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Urinary iodine concentration during pregnancy in an area of unstable dietary iodine intake in Switzerland

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ABSTRACT. We prospectively investigated urinary iodine concentration (UIC) in pregnant women and in female, non-pregnant controls in the canton of Berne, Switzerland, in 1992. Mean UIC of pregnant women [205±151 µg iodine/g creatinine (µg I/g Cr); no.=153] steadily decreased from the first (236±180 µg I/g Cr; no.=31) to the third trimester (183±111 µg I/g Cr, $p<0.0001$; no.=66) and differed significantly from that of the control group (91±37 µg I/g Cr, $p<0.0001$; no.=119). UIC increased 2.6-fold from levels indicating mild iodine deficiency in controls to the first trimester, demonstrating that high UIC during early gestation does not necessarily reflect a sufficient iodine supply to the overall population. Pregnancy is accompanied by important alterations in the regulation of thyroid function and iodine metabolism. Increased renal iodine clearance during pregnancy may explain increased UIC during early gestation, whereas increased thyroidal iodine clearance as well as the iodine shift from the maternal circulation to the growing fetal-placental unit, which both tend to lower the circulating serum levels of inorganic iodide, probably are the causes of the continuous decrease of UIC over the course of pregnancy. Mean UIC in our control group, as well as in one parallel and several consecutive investigations in the same region in the 1990s, was found to be below the actually recommended threshold, indicating a new tendency towards mild to moderate iodine deficiency. As salt is the main source of dietary iodine in Switzerland, its iodine concentration was therefore increased nationwide in 1998 for the fourth time, following increases in 1922, 1965 and 1980.

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INTRODUCTION

Dietary iodine supply, usually assessed by measuring urinary iodine concentration (UIC), has received considerable attention worldwide (1, 2). About one fifth of Earth's population is at risk of iodine deficiency (ID), 200-300 million people present with disturbed thyroid function or a goiter caused by ID, about 20 million suffer from ID-induced mental retardation and about 6 million are cretins (3). Goiter is endemic in most European countries, and a recommended minimal iodine supply of 150 µg/day for adults and of 175-200 µg/day for pregnant women (4) [or a urinary concentration of 150 µg iodine/g creatinine (µg I/g Cr) and 175-200 µg I/g Cr, respectively, assuming a mean 24 h urinary creatinine excretion of 1.0 g in women (5)] is achieved only in a few regions (6, 7). Thyroid disorders caused by ID range from discrete functional disturbances to mild intellectual impairment to full-blown cretinism (8, 9).

In pregnant women, a tendency towards an increase of TSH within physiological limits was observed even under conditions of only mild to moderate ID (with UIC of 50-100 µg iodine/day [µg I/d]) (10, 11). Continuous monitoring of a group at risk of developing latent hypothyroidism under conditions of marginal iodine supply, such as pregnant women, is essential (10, 11).

Key-words: Iodine, metabolism, pregnancy, salt, urine, women.

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The goal of the present study was to evaluate random individual and sequential UIC data of pregnant women in the Bernese region in Switzerland in 1992, in order to compare them with data in the literature. Determining UIC levels of pregnant women in Switzerland seemed an important topic of research, especially since UIC levels which had been shown to be adequate in Switzerland in the 1980s appeared to be moderately insufficient in the 1990s in the same region (12-14). This insufficiency probably reflects a decrease in dietary iodine supply, and is assumed to be due to changes in nutritional habits (12, 13).

MATERIAL AND METHODS

Subjects

From the end of February to early April 1992 we investigated UIC and urinary creatinine concentration (UCC) in spot urine samples of 192 pregnant women from six different regions in the canton of Berne, Switzerland (Interlaken, Heimberg, Burgdorf, Biel, Thun and Berne) and of 124 healthy, non-pregnant women from the regions of Berne (no.=71) and Burgdorf (no.=53) who served as controls.

After written informed consent was obtained, gynecologists and general practitioners collected spot urine samples of consecutive pregnant (at any stage of pregnancy) and non-pregnant women, respectively, on the occasion of routine consultations at various times of the day. The samples were collected in conventional 10 ml plastic tubes and frozen immediately (no.= 50, 66, and 76 samples from the first, second and third trimesters, respectively). Significant circadian (15) and seasonal (16) rhythms of UIC, with higher UIC values in late afternoon compared to early morning and during winter compared to summer, were not reported in the medical literature until after the sampling period, and thus were not taken into consideration in the study design.

All women completed a questionnaire on preexisting thyroid diseases, consumption of iodized *vs* non-iodized salt at home, special diets, intake of medicines (in particular multiple vitamins or oligoelements) and exposure to contrast media or other iodine-containing pharmaceuticals.

