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Iodine Sufficiency during Pregnancy in Latvia

Summary of the Doctoral Thesis for obtaining the scientific degree "Doctor of Science (*PhD*)"

Sector – Medical and Health Sciences

Sector – Clinical Medicine

Sub-Sector – Obstetrics and Gynaecology

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Abbreviations used in the Thesis

ALSPAC	Avon Longitudinal Study of Parents and Children
Anti-TPO	thyroid peroxidase antibodies
ATA	American Thyroid Association
CDPC	Centre for Disease Prevention and Control of Latvia
CI	confidence interval
CM	Cabinet of Ministers
CNS	central nervous system
Cr	creatinine
EPIC	European Prospective Investigation into Cancer and Nutrition
FAO	Food and Agriculture Organization of the United Nations
FT4	free tetraiodothyronine
GPX	glutathione peroxidase
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
IQ	intelligence quotient
IQR	interquartile range
LH	luteinising hormone
OR	odds ratio
SC	schoolschildren
SD	standard deviation
SE	standard error
SEPP	selenoprotein P
TPO	thyroid peroxidase
TSH	thyroid-stimulating hormone
T3	triiodothyronine
T4	tetraiodothyronine
UIC	urine iodine concentration

UNICEF	United Nations Children's Fund
USA	United States of America
USI	universal salt iodisation
WHO	World Health Organization

Introduction

“Every child has the right to an adequate supply of iodine to ensure his (or her) normal development.”

“Every mother has the right to an adequate iodine nutrition to ensure that her unborn child experiences normal mental development.”

These are Declarations emanating from the Convention on the Rights of the Child, United Nations Assembly, New York, 1989; World Summit for Children, United Nations, New York, 1990: Declaration for the Survival, Protection and Development of Children; World Conference on Micronutrients: Eliminating Hidden Hunger, Montreal, 1991, UNICEF, WHO, FAO, ICCIDD; World Conference on Nutrition, Rome, 1992, WHO, FAO. They clearly highlight the significant consistency of disruptions caused by iodine deficiency and calls on countries to organise and implement initiatives to ensure sufficient supply of iodine to the population. (1)

Universal salt iodisation (USI) is a key strategy recommended by the World Health organization (WHO) to prevent the iodine deficiency that has been successfully implemented in many countries over the past 25 years. The number of households using iodised salt has increased from 20 % in 1990 to 70 % in 2000 and to 88 % in 2019 worldwide. (2) In parts of Asia, Africa and South America, the United States of America (USA), the iodine deficiency has been effectively alleviated, but in many regions around the world, including Europe, iodine intake in the population remains insufficient. (3,4) It is estimated that in Europe up to 70 % of women during pregnancy have decreased iodine intake than recommended, as most European countries do not have mandatory USI programme and use of iodine-enriched salt in households is voluntary. (5)

Globally, iodine deficiency is the next most common cause after starvation, leading to potentially preventable brain damage. Although severe iodine deficiency and consequences in certain areas of the world has been eradicated, about a quarter of the planet's population is still exposed to the development of disruptions caused by different spectrum of iodine deficiency. Developmental deficiency of central nervous system (CNS), which is irreversible after birth, is the most common consequence of iodine deficiency during pregnancy and its elimination is an important aim to be achieved with sufficient iodine supply in the population. (6)

The iodine is essential micronutrient for production of thyroid hormones. During pregnancy, normal secretion of thyroid hormones and transplacental transmission are essential for foetal brain development. Thyroxine (T4) can be detected in the foetal celomic fluid from 6 weeks of pregnancy onwards, and maternal FT4 is crucial for foetal demands until mid – pregnancy, when hormone synthesis is enhanced in the foetal thyroid gland. Thyroid hormone receptors are present in foetal brain cells even before foetal thyroid function begins, and maternal thyroid hormones in the first trimester are essential for differentiation and myelination of oligodendrocytes, as well as proliferation and migration of neurons. (5)

Demands of iodine increases by 50 % during pregnancy in association with more intensive maternal thyroid hormone synthesis, increased urinary iodine excretion and transplacental transfer of iodine for foetal hormone synthesis. In circumstances of iodine deficiency, T4 production is restricted to save resources of iodine, meanwhile T3 synthesis is enhanced, resulting in maternal hypothyroxinemia. Thyroxine is the main transplacental circulating maternal hormone and reduced T4 secretion plays a significant negative role in foetal development, especially in the CNS.

Research conducted in recent decades reveals a link to mild and moderate iodine deficiency during pregnancy and persistent changes in a child's neurocognitive development after birth – reduced memory capacity, learning, reading and language difficulties, for 6–7 point reduced intelligence ratio (IQ).

The iodine deficiency during pregnancy is attributed to the development of autism spectrum disorders, attention deficit and hyperactivity syndrome. (7)

The mandatory USI has not been implemented in Latvia and the use of iodised salt in households is voluntary. One of the indicators to measure iodine sufficiency in population is median urinary iodine concentration (UIC) in schoolchildren (SC). In a cross-sectional study conducted in Latvia in 2000, the median urinary iodine among SC (n 587) was 59 µg/l, which confirms the moderate iodine deficiency in the population. Another significant indicator of population iodine supply, newborn's TSH screening, also indicates mild iodine deficiency – in 2000, the proportion of new-born infants with TSH > 5 mIU/L was 16.5 %. (8)

Later study in 2009 and 2010 revealed the seasonal difference of iodine sufficiency among SC – mild iodine deficiency was observed in spring when measured median UIC was 78.3 µg/g Cr, whereas median UIC in autumn was 129.7 µg/g Cr, confirming sufficient iodine intake among SC. The median UIC, excluding seasonal differences, was 107.3 (IQR 69.1–161.7) µg/g Cr. According to this indicator, in 2013, the International Council for the Control of iodine deficiency disorders (ICCIDD) ranked Latvia among the countries with no formal iodine deficiency. Meanwhile, the register of newborn's TSH in 2009 and 2010 still confirm mild iodine deficiency. (9, 10)

Particularly vulnerable part of the population in mild to moderate iodine deficiency regions are pregnant women – demand of iodine significantly increases already in first weeks of pregnancy. Thus, sufficient intake of iodine during pregnancy is particularly important not only in individual terms, but also affects the national social and economic development – lower intelligence quotient (IQ) is related to decreased learning capacity and lower educational levels, hence lower income and welfare. Therefore, appropriate recommendations and strategies to prevent iodine deficiency during pregnancy demand special attention. (11)

Aim of the Thesis

1 To evaluate iodine sufficiency among pregnant women in Latvia.
2 To assess whether information activities carried out among health care professionals and society after results of study performed in 2013, is associated with improved iodine sufficiency during pregnancy in Latvia.

Tasks of the Thesis

1 Determine iodine sufficiency among pregnant women in Latvia using two relevant indicators – median UIC and newborn's TSH data.
2 Analyse dietary habits regarding iodine and selenium rich product consumption and use of iodine and selenium containing supplements during pregnancy and the impact on iodine sufficiency.
3 Assess whether informing activities carried out among healthcare professionals and society emphasizing importance of iodine supply have improved iodine sufficiency during pregnancy in Latvia within 5 years.
4 Determine whether iodine sufficiency, iodine supplementation affect thyroid function, organ-specific autoimmunity, as well as serum selenium levels.

Hypotheses of the Thesis

1 Iodine intake during pregnancy is not sufficient in Latvia.
2 After implemented recommendations, consumption of iodine rich products and iodine containing supplements increases and iodine sufficiency during pregnancy improves.
3 Sufficiency of selenium among pregnant women in Latvia is not optimal.

Novelty of the Thesis

Mild to moderate iodine deficiency has been estimated in Latvia, based on previous studies of median UIC among SC and newborn's TSH data, nevertheless iodine sufficiency during pregnancy has not been studied in Latvia.

The USI recommended by WHO as the most effective strategy to prevent iodine deficiency, has not been implemented in Latvia. Consequently, the hypothesis, that during pregnancy, when iodine demand increases, iodine deficiency persists and potentially negative effect on neurocognitive development and permanently reduces intellectual potential for each next generation, remains relevant.

In absence of mandatory USI, dietary recommendations regarding consumption of iodine rich products and supplements are crucial for optimal iodine intake. National recommendations for iodine intake during pregnancy has been published and various information activities for health care professionals and society emphasizing importance of iodine during pregnancy have been carried out in recent years. Therefore, it is important to assess whether the existing strategy is safe and effective and whether it has improved iodine sufficiency among pregnant women in Latvia.

The supply of selenium, which plays an important role in the pathogenesis of autoimmune thyroid processes, has not been studied among pregnant women in Latvia so far.

However, iodine intake has a U-shaped effect – both very high and low concentrations can be harmful. The higher iodation of thyroglobulin is associated with higher autoantigenicity whereas selenium as a cofactor of selenoenzymes may reduce autoimmune reactions. Therefore, the detection of serum selenium levels is important aspect in context of thyroid autoimmunity and iodine intake. Until now serum selenium during pregnancy in Latvia has not been evaluated.

1 Materials and methods

1.1 Structure of the study

The study consists of three parts:

1) Sufficiency of iodine and its association with thyroid function during pregnancy in different regions of Latvia in 2013.
2) Sufficiency of iodine and selenium during the first trimester of pregnancy in 2018.
3) Iodine intervention study in pregnant women in 2018.

The latter two parts are interconnected: measurements of serum selenium were carried out in pregnant women in the iodine intervention study during the first trimester in addition to the determination of dietary habits, thyroid parameters and UIC (Figure 1.1).

The author's contribution – during the first study Vija Veisa, ensured communication with regional doctors, organised collection and delivery of questionnaires, consent forms, urine samples to coordination site of the study. In the second and third studies, Vija Veisa created study protocol and information material for study participants about the importance of iodine intake during pregnancy, organised study and control groups. Also, the delivery of urine and serum samples to laboratories, data collection, processing, analysis and interpretation was carried out by the author.

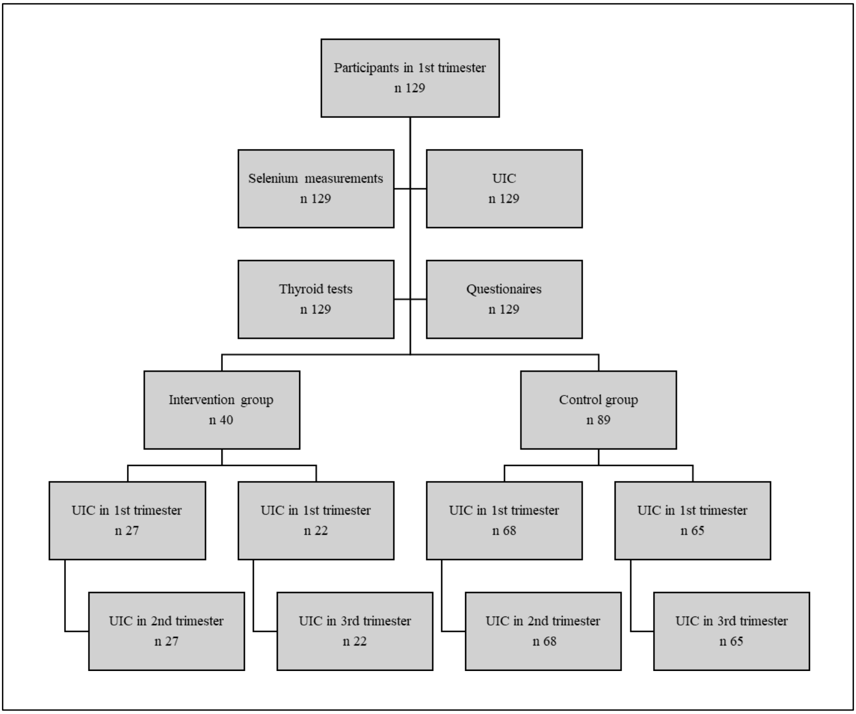

Figure 1.1 **Inclusion of participants in the studies "Sufficiency of iodine and selenium during the first trimester of pregnancy" and "Iodine intervention study in pregnant women", 2018**

1.2 Inclusion of participants in the study

1.2.1 Sufficiency of iodine and its association with thyroid function during pregnancy in different regions of Latvia in 2013; I study

To obtain results that could be extrapolated to all pregnant women in Latvia, a twenty-cluster survey was performed in all regions of Latvia during the spring and autumn seasons in 2013, with at least twenty women per cluster (Figure 1.2).

