 1T was 1.20 (0.70–1.73) µUI/mL, and a progressive low increase of TSH was observed during the whole pregnancy, with a 2T TSH value of 1.42 (1.03–1.82) µUI/mL ($P < 0.001$ compared to 1T TSH) and a 3T TSH value of 1.74 (1.25–2.22) µUI/mL ($P < 0.001$ compared to 1T TSH and to 2T TSH). (ii) High-increasing TSH (class 2 (C2)) was described in 40 pregnant women (9.7%). The 1T TSH value was 1.87 (1.28–2.75) µUI/mL, and a progressive high increase of TSH was observed at the 2T (3.10 (2.40–3.49) µUI/mL ($P < 0.001$ compared to 1T TSH)) and the 3T 3.52 (3.20–4.26) µUI/mL ($P < 0.001$ compared to 1T TSH and $P=0.004$ compared to 2T TSH)). (iii) Decreasing TSH (class 3 (C3)) was described in 18 pregnant women (4.3%). The 1T TSH was 3.37 (2.82–3.96) µUI/mL, and a decrease of TSH was observed during the 2T (TSH 2.42 (2.26–3.19) µUI/mL ($P=0.142$ compared to 1T TSH)) and the 3T (TSH 2.98 (2.45–3.52) µUI/mL ($P=0.004$ compared to 1T TSH and $P=0.028$ compared to 2T TSH)) from the baseline, with a slight decline regarding 2T. TSH trajectories in negative TAI participants are shown in Fig. 3, finding the same latent classes as the general cohort with similar percentages.

Baseline characteristics

Baseline clinical and analytical characteristics of the three TSH trajectories groups are described in Tables 2 and 3, respectively. Maternal age was significantly different among the three groups, with older women in C1 and younger women in C3. Differences in initial maternal weight (before 10 weeks of gestational age) were also observed among the three groups, with women with higher weight in C3 and women with

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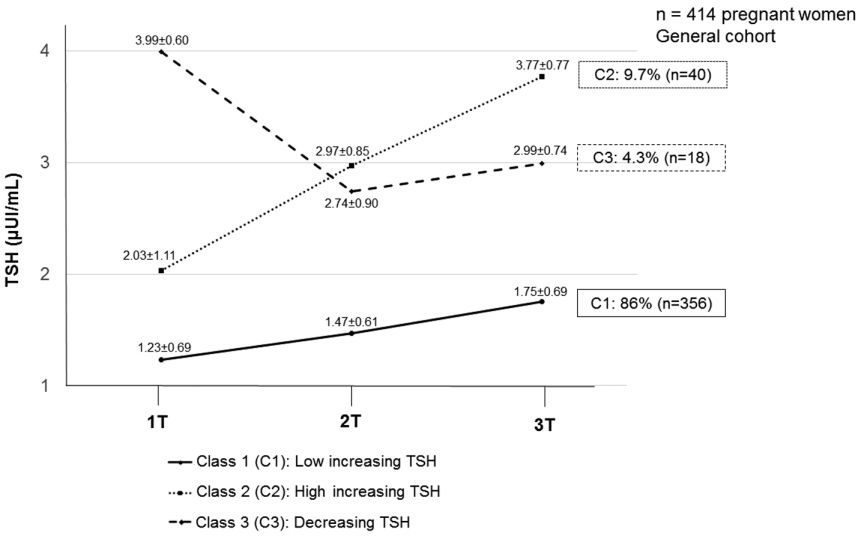

Figure 2
TSH latent classes during pregnancy of the general cohort. 1T, first trimester of pregnancy; 2T, second trimester of pregnancy; 3T, third trimester of pregnancy; C1, class 1; C2, class 2; C3, class 3; TSH, thyrotropin.

lower weight in C2. Parity was different between the three groups ($P=0.04$), with a higher percentage of the first gestation in C3 women. No differences in previous obstetric and fetal complications were observed, neither in the level of education nor smokers. Less than half of the women in each group consumed iodized salt on the first visit, with no significant differences between trajectory groups. Measurement of urinary iodine indicated that the three trajectory groups presented similarly high percentages of adequate iodine status according to guidelines recommendations for pregnancy (Table 3), which ranged from 60 to 83.4% of urinary iodine within recommended ranges. However, differences were observed in the gestational age of onset of iodine supplementation between the three category groups ($P=0.002$), with a higher percentage of pre-conceptional or before the 6 weeks of gestational age onset in C3 and with a higher rate after 6 weeks of gestational age onset in C2.