In order to confirm the low initial UIC values of part of the Berne control group and to exclude a transiently insufficient supply, 36 non-pregnant control women with values <100 µg I/l were reevaluated (= Berne repetition) in November 1992.

The results of the group of pregnant women from the region of Burgdorf were confusing. The mean UIC values of this group (859±504 µg I/g Cr; or 583±345 µg I/l; no.=27, $p<0.001$) significantly exceeded those of all other groups. 85% of the values exceeded 300 µg I/g Cr, and 44% even exceeded 1000 µg I/g Cr. There were no differences regarding the socio-demographic characteristics, results from the questionnaires and UCC compared with the groups from other regions. Perineal or vaginal disinfecting with an iodine-containing solution at the gynecologist's was ruled out. When an evaluation of healthy, non-pregnant women in Burgdorf one year later (91±42 µg I/g Cr; or 95±73 µg I/l; no.=50) revealed a mean UIC in line with the values of the non-pregnant women from the region of Berne, we assumed a transient and short-term iodine contamination of unknown origin and excluded the whole Burgdorf group of pregnant women from the calculations.

After exclusion of extreme UIC values (see statistics), a total of 153 spot urine samples from pregnant women (no.=31, 56 and 66 in the first, second and third trimesters, respectively) and of 119 samples from non-pregnant women remained. In order to compare our UIC findings with data from the literature, we calculated the mean UIC (and not medians, as used in other epidemiological studies) of the groups. Though the controls were not matched for age, the pregnant women (29.7±4.4 yr) and the controls (27.8±5.6 yr) did not differ significantly.

In accordance with previously published studies (10, 17-20), pregnancy was divided arbitrarily into weeks 1-16, 17-29, and 30 to delivery, corresponding to the first, second and third trimesters, respectively. Of the 50 pregnant women who had been included during the first trimester, 34 and 31 women collected a further urine sample during the second and third trimesters, respectively. In 15 women, UIC could be studied sequentially (one urine sample from each trimester).

Analytical methods

All laboratory analyses were performed at the Division of Clinical Chemistry, Inselspital, University of Berne, Switzerland. Total iodine was determined using the wet ash method based on the Sandell-Kolthoff reaction (21) and with the same Technicon Autoanalyzer (Technicon, Tarrytown, NY) used in previous studies in this region since 1975 (13, 22, 23). Creatinine was determined with a Hitachi 911 Autoanalyzer (Boehringer, Mannheim, Germany) using the picric acid method of Jaffé. A detailed description of the analytical methods has been given previously (14, 24). The method used in the present study for iodine measurement gives results closely comparable to a modified Sandell-Kolthoff procedure (24), which again correlates very well with a method using inductively coupled plasma mass spectrometry (25). The iodine/creatinine ratio in urine samples was shown to provide a reliable estimation of iodine intake (26) and has been used in literature on urinary iodine measurements. Since the renal clearances of iodine and creatinine are altered to the same extent in pregnancy, the iodine/creatinine ratio represents a valid parameter for longitudinal studies of urinary iodine concentration during gestation (27, 28).

Statistics

The results were analyzed statistically using *t* test. Extreme values were identified by the formula T=(x-d)/ Standard deviation (SD), in which x = presumptive extreme value, d = mean value of the group without x, and SD without x. Provided there is a normal distribution, T will have a maximum value of 3.402 within groups of 30 members, for a level of significance of 99%.

RESULTS

UIC in pregnant women

As summarized in Table 1, the mean ±SD UIC of all pregnant women (205±151 µg I/g Cr; or 204±202 µg I/l; no.=153) differed significantly from the control group (91±37 µg I/g Cr or 91±68 µg I/l; $p<0.0001$; no.=119). Except for the group

from the region of Thun, every single group of pregnant women differed significantly from the control group. Age, preexisting thyroid diseases and diets did not influence UIC. None of the study participants declared an intake of pre-natal foodstuffs or of pharmaceuticals with known relevant iodine contents.

The mean UIC increased 2.6-fold during the first trimester compared with the control group and thereafter steadily decreased from the first (236±180 µg I/g Cr; or 267±317 µg I/l; no.=31) to the second (213±170 µg I/g Cr; or 206±175 µg I/l; no.=56) and the third (183±111 µg I/g Cr; or 172±138 µg I/l; $p<0.0001$; no.=66) trimester. The median (range) values (extreme values not excluded) were 85 (24-575) µg I/g Cr (no.=124) for the controls and 183 (46-5335) µg I/g Cr (no.=36), 153 (69-729) µg I/g Cr (no.=59) and 143 (58-2205) µg I/g Cr (no.=67) for the first, second and third trimester, respectively.

