Oral Contraceptive Intake and Iodine Status in Young Women

Carola Deischinger^a Doris Deischinger^a Irina Gessl^b Michael Krebs^a
Rodrig Marculescu^c Alexandra Kautzky-Willer^a Lana Kosi-Trebotic^a

^aClinical Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Unit of Gender Medicine, Vienna, Austria; ^bClinical Division of Rheumatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria; ^cClinical Institute for Medical and Chemical Laboratory Diagnostics, Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

Keywords

Iodine · Urinary iodine concentration · Women · Oral contraceptive · Iodine deficiency

Abstract

Objective: Similar to pregnant women, women taking an oral contraceptive (OC) might have elevated iodine requirements due to the altered hormonal state. This is the first study aimed at investigating the prevalence of iodine deficiency and possible influences of OC intake on urine creatinine and iodine levels in young women. **Methods:** One hundred fifty-five women between the age of 18 and 35 years (62 taking an OC and 93 controls) participated in a cross-sectional pilot study at the Medical University of Vienna, which included a 1-spot urine sample and a questionnaire on OC intake as well as a food questionnaire. **Results:** The median urinary iodine concentration (UIC) in this study was 68 µg/L (41, 111 µg/L) suggesting an inadequate iodine status in the women according to the WHO guidelines. Median UIC (OC: 89 µg/L, IQR 55–120; control: 59 µg/L, IQR 39–91, $p = 0.010$) and urine creatinine (OC: median = 99.0 µg/L, IQR 74.9–175.5; control: 77.0 µg/L, IQR 49.6–147.2, $p = 0.030$) lev-

els were significantly higher in OC women than in the control group. UIC corrected for urine creatinine was comparable between both groups. **Conclusion:** With similar creatinine-corrected UICs in both groups, OC intake might not have a significant impact on iodine status. However, the low median UIC in a vulnerable group of young women potentially conceiving in the following years points at the necessity of optimizing the iodine intake in the Austrian population and reiterates the insufficiency of the current iodine supplementation measures.

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Introduction

Iodine is a critically important nutrient well known for its role in thyroid health [1]. However, almost a third of all countries worldwide are still considered iodine deficient [2]. This is of utmost importance in pre-gestation and gestation due to its effects on neurodevelopment and fecundability [3, 4]. The relevance of adequate iodine supply during pregnancy is especially evident due to its influence on the neurodevelopment of the unborn child

[5, 6], which begins in the third to fourth week of gestation and may be affected by the mother's thyroid and pregestational iodine status [3, 7]. It is therefore essential to identify potential mediators of the iodine status in women at child-bearing age.

In Austria, according to a previously conducted study by Lindorfer et al. [8], 82.2% of all included pregnant Austrian women had an iodine deficiency varying from slight to severe. Pregnant women are more susceptible to iodine deficiency due to a 50% increased thyroid hormone synthesis, passage of iodine through the placenta to aid in fetal thyroid hormone production, and 30–50% higher renal iodide loss due to progressively increasing glomerular filtration rate (GFR) and renal plasma flow [1, 3, 9–12]. Oral contraceptives (OCs), the most frequent form of contraception, are also known to increase GFR [13, 14], which could result in increased renal iodine loss as well. Possible explanations for the higher GFR while on OC include a vasodilative effect of the estrogen component [15] and progesterone causing natriuresis, potentially predisposing to a loss of iodine [10]. Furthermore, iodine is an essential component in thyroid hormone production [11]. According to the free thyroid hormone hypothesis, thyroxine-binding globulin (TBG) concentrations rise when excess estrogen is present [11]. Accordingly, pregnant women and women using birth control pills have similarly high total and free TBG binding capacity due to more thyroxine (T4) being bound to TBG [16]. An increased TBG concentration leads to a free T4 reduction and a compensatory increase in thyroid hormone production for which iodine is needed [11].

As data on the possible role of estrogen and progesterone on thyroid and iodine levels are still insufficient [17, 18], women using OC might be at risk of developing iodine deficiency. Therefore, we aimed at investigating the iodine status (urinary iodine concentration – UIC; creatinine-corrected UIC) of Austrian women from the age of 18 to 35 and OC as a potential influence.

Study Design and Methods

This cross-sectional pilot study is the analysis of UIC, creatinine levels, and creatinine-corrected UIC in 155 (61 in the OC group and 93 in the control group) nulliparous, Caucasian, female students at the Medical University of Vienna between December 2016 and December 2019. The women were currently either taking a combination OC or had not been taking a form of OC within 6 months before the participation (control group). Women in the OC group ought to have taken an OC for at least 3 months prior to the submission of the urine sample. Primary outcomes are UIC and creatinine-corrected UIC to establish the iodine status of the

