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Preference-Based Assessments

The Impact of Subclinical Hypothyroidism on the Quality of Life During Pregnancy: Mapping 5-Level Version of EQ-5D and ThyPRO-39

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ABSTRACT

Objectives: To describe how subclinical hypothyroidism (SubHypo) influences the quality of life (QoL) during pregnancy.

Methods: In primary data collection (NCT04167423), thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroid peroxidase antibodies, generic quality of life (QoL; 5-level version of EQ-5D [EQ-5D-5L]), and disease-specific QoL (ThyPRO-39) were measured among pregnant women. SubHypo during each trimester was defined according to the 2014 European Thyroid Association guidelines (TSH $>$ 2.5, 3.0, and 3.5 IU/L, respectively; with normal FT4). Path analysis described relationships and tested mediation. Linear ordinary least squares, beta, tobit, and two-part regressions were used to map ThyPRO-39 and EQ-5D-5L. Alternative SubHypo definition was tested in sensitivity analysis.

Results: A total of 253 women at 14 sites (31 $\pm$ 5 years old, 15 $\pm$ 6 weeks pregnant) completed the questionnaires. Sixty-one (26%) had SubHypo and differed from 174 (74%) euthyroid women in smoking history (61% vs 41%), primiparity (62% vs 43%) and TSH level (4.1 $\pm$ 1.4 vs 1.5 $\pm$ 0.7 mIU/L, $P < .001$). EQ-5D-5L utility in SubHypo (0.89 $\pm$ 0.12) was lower than that in euthyroid (0.92 $\pm$ 0.11; $P = .028$) even after adjustment (difference -0.04, $P = .033$), whereas ocular ($P = .001$, ThyPRO-39), cognitive symptoms ($P = .043$), anxiety ($P < .0001$), and the composite score were higher. The impact of SubHypo on utility was mediated by anxiety. Results were confirmed by sensitivity analysis. Final mapping equation (ordinary least squares) includes goiter symptoms, anxiety, upset stomach, composite score (ThyPRO-39), FT4 levels, and week of pregnancy (determination coefficient 0.36).

Conclusion: This is the first QoL mapping of SubHypo during pregnancy and the first evidence that SubHypo is associated with a negative impact on QoL. The effect is mediated by anxiety. EQ-5D-5L utilities can be generated based on ThyPRO-39 scores collected in pregnant euthyroid and patients with SubHypo.

Keywords: EQ-5D, hypothyroidism, pregnancy, quality of life, ThyPRO-39.

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Introduction

Elevated thyroid stimulating hormone (thyrotropin, TSH) concentrations with normal serum-free thyroxine (nonprotein bound p-thyroxine, FT4) levels define subclinical hypothyroidism (SubHypo), the most common thyroid dysfunction after conception.[1] This condition is associated with an increased risk of preeclampsia,[2] gestational diabetes,[3] gestational hypertension, placental abruption,[4] pregnancy loss,[4] preterm delivery,[5,6] postpartum hemorrhage, low birth weight infants,[7] neonatal death,[4,8] and, probably, also offspring cognitive development.[9,10]

We have previously shown that after 25 years of investigation, the effect of thyroid dysfunction and, or thyroid autoimmunity on well-being during pregnancy is still unsettled.[11] More specifically, it is unknown whether SubHypo is accompanied by specific symptoms,[11] meaning that case findings of women at risk cannot be effectively evaluated in everyday practice. In addition, it is unknown if SubHypo affects the quality of life (QoL) during pregnancy.[11] Using the terminology of health technology assessments, it is difficult to attribute any utility to this health state. This evidence gap represents an obstacle to creating cost-utility models that can serve as an argument for population-wide screening programs.

Per protocol, the primary aim of this project was to compare the health-related QoL between pregnant women with normal thyroid function and those with SubHypo. The secondary aim was to map thyroid-related QoL with specific symptoms and to estimate their individual effect on the overall QoL.

Methods

Study Design

This was a cross-sectional primary online data collection of questionnaires and test results (TSH, FT4, and thyroid peroxidase antibodies [TPO-Ab]) from pregnant women attending gynecology

or endocrinology offices between January 2020 and April 2022. Hospitals and outpatient private gynecology clinics in the Czech Republic were chosen to achieve geographical coverage of 6 regions. A questionnaire was presented to all attending pregnant women who (1) were able to complete the online questionnaires, (2) were screened for thyroid function at any time during the index pregnancy, and (3) had TSH and FT4 values available. In the presented analyses, we included euthyroid women and women with SubHypo (increased TSH and normal FT4), irrespective of TPO-Ab. Normal thyroid function during each trimester was defined according to the 2014 European Thyroid Association (ETA) guidelines (TSH 0.1-2.5; 0.2-3.0; and 0.3-3.5 mIU/L, for trimesters 1-3, respectively)[12] and Czech population reference range (FT4 9.55-23 pmol/L).[13] Women with laboratory results indicating other thyroid pathologies were excluded (Fig. 1[12,13]).

Potential confounders were collected according to reviewed factors influencing the QoL during pregnancy[14]: age, week of pregnancy, parity, characteristic of previous labor, type of index conception, other significant comorbidities, TPO-Ab levels, education, abuses, emotional relationship to the index pregnancy, subjective social and financial distress, subjective perception of having friends and family, and regular physical activity/exercise (detailed wording in Table 1[12,14]).

The generic QoL was estimated using the validated Czech version of the 5-level version of EQ-5D (EQ-5D-5L) questionnaire,[15] and utilities (the measure of the preference or value that an individual or society gives a particular health state, a score between 0 and 1) were generated from the UK value set (the Czech value set has not yet been created). The thyroid-related QoL was estimated through the ThyPRO-39 questionnaire.[16] The Czech version of the ThyPRO-39 was prepared and validated in collaboration with the authors of this questionnaire in line with the good practice[17] using the standardized procedure consisting forward and backward translations (3 forward translators and 1 backward native/bilingual translator), reconciliation with author team, and construction of the consensus version. Pilot readability testing was done using 5 patients with thyroid disease but not participating in this project. The Czech version of the questionnaire, along with the details on the translation process and cognitive debriefing, is enclosed in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015.