Once excluding those women with TAI (Table 4), the clinical characteristics of the three latent classes show some changes: the difference in maternal weight did not reach statistical significance, whereas there were statistical differences in the level of education (higher level in C3) or the antecedent of miscarriage (higher level in C1).

Differences in TSH were observed in each trimester between the three groups, with higher 1T TSH value in C3 (C1: 1.20 (0.70–1.73) µUI/mL, C2: 1.87 (1.28–2.75) µUI/mL, C3: 3.37 (2.82–3.96) µUI/mL; $P=0.001$), higher 2T TSH value in C2 (C1: 1.42 (1.03–1.82) µUI/mL,

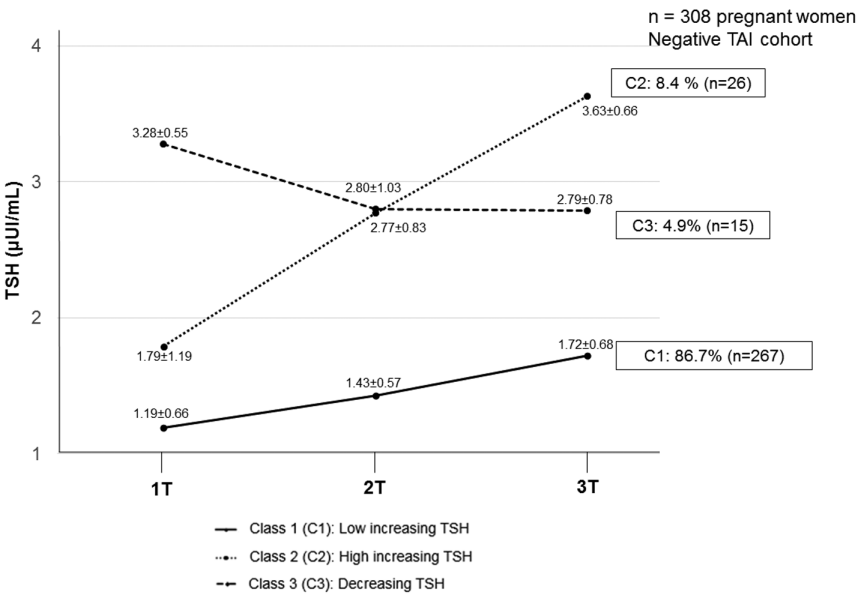

Figure 3
TSH latent classes during pregnancy of the negative TAI cohort. 1T, first trimester of pregnancy; 2T, second trimester of pregnancy; 3T, third trimester of pregnancy; C1, class 1; C2, class 2; C3, class 3; TAI, thyroid autoimmunity; TSH, thyrotropin.

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Table 2 Basal characteristics of the TSH latent classes.