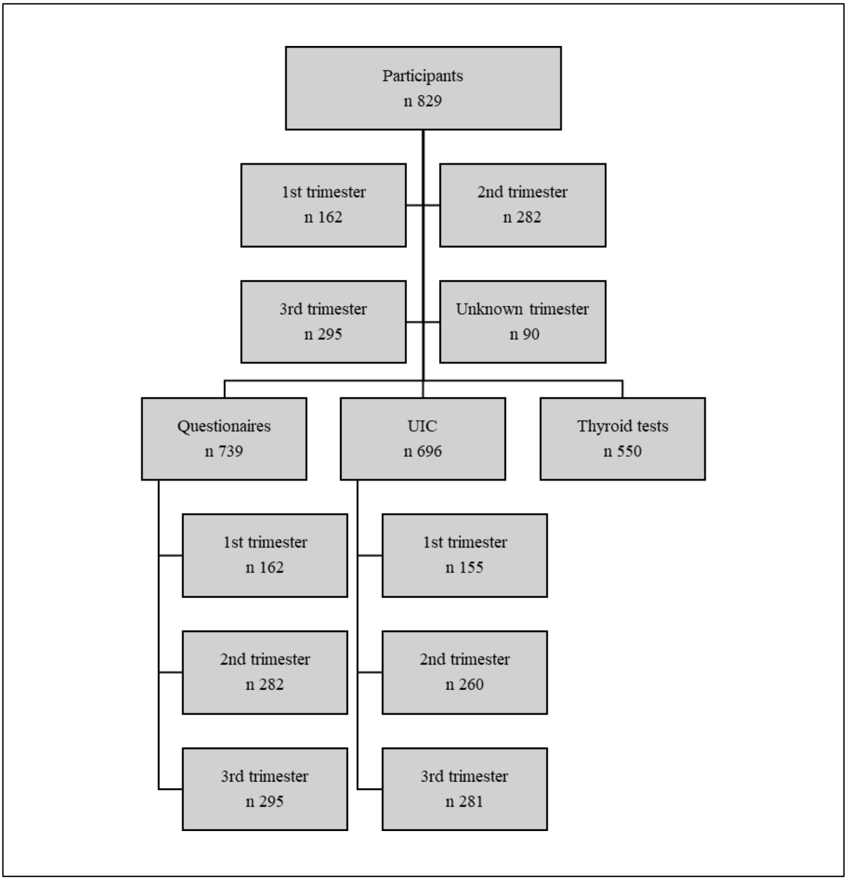

Figure 1.2 **Inclusion of the participants in the study "Sufficiency of iodine and its association with thyroid function during pregnancy in different regions of Latvia in 2013"**

Sample size calculation was based on an estimated 70.4 % prevalence of UIC < 150 µg/l, a 95 % confidence interval (CI), a design effect of 2 and an absolute precision 5 %, resulting in a total sample size of 642 women. This prevalence figure was based on a population survey among Latvian schoolchildren. (10)

After receiving a detailed explanation from the study doctor (or midwife), the study participants independently completed a questionnaire concerning the use of iodine supplements and the consumption of seafood, dairy products and iodised household salt, as well as smoking history, previous thyroid diseases and parity. From each participant a single blood sample (for FT4, TSH, anti-TPO testing) and morning urine sample (for urinary iodine measurement) were collected for laboratory tests.

1.2.2 Sufficiency of iodine and selenium during the first trimester of pregnancy in 2018; II study

The study consists of two parts:

1 **Urinary iodine, serum selenium and thyroid function measurements during first trimester.**

Pregnant women without any health problems were recruited at three different outpatient medical institutions in Riga at the beginning of antenatal care. Overall, 129 women were enrolled in the first trimester of pregnancy during their first antenatal visit (week 6–9), and their serum selenium and serum selenium protein levels, UIC in morning urine sample, thyroid function, and anti – TPO levels, which are indicative of autoimmune processes, were measured. To determine dietary iodine sources, women were asked to complete the questionnaire concerning the use of iodine/selenium supplements and the consumption of seafood, dairy products and iodised household salt, as well as smoking history, previous thyroid diseases and parity.

2 **Analysis of iodine and selenium containing products consumption among reproductive age (15–49) women in the general population of Latvia.**

Iodine and selenium sufficiency in early pregnancy largely depends on dietary habits before pregnancy. Therefore, analysis of secondary data from the population study of the Centre for Disease Prevention and Control (CDPC) about use of iodine and selenium-containing food products among women of reproductive age has been carried out.

This part of the study was estimated from health survey data. The Health Behaviour Survey among the Latvian Adult Population is a population-based survey that has been repeated every two years since 1998 (from 1998 to 2008, a collaborative project of the Finbalt Health Monitor). In 2010, the method of data collection was changed from a postal survey with self-administered questionnaires to face-to-face interviews; therefore, we included surveys from 2010 to 2018 in our data analysis. The representative sample from the general population aged 15–64 (surveys 2010–2014) or 15–74 (surveys 2016 and 2018) was selected using stratified random multistage sampling. Sample size estimates and stratification by age, sex, region and urbanization were based on the latest available population data provided by the Central Statistical Bureau of Latvia. After random selection of initial interview points, the random route procedure and quota method were used. For purposes of our study, we restricted analysis of survey data to the reproductive age women (from 15 to 49 years).

1.2.3 Iodine intervention study in pregnant women in 2018; III study

In 2018, pregnant women who started antenatal care at 6–9 weeks' gestation at Riga Maternity Hospital, I. Katlapa's Medical Practice and Health Centre 4 were invited to participate in the study. Women with a history of thyroid disease were not included. Pregnant women attending the Riga Maternity Hospital were given 150 µg iodine-containing supplements in tablet form for daily use throughout pregnancy.

Pregnant women in the control group were observed in I. Katlapa’s Medical practice and Health Center 4, routine dietary recommendations regarding iodine rich products, iodised salt were provided to them, but no free iodine supplements were handed out.

To analyse consumption of iodine-containing products, women completed a questionnaire about dietary habits, use of dietary supplements at the start of the study, as well as during the second and third trimesters of pregnancy. In both oral and written form, all women were provided with information about the importance of iodine use during pregnancy, as well as iodine-containing foods. At the start of the study and during the second and third trimesters of pregnancy, morning urine samples for iodine testing were collected, and serum testing of TSH, FT4 and anti-TPO was performed.

1.3 Laboratory measurements

1.3.1 Urinary iodine measurements

The measurement of urinary iodine concentration (UIC) was based on the Sandell-Kolthoff reaction. (12) In detail, 40 µL of urine samples were added to 160 µL of 1.0 M ammonium persulfate and heated for 60 min at 100 °C. The samples were cooled to room temperature, and 400 µL of arsenious acid solution (0.1 M in 0.5 M H2SO4) was added. The samples were mixed, and 200 µL of each sample was pipetted into a 96-well plate and allowed to stand for 15 min at room temperature. Then, 16 µL of ceric ammonium sulphate solution (0.15 M in 1.75 M H2SO4) was added to each sample and quickly mixed.

Absorption was measured at 405 nm after a 30 min incubation at room temperature using a µQuant™ Microplate Spectrophotometer (BioTek, Winooski, USA). In parallel, standard iodine solutions (concentrations of 300, 200, 150, 100, 50, 20, and 0 µg/l) were treated identically. To clarify so-called matrix effects, methods used for iodine level measurement were validated by preparing standard solutions of iodine using different matrices (water or a random urine sample). The standard curves created using water and urine as the matrix were identical, indicating that the method was accurate and that the matrix effect on urinary iodine measurements was low.

1.3.2 The urinary creatinine concentration

The creatine-standardised UIC was calculated as a more reliable measure than random spot UIC measurement considering the great day-to-day variability in water intake. (13)

The urinary creatinine concentration was measured using the Jaffe method so that the iodine concentration adjusted for the creatinine concentration (iodine/Cr) could be calculated. (14) Urinary iodine, creatinine measurements and standardisation of urine iodine and creatinine were performed at the Latvian Institute of Organic Synthesis.

1.3.3 Thyroid testing

Serum thyroid-stimulating hormone, FT4 and anti – TPO levels were measured by a chemiluminescence immunoassay (Siemens, Malvern, PA, USA), which was performed on an Advia Centaur XP (Siemens) analyser by the E. Gulbis Laboratory (Riga, Latvia), which operates according to EN ISO 15189 standards. In addition, through the EUthyroid project (a European Union-funded research project evaluating current national efforts aimed at preventing iodine deficiency disorders), urine and serum samples were re-analysed at the central EUthyroid laboratory in Helsinki to compare and harmonise UIC and serum TSH, FT4, and anti-TPO values with those obtained by other EUthyroid partner countries throughout Europe.

In the nationally representative pregnancy survey (2013), thyroid function (TSH to be specified) were evaluated based on the reference intervals recommended by the American Thyroid Association guidelines in 2011 (15): normal range for TSH during the first trimester was considered 0.1–2.5 mIU/L; 0.2–3.0 mIU/L in the second trimester; in the third trimester, 0.3–3.0 mIU/L, and anti-TPO 0–64 IU/ml.

In the next studies, the reference intervals were chosen according to American Thyroid Association guidelines published in 2017 and were, 0.4–4.0 mIU/ml for all trimesters. (16)

1.3.4 Serum selenium measurements

Serum Selenium measurements were performed in Scientific Laboratory of Biochemistry, Rīga Stradiņš university. The plasma selenium concentration was determined fluorometrically by using a "Cary Eclipse" fluorescence spectrophotometer (Varian, Inc., Houten, The Netherlands). Interlaboratory quality control was conducted by employing two standards – selenium AAS solution (Aldrich, St. Louis, MO, USA, Cat#24, 792–8) and Seronorm TE Serum Level I (Sero AS, Cat#201 405, Billingstad, Norway) – for the Seronorm™ Trace Elements-Controls Programme. External Quality Assessment Services were performed by Labquality Oy, Finland. Selenoprotein P (SEPP) concentrations were measured using a Spark® multimode microplate reader (Tecan Group Ltd., Mannedorf, Switzerland) by a validated commercial SELENOP-specific ELISA kit (Cusabio, Wuhan, China) for human cells and a Rat Selenoprotein P (Selenop) ELISA kit (Cusabio, Wuhan, China) according to the instructions of the supplier.

1.3.5 TSH screening for newborns

Neonatal TSH screening results from 2019 and 2022 in Children's Clinical University Hospital (Riga) have been used to evaluate neonatal TSH screening data as indicator of population iodine supply in Latvia.

Newborns TSH screening in Latvia is organised according to Regulations of Cabinet of Ministers (CM) No. 611 with focus to reveal sporadic hypothyroidism after birth. The heel-prick blood samples from newborns routinely are collected 48–72 hours after birth.

Fully dried filter paper cards are stored at room temperature between +18 °C and +25 °C until delivery to the laboratory. Blood samples dried on filter paper are tested by immunofluorescence (Labsystems Diagnostics Neonatal hTSH FEIA Plus) in Laboratory of Children's Clinical University Hospital.

1.4 Statistical analysis

The results are expressed as means and standard deviations (SD) or as medians and interquartile ranges (IQR) and as the percentage of participants in the study. Two-sided Student's t-test and the Mann-Whitney U test (or Kruskal-Wallis test) was used to compare UIC differences between the two subgroups. Differences in prevalence estimates were tested using the χ^2 test or Fisher's exact test, as appropriate. Pearson's or Spearman's correlation coefficients were calculated depending on the normality of the data. P values below 0.05 were considered statistically significant. For category type variables, the percentage and its 95 % confidence interval (CI) were calculated. Multivariate linear regression was used to analyse the factors associated with logarithmically transformed creatinine-standardised UIC, and multivariate logistic regression was used to analyse the factors associated with elevated TPO-Ab (>60 IU/ml). The odds ratio (OR) and its 95 % confidence interval were calculated from the logistical regression model. Only women with complete records were included in multivariate regression analyses. The compatibility of the study variable distribution with normal distribution was verified by Kolmogorov-Smirnov (Kolmogorov-Smirnov) and Shapiro-Wolf (Shapiro-Wilk) tests. The UIC between trimesters were compared with paired data from Wilcoxon's mark rank tests (Wilcoxon ignited rank test for paired samples). The proportion of iodine containing foods consumers was compared in trimesters to paired data from McNemar tests (McNemar test on Paired proportions). The data were analysed using the IBM SPSS 19·0 statistical software package and the Confidence Interval Analysis software.

1.5 Ethical Aspects and Permissions

All parts of the study were conducted according with international and national lows and regulations, Helsinki and Taipei declarations. Before starting the study, women were provided with patient's information and signed informed consent form to participate in the study.

The study protocols were approved by Ethical Committee of Rīga Stradinš University and Ethical Committee of Pauls Stradiņš Clinical University Hospital.

The Centre for Disease Prevention and Control is the owner of the fully anonymised population health survey data; the research datasets were prepared by the Centre staff and released to the researchers.

The 150 µg iodine-containing food supplements were specially produced for the study by the Latvian pharmaceutical company Lotos Pharma, which operates in accordance with the Codex GMP (Codex good manufacturing practice) certificate and quality certificate ISO 22000 and is registered in accordance with the requirements in Latvia.

2 Results

2.1 Sufficiency of iodine and its association with thyroid function during pregnancy in different regions of Latvia in 2013

Of the 829 pregnant women enrolled in the current study, 739 women completed the study questionnaire (Table 2.1). Of the 162 women in the first trimester of pregnancy at the time of evaluation, 50.3 % (n 81) reported regular use of any dietary supplements irrespective of iodine content. The percentage of women using supplements was 63.6 % (n 178) in the second trimester and 65.5 % (n 190) in the third trimester; both values were significantly greater than those of women in the first trimester who used supplements ($p = 0.006$ and $p = 0.002$, respectively). Only 3.1 % (n 5) of women used supplements containing ≥ 150 μg iodine in the first trimester. The percentage of women using these supplements was also significantly greater in the second trimester ($p = 0.008$), reaching 10.0 % (n 28), but the percentage was not significantly greater in the third trimester (5.9 % (n 17)) compared with the first trimester ($p = 0.193$).