The protocol was registered prospectively in the clinicaltrials.gov registry under the identifier NCT04167423 and approved on November 7, 2019 by the multicenter ethics committee of Faculty Hospital in Hradec Králové under the identifier 201911S14O. We report in line with the Mapping onto Preference-based measures reporting Standards (MAPS) statement.[18]

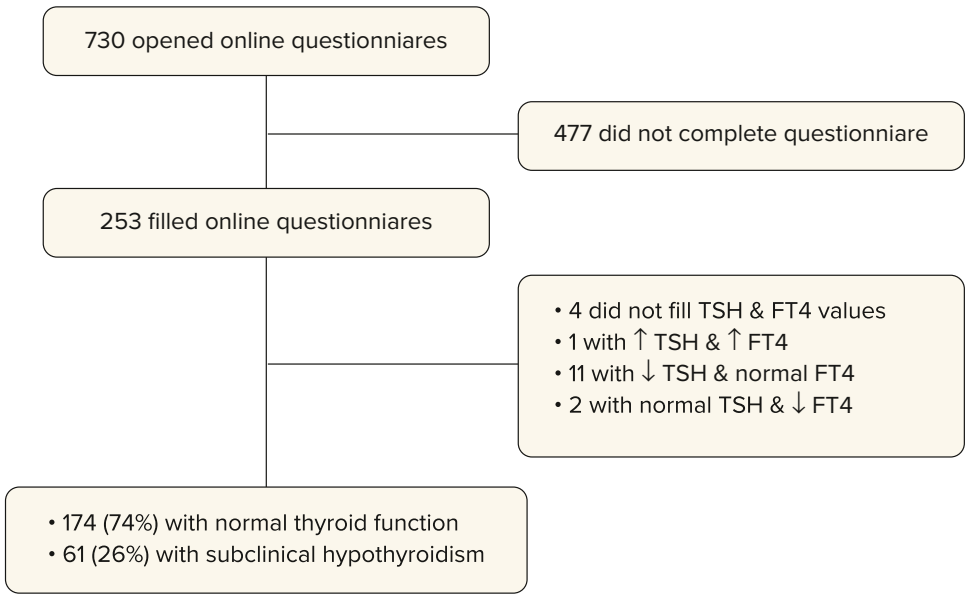
Statistical Approaches

Differences in baseline characteristics were tested using the Mann-Whitney test with ties and the chi-squared test. Differences in outcomes were tested using a *t* test and adjusted via multivariate linear regression. A consensual alpha level of 0.05 was used to assess statistical significance. We used only complete records; no imputation was done for missing data. All calculations were done with Stata software (version 15.0; StataCorp LP, College Station, TX).

Path Analysis

We used structural modeling to explain pathways suggesting underlying effects/influences between individual constructs (eg,

Figure 1. Patient flow. Of the 730 opened online questionnaires, 253 (35%) completed all mandatory answers (hormonal levels and both the EQ-5D-5L and the ThyPOR-39), and 235 (93%) were used for the present analysis. The study included 61 (26%) women with subclinical hypothyroidism and 174 (74%) euthyroid women. Normal thyroid function during each trimester was defined according to the 2014 ETA guidelines (TSH 0.1-2.5; 0.2-3.0; and 0.3-3.5 mIU/L)[12] and FT4 according to Czech population reference ranges (9.55-23.0 pmol/L).[13] For the presented analyses, we included euthyroid women and women with subclinical hypothyroidism (increased TSH and normal FT4) irrespective of the presence of TPO-Ab, the prevalence of which was comparable in both groups. Women with other thyroid pathologies were excluded.



EQ-5D-5L indicates 5-level version of EQ-5D; ETA, European Thyroid Association; FT4, free thyroxine; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

Table 1. Characteristics of pregnant women with normal thyroid function and with subclinical hypothyroidism.

Group characteristic	Normal thyroid function	Subclinical hypothyroidism	*P* value
Number of women	174 (74%)	61 (26%)	
Age, years	30.94 ± 4.95	30.51 ± 5.92	.290
TSH, mIU/L	1.48 ± 0.67	4.14 ± 1.40	< .001
FT4, pmol/L	13.94 ± 1.88	13.93 ± 1.87	.956
TPO-Ab positivity	111 (66%)	41 (69%)	.593
Week of pregnancy	14.84 ± 6.48	14.00 ± 5.74	.401
Primiparous	75 (43%)	38 (62%)	.010
Previous cesarian section	24 (24%)	4 (17%)	.482
Assisted reproduction (index pregnancy)	10 (6%)	6 (10%)	.275
Other medical condition	17 (10%)	8 (13%)	.466
Education basic	6 (3%)	3 (5%)	.444
Education intermediate	72 (41%)	30 (49%)	.444
Education university	96 (55%)	28 (46%)	.444
Positive smoking history	71 (41%)	37 (61%)	.007
Current smoker	10 (6%)	2 (3%)	.451
Current alcohol consumer	14 (8%)	4 (7%)	.707
Not using other substances	174 (100%)	61 (100%)	-
I am happy to be pregnant. This pregnancy is a positive event.	173 (99%)	60 (98%)	.436
I am feeling financially or socially distressed.	4 (2%)	2 (3%)	.676
I feel like I have good friends who can help me if I need it.	171 (99%)	58 (97%)	.104
I feel like I have a good family who can help me if I need it.	173 (99%)	60 (98%)	.436
Weekly exercises/physical activity	2.48 ± 2.23	2.21 ± 2.17	.388

Note. Subclinical hypothyroidism during each trimester was defined according to the 2014 ETA guidelines (TSH 0.1-2.5; 0.2-3.0; and 0.3-3.5 mIU/L).[12] The relevant factors and potential confounders were collected according to Lagadec et al.[14] Continuous variables are represented as mean ± standard deviation, binary variables as count (%). Differences between groups were tested using the Kruskal Wallis and chi-squared tests with no correction for multiplicity testing. Albeit anonymous, all answers were reported by the patient; thus, the answers to substance abuse might be biased. A consensual alpha level of 0.05 was used to assess statistical significance.
ETA indicates European Thyroid Association; FT4, free thyroxine; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

anxiety or QoL) and to test mediation. Structural equation modeling was done using the Stata package *sem*; standardized coefficients were estimated using the maximum likelihood algorithm. The fit and validity of the model were assessed using the *estat gof* and *estat mindices* packages. The final model was chosen based on the likelihood ratio test comparing the model with a saturated model, the root mean squared error of the approximation (RMSEA), coefficient of determination, and the comparative fit index.[19] The mediation was tested using the postestimation command *medsem*[20] comparing the direct and indirect effect per Baron and Kenny[21] modified by Iacobucci.[22] The Monte Carlo test verified the result.

