

Iodine deficiency in pregnancy is prevalent in vulnerable groups in Denmark

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ABSTRACT

INTRODUCTION: Iodine is essential for the production of thyroid hormones. In pregnancy, physiological changes occur that can lead to iodine deficiency and impairment of fetal neurological development. We aimed to assess the iodine intake in pregnant women in Eastern Denmark, compare iodine levels in Eastern and Western Denmark and to identify potentially vulnerable groups.

METHODS: This was a cross-sectional cohort study of pregnant Danish women (n = 240). Questionnaires and urine samples were collected at the Ultrasound Clinic, Hvidovre Hospital, Denmark, and urinary iodine concentrations (UIC) ($\mu\text{g}/\text{l}$) were measured. Predictors of iodine supplement use were examined by multivariate logistic regression models.

RESULTS: The pregnant women from Eastern Denmark had a median age of 30 years and the median gestational week at which they were included in the study was week 19. The majority took iodine-containing supplements (86%). The median UIC was 118 (interquartile range (IQR): 79-196) $\mu\text{g}/\text{l}$ in iodine supplement users and 82 (IQR: 41-122) $\mu\text{g}/\text{l}$ in non-users ($p < 0.001$). Predictors of not using iodine supplement in Eastern and Western Denmark were short maternal education, non-Danish origin and pre-pregnancy obesity.

CONCLUSIONS: The iodine status in Danish pregnant women was below WHO recommendations. Iodine supplement non-users are at a particular risk of iodine deficiency. Low maternal education, non-Danish origin and pre-pregnancy obesity are predictors of non-iodine supplement use. An increase in iodine fortification may be recommended to improve the iodine status in pregnant Danish women.

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Iodine is essential for the production of thyroid hormones and is obtained mainly from dairy products, drinking water, fish and seaweed or from iodised food or iodine-containing supplements. Previous reports have shown that organic milk contains less iodine than non-organic milk. In the pregnant state, physiologic changes in iodine metabolism and thyroid hormone production occur; i) the thyroid hormone production increases with approximately 50% [1], ii) the excretion of iodide in the urine increases due to an increased renal plasma flow

and a heightened glomerular filtration rate [2], and iii) the breakdown of thyroid hormones increases in the placenta due to increased activity of iodothyronine deiodinating enzymes [3]. The increased demand can lead to moderate or severe iodine deficiency, which may impair the growth and the neurological development of the foetus [4, 5].

Denmark has been iodine-deficient with regional differences due to different levels of iodine in the drinking water; the iodine deficiency in West Denmark was most pronounced [6]. In the year 2000, a mandatory iodine fortification programme was implemented including iodine fortification of household salt and salt used for commercial production of bread (13 μg per 1 g salt). The Danish Investigation of Iodine Intake and Thyroid Disease has been monitoring the iodine status before and after the implementation of the mandatory iodine fortification programme. A significant increase in median urinary iodine concentration (UIC) in the general population was demonstrated as a result of the initiative [7]. However, the iodine intake among adult Danes remains below the recommended level, especially in people not taking individual iodine supplements [8].

According to WHO, the International Council for the Control of Iodine deficiency Disorders and UNICEF, an adequate intake of iodine in the pregnant state is defined as 250 μg per day, which corresponds to a median UIC of 150-249 $\mu\text{g}/\text{l}$ [9]. However, if the population in general has an adequate iodine intake with a median UIC > 100 $\mu\text{g}/\text{l}$ for at least two years, it is anticipated that the iodine stores in the thyroid will be sufficient and capable of covering the extra needs associated with pregnancy [10], and no intake of iodine supplements during pregnancy is recommended [11]. A recent study of pregnant women in Western Denmark reported a median UIC below this recommended level for the pregnant state for iodine supplement users and especially for iodine supplement non-users [12].