Table 2.1

Characteristics of pregnant women population (n 739), Latvia

	(%)	n
Trimester		
First	21.9	162
Second	38.2	282
Third	39.9	295
First pregnancy		
Yes	45.3	335
No	54.7	404
Season		
Spring	53.9	398
Autumn	46.1	341
Use of supplements containing iodine		
≥ 150 μg	6.8	50
100–149 μg	10.4	77
< 100 μg	81.7	604
Not known	0.1	1

Table 2.1 continued

	(%)	n
Use of iodised salt		
Always	8.9	66
Sometimes	36.1	267
Never	54.8	405
Not known	0.1	1
Consumption of milk and dairy products		
2–4 servings per day	37.5	277
1 serving per day	50.3	372
Rarely/ less than once daily	11.0	81
Not known	0.1	1
Consumption of seafood		
2–3 per week	5.0	37
Once weekly	45.9	339
Less than once weekly	47.9	354
Not known	1.2	9
Smoking		
Yes	7.2	53
Stopped during pregnancy	35.2	260
No	56.2	415
Not known	1.5	11
History of thyroid disease		
Yes	9.6	71
No	90.0	665
Not known	0.4	3
Anti-TPO > 60 IU/ml		
Yes	10.7	79
No	63.6	470
Not known	25.7	190
Elevated trimester specific TSH*		
Yes	3.8	28
No	70.6	522
Not known	25.6	189
Decreased FT4		
Yes	3.8	28
No	70.6	522
Not known	25.6	189

* According to the guidelines of the American Thyroid Association: first trimester, > 2.5 mIU/L; second trimester, > 3.0 mIU/L; third trimester, > 3.0 mIU/L (15).

The UIC was measured in 696 pregnant women (Figure 2.1). The median UIC among pregnant women was 80.8 (IQR 46.1–130.6) µg/g Cr, the 0.5 % percentile was 3.0 µg/g Cr and the 99.5 % percentile was 621.4 µg/g Cr. Of these women, 81 % had UIC measurements below 150 µg/g Cr.

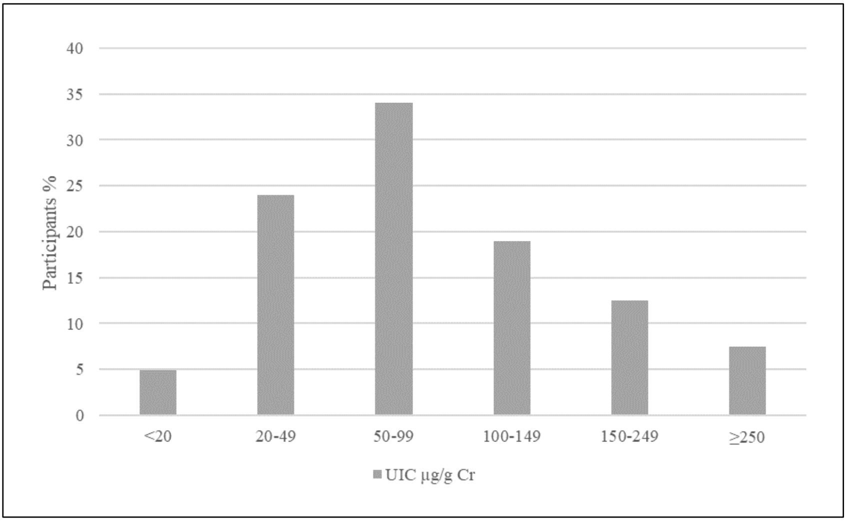

Figure 2.1 **Frequency distribution of urinary iodine excretion among pregnant women in Latvia (n 696)**

Only 7 % of the pregnant women exceeded UIC of 249.9 µg/g Cr and 1 % (n 7) had UIC above 500 µg/g Cr. The median standardised UIC in the first trimester was significantly lower than that in the second and third trimesters ($p < 0.001$ for both; Figure 2.2).

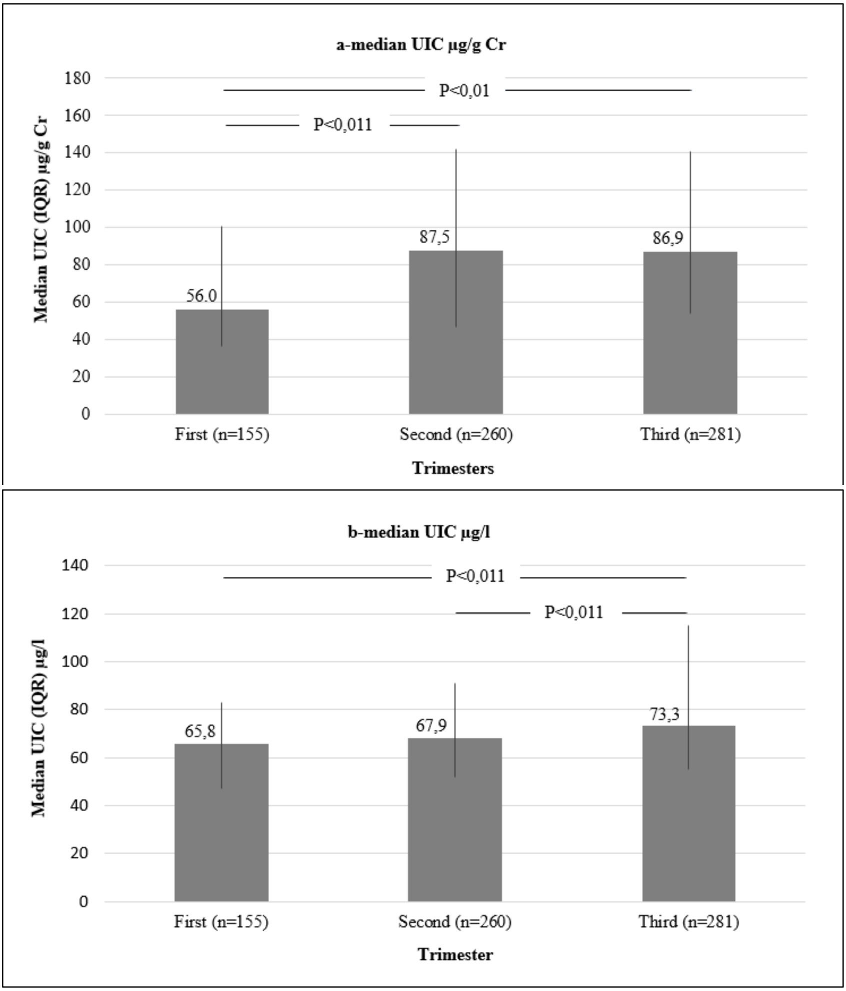

Figure 2.2 **Median urinary iodine excretion during pregnancy trimesters (n 696)**

A significant negative correlation between the gestational week and FT4 concentration was observed (Spearman's $\rho = -0.367$, $p < 0.001$). The median FT4 concentration was 14.4 pmol/l in the first trimester, 13.1 pmol/l in the second trimester and 12.5 pmol/l in the third trimester ($p < 0.001$). Hypothyroxinaemia (as defined by FT4 concentration below 10.3 pmol/l) was not detected in the first trimester but reached the prevalence of 2.5 % in the second trimester and 10.7 % in the third trimester ($p < 0.001$). In the setting of mild maternal iodine deficiency, hypothyroxinaemia was not associated with UIC and anti-TPO.

The median UIC was 80.3 (IQR 45.8–127.9) µg/g Cr in the group of women who did not use iodine-containing supplements or used supplements with an iodine content of < 100 µg. A non-significantly higher median UIC of 86.2 µg/g Cr was detected in women using supplements with 100–149 µg iodine and 96.2 µg/g Cr with ≥ 150 µg iodine (p = 0·471). Women who regularly used iodised salt had a non-significantly higher median UIC than did those who used regular salt, at 86.2 and 79.9 µg/g Cr, respectively ($p = 0.234$). Women who reported only rarely consuming milk products had a median UIC of 65.2 µg/g Cr, which was significantly lower than that in the group of women consuming approximately three servings of milk products daily (87.6 µg/g Cr; $p = 0.002$) and the women consuming one portion of milk products daily (80.1 µg/g Cr; $p = 0.047$). The difference between the latter two groups was non-significant ($p = 0.076$). (Table 2.2)

Table 2.2

UIC (µg/g Cr) according to the participants' characteristics and dietary habits among pregnant women in Latvian

	n	Median UIC ug/gCr	IQR	p	UIC < 150 µg/g Cr (%)	p for trend χ2 tests
Use of supplements containing iodine						
≥ 150 µg	48	96.2	51.9–140.3	-	81.2	-
100–149 µg	70	86.2	46.6–156.9	-	71.4	-
< 100 µg	570	80.3	45.8–127.9	0.471*	81.9	0.295
Use of iodised salt						
Always	60	86.2	50.9–153.6	-	75.0	-
Sometimes	254	82.8	48.7–133.2	-	80.3	-
No	381	79.9	43.6–126.3	0.465*	81.9	0.243

Table 2.2 continued

	n	Median UIC ug/gCr	IQR	p	UIC < 150 µg/g Cr (%)	p for trend χ2 tests
Consumption of milk and dairy products						
2–4 servings per day	263	87.6	50.8–143.9	-	77.9	-
1 serving per day	347	80.1	44.6–134.6	-	81.3	-
Rarely/ less than once daily	77	65.2	40.0–101.7	0.007*	88.3	0.048
Consumption of seafood						
2–3 times per week	36	83.8	42.6–173.7	-	69.4	-
Once weekly	319	86.8	47.7–141.0	-	79.0	-
Less than once weekly	332	76.9	45.0–115.1	0.061*	83.7	0.023
Smoking						
Yes	52	75.6	41.7–115.1	-	88.5	-
Stopped during pregnancy	242	82.2	47.9–134.8	-	79.8	-
No	391	82.1	46.0–132.5	0.285*	80.6	0.429
Season						
Sring	370	82.9	47.4–132.6	-	81.4	-
Autumn	326	79.7	43.9–131.2	0.608†	80.1	0.667
First pregnancy						
Yes	318	79.9	47.4–131.5	-	80.5	-
No	378	82.8	45.5–132.6	0.715†	81.0	0.881
Trimester						
First	155	56.0	36.4–100.6	-	88.4	-
Second	260	87.5	46.4–141.7	-	78.5	-
Third	281	86.9	53.8–140.6	< 0.001*	78.6	0.027
Age						
< 28 years	346	79.6	45.1–127.9	-	81.5	-
≥ 28 years	350	83.2	46.3–135.9	0.345†	80.0	0.615

* p value from Kruskal-Wallis test.
†p value from Mann-Whitney U test.

Multivariate linear regression analysis was performed to assess the demographic and dietary factors associated with creatinine-standardised UIC in the present study. As shown in Table 2.3, the women's age, gestational age, milk consumption (at least one serving daily) and seafood consumption (once weekly) were independently associated with a higher UIC, but parity was associated with a lower UIC.

Table 2.3

The association between dietary factors and participants' characteristics and logarithmically transformed UIC (μg/g Cr) in multiple linear regression analysis (n 683)

	β	SE	95 % CI	p
Age (years)	0.007	0.003	0.002, 0.013	0.011
Gestational age (weeks)	0.006	0.001	0.003, 0.008	< 0.001
Parity (number of previous pregnancies)	−0.034	0.016	−0.066, −0.002	0.038
Use of iodine containing supplements				
≥ 150 μg	0.052	0.052	−0.050, 0.155	0.319
100–149 μg	0.033	0.044	−0.054, 0.119	0.459
< 100 μg	0	–	–	–
Use of iodised salt				
Always	0.008	0.050	−0.091, 0.107	0.871
Sometimes	−0.012	0.030	−0.070, 0.046	0.690
No	0	–	–	–
Consumption of milk and dairy products				
2–4 servings per day	0.115	0.046	0.024, 0.205	0.013
1 serving daily	0.087	0.044	0.000, 0.175	0.049
Rarely/ less than once daily	0	–	–	–
Consumption of seafood				
2–3 times per week	0.092	0.063	−0.099, 0.111	0.915
Once weekly	0.064	0.028	0.009, 0,120	0.024
Less than once weekly	0	–	–	–
Smoking				
Yes	0.006	0.053	−0.099, 0.111	0.915
Stopped during pregnancy	0.031	0.029	−0.025, 0.088	0.277
No	0	–	–	–
Season				
Spring vs autumn	0.02	0.027	−0.050, 0.055	0.930

Because the issue of anti-TPO positivity in relation to iodine supplementation is clinically relevant, only pregnant women without known pre-existing thyroid disease were selected for the statistical analysis (n 496). The prevalence of anti-TPO concentration above 60 U/ml in spring was 17.3 %, which was significantly higher than that in autumn, 8.9 % ($p = 0.005$); (Table 2.4).