Sensitivity Analysis

Additionally, we tested the sensitivity of our conclusions relative to the definition of SubHypo established in the 2014 ETA guidelines.[12] The differences in generic, disease-specific QoL, and anxiety were additionally compared with an identical sample in which normal thyroid function was defined more strictly, that is, according to Czech population reference ranges for the first trimester (TSH 0.16-3.43) and the normal reference range for the second and third trimester, that is, TSH 0.4-4.0 mIU/L.[23] The same definition was also used for path and mediation analysis.

Mapping

We used a simple ordinary least squares regression (OLS) to identify candidate variables with the capacity to predict the EQ-5D utility (ie, having a *P* value of the coefficient from the multiple regression below .05). The final selection of covariates was tested in OLS, beta, tobit, and two-part regressions (Stata packages *betareg*, *tobit*, and *twopm*), allowing the generation of the most explanatory mapping equation.[24] The fit and validity of the models were assessed using the coefficient of determination, Akaike information criterion and mean squared error between the observed versus predicted values. The methods used are described in detail the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015.

Results

Of 730 opened links to the online questionnaires, we selected questionnaires with all mandatory answers completed (hormonal levels and both the EQ-5D and the ThyPOR-39 questionnaires) from 253 pregnant women (Fig. 1[12,13]) from 14 sites in 6 regions of the Czech Republic between January 16, 2020 and April 13, 2022. We excluded from analysis 4 women

Table 2. Patient-reported outcomes among pregnant women with normal thyroid function and subclinical hypothyroidism.

Group characteristic	Normal thyroid function	Subclinical hypothyroidism	*P* value	Adjusted difference*	*P* value
Number of pregnant women	174 (74%)	61 (26%)			
ThyPRO-39 scores	(Mean ± SD)	(Mean ± SD)		Mean (95% confidence interval)	
Goiter symptoms	5.37 ± 7.91	6.98 ± 7.95	.087	1.98 (−0.45 to 4.42)	.111
Hyperfunction symptoms	13.26 ± 11.13	15.95 ± 12.10	.057	1.74 (−1.84 to 5.32)	.339
Hypofunction symptoms	15.05 ± 13.13	19.16 ± 15.22	.023	3.19 (−1.12 to 7.52)	.147
Eye symptoms	4.25 ± 6.75	7.97 ± 8.58	< .001	3.97 (1.66-6.28)	.001
Tiredness	41.86 ± 19.98	49.30 ± 21.52	< .001	6.18 (−0.03 to 12.39)	.051
Cognition	8.28 ± 12.41	12.98 ± 13.60	.007	4.17 (0.13-8.21)	.043
Anxiety	12.53 ± 13.50	22.08 ± 20.02	< .001	9.38 (4.63-14.12)	<.001
Depression	21.42 ± 14.72	26.46 ± 14.42	.011	3.70 (−0.84 to 8.23)	.110
Emotional susceptibility	23.77 ± 15.95	29.28 ± 16.27	.011	4.13 (−0.76 to 9.01)	.098
Social life impairment	6.29 ± 12.60	9.38 ± 11.87	.048	2.34 (−1.58 to 6.26)	.240
Daily life impairment	11.13 ± 15.21	12.56 ± 17.42	.273	1.72 (−3.30 to 6.73)	.501
Cosmetic complaints	3.49 ± 8.92	5.85 ± 12.10	.054	2.05 (−1.00 to 5.10)	.186
Composite score	17.76 ± 10.70	23.16 ± 12.23	< .001	4.62 (1.15-8.10)	.009
Overall impact on the quality of life	4.89 ± 12.80	7.38 ± 15.37	.110	2.31 (−1.97 to 6.60)	.289
EQ-5D-5L scores	Mean ± SD	Mean ± SD		Mean (95% confidence interval)	
Utility	0.92 ± 0.11	0.89 ± 0.12	.028	−0.036 (−0.069 to −0.003)	.033
VAS[†]	86.66 ± 17.37	80.66 ± 27.61	.025	−6.53 (−12.81 to −0.22)	.043

Note. Crude differences were tested using a one-sided *t* test. A consensual alpha level of 0.05 was used to assess statistical significance. The items in bold were significantly different.
EQ-5D-5L indicates 5-level version of EQ-5D; TPO-Ab, thyroid peroxidase antibodies; VAS, visual analog scale.
*Adjusted for age, trimester, presence of TPO-Ab, primiparity, other preceding health conditions, education level, and smoking history.
[†]The respondent's self-rated health status on a graduated (0-100) scale, with higher scores for higher health-related quality of life.

who did not fill either TSH or FT4 values, 1 who indicated increased both TSH and FT4, 11 with SubHypo, 2 with isolated hypothyroxinemia. The mean age was 31 ± 5 years; women were in the 15 ± 6 weeks of pregnancy (60%, 29%, and 11% of laboratory results from the first, second, and the third trimester, respectively) and exercised on average 2.4 ± 2.2 times per week (question: "How many times a week do you exercise or perform a physical activity, such as yoga, Pilates, walking etc."). Seven percent of conceptions were assisted, 97% women reported a satisfactory financial situation (disagreement with the statement, "I am feeling financially or socially distressed"), 97% had helping friends (statement, "I feel like I have good friends who can help me if I need it"), and 99% had helping family (statement, "I feel like I have a good family who can help me if I need it") (more in Table 1[12,14]). Sixty-one (26%) women had SubHypo and were comparable in all characteristics with the 174 (74%) women with normal thyroid function, except for smoking history (61% vs 41%, $P = .007$), primiparity (62% vs 43%, $P = .010$), and TSH level (4.1 ± 1.4 mIU/L vs 1.5 ± 0.7 mIU/L, $P < .001$) (Table 1[12,14]). Plasma FT4 levels were perfectly balanced between euthyroid and women with SubHypo (13.94 ± 1.88 pmol/L vs 13.93 ± 1.87 pmol/L), as was the number of TPO-Ab positive women (66% vs 69%, $P = .593$).

