CLINICAL STUDY

Parity is associated with increased thyroid volume solely among smokers in an area with moderate to mild iodine deficiency

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Abstract

Objective: Pregnancy has been suggested as part of the explanation of the gender difference in the prevalence of goitre, but opposing results have been reported on the association between pregnancy and goitre. We investigated the association between parity and thyroid volume and a possible impact of iodine deficiency and tobacco smoking on this association.

Design: A comparative, cross-sectional study of 3712 women randomly sampled from the general population in two geographical areas with moderate and mild iodine deficiency.

Methods: The participants answered questionnaires with an obstetric anamnesis, and ultrasonography of the thyroid was performed. Data were analysed in linear models and logistic regression analysis to adjust for age, iodine status, use of oral contraceptives and smoking habits. Women with present or recent pregnancies were excluded from the analyses.

Results: A higher thyroid volume was found among parous than among nulliparous women ($P=0.007$). The association between parity and thyroid volume was strongest in the youngest age groups, in the region with the most severe iodine deficiency, and among smokers. No association was found between parity and the prevalence of solitary or multiple thyroid nodules. Number of births, age at menarche or menopause, the number of fertile years, and age at first childbirth were not associated with thyroid volume.

Conclusion: Pregnancy increases thyroid volume, particularly when combined with tobacco smoking and iodine deficiency. The effect is probably reversible seen over a spectrum of several years.

European Journal of Endocrinology 146 39–43

Introduction

Goitre is more prevalent among women than among men. The pathogenesis of this gender difference is not known in detail. It may be due to genetic differences mediated by differences in sex hormone levels, or it may be due to environmental factors. One environmental factor could be parity, as it has been suggested that pregnancy increases the risk of goitre and may be responsible for the gender difference in goitre prevalence (1).

Thyroid volume and goitre prevalence increase during pregnancy in iodine-deficient areas even if goitre is not endemic (2–5), whereas the increase in thyroid volume in iodine-replete areas is smaller or absent (6, 7). The increase in goitre prevalence and thyroid volume in iodine-deficient areas can be prevented by supplementation with iodine during

pregnancy (8, 9), further supporting that it is mediated by an exacerbation of iodine deficiency. This could be due to increased demands through gestation, but increased urinary loss of iodine due to increased glomerular filtration has also been suggested, based on increased iodine excretion during pregnancy irrespective of iodine supplementation (3, 10).

Within the first year after term, thyroid volume declines (4, 6, 8, 11), but it is unclear if thyroid volumes return to pre-pregnancy values. Two studies have investigated the long-term consequences of pregnancy and found increased thyroid volume among parous women in an iodine-deficient area (12), whereas no association between previous pregnancies and thyroid volume was found in an iodine-sufficient area (13).

We studied the association between previous pregnancies and thyroid volume in a randomly selected

cohort from the general population in two geographical areas with moderate and mild iodine deficiency. We further tested the combined impact of parity and other risk factors for goitre.

Subjects and methods

A cohort of 7286 women was invited by letter, and 3712 (50.9%) participated. This study population represents the female population from a cohort that has previously been described in detail (14). The women were chosen in age groups to represent groups dominated by women before childbearing age (18–22 years), within childbearing age (25–30 years), after childbearing age and pre-menopausal (40–45 years), and post-menopausal (60–65 years). The cohort was randomly sampled from the Civil Registration System in which all subjects with residence in Denmark are registered by a unique ten-digit number. The cohort was sampled in two urban areas: the central part of Aalborg, a city in the western part of Denmark, and the northern part of the municipality of Copenhagen in the eastern part of Denmark. The two regions represent different degrees of iodine deficiency, as iodine concentrations in casual urine samples delivered by 98.8% of participants were 45 µg/l in Aalborg (moderate iodine deficiency) and 61 µg/l in Copenhagen (mild iodine deficiency) after exclusion – for this classification only – of subjects taking individual iodine supplementation ($P < 0.001$).

The participants answered questionnaires with an obstetric anamnesis including the number of childbirths and age at the first birth as well as the number of pregnancies. Previous or present use of oral contraceptives

was registered, and age at menarche and menopause was noted.

The questionnaires contained questions concerning previous thyroid disease. This information was confirmed in an interview with a doctor and in ambiguous cases by tracing of medical records. Further questions were asked about smoking habits, alcohol consumption and individual iodine supplementation in the form of iodine-containing vitamin/mineral tablets. The participants were divided into four groups according to smoking habits: never smokers, ex-smokers, moderate smokers (1–19 cigarettes/day), and heavy smokers (minimum 20 cigarettes/day).