Table 2.4

The association between patients' characteristics and dietary factors and the prevalence of elevated TPO-Ab (>60 U/ml) during pregnancy in multiple logistic regression analysis (n 496)

	Number of participants in subgroup	Prevalence of elevated anti-TPO (%)	OR	95 % CI	p
Age (years)	–	–	1.04	0.98, 1.11	0.194
Gestational age (weeks)	–	–	0.98	0.95, 1.01	0.198
Parity (number of previous pregnancies)	–	–	0.88	0.62, 1.25	0.473
Use of supplements containing iodine					
≥ 150 µg	39	12.8	1.17	0.42, 3.30	0.473
100–149 µg	56	8.9	0.80	0.29, 2.20	0.665
< 100 µg	393	13.7	1.00	–	–
Use of iodised salt					
Always	42	7.1	0.66	0.18, 2.42	0.535
Sometimes	174	14.4	1.04	0.56, 1.95	0.895
No	280	12.9	1.00	–	–
Consumption of milk and dairy products					
2–4 servings per day	181	13.3	0.52	0.22, 1.20	0.124
1 serving per day	250	10.8	0.38	0.17, 0.85	0.019
Rarely/ less than once daily	56	23.2	1.00	–	–
Consumption of seafood					
At least once weekly	244	12.3	0.90	0.49, 1.65	0.735
Less than once weekly	243	14.0	1.00	–	–
Smoking					
Yes	34	20.6	1.73	0.63, 4.74	0.0291
Stopped during pregnancy	168	11.3	0.77	0.40, 1.48	0.425
No	285	13.3	1.00	–	–

Table 2.4 continued

	Number of participants in subgroup	Prevalence of elevated anti-TPO (%)	OR	95 % CI	p
Season					
Spring	237	17.3	1.97	1.09, 3.54	0.024
Autumn	259	8.9	1.00	–	–
Elevated trimester-specific TSH					
Yes	23	21.7	3.00	0.97, 9.35	0.058
No	473	12.5	1.00	–	–
FT4 (pmol/I)			0.90	0.77, 1.04	0.158
UIC (µg/Cr)			1.00	0.99, 1.00	0.204

The prevalence of anti-TPO concentration above the reference range in the group of women with TSH concentration within the trimester-specific range was 12.5 %, but it reached a higher prevalence of 21.7 % in women with an elevated trimester specific TSH concentration, although the difference was not statistically significant ($p = 0.201$). No association between higher prevalence of elevated anti-TPO concentration and iodine content in supplements was detected in our study (p for trend = 0.565). Multivariate logistic regression analysis indicated that the odds of having an elevated anti-TPO concentration were almost two times greater in spring than in autumn (OR = 1.97; 95 % CI 1.09, 3.54) and nearly three times lower in women consuming one serving of dairy products daily than in women rarely consuming dairy products (OR = 0.38; 95 % CI 0.17, 0.85).

The odds of having anti-TPO concentration > 60 U/ml were not increased by using supplements containing iodine, consuming iodised salt or fish, age, gestational age, parity or smoking habits.

2.2 Sufficiency of iodine and selenium during the first trimester of pregnancy in 2018

2.2.1 Dietary sources of iodine and selenium in reproductive age women

Iodine and selenium sufficiency during first trimester largely depends on dietary habits before pregnancy. Therefore, analysis of secondary data from the population study of the Centre for disease Prevention and Control (CDPC) about use of iodine and selenium-containing food products among women of reproductive age has been carried out. Data analysis includes studies carried out between 2010 and 2018.

The main sources of iodine and selenium in women of reproductive age in Latvia according to the population health survey and food questionnaire are presented in Figure 2.3.

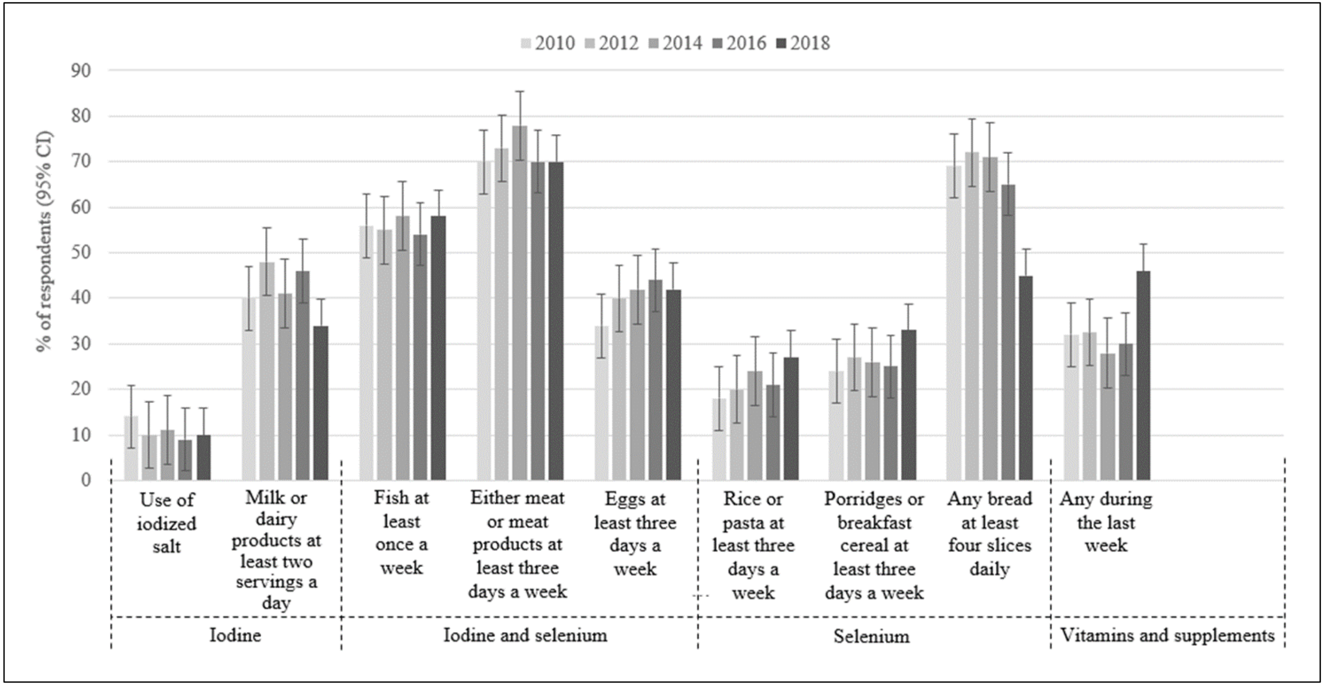

Figure 2.3 **The main sources of iodine and selenium in women of reproductive age according to population-based health surveys in Latvia**

The use of iodised salt was the highest in 2010 ($p < 0.001$), when 13.4 % of women reported that iodised salt was usually used at home; since then, less than 10 % reported such behaviour.

Consumption of milk and dairy products as potential sources of iodine was substantially lower in 2018 than in previous survey years ($p < 0.001$); only 33.4 % of women reported having at least two servings of milk or dairy products a day compared to 41–48 % in earlier years. This decrease was observed in all age groups (Table 2.5).

In addition, intake of bread as one of the main sources of selenium showed a significant decrease in recent years ($p < 0.001$): approximately 70 % of reproductive age women reported consumption of more than three slices of any type of bread per day from 2010–2014, while only 54.7 % and 45.5 % of women reported it in 2016 and 2018, respectively. The same tendency was observed for all age groups (Table 2.5).

Furthermore, the consumption of important sources of selenium and iodine such as meat and fish did not change substantially; approximately 70 % of respondents reported eating either meat or meat products at least three days a week, and almost 60 % reported eating some kind of fish at least once per week. However, in all surveys, fish intake was significantly lower among younger women ($p < 0.001$): only 39.4–48.2 % of 15- to 24-year-old women had eaten fish at least once per week (Table 2.5).

Table 2.5

The main dietary sources of iodine and selenium in women of reproductive age; population-based health survey in Latvia (2010–2018)

Year of survey/ Age	n	Respondents (%) (95 % CI)								
		Iodine		Iodine and selenium			Selenium			
		Use of iodised salt	Milk or dairy products at least two servings a day	Fish at least once a week	Either meat or meat products at least three days a week	Eggs at least three days a week	Rice or pasta at least three days a week	Porridges or breakfast cereal at least three days a week	Any bread at least four slices a day	Any vitamins and supplements during the last week
2010										
15–24	272	9.6 (6.6–13.6)	42.2 (36.4–48.2)	47.8 (41.9–53.7)	66.2 (60.4–71.5)	22.4 (17.9–27.8)	16.5 (12.6–21.4)	19.5 (15.2–24.6)	68.9 (63.1–74.1)	30.5 (25.4–36.2)
25–29	141	14.9 (9.9–21.7)	41.2 (33.3–49.6)	46.8 (38.8–55.0)	75.9 (68.2–82.2)	33.3 (26.1–41.5)	16.3 (11.1–23.3)	26.2 (19.7–34.1)	69.1 (61.0–76.2)	34.8 (27.4–42.9)
30–34	163	20.2 (14.8–27.1)	39.9 (32.7–47.5)	62.0 (54.3–69.1)	70.6 (63.1–77.0)	42.3 (35.0–50.0)	25.8 (19.7–33.0)	27.6 (21.3–34.9)	61.7 (54.0–68.9)	35.0 (28.1–42.6)
35–49	480	12.9 (10.2–16.2)	40.1 (35.8–44.6)	62.7 (58.3–66.9)	69.6 (65.3–73.5)	38.8 (34.5–43.2)	18.1 (14.9–21.8)	22.7 (19.2–26.7)	70.0 (65.7–73.9)	30.2 (26.3–34.5)
Total	1056	13.4 (11.5–15.6)	40.8 (37.8–43.8)	56.6 (53.6–59.6)	69.7 (66.9–72.4)	34.4 (31.6–37.3)	18.7 (16.4–21.1)	23.1 (20.7–25.7)	68.3 (65.4–71.1)	31.6 (28.9–34.5)

Table 2.5 continued

		Respondents (%) (95 % CI)								
		Iodine		Iodine and selenium			Selenium			
Year of survey/ Age	**n**	**Use of iodised salt**	**Milk or dairy products at least two servings a day**	**Fish at least once a week**	**Either meat or meat products at least three days a week**	**Eggs at least three days a week**	**Rice or pasta at least three days a week**	**Porridges or breakfast cereal at least three days a week**	**Any bread at least four slices a day**	**Any vitamins and supplements during the last week**
2012										
15–24	275	6.6 (4.2–10.1)	47.6 (41.8–53.5)	44.7 (39.0–50.6)	72.7 (67.2–77.7)	34.9 (29.5–40.7)	19.6 (15.4–24.7)	26.9 (22.0–32.4)	65.5 (59.7–70.8)	27.6 (22.7–33.2)
25–29	146	13.0 (8.5–19.4)	50.7 (42.7–58.7)	60.3 (52.2–67.9)	75.3 (67.8–81.6)	43.2 (35.4–51.3)	23.3 (17.2–30.8)	29.5 (22.7–37.3)	72.6 (64.9–79.2)	37.0 (29.6–45.1)
30–34	152	12.5 (8.2–18.7)	48.0 (40.2–55.9)	64.5 (56.6–71.6)	74.3 (66.9–80.6)	42.1 (34.5–50.1)	19.1 (13.6–26.1)	28.3 (21.7–35.9)	64.5 (56.6–71.6)	36.2 (29.0–44.1)
35–49	484	8.5 (6.3–11.3)	47.4 (43.0–51.9)	58.1 (53.6–62.4)	71.5 (67.3–75.3)	42.1 (37.8–46.6)	21.5 (18.1–25.4)	26.9 (23.1–31.0)	76.2 (72.2–79.8)	32.4 (28.4–36.7)
Total	1057	9.2 (7.6–11.1)	48.0 (45.0–51.0)	55.8 (52.8–58.8)	72.8 (70.0–75.4)	40.4 (37.5–43.4)	20.9 (18.6–23.5)	27.4 (24.8–30.2)	71.2 (68.4–73.9)	32.4 (29.6–35.2)

Table 2.5 continued

		Respondents (%) (95 % CI)								
		Iodine		**Iodine and selenium**			**Selenium**			
Year of survey/ Age	**n**	**Use of iodised salt**	**Milk or dairy products at least two servings a day**	**Fish at least once a week**	**Either meat or meat products at least three days a week**	**Eggs at least three days a week**	**Rice or pasta at least three days a week**	**Porridges or breakfast cereal at least three days a week**	**Any bread at least four slices a day**	**Any vitamins and supplements during the last week**
2014										
15–24	218	8.3 (5.3–12.7)	40.8 (34.5–47.5)	46.3 (39.8–53.0)	73.4 (67.2–78.8)	35.3 (29.3–41.9)	29.4 (23.7–35.7)	22.9 (17.8–29.0)	69.7 (63.3–75.4)	25.2 (19.9–31.4)
25–29	153	12.4 (8.1–18.6)	37.9 (30.6–45.8)	56.2 (48.3–63.8)	78.4 (71.3–84.2)	38.6 (31.2–46.5)	25.5 (19.2–32.9)	28.1 (21.6–35.7)	68.0 (60.2–74.9)	26.8 (20.4–34.3)
30–34	162	11.1 (7.1–16.9)	43.2 (35.8–50.9)	61.1 (53.4–68.3)	82.1 (75.5–87.2)	46.9 (39.4–54.6)	19.8 (14.3–26.6)	28.4 (22.0–35.8)	63.6 (55.9–70.6)	32.1 (25.4–39.6)
35–49	465	92 (6.9–12.2)	41.3 (36.9–45.8)	63.2 (58.7–67.5)	76.1 (72.0–79.8)	43.9 (39.4–48.4)	23.4 (19.8–27.5)	25.8 (22.0–30.0)	71.6 (67.3–75.5)	27.1 (23.3–31.3)
Total	998	9.8 (8.1–11.8)	41.0 (38.0–44.1)	58.1 (55.0–61.1)	76.9 (74.1–79.4)	41.7 (38.7–44.8)	24.4 (21.9–27.2)	26.0 (23.3–28.8)	69.3 (66.4–72.1)	27.5 (24.8–30.3)