This pattern was confirmed in the spot urine samples from the 15 sequentially studied women, with a significant decrease of mean UIC from the first (258±192 µg I/g Cr; or 325±353 µg I/l) to the third trimester (153±70 µg I/g Cr; or 183±121 µg I/l; $p<0.0001$), while UCC remained unchanged (Table 2).

Distribution of the UIC data

Although the mean UIC of all pregnant women exceeded the recommended lower threshold of 175 -200 µg I/g Cr (4), 96 values (63%) were found below this limit and 28 values (18%) were found in the range of 50-100 µg I/g Cr. Thirty one (20%) and twenty-nine (19%) of the pregnant women compared to zero and three (3%) of the non-pregnant women had UIC data above 300 µg I/g Cr and 300 µg I/l urine, respectively. Five, three and one of the excluded extreme UIC values from pregnant women were from the first, second and third trimester, respectively (see statistics and Table 1).

Table 1 – *Urinary iodine concentration of pregnant and non-pregnant women from various regions in the canton of Berne, Switzerland.*

Region	N (2)	UIC µg I/g Cr mean ± 1 SD	UCC mmol/l mean ±1 SD	Single extreme values (6) µg I/g Cr (see statistics)
Berne	69	91±34	9.3±6.0	343; 305
Burgdorf (1)	50	91±42	10.3±7.1	575; 439; 260
Controls, all (2)	119	91±37	9.7±6.5	
Interlaken	28	142±71(4)	8.6±5.3 (3)	916; 532
Thun	29	103±30 (3)	8.9±5.0 (3)	208
Heimberg	35	236±163 (5)	9.1±5.1 (3)	5335; 2205; 1845
Biel	27	160±52 (5)	6.9±2.7 (4)	958; 569; 428
Berne	34	346±184 (5)	10.6±5.4 (4)	None
Pregnant, all (2)	153	205±151 (5)	8.9±5.0 (3)	

(1) Urine samples collected one year after those from Berne. (2) Without extreme values (see statistics). Significance *vs* controls: (3) not significant, 4) $p<0.001$, (5) $p<0.0001$. (6) Excluded from calculations. UIC = urinary iodine concentration, UCC = urinary creatinine concentration, µg I/g Cr = µg iodine/g creatinine. To convert UCC from mmol/l to g/l divide by 8.840.

Table 2 – *Urinary iodine concentration and urinary creatinine concentration in the course of pregnancy and in controls.*

	N (1)	UIC µg I/l urine mean ±1 SD	µg I/g Cr mean ±1 SD	UCC mmol/l mean ±1 SD
Control group	119	89±63	91±37	9.7±6.5
Individual samples				
1st trimester	31	267±317 (3)	236±180 (3)	9.2±5.6 (2)
2nd trimester	56	206±175 (3)	213±170 (3)	9.1±5.0 (2)
3rd trimester	66	172±138 (3,4)	183±111 (3,4)	8.6±4.6 (2)
Sequential samples				
1st trimester	15	325±353	258±192	10.4±7.2
2nd trimester	15	166±100	183±82	8.4±4.8
3rd trimester	15	183±121 (4)	153±70 (4)	10.0±3.7

(1) Numbers of samples after exclusion of extreme values (see statistics and Table 1). Significance *vs* controls: (2) none, (3) $p<0.0001$. Significance *vs* 1st trimester: (4) $p<0.0001$. Trimesters 1, 2 and 3 denote weeks 1-16, 17-29 and 30 to delivery, respectively. UIC = urinary iodine concentration, UCC = urinary creatinine concentration, µg I/l urine = µg iodine/l urine, µg I/g Cr = µg iodine/g creatinine. To convert UCC from mmol/l to g/l divide by 8.840.

DISCUSSION

In the Bernese region, where mild ID prevailed, UIC in 153 pregnant women was found to be significantly higher than in a control group of non-pregnant women. Compared to the controls, the UIC during the first trimester of pregnancy increased 2.6-fold and decreased progressively over the second to the third trimester. However, even in the third trimester, UIC values were still significantly higher in pregnant women than in non-pregnant controls.

UIC throughout pregnancy

As summarized in Fig. 1, the available data from the literature suggest an increased mean UIC during gestation, unless the mean UIC in the reference populations is below approximately 75 µg I/g Cr (or <75 µg I/l urine).

