



# Iodine Status of Pregnant Women in Bulgaria

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**Abstract:** Universal iodization of salt on the whole territory in Bulgaria was introduced in 1994. The external evaluation of an International expert group conducted in 2005, placed the country among those who successfully overcame the problem of iodine deficiency. AIM of the present study is to update the data on iodine intake of pregnant women in Bulgaria, given that there have been no studies in the last 8 years. MATERIAL: A total number of 537 pregnant women were recruited in the study with an average age  $30.49 \pm 5$  y, distributed by gestational weeks and according to the intake of (vitamins and minerals preparations) preparations containing vitamins with minerals. The study was conducted as a cross-sectional, multicenter population-based in 10 regions of Bulgaria (a total of 84 settlements), without pre-selection and 98.3% of the examined pregnant women use Bulgarian iodized salt according to the data from the Questionnaire. METHOD: A spot morning urine samples were collected for determination of urinary iodine concentration. The frozen samples in a special container were transported to the accredited Limbach laboratory in Heidelberg, Germany. The iodine in urine was determined by inductively coupled plasma mass spectrometry (ICP-MS) method. The statistical analysis was performed using standard SPSS 13.0 for Windows. RESULTS: The median urinary iodine concentration (mUIC) for the whole group of pregnant women (n=537) was  $170 \mu\text{g/L}$  (95% CI 161.00 - 177.00). Normal iodine excretion is present in 39.3%, low – in 41.2% and over-optimal – in 19.6% of pregnant women. Significantly lower levels of iodine in urine were found in the third trimester of pregnancy compared to the first trimester ( $P < 0.012$ ) and compared to the second trimester ( $P < 0.001$ ). The median iodine concentration in pregnant women from the group supplemented with combined vitamins with minerals was significantly higher compared to the group without supplementation – 175 (95% CI 166.00 - 199.00) against 149 (95% CI 123.00 - 168.00),  $P < 0.021$ . CONCLUSION: During pregnancy, additional supplementation with combined vitamins with minerals containing iodine is required, regardless of the universal iodization of salt, introduced in Bulgaria for more than twenty-five years.

**Keywords:** Pregnant Women, Universal Salt Iodization, Urinary Iodine Concentration, Supplementation

## 1. Introduction

Iodine deficiency is a serious public health and social problem that affects huge population groups in the so-called “endemic” areas with low iodine content in the environment. High risk groups for low iodine intake are pregnant women and infants, as the trace element is involved in the formation of brain structures and inadequate iodine intake during pregnancy and infancy seriously affects the cognitive development of the fetus and newborn [1-3]. With the introduction of “universal” salt iodization, an effective and

inexpensive strategy to increase iodine intake by the general population, the problem of iodine deficiency has been eliminated worldwide [4, 5]. The reference group for assessing the effect of iodine prophylaxis are schoolchildren, aged 6-10 years, and the most convenient indicator for assessing iodine intake is the determination of the concentration of iodine in the urine [6-8]. This biochemical marker is used in the application of appropriate sampling and is a sensitive and specific analytical indicator. Iodine concentration in urine reflects immediate iodine intake and is a reliable screening indicator for population groups for which

reference intervals have been determined for both school children and pregnant women [9]. However, there are still discussions about the epidemiological criteria for assessing iodine status during pregnancy [10, 11]. Universal iodization of salt on the whole territory in Bulgaria was introduced in 1994. In 2005, the evaluation of an international expert group acknowledged the country among those who successfully solved the problem of iodine deficiency [12, 13]. According to international criteria, no additional iodine supplementation is recommended for pregnant women in a country that has eliminated iodine deficiency [14]. Results of national surveys for an assessment the progress of the prevention program conducted in 2003, 2008 and 2012 show that iodine intake in schoolchildren is adequate, but in the small number of pregnant women studied – the median iodine is closer to the lower limit of the reference interval 165.0 µg/L, 158.5 µg/L and 161.0 µg/L, respectively.

The aim of the present study is to update the data on iodine intake in pregnant women in Bulgaria, given that no studies have been performed in the last 8 years.

## 2. Study Design

A cross sectional, multicenter population-based study was conducted from September 25 to November 6, 2019 in 10 regions of Bulgaria (Sofia and Sofia region – Samokov, Pirdop; Smolyan and the region; Gotse Delchev; Gabrovo and the region; Troyan-Apriltsi; Burgas and the region; Stara Zagora and region; Pleven and the region), including small towns and villages from each region or a total of 84 settlements. The regions were not randomly selected. Regions with a known iodine deficiency in the past were included, such as Sofia city, Sofia district, Smolyan, Gotse Delchev, Gabrovo, Troyan, as well as regions with iodine sufficiency – Burgas, Stara Zagora, Pleven and their districts. The study was conducted with the assistance of 104 endocrinologists and gynecologists from the selected areas. From their lists of registered pregnant women, a total of 630 women were invited to participate corresponding to a recruiting rate of 85.2% (n=537).