Table 2.5 continued

Year of survey/ Age	n	Respondents (%) (95 %CI)								
		Iodine		Iodine and selenium			Selenium			
		Use of iodised salt	Milk or dairy products at least two servings a day	Fish at least once a week	Either meat or meat products at least three days a week	Eggs at least three days a week	Rice or pasta at least three days a week	Porridges or breakfast cereal at least three days a week	Any bread at least four slices a day	Any vitamins and supplements during the last week
2016										
15–24	277	5.4 (3.3–8.7)	45.5 (39.7–51.4)	39.4 (33.8–45.2)	69.0 (63.3–74.1)	39.4 (33.8–45.2)	22.4 (17.9–27.7)	20.2 (15.9–25.3)	60.6 (54.8–66.2)	24.2 (19.5–29.6)
25–29	158	8.2 (4.9–13.6)	51.3 (43.5–58.9)	51.9 (44.2–59.6)	73.4 (66.0–79.7)	43.7 (36.2–51.5)	20.3 (14.7–27.2)	34.8 (27.8–42.5)	45.6 (38.0–53.4)	34.8 (27.8–42.5)
30–34	190	8.4 (5.2–13.2)	44.7 (37.8–51.8)	55.8 (48.7–62.7)	78.4 (72.0–83.7)	42.6 (35.8–49.7)	20.5 (15.4–26.8)	25.8 (20.1–32.5)	51.1 (44.0–58.1)	25.8 (20.1–32.5)
35–49	542	9.4 (7.2–12.2)	46.5 (42.3–50.7)	59.4 (55.2–63.5)	67.3 (63.3–71.2)	45.4 (41.2–49.6)	17.3 (14.4–20.8)	24.4 (20.9–28.1)	55.5 (51.3–59.7)	32.1 (28.3–36.2)
Total	1167	8.1 (6.7–9.9)	46.6 (43.8–49.5)	53.0 (50.2–55.9)	70.4 (67.7–72.9)	43.3 (40.5–46.1)	19.5 (17.3–21.8)	25.0 (22.6–27.6)	54.7 (51.8–57.5)	29.6 (27.0–32.2)

Table 2.5 continued

Year of survey/ Age	n	Respondents (%) (95 %CI)								
		Iodine		Iodine and selenium			Selenium			
		Use of iodised salt	Milk or dairy products at least two servings a day	Fish at least once a week	Either meat or meat products at least three days a week	Eggs at least three days a week	Rice or pasta at least three days a week	Porridges or breakfast cereal at least three days a week	Any bread at least four slices a day	Any vitamins and supplements during the last week
2018										
15–24	247	3.2 (1.6–6.3)	30.4 (25.0–36.4)	48.2 (42.0–54.4)	61.9 (55.7–67.8)	34.0 (28.4–40.1)	35.2 (29.5–41.4)	35.2 (29.5–41.4)	40.5 (34.6–46.7)	38.9 (33.0–45.1)
30–34	152	17.8 (12.5–24.6)	32.2 (25.3–40.0)	59.9 (51.9–67.3)	75.0 (67.6–81.2)	46.1 (38.3–54.0)	28.3 (21.7–35.9)	38.8 (31.4–46.8)	40.8 (33.3–48.7)	49.3 (41.5–57.2)
35–49	454	10.8 (8.3–14.0)	35.2 (31.0–39.7)	60.8 (56.2–65.2)	73.6 (69.3–77.4)	47.8 (43.2–52.4)	22.2 (18.7–26.3)	30.6 (26.5–35.0)	51.8 (47.2–56.3)	51.1 (46.5–55.7)
Total	991	9.4 (7.7–11.4)	33.4 (30.5–36.4)	57.9 (54.8–61.0)	69.9 (67.0–72.7)	42.2 (39.1–45.3)	28.2 (25.4–31.0)	33.8 (30.9–36.8)	45.5 (42.4–48.6)	48.2 (45.1–51.4)

Table 2.6 presents the prevalence of the consumption of food items among both pregnant women in the study and women of reproductive age in the general population. The direct comparison of product intake was limited due to differences in the questionnaires. Nevertheless, in both populations, there was an association between the use of iodised salt and age: the older the women were, the greater the proportion who reported using iodised salt ($p = 0.016$ in pregnant women and $p < 0.001$ in the general population).

Table 2.6

The use of iodine-rich products by age group according to pregnant women's questionnaire responses and the 2018 population-based health survey

(Proportion of participants % (95 % CI))

Age/years	n	Use of iodised salt always/ sometimes	Consumption of dairy products at least 2 servings a day	Seafood at least once a week	Vitamins and supplements during last three weeks
Pregnant women					
Total	129	37.2 (29.4–45.8)	31.0 (23.7–39.4)	48.1 (39.6–56.6)	68.2 (59.8–75.6)
17–24	20	15.0 (5.2–36.0)	15.0 (5.2–36.0)	30.0 (14.6–51.9)	65.0 (43.3–81.9)
25–29	51	37.3 (25.3–51.0)	33.3 (22.0–47.0)	49.0 (35.9–62.3)	66.7 (53.0–78.0)
30–34	42	40.5 (27.0–55.5)	31.0 (19.1–46.0)	47.6 (33.4–62.3)	66.7 (51.6–79.0)
35–40	16	56.3 (33.2–76.9)	43.8 (23.1–66.8)	68.8 (44.4–85.8)	81.3 (57.0–93.4)
p for trend ($\chi 2$ tests)		0.016	0.124	0.049	0.381
p ($\chi 2$ test)		0.075	0.291	0.146	0.693
Population based health survey; reproductive age women					
Total	991	9.4 (7.4–11.4)	33.4 (30.5–36.4)	57.9 (54.8–61.0)	48.2 (45.1–51.4)
15–24	247	3.2 (1.6–6.3)	30.4 (25.0–36.4)	48.2 (42.0–54.4)	38.9 (33.0–45.1)
25–29	138	6.5 (3.5–11.9)	34.1 (26.7–42.3)	63.8 (55.5–71.3)	54.4 (46.0–62.4)
30–34	152	17.8 (12.5–24.6)	32.2 (25.3–40.0)	59.9 (51.9–67.3)	49.3 (41.5–57.2)
35–49	454	10.8 (8.3–14.0)	35.2 (31.0–39.7)	60.8 (56.2–65.2)	51.1 (46.5–55.7)
p for trend ($\chi 2$ tests)		< 0.001	0.227	0.006	0.014
p ($\chi 2$ test)		< 0.001	0.607	0.004	0.001

Overall, the proportion of pregnant women who always used iodised salt was 8.5 % (95 % CI 4.8–14.5 %). This number does not differ from the 9.4 % of regular users of iodised salt among women in reproductive age in general population.

On the other hand, a slight increase in the use of grain products and cereals was observed in 2018 compared to the previous survey years; 28.2 % of women reported eating rice or pasta, and 33.8 % reported eating porridge or breakfast cereal at least three days a week. In addition, in 2018, there was a substantial increase in the use of vitamins and supplements, which may have contributed to the intake of both iodine and selenium ($p < 0.001$). In the latest survey, 48.2 % of reproductive age women reported the use of some vitamins and supplements in the last week, whereas approximately 30 % did so in from 2010–2016. This increase was observed in all age groups. Similarly, in both populations, there were age-dependent differences in fish and/or seafood consumption. Among pregnant women, younger women reported a lower intake of seafood, but the proportion of individuals who ate seafood at least once per week was the highest in the 35- to 40-year-old group at 68.8 % ($p = 0.049$ according to age).

A high proportion (68.2 %) of pregnant women were already using vitamins and supplements at their first antenatal visit; the percentage of users was particularly high among older pregnant women – more than 80 % – but the difference age-related was not statistically significant. However, only 19 (14.7 %) pregnant women used supplements containing sufficient concentration (150 µg) of iodine and only 13 (10.1 %) used supplements containing selenium (60 µg/day).

2.2.2 Information activities among health care professionals and society emphasizing importance of iodine supply during pregnancy from 2013 to 2018

In countries with absent USI strategy, targeted dietary recommendations to achieve optimal iodine sufficiency during pregnancy are crucial. Since 2005, when the draft of amendments to regulate obligatory salt iodisation was rejected in Latvia (see section 3.1 for more details), there is no national strategy and proposition for eliminating iodine deficiency in the population, including pregnant women.

During antenatal period women is in care of healthcare professionals (most often a gynaecologist, obstetrician, including midwife, general practitioner, in case of endocrine disorders – also an endocrinologist), therefore, recommendations about iodine containing food products and supplements, given by specialists are important and helpful to ensure optimal iodine intake. After conducted nationwide study of pregnant women in 2013, where iodine deficiency was assessed, specialists (Latvian Association of Gynaecologists and Obstetricians, in collaboration with Latvian Society of Endocrinologists) started initiative to increase knowledge and awareness of iodine importance during pregnancy. In 2015 the interdisciplinary conference about significance and requirements and iodine and selenium during pregnancy was organised with participation of recognizable nutrition science professor of Margaret Rayman (United Kingdom).

In 2015, the Latvian Association of Gynaecologists and Obstetricians in collaboration with the Ministry of Health and the CDPC established training course "Basic antenatal care – examinations, interpretation and education of a pregnant woman for the best pregnancy outcome", with included recommendations about healthy diet and supplements (emphasizing iodine intake) during pregnancy. The course was for gynaecologists, obstetricians, as part of postgraduate training to implement recertification.

In addition, based on previous studies of iodine sufficiency in Latvia and international guidelines, the national recommendations for iodine intake during pregnancy were created and published in the Proceedings of Latvian Academy of Sciences. (17) They highlight importance of following dietary recommendations – iodine rich foods and iodised salt consumption during pregnancy and include recommendations for 150 µg iodine supplementation daily throughout pregnancy and breastfeeding.

Under the guidance of the Ministry of Health in collaboration with the WHO, the recommendations for health care professionals about healthy diet and relevant supplements (including iodine) during pregnancy – "Healthy nutrition recommendations for women during pregnancy" (18) and "Appropriate nutrition when planning pregnancy and during pregnancy – the basis for healthy start" was created and published in 2017. (19) Information materials about pregnancy, including dietary recommendations and particularly recommendations about healthy diet during pregnancy were created by CDPC and are with public access in both, print and digital form ("I want to be mum," "Healthy nutrition recommendations for women during pregnancy,") as well as other informative online materials for women during pregnancy and lactation, including nutritional recommendations. (20)

2.2.3 Urinary iodine, serum selenium and thyroid function during first trimester

In 2018 among pregnant women at 6–9 weeks of gestation, the median UIC was 147.2 (IQR 90.0–248.1) µg/gCr, and 52.8 % of participants had a UIC below 150 µg/gCr (Figure 2.4). The mean serum selenium was 101.5 (SD 35.6) µg/l, with 72.6 % of participants having selenium levels below 120 µg/l and 30.1 % having selenium levels below 80 µg/l, whereas the median selenoprotein P was 6.9 (3.1–9.0) mg/L. Thyroid function was normal in all pregnant women. The mean TSH level was 1.1 (SD 0.7) mIU/L, and the mean

FT4 level was 14.2 (SD 2.7) pmol/l, whereas 13.9 % of women had anti-TPO level above 60 IU/mL.

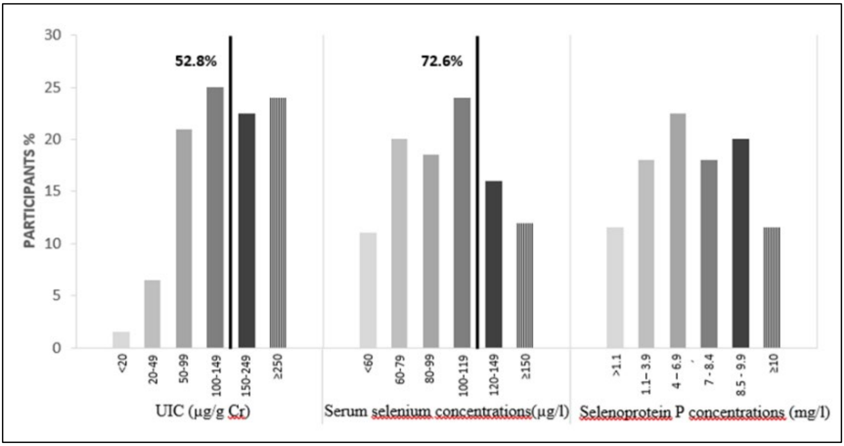

Figure 2.4 **Frequency distribution of UIC, serum selenium concentrations and selenoprotein P concentrations in in pregnant women in Latvia in first trimester**

The differences in urinary iodine excretion, serum selenium concentration, selenoprotein P concentration and anti-TPO levels between subgroups were not statistically significant (Table 2.7). However, the number of dietary sources of iodine (iodised salt, milk and dairy products, seafood and vitamins/supplements, as listed and dichotomised in Table 2.7) showed a positive correlation with the UIC (Spearman's rho = 0.217, p = 0.016). There was no significant correlation between serum selenium and SEPP levels in our population (p = 0.636).