participating women. The participants submitted a morning spot urine sample (10 mL per person, after at least an 8-h fast) and completed a questionnaire on their contraceptive pill intake (duration, type of OC, and brand), 24-h recall of foods containing high amounts of iodine, height, weight, and smoking status. The 24-h diet recall included questions on milk, cheese, yoghurt, seafood, and fish consumption due to their high iodine content [19]. None of the women had consumed seafood within the past 24 h. Therefore, seafood consumption was excluded from all further analyses. Exclusion criteria were exposure to iodinated contrast media, an iodine-containing disinfecting agent in the last 6 weeks, amiodarone within the past 24 months, pregnant or breastfeeding in the last 6 months, hyperthyroidism within the past 12 months, and progestin-only birth control pills or any other nonoral contraceptives. Individuals with diagnosed liver problems or renal insufficiency were excluded as well because UIC might not correctly reflect iodine status. Of 185 screened women, 30 were excluded, leaving 155 women for the analysis. Women were predominantly excluded due to the intake of progestin-only birth control or the use of nonoral contraceptives, which resulted in a higher number of women in the control group (93) than in the OC group (62). In the urine analysis, creatinine levels in milligrams per deciliter and iodine levels in micrograms per liter via a microphotometric method (Sandell-Kolthoff method) were measured. All samples were analyzed in our ISO 9001-certified central laboratory at the General Hospital in Vienna (AKH Wien). Methods are available under the homepage of the institute of laboratory medicine, www.kimcl.at. Creatinine-corrected iodine levels were calculated using the measured creatinine and iodine levels.

Statistical Methods

Normal distribution was checked via the calculation of skewness using the Kolmogorov-Smirnov test. Nonparametric data were described as median and interquartile range (IQR), normally distributed data as mean and standard deviation, and categorical baseline characteristics as percentages and frequencies. Potential differences in normally distributed baseline characteristics such as weight, height, and age were assessed with independent samples *t* tests. To compare the nonparametric variables iodine, creatinine, milk, cheese, yoghurt, seafood, and fish consumption between the OC and the control group, each of these variables was log10 transformed, and a *t* test and an ANCOVA correcting for smoking status, BMI, age, milk, cheese, yoghurt, and sea fish consumption were performed. A linear regression was calculated to evaluate potential influencing factors of creatinine-corrected iodine. The collected data were analyzed with SPSS (Version 25).

Results

As presented in Table 1, baseline characteristics such as age, height, weight, and smoking behavior were not significantly different between the 2 groups. Concerning the 24-h recall on iodine-containing foods, the consumption of iodine-rich foods was similar in the OC and the control group (see Table 1). The mean time on OC was 62 months (± 39), ranging from 3 to 156 months.

Table 1. Baseline characteristics of women taking OC and controls

Baseline characteristics	OC (N = 62)		Control group (N = 93)	
	mean	SD	mean	SD
Age, years	26.2	12.3	26.9	5.2
Height, cm	168	6	168	7
Weight, kg	61.1	8.4	61.8	10.3
Duration of OC intake, months	62	39		
Estrogen content of OC, mg	1.11	1.12		
Progesterone content of OC, mg	0.05	0.19		
Food and lifestyle questionnaire				
Milk consumption, mL	103	126	133	187
Cheese consumption, g	32	37	34	40
Yoghurt, g	50	93	67	118
Sea fish, g	20	68	48	108
Smoking prevalence, %	14.5 (9/62)		15.1 (14/93)	
	median	IQR	median	IQR
Urine spot analysis				
UIC, µg/L	89**	55–120	59**	39–91
Urine creatinine, mg/dL	99.0*	74.9–175.5	77.0*	49.6–147.2
Creatinine-corrected iodine, g/gCr	74	52–120	74	49–147

Continuous variables were summarized by mean $\pm$ standard deviation and median and interquartile range and categorical variables by percentages. To assess differences between women on birth control and the control group, an independent samples *t* test was performed. OC, oral contraceptive; UIC, urinary iodine concentration. * The significance level is $p < 0.05$. ** The significance level is $p < 0.01$.

In the *t* test, UIC ($p = 0.010$) and urine creatinine ($p = 0.030$) were significantly higher in women on an OC than in the control group. However, in an ANCOVA corrected for smoking status, BMI, age, milk, cheese, yoghurt, and sea fish intake, the creatinine-corrected iodine did not differ between the groups (mean difference = 0.035, $p = 0.506$).

A linear regression model investigating creatinine-corrected iodine ($p = 0.286$, $R^2 = 0.014$) showed no relevant impact of smoking status ($\beta = -0.001$, $p = 0.497$), BMI ($\beta = -0.066$, $p = 0.207$), age ($\beta = 0.022$, $p = 0.394$), cheese intake ($\beta = 0.098$, $p = 0.112$), sea fish intake ($\beta = 0.033$, $p = 0.343$), duration of OC intake ($\beta = -0.030$, $p = 0.356$), and estrogen ($\beta = -0.003$, $p = 0.483$)/progesterone ($\beta = 0.067$, $p = 0.203$) content of the OC. Only milk ($\beta = 0.160$, $p = 0.023$) and yoghurt consumption ($\beta = 0.164$, $p = 0.021$) had a significant impact on creatinine-corrected iodine levels. According to the WHO guidelines [20], which defines an inadequate iodine status as a median UIC below 100 µg/L, the median (IQR) UIC of 89 µg/L (55, 120 µg/L) in the OC group, 59 µg/L (39, 91 µg/L) in the control group, and a median UIC of 68 µg/L (41, 111 µg/L) in the whole population indicate an inadequate iodine status in the participating women.

