Iodine deficiency in Danish pregnant women

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ORIGINAL ARTICLE

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ABSTRACT

INTRODUCTION: Maternal iodine requirements increase during pregnancy. Studies performed before the introduction of mandatory iodine fortification of salt in Denmark in 2000 showed that pregnant women with no intake of iodine-containing supplements were moderately iodine-deficient and showed signs of thyroidal stress. We investigated the intake of iodine-containing supplements and urinary iodine excretion in Danish pregnant women after the introduction of iodine fortification of salt.

MATERIAL AND METHODS: We conducted a cross-sectional study between June and August 2012 in an area of Denmark where iodine deficiency had previously been moderate. Pregnant women coming to Aalborg University Hospital for obstetric ultrasound were recruited consecutively. Participants filled in a questionnaire and handed in a spot urine sample for measurement of iodine and creatinine.

RESULTS: Among the pregnant women included (n = 245), 84.1% reported an intake of iodine-containing supplements, and compared with those not taking iodine supplements the median urinary iodine concentration was significantly higher in this group: 109 g/l (25th-75th percentile: 66-191 µg/l). On the other hand, the median urinary iodine concentration was considerably below the recommended level, even for the non-pregnant state in pregnant women with no iodine supplement intake: 68 µg/l (35-93 µg/l), $p < 0.001$.

CONCLUSION: The majority of pregnant women took iodine-containing supplements, but the subgroup of non-users was still iodine-deficient after the introduction of iodine fortification of salt. Iodine supplement intake during pregnancy in Denmark should be officially recommended.

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TRIAL REGISTRATION: not relevant.

Adequate maternal iodine intake is required for thyroid hormone synthesis, and thyroid hormones, in turn, are essential for foetal growth and development, especially for early brain development [1, 2]. Maternal iodine requirements increase during pregnancy [3]. In their guidelines, the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) define an adequate intake of iodine during pregnancy as 250 µg/day, which corresponds to a median urinary iodine concentration of 150-249 µg/l in a population of pregnant women [4]. By contrast, a median urinary iodine concentration in the 100-199 µg/l range is considered a sufficient iodine intake in the non-pregnant state [4].

Iodine intake may stem from drinking water and from dietary iodine contents, from food fortified with iodine (typically salt), or from intake of iodine-containing supplements [5]. Denmark was previously iodine-deficient with regional differences caused by regional variation in the levels of iodine in the drinking water: moderate iodine deficiency was observed in Western Denmark and mild iodine deficiency in Eastern Denmark [6, 7]. A mandatory iodine fortification of salt was introduced in the year 2000 [8], and this programme had increased urinary iodine concentration to the lower threshold of the recommended level in the Danish population in 2004-2005 [9]. On the other hand, a recent study performed in 2008-2010 found that urinary iodine concentration had again decreased in the Danish population [10].

In studies of Danish pregnant women before the year 2000, pregnant women with no intake of iodine-containing supplements had a low urinary iodine concentration corresponding to moderate iodine deficiency, increased thyroid volume and high serum thyroglobulin (Tg), and their serum thyroid-stimulating hormone (TSH) levels increased during pregnancy [11, 12]. In a study conducted in five Danish cities [13], 36% of the pregnant women reported an intake of iodine-containing supplements when asked upon arrival for delivery. No previous study has specifically addressed the iodine intake and the use of iodine supplements during pregnancy in Denmark after the introduction of iodine fortification of salt.

The aim of the present study was to investigate if pregnant women living in an area of Denmark with previously moderate iodine deficiency took iodine-containing supplements, to examine predictors of iodine supplement intake and to evaluate iodine intake during pregnancy by measurement of urinary iodine concentration.