Table 2.7

Iodine and selenium status in pregnant women in association with demographic and dietary factors

	n	UIC ug/gCr		Serum selenium concentration. pg/L		Selenoprotein P concentration. mg/L	Anti-TPO level
		Median (IQR)	< 150 µg/g Cr (%)	Mean (SD)	< 120 pg/L (%)	Median (IQR)	> 60 1U/ml (%)
Age (years)							
17–24	20	128.2 (78.5–184.5)	57.9	96.4 (27.6)	77.8	8.4 (3.8–9.5)	10.0
25–29	51	147.2 (114.0–281.7)	55.1	103.0 (40.1)	73.5	6.0 (1.4–8.8)	9.8
30–34	42	134.5 (80.6–272.1)	52.5	98.8 (32.9	67.6	7.2 (4.4–9.2)	18.4
35–40	16	171.0 (106.8–229.0)	40.0	103.2 (25.9)	81.8	4.4 (3.0–6.0)	23.1
First pregnancy							
Yes	60	154.9 (110.5–248.1)	49.2	101.6 (33.0)	73.6	6.9 (1.8–9.1)	10.2
No	69	134.0 (88.2–263.4)	56.3	99.8 (36.4)	72.9	7.0 (3.7–8.8)	17.5
Use of iodised salt							
Always or sometimes	48	153.8 (110.8–293.1)	44.4	97.3 (29.8)	82.1	6.8 (1.5–8.9)	19.6
No	81	134.0 (82.5–201.0)	57.7	102.5 (31)	68.5	7.1 (3.4–9.0)	10.5
Consumption of milk or dairy products							
At least 2 servings a day	40	149.0 (114.0–330.4)	51.4	101.2 (35.1)	75.7	5.9 (2.0–8.9)	22.5
Less than 2 servings a day	89	145.2 (82.5–195.4)	53.5	100.4 (34.7)	71.7	7.1 (3.2–9.0)	9.8
Consumption of seafood							
At least once a week	62	147.2 (102.8–265.3)	52.5	97.0 (36.5)	75.0	5.8 (2.5–9.3)	14.0
Less than once a week	67	146.0 (89.5–195.8)	53.1	103.8 (33.0)	71.7	7.1 (3.5–8.9)	13.8
Use of any vitamins and supplements during the last three weeks							
Yes	88	154.4 (105.8–238.1)	47.7	97.5 (35.8)	76.3	6.0 (1.7–9.0)	14.8
No	41	124.5 (87.2–250.2)	64.9	109.7 (34.1)	64.9	7.8 (4.4–9.0)	12.2
Total	129	147.2 (90.0–248.1)	52.8	101.5 (35.6)	72.6	6.9 (3.1–9.0)	13.9

Serum Se and SEPP levels did not differ between pregnant women with high levels of anti-TPO and those with normal levels ($p = 0.248$ and $p = 0.938$, respectively). No significant correlation was found between serum selenium or SEPP and TSH levels ($p = 0.225$ and $p = 0.532$, respectively). In addition, no association was detected between serum selenium or SEPP levels and age ($p = 0.675$ and $p = 0.495$, respectively). There was no statistically significant correlation between any of the clinical and nutritional markers except anti-TPO levels, which were positively correlated with TSH levels (Spearman's ρ 0.28, $p = 0.002$).

2.3 Iodine intervention study in pregnant women in 2018

2.3.1 Characteristics of pregnant women in study

The analysis includes data about 129 women who completed questionnaires about their dietary habits. In the first trimester of pregnancy, UCI was detected for 123 pregnant women, in the second and third trimesters 99 and 90 respectively.

In first trimester median UIC in was 147.2 (IQR 89.9–228.9) µg/g Cr. Mean TSH in the first trimester was 1.13 (SD 0.69) mIU/ml, with no TSH exceeding the reference range of 4.0 mIU/ml. (16) In the second trimester, the mean TSH was 1.36 (SD 0.66) mIU/mL and for one woman in the control group TSH was above normal (4.4 mIU/mL), while in the third trimester the mean TSH was 1.33 (SD 0.57) mIU/mL and in both, the intervention and control groups, it was at the normal reference values.

The median FT4 in pregnant women was 14.2 (SD 2.67) pmol/l, three women had hypothyroxinaemia with FT4 < 10.3 pmol/l in the first trimester, with one remaining hypothyroxinaemia in the second and third trimesters.

Elevated anti-TPO above 60 IU/ml were in 13.9 % (95 % CI 8.9–21.2 %) of pregnant women. No increase of anti-TPO was observed with the progress of pregnancy neither in control, nor intervention group.

The average age of pregnant women was 29 years (17 to 40 years), for 46 % of women this was first pregnancy.

Analysis of dietary habits revealed that in first trimester iodised salt (always/sometimes) were using 37.2 % (95 % CI 29.4–45.8 %) of participants. Women who always/sometimes used iodised salt, had higher median UCI (153.8 (IQR 110.8–293.1 µg/g Cr) than those who did not (130.7 (IQR 82.5–216.9 µg/g/Cr), although the difference is not statistically significant ($p = 0.088$).

In first trimester fish/seafood consumption at least once weekly was reported by 48.1 % (95 % TI 39.6–56.6 %) of women. Although, women who consumed fish and seafood at least once per week had higher median UCI trend 147.2 (IQR 102.8–253.3) µg/g/Cr compared to those who ate less fish and sea products 137.7 (IQR 89.5–195.3) µg/g Cr), the difference was not statistically significant ($p = 0.491$).

During the first trimester of pregnancy, 52.7 % (95 % CI 44.1–61.1 %) used 1 portion of dairy products per day, while 31.0 % (95 % CI 23.7–39.4 %) used for 2–4 portion per day. In pregnant women who consumed at least 2 portions of milk products per day, median UCI was higher (149.0 (IQR 114.0–305.6) µg/g Cr) compared to those who consumed less milk products daily (140.9 (IQR 82.5–206.0) µg/g Cr), however the difference was not statistically significant ($p = 0.086$).

2.3.2 Comparison of intervention and control groups

In the intervention group 150 µg iodine-containing supplement received 40 pregnant women, 89 women were enrolled in the control group.

At the beginning of the study median UIC was 93.9 (IQR 51.1–252.6) µg/g Cr in the intervention group, while 151.1 (IQR 112.6–243.3) µg/gCr ($p = 0.007$) in the control group.

In both study groups, median UIC increased throughout pregnancy and statistically significant increase of median UIC was observed in the control group, both – when compared first trimester to second and third trimesters (Table 2.8).

Table 2.8

Changes of UIC during pregnancy in intervention and control groups

	Trimester	Median UIC µg/g Cr (IQR)	p value in comparison with 1st trimester
Intervention group	First	113.1 (63.1–362.3)	–
	Second	121.9 (83.1–334.6)	0.442
	Third	165.0 (84.8–377.9)	0.200
Control group	First	151.1 (112.6–243.3)	–
	Second	181.9 (120.5–401.6)	0.007
	Third	214.4 (144.5–427.6)	0.001

Analysis of dietary habits (Table 2.9) revealed that with progression of pregnancy women more likely consumed iodised salt in both study groups, furthermore, more frequent use of iodised salt compared first trimester to second and third, was observed in control group ($p = 0.001$).

The use of dairy products did not change in any of the study groups throughout the pregnancy.

However, along the progression of pregnancy changes in fish and seafood consumption were observed – in the intervention group frequency of fish and seafood intake significantly increased comparing first trimester with second ($p = 0.034$).

Table 2.9

Changes of dietary habits during pregnancy in intervention and control groups

	Trimester	Pregnant women (%)	95 CI (%)	p value in comparison with 1st trimester
Use of iodised salt always/sometimes				
Intervention group	First	40.0	26.3–55.4	–
	Second	44.4	27.6–62.7	0.414
	Third	48.1	30.7–66.0	0.257
Control group	First	36.0	26.8–46.3	–
	Second	55.9	44.1–67.1	< 0.001
	Third	54.2	42.7–65.2	< 0.001
Fish and seafood at least once a week				
Intervention group	First	40.0	26.3–55.4	–
	Second	55.6	37.3–72.4	0.034
	Third	55.6	37.3–72.4	0.096
Control group	First	51.7	41.5–61.8	–
	Second	58.8	47.0–69.7	0.096
	Third	54.2	42.7–65.2	0.366
Dairy products ≥ 2 servings a day				
Intervention group	First	17.5	8.7–31.9	–
	Second	22.2	10.6–40.8	0.564
	Third	25.9	13.2–44.7	0.564
Control group	First	37.1	27.8–47.5	–
	Second	42.6	31.6–54.5	0.782
	Third	44.4	33.5–55.9	0.317

Importance of sufficient iodine intake during pregnancy (the use of iodine rich foods and iodised salt) was emphasized in written and oral form to both study groups. Consequently, in first trimester 18 % of pregnant in control group (95 % CI 11.4–27.2 %) voluntarily used iodine containing food supplements with iodine 150 µg per day, and 15.7 % (95 % CI 9.6–24.7 %) and 19 % (95 % CI 12.3–28.5 %), in the second and third trimesters, respectively. In view of this fact, we calculated changes of UIC in trimesters among actual iodine users and non-users, thus increasing the number of 150 µg iodine user group (intervention group) with individuals using iodine from control group (Table 2.10).

Table 2.10

Changes of median UIC during pregnancy – original study groups and actual iodine 150 µg users and non-users

Median UIC 1st trimester	Median UIC 2nd trimester	Median UIC 3rd trimester	p	Pregnant women n*
Original intervention and control groups				
Intervention group				
113.1 (IQR 63.1–362.3)	121.9 (IQR 83.1–334.6)	–	0.441	27
99.8 (IQR 46.2–280.6)	–	165.0 (IQR 84.8–377.9)	0.2	22
Control group				
151.1 (IQR 112.6–243.3)	181.9 (IQR 120,5–401,6)	–	0.007	68
149.0 (IQR 111.5–210.3)	–	214.4 (IQR 144.5–427.6)	0.001	65
Actual iodine 150 µg users and non-users				
Iodine 150 µg users				
131.4 (IQR 88.6 –291.9)	152.0 (IQR 97.9–352.1)	–	0.121	41
127.4 (IQR 84.5–273.4)	–	193.5 (IQR 122.7–466.3)	0.006	36
Iodine non-users				
151.1 (IQR 112.5–233.8)	184.66 (IQR 76.6–184.7)	–	0.028	54
147.8 (IQR 106.8–196.9)	–	199.7 (IQR 133.0–360.9)	0.003	51

*The different number of pregnant women (n) in control and intervention groups is explained by the different number of available UIC in 1st and 2nd or 1st and 3rd trimesters respectively.

The calculations, reveal statistically significant increase of median UIC not only in the control group during the second and third trimesters compared to the first, but also in the intervention group – median UIC increased statistically significantly in the third trimester compared to the first (p = 0.006). Although, the trend of UIC improve was observed in originally formed intervention and study groups, probably, the statistical significance of increase in interventional group was not seen due to small number of participants.

3 Discussion

3.1 Sufficiency of iodine and its association with thyroid function during pregnancy in different regions of Latvia in 2013

Several studies in schoolchildren have been carried out to assess iodine sufficiency in Latvian population. The comprehensive cross-sectional survey in spring 2000 involved 587 schoolchildren. The median UIC in was 59 µg/l, ranking Latvia among countries with mild iodine deficiency in the population. (9) Severe iodine deficiency was found in 19.2 % of participants. Another significant indicator of iodine sufficiency in the population, the newborn TSH screening data, also shows mild iodine deficiency. In 2000, the proportion of newborns with TSH > 5 mIU/L was 16.5 %, but in 2001 and 2002 it was 10.4 % and 8.4 %, respectively. (8)

In 2003, the Ministry of Health started active work on normative documents, to implement strategy for prevention of iodine deficiency in country. The drafted amendments of the "Law on Food Chain supervision" and appropriate Regulations of CM included changes that salt, purchased in retail and used for the production of bread, mayonnaise and ketchup, is fortified with iodine. The defined iodine ion concentration in salt for daily household consumption had to be 0.002 to 0.005 %, while in salt for food production 0.004 to 0.01 %. The invention of mandatory salt iodisation in Latvia was planned to start in 2004 – according to the final Declaration of the Special Session on children of the United Nations General Assembly of New York, adopted in May 2002, to which Latvia was joined. (21)

However, in 2005, the amendments were rejected largely due to the diversity and resistance of public opinion. In result concerns raised about increase salt price and people started active salt purchasing for households needs. Mandatory requirements for salt iodisation were no longer included in the draft of amendments for CM regulations and the food producers could decide about salt iodisation voluntary. Both table salt and iodised salt still can be purchased in retail. As a result, the use of iodised salt in Latvia has been and continues to be a voluntary choice in both domestic use and food production. (22)

Another survey was conducted in 2010. Altogether 915 schoolchildren at age 9–12 years from 46 Latvian schools were involved in study. Urinary iodine excretion in the morning urine portion was spectrophotometrically determined and standardised against creatinine. Parents were asked to complete a questionnaire about the dietary habits regarding iodine containing products consumption. The study revealed the seasonality of iodine supply – mild iodine deficiency was seen in spring when median UIC was 78.3 μg/g Cr, while no iodine deficiency was observed in autumn (median UIC was 129.7 μg/g Cr). The median standardised UIC excluding seasonal differences, was 107.3 (IQR 69.1–161.7) μg/g Cr. According to this indicator, in 2013, the International Council for the Control of Iodine deficiency disorders (ICCIDD) ranked Latvia among the countries with no formal iodine deficiency (median UIC 100–199 μg/l corresponds to sufficient iodine intake in schoolchildren according to WHO). (23, 24) Despite the fact that the overall median UIC in schoolchildren remained within the low normal range, a large percentage of the Latvian population have suboptimal iodine intake and were found to be iodine deficient. This occurs in pregnancy, when maternal demands of iodine significantly increase due to more intense thyroid function, transplacental transfer of iodine and thyroid hormones to the foetus and due to increase in maternal renal iodine clearance.

