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Published in:
Clinical Endocrinology

DOI (link to publication from Publisher):
10.1111/cen.14797

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Received: 20 April 2022 | Revised: 16 June 2022 | Accepted: 29 June 2022

DOI: 10.1111/cen.14797

ORIGINAL ARTICLE

WILEY

Iodine status in Danish pregnant women after an increase in iodine fortification

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Funding information

Stofskifteforeningen; Novo Nordisk Foundation, Grant/Award Numbers: NNF18OC0033520, NNF20OC0059465

Abstract

Objective: Iodine fortification programmes are implemented in many countries and often associated with an increase in population iodine intake. However, the initial attempt may not be sufficient and in Denmark the level of iodine added to salt was increased in 2019. Sparse evidence is available on the impact of such modification in iodine fortification. The aim of this study was to evaluate iodine status in Danish pregnant women in 2021 after this increase in iodine fortification and compare to iodine status in 2012.

Design: Cross-sectional study.

Patients: Pregnant women in the North Denmark Region referred for routine obstetric ultrasound in 2021.

Measurements: Participants filled out a questionnaire and delivered a spot urine. Median urinary iodine concentration (UIC) was calculated and assessed according to the recommended range in pregnancy (150–249 µg/L).

Results: Altogether 147 pregnant women were included and 88% used iodine-containing supplements. Median UIC was overall 77 µg/L [95% confidence interval (CI): 61–96 µg/L], which was lower than in 2012 (101 µg/L [95% CI: 89–111 µg/L]) ($p < 0.001$). Considering sources of iodine intake in pregnancy, lower daily intake of dairy products ($p = 0.008$) and bread ($p < 0.001$) and a lower content of iodine in the supplement used ($p < 0.001$) was seen in 2021 compared to 2012.

Conclusion: Despite an increase in iodine fortification and frequent use of iodine-containing supplements, iodine status in pregnant women in the North Denmark Region was insufficient. Results call for continued monitoring and attention to ensure adequate iodine status during pregnancy in Denmark.

KEYWORDS

iodine, iodine status, urinary iodine concentration, iodine fortification, pregnancy

1 | INTRODUCTION

Iodine is an essential micronutrient required for the synthesis of thyroid hormones needed for foetal growth and brain development.[1] In pregnant women, the iodine requirements increase due to several pregnancy-related physiological changes.[2] One of the most serious adverse effects of iodine deficiency in pregnancy is impaired neurodevelopment, and the prevention of cretinism was one of the main goals with the implementation of a global strategy for prevention and control of iodine deficiency.[2,3] The local strategy for prevention of iodine deficiency varies between populations, however, a common method is the implementation of an iodine fortification programme, and in many settings iodine is added to salt.[4,5] Iodine fortification programmes necessitate close monitoring of population iodine intake since the association between iodine intake and the occurrence of thyroid disease is U-shaped.[3,4] Substantial evidence has described the impact of the implementation of iodine fortification programmes in different countries, in different population groups, and in populations with a different *a priori* iodine status.[5] On the other hand, the impact of a change in population iodine fortification, for example, a modification of the level of iodine added to salt, is less studied.[6]

The Danish population was previously iodine deficient with regional differences reflected by mild iodine deficiency in East Denmark and moderate iodine deficiency in West Denmark.[7] A mandatory iodine fortification of salt at a level of 13 ppm was introduced in Denmark in the year 2000, which increased the iodine intake in the general Danish population.[7–9] However, median urinary iodine concentration (UIC) in adults was still below the recommended range (100–299 μg/L)[4,10] after 11 years.[9] Iodine status in Danish pregnant women was evaluated in 2012 in West Denmark[11] and in 2014 in East Denmark[12] and was considered insufficient in both regions with median UIC below the recommended range (150–249 μg/L).[4] The insufficient iodine status in pregnant as well as nonpregnant adults led the Danish authorities to implement an increase from 13 to 20 ppm in the level of iodine added to salt from July 1, 2019.[13] The marked increase raises a need for monitoring of population iodine intake, especially in vulnerable groups such as pregnant women.