Under conditions of severe ID in a region of former Eastern Germany (mean UIC 21±14 µg I/g Cr in non-pregnant women aged 18-35 yr), mean UIC values in mid- and late gestation were found to be lower than those of the respective controls (columns A and C in Fig. 1) (17, 18). This was also true after improvement of iodine supply to about 50-75 µg/day [mean UIC in the control group estimated from Fig. 2 in reference (18) at about 70 µg I/g Cr, indicating moderate ID]. In a small group from another severely iodine-deficient region in Italy (not shown in Fig. 1), UIC during pregnancy was found to be clearly below that of the control population (29±16 µg I/g Cr; no.=16 *vs* 49±43 µg I/g Cr; level of significance not reported) (29). One study performed in Denmark (not shown in Fig. 1) and one study from Belgium (columns B in Fig. 1), both with a mean UIC of about 50-75 µg I/day (or 50-75 µg I/l urine) in the respective reference populations, revealed an unchanged UIC during pregnancy (10, 30, 31). In two Irish populations with a UIC of 80±1.6 µg I/l and 94±6.8 µg I/g Cr in the non-pregnant controls, UIC throughout pregnancy was significantly increased in comparison with the respective controls (columns D and E in Fig. 1) (19, 20). In a region of Iran with a comparably high UIC of about 200 µg I/l in the controls, UIC during pregnancy did not differ significantly from non-pregnant women (not shown in Fig. 1) (32).

UIC in early gestation (1st trimester)

The mean UIC in the present study was found to be highly significantly increased during the first trimester (236±180 µg I/g Cr) compared with the control group (91±37 µg I/g Cr; columns F in Fig. 1). Similar results have been reported from Ireland,

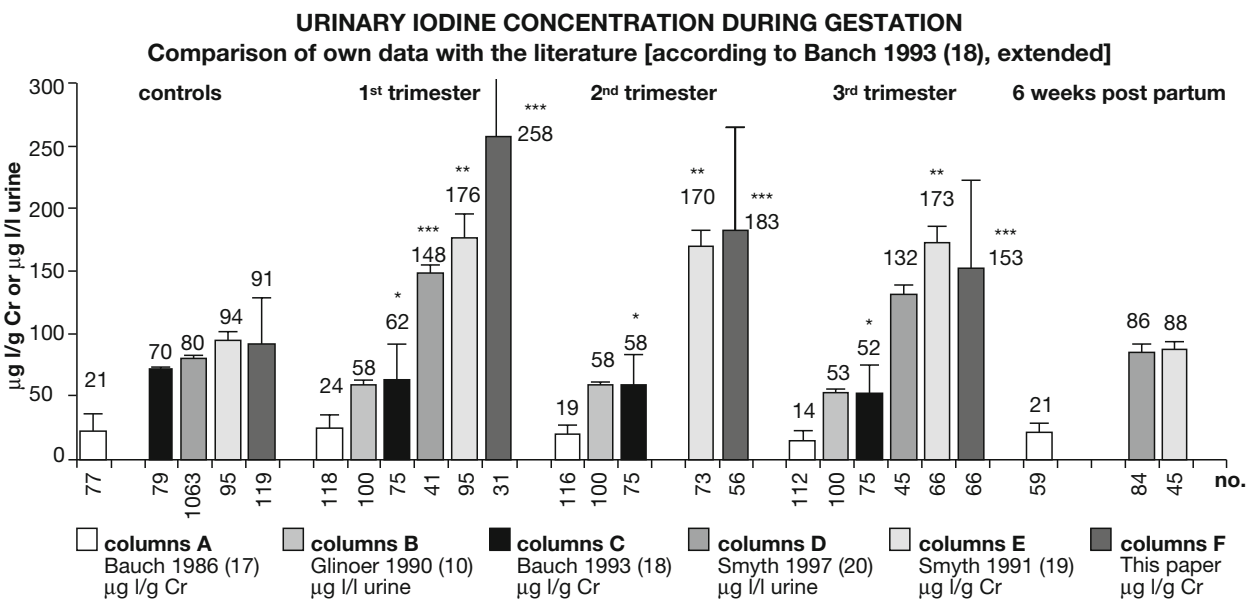

Fig. 1 - *In studies with a mean UIC in the controls above approximately 75 µg I/l urine or µg I/g Cr (columns D, E, F), mean UIC during pregnancy is increased. In studies with a mean UIC in the controls below approximately 75 µg I/l urine or µg I/g Cr (columns A, B, C), mean UIC during pregnancy remains stable or even decreases. Mean urinary iodine concentration of the control group Bauch 1993 was estimated from Figure 2 in reference (18). Data comparison between the different authors and regions is limited, since values are reported in different units. µg I/g Cr = µg iodine/g creatinine. µg I/l urine = µg iodine/l urine. no. = number of spot urine samples. Columns and the values above the columns refer to mean UIC data; vertical lines indicate standard deviations (+ 1 SD). Significance* vs *respective controls:* *p<0.05; **p<0.01; ***p<0.0001.