Differences Between the QoL and Individual Symptoms

The average EQ-5D-5L utility in pregnant women with SubHypo was lower than that in euthyroid pregnant women (0.89 ± 0.12 vs 0.92 ± 0.11; $P = .028$) even after adjusting for age, trimester, presence of TPO-Ab, parity, preceding health conditions, education level, and smoking history (the adjusted difference was 0.036, $P = .033$) (Table 2). The main contribution to decreased utility measured by EQ-5D-5L in women with SubHypo was the depression/anxiety domain (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015). The histogram of EQ-5D utilities is available as Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015.

A comparison of ThyPRO-39 domains between SubHypo and euthyroid pregnant women uncovered pronounced symptoms of hypothyroidism ($P = .023$), ocular symptoms ($P < .001$), fatigue ($P = .008$), cognitive symptoms ($P = .007$), anxiety ($P < .001$),

depression (P = .011), emotional susceptibility (P = .011), impaired social life (P = .048), and overall QoL impact (ThyPRO-39 composite score) (P = .001). Differences (ie, increased scores) remained significant after adjustment in the ocular (adjusted difference 1.66-6.28; P = .001), cognitive symptoms (0.13-8.21; P = .043), anxiety (4.63-14.12; P = .000), and the composite score (1.15-8.10; P = .009) (Table 2).

Broken down by individual ThyPRO-39 items, the results show that women with SubHypo were troubled by the following symptoms: palpitations (adjusted P value = .014); eye dryness or grittiness (P = .001); impaired vision (P = .026); dry skin (P = .037); difficulty getting motivated to do anything (P = .003); unclear thinking (P = .012); being afraid or anxious (P = .015); feeling tense ($P < .001$); feeling uneasy ($P < .001$); and feeling sad (P = .010). More details are in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015.

How SubHypo Influences the QoL: Path Analysis

We first fit a structural model in which the state of SubHypo predicts all ThyPRO-39 domains/symptoms, which, at the same time, predicts the EQ-5D utility (model 1; Table 3). In such a setting, SubHypo predicts symptoms of hypofunction, eye symptoms, tiredness, cognition, anxiety, depression, emotional susceptibility, and social life impairment. On the other hand, goiter symptoms, anxiety, and daily life impairment predict the EQ-5D utility. From these observations, it is clear that anxiety represents the principal axis between thyroid function and the generic QoL because it is the only symptom that is predicted by SubHypo and, at the same time, predicts the EQ-5D utility.

In the next step, we looked for the predictors of anxiety. In OLS model 2, we identified SubHypo, financial/social distress, and helping friends as predictors of anxiety (Table 3). Next, we looked for predictors of EQ-5D utility among patient characteristics adjusted to anxiety symptoms (OLS model 3), and we identified the week of pregnancy, positive smoking history, and being happy to be pregnant as the candidate variables. In the final step, we put these observations together and built the structural model 4. For the sake of parsimony, we dropped the positive smoking history, because it did not improve the model explanatory power (coefficient of determination). This final model included ThyPRO-39 anxiety, week of pregnancy, and "being happy to be pregnant" as predictors of EQ-5D-5L utility. The anxiety was predicted with SubHypo, financial distress, and "having helping friends" (Fig. 2). Although we could not explain a large portion of the variability in EQ-5D utility (77% error term), the fit of model 4 seems rather strong based on the likelihood ratio test (P = .457), the coefficient of determination (0.182), RMSEA (0.000), and the comparative fit index (1.000). In Table 3 and Figure 2, we report standardized coefficients for structural models because they reflect the effect size (similar Cohen's D). For predictions. Nevertheless, the nonstandardized coefficients need to be used; hence, model 4 can be transcribed into the following equations:

$$\text{EQ}-5\text{D utility (predicted)} = 0.803 + 0.200 \times \text{happy to be pregnant (yes/no)} - 0.0029 \times (\text{ThyPRO}-39\ \text{Anxiety}) - 0.0031 \times (\text{week of pregnancy})$$

$$\text{ThyPRO}-39\ \text{Anxiety (predicted)} = 37.6 - 25.5 \times \text{helping friends (yes/no)} + 14.9 \times \text{financial distress (yes/no)} + 8.1 \times \text{SubHypo (yes/no)}$$

By fitting the same structural equation model in which the utility was both directly and indirectly affected by SubHypo (Table 3, model 5) as indicated by the crossed arrow in Figure 2, the comparative fit index drops to 0.993, and the RMSE increases to 0.026. The mediation analysis (ie, comparison of direct and indirect effects) suggests that 86% of the effect of SubHypo on the QoL is mediated through anxiety (because we prefer not to derive effect size [Cohen's D] based on nonsignificant standardized path coefficients, we decided to measure the indirect effect on percentual scale, that is, by dividing the product of nonstandardized path coefficients by the overall effect. More specifically, we divide the product of 2 nonstandardized path coefficients for SubHypo → Anxiety and Anxiety → EQ-5D utility [8.133 × − 0.0028] by the sum of this product and the coefficient for direct effect SubHypo → EQ-5D [8.133 × − 0.0028] − 0.0037.[20]). Such observation was corroborated by the Monte Carlo test (P = .001), indicating that this mediation is complete.