In the present study, we aimed to evaluate urinary iodine status in pregnant women in the North Denmark Region after the increase in iodine fortification of salt. The North Denmark Region is part of West Denmark and of main interest as this region previously had the most pronounced iodine deficiency.[7] Furthermore, the current study included pregnant women from the same geographical area as the study in 2012[11] which allows for comparison with the iodine status of Danish pregnant women before the increase in iodine fortification.

2 | MATERIALS AND METHODS

2.1 | Study population

We performed a cross-sectional study among Danish pregnant women in the North Denmark Region which is in West Denmark. Study participants were recruited consecutively from September 8 until October 12, 2021, when they arrived for routine obstetric ultrasound in the Department of Obstetrics, Aalborg University Hospital. Every pregnant woman in Denmark is offered such ultrasound as part of the nationwide prenatal screening programme, and the rate of participation is above 90%.[14] Altogether 172 pregnant women provided informed consent for participation in the study and were asked to deliver a spot urine sample and to fill out an electronic questionnaire with information on maternal health, socio-demographic characteristics, dietary habits, and use of dietary supplements. A total of 147 women provided complete information and were included in the final study population excluding multiple pregnancies ($n = 3$) and women with known thyroid disease ($n = 3$) or gastrointestinal disease associated with malabsorption (inflammatory bowel disease and coeliac disease) ($n = 3$).

The study was registered according to the General Data Protection Regulation in the North Denmark Region (2021-111) and study data were collected and managed using REDCap electronic data capture tools hosted at the North Denmark Region.[15,16] The local institutional Committee on Health Research Ethics deemed the project exempt from review.

2.2 | Biochemical analyses

A nonfasting spot urine sample was collected from each woman at the time of inclusion (ranging from 8 a.m. and 15 p.m.). Each urine sample was stored at −20 degrees Celsius before the biochemical analyses. Analyses of urinary iodine were performed in four batches in the Department of Endocrinology, Aalborg University Hospital, which is certified by the U.S. Centres for Disease Control and Prevention's EQUIP Programme. UIC was determined by spectro-photometric measurements of the Sandell-Kolthoff reaction with cerium and arsenite reagents after alkaline ashing modified by Wilson and van Zyl,[17] as previously described in detail.[18] A total of 21 samples with iodine concentrations in the range from 25 to 600 μg/L from the study in 2012[11] were randomly included in the present batch-analyses to assess comparability with previous results. Relative mean bias between the results in 2012 and the re-analyses was −1.1% (95% CI: −3.5% to 1.3%). Urinary creatinine was analysed in the Department of Clinical Biochemistry, Aalborg University Hospital, using Cobas 8000 (Roche Diagnostics).

2.3 | Statistical analyses

Urinary iodine excretion was expressed as UIC (μg/L), iodine/creatinine ratio (μg/g) and the estimated 24-h excretion of iodine using a urinary excretion of creatinine on 1.09 g per 24-h previously measured in Danish pregnant women.[19] Categorical variables were described by the number (n) and the frequency (%). Continuous variables showed skewed distribution and were described by medians with interquartile range (IQR) or a 95%

binomial-based confidence interval (95% CI).[10] Chi-squared test and Fischer's exact test were used as appropriate for the comparison of categorical variable and Mann–Whitney *U*-test for the comparison of continuous variables between two groups. Statistical analyses were performed using Stata 17.0 (StataCorp LLC) with a 5% level of significance.

3 | RESULTS

A total of 147 singleton pregnant women were included in the study. The time of inclusion was mainly in the first or second trimester (Table 1), and median maternal age was 29.8 years. Most women were of Danish origin, had normal BMI, middle to high educational level and were nonsmokers (Table 1). Almost all women ($n = 145$) reported a use of dietary supplements. A total of 130 women (88.4%) used an iodine-containing dietary supplement (Table 1), and the recommended daily dose of iodine was most frequently 75 µg (18.5%) or 175 µg (56.2%). The majority initiated their intake of iodine-containing supplements during the pregnancy (72.3%) and often in the early pregnancy before the ninth week of pregnancy (60.0%).