where in two different studies a mean UIC of 148±6 µg I/g Cr (control group 80±1.6 µg I/g Cr, $p<0.001$; columns D in Fig. 1) and 176±18 µg I/g Cr (control group 94±7 µg I/g Cr, $p<0.01$; columns E in Fig. 1) were found in the first trimester (19, 20). Under conditions of mild to severe ID, UIC in the first trimester was reported to increase slightly (no level of significance reported) in another study (columns A in Fig. 1) (17). The exact UIC values of the control populations of two other studies (columns B and C in Fig. 1) from regions with mild ID are not available (UIC in the control group about 50-75 µg I/g Cr) (10, 18).

Decrease of UIC in the 2nd and 3rd trimesters

In our sequentially studied urine samples of 15 women, the mean UIC decreased significantly from the first to the third trimesters, while the mean UCC remained unchanged (Table 2). As summarized in Fig. 1, UIC decreased in the course of pregnancy in the present and in most of the previously published investigations (10, 18, 19, 20). In a large group of pregnant women from Belgium (not shown in Fig. 1), a similar decreasing shift from 58±2 µg I/l in early gestation to 49±2 µg I/l in late gestation was reported (33).

The increase of UIC in early gestation as well as the decrease during the course of pregnancy probably reflects two major physiological changes.

First, with pregnancy, renal clearance of iodide increases significantly due to an increased glomerular filtration rate (27, 28). This iodide loss tends to lower the circulating levels of inorganic iodide and induces, in turn, a compensatory increase in the thyroidal iodide clearance (11, 27, 34). The rapid postpartum return of UIC to pre-pregnant values documented in the literature is probably due to normalization of renal clearance as well as placental loss, and suggests a direct effect of pregnancy on urinary iodine output (11, 17, 19, 20). In areas with moderate ID, serum inorganic iodide levels decrease already during early gestation (11, 27). This may explain why in such regions mean UIC throughout pregnancy does not increase or even decreases as compared to that of non-pregnant women (10, 17, 18, 29, 30).

Second, later on during gestation, a part of the available iodide pool is shifted from the maternal circulation to the expanding fetal-placental unit (11, 35), leading to an additional, progressive decrease of circulating levels of inorganic iodide. The increased thyroidal iodide clearance and the shift to the fetal-placental unit may explain the observations of progressive UIC decrease during gestation. To our knowledge, there are no available data concerning the existence and location of an active regulation system of renal retention or secretion of halogens and especially of iodide.

High individual UIC values during pregnancy

In the present study, the mean UIC of all pregnant women exceeded the recommended lower threshold of 175-200 µg I/g Cr (4). One-fifth of the pregnant women compared to zero of the non-pregnant women had UIC values above 300 µg I/g Cr. Nevertheless, two-thirds of the UIC values from pregnant women did not reach the 175 µg I/g Cr threshold and one-fifth was even found to be in the low range of 50-100 µg I/g Cr. The existence of high intra-individual variability (13), as well as the significant relevance of a circadian rhythm of UIC (15), was unknown in 1992 when the urinary samples for the present study were collected. We cannot exclude that urine spots in the controls might have been sampled more often during morning hours, whereas pregnant women might have sampled throughout the day. As UIC has been found to be lower in the morning than in the afternoon, this potential methodological bias may represent an additional explanation for the higher frequency of high and sometimes very high UIC data in pregnant women compared with the controls.

In another Swiss study performed after salt iodide concentration had been increased in 1998, *i.e.*, under different baseline conditions than in the present study, roughly one-fifth of 511 pregnant women [estimated from Fig. 2 in reference (36)] had a UIC above 300 µg I/l throughout pregnancy. In this study 13% of all pregnant women declared consumption of an iodine-containing supplement (36) compared to none in the present investigation.

Higher mean UIC values in early compared to late gestation are unlikely to result from a methodological bias, as the UIC pattern throughout pregnancy found in the random individual (expressed as mean and median values) as well as in the sequential samples were closely comparable. Since UIC decreases in the course of pregnancy, and because mid- (no.=56/153) and late- (no.=66/153) gestational periods were somewhat over-represented in our sample series, the average UIC over the whole pregnancy as well as the average UIC during the first trimester could likely have shifted to even higher values in a numerically more balanced study population.