The aim of the present study was to assess the iodine intake in a population of pregnant women in Eastern Denmark after implementation of the mandatory iodine fortification programme. Furthermore, we aimed to compare the iodine intake in pregnant women

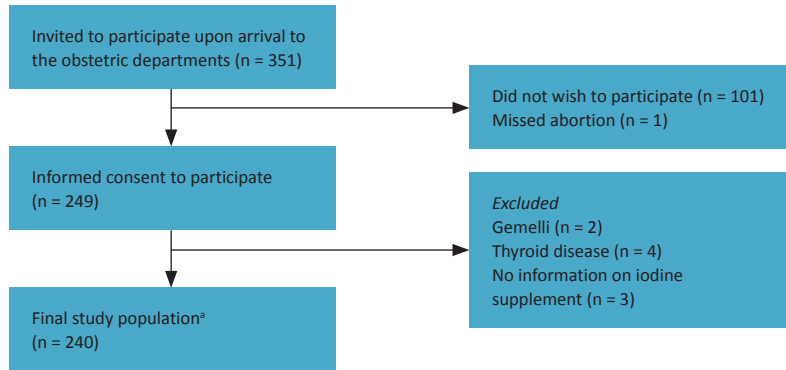
ORIGINAL ARTICLE

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FIGURE 1

Flow chart of final study population.



a) Urinary samples, n = 236.

in Eastern and Western Denmark, and to evaluate if some vulnerable groups were at special risk for iodine deficiency during their pregnancy.

METHODS

We conducted a cross-sectional study between 12 May and 20 July 2014 at the ultrasound Clinic at Hvidovre Hospital, Capital Region of Denmark.

From the digital patient registration system we identified all pregnant women booked for ultrasound assessment in their first, second and third trimesters. We primarily excluded gemelli pregnancies and pregnant women assigned for control of comorbidities including thyroid disease. Included women (**Figure 1**) were informed about the project in the waiting room when they showed up for the ultrasonography session. After information was given, the women were invited to sign a consent form and fill in a questionnaire concerning socio-demographic issues, obstetric history, smoking habits and information on intake of iodine containing food sources (milk, bread, fish) and vitamin supplements. The information about vitamins was further elaborated in a short interview. The women were not informed about the fortification and monitoring programme on iodine in Denmark prior to their participation. When language barriers were observed, the entire questionnaire was translated verbally into English. At the end of session, the women provided a urine sample.

In Western Denmark, a cross-sectional study was conducted between 13 June and 10 August 2012 using similar methods as described in detail previously [12].

All urine samples were collected between 8 am and 3 pm and then stored at -20°C until analysis in the iodine laboratory, which analysed the samples from the previous study in West Denmark [12]. The laboratory is

certified by the U.S. Centers for Disease Control and Prevention's EQUIP programme. Urinary iodine concentrations ($\mu\text{g/l}$) were measured by the cerium/arsenite method after alkaline ashing [13]. Urinary creatinine concentrations were measured on the Cobas 8,000 system (Roche).

The study was approved by the local ethics committee (record no.: N-VN-19960208MCH).

Statistics

Descriptive characteristics of the pregnant women in terms of iodine supplement use were analysed using the Chi squared test or Fisher's exact test, as appropriate. Predictors of iodine supplement use were examined in univariate analyses and in multivariate logistic regression models. Urinary iodine excretion was expressed as spot urine concentrations (μg iodine/l). The estimated 24-h iodine excretion (μg iodine/24 h) was calculated using the mean 24-h urinary creatinine excretion observed previously in Danish pregnant women ($1.09\text{ g creatinine}/24\text{ h}$) [14]. The Mann-Whitney test was used to compare urinary iodine excretion when stratified by iodine supplement use. Statistical analyses were performed using IBM SPSS Statistics 22 and Stata 11 (Stata Corp, Tx, USA).

Trial registration: not relevant.

RESULTS

Study population in Eastern Denmark

The final study population in Eastern Denmark consisted of 240 women (**Figure 1**), corresponding to 68% of all of the women who were invited to participate at the Ultrasound Clinic, Hvidovre Hospital, Denmark. The median age at the time of enrolment was 30 years (range: 20-42 years) and the median gestational age at the time of enrolment was week 19 (range: week 9-38). The majority of the participants were expecting their first or second child (77%), and 47 (20%) were of non-Danish origin.