The overall median UIC was 77 µg/L, and when stratified by the use of iodine-containing supplements median UIC was 80 µg/L in users and 59 µg/L in nonusers ($p = 0.080$) (Figure 1). When adjusting for maternal urinary creatinine these findings were supported and iodine excretion was highest among iodine-containing supplement users as compared to nonusers (Table 2). Compared with the figures on iodine status in Danish pregnant women in 2012, median UIC was lower in 2021 overall and among iodine-containing supplement users ($p < 0.001$), but similar among nonusers ($p = 0.581$) (Figure 1). Considering the timing of the most recent intake of iodine supplement, median UIC was higher when the most recent intake was the same day before the urine sampling (Figure 2A). When stratified by the daily dose of iodine obtained from a dietary supplement, there was no considerable difference in median UIC when comparing users of minimum 150 µg iodine/day to nonusers (Figure 2B). Furthermore, no difference in median UIC was observed when stratified by the different trimesters of pregnancy: first trimester: 78 µg/L (95% CI: 60–100 µg/L), second trimester: 74 µg/L (95% CI: 57–97 µg/L), $p = 0.887$.

Finally, we assessed if differences between the cohorts could explain the decrease in median UIC from 2012 to 2021 (Table 3). Main maternal characteristics appeared similar in the cohorts, but a change in dietary habits was seen. Thus, less women reported daily intake of bread and dairy products in 2021 as compared to 2012 (Table 3). The frequency of iodine-containing supplement use in pregnancy was similar between the cohorts (83.6% in 2012 vs. 88.4% in 2021, $p = 0.192$), but a considerable increase in the number of women using iodine supplements with a dose of less than 150 µg iodine/day was seen in 2021 (Table 3).

TABLE 1 Maternal characteristics of the pregnant women included in the study population ($n = 147$)

	n	%
Trimester at urine sampling		
First trimester	61	41.5
Second trimester	80	54.4
Third trimester	6	4.1
Age (years)		
<25	9	6.1
25–35	120	81.6
>35	18	12.3
Prepregnancy body mass index (BMI) (kg/m^2)[a]		
<25.0	96	66.7
25.0–29.9	30	20.8
≥30.0	18	12.5
Ethnicity		
Danish	130	88.4
Other than Danish	17	11.6
Education[b]		
Basic	8	5.4
Low	24	16.3
Middle	62	42.2
High	53	36.1
Smoking		
Never	89	60.6
Previous	54	36.7
Current	4	2.7
Iodine containing supplements		
Users	130	88.4
Nonusers	17	11.6

[a]Missing value on prepregnancy BMI not included: $n = 3$.
[b]Highest achieved educational level. Basic: primary and general upper secondary education (not qualifying for a profession); Low: vocational education and training; Middle: academy profession and bachelor programmes; High: master programmes and PhD.

4 | DISCUSSION

Two years after an increase in iodine fortification of salt, the overall median UIC among pregnant women within the North Denmark Region was below the recommended range of adequate iodine status in pregnancy. Moreover, the median UIC was at present lower than when evaluated among Danish pregnant women in the same region nearly one decade ago. In the present study, the highest median UIC was observed among users of iodine-containing supplements in pregnancy. However, regardless of iodine supplement use, the iodine