Sensitivity of the Results Relative to the Definition of SubHypo

For sensitivity analysis (Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015), we tested whether the difference in EQ-5D utility, ThyPRO-39 anxiety, and composite score depend on the definition of SubHypo. Using alternative diagnostic criteria based on the Czech population reference range[23] (see Methods), we divided the sample into 196 (84%) euthyroid and 37 (16%) women with SubHypo. The difference in anxiety (P = .003) and the ThyPRO-39 composite score (P = .045) remained significant even after adjustment. The adjusted EQ-5D-5L disutility increased to 0.057 (P = .005).

The structural model, presented in Figure 2, fitted with the abovementioned stricter definition of SubHypo (Table 3; model 6), has comparable performance to the original structural model 4: the likelihood ratio test (P = .243), the coefficient of determination (0.158), RMSEA (0.039), and the comparative fit index (0.979). Mediation analysis shows that 56% of the effect of SubHypo is mediated by anxiety (the Monte Carlo test P = .020 indicates complete mediation).

Mapping EQ-5D and ThyPRO-39

Various disease-specific QoL measures are used in clinical trials focused on thyroid disorders[25]; unfortunately, few have also collected generic measures allowing estimates of the utility value,[26] a key input for the economic evaluation of diagnostic and/or treatment interventions. For readers encountering this obstacle, we provide a full specification of several regression models (Table 4) that allow to generate EQ-5D utilities when only ThyPRO-39 scores have been collected.

We used ThyPRO-39 domains/symptoms along with patient characteristics to identify the relevant variables in a simple linear regression (model 1, Table 4). Because of the collinearity between the individual ThyPRO-39 domains and the composite

Table 3. Development of the structural model.

No.	Model 1 (structural)				Model 2 (OLS)		Model 3 (OLS)	
Model description	SubHypo → symptom		symptom → EQ-5D		→ Anxiety		→ EQ-5D	
ThyPRO-39 scores	coef	*P* value	coef	*P* value	coef	*P* value	coef	*P* value
Goiter symptoms	0.089	.167	−0.135	.037				
Hyperfunction symptoms	0.103	.109	−0.087	.264				
Hypofunction symptoms	0.131	.040	−0.047	.511				
Eye symptoms	0.220	.000	0.057	.431				
Tiredness	0.159	.012	−0.114	.173				
Cognition	0.161	.011	0.077	.339				
Anxiety	0.263	<.001	−0.319	<.001			−.003	<.001
Depression	0.150	.018	0.014	.852				
Emotional susceptibility	0.150	.018	−0.054	.500				
Social life impairment	0.109	.091	−0.056	.435				
Daily life impairment	0.040	.542	−0.151	.046				
Cosmetic complaints	0.105	.102	−0.116	.063				
Constant term					29.9	.153	0.626	<.001
SubHypo					8.27	.001		
Age					0.21	.352	0.001	.255
TPO-Ab positivity					−2.25	.308	−0.003	.803
Week of pregnancy					0.03	.860	−0.003	.006
Primiparous					−1.20	.602	−0.006	.672
Assisted reproduction					−4.66	.275	−0.038	.157
Other medical condition					6.01	.070	−0.031	.138
Education category					1.23	.567	0.009	.499
Positive smoking history					−0.46	.842	0.033	.023
Current smoker					1.55	.750	0.025	.413
Current alcohol consumer					2.89	.444	0.029	.219
Happy to be pregnant					−5.66	.602	0.182	.008
Financially or socially distressed					16.8	.009		
Good friends					−24.7	.006		
Good family					2.13	.845	0.109	.118
Weekly physical activity					0.62	.201	0.003	.385
Coefficient of determination	0.221				0.10		0.26	
RMSE	0.230				14.9		0.09	
Likelihood ratio test	<0.001							
Comparative fit index	0.134							
Akaike information criterion	22 194				1811		−400	

Note. When building the structural model, our aim was to capture the relationships between individual symptoms and patient characteristics along with their impact on the generic quality of life. We did not consider the ThyPRO-39 composite score and the overall impact because these represent a multifactorial construct—a sum of individual symptoms and may mask their individual contribution. We report standardized coefficients for structural models because they reflect the effect size.
→ indicates "predicts"; coef, coefficient; OLS, least squares regression; RMSE, root mean squared error; SubHypo, subclinical hypothyroidism; TPO-Ab, thyroid peroxidase antibodies.

score, we additionally tested these separately (model 2 and model 3, Table 4) to find the set of candidate variables (model 4) to which we add one symptom of ThyPRO-39 "upset stomach" and remove those that are not expected to be routinely collected (model 5). More details on individual steps in model development can be found in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015. To improve the fit on the collected data, we used the final predictors (model 5) to predict EQ-5D utilities via beta (model 6), tobit (model 7) and two-part (model 8) regressions. Although these approaches allowed us to avoid prediction of utility above 1 (7% in OLS vs 0% in beta, tobit, and two-part