Ultrasonography of the thyroid was performed with a Siemens Sonoline ultrasonography equipment (Siemens, Munich, Germany) with a 7.5 MHz 70 mm linear transducer, and thyroid volume was calculated as the sum of length $\times$ width $\times$ depth $\times$ 0.52 of each lobe as previously described (15). A thyroid volume exceeding 18 ml was regarded as thyroid enlargement (16). The number of thyroid nodules exceeding 5 mm in diameter was registered; however, only the nodules exceeding 10 mm in diameter were used for classification of the thyroid glands as regular, uninodular or multinodular.

Blood samples were drawn and analysed for thyrotrophin (TSH), free tri-iodothyronine (T_3) and free thyroxine (T_4) with a LUMI test (Brahms, Berlin, Germany). The functional sensitivity of the TSH assay was 0.01 mU/l.

Among the 3712 women, 207 had known thyroid disease and 144 were pregnant or had given birth within 12 months prior to the study and were excluded, leaving 3361 women eligible for the analyses. The distribution of these women on some of the central variables is shown in Table 1.

Table 1 The distribution of the cohort on some of the central variables, divided into age groups.

Variable	Parameter	Number in age group (years)			
		18–22	25–30	40–45	60–65
Iodine status	Mild iodine deficiency	486	443	469	385
	Moderate iodine deficiency	444	376	403	355
Childbirths	None	908	604	151	91
	One	17	128	214	113
	Two	4	77	378	270
	Three or more	1	9	96	170
Thyroid enlargement*	Yes, volume > 18 ml	43	65	231	210
	No, volume $\leq$ 18 ml	887	753	640	527
Thyroid nodularity*	No nodules > 10 mm	910	778	661	450
	Solitary nodule > 10 mm	13	20	77	78
	Multiple nodules > 10 mm	7	20	133	209
Tobacco smoking**	Never	547	409	282	288
	Ex	95	125	188	209
	1–19 cigarettes/day	231	197	219	169
	>20 cigarettes/day	57	87	183	74

* Thyroid ultrasonography missing for five participants.

** Smoking anamnesis missing for one participant.

Statistics

All data processing was done with the statistical software SPSS version 8.0.2. To allow adjustment for possible confounding by other factors, data were analysed in linear models and logistic regression analyses. As the distribution of thyroid volumes and serum TSH were skewed towards higher values, analyses were done after logarithmic transformation. Data were generally analysed in univariate models and in a simple model adjusting for age, region of inhabitancy (and thereby iodine status) and use of oral contraceptives. In a multivariate model, also smoking, alcohol intake, individual iodine supplementation and familial occurrence of thyroid disease were considered as confounders. The main effects of age, region of inhabitancy (14), alcohol consumption (17) and smoking (18) have been published previously; they were all significantly associated with thyroid volume. First-order interactions were tested, and significant interactions were included in the models and quantified. The between-groups comparisons in the figures were performed as analyses of the parameters in the interaction terms in linear models.

The level of significance was set to 5%.

Figure 1 Thyroid volume among women with and without previous childbirths and the relationship with age. Figures are mean values from a linear model after adjustment for region of inhabitancy and use of oral contraceptives; thyroid volume was analysed after logarithmic transformation. Vertical bars are s.e. Comparison of parous vs nulliparous women: 18–22 years, $P = 0.13$; 25–30 years, $P < 0.001$; 40–45 years, $P = 0.04$; 60–65 years, $P = 0.59$.

Results

Thyroid volume at ultrasonography was associated with parity in linear models. However, the number of childbirths was not associated with thyroid volume, as women with one, two or three or more childbirths had similar thyroid volumes, and consequently women were only categorized as parous or nulliparous in further analyses. In a univariate analysis, we found a mean thyroid volume of 10.7 ml in nulliparous and 14.1 ml in parous women ($P < 0.001$). After adjustment for age and region of inhabitancy, this difference diminished, but was still significant (11.8 vs 12.5 ml, $P = 0.007$).

An interaction term in the linear model suggested that the association of thyroid volume with parity was strongest in the youngest age groups (Fig. 1), although the interaction term was insignificant ($P = 0.11$). The association between parity and thyroid volume was more pronounced in the area with the lowest iodine excretion (Fig. 2) as demonstrated by the interaction term in the linear model ($P = 0.049$).

When including life style factors in the analysis, smoking interacted with parity in the association with thyroid volume (Fig. 3). For non-smokers or ex-smokers, thyroid volume was similar among parous and among nulliparous women, whereas a strong association with parity was found among smokers ($P < 0.001$ for interaction). The interaction between smoking and parity was still significant after adjust-

Figure 2 The association between thyroid volume and parity in two Danish regions with mild and moderate iodine deficiency. Figures are mean values from a linear model after adjustment for age and use of oral contraceptives; thyroid volume was analysed after logarithmic transformation. Vertical bars are s.e. Comparison of parous vs nulliparous in moderate iodine deficiency, $P < 0.001$; in mild iodine deficiency, $P = 0.24$.