Pregnancy and iodine metabolism

Pregnancy constitutes a challenge for both the maternal and fetal thyroid glands and induces ma-

jor alterations of iodine metabolism (11, 37). Two excellent and comprehensive surveys concerning regulation of thyroid function during pregnancy have been published (11, 35). The increased frequency of goiter during or after pregnancy has repeatedly been confirmed (10, 11, 20, 30, 38). The pathogenesis of goiter has also been discussed in detail recently (39-41). Thyroid disorders are observed four- to five-fold more frequently in women than in men (11). Whether thyroid stimulation during gestation is causal and sufficient to explain later development of autonomous thyroid growth and function in women is still unknown.

Iodine supplementation during pregnancy

In regions with mild to severe ID, supplementation by iodine or by iodine plus L-thyroxine during pregnancy prevented an increase of the thyroid volume in the mothers and the newborns and attenuated or suppressed an increase of maternal TSH levels in several published studies (17, 30, 31). One single study, however, reported an increase of thyroid volumes in pregnant women despite supplementation by 300 µg I/d and no effect on the maternal TSH levels (42). It might be possible that these contradictory results are due to a lack of compliance in some of the subjects (as UIC data in a quarter of the treated pregnant women remained very low) or to the higher supplementation dose in comparison with other studies.

The available literature does not definitely answer questions on the optimal dose, timing, or duration of iodine supplementation with relation to pregnancy. Whether it is beneficial to give iodine supplements to pregnant women under conditions of only borderline ID remains unknown and requires further evaluation. Nevertheless, since a tendency towards an increase of TSH levels arises even under conditions of only mild to moderate ID (with UIC of 50-100 µg I/d) in pregnant women (10, 11), iodine supplementation (with 150-200 µg I/d) during pregnancy should seriously be considered, at least until a sufficient level of UIC has been documented in women of child-bearing age within the population. It cannot be stressed enough that even if children have UIC levels indicating sufficient iodine supply, women of child-bearing age in the same population may present UIC indicating significant ID (43).

Low UIC in the control group

After table salt in Switzerland had been supplemented with increasing concentrations of potassium iodide in 1922, 1965 and 1980 (with 5, 10 and 20 mg/kg, respectively), urinary iodine concentration rose from less than 30 µg I/24 h in 1920 to a UIC of more than 150 µg I/g Cr in the 1980s, indicating sufficient supply (23). However, average UIC in our control group of 119 non-pregnant women (91±37 µg I/g Cr) was in good agreement with data from a parallel investigation of adults (87±40 µg I/g Cr; no.=54) (12), with two later studies in the same region (15) and in different parts of Switzerland (44, 45), indicating a new tendency towards mild to moderate ID, especially in young female adults (43). Because in the present study UIC values of some non-pregnant women from Berne (Berne repetition) were confirmed unchanged by a second measurement seven months after the initial collection, a transiently insufficient iodine supply could be ruled out. Only 6% of our individual values reached the recommended threshold of 150 µg I/g Cr (4), and as much as 8% of the values were found to be below 50 µg I/g Cr.

Two potential biases may be ruled out. The UCC of our controls did not differ from previous investigations in the same region (46), and a seasonal variation of UIC related to the intake of milk and fresh milk products was shown to be significant only in children, who have a high milk intake, but not in adult women, who consume much less milk (16).

As a consequence, given that in Switzerland salt is still the main source of dietary iodine, supplementation was increased nationwide in 1998 for the fourth time.

CONCLUSIONS

In conclusion, UIC during early pregnancy increases under conditions of mild to moderate ID and decreases from early to late gestation. These variations are caused by physiological adaptations of thyroid and renal clearances of iodide. Therefore, as UIC during pregnancy does not necessarily reflect the actual iodine supply, interpretation of UIC during pregnancy has to be performed with caution. The question of which UIC threshold in pregnant women reliably reflects sufficient iodine supply requires further evaluation.