	Class 1	Class 2	Class 3	*P*
Number (%)	356 (86)	40 (9.7)	18 (4.3)	
Age (years, mean ± S.D.)	32.37 ± 5.00	30.57 ± 5.05	30.22 ± 4.43	**0.027**[a]
Weight (kg, mean ± S.D.)	64.54 ± 13.11	60.24 ± 11.26	68.94 ± 13.58	**0.043**[a]
BMI (kg/m^2, mean ± S.D.)	25.23 ± 5.45	24.68 ± 4.73	25.87 ± 4.69	0.192[a]
Parity (*n* (%))				**0.042**[b]
Nulliparous	117 (32.9)	15 (37.5)	11 (61.1)	
Multiparous	239 (67.1)	25 (62.5)	7 (38.9)	
Previous miscarriages (*n* (%))	136 (38.2)	15 (37.5)	4 (22.2)	0.393[b]
Previous HGT (*n* (%))	5 (1.4)	0 (0)	1 (5.56)	0.257[b]
Previous GDM (*n* (%))	8 (2.2)	0 (0)	0 (0)	0.515[b]
Previous PTB (*n* (%))	10 (2.8)	1 (2.5)	0 (0)	0.768[b]
Current spontaneous pregnancy (*n* (%))	333 (93.5)	38 (95)	16 (88.9)	0.804[b]
Level of education (%)				0.096[b]
None/primary	90 (25.3)	14 (35)	4 (22.2)	
Secondary	173 (48.6)	14 (35)	5 (27.8)	
Higher education	93 (26.1)	12 (30)	9 (50)	
Smoking habit (*n* (%))	72 (20.3)	4 (10)	2 (11.1)	0.467[b]
Consumption of iodized salt (*n* (%))				0.943[b]
No	197 (55.3)	23 (57.5)	9 (50.0)	
Yes	93 (26.1)	9 (22.5)	6 (33.3)	
Don't know/no answer	66 (18.5)	8 (20.0)	3 (16.7)	
Iodine prophylaxis (%)				0.390[b]
None	114 (32.0)	16 (40)	3 (16.7)	
Potassium iodide	109 (30.6)	10 (25)	5 (27.8)	
Multivitamin	133 (37.4)	14 (35)	10 (55.6)	
Onset of iodine prophylaxis (*n* (%))				**0.002**[b]
Preconceptional	54 (15.2)	3 (7.5)	5 (27.8)	
Before 6 w ga	121 (34)	5 (12.5)	7 (38.9)	
After 6 w ga	175 (49.2)	31 (77.5)	5 (27.8)	
Missing data	6 (1.7)	1 (2.5)	1 (5.6)	

[a]ANOVA test; [b]Chi-squared test. Bold indicates statistical significance, $P < 0.05$.
1T, first trimester of gestation; 2T, second trimester of gestation; 3T, third trimester of gestation BMI, body mass index; ga, gestational age; GDM, gestational diabetes mellitus; GHT, gestational hypertension/preeclampsia; IK, potassium iodine; PTB, preterm birth; S.D., standard deviation; w, weeks.

C2: 3.10 (2.40–3.49) µUI/mL, C3: 2.42 (2.26–3.19) µUI/mL; $P = 0.001$) and higher 3T TSH value in C2 (C1: 1.74 (1.25–2.22 µUI/mL, C2: 3.52 (3.20–4.28) µUI/mL, C3: 2.98 (2.45–3.52) µUI/mL; $P = 0.001$).

Additionally, no differences in TSH values were observed between pregnant women of male fetuses (MF) and those with female fetuses (FF) in each trimester of gestation in the entire cohort and after excluding positive TAI women (data not shown).

The percentage of subclinical hypothyroidism in 1T, defined as TSH > 3.78 mIU/mL (the upper limit of reference ranges of our population (7)), was analyzed. Significant differences among the three groups were observed ($P < 0.001$), with a higher percentage in C3 (five patients, 27.8%) compared with C1 (zero patients, 0%) and C2 (three patients, 7.5%). No differences in FT4 were observed in each trimester between the three latent classes. Also, no differences in positive anti-thyroid antibodies (aTPOAb and aTgAb) were observed between the three groups throughout pregnancy.

Urinary iodine was similar in all three groups during 1T, 2T, and 3T, being all values within those recommended for pregnancy. hCG levels in 1T were also different in the three groups, higher in C2 and lower in C3 (C1: 126,566 (92,838.83–166,926.12) mUI/mL, C2: 135,145.96 (104.796.08–200,232.27) mUI/mL, C3: 92,699.41 (76,765.225–126,777.94) mUI/mL; $P = 0.014$)).