At the time of enrolment, nearly all women took a supplement (96.7%). The majority had initiated the supplement intake during pregnancy (74.3%) at a median gestational week 6 (range: week 1-19). The supplements contained iodine in 86% of all cases, while 14% of the supplements contained no iodine. Typically, the iodine content was $175\text{ }\mu\text{g/day}$ (82.7%), while 15.8% had an intake of less than $175\text{ }\mu\text{g/day}$, and two women had an excess intake of $325\text{--}350\text{ }\mu\text{g}$ iodine per day. Details on the study population in Western Denmark have been given previously [12].

Iodine status in pregnancy

Various estimates of urinary iodine excretion in pregnant women from Eastern and Western Denmark are

presented in **Table 1**. Similar to previous Danish studies, urinary iodine excretion was higher in Eastern Denmark with a higher iodine ground water content than in Western Denmark.

As expected, women who took iodine-containing supplements had higher urinary iodine excretion than women taking no such iodine supplements. Urinary iodine concentrations in women taking no iodine supplements were well below the recommended level even for non-pregnant adults in both regions.

Predictors of iodine supplement use

Because iodine supplement intake was so important for the iodine status of the pregnant women studied, we explored in more detail the characteristics of women who took no supplements. **Table 2** lists a number of characteristics that might potentially be of importance, and comparisons between users and non-users of iodine supplements were performed in univariate analyses. Low maternal education and maternal unemployment, as well as maternal pre-pregnancy obesity were highly significant predictors of non-use of iodine supplements. In these analyses, non-use of iodine supplements was also more common in women who had a non-Danish origin and in women above the age of 35 years, but these findings were not statistically significant (Table 2).

The factors associated with the use of iodine supplements as shown in Table 2 ($p < 0.10$) were subsequently evaluated in a multivariate model as illustrated in **Table 3**. Maternal low education, pre-pregnancy obesity and non-Danish origin were significantly associated with the non-use of iodine-containing supplements.



Iodine supplements during pregnancy are important.

DISCUSSION

Principal findings

Through this cross-sectional study of 240 pregnant women living in Eastern Denmark, we were able to demonstrate a deficient iodine status despite ten years with mandatory iodine fortification of salt in Denmark. Thus, the fortification of 13 μg of iodine per 1 g salt is not sufficient to meet the recommended level for pregnant women. Pregnant women with no use of iodine-containing supplements were at particular risk; with median urinary iodine concentrations below the WHO recommended levels even for the non-pregnant state [9]. However, iodine excretion was also below the recommended level in pregnant women taking a supplement with 175 μg of iodine per day. No difference in the intake of iodine containing food sources was identified between iodine supplement users and non-users, and the contribution of iodine may therefore be considered



TABLE 1

Urinary iodine concentration, estimated 24-h iodine excretion and iodine to creatinine ratio in pregnant women in Eastern and Western Denmark according to region and intake of iodine containing supplements^a.

| | All | Iodine supplements | No iodine supplements | p-value ^b |
|--|---------------|--------------------|-----------------------|----------------------|
| <i>Eastern Denmark</i> | | | | |
| Pregnant women, n ^c | 236 | 196 | 40 | |
| Urinary iodine concentration, median (25th-75th percentile), $\mu\text{g}/\text{l}$ | 114 (67-175) | 118 (79-196) | 82 (41-122) | < 0.001 |
| Estimated 24-h iodine excretion, median (25th-75th percentile), μg^{d} | 173 (118-303) | 199 (132-325) | 109 (79-142) | < 0.001 |
| Iodine to creatinine ratio, median (25th-75th percentile), $\mu\text{g}/\text{g}$ | 158 (108-278) | 183 (121-298) | 100 (72-130) | < 0.001 |
| <i>Western Denmark</i> | | | | |
| Pregnant women, n ^b | 238 | 199 | 39 | |
| Urinary iodine concentration, median (25th-75th percentile), $\mu\text{g}/\text{l}$ | 101 (63-167) | 109 (66-191) | 68 (35-93) | < 0.001 |
| Estimated 24-h iodine excretion, median (25th-75th percentile), μg^{d} | 150 (96-257) | 167 (114-280) | 80 (59-109) | < 0.001 |
| Iodine to creatinine ratio, median (25th-75th percentile), $\mu\text{g}/\text{g}$ | 138 (89-236) | 153 (105-257) | 73 (54-100) | < 0.001 |

a) Mann-Whitney test: Eastern Denmark vs. Western Denmark for the estimated 24-h iodine excretion: all (median 173 vs. 150 $\mu\text{g}/24\text{ h}$), $p = 0.003$; iodine supplements (median 199 vs. 167 $\mu\text{g}/24\text{ h}$), $p = 0.01$; no iodine supplements (median 109 vs. 80 $\mu\text{g}/24\text{ h}$), $p = 0.002$.