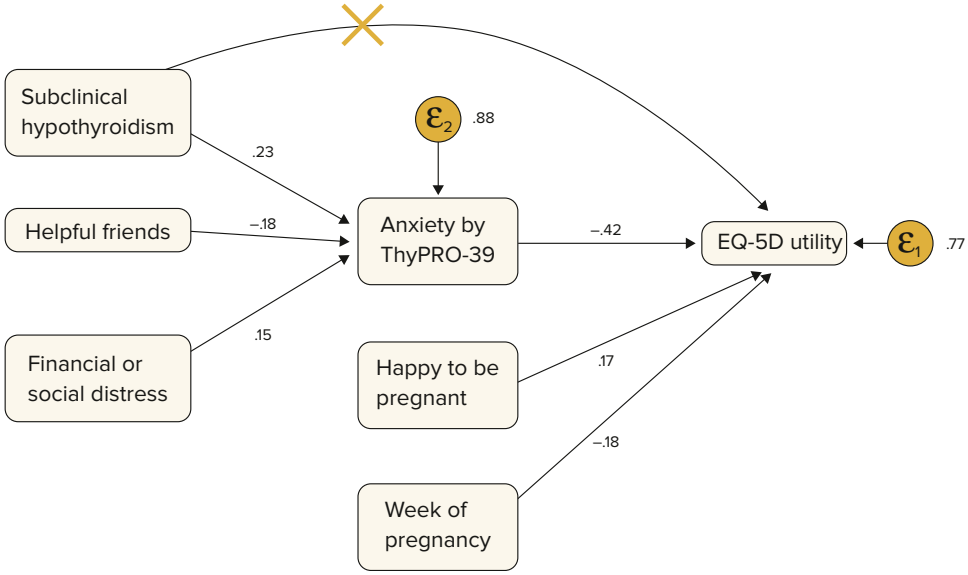
Table 3. Continued

Model 4 (structural)				Model 5 (structural)				Model 6 (structural)			
→Anxiety		→EQ-5D		M4 with direct effect SubHypo→EQ-5D				M4 with alternative definition of SubHypo			
				→Anxiety		→EQ-5D		→Anxiety		→EQ-5D	
coef	*P* value	coef	*P* value	coef	*P* value	coef	*P* value	coef	*P* value	coef	*P* value
		−0.418	<.001			−0.141	<.001			−0.424	<.001
2.37	<.001			2.37	<.001			2.56	<.001		
0.227	<.001			0.227	<.001	−0.015	.803	0.185	.012		
		−0.181	.002			−0.182	.002			−0.184	.001
		0.173	.003			0.172	.003			0.170	.003
0.152	.014			0.152	.014			0.155	.013		
−0.185	.003			−0.185	.003			−0.202	.001		
0.182				0.182				0.158			
<0.001				0.026				0.039			
0.457				0.329				0.243			
1.000				0.993				0.979			
2236				2238				2183			

regressions), they did not significantly improve the determination coefficients and did not have the capacity to utilize the information coming from the ThyPRO-39 Anxiety or Composite score and the FT4. With that in mind and for the sake of straightforward usage, we used model 5 (OLS) to derive the final mapping equation:

$$\text{EQ}-5\text{D Utility(predicted)} = 1.168 - 0.0017 \times (\text{ThyPRO}-39\ \text{Goiter symptoms}) - 0.0017 \times (\text{ThyPRO}-39\ \text{Anxiety}) - 0.0017 \times (\text{ThyPRO}-39\ \text{Composite}) - 0.0209 \times (\text{ThyPRO}-39\ \text{Upset stomach}) - 0.0076 \times (\text{FT4 [pmol/L]}) - 0.0039 \times (\text{week of pregnancy})$$

Figure 2. Path analysis. We used structural equation modeling to explain underlying relationships between individual constructs (e.g., anxiety or quality of life) and to test mediation, that is, to identify pathways in which an independent variable influences the mediator variable, which, in turn, influences the dependent variable. The final model showed ThyPRO-39 anxiety, week of pregnancy, and "being happy to be pregnant" to be strong predictors of EQ-5D utility. Squares represent individually measured constructs, and circles represent error terms (ε; the amount of variation unexplained by the model: 77% of utility and 88% of anxiety). Standardized coefficients (numbers above the arrows; divided by the variance) represent the strength of association on a scale of 0 to 1, hence, all associations presented are medium-to-weak. A negative coefficient indicates an inverse association; for instance, increasing anxiety is associated with decreasing quality of life. To predict the 2 constructs, the following equations based on nonstandardized coefficient should be used:



EQ-5D utility (predicted) = 0.803 + 0.200 × happy to be pregnant (yes/no) − 0.0029 × (ThyPRO-39 Anxiety) − 0.0031 × (week of pregnancy)ThyPRO-39 Anxiety (predicted) = 37.6 − 25.5 × helping friends (yes/no) + 14.9 × financial distress (yes/no) + 8.1 × subclinical hypothyroidism (yes/no)The mediation analysis (that is, the comparison of direct and indirect effects) suggests that 86% of the effect of subclinical hypothyroidism on the quality of life was mediated via anxiety (axis subclinical hypothyroidism→anxiety→quality of life). Additional testing confirmed that, apart from anxiety, there were no other ways that subclinical hypothyroidism affected the quality of life (crossed arrow). EQ-5D-5L indicates 5-level version of EQ-5D.

Of note, the coefficients presented are only transferrable to populations comparable with the present sample, that is, pregnant euthyroid and women with SubHypo.

For those keen to elaborate more on this matter, we made the original dataset available in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015.

Discussion

To date, none have described the QoL of those with SubHypo during pregnancy. Our adjusted comparative analysis shows that this condition is associated with a slight but measurable decrease in the QoL. Statistically significant disutility can be assessed with a generic tool (EQ-5D-5L), confirmed throughout several analyses even when adjusted to third factors. The clinical relevance of this difference remains a matter of discussion, and we can argue that it is rather the specific symptoms that add a piece of evidence to the everyday practice of a gynecologist or endocrinologist.

Previous Coretti's[27] literature review focused on the minimal clinically important difference in the EQ-5D utility and concluded that the lower range reported in the literature was 0.03. This places our estimate of 0.04 on the edge of clinical relevance. On the other hand, the generic QoL estimates provides a vital input for the decision analytic modeling, because they allow to characterize the individual health states. This is of particular importance, notably when building cost-effectiveness models for thyroid screening programs. Interestingly, our estimate of utility (0.89) was not very different from values reported in nonpregnant women (0.87)[28] but was lower than the expert estimates used in previous economic models (0.9 and 1.0).[29] Nonetheless, the true impact of our utility estimates can be assessed only when updated models are constructed.

In addition to generic QoL, a disease-specific QoL questionnaire (ThyPRO-39), which is likely to be much more sensitive than EQ-5D, showed that specific SubHypo symptoms were more prevalent and more pronounced compared with euthyroid women during pregnancy. Interestingly, these symptoms differ from those consensually attributed to hypothyroidism (Table 2), notably depression.[11] In our cohort, pregnant women with SubHypo showed significantly increased scores relative to eye symptoms, decreased cognition, and increased anxiety; yet, only anxiety affected their overall well-being.