Concerning iron metabolism, no differences in serum ferritin levels were observed in the three trimesters among the three classes; the ferritin concentrations were within the normal range for all three classes during the 1T and low during the 2T and 3T, compatible with iron deficiency (defined as ferritin < 20 ng/mL). However, there were significant differences in hemoglobin (Hb) and hematòcrit (Hct) levels according to the three trajectories in the 2T, being lower in C2, which presented higher TSH levels in 2T (Supplementary Table 2). These differences were not present in 1T and 3T.

In multinomial logistic regression analysis, maternal age significantly correlated with the latent

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Table 3 Biochemical characteristics of the TSH latent classes.

	First trimester (1T)	***P***	**Second trimester** (2T)	***P***	**Third trimester** (3T)	***P***
TSH (μUI/mL)	1.41 (0.82–2.07)	**0.001**[a]	1.54 (1.11–2.10)	**0.001**[a]	1.88 (1.33–2.56)	**0.001**[a]
Class 1	1.20 (0.70–1.73)		1.42 (1.03–1.82)		1.74 (1.25–2.22)	
Class 2	1.87 (1.28–2.75)		3.10 (2.40–3.49)		3.52 (3.20–4.26)	
Class 3	3.37 (2.82–3.96)		2.42 (2.26–3.19)		2.98 (2.45–3.52)	
FT4 (ng/dL)	0.96 (0.90–1.03)	0.090[a]	0.80 (0.76–0.86)	0.924[a]	0.79 (0.73–0.84)	0.545[a]
Class 1	0.97 (0.91–1.04)		0.80 (0.76–0.86)		0.79 (0.74–0.84)	
Class 2	0.96 (0.89–1.01)		0.80 (0.76–0.87)		0.82 (0.73–0.83)	
Class 3	0.93 (0.87–1.03)		0.83 (0.72–0.90)		0.77 (0.71–0.84)	
β-hCG (mUI/mL)	120,659.92 (86,764.06–167,437.77)	**0.014**[a]				
Class 1	126,566 (92,838.83–166,926.12)					
Class 2	135,145.96 (104,796.08–200,232.27)					
Class 3	92,699.41 (76,765.25–126,777.94)					
Urinary iodine (μg/L)	131.2 (86.70–197.20)	0.542[a]	178.3 (118.55–260.25)	0.163[a]	175.8 (114.40–237.60)	0.269[a]
Class 1	124.10 (84.60–188.45)		175.60 (115.90–257.60)		173.40 (109.80–230.45)	
Class 2	144.40 (72.25–253.76)		212.20 (144.40–280.30)		194.60 (121.75–314.10)	
Class 3	101.55 (92.88–171.05)		211.20 (163.48–284.10)		181.80 (128.10–248.00)	
Positive aTPOAb (*n* (%))	37 (8.9)	0.118[b]	30 (7.2)	0.220[b]	18 (4.3)	0.562[b]
Class 1	28 (7.9)		23 (6.5)		14 (3.9)	
Class 2	7 (17.5)		6 (15.0)		3 (7.5)	
Class 3	2 (11.1)		1 (5.6)		1 (5.6)	
Positive aTgAb (*n* (%))	49 (11.8)	0.868[b]	38 (9.2)	0.807[b]	38 (6.8)	0.681[b]
Class 1	42 (11.8)		31 (8.7)		23 (6.5)	
Class 2	4 (10.0)		5 (12.5)		4 (10.0)	
Class 3	3 (16.7)		2 (11.1)		2 (11.1)	

[a] Kruskal–Wallis test; [b] ANOVA; [c]units are expressed as median (25th–75th percentiles). Bold indicates statistical significance, $P < 0.05$.
aTgAb, anti-thyroglobulin antibodies; aTPOAb, anti-thyroid peroxidase antibodies; β-hCG, beta-human chorionic gonadotropin hormone; FT4, free thyroxine; TSH, thyrotropin.

class of gestational thyroid function, independently of the presence or not of TAI. The level of education was associated with trajectories when women with TAI were included (Supplementary Table 3); meanwhile, the onset of iodine supplementation predicted latent class after excluding the TAI pregnant women (Supplementary Table 4).