Discussion

To the best of our knowledge, no previous study on this topic has been published. Contrary to what was hypothesized, women who were taking an OC did not display less advantageous iodine statuses than the control group. Median UIC was higher in the OC group while creatinine-corrected UIC did not display differences between the 2 groups in this study. Creatinine-corrected UIC is considered a more reliable measure of iodine excretion as it allows to take variability in hydration level, muscle mass, and physical activity into account [21]. The higher levels of urine creatinine and iodine excretion in women who were taking an OC might be explained by the association of OC intake with a higher GFR [13]. The vasodilative effect of estrogen increases GFR; the natriuretic effect of synthetic progesterone predisposes to a renal loss of iodine [13, 15]. Since the spironolactone-derivative drospirenone is similar to progesterone, drospirenone-containing oral contraceptives might exert a similar effect and lead to an increased urine iodine excretion. In pregnancy, women have a higher UIC/increased renal iodine loss [22], which the adjusted thresholds in preg-

nant women take into account [20]. The same effect could apply to the women taking OCs in this study though and, therefore, potentially masking an iodine deficiency [21]. However, our analysis did not demonstrate any effect of estrogen and progesterone dosages on UIC or creatinine-corrected UIC.

In the whole cohort, the median UIC of 68 µg/L (41, 111 µg/L) suggests an inadequate iodine status in the participating women according to the WHO guidelines [20]. In general, a one-time urine sample is not the gold standard for approximating the iodine status in an individual person due to its daily fluctuations and dependence on factors such as diet and water intake. When examining larger sample sizes, these variations are mostly expected to level out [23]. According to König et al. [24], another way of increasing the precision of our analysis would have been to use 10 spot urine samples per person. To improve the reliability of the spot urine samples in this study, we creatinine-corrected iodine levels to account for variability in hydration levels and collected information on high-iodine food intake in a 24-h diet recall. Except for milk and yoghurt consumption, which only exerted a negligible effect, none of the iodine-containing foods in our 24-h recalls were significantly related to UIC in our analysis, and there were no differences in milk, cheese, yoghurt, and sea fish intake between the OC and the control group. What we were not able to account for is voluntary salt reduction or the substitution of iodized salt with perceived “healthier” alternatives such as Himalayan salt, which might also have an influence on the proportion of low UIC indicating iodine deficiency in our population rather than insufficient salt fortification strategies.

Another lifestyle factor, namely, smoking, was accounted for in our analysis due to the antithyroid effect of thiocyanate in cigarettes [25]. Thiocyanate in cigarettes can act as an antithyroid agent by inhibiting iodide transport, iodine organification, and increasing iodide efflux [25]. Furthermore, smoking has been associated with goiter [26], an increased risk for autoimmune disorders of the thyroid gland [27] and lower thyrotropin (TSH) levels [28]. However, smoking status had no significant effect on UIC or creatinine-corrected UIC in this analysis.

A limitation of this study is that it is a small, 1-site pilot study, and there are significant differences in iodine levels between the east and west of Austria [29]. Therefore, the results of this study might not be transferable onto areas in the west. However, the homogeneity of the pool of study participants in other baseline characteristics such as age, weight, height, and smoking status is also one of

the main strengths of this study. Information on thyroid status such as free tri-iodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), and TBG would have been beneficial in this pilot study and should be incorporated in potential future investigations on this topic. Furthermore, potential follow-up studies would be advised to use at least 10 spot urine analyses per person to increase the reliability of the UIC measurements.

Considering the creatinine-corrected UIC was not significantly different between the 2 groups, the higher UIC in women taking OCs might be due to variability in factors such as water intake rather than depicting the actual iodine status. Although we were glad to see that OCs do not negatively affect women’s iodine status, still the median UIC of the participating women suggests an inadequate iodine intake despite decades of salt iodization. Therefore, current strategies for salt fortification with iodine might be insufficient. Our results indicate a poor iodine status even in nonpregnant young women in Austria which makes this topic a highly relevant public health issue [8, 30]. Considering the likelihood of young women between the age of 18 and 35 getting pregnant, achieving adequate preconception iodine levels in this subgroup is especially important for the future of our children and a sensible recommendation regardless of OC intake.

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Statement of Ethics

The study was approved by the local ethics committee (Ethics Committee of the Medical University of Vienna, No. 1190/2016) and performed in accordance with the Declaration of Helsinki. All participants gave written informed consent for participation in the study.

Conflict of Interest Statement

All authors have no conflicts of interest to disclose.

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Author Contributions

C.D. wrote the manuscript and researched data. D.D., I.G., and A.G. researched data and contributed to the methods. R.M. contributed to the methods and reviewed the manuscript. M.K.,

L.K.-T., and A.K.-W. contributed to the discussion and reviewed/edited the manuscript. L.K.-T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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