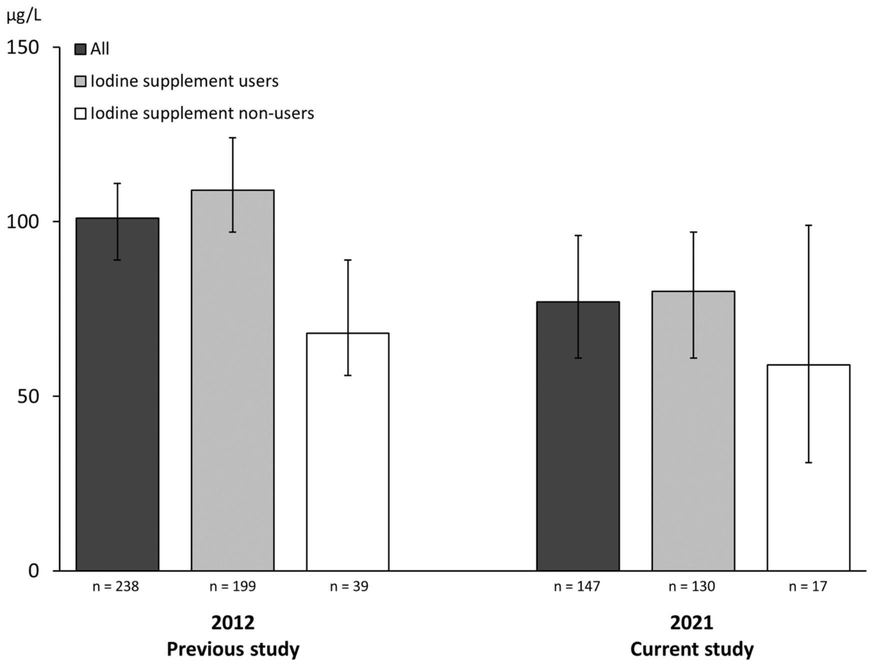

FIGURE 1 Median urinary iodine concentration with 95% confidence intervals among pregnant women in 2012 (previous study; reproduced from Andersen et al.[11]) and in 2021 (current study). Dark grey bars illustrate the overall median urinary iodine concentration whereas light grey bars and white bars illustrate the stratification according to use of iodine-containing supplements.

TABLE 2 Overall iodine/creatinine ratio and estimated 24-h iodine excretion and according to maternal use of iodine-containing supplements

		All		Iodine-containing supplements				
				Users		Nonusers		
		n = 147		*n* = 130		*n* = 17		
	Unit	Median	95% confidence interval (95% CI)	Median	95% CI	Median	95% CI	*p*[a]
Urinary iodine/creatinine ratio	µg/g	116	103–133	119	106–146	87	67–123	0.029
Estimated 24-h iodine excretion[b]	µg	127	112–145	130	115–159	94	73–134	0.029

[a]Mann-Whitney *U*-test (users vs. nonusers).

[b]Calculated from 24-h urinary creatinine excretion previously measured in Danish pregnant women: 1.09 g/24-h.[19]

status was insufficient for pregnant women and median UIC was even below the recommended range for school-aged children and nonpregnant adults, corresponding to mild iodine deficiency.

Iodine status of the Danish population has been a concern for decades and geographical difference in iodine intake within the country are well-known. Historically, these differences linked back to the ice age[20] and the lower iodine intake in West Denmark compared to East Denmark is evident from differences in iodine content of drinking water.[21] Iodine status in Danish pregnant women has throughout the past three decades been insufficient, even though a marked increase in median UIC was found after the implementation of mandatory iodine fortification of salt in Denmark.[11,12,19,22] Historically, some of the earliest reported assessments of iodine intake in Danish pregnant women were performed in West Denmark in 1988–1993.[19,22] Here it was found that pregnant women had moderate iodine deficiency (median UIC around 50 µg/L) along with signs of thyroidal stress as evident from increased TSH, high levels of thyroglobulin, and increased thyroid volume in pregnancy.[19,22] These findings raised a serious concern, and along with the findings of moderate to mild iodine deficiency in the general Danish population, and a high frequency of goitre, the observations formed the rationale to implement mandatory iodine fortification of salt in Denmark in the year 2000.[7] The implementation of iodine fortification was followed by a close monitoring in the general Danish population as part of the Danish investigation of iodine intake and thyroid disease (DanThyr).[7] As expected, iodine fortification increased iodine intake in the Danish population, and the median UIC was just within the recommended range (101 µg/L) when evaluated in 2004–2005.[8] It was not until 2012–2014 that iodine status in Danish pregnant women specifically was evaluated after the implementation of iodine fortification. Compared with the previous investigations,[19,22] iodine intake among pregnant women was higher at this time point in West (median UIC 101 µg/L)[11] and in East Denmark (median UIC 114 µg/L).[12] Thus, within recommendations in nonpregnant adults, but below the recommended median UIC of 150 µg/L in pregnancy.[4] Meanwhile, the population monitoring showed a decreasing median UIC (83 µg/L) among adults in the general population[9] and examination of Danish school children in East Denmark showed a median UIC of