Maternal and neonatal outcomes

Maternal and neonatal outcomes of the three TSH latent classes are described in Table 5. A low number of some pregnancy outcomes were observed in C2 and C3, such as fetal malformations, intrauterine growth restriction, gestational hypertension/preeclampsia, gestational diabetes, or maternal hospital admissions. Maternal weight gain during pregnancy differed between the three groups, with a higher increase in C3 (C1: 12.45 ± 4.60 kg, C2: 11.51 ± 3.88 kg, C3: 15.96 ± 4.69 kg; $P=0.006$). When TAI pregnant women were excluded, this difference remained (C1: 12.31 ± 4.68 kg, C2: 11.41 ± 4.40 kg, C3: 16.23 ± 5.27 kg; $P=0.021$). The second stage of labor differed significantly between the three groups of TSH trajectories, with a lower percentage of spontaneous labor and a higher percentage of induction in C3 ($P=0.003$). However, no differences in the type of labor (spontaneous, induced, or cesarean section) were observed. No differences in weight, sex newborn or neonatal unit admissions were described.

Discussion

We performed a prospective study to evaluate different trajectories of thyroid function during pregnancy using LCGA in a group of healthy pregnant women without high-risk factors living in Catalonia. Based on TSH, three latent classes were identified: low increasing TSH, present in most pregnant women (86%), a second one with a high increasing TSH and a less prevalent one characterized by a decreasing TSH pattern. These three patterns in our cohort agree with those in a previously published study on this issue (8). The study by Pop *et al.* was conducted in a larger cohort than ours. Still, the same trajectories of thyroid function during pregnancy as in our study were identified, with the low-increasing TSH class also being the most common; the replication of results obtained

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Table 4 Basal characteristics of the latent classes of thyroid function (excluding those with thyroid autoimmunity (TAI): anti-TPO and/or anti-Tg antibodies).

	Class 1	Class 2	Class 3	*P*
Number (%)	267 (86.7)	26 (8.4)	15 (4.9)	
Age (years, mean ± S.D.)	32.24 ± 4.90	29.69 ± 5.05	30.13 ± 4.43	**0.014**
Weight (kg, mean ± S.D.)	65.21 ± 13.42	60.47 ± 9.24	68.72 ± 12.78	0.113
BMI (kg/m^2, mean ± S.D.)	24.94 ± 4.80	23.48 ± 3.93	25.56 ± 4.56	0.272
Parity (*n* (%))				**0.005**
Nulliparous	78 (29.2)	11 (42.3)	10 (66.7)	
Multiparous	189 (70.8)	15 (57.7)	5 (33.3)	
Previous miscarriages (*n* (%))	110 (41.2)	7 (26.9)	2 (13.3)	**0.043**
Previous GHT (*n* (%))	4 (1.5)	0 (0)	1 (6.7)	0.241
Previous GDM (*n* (%))	7 (2.6)	0 (0)	0 (0)	0.577
Previous PTB (*n* (%))	6 (2.2)	0 (0)	0 (0)	0.625
Current spontaneous pregnancy (*n* (%))	249 (96.5)	24 (96)	13 (92.9)	0.777
Level of education (%)				**0.011**
None/primary	76 (28.5)	11 (42.3)	2 (13.3)	
Secondary	128 (47.9)	8 (30.8)	4 (26.7)	
Higher education	63 (23.6)	7 (26.9)	9 (60)	
Smoking habit (*n* (%))	59 (22.1)	3 (11.5)	1 (6.7)	0.447
Consumption of iodized salt (*n* (%))				0.730
No	148 (55.4)	16 (61.5)	7 (46.7)	
Yes	68 (25.5)	6 (23.1)	6 (40.0)	
Don't know/no answer	51 (19.1)	4 (15.4)	2 (13.3)	
Iodine prophylaxis (%)				0.386
None	92 (34.5)	10 (38.5)	2 (13.3)	
IK	77 (28.8)	5 (19.2)	5 (33.3)	
Multivitamin	98 (36.7)	11 (42.3)	8 (53.3)	
Onset of iodine prophylaxis (*n* (%))				**0.010**
Preconceptional	40 (15.2)	1 (4)	5 (33.3)	
Before 6 w ga	87 (33.1)	4 (16)	6 (40)	
After 6 w ga	136 (49.2)	20 (80)	4 (26.7)	