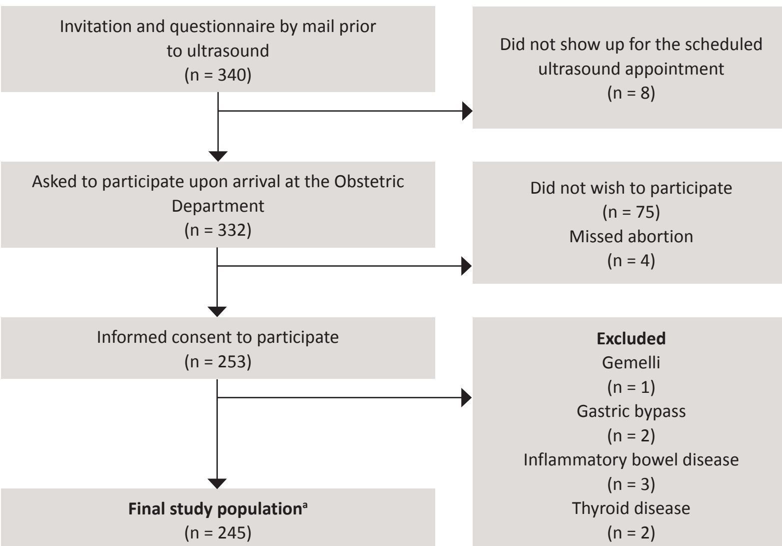
MATERIAL AND METHODS

Study population and design

We conducted a cross-sectional study between 13 June and 10 August 2012 in an area of Denmark with previously moderate iodine deficiency [8]. We consecutively recruited healthy, pregnant women referred to Aalborg

FIGURE 1

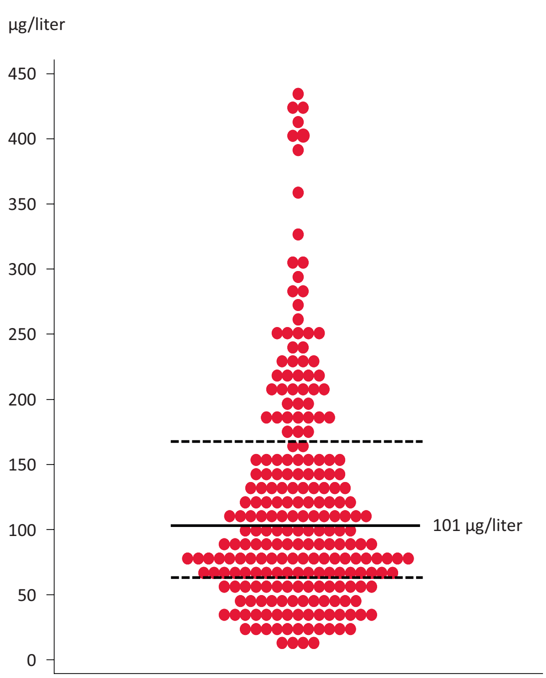
Flow chart illustrating the number of pregnant women invited, participating and included in the final study population.



a) Urinary samples (n = 238).

FIGURE 2

Overall urinary iodine excretion among the pregnant women (n = 238). Horizontal lines illustrate median (solid line) and interquartile range (dashed lines).



Urinary iodine concentrations in range from 460-1000 µg/liter (n=8) not illustrated.
Values were stratified into 40 bands in the range from 7-440 µg/liter; each band corresponding to 10.8 µg/liter.

University Hospital for obstetric ultrasound as part of the antenatal investigation programme [14]. Two of the pregnant women were excluded (**Figure 1**), because they had a diagnosis of hypothyroidism and took levothyroxin replacement therapy at the time of enrollment. None of the remaining women had a history of thyroid disease verified by a doctor.

After providing informed consent, participants were asked to fill out a questionnaire including obstetric history, socio-demographics and smoking habits, and to list detailed information on any medication and intake of vitamin and/or mineral supplements. Information about dietary supplements was verified by interview; and at the time of enrollment, the women were asked to provide a spot urine sample. The time of sampling was between 8 am and 1 pm, except for two women who had sampled the urine at home the same day prior to inclusion into the study (at 6:00 a.m. and 7:10 a.m., respectively). The study protocol was approved by the local ethics committee.

Laboratory procedures

Urine samples were stored at –20 °C until measurement of urinary iodine concentration in runs during the time of study inclusion. Urinary iodine concentrations (µg/l) were determined by the cerium/arsenite method after alkaline ashing, as previously described [15]. The analytical sensitivity was 2 µg/l. The iodine laboratory was certified by the U.S. Centers for Disease Control and Prevention's EQUIP Programme. Urinary creatinine concentrations (µmol/l) were measured immediately after urinary sampling on a Cobas 8,000 system. The equipment was calibrated according to the manufacturer's instructions, and external standards were included.