Indeed, our study with median UIC (80.8 (IQR 46.1–130.6) μg/g Cr) confirms iodine deficiency during pregnancy in Latvia (median UIC 150–249 μg/l corresponds to sufficient iodine intake in pregnant population according to WHO). (24) Low median UIC in first trimester indicates deficiency even before pregnancy and during the first embryonic weeks, when organogenesis, including foetal brain development, is intensively progressing. Iodine deficiency in early pregnancy and consequently impaired FT4 synthesis is attributable to suboptimal cognitive development in later childhood – children born to women with UIC 50–150 µg/g Cr have lower verbal IQ and lower reading ability at age 8. (25) Therefore, in mild to moderate iodine deficiency regions, the use of dietary supplements with iodine concentrations of at least 150 µg should be recommended already before pregnancy. (26)

The present study among pregnant women in Latvia also indicates that the median UIC was significantly higher in the second and third trimesters, which could be attributed to the intake of iodine containing supplements, recommended by health care specialists. However, the intake of iodine supplements containing 150 µg iodine, as recommended by the American Thyroid Association (15), did not explain that association and did not appear to be more effective in reducing the iodine deficiency during pregnancy. This might be attributed to the fact that in our study there were small number of women taking supplements containing ≥ 150 µg iodine to find the difference between subgroups statistically significant. Our data support the notion that the iodine deficiency was most likely already present before pregnancy.

Previous studies in Latvia among schoolchildren (10, 23), along with others (27, 28), have confirmed seasonal UIC fluctuations in mild iodine-deficient regions of Europe. However, in the present study, we did not find significant seasonal differences in UIC in pregnant women.

This may be attributable to different sources of iodine in the dietary intake during pregnancy (supplements, iodised salt, fish and seafood), which masks the effect of seasonal pattern-dependent food sources, such as milk and milk products. There is evidence that the seasonal changes of UIC observed in schoolchildren is attributable to the consumption of milk and dairy products During the spring–summer period, when iodine concentration in milk is lower, lower median UIC is observed in schoolchildren compared to the autumn–winter period. Seasonal changes of UIC, is not observed among adults who consume milk and dairy products less frequently and other sources of iodine, such as iodised salt, fish and seafoods prevail in their diet. (29–31)

Surprisingly, contrary to the finding of no seasonality effect in the UIC values, our study reports that the prevalence of elevated anti-TPO concentration was approximately two times higher in spring than in autumn. This finding is the first time that such an observation has been reported in pregnant women. The aetiology of thyroid autoimmunity is multifactorial, with both endogenous predisposition and environmental factors, including infections, playing an important role in the development of autoimmune diseases. (32, 33) We have no information regarding previous anamnesis, nor did we test for infection in our study population, therefore the idea that infection is a contributing factor to the increase of anti-TPO remains speculative, although theoretically possible. In addition, a role of vitamin D sufficiency, whose immunomodulatory properties have been extensively studied in recent years, is discussed in thyroid autoimmunity. A number of studies confirm the association of low vitamin D levels with the activity of autoimmune thyroid diseases, but unambiguous prospective and randomised study data on the role of vitamin D in the aetiology and treatment of autoimmune thyroid diseases are still lacking. (34–36)

Nine randomised controlled studies conducted in mild to moderate iodine deficiency regions suggest that the use of iodine-containing supplements during pregnancy has a positive effect: it prevents thyroid volume and TSH levels from increasing and reduces thyroglobulin levels. (37) However, increased iodine intake can activate thyroid autoimmunity and raise anti-TPO. (38–40)

Elevated levels of anti-TPO during pregnancy are associated with a higher risk of postpartum thyroiditis, nevertheless women with postpartum thyroiditis were observed to have higher median UIC (231.9 µg/l and 199.99 µg/l, respectively; $p = 0.00153$). (41) Consequently, increased dietary intake of iodine is associated with a higher risk of developing post-natal thyroiditis and an increase in anti-TPO titre, but this is observed in a population with significantly higher iodine intake and higher median UIC, whereas in regions with mild to moderate iodine deficiency, post-natal thyroiditis was not observed in anti-TPO positive pregnant women with additional iodine 150 µg/day. (37, 42)

Excessive use of iodine during pregnancy may negatively affect thyroid function leading to increased TSH. Elevated TSH was seen more frequently in pregnant women taking 200 µg of iodine per day compared to 100 µg of iodine, and lower median FT4 (10.09 pmol/l) was associated with higher median UIC (168 µg/L) and with more frequent use of supplements (93 %). (43) A cross-sectional study conducted in China included 7190 pregnant women during the first trimester and demonstrated "U" shaped effect in relationship between thyroid function and UIC. The lowest levels of TSH and thyroglobulin were found in women with UIC 150–249 µg/L, while iodine use of more than 250 µg/day in a population of already adequate iodine sufficiency increased the risk of subclinical hypothyroidism, and UIC of more than 500 µg/L was associated with an increased risk of isolated hypothyroxinaemia. (42,44)

In the present study, we did not observe any association between UIC and elevated anti-TPO values. When more than 80 % of the pregnant women have UIC lower than 150 µg/g Cr, iodine supplementation is not expected to trigger thyroid autoimmunity, a result that has been noted in populations with UIC that were approximately three times greater. In countries such as Latvia, excessive iodine intake is unlikely, even when regularly consuming iodised salt at the WHO recommended amount and seafood once weekly during the pregnancy.

3.2 Sufficiency of iodine and selenium during the first trimester of pregnancy in 2018

Since the study in 2013, where iodine deficiency in the pregnant population was assessed (median UIC 80.8 µg/g Cr), the importance of sufficient iodine intake during pregnancy and lactation has been emphasized in various ways among health care professionals and society (for details, see section 2.2.2).

Assessing the changes of median UIC in pregnant women over five years, it can be concluded that iodine sufficiency has improved since 2013. In 2013, median UIC during first trimester was 56.0 µg/g Cr, however, in 2018 median UIC in first trimester has increased to 143.1 µg/g Cr. Although the median UIC reflects a positive trend in iodine intake during pregnancy, optimal iodine sufficiency during the first trimester, when it is crucial for early foetal CNS development, has not yet been achieved.

A comparison of the dietary habits of pregnant women in 2013 and 2018 shows an increase in the number of women taking at least 150 µg of iodine-containing supplements in the first trimester (3.1 % in 2013, 14.7 % of pregnant women in 2018).

The analysis of the survey data from women of reproductive age showed that in the period from 2010 to 2018, the consumption of several iodine- or selenium-rich products, such as dairy products and bread, decreased. Only 1/3 of women in 2018 reported consuming at least two servings of milk or dairy products a day (compared to 40 % or more in previous surveys). The consumption of bread has decreased 1.5 times (the percentage of individuals who reported consuming at least four slices of any bread daily decreased from 70 % to 45.5 %).

Since the 2012 survey, less than 10 % of women have reported using iodised salt. On the other hand, there was an increase in the consumption of grain products (rice, pasta, porridge, and breakfast cereal) observed in 2018. However, the most striking increase was in the use of vitamins and supplements: almost half (48.2 %) of women of reproductive age in Latvia reported using supplements in the 2018 survey. In pregnant women, the proportion using vitamins and supplements was even higher – 68.2 %. However, only 10–15 % used supplements containing sufficient concentration of iodine or selenium.

The results of the present study showed that approximately half of pregnant women reach adequate iodine supply in the first trimester of pregnancy despite no obvious changes in dietary habits in past years. One possible explanation for improved iodine nutrition might be increased consumption of imported foods from countries where salt fortification with iodine is mandatory and iodised salt is used in industrial food production. The use of iodised salt in the manufacturing of frequently consumed processed foods may have a more considerable impact on the daily iodine intake of consumers than the use of iodised salt in the household. The survey data for young (18- to 35-year-old) adults in Latvia revealed that grain products (bread, breakfast cereals, biscuits, and cakes) and meat and meat products were the main sources of salt intake (each group accounted for 29.5 % of the daily intake). (45) Furthermore, the import of these products has increased over time, and in 2017, the dominant country from which products were imported was Poland, where a mandatory iodine deficiency prevention program had been introduced; all meat and edible meat offal products imported from European countries, 21.4 % were from Poland. (46) In addition, the second largest importer of meat and edible meat offal products in 2017 was Denmark (11.2 % of total meat imports), where salt fortification with iodine is also mandatory. Poland was also the leader in importing prepared cereals, flour, starch, milk or pastry products in 2017 (14.8 % of the total import of these products).

Approximately 25–70 % of the recommended daily amount of iodine is consumed with milk and dairy products, which are considered as significant source of dietary iodine. However, the iodine concentration in milk varies from 33 to 534 µg/L in different countries and depends on the iodine concentration in feed and season, on the use of iodine-containing disinfectants in the treatment of cows' udders, on the type of farming and dairy processing. (47) Analysis of 20 milk samples from various Latvian milk producers and farms shows that the average iodine concentration is relatively high – (457.6 µg/l) in comparison to other countries, because of iodine-rich cattle feed supplement use and iodine-containing disinfectants used by farms. In addition, iodine fortification on large farms has increased during the last three years, and locally produced dairy products are preferred by the population in Latvia. (48)

In addition, more common use of supplements, even those with relatively low iodine content, may lead to better iodine status in pregnant women in Latvia comparing to 2013.

Although, register of thyroid autoimmune diseases has not been established in Latvia, but indirectly the prevalence may be evaluated by frequency of medications used in treatment of thyroid disorders. Analysis of levothyroxine and thiamazole use in Latvia from 2011 to 2014 showed that the frequency of medications use increased in all age groups. (49) As known the most common thyroid disorders are autoimmune or Hashimoto thyroiditis and Grave’s disease and increase in drug consumption implies an increase in the incidence of these thyroid autoimmune diseases.

In the case of autoimmune thyroiditis, optimal selenium intake is essential and associated with a reduction in oxidative stress and inflammatory responses in the thyroid gland. (50)

Serum selenium levels in the first trimester (101.5 µg/l) were lower in our population than in populations of some countries, such as the United States (151 µg/l), Japan (140.2 ± 12.4 µg/l), Nigeria (107.4 ± 15.8 µg/l), and Finland (106 ± 15 µg/l), but higher than values reported in other countries, such as Germany (89 ± 1 µg/l), Serbia (63 µg/l), Finland (59 µg/l), and Poland (53.4 ± 8.0 µg/l). Approximately one third (30.1 %) of pregnant women in Latvia had selenium levels below 80 µg/l, which corresponds to a status of selenium deficiency. (51)

Selenium intake levels vary among different regions and largely depend on the selenium content of foods. The main sources of selenium for the Latvian population are bread, cereals, meat, and fish. In 2011, dietary selenium intake was assessed in 990 pregnant women in Latvia using 24-h dietary recalls on two consecutive days. The average selenium intake was 50.3 µg/day, which is below the recommended daily intake of 60 µg/day for pregnant women according to European authorities and below the new value of adequate intake of 70 µg/day for women in pregnancy set by the European Food Safety Authority in 2014. (52) However, daily dose recommendations for selenium vary from one country to another.