Bold indicates statistical significance, $P < 0.05$.1T, first trimester of gestation; 2T, second trimester of gestation; 3T, third trimester of gestation BMI, body mass index; ga, gestational age; GDM, gestational diabetes mellitus; GHT, gestational hypertension/preeclampsia; IK, potassium iodine; PTB, preterm birth; S.D., standard deviation; w, weeks.

in the present study suggests that this phenomenon may generally apply to pregnant women cohorts. In our study, significant differences in TSH values were observed in the three trimesters of gestation between the different classes.

hCG, a hormone that increases once fertilization occurs and has as its principal function to prepare the endometrium for the initial implantation of the embryo, has a thyrotropin-like effect in the 1T that implies a decrease in TSH and an increase in T4 (12). In our study, significant differences were observed in 1T β-hCG levels between the different classes, higher in C2 (High increasing TSH pattern) and lower in C3 (Decreasing TSH pattern). This fact could have been translated into a different stimulating T4 secretion capacity by the maternal thyroid, as FT4 concentrations between groups did not differ, indicating that the higher level of TSH in C3 may have accounted for a compensatory mechanism. In contrast, in the study by Pop *et al.* no significant differences were observed concerning β-hCG levels at 12 weeks between the three classes (8); in our cohort, however, β-hCG samples were drawn earlier, between 6 and 9 weeks of gestational age. In addition, the thyrotropic effect of β-hCG can also be modulated by factors such as maternal age, parity, BMI, or TAI (13). Maternal age has been reported as a risk factor for developing hypothyroidism during pregnancy (6), and it may also influence the maternal capacity to secrete β-hCG. Maternal age is one of the principal factors determining the recommendations for performing the 1T selective screening for thyroid dysfunction in most guidelines (6). In our study, there was a significant difference in maternal age between the different classes, being higher in C1 (32.3 ± 5 years), although differences with the other classes did not exceed 2 years in absolute value. However, in logistic regression analysis, maternal age correlated with maternal thyroid function trajectories.

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Table 5 Maternal and neonatal outcomes.

	Class 1	Class 2	Class 3	*P*
Number (%)	356 (85.99)	40 (9.7)	18 (4.3)	
Fetal malformations (*n* (%))	6 (1.7)	0 (0)	0 (0)	0.611
Intrauterine growth restriction (*n* (%))	26 (7.3)	2 (5.0)	2 (11.1)	0.699
Intrauterine growth alteration (*n* (%))	29 (8.1)	2 (5.0)	2 (11.1)	0.957
Weight gain during pregnancy (kg, mean ± S.D.)	12.45 ± 4.60	11.51 ± 3.88	15.96 ± 4.69	**0.006**
GHT (*n* (%))	33 (9.3)	3 (7.5)	0 (0)	0.384
GDM (*n* (%))	37 (10.4)	2 (5.0)	1 (5.6)	0.464
Anemia (*n* (%))	148 (41.6)	18 (45.0)	4 (22.2)	0.227
Maternal hospital admissions (*n* (%))	12 (3.4)	2 (5.0)	0 (0)	0.622
Beginning of labor (*n* (%))				
Spontaneous	221 (62.1)	26 (65)	5 (27.8)	**0.003**
Induction	90 (25.3)	9 (22.5)	12 (66.7)	
Elective (cesarean)	29 (8.1)	3 (7.5)	0 (0)	
Missing data	16 (4.5)	2 (5)	1 (5.6)	
Type of birth (*n* (%))				
Eutocic	206 (58.9)	24 (60)	11 (61.1)	0.508
Instrumental	46 (12.3)	8 (20)	3 (16.7)	
Cesarean	88 (24.7)	6 (15)	3 (16.7)	
Missing data	16 (4.5)	2 (5)	1 (5.6)	
Newborn weight (g, mean ± S.D.)	3265.73 ± 479.73	3135.00 ± 377.90	3439.09 ± 566.14	0.138
Female newborn (*n* (%))	182 (51.1)	20 (50)	6 (33.3)	0.430
Newborn neonatal unit admission (*n* (%))	30 (8.4)	4 (10)	4 (22.2)	0.130