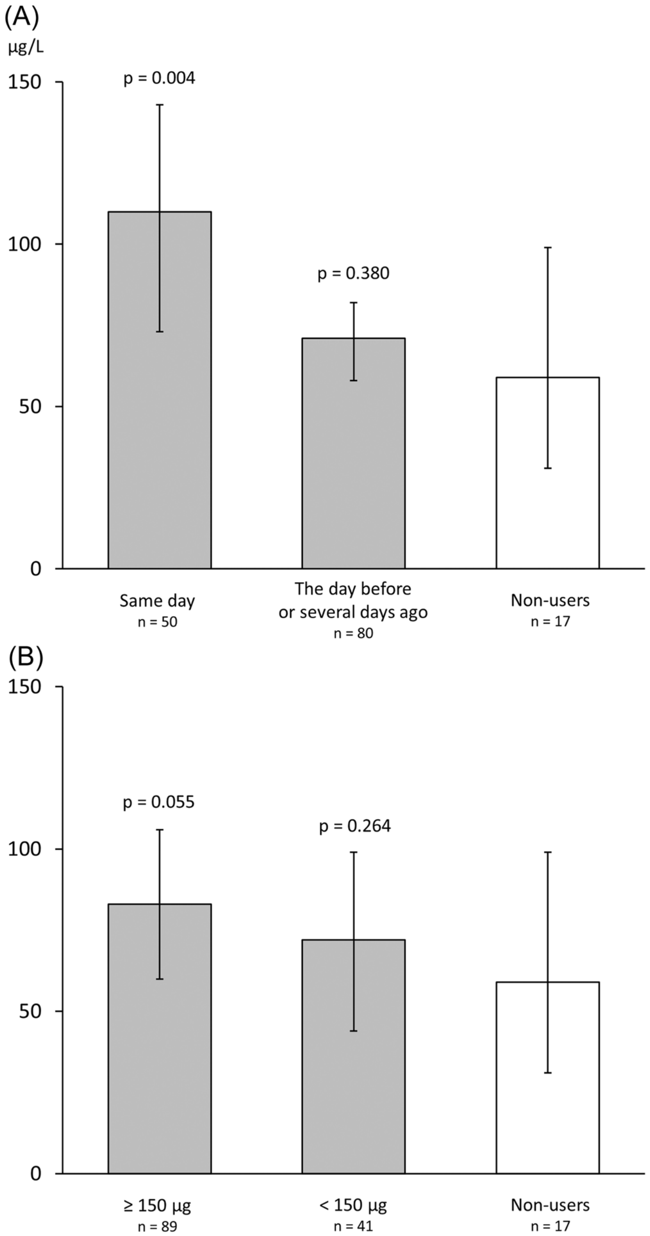

FIGURE 2 Median urinary iodine concentration with 95% confidence intervals stratified according to: (A) the most recent iodine supplement intake before the urine sampling and (B) the daily amount of iodine intake from supplements. *p*-Values are the result of comparison to the group of nonusers (white bars) using Mann–Whitney *U*-test.

145 μg/L.[23] Thus, a need for increased iodine fortification of salt was considered, and it was concluded that an increase from 13 to 20 ppm in the level of iodine added to salt was not expected to have negative consequences among children.[23] This led the authorities to implement an increase in iodine fortification from July 1, 2019.[13]

Our study is the first study to report data on urinary iodine status in the Danish population after the 2019-increase in iodine fortification. It is a marked increase, and monitoring is important. A recent Danish study[24] aimed to assess the effect of the current iodine fortification level of 20 ppm on iodine intake in the Danish population. They used data on population dietary habits from 2011 to 2013 and applied the current level of iodine fortification for their simulation. They concluded that iodine intake in the Danish population appears adequate with the current iodine fortification level, but their simulations pointed towards a risk of inadequate iodine intake in young females and a risk of excessive iodine intake in the youngest age groups.[24] However, no measurements of urinary iodine excretion were included and the simulations were not performed in pregnant women specifically, but their estimates encourage focus on specific vulnerable groups such as women of reproductive age.[24]

In the present study, we evaluated iodine status in Danish pregnant women from the measurement of UIC in spot urine samples. It was an unexpected finding that the median UIC among pregnant women significantly decreased from 2012 to 2021, and we can only speculate on possible mechanisms. First, we used the same method for measurement of UIC in the two studies and re-analyses of samples from 2012 in 2021 identified no significant difference in the biochemical method. Furthermore, we included women from the same hospital in the same geographical area during the summer and autumn season using the same inclusion and exclusion criteria. In line with this, we observed no differences in the main maternal characteristics between the cohorts. However, differences were seen when looking into detail on maternal sources of iodine intake as discussed below.