Statistical analyses

Characteristics of the pregnant women according to intake of iodine containing supplements were compared using Fisher's exact test, and predictors of iodine supplement intake were examined in multivariate logistic regression. Urinary iodine excretion was expressed as spot urine concentration (µg iodine/l), iodine/creatinine ratio (µg iodine/g creatinine) and estimated 24-h iodine excretion (µg iodine/24 h) calculated from the mean 24-h urinary creatinine excretion (1.09 g creatinine/24 h) previously measured in Danish pregnant women [11]. Urinary iodine concentrations showed a skewed distribution, and the results were expressed as medians with 25th and 75th percentiles. Non-parametric tests were used to compare urinary iodine excretion stratified by iodine supplement intake (Mann-Whitney test) and by gestational week (Kruskal-Wallis test). Statistical analyses were performed using Stata 11 (StataCorp, College Station, TX, USA), and a 5% level of significance was chosen.

Trial registration: not relevant.

RESULTS

Study population

A total of 245 women were included in the final study population (Figure 1), corresponding to 73.8% of the women invited to participate upon arrival at the Obstetric Department. The median age at the time of enrollment was 30.5 years (range 18.4-41.2 years), the median gestational age was week 20 (range week 10-37), and approximately half of the women were expecting their first child (**Table 1**).

Use of iodine-containing supplements

Nearly all of the pregnant women used dietary supplements (95.9%) at the time of enrollment, and 206 women (84.1%) reported a regular intake of iodine-containing supplements, whereas 39 women (15.9%) were taking either no vitamin and/or mineral supplements (n = 10) or vitamin and/or mineral supplements not containing iodine (n = 29).

The iodine containing supplements typically contained 175 µg iodine/day (81.1%); less often 150 µg iodine per day (17.0%); and a few women (1.9%) took iodine-containing supplements different from the recommended dose (87.5 and 375 µg iodine per day, respectively). The intake of the iodine supplement was often initiated during pregnancy (75.2%) at median gestational week 6 (range week 1-32), but some of the pregnant women had initiated iodine supplement intake in the year preceding the pregnancy (16.5%) at median 10 weeks before conception (range 2-52 weeks), or more than a year before conception (8.3%). Among iodine supplement users, 38 women reported intake of another iodine-containing supplement before their current supplement, and eight of the current non-users had stopped iodine supplement intake during the pregnancy before study inclusion.

Predictors of iodine supplement intake

In the univariate analyses, only maternal age significantly differed according to intake of iodine-containing supplements (Table 1). In the multivariate analyses including all variables listed in Table 1 as categoricals, lower maternal age (≤ 35 years, p = 0.001) and maternal education, i.e. qualifying for a profession (vocational or higher education versus primary/secondary school only, p = 0.039), were significant predictors of maternal intake of iodine-containing supplements. On the other hand, the total number of years of education did not significantly predict iodine supplement intake.

Urinary iodine excretion

The overall median urinary iodine concentration (**Figure 2**) was just within the recommended range for the non-pregnant state (100-199 µg/l), but below the recommended level during pregnancy (150-249 µg/l). The median urinary iodine concentration was higher in the group of pregnant women reporting an intake of iodine-

TABLE 1

Characteristics of the pregnant women in the final study population at the time of enrollment and according to intake of iodine-containing supplements.