Bold indicates statistical significance, $P < 0.05$.GDM, gestational diabetes; GHT, gestational hypertension/preeclampsia; S.D., standard deviation.

It is also known that weight and BMI influence thyroid function variations in adults; thus, high weight and BMI are related to increasing TSH and decreasing FT4 mainly through leptin modulation of TSH secretion (14, 15). Higher maternal TSH and lower FT4 levels have also been associated with higher pregestational BMI in the early stages of pregnancy (16). In agreement with Collares *et al.* study, we observed differences in maternal weight in the first trimester between the three classes. Class 3 (decreasing TSH pattern) pregnant women, who had higher 1T TSH levels, had higher maternal weight than C2 and C1, and reciprocally, those in C1 (low-increasing TSH pattern), with lower 1T TSH levels had a lower maternal weight in the first trimester. However, there were no statistical differences in BMI in the 1T between the three classes, although BMI may not be a good parameter for measuring adiposity, particularly in pregnant women.

Iodine is an essential component of thyroid hormones, and iodine deficiency causes inadequate thyroid hormone production; during pregnancy, it may impair the growth and neurodevelopment of the offspring and increase infant mortality (17). Urinary iodine levels did not show iodine deficiency in any group or in any trimester of gestation. Therefore, none of the results observed regarding urinary iodine in our cohort may be applied in detecting different trajectories of thyroid function. However, earlier initiation of iodine supplementation could influence a higher 1T TSH value due to a possible adaptative glandular hyperplasia, as was described by Glinoer (18). In our study, the C3 (decreasing TSH pattern class) presented a higher 1T TSH value and a higher percentage of women who initiated iodine prophylaxis before 6 weeks of gestational age than the other two classes. In the literature, it is always written that TSH increases with increasing term; however, in both studies, it is found that a (small) subgroup of women show a decreasing pattern of TSH. The fact is probably a nice example of the alleviation of the auto-immune response with increasing term of gestation.

It has been suggested that TAI could play a role in thyroid trajectories during pregnancy (8). In our cohort, the overall prevalence of TAI was lower than the one reported by Pop *et al*. However, to elucidate the role of TAI as a potential confounder in our study, we performed the statistical analysis twice: including and excluding TAI pregnant women. First of all, the differences in maternal weight according to latent classes disappeared when removing the TAI ones, which can be interpreted as a potential confounder in the relationship between maternal weight and TSH, as we have previously demonstrated (19). In the study by Pop *et al.* (8), we also observed a decrease in the percentage of positive aTPOAb throughout pregnancy in the three TSH trajectories groups, consistent with a special immunomodulatory regulation status specific to pregnancy.