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REFERENCES

1. Laurberg P. Iodine intake - what are we aiming at? J. Clin. Endocrinol. Metab. 1994, *79:* 17-19.
2. Dunn J. Seven deadly sins in confronting endemic iodine deficiency, and how to avoid them. J. Clin. Endocrinol. Metab. 1996, *81:* 1332-1335.
3. Dunn J.T., van der Haar F. A practical guide to the correction of iodine deficiency. International council for control of iodine deficiency disorders (ICCIDD). Dunn JT, van der Haar F. (Eds.), 1990, p. 10.
4. Delange F. Requirements of iodine in humans. In: Delange F., Dunn J.T., Glinoer D. (Eds.), Iodine deficiency in Europe, a continuing concern. Plenum Press, New York, 1993, p. 5.
5. Schmid M., Schulthess C., Bürgi H., Studer H. Jodmangel in der Schweiz noch immer endemisch. Schweiz. Med. Wochenschr. 1980, *110:* 1290-1295.
6. Delange F., Bürgi H. Iodine deficiency disorders in Europe. Bull. World Health Organ. 1989, *67:* 317-325.
7. Gaitan E., Dunn J.T. Epidemiology of iodine deficiency. Trends Endocrinol. Metab. 1992, *3:* 170-175.
8. Boyages S.C. Iodine deficiency disorders. J. Clin. Endocrinol. Metab. 1993, *77:* 587-591.
9. Delange F. The disorders induced by iodine deficiency. Thyroid. 1994, *4:* 107-128.
10. Glinoer D., De Nayer P., Bourdoux P., *et al*. Regulation of maternal thyroid during pregnancy. J. Clin. Endocrinol. Metab. 1990, *71:* 276-287.
11. Glinoer D. The regulation of thyroid function in pregnancy: Pathways of endocrine adaptation from physiology to pathology. Endocr. Rev. 1997, *18:* 404-433.
12. Als C., Gerber H., Brander L., Luescher D., Lauber K., Roesler H. Iodine supply varies over time in an affluent society such as Switzerland. Exp. Clin. Endocrinol. 1994, *300* (Suppl 1): 189 (Abstract).
13. Als C., Lauber K., Brander L., Luescher D., Roesler H. The instability of dietary iodine supply over time in an affluent society. Experientia 1995, *51:* 623-633.
14. Brander L. Untersuchung zur Jodversorgung schwangerer Frauen im Kanton Bern. Medical dissertation. University of Bern, 1997.
15. Als C., Helbling A., Peter K., Haldimann M., Zimmerli B., Gerber H. Urinary iodine concentration follows a circadian rhythm: a study with 3023 spot urine samples in adults and children. J. Clin. Endocrinol. Metab. 2000, *85:* 1367-1369.
16. Als C., Haldimann M., Bürgi E., Donati F., Gerber H., Zimmerli B. Swiss pilot study of individual seasonal fluctuations of urinary iodine concentration over two years: is age-dependency linked to the major source of dietary iodine? Eur. J. Clin. Nutrition. 2003, *57*: 636-646.
17. Bauch K., Meng W., Ulrich F.E., *et al*. Thyroid status during pregnancy and post partum in regions of iodine deficiency and endemic goiter. Endocrinol. Exp. (Bratisl.) 1986, *20:* 67-77.
18. Bauch K., Einenkel D., Alexander W., *et al*. Goiter in pregnancy in Germany. In: Delange F., Dunn J.T., Glinoer D. (Eds.), Iodine deficiency in Europe. Plenum Press, New York, 1993, p. 191.
19. Smyth P.P.A., Hetherton A.M., Ryan R., O'Herlihy C. Alterations in iodine status and thyroid volume during pregnancy. In: Beckers C., Reinwein D. (Eds.), The thyroid and pregnancy. Schattauer-Verlag, Stuttgart-New York, 1991, p. 55.
20. Smyth P.P.A., Hetherton A.M.T., Smith D.F., Radcliff M., O'Herlihy C. Maternal iodine status and thyroid volume during pregnancy: Correlation with neonatal iodine intake. J. Clin. Endocrinol. Metab. 1997, *82:* 2840-2843.
21. Sandell E.B., Kolthoff J.M. Chronometric method for the determination of micro quantities of iodine. J. Am. Chem. Soc. 1934, *56:* 1426.
22. Lauber K. Iodine determination in biological material. Kinetic measurement of the catalytic activity of iodide. Anal. Chem. 1975, *47:* 769-771.
23. Bürgi H., Supersaxo Z., Selz B. Iodine deficiency diseases in Switzerland one hundred years after Theodor Kocher's survey: A historical review with some new goiter prevalence data. Acta Endocrinol. (Copenh.) 1990, *123:* 577-590.
24. Wüthrich C. Jodresorption bei der Mundspülung mit standardisierter PVP-Jod-Lösung unter besonderer Berücksichtigung des Gehaltes an Jodid und Jodat. Pharmaceutical Dissertation. University of Bern, 1995.
25. Haldimann M., Zimmerli B., Als C., Gerber H. Direct determination of urinary iodine by inductively coupled plasma mass spectrometry using isotope dilution with iodine-129. Clin. Chem. 1998, *44:* 817-824.
26. Bourdoux P., Delange F., Filetti S., Thilly C., Ermans A.M. Reliability of the iodine/creatinine ratio: a myth? In: Hall R., Köbberling J. (Eds.), Thyroid disorders associated with iodine deficiency and excess. Raven Press, New York, 1985, *22:* 145-153.
27. Aboul-Khair S.A., Crooks J., Turnbull A.C., Hytten F.E. The physiological changes in thyroid function during pregnancy. Clin. Sci. 1964, *27:* 195-207.
28. Dafnis E., Sabatini S. The effect of pregnancy on renal function: physiology and pathophysiology. Am. J. Med. Sci. 1992, *303:* 184-205.
29. Vermiglio F., Lo Presti V.P., Scaffidi Argentina G., *et al*. Maternal hypothyroxinaemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. Clin. Endocrinol. (Oxf.) 1995, *42:* 409-415.
30. Pedersen K.M., Laurberg P., Iversen E., *et al*. Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. J. Clin. Endocrinol. Metab. 1993, *77:* 1078-1083.
31. Glinoer D., De Nayer P., Delange F., *et al*. A randomized trial for the treatment of mild iodine deficiency during pregnancy: Maternal and neonatal effects. J. Clin. Endocrinol. Metab. 1995, *80:* 258-269.
32. Rezvanian H., Aminorroaya A., Majlesi M., *et al*. Thyroid size and iodine intake in iodine-repleted pregnant women in Isfahan, Iran. Endocr. Pract. 2002, *8:* 23-28.