In Denmark, there are no official recommendations on the specific use of iodine-containing supplements in pregnancy. However, many Danish pregnant women take a multivitamin supplement, which in many cases contains iodine. Thus, it was a consistent finding in 2012 and 2021 that more than 80% of the pregnant women reported current use of iodine-containing supplements and in all cases, iodine was obtained from the intake of a multivitamin supplement. Hence, the use of iodine-containing supplements in Danish pregnant women appears stable within the latest decade and is higher than in 1988–1990 when one-third of pregnant women reported intake of iodine-containing supplements.[25]

A notable difference between the 2012 and 2021 cohort was the content of iodine in the supplements used. Whereas in 2012 nearly all iodine supplements used by the pregnant women had a content of minimum 150 μg iodine/day, one-third of the iodine supplements used in 2021 had a content of less than 150 μg iodine/day. This may to some extend be explained by an update in the Danish guidance on the regulation of food supplements in 2019,[26] in which a recommended maximum daily dose of 83 μg iodine in supplements for adults is stated. Thus, in recent years companies may have formulated or reformulated their iodine-containing supplements, including their pregnancy-specific multivitamins, accordingly. Since numbers were small in the stratified analyses, we were not able to make definite conclusions on differences in median UIC between groups with a daily dose of iodine above or below 150 μg.

Another difference between the study cohorts was a less frequent use of iodine-rich food items such as dairy products and bread among

TABLE 3 Maternal characteristics, dietary habits, and details on the use of iodine-containing supplements among pregnant women in 2012 and 2021

	2012[a]		2021		p[b]
Pregnant women (*n*)	**238**		**147**		
Maternal characteristics					
Pregnancy week at urine sampling (median, interquartile range [IQR])	21	14–21	20	13–21	0.010
Age in years (median, IQR)	30.5	27.0–33.4	29.8	27.3–32.4	0.485
Prepregnancy body mass index in kg/m^2 (median, IQR)[c]	23.5	21.3–27.7	23.4	21.5–26.6	0.560
Dietary habits					
Fish (*n*, %)[d]					
Yes	214	89.9	131	89.1	
No	24	10.1	16	10.9	0.803
Bread (*n*, %)[e]					
Daily	215	90.3	119	81.0	
Occasionally/never	23	9.7	28	19.0	0.008
Dairy products (*n*, %)[e]					
Daily	205	86.1	103	70.1	
Occasionally/never	33	13.9	44	29.9	<0.001
Iodine-containing supplement users (*n*)	**199**		**130**		
Daily iodine intake from supplements (*n*, %)					
<150 µg/day	3	1.5	41	31.5	
≥150 µg/day	196	98.5	89	68.5	<0.001
Recent intake before urine sampling (*n*, %)					
Same day	98	49.3	50	38.5	
The day before or several days ago	101	50.7	80	61.5	0.055

[a]Data reproduced from Andersen et al.[11]

[b]Mann-Whitney U-test for the comparison of continuous variables and chi-squared test or Fischer's exact test as appropriate for the comparison of categorical variables (2012 vs. 2021).

[c]Missing value on prepregnancy BMI not included: 2012: $n = 4$; 2021: $n = 3$.

[d]Do you eat fish?

[e]How often do you eat bread/dairy products?

the pregnant women included in 2021. It has previously been proposed, that the decrease in iodine intake observed in the general Danish population after the implementation of iodine fortification in the year 2000 may be explained by a decrease in the iodine content of milk.[27] Additionally, all salt used in the commercial bread production in Denmark is iodised, thus, bread is one of the primary sources of iodised salt. Consequently, dairy products and bread have recently been identified among the main contributing food items to iodine intake in the Danish population and recent simulations indicated that the exclusion of dairy products or bread may pose a risk of inadequate iodine intake, especially in females of reproductive age.[24] Furthermore, the consumption of milk has been shown to be an important dietary source of iodine in women of reproductive age, with an increasing effect of milk consumption on median UIC in a randomised controlled trial.[28] Consequently, a less frequent use of such iodine rich food items may lead to inadequate iodine intake.

Finally, a methodological aspect on the timing of spot urine sampling must be considered when comparing different cohorts.[29] In both cohorts, the timing of urine sampling during the daytime and the location of urine sampling in hospital were comparable. In line with previous findings,[29] the median UIC was dependent of the timing of the intake of the last iodine-containing supplement before urine sampling. However, the timing of most recent supplement intake before urine sampling did not considerably differ among women included in 2012 and in 2021 and is unlikely to explain the differences in median UIC.