Selenium may reduce thyroid inflammatory activity and the development of postpartum thyroiditis and permanent hypothyroidism in patients with autoimmune thyroiditis. Prospective randomised placebo-controlled study confirms that anti-TPO positive pregnant women treated with selenium 200 µg per day during pregnancy and postpartum had a significantly lower incidence of postpartum thyroiditis and permanent hypothyroidism compared to those in the untreated group. (53) However, the results of another double-blind randomised placebo-controlled study where selenium during pregnancy was administered at a lower daily dose (60 µg), did not indicate any change in anti-TPO levels in the study and control groups. (54) Currently there is a lack of sufficient evidence to recommend routine selenium supplementation during pregnancy in anti-TPO positive women, further randomised studies should be conducted on this subject. (16)

The selenium status in the Latvian general population has not been assessed, but our study reported a mean serum selenium level of 101.5 µg/l in pregnant women in Latvia (~30 % being deficient, below 80 µg/l). The optimal selenium status and the best biomarker of selenium sufficiency in pregnancy have not been clearly defined by international experts. The SEPP concentration reflects selenium resources in the organism and appears to be a better marker of selenium status than the concentration of plasma selenium, which also includes selenomethionine incorporated in the protein structure. (55) Although several commercial kits for the quantification of SEPP in the plasma are available, reference values for SEPP are not currently established as there are significant variations in the serum concentrations of SEPP obtained by different techniques, immunoassays, and laboratories. (56) In the current study, the median SEPP level was 6.9 (3.1–9.0) mg/L. In comparison, the median SEPP level in controls (n = 993) in the study nested within a Danish cohort was 5.5 (3.5–8.0) mg/L. (57) Concentrations of the SEPP were measured in 966 healthy individuals participating in the large European Prospective Investigation into Cancer and Nutrition (EPIC) study and the mean SEPP level was 4.4 mg/L. (58) A reference range of 2.56–6.63 mg/L for serum SEPP concentration has recently been proposed based on the data obtained from EPIC study. (59) However, data on SEPP concentrations in pregnant women are scarce.

During pregnancy, 13–17 % of selenium is incorporated into plasma GPX, 50–60 % is incorporated into SEPP, and 23–32 % is bound to albumins. (60)

We did not find any significant correlation between serum selenium and SEPP levels in early pregnancy, indicating that either the selenium status of pregnant women was at the level needed for full expression of selenoproteins or, more likely, that increasing oestrogen levels increase SEPP levels, similarly to thyroxine-binding globulin and cortisol-binding globulin. (61) Therefore, more robust evidence of the efficacy of SEPP levels as a biomarker of selenium status in pregnancy is needed.

3.3 Iodine intervention study in pregnant women in 2018

Compared to the study of pregnant population in Latvia performed in 2013, iodine sufficiency in the first trimester during past 5 years has improved, however, it does not reach optimal level neither in intervention group nor study group. In chapter 3.2. is discussed potential factors, associated with better iodine intake in absence of mandatory USI strategy in Latvia. Overall, improvement of iodine sufficiency is multifactorial and can be attributed to food production (e.g. use of iodine-containing disinfectants in dairy farming) (48), the import of foods from countries (Poland, Denmark) with mandatory USI (46) and the increased use of iodine-containing dietary supplements during pregnancy (at least 150 µg of iodine was used by 3.1 % in 2013, 14.7 % of pregnant women in 2018).

It might be hypothetical that the availability (free of charge) and use of 150 µg iodine supplement during pregnancy might be associated with better median UIC, results suggested that iodine sufficiency improved in both study groups along the progression of pregnancy – moreover in controls increase of median UIC in second trimester was significant and reached optimal level according to WHO criteria (181.9 µg/g Cr).

Alongside the use of iodine supplements, dietary recommendations related to the consumption of iodine rich products and iodised salt, provided by antenatal care professionals have an important role. Both – use of iodised salt and intake of fish and seafood increased as pregnancy progressed, thus having a positive impact on iodine supply during the second and third trimesters. Similar results were obtained from an observation study conducted in Catalonia involving 633 pregnant women on their first antenatal visit, where women received information about importance of iodine during pregnancy and recommendations about foods rich in iodine. Dietary intake of iodine containing food products and UIC were evaluated during the first, second and third trimesters of pregnancy. It was observed that the consumption of dairy products, iodised salt and iodine supplements increased with the progression of pregnancy and was associated with improve of iodine sufficiency and median UIC above 150 mg/L, confirming the importance of recommendations given by healthcare professionals. (62)

All women involved in study received information about the importance of iodine intake during pregnancy at their first antenatal appointment, therefore, 19 % of pregnant women in the control group took iodine (150 µg) voluntary, which should be taken into account when evaluating UCI in controls. It should be mentioned that the benefits of iodine supplementation during pregnancy in regions of mild to moderate iodine deficiency are still unclear and there is a lack of broad randomised, placebo-controlled studies to draw conclusions. However, ethical aspects of conducting such designed studies are associated with several concerns, highlighting the potential risk of control groups and placebo recipients for developing iodine deficiency disorder. A randomised placebo-controlled trial of 150 μg iodine in the intervention group started in Australia was stopped due to published national recommendations – iodine containing supplements should be recommended to all women during pregnancy. (63) Another important ethical aspect of placebo-controlled studies is potentially negative effects of excessive iodine intake.

Use of iodine in a large population raises concerns about potential increase of thyroid autoimmunity and impairment of hormonal synthesis. This aspect has delayed implementation of mandatory USI in many regions of the world. Iodine induced thyroid hyperfunction was observed in Zimbabwe and the Democratic Republic of Congo, when after implementation of mandatory USI program, excessive iodine intake was observed in previously severely deficient regions, and this was associated with poorly monitored salt iodisation. Increase of hyperthyroidism was related to excessive iodine intake predominantly among elderly people with thyroid nodules, associated with lack of proper thyrocyte response to TSH and autonomy of thyroid nodules. (64) On the other hand, in Denmark, starting gradual USI in regions with moderate and mild iodine deficiency (Alborg and Copenhagen, respectively) higher incidence of hypothyroidism in young and middle-aged people was experienced (65), as well as an increased incidence of hyperthyroidism in both women and men in all age groups. (66)

In China, when comparing three cohorts with mild iodine deficiency, with iodine supply above optimal and excessive iodine intake, the cumulative incidence of autoimmune thyroiditis was observed at 0.2 %, 2.6 % and 2.9 %, respectively. Over a five-year period, individuals with thyroid antibodies and euthyroidism in cohorts with iodine intake above optimal and excessive iodine intake were more likely to experience an increase in TSH compared to a mild iodine deficiency cohort. This leads to the conclusion that excessive intake of iodine is associated with more frequent development of hypothyroidism and autoimmune thyroiditis. (67)

In conclusion, to evaluate effectiveness of salt iodisation and to avoid excessive iodine intake, careful monitoring is required when salt iodisation strategies are implemented in large population. At the same time, even mild and moderate iodine deficiency in population, is attributed to potentially higher risks and consequences (e.g. pregnancy failure, neurocognitive deficiency in offspring, struma, etc.) than possible risks associated with excessive iodine intake. (64)

Administration of 150 µg containing iodine supplement per day and dietary recommendations about iodine containing product consumption, use of iodised salt in household are safe recommendations for pregnant women and have been recommended as early as three months before pregnancy in accordance with ATA guidelines. (16, 68)

In the present study, median ioduria did not indicate excessive iodine intake in any of the groups at different trimesters of pregnancy, and no increase in antiTPO was observed in any of the study groups. Administration of iodine 100 and 150 µg daily in pregnant women is not associated with anti-TPO changes – similar are conclusions from a small retrospective study of pregnant women in Germany. (69)

3.4 Screening of newborn TSH as indicator of iodine sufficiency in Latvian population

In 2019, in newborn TSH screening involved 18.593 newborns and 5.6 % (95 % CI 5.2–5.9 %) of them were detected in TSH > 5 mIU/L, while in 2022 TSH screening was performed in 15,664 newborns and 8.8 % (95 % CI 8.4–9.3 %) had TSH > 5 mIU/L. According to the criteria recommended by WHO (neonatal proportions of 3.0–19.9 % with TSH 5 mIU/L indicate mild iodine deficiency in the population (24)), neonatal TSH screening data confirm that Latvia belongs to the mild iodine deficiency region.

Previous TSH screening analysis in 2000–2002 also confirmed mild iodine deficiency. Newborns with TSH > 5 mIU/L were 16.5 % in 2000, 10.4 % in 2001 and 8.4 % in 2002. (8) Similarly, in 2009, 8.2 % (95 % CI 7.8–8.7 %) and, in 2010, 9.3 % (95 % CI 8.8–9.7 %) of newborn had TSH > 5 mIU/L, confirming mild iodine deficiency in the population. In addition, there is a statistically reliable regional difference in iodine insecurity, with 13.1 % (95 % CI 12.1–14.1 %) in Latgale region, while 5.8 % (95 % CI 5.1–6.6 %) of newborns with TSH > 5 mIU/L. (23) in Kurzeme.

Neonatal TSH values improve with changes in iodine supply during pregnancy (70) , which coincides with better median ioduria in pregnant women, but although the TSH screening registry reflects an improving trend in iodine supply, Latvia still belongs to a region with mild iodine deficiency.

Weaknesses of the Study

The study had several limiting factors:

1. **Low number of participants in the intervention study**. Successful implementation of study, which includes various sequential research activities (questionnaires, serum testing for thyroid parameters, collection of urine samples in each trimester of pregnancy), requires accuracy from both – the specialists involved and respondents. Failure to track answered questionnaires, urine and serum samples led to missing data and to consequently low number of respondents for the data analysis.
2. **"Purity" of the control group.** The importance of sufficient iodine intake during pregnancy is not in doubt, therefore, in the study control group, iodine supplements were voluntarily used by a certain number of pregnant women, and the researcher was not entitled to limit that for ethical reasons.
3. **Initial differences of median UIC in intervention and control groups.** Although the involvement of pregnant women in the study was organised randomly (three different outpatient medical centers where the antenatal care is state covered and it is provided by gynaecologist/obstetrician and) , the first trimester median UIC were different in both groups, with lower rates in the iodine user group. Consequently, the hypothetical claim that use of iodine supplements is associated with better iodine sufficiency in intervention group could not be confirmed, which was also affected by the relatively low number of respondents.
4. **Lack of information about the use of selenium-containing products during pregnancy.** Questionnaires originally did not contain questions about dietary habits associated with selenium intake. Therefore, information on selenium-containing products in pregnant women is

incomplete and secondary data from the SPCC study about dietary habits among reproductive age women were analysed.

5. **Measurements of selenium sufficiency.** There is still a lack of consensus opinion among international organisations of professionals on the most informative selenium markers and their reference values, especially in the pregnant population. Consequently, the optimal selenium sufficiency, testing and additional use during pregnancy remain relevant and need to be clarified further.

Conclusions

1 Median UIC confirms that iodine intake during pregnancy in Latvia is insufficient. The lowest median UIC was assessed in the first trimester. There are no territorial or seasonal differences in the supply of iodine during pregnancy in Latvia. Data from the neonatal TSH screening registry also confirm mild iodine deficiency in the population.

2 Around half of pregnant women take supplements during the first trimester, but only a small part of them contains iodine more than 100 µg. The use of supplements with iodine content at least 100 µg and above statistically significantly improves iodine supply. The use of iodised salt, dairy products, fish and seafood is also associated with higher median UIC. Selenium levels in around 30 % of pregnant women were less than 80 µg/L, corresponding to selenium deficiency. Only a small proportion (10.1 %) of the supplements used by pregnant contained selenium > 60 µg.

3 National recommendations, various information activities and materials for healthcare professionals and the society can be attributed to improvement of iodine sufficiency during pregnancy, reveals 1st trimester median UIC in 2018 compared to 2013. However, optimal iodine intake during first trimester, when it is particularly important for the early development foetal CNS, has not yet been achieved. Despite the published national recommendations emphasizing use of 150 µg iodine as a daily dietary supplement during pregnancy, a small proportion of pregnant women is following this recommendation.

4 For improvement the iodine sufficiency in Latvia, nutritional recommendations regarding daily consumption of iodised salt, milk products, seafood and fish, as well as intake of at least 150 µg iodine – containing supplements during pregnancy are important. These interventions are safe – in none of the groups did the median ioduria at

different trimesters of pregnancy indicate excessive iodine intake, and no increase in anti-TPO or changes in thyroid function were observed. Serum selenium and selenium protein P levels were not different in women with normal and elevated anti-TPO levels. Similarly, there was no significant correlation between selenium, selenoprotein P and TSH levels.

Proposals

1 There is need to develop and implement **a strategy for the elimination** iodine deficiency in the population at the level of the Ministry of Health and the CDPC in Latvia.

2 Targeted information and education about the importance of optimal iodine intake during pregnancy and lactation should focus on:
   - healthcare professionals (gynaecologists/obstetricians, general practitioners, endocrinologists, midwives, nutritionists, including pharmacists) involved in the care of the pregnant and breastfeeding women;
   - pregnant and breastfeeding women;
   - women with childbearing potential planning pregnancy;
   - specialist organisations (gynaecologists/obstetricians, endocrinologists, general practitioners) should define consensus recommendations for the use of iodine and selenium supplements in specific clinical situations and pregnancy (autoimmune thyroiditis, levothyroxine use, etc.).

3 The iodine sufficiency of population should be monitored periodically (at least every five years) using the WHO recommended indicators (neonatal TSH screening, median UIC in the schoolchildren and pregnant population) to evaluate the effectiveness of interventions implemented.

4 For a certain social risk groups during pregnancy, supplements should be state covered (folic acid, iodine, vitamin D, iron).

5 Further studies are needed to evaluate selenium sufficiency in the general and pregnant population in Latvia to develop recommendations for additional use of selenium.

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