	All		Iodine supplements		No iodine supplements		
	n	%	n	%	n	%	p[a]
Pregnant women	245	100.0	206	84.1	39	15.9	–
Gestational week at enrollment							0.51
10-15	87	35.5	74	35.9	13	33.3	
19-21	133	54.3	109	52.9	24	61.6	
28-37	25	10.2	23	11.2	2	5.1	
Parity[b]							0.47
1	132	53.9	112	54.4	20	51.3	
2	88	35.9	75	36.4	13	33.3	
≥ 3	25	10.2	19	9.2	6	15.4	
Age, years							0.006
< 25	27	11.0	24	11.7	3	7.7	
25-35	180	73.5	157	76.2	23	59.0	
> 35	38	15.5	25	12.1	13	33.3	
Cohabitation							1.00
Living with partner	233	95.1	196	95.2	37	94.9	
Not living with partner	12	4.9	10	4.8	2	5.1	
Ethnicity							1.00
Danish	227	92.7	191	92.7	36	92.3	
Other than Danish	18	7.3	15	7.3	3	7.7	
Education[c]							0.26
Basic	23	9.4	16	7.8	7	17.9	
Low	64	26.1	56	27.2	8	20.5	
Middle	98	40.0	83	40.3	15	38.5	
High	60	24.5	51	24.7	9	23.1	
Occupation							0.48
Employed	181	73.9	153	74.3	28	71.8	
Student	28	11.4	25	12.1	3	7.7	
Unemployed/not a student	36	14.7	28	13.6	8	20.5	
Pre-pregnancy BMI[d], kg/m²							0.36
< 25.0	143	59.3	119	58.6	24	63.2	
25.0-29.9	59	24.5	53	26.1	6	15.8	
≥ 30.0	39	16.2	31	15.3	8	21.0	
Smoking							0.92
Current	14	5.7	12	5.8	2	5.1	
Previous	82	33.5	70	34.0	12	30.8	
Never	149	60.8	124	60.2	25	64.1	
Organic milk[e]							0.26
Yes	79	32.2	63	30.6	16	41.0	
No	166	67.8	143	69.4	23	59.0	

BMI = body mass index.
a) Fisher's exact test: iodine supplements vs. no iodine supplements.
b) Previous live births and stillbirths including index pregnancy.
c) Highest educational level achieved or initiated. General education: "basic" (primary/secondary education only; 9-13 yrs). General education and education qualifying for a profession: "low" (vocational education and training: 9-13 yrs), "middle" (short- or medium cycle higher education: 14-16 yrs), "high" (long-cycle higher education: ≥ 17 yrs).
d) Missing value on BMI (n = 4) not included, 7 women had a BMI < 18.5 kg/m² (all iodine supplement users).
e) Do you mainly buy organic milk? (yes/no). Included as an indicator variable for maternal food-buying habits.

TABLE 2

Urinary iodine concentration, iodine/creatinine ratio and estimated 24-h iodine excretion according to maternal intake of iodine-containing supplements.

	Iodine supplements	No iodine supplements	p[a]
Pregnant women, n[b]	199	39	
Urinary iodine concentration, μg/l, median (25th-75th percentile)	109 (66-191)	68 (35-93)	< 0.001
Iodine/creatinine ratio, μg/g, median (25th-75th percentile)	153 (105-257)	73 (54-100)	< 0.001
Estimated 24-h iodine excretion, μg, median (25th-75th percentile)[c]	167 (114-280)	80 (59-109)	< 0.001

a) Mann-Whitney test: iodine supplements versus no iodine supplements.
b) Pregnant women with no urinary sample (n = 7) not included.
c) Calculated from 24-h urinary creatinine excretion previously measured in Danish pregnant women: 1.09 g creatinine/24 h [11].

containing supplements (**Table 2**) and below the lower recommended level for even the non-pregnant state in the group with no iodine supplement intake. The findings were similar when urinary iodine excretion was expressed as an iodine/creatinine ratio and estimated 24-h iodine excretion (Table 2). There was no significant difference in urinary iodine concentrations among iodine supplement users when stratified by gestational age; median urinary iodine week 10-15 (n = 73): 107 μg/l (25th-75th percentile: 66-197 μg/l), week 19-21 (n = 103): 102 μg/l (65-170 μg/l), week 28-37 (n = 23): 140 μg/l (91-252 μg/l), p = 0.06.

DISCUSSION

Principal findings

More than ten years after the introduction of mandatory iodine fortification of salt in Denmark, pregnant women living in an area previously characterized by moderate iodine deficiency had urinary iodine concentrations below the level recommended during pregnancy. As expected, pregnant women who took iodine-containing supplements had a higher median urinary iodine concentration than pregnant women with no intake of iodine supplements, and the median urinary iodine concentration was within the recommended level for the non-pregnant state in this group. The frequency of iodine supplement intake during pregnancy in Denmark had increased steeply compared with a previous study and was significantly predicted by maternal age and education. However, a subgroup of women still took no iodine supplements during pregnancy, and in this group the median urinary iodine concentration was considerably below the level recommended even for the non-pregnant state.