Urinary iodine excretion is considered an appropriate method for the assessment of recent iodine intake since the urinary iodine excretion exceeds more than 90% of ingested iodine.[30,31] Iodine intake can be estimated from different urinary iodine measurements, and median UIC from spot urine samples is a recommended marker for the assessment of iodine status in a population.[4,31] However, UIC is prone to variations in the individual daily iodine intake as well as differences in urine volume which in some cases may lead to misinterpretations.[31,32] During pregnancy, a wide range of physiological changes occur and especially the increase in plasma volume and glomerular filtration rate[33] are important factors when considering iodine excretion in pregnant women. Thus, we evaluated urinary iodine excretion in relation to the urinary creatinine concentration to adjust for variation in UIC due to urine dilution. Since the daily excretion of creatinine is rather constant in healthy individuals and previously measured to be approximately 1 g (1.09 g) in Danish pregnant women,[19] the iodine/creatinine ratio approximates the 24-h iodine excretion. If the total urine volume is 1 L/day, the 24-h iodine excretion would be interchangeable with UIC.[32] However, daily urine volume is assumed to be higher in pregnant women and in Norwegian pregnant women it was recently shown to be 1.4 L/day.[34] Hence, in accordance with the figures in the present study and previous reports among Danish pregnant women,[11,12] the estimated 24-h iodine excretion would tend to be higher than the UIC in a pregnant population. Notably, the estimated 24-h urinary iodine excretion also did not reach the recommended range for adequate iodine status in the pregnant state, thus, the creatinine-adjusted measures of iodine excretion corroborate that iodine status in pregnant women in this region of Denmark remains insufficient.

In this study, we consecutively recruited pregnant women when they arrived for routine obstetric ultrasound. We cannot exclude a risk of selection bias among women who declined to participate. Furthermore, data were collected using an electronic questionnaire which may introduce the risk of information bias and misclassification according to the use of iodine-containing supplements, the dose of daily iodine intake from supplements as well dietary habits. Due to the variation in urinary iodine excretion, a sample size of 125 urine samples is required to estimate median UIC with 95% confidence within a precision range of ±10% in a population.[35] Thus, the sample size in the present study enabled the estimation of an overall median UIC with an acceptable precision. Similarly, the sample size was sufficient for a valid assessment of median UIC among users of iodine-containing supplements, however, the number of nonusers and pregnant women in further stratified analyses was limited and these results should be interpreted with caution. Our study was regional, and our findings may not apply to pregnant women living in other parts of Denmark. Finally, no information was available on maternal thyroid function or levels of thyroglobulin. Such data would be warranted to further evaluate iodine status in Danish pregnant women.

5 | CONCLUSION

After more than 20 years of mandatory iodine fortification and a recent increase in the level of iodine added to salt, iodine status in pregnant women within the North Denmark Region was insufficient with a median UIC lower than previously found. Our findings raise a concern about inadequate iodine status in Danish pregnant women and do not indicate a higher iodine intake after the recent increase in the level of iodine added to salt. The frequency of iodine-supplement use was unaltered high in Danish pregnant women; however, results indicate a decrease in iodine content of supplements used as well as alterations in dietary habits, and further assessment of underlying factors is needed. The findings call for continued attention to ensure adequate iodine status during pregnancy in Denmark and to monitor population iodine status as well as thyroid markers of iodine deficiency after a marked change in the nationwide iodine fortification programme.

ACKNOWLEDGMENTS

This study was supported by a grant from "Stofskifteforeningen" and from the Novo Nordisk Foundation (NNF18OC0033520 and NNF20OC0059465).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data cannot be shared due to regulatory restrictions that apply to the availability of data generated and analysed during this study to preserve patient confidentiality and according to the GDPR regulations.

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How to cite this article: Knøsgaard L, Andersen S, Hansen AB, Sørensen A, Vestergaard P, Andersen SL. Iodine status in Danish pregnant women after an increase in iodine fortification. *Clin Endocrinol (Oxf)*. 2023;98:407-414. doi:10.1111/cen.14797