According to the annual reports of the National Statistical Institute (NSI) of Bulgaria in recent years there are usually about 60 000 live births per calendar year. This determined the projected number of pregnant women for inclusion in the screening given that up to about 1% of their total number for the country should be examined. For 2019, the NSI reports 61 538 live births. The current screening includes 537 or 0.87% of pregnant women for 2019 [15].

## 3. Material and Methods

We studied 537 pregnant women, mean age 30.49±5 y [95% CI: 30.06 - 30.91], median – 30 (18 - 47), [95% CI: 30 - 31]. Their distribution by age categories was as follows: 18 - 22 y – 31 (5.78%), 23 - 27 y – 114 (21.22%), 28 - 32 y – 214 (39.86%), 33 - 37 y – 128 (23.84%), 38 - 42 y – 46 (8.56%), 43 - 47 y – 4 (0.74%). The examined pregnant women were distributed by trimesters according to the gestational week, as

follows: first – 109 (20.3%), second – 269 (50.1%), third – 159 (29.6%).

All participants signed an informed consent, approved by the local Ethics Commission at Sofamed University Hospital, Sofia University “St Kliment Ohridski”, and it was prepared in accordance with ethical standards according of the Helsinki-1964 Declaration and its later additions.

Each pregnant woman filled in a Questionnaire personally with the assistance of a specially designated medical person from the “face to face” team in order to correctly collect data on pregnancy history, intake of combined vitamins and minerals, other medications by type and dose, available thyroid or other diseases. Pregnant women were admitted to the screening at random without pre-selection, as 458/537 (85.28%) of them took medication [Magnesium supplements – 125 (23.27%), Acid Folic – 118 (21.9%), Micronized progesterone – 23 (4.2%), Iron supplements – 64 (11.9%), Antispasmodics – 32 (5.9%), Aspirin – 30 (5.5%), Low molecular weight heparins – 27 (5.0%), Levothyroxine – 79 (14.7%), Methyldopa – 4 (0.7%)] – alone or in various combinations. However, mainly in 50.46% (271/537) of the cases these were combined preparations containing vitamins and minerals taken alone or together with other medications, which is according to the protocol of gynecologists and thus provides 150 µg iodine per day. The most common drugs are magnesium, folic acid and iron (57.1%), while the other drugs are given to individual pregnant women in order to preserve the pregnancy and bring it to a successful delivery – antispasmodics, progestin, and anticoagulants. Levothyroxine substitution was found in 79 (14.7%) pregnant women with a known thyroid disease. All participants were of Caucasians, with no evidence of liver, kidney disease or evidence of malabsorption. Pregnant women had followed their usual daily routine in the previous months.

After completing the personal questionnaire, the actual weight and height were measured for each pregnant woman. The pre-pregnancy weight was also registered in the Questionnaire. The body mass index (BMI - kg/m<sup>2</sup>) before pregnancy and the current one were calculated. Data on dietary supplement use were obtained from Questionnaire, and women were classified as supplement users (using combined vitamins containing ≥ 150 µg iodine/day) and nonsupplement users. The cut-off of 150 µg was chosen in accordance with the recommended level for iodine supplementation during pregnancy in many countries [16, 17] and as the most popular combined vitamin with minerals tablets in our country contain 150 µg iodine.

The main indicators that determine the presence of iodine deficiency are: the concentration of urinary iodine, TSH level, thyroid size (volume). The first most important is the amount of iodine in the urine, which reflects the intake of iodine with food (90% is excreted passively in the urine depending on estimated glomerular filtration rate, eGFR) [18]. Thus, the concentration of iodine in urine (Urinary iodine concentration, UIC) in a sustained diet represents the balance between dietary intake, thyroid iodine extraction, total thyroid hormone depot and GFR.

### 3.1. Laboratory Test

Urinary iodine concentration was determined. The Pregnant women gave a single portion of the morning fresh midstream urine ~20 ml using the clean plastic cups to test iodine. The samples were immediately transported at room temperature in neutral monocuvets to the Central Laboratory (for transport shorter than 8 h, they were transported a room temperature, which does not influence their quality) and the aliquots of all urine samples were frozen at -20° until analysis. The next day the frozen samples were transported in special containers to the accredited Limbach laboratory in Heidelberg, Germany. The analysis was performed using the accredited inductively coupled plasma mass spectrometry (ICP-MS) method with the following characteristic: linearity in the range of 0 – 4000 µg/l, precision in the series at 304 mcg/l RSD 0.8%, inter-assay SNU=304 µg/l, 15 shifts, RSD 4.5%; accuracy percentage deviation from adjusted nominal value of the certified reference material Seronorm™ Trace Elements urine (SNU) (304 µg/l): 4.0% (data set=4x12), recovery 104%. The results are presented in µg/L.