Iodine supplement use in Danish pregnant women

In a previous study [13] conducted in Denmark before the year 2000, nearly all pregnant women reported taking vitamin and/or mineral supplements (93.4%) when asked upon arrival for delivery, but only 36% reported an intake of iodine-containing supplements (150 μg iodine/day). Thus, the frequency of dietary supplement during pregnancy before the year 2000 was comparable to that observed in our study population (95.9%), but the use of iodine-containing supplements had increased considerably. The reasons for this increase are not completely clear. There are no current official recommendations on the intake of iodine-containing supplements during pregnancy in Denmark. Iodine supplement was obtained by intake of a multivitamin pill, and official recommendations on the intake of folic acid, vitamin D and iron during pregnancy do exist [14]. Thus, it seems likely that iodine supplement intake is incidental to other recommendations during pregnancy in Denmark. The gestational age of the women included in our study ranged 10-37 weeks. No previous study specifically addressed the use of iodine supplements in early pregnancy in Denmark.

Urinary iodine excretion in Danish pregnant women

Several of the previous studies on urinary iodine excretion in Danish pregnant women examined pregnant women living in Western Denmark, an area where moderate iodine deficiency was previously observed. In the studies by Pedersen et al [11, 12], the median urinary iodine concentration was low (approximately 50 and 40 μg/l in gestational weeks 17 and 37, respectively) and serum Tg was high in pregnant women with no intake of iodine-containing supplements. Furthermore, thyroid volume as well as TSH tended to increase during pregnancy. These changes were ameliorated by iodine supplement intake, and urinary iodine increased to 106 μg/l in late pregnancy after iodine supplement intake during the pregnancy [12], which was also shown in a study by Nohr et al [16].

Remember iodine!

Thus, our results indicate that the median urinary iodine concentration has increased in pregnant women with no iodine supplement intake, which corresponds to the general increase in the median urinary iodine concentration after the introduction of iodine fortification of salt in Denmark [9]. However, pregnant women with no intake of iodine-containing supplements still have urinary iodine concentrations substantially below the recommended level for pregnancy [4] and even below the recommended range for the non-pregnant state [4].

In the Danish population, the iodine fortification of salt increased urinary iodine to the lower threshold within the recommended range, but results from the DanThyr study (The Danish investigation on iodine intake and thyroid disease) [8] recently showed a modest decrease in urinary iodine concentration [10]. The present study confirms that the current level of iodization of salt in Denmark is insufficient, i.e. that it will not produce a urinary iodine concentration within the recommended range.

Strengths and limitations

Urinary iodine excretion is a recommended marker of recent iodine intake [4], and spot urine samples can be used in population studies [17]. The relatively large number of pregnant women included in our study increased the precision of the estimated iodine excretion [18]. However, the number of pregnant women in the stratified analyses was limited in some groups.

Our study only included women referred to Aalborg University Hospital, and we cannot exclude that differences in the use of dietary supplements during pregnancy may exist across Denmark. In a previous study performed in five Danish cities, the frequency of iodine supplement intake during pregnancy ranged from 21% to 50% when stratified by city [13]. The level of iodine in drinking water and urinary iodine excretion in the area investigated in our study was previously reported to correspond to the level observed in most parts of Western Denmark (i.e. west of the Great Belt) [6, 7].

We consecutively recruited healthy, pregnant women and the rate of participation was high. However, we cannot exclude some degree of selection bias.

CONCLUSION

Danish pregnant women living in an area previously characterized by moderate iodine deficiency still have urinary iodine concentrations below the recommended level for the pregnant state after the introduction of the mandatory iodine fortification of salt in Denmark. Pregnant women with no intake of iodine-containing supplements are at particular risk of insufficient iodine intake. Results indicate a need for more attention among healthcare professionals to ensure sufficient iodine status in Danish pregnant women. Intake of iodine-containing supplements during pregnancy in Denmark should be officially recommended, and our results may indicate a need for a modest increase in the level of iodine added to salt in Denmark.

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