Although increased plasma TSH levels define SubHypo, there has been a lack of local and global consensus on the ranges used for reference.[5] Practice guidelines provide indicative diagnostic criteria; yet, population-derived reference ranges, if available, should be preferred over universal values.[12,30,31] For the sake of the generalizability of our conclusions, we used the universal values proposed by ETA[12] in the primary analysis. Additionally, we tested whether our results still hold under an alternative definition of hypothyroidism. We used stricter diagnostic criteria for the sensitivity analysis to divide our cohort into euthyroid and

SubHypo. Using reference ranges derived from the Czech cohort of pregnant women[23] instead of the universal values proposed by ETA,[12] only 60% (37/61) of women were considered hypothyroid compared with the primary analysis. Nevertheless, we still managed to show a measurable difference in the QoL and confirm the principles indicated by the path analysis. Our general finding (not the effect size) seems partially independent of the reference ranges used.

Unlike the EQ-5D-5L questionnaire, which contains a single question for both anxiety and depression, the ThyPRO-39 calculates the anxiety score based on the answers to 3 specific questions (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015). The coefficients presented in Figure 2 indicate that part of the generic QoL was negatively influenced by ThyPRO-39 anxiety. Also, we observed that SubHypo was the most substantial contributor to the anxiety scores. Even more importantly, in our mediation analysis, SubHypo does not significantly affect the generic QoL in ways other than through anxiety. These observations suggest the important role of anxiety as a mediating factor of disutility resulting from SubHypo. Nevertheless, it should be noted that structural equation modeling remains a statistical framework; thus, any relationships between individual constructs should be perceived as associations rather than proofs of causal relationships, notably in a cross-sectional setting. Also, it must be noted that most (77%) of the generic QoL and most of the observed anxiety (88%) could not be explained by our model. Such amount of residual variance points at latent factors that may be in play.

Although this study provides a starting point for future research, it is subject to several limitations. First, hormonal balance undergoes dynamic changes during pregnancy, notably in the first trimester.[32] A shortcoming of our data collection is that about one-half of the subjects could not precisely report the time of therapy initiation. Nevertheless, we adjusted the analyses to the available answers using multivariable regression, which did not affect the difference in outcomes between patients with SubHypo and the euthyroid (data not shown).

Another shortcoming of our data collection was that we could not establish the effect of hormonal substitution. Although women with SubHypo reported receiving hormonal substitution more often (7.5% vs 36.1%), they could not precisely report the time of therapy initiation; that is, we could not ascertain whether the therapy was initiated based on the index test results or before the index test results; there were many incomplete or missing responses. For example, only 20 women answered the question "to what extent (0 to 100) does hormonal substitution affect your daily life," showing a mean impact of 11.9 ± 18.5, which can be considered negligible. Notably, a previous meta-analysis[33] showed that among nonpregnant adults with SubHypo, the use of thyroid hormone therapy was not associated with improvements in the general QoL or thyroid-related symptoms even after 18 months of hormonal substitution. Extrapolating Feller's conclusion[33] to our cohort of pregnant women, it seems unlikely that hormonal substitution indicated after the index test results would have influenced the QoL of those who put off completing the questionnaire by up to several weeks. Inversely, long-standing hormonal substitution that started before conception is reflected in the TSH and FT4 levels measured and hence, accounted for in our analysis.

During our data collection, women reported their blood test results online based on the medical report they obtained from their treating physician. A third, most important limitation of the study was that women were not blinded to test results, and some may have become aware of their new diagnosis, that is, SubHypo, because it was indicated in their medical records. Therefore, we cannot rule out that, for some, the QoL assessment might have been affected by this new information (a self-reporting bias). In roughly one-half of the questionnaires, data entry was not done directly in the gynecological outpatient clinic, and the women filled questionnaires from home. It cannot be excluded that women confronted with the new diagnosis might have searched other sources for information on thyroid disease and found a list of typical symptoms, which could have biased their answers. This limitation, however, could not be avoided by blinding toward the test results because of ethical reasons. Moreover, our study design reflects the real-world setting, because, in the common practice, the patient would also not be blinded. We believe that, if any disutility is related to the screening procedure per se, this should be reflected by the decision analytic procedure, meaning that our unblinded estimates can be effectively used for future cost-utility modeling.

The last limitation, the prevalence of SubHypo in our cohort, can seem high (26%). Although this may indicate that patients with SubHypo with significant symptoms affecting the QoL were more likely to take the survey, we believe that rather those who received results deemed positive by the laboratory decided to complete the survey irrespective if symptomatic or not. Moreover, the review by Dong et al[1] showed a prevalence ranging between 1.5% and 42.9%. Furthermore, of 25 studies using the American Thyroid Association 2011 reference ranges[34] comparable to our definition, 3 studies had comparable and 5 had an even higher prevalence.[1] In light of this literature review, our prevalence does not seem that outstanding.

An essential strength of our study was the primary data collection that assessed a wide range of confounding factors that allowed us to more accurately evaluate the actual effect of subclinical thyroid hypofunction on the overall QoL. Of particular note was that our utility estimate from euthyroid pregnant women differed, meaningfully, from those previously used[29]; thus, we believe that an update of current economic modeling is worth considering.

Our second aim was to develop mapping equation allowing to predict EQ-5D utilities in which only ThyPRO-39 scores are available. We chose 6 variables: 3 domains and 1 subscore from ThyPRO-39, the level of FT4, and the week of pregnancy. With residual variance of about 60%, this is not a particularly strong model. One-half of patients reported utility = 1 (Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.02.015), which we hoped to tackle using two-part regression.[24] Against expectation, the advanced models did not provide better explanatory power than OLS. Having tested numerous linear and 3 nonlinear models, we believe to have made the best possible use of the source data. The limited sample size thus remains the largest limitation.

Mapping in pregnant women is very rarely done and in the few published reports,[35,36] a large portion (56%-89%) of EQ-5D utility variance remains also unexplained. After all, we believe to have brought a piece of evidence, because, at this point, our mapping is the only one available. In future projects, we suggest to analyze panel observations by multilevel models, which may allow quantification and adjusting for the intraindividual variance.[37]

Table 4. Multivariate regression models predicting the EQ-5D utility (mapping).