Figure 3 The dependency on smoking of the association between parity and thyroid volume. Figures are means in a linear model after adjustment for region of inhabitancy, age and use of oral contraceptives; logarithmic transformation of thyroid volumes was used in the analyses. Vertical bars are S.E. Comparison of parous vs nulliparous women within each group according to smoking habits: never smokers, $P = 0.82$; ex-smokers, $P = 0.27$; moderate and heavy smokers, $P < 0.001$.

ment for alcohol consumption, iodine supplementation, and familial occurrence of thyroid disease ($P = 0.002$).

Thyroid enlargement at ultrasonography was also associated with parity in a logistic regression analysis with an odds ratio of 1.33 (95% confidence interval 1.01–1.75) for parous compared with nulliparous women after adjustment for age, region and use of oral contraceptives. Again, a significant interaction was found between smoking and parity ($P = 0.04$). Odds ratio among smokers was 1.71 (1.03–2.8) for parous women compared with nulliparous women. Among non-smokers, no association with parity was found.

A possible association between parity and thyroid nodules was investigated. Solitary nodules and multinodularity were both associated with parity in a univariate analysis. After adjustment for age, these associations became insignificant, e.g. odds ratio for a solitary thyroid nodule was 1.5 (0.9–2.5) for parous compared with nulliparous women.

Women who had been pregnant but who were nulliparous had insignificantly higher thyroid volumes than women who had never been pregnant in a multivariate analysis (12.1 vs 11.7 ml, $P = 0.18$). Age at the first childbirth was negatively associated with thyroid volume in the simple model ($P = 0.004$), but this association became insignificant after adjustment for

smoking habits ($P = 0.63$). Age at menarche or menopause or the number of fertile years was not associated with thyroid volume.

Serum TSH was significantly higher among nulliparous women than among parous women (1.34 vs 1.22 mU/L, $P = 0.02$). This difference disappeared if adjustment for thyroid volume was included in the model. No association was found between parity and levels of free T_3 and free T_4 .

Discussion

In this random sample of 3712 women from the general population, we found a significant, positive association between parity and thyroid volume and similarly an association between parity and thyroid enlargement. An association with thyroid volume has recently been demonstrated in an area with moderate iodine deficiency (12), but was absent in an iodine-sufficient area (13). Similarly, a comparative study on palpable goitre showed a larger impact of pregnancies on goitre prevalence in Scotland with iodine deficiency than in Iceland with iodine repletion (19). In our study, this association was highly dependent on iodine status, as the association was significantly stronger in the area with the most pronounced iodine deficiency, although the difference in iodine excretion between the two regions in the investigation was only modest with median iodine concentrations of 45 and 61 $\mu\text{g/l}$ in spot urine samples. This difference was, however, also related to a substantial difference in goitre prevalence (14). The lower serum TSH levels observed among parous women are also explained by an effect of iodine deficiency, as goitre in moderate iodine deficiency is associated with lower serum TSH levels (20).

Another striking feature of the association between parity and thyroid volume was that the association was only found among smokers. Smoking probably affects the thyroid through the inhibition of iodine uptake and organification (21). Thus, an interaction between parity and smoking is a further indicator of an effect of parity on thyroid volume being mediated by an exacerbation of iodine deficiency throughout pregnancy.

As women with childbirth within the last year and pregnant women were excluded from the analyses in this study, the finding of an association between parity and thyroid volume shows that this is not a readily reversible phenomenon. Conversely, the association was no longer present among women in the age group 60–65 years. Thus, the association seems to last some years after childbirth but is probably not life-long, and it is possible that other factors play a more dominating role than parity in the determination of thyroid volume later in life; a cohort effect should be considered, however. Some reversibility is in line with

previous reports (4, 6, 8, 11), although long-term effects could not be evaluated in these studies.

We found no significant association between parity and the prevalence of thyroid nodules, either solitary or multiple nodules, after adjustment for age in the analyses. This is in contrast to a previous German study from an area with similar iodine status (22); in that study, apparently no adjustment was made for the age of the women, and it is possible that the association was actually an age effect, although the age spectrum was smaller than ours.

In conclusion, parity was associated with increased thyroid volume. This association seems to rely on aggravation of iodine deficiency during pregnancy, and is thus only present in areas with some degree of iodine deficiency in the population. The effect of pregnancy is synergistic with other factors aggravating iodine deficiency, for instance smoking.

Acknowledgements

This study was supported by grants from the Tømmerhandler Vilhelm Bang Foundation, the Copenhagen Hospital Corporation Research Foundation, the 1991 Pharmacy Foundation, the Danish Medical Foundation, the Health Insurance Foundation and North Jutland County Research Foundation. We also express our thanks to Inge-Lise Legaard and Rene Fiege who carefully performed the ultrasonographies.

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Received 7 June 2001

Accepted 26 September 2001