### 3.2. Statistical Processing

Statistical analysis was performed using standard SPSS 13.0 for Windows: descriptive statistics (mean, medians, standard deviation), correlation analysis and analysis of variance (ANOVA, post-hoc test - with Bonferroni alpha correction), using parametrical and non-parametrical methods, including - Chi-Square Test, Fisher's Exact Test, Kolmogorov-Smirnov, Shapiro-Wilk Tests, Levene's Test for Equality of Variances, Student's t-test, Kruskal-Wallis test and Mann-Whitney test. All quantitative variables were presented as mean with standard deviation, median or percentage (unless specified otherwise), p values below 0.05 were accepted as statistically significant.

## 4. Results and Discussion

The median urinary iodine concentration (mUIC) for the whole group of pregnant women (n=537) was 170 µg/L (95% CI: 161.00 - 177.00). Figure 1 graphically presents iodine in urine for the whole group of 537 pregnant women.

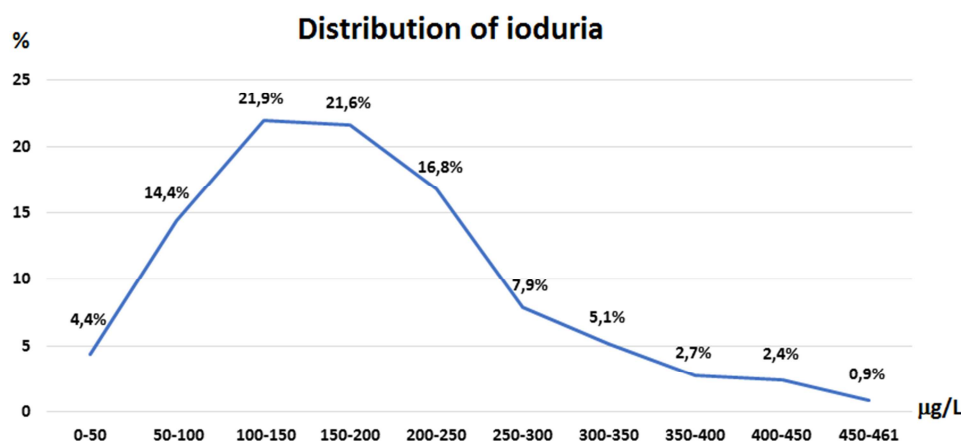


Figure 1. Graphical representation of the distribution of ioduria for the whole group (n=537).

The Table 1 shows the distribution into three main groups according to the size of urinary iodine a. The results show that 211 pregnant women (39.3%) from the study group had normal iodine excretion in the range of 150 - 250 µg/L, which reflects adequate iodine intake. Below 150 µg/L – lower limit of the reference range of iodine in urine for pregnant women, were 221 women (41.2%). There were no cases of excessive iodine intake (iodine in urine > 500 µg/L), and 105 (19.6%) women had over-optimal iodine intake (250 - 497 µg/L).

Table 1. Distribution in three main groups according to the level of urinary iodine concentration (UIC) low, normal, over-optimal.

Parameter	Number	Level (µg/L)	%
Low UIC	221	1-149	41.2
Normal UIC	211	150-249	39.3
Over-optimal UIC	105	249-497	19.6

Table 2 shows UIC by trimester. Significantly lower level of iodine in urine in the third trimester was found compared to the first ( $P < 0.012$ ) and the second trimester ( $P < 0.001$ ).

These results may be related to the development of the fetal thyroid gland and the need for more substrate to produce hormones by both the mother and already from the fetus.

Table 2. Mean values and median of urinary iodine concentration by trimesters of pregnancy of the study population.

Trimester	Mean	Std. Deviation	N	Median
First	185,28	94,09	109	166
Second	195,13	97,68	269	185
Third	156,97	81,86	159	145
Total	181,88	93,84	537	170

The intake of medications and combined vitamins with minerals during pregnancy was additionally analyzed and it was found that only 79 (14.7%) pregnant women did not take anything and the remaining 458 (85.29%) did. It turned out that in the whole studied group of pregnant women (n=537) the most commonly taken drugs were the combined vitamins with minerals – 271 (50.47%). It was specified that among 458 pregnant women taking medication, 271 of them (59.17%)

took combined vitamins with minerals alone or together with other medications (in over 57% of cases it was folic acid, magnesium, iron, antispasmodic for successful completion of pregnancy and following a standard protocol). Pregnant women under the substitution of combined vitamins with minerals took another 150 µg of iodine in addition to the usual diet. Therefore, three groups were formed:

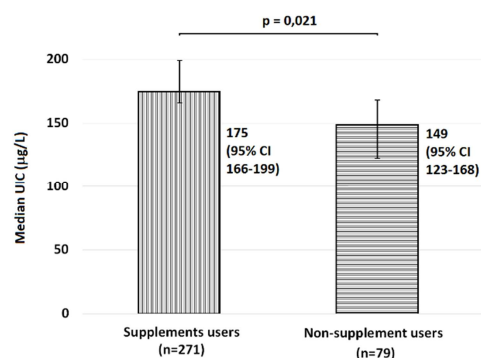
1. Group 1 – pregnant women not taking anything (n - 79)
2. Group 2 – pregnant women taking combined vitamins with minerals – alone or with other medications (n - 271)
3. Group 3 – pregnant women taking any medication but not combined vitamins with minerals (n - 187)

Table 3 divides pregnant women from the three groups described according to medication intake.

**Table 3.** Distribution of pregnant women according to the use of medications.

Group	Group 1 Not taking anything	Group 2 Taking Vitamins	Group 3 Taking other medications
number	79	271	187
Mean	158.0	191.8	176.7
SD	92.8	95.5	89.5
95% Confidence Interval for Mean	137.1-178.9	180.3-203.2	163.7-189.7
Median	149	175	170
95% Confidence Interval for Median	123-168	166-199	151-185
<149 µg/L	53.1%	36.9%	42.2%
150-249 µg/L	32.9%	39.4%	41.7%
>250 µg/L	13.9%	23.6%	16.6%

The results of UIC presented in the table 3 show that nearly 1/3 (32.91%) of pregnant women who have normal iodine excretion do not take any mineral-vitamin supplements. Probably the normal iodine excretion is a result of the universal salt iodization, which includes also the use of iodized salt by the food processing industry (bread, cheese, sausages, etc). Universal iodization of salt in Bulgaria was introduced in 1994 and in 2005 Bulgaria was declared a country that successfully eliminated deficiency among the population [12, 13]. It turns out that the median iodine concentration of pregnant women of group 2 (with supplementation) is significantly higher than in group 1 (without supplementation) [175 (95% CI: 166.00 - 199.00) vs. 149.00 (95% CI: 123.00 - 168.00),  $P < 0.021$ ], figure 2.



**Figure 2.** Comparison of median (95% Confidence Interval for Median) between groups 1 and 2.

As can be seen from Table 3, a comparison between Group 1 and Group 2 revealed a difference between the frequency of urinary iodine in the subgroup  $< 149 \mu\text{g/L}$ , which is logically significantly more common in Group 1 (non-supplemented) than in Group 2 (supplemented with combined vitamins with minerals) – 53.17% against 36.90%,  $P < 0.01$ . The frequency of high iodine excretion in the subgroup  $> 250 \mu\text{g/L}$ , on the contrary, was significantly higher in Group 2 (supplemented with combined vitamins with minerals) compared to Group 1 (not supplemented) – 23.62% vs. 13.92%,  $P < 0.05$ .

A special place was given in the Questionnaire regarding the type of salt used in the household -Bulgarian iodized table salt, Himalayan salt or combination of both types of salt. It turned out that 483 (90.45%) of all pregnant women use Bulgarian iodized salt, 9 (1.69%) – Himalayan salt and 42 (7.86%) – both types of salt. Obviously, the percentage of pregnant women who do not use Bulgarian iodized salt is negligible – 1.69% (n - 9) and this is an excellent certificate for the Bulgarian population – 98.31% cook with iodized salt.

Moreover, the recommendations for reducing salt intake and using only iodized salt instead of any other non-iodized varieties remain disputable [19, 20].

## 5. Conclusion

The study for evaluation of the current iodine intake of pregnant women under the circumstances of eliminated iodine deficiency by the universal iodization of salt allows to draw several main conclusions. Mass iodine prophylaxis, involving the use of iodized salt in food production and for direct use, provides adequate iodine intake even from population groups with increased needs, such as pregnant women proven to have normal iodine excretion.

Despite the effectiveness of universal iodization of salt and in particular the exclusive use of only iodized salt in the food industry, during pregnancy it is recommended to take additional iodine-containing combined preparations, proven by iodine excretion closer to the optimal reference values for population assessment in the supplemented group.

Due to the widespread recommendation to reduce salt consumption (iodized and non-iodized), including during pregnancy, it is appropriate to recommend to all pregnant women to be supplemented with iodine-containing preparations of vitamins and minerals, regardless of the proven successful elimination of iodine deficiency in Bulgaria.

## Conflicts of Interests

All the authors do not have any possible conflicts of interest.

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