b) Mann-Whitney test: iodine supplements vs. no iodine supplements.

c) Pregnant women with no urinary sample (Eastern Denmark $n = 4$, Western Denmark $n = 7$) not included.

d) Calculated from 24-h urinary creatinine excretion previously measured in Danish pregnant women: 1.09 g creatinine/24 h [14].

TABLE 2

Predictors of iodine supplement intake in pregnant women in Eastern and Western Denmark. The values are n (%)^a.

| | Iodine supplement (N = 405 (83.5%)) | No iodine supplement (N = 80 (16.5%)) | p-value ^b |
|--|--|--|----------------------|
| <i>Region of Denmark</i> | | | 0.73 |
| East | 199 (82.9) | 41 (17.1) | |
| West | 206 (84.1) | 39 (15.9) | |
| <i>Gestational age, weeks</i> | | | 0.82 |
| ≤ 20 | 335 (83.3) | 67 (16.7) | |
| > 20 | 70 (84.3) | 13 (15.7) | |
| <i>Mode of conception^c</i> | | | 0.51 |
| Spontaneous | 368 (83.8) | 71 (16.2) | |
| Assisted | 36 (80.0) | 9 (20.0) | |
| <i>Maternal parity^d</i> | | | 0.13 |
| 1-2 | 342 (84.7) | 62 (15.3) | |
| ≥ 3 | 63 (77.8) | 18 (22.2) | |
| <i>Maternal age, yrs^c</i> | | | 0.086 |
| < 35 | 340 (85.0) | 60 (15.0) | |
| ≥ 35 | 65 (77.4) | 19 (22.6) | |
| <i>Maternal origin</i> | | | 0.058 |
| Danish | 356 (84.8) | 64 (15.2) | |
| Other than Danish | 49 (75.4) | 16 (24.6) | |
| <i>Maternal cohabitation</i> | | | 0.80 |
| Living with partner | 350 (83.3) | 70 (16.7) | |
| Not living with partner | 55 (84.6) | 10 (15.4) | |
| <i>Maternal education^{c, e}</i> | | | 0.001 |
| Education qualifying for a profession | 361 (85.3) | 62 (14.7) | |
| No education qualifying for a profession | 38 (67.4) | 18 (32.1) | |
| <i>Maternal employment^c</i> | | | 0.012 |
| Employed/student | 357 (85.0) | 63 (15.0) | |
| Unemployed/not a student | 44 (72.1) | 17 (27.9) | |
| <i>Maternal pre-pregnancy BMI, kg/m^{2c}</i> | | | 0.012 |
| < 30 | 358 (85.0) | 63 (15.0) | |
| ≥ 30 (obesity) | 41 (71.9) | 16 (28.1) | |
| <i>Maternal smoking</i> | | | 1.00 |
| Current smoking during the pregnancy | 21 (84.0) | 4 (16.0) | |
| No current smoking | 384 (83.5) | 76 (16.5) | |
| <i>Milk daily^c</i> | | | 0.295 |
| Yes | 333 (84.5) | 61 (15.5) | |
| No | 72 (80.0) | 18 (20.0) | |
| <i>Bread daily^c</i> | | | 0.564 |
| Yes | 341 (83.2) | 69 (16.8) | |
| No | 61 (85.9) | 10 (14.1) | |
| <i>Fish daily^c</i> | | | 0.883 |
| Yes | 6 (85.8) | 1 (14.2) | |
| No | 399 (83.6) | 78 (16.4) | |
| <i>Mainly buys organic milk^c</i> | | | 0.23 |
| Yes | 169 (81.3) | 39 (18.7) | |
| No | 233 (85.4) | 40 (14.6) | |

a) % were calculated as the frequency of iodine supplement/no iodine supplement within each horizontal group; b) p-value is the result of the χ^2 -test (iodine supplement vs. no iodine supplement) except for maternal smoking, which is the result of Fisher's exact test; c) Missing values not included: mode of conception (n = 1), maternal age (n = 1), education (n = 6), employment (n = 4), pre-pregnancy BMI (n = 7), milk daily (n = 1), bread daily (n = 4), fish daily (n = 1), mainly buys organic milk (n = 4); d) Previous live and still births, including the index pregnancy; e) Highest educational level achieved, education qualifying for a profession: 14-17 yrs of school/education, no education qualifying for a profession: 9-13 yrs of school/education.