33. Glinoer D. The thyroid function during pregnancy: maternal and neonatal aspects. In: Beckers C., Reinwein D. (Eds.), The thyroid and pregnancy. Schattauer-Verlag; Stuttgart-New York, 1991, p. 35.
34. Halnan K.E. The radioiodine uptake of the human thyroid in pregnancy. Clin. Sci. 1958, *17:* 281-290.
35. Burrow G.N., Fisher D.A., Larsen P.R. Maternal and fetal thyroid function. N. Engl. J. Med. 1994, *331:* 1072-1078.
36. Hess S.Y., Zimmermann M.B., Torresani T., Bürgi H., Hurrell R.F. Monitoring the adequacy of salt iodization in Switzerland: a national study of school children and pregnant women. Eur. J. Clin. Nutr. 2001, *55:* 162-166.
37. Glinoer D., Delange F., Laboureur I., *et al*. Maternal and neonatal thyroid function at birth in an area of marginally low iodine intake. J. Clin. Endocrinol. Metab. 1992, *75:* 800-805.
38. Crooks J., Tulloch M.J., Turnbull A.C., Davidsson D., Skulason T., Snaedal G. Comparative incidence of goiter in pregnancy in Iceland and Scotland. Lancet 1967, II: 625-627.
39. Bürgi U., Gerber H., Studer H. Goitrogenesis in iodine deficiency. In: Delange F., Dunn J.T., Glinoer D. (Eds.), Iodine deficiency in Europe. Plenum Press, New York, 1993, p. 61.
40. Gerber H., Bürgi U., Peter H.J., Wagner H.E. The transformation of normal thyroid cells to goiter: the role of iodine depletion and repletion. In: Naumann J., Glinoer D., Braverman L.E., Hostalek U. (Eds.), The thyroid and iodine. Schattauer-Verlag, Stuttgart-New York, 1996, p. 65.
41. Peter H.J., Bürgi U., Gerber H. Pathogenesis of nontoxic diffuse and nodular goiter. In: Braverman L.E., Utiger R. (Eds.), The Thyroid, ed 7. Lippincott, Philadelphia, 1996, p. 890.
42. Liesenkötter K.P., Göpel W., Bogner U., Stach B., Grüters A. Earliest prevention of endemic goiter by iodine supplementation during pregnancy. Eur. J. Endocrinol. 1996, *134*: 443-448.
43. Als C., Keller A., Minder C., Haldimann M., Gerber H. Age- and gender-dependent urinary iodine concentrations in an area-covering population sample from the Bernese region in Switzerland. Eur. J. Endocrinol. 2000, *143*: 629-637.
44. Truong T.H., Gerber H., Haenel A.F., Bürgi H. Jodversorgung in verschiedenen Lebensphasen und sonographische Schilddrüsenvolumina bei Schulkindern in einer Gegend der Schweiz. Schweiz. Med. Wochenschr. 1997, *127:* 715-721.
45. Solcà B., Jaeggi-Groisman S.E., Saglini V., Gerber H. Iodine supply in different geographical areas of Switzerland: comparison between rural and urban populations in the Berne and the Ticino regions. Eur. J. Clin. Nutr. 1999, *53:* 754-755.
46. Mordasini C., Abetel G., Lauterburg H., *et al*. Untersuchung zum Kochsalzkonsum und zur Jodversorgung der schweizerischen Bevölkerung. Schweiz. Med. Wschr. 1984, *114:* 1924-1929.