	Model 1 OLS		Model 2 OLS		Model 2 OLS		Model 3 OLS	
ThyPRO-39 scores	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Goiter symptoms	−0.0017166	.051	−0.001733	.045				
Hyperfunction symptoms	−0.0011233	.119	−0.0007758	0.281				
Hypofunction symptoms	−0.0000405	.942	−0.0003443	0.522				
Eye symptoms	0.0011315	.286	0.0007837	0.447				
Tiredness	−0.0021433	.226	−0.0005645	0.187				
Cognition	−0.0007118	.748	0.0006073	0.360				
Anxiety	−0.0034813	.054	−0.0020331	<0.001				
Depression	−0.0015859	.414	0.0000991	0.856				
Emotional susceptibility	−0.0019389	.343	−0.0003414	0.511				
Social life impairment	−0.0016717	.195	−0.000462	0.449				
Daily life impairment	−0.0015088	.251	−0.0009739	0.055				
Cosmetic complaints	−0.0013568	.046	−0.0011953	0.074				
Composite score	0.010578	.392			−0.0047585	<.001		
Overall impact on the QoL	−0.0014214	.307						
Upset stomach								
Age, years	0.0003312	.818					0.0006113	.698
TSH, mIU/L	−0.0011979	.792					−0.0063372	.207
FT4, pmol/L	−0.008704	.013					−0.0055037	.159
TPO−Ab positivity	0.0017267	.899					0.0082736	.592
Week of pregnancy	−0.0032553	.003					−0.0029218	.015
Primiparous	−0.0111324	.426					−0.003819	.807
Assisted reproduction	−0.0336816	.200					−0.0228821	.441
Other medical condition	−0.017536	.408					−0.0486324	.034
Education category	0.0097289	.465					0.0060605	.684
Positive smoking history	0.0392181	.007					0.0326088	.043
Current smoker	0.0173278	.562					0.0176786	.599
Current alcohol consumer	0.0066534	.779					0.0174871	.504
Happy to be pregnant	0.0997406	.162					0.1931224	.011
Financially or socially distressed	0.001347	.975					−0.0894311	.042
Good friends	0.0661152	.243					0.1591673	.010
Good family	0.1014332	.130					0.1031506	.172
Weekly physical activity	0.0006809	.823					0.0008543	.797
Constant term	0.872	<.001	1.010	<.001	1.00	<.001	0.548	.001
R^2 observed vs predicted	0.432		0.312		0.274		0.186	
Adjusted R^2	0.337		0.275		0.244		0.1163	
Akaike information criterion	−407		−437		−437		−357	
MSE observed vs predicted	0.007		0.008		0.009		0.010	
% utilities predicted above 1	8.7%		0.4%		0.4%		0%	

Note. We used a simple OLS to identify variables with the potential to predict the EQ-5D utility (ie, having *P* value of the coefficient from the multiple regression below .05). We excluded variables that were not significant predictors and those that did not improve the determination coefficient. Final selection of covariates was tested in OLS (model 5), beta (model 6), tobit (model 7), and two-part regressions (model 8) with the aim to predict coefficients to build the most explanatory mapping equation. Of note, the nonlinear models did not have the capacity to utilize the information coming from the ThyPRO-39 Anxiety or Composite score and the FT4, leaving it a nonsignificant predictor. With respect to determination coefficient, and also the simplicity of interpretation, we choose linear model 5 to derive the final mapping equation.

FT4 indicates free thyroxine; MSE, mean squared error; OLS, ordinary least squares regression; QoL, quality of life; TSH, thyroid stimulating hormone.

*For the purpose of beta regression, the utility was transformed by subtracting 10^{-6} from the original values.

†For the purpose of two-part regression, the utility was transformed by subtracting 1 from the original values and multiplying by −1.

Conclusion

Our analysis is novel in 4 ways: first, it provides the first Czech translation of the ThyPRO-39 questionnaire; second, it is the first use of the ThyPRO-39 in pregnant women; and third, it is the first use of the EQ-5D-5L and ThyPRO-39 during pregnancy and the first evidence that SubHypo in pregnancy is associated with a decrease in the QoL. Our results strongly suggest that specific symptoms characterize SubHypo and that its impact on the QoL during pregnancy is mediated by anxiety. The main limitation of

Table 4. Continued

Model 4 OLS		Model 5 OLS		Model 6 beta*		Model 7 tobit		Model 8 two-part†			
Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value	Coef (logit)	*P* value	Coef (OLS)	*P* value
−0.0023077	.004	−0.0016585	.035	−0.0292447	.001	−0.0033706	.030	0.056111	.012	−0.0003215	.619
−0.0025034	<.001	−0.0017125	.002	−0.0171422	.009	−0.0030294	.009	0.0300707	.055	0.0009847	.056
		−0.0017184	.046	−0.0114044	.218	−0.0030845	.080	0.0533102	.050	0.0006268	.446
		−0.0209329	<.001	−0.1679021	.026	−0.0382223	.002	0.3805721	.013	0.0142439	.008
−0.0084491	.011	−0.0076313	.018	−0.0658749	.108	−0.0168939	.014	0.1939709	.026	0.0039872	.197
−0.0031772	.002	−0.0039478	<.001	−0.0302941	.007	−0.0071173	<.001	0.0649288	.011	0.0031289	.001
−0.030011	.135										
0.0208923	.094										
0.1572887	.019										
−0.0307219	.433										
0.0802517	.147										
0.887	<.001	1.168	<.001	0.741 (4.917)	<.001	1.509	<.001	−6.129 (0.041 nonsignificant)			
0.320		0.364		0.310		0.361		0.390			
0.291		0.347		NA		0.563		0.221 (0.236)			
−424		−447		−2946		82		−17			
0.008		0.008		0.009		0.008		0.007			
0.8%		7.0%		0%		0%		0%			

our conclusion is potential confounding by the knowledge of the diagnosis.

Utility values for future economic modeling can be generated using the mapping equation presented.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2023.02.015.

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