TABLE 3

Odds ratio (OR) with 95% confidence interval (CI) and p-value for no iodine supplement use in 485 pregnant women in Eastern and Western Denmark. The adjusted model included maternal education, pre-pregnancy BMI, origin, age and employment (p-value < 0.1 in univariate analysis).

| | OR (95% CI) | p-value |
|---|------------------|---------|
| <i>Maternal education</i> | | 0.014 |
| Education qualifying for a profession | 1.0 ^a | |
| No education qualifying for a profession | 2.3 (1.2-4.6) | |
| <i>Maternal pre-pregnancy BMI, kg/m²</i> | | 0.018 |
| < 30 | 1.0 ^a | |
| ≥ 30 (obesity) | 2.2 (1.1-4.4) | |
| <i>Maternal origin</i> | | 0.026 |
| Danish | 1.0 ^a | |
| Other than Danish | 2.1 (1.1-4.7) | |
| <i>Maternal age, yrs</i> | | 0.055 |
| < 35 | 1.0 ^a | |
| ≥ 35 | 1.8 (1.0-3.3) | |
| <i>Maternal employment</i> | | 0.17 |
| Employed/student | 1.0 ^a | |
| Unemployed/not a student | 1.6 (0.8-3.2) | |

a) Reference.

[15], which may be a result of differences in the methods used for collection of information. Nonetheless, the majority reported a daily intake of bread, and bread may still be considered an appropriate source of fortification.

In the general population, the iodine status has improved after the introduction of mandatory iodine fortification of salt in 2000. Our results from Eastern Denmark indicate that pregnant women are at particular risk of iodine deficiency. This is consistent not only with previous studies from Western Denmark, but also with recent studies from other parts of Europe [16, 17].

Regional differences in iodine concentrations in Denmark are well-documented and are due to different levels of iodine in the drinking water [18]. A similar regional difference was found among pregnant women, with the highest iodine concentrations being measured in Eastern Denmark. Nonetheless, pregnant Danish women with no intake of iodine-containing supplements were at particular risk of iodine deficiency.

Vulnerable groups

Low maternal education, pre-pregnancy obesity and non-Danish origin were identified as independent risk factors for Danish pregnant women's consumption of supplements with no content of iodine. Previous studies in Danish women have found that a high educational level, but not a high BMI, was significantly associated with use of multivitamins [19]. Likewise, a high educational level has been found to be significantly associated with the use of folic acid supplements before pregnancy and with iron supplements during pregnancy [20].

equivalent. However, a relatively high amount of women stated that they had no daily intake of bread and milk compared with the Danish investigation of dietary habits

Strengths and limitations

This is an investigation of two regional cohorts, which limits our ability to generalise the results to the total pregnant population in Denmark. Furthermore, there is a risk of selection bias due to recruitment at the ultrasound clinic, which may limit the number of participants from both ethnic groups, resource-limited groups and busy working groups. The questionnaires were filled out in the waiting area with a risk of recall bias with respect to, e.g., iodine supplement use in the initial phase of pregnancy.

The urine samples were collected at the same time of day and through the same months of year in Eastern and Western Denmark which strengthens the ability to compare the urinary iodine concentrations without any adjustments. Furthermore, the urine samples were stored under similar conditions and were analysed using the same certified laboratory equipment.

CONCLUSIONS

Despite mandatory iodine fortification, iodine excretion was below WHO recommendations in pregnancy in two Danish cohorts. Non-users of iodine supplements are at particular risk of insufficient iodine intake during pregnancy. The pregnant women with no intake of iodine supplements were characterised by low education, pre-pregnancy obesity and non-Danish origin. An increase in the iodine fortification in Denmark may be recommended to improve iodine status in pregnant women.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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