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Iron deficiency is frequent during pregnancy. Recent and previous data showed that there is an impact of iron deficiency on thyroid function (higher TSH and lower FT4 levels) and autoimmunity (aTPOAb) during pregnancy (20, 21, 22). In our study, no differences in the percentage of TAI and FT4 levels were observed among the three classes in the three trimesters. However, as mentioned before, we observed differences in TSH levels among the three classes in each trimester. Concerning iron deficiency, no differences were observed in the three trimesters in serum ferritin levels among the three classes, being compatible with iron deficiency (ferritin < 20 ng/mL) in 2T and 3T in the three classes. However, Hb and Hct levels were lower in 2T in the C2 women who had higher TSH levels in 2T. This may indicate that other iron parameters may be altered; thus, further investigation with additional indicators of iron metabolism is required to explain these results and to better understand the role of iron deficiency in thyroid function and autoimmunity during pregnancy.

Our study observed differences in weight gain during pregnancy among the three maternal thyroid function trajectories, with a higher weight increase in C3 (decreasing TSH pattern), the class with a higher baseline weight, and higher TSH levels in 1T. This difference remained even after excluding positive TAI pregnant women. These results agree with those described in several articles, where pregnant women with higher TSH in the 1T have higher weight and BMI and more significant weight gain during pregnancy (15). In the study by Pop *et al.*, small for gestational age babies were associated with specific maternal thyroid function latent classes groups (8), with a higher percentage in the high increasing TSH group. We did not observe differences in fetal growth among the three latent classes, probably due to the size of our study cohort compared to the later study. However, we found differences in the labor initiation modality, with a higher percentage of induced labor in C3, which was the group with a higher proportion of primiparous women (72%), a fact that could explain this difference.

Recent data have also shown that the fetal gender might lead to changes in thyroid function (23). In our study, no differences were observed in TSH values between pregnant women who gave birth to MF and those who gave birth to FF in each trimester.

Finally, 37% of women that participated in our study had the antecedent of a previous miscarriage. This percentage may likely be due to a selection bias. Pregnant women with previous miscarriages may be more prone to participate in an observational study with monthly obstetric surveillance and will accept additional appointments more easily. However, no differences in the previous miscarriage's percentage were found among the trajectory groups.

One of the strengths of our study is that it was performed in a prospective cohort of pregnant women recruited before 10 weeks of gestational age, and we collected clinical, physical activity, and nutritional data. Although it is a relatively smaller cohort compared to other studies, we found similar results with the same categories of maternal thyroid function trajectories, which confirms previously described results and lends consistency to our study.

Latent classes growth analysis allows to identify different patterns of TSH probably related to the dynamic adaptation process to pregnancy changes: the effect of hCG on TSH in 1T, modulated by maternal age and weight, seems to determine in part the longitudinal trend of thyroid parameters throughout the three trimesters of gestation as well as some perinatal outcomes. As Pop *et al.* stated, those patterns might also reflect differences in pregnancy-specific immune tolerance between nulliparous and multiparous women.

Although our sample size limits to a certain extent the prevalence of positive TAI or adverse maternal and adverse neonatal outcomes, the higher percentage of subclinical hypothyroidism and the higher percentage of inductions in C3 group in our study strengthen the findings of the study by Pop *et al*.

In conclusion, our study confirms the existence of at least three different maternal TSH trajectories, being the low-increasing TSH class the most frequent, involving 86% of cases. Maternal age correlated with maternal thyroid function trajectories. Additional studies may identify other factors that may participate in the mechanistic explanation of such classes and be involved in the development of prediction models of maternal thyroid trajectories and thereby helping to unravel the implication of each thyroid trajectory class in maternal and neonatal outcomes.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-23-0016.

Declaration of interest

None of the authors have any conflicts of interest to declare.

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Author contribution statement

Conception and design of the study: BS, IV, and MP-D. Acquisition of data: CM, LF, APMO. Statistical analysis: YD, LE-C, JC. Analysis and/or interpretation of data: BS, IV, YD, LE-C, JC, MP-D. Drafting or revising the article critically for important intellectual content: BS, IV, MP-D. All authors give final approval of the article to be submitted.

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