General discussion

Severe maternal iodine deficiency during pregnancy can lead to dwarfism and intellectual disability (i.e., cretinism). Despite increasing efforts to eliminate iodine deficiency and prevent thyroid-related diseases world-wide, mild-to-moderate iodine deficiency is still common, especially in pregnant women. The potential effects of mild-to-moderate iodine deficiency during pregnancy for thyroid function and child neurodevelopment are less well known. For this reason, the aims of this thesis were to explore the determinants of iodine status, to examine the association of maternal iodine status with thyroid function during pregnancy, and to investigate if maternal iodine status and thyroid function during pregnancy are associated with child neurodevelopment outcomes. In this chapter the main results will be discussed in light of methodological considerations, together with the clinical implications and suggestions for further research.

Main findings and interpretation

Determinants of iodine status

In chapter 2, we demonstrated that younger women, with a higher pre-pregnancy BMI, and with low intake of milk and dairy products are more likely to have a low urinary iodine-to-creatinine ratio (UI/Creat) during pregnancy. We also identified cohort-specific determinants of maternal UI/Creat, such as intake of fish and shellfish in INMA and ALSPAC, and intake of eggs and cereal products in Generation R. The cohort-specific associations may be a reflection of differences between populations in the consumption of dietary iodine sources (i.e., the average fish consumption is higher in INMA and ALSPAC than in Generation R), the availability of iodized salt (i.e., the estimated penetration rate of iodized salt in household is 60-70% in the Netherlands, 16% in Spain, and 2% in the UK [1]; eggs are assumed to be eaten with salt), and the implemented iodine fortification program in the specific countries (i.e., bread is fortified with iodized salt in the Netherlands, and therefore a great source of iodine in this population [2]). These cohort-specific associations of maternal characteristics and dietary habits with iodine status suggest that public health interventions targeted to achieve iodine sufficiency in pregnancy probably need to be country-specific.

Iodine status and maternal thyroid function

In Chapter 3, we showed that in a population of 2009 pregnant women with a median UI/Creat of 85 µg/g (indicating mild-to-moderate iodine deficiency during pregnancy), the clinical reference ranges of thyroid function tests were not meaningfully different among subgroups of women differing in iodine status. We therefore question the current recommendation to calculate reference ranges for thyroid function during pregnancy solely in iodine sufficient populations. Furthermore, we examined the cross-sectional associations of maternal UI/Creat with TSH, FT4, FT3, TT4, TT3, TPOAb and TgAb positivity. Lower

iodine availability was associated with a slightly higher TT4 and a lower TSH, while women with adequate iodine intake (i.e., UI/Creat of 150-249 µg/g) had the lowest risk of TPOAb positivity. The latter results are in line with the current recommendations that define an iodine concentration between 150-249 µg/L as optimal during pregnancy [3]. The lack of an association of UI/Creat with the FT4/FT3 and TT4/TT3 ratios indicated that there was no increase in T3 over T4 secretion or higher peripheral deiodination of T4, both well-known adaptive mechanisms to chronic low iodine intake. The severity of iodine deficiency in this population may have been too mild to deplete the intra-thyroidal iodine storage and thus caused no shift in these ratios. Unfortunately, we could not study if the mild changes in thyroid function that were found in our study (i.e., higher TT4 and TPOAb positivity), were also associated with neurodevelopmental outcomes in the offspring from the SELMA cohort. Hence, we can only speculate about the clinical relevance of the observed associations. The association of TT4 during pregnancy with child neurodevelopmental outcomes has not yet been studied in great detail, though research in the iodine sufficient Generation R cohort showed that TT4 was not associated with child IQ after correction for FT4 [4]. TPOAb positivity during pregnancy has been associated with pregnancy outcomes, such as preterm birth [5], and with a higher risk of ADHD [6], and a lower IQ score in the offspring [7]. The latter was however only observed in the iodine sufficient population of Generation R but not in the mild-to-moderate iodine deficient population of ALSPAC.

Maternal iodine status and child neurodevelopment

In chapter 4.1, a pooled analysis of individual-participant data in 6180 mother-child pairs showed a positive curvilinear association of UI/Creat with mean verbal IQ. The results further suggested that particularly the first 14 weeks of gestation constitute a vulnerable period for fetal exposure to maternal iodine deficiency. This supports the notion that it is important for pregnant women to have adequate iodine stores in early or even before pregnancy. We were unable to show that the association of maternal iodine status with child verbal IQ was mediated through maternal thyroid function; UI/Creat was not associated with TSH or FT4. The absence of such an association might be explained through possible flaws of UI/Creat as a proxy for individual iodine status or thyroidal iodine availability, or suggest that the association is mediated by fetal thyroid function. Iodine “deficiency” (i.e., UI/Creat below 150 µg/g) and iodine “excess” (i.e., UI/Creat above 150 µg/g) were not associated with lower verbal or non-verbal IQ. In chapter 4.2, we describe that there is no evidence for an association between iodine deficiency during pregnancy and the child’s ADHD or autistic traits. The associations of maternal FT4 or TSH with ADHD or autistic traits did not depend on maternal iodine status.

Maternal thyroid function and child neurodevelopment

In chapter 5.1, our meta-analysis of individual-participant data in 9036 mother-child pairs showed that low maternal FT4 in early pregnancy was associated with lower non-verbal and verbal child IQ scores. The association of low FT4 with the non-verbal IQ score was robust in all three cohorts, showing a 3.9-point lower non-verbal IQ score in children born to women with FT4 <2.5th percentile as compared with those born to women with FT4 between the 25th to 75th percentile range. We could not replicate the association of high FT4 with lower non-verbal IQ that had previously been demonstrated in the Generation R cohort [8]. Firm conclusions about the association of maternal thyroid function with autistic traits could not be made due to the small number of children scoring within the clinical range and the inconsistency of the results when using different cut-off values in the extreme ends of the FT4 distribution. In chapter 5.2, we show that in 7669 mother-child pairs maternal TSH or FT4 was not associated with child ADHD or with high ADHD symptom scores. Further investigation of effect modification by gestational age showed no consistent differential effect across the two outcomes.

No association was observed between TSH and IQ, ADHD, or autistic traits in any of the studies published in chapter 5. We therefore question whether maternal FT4 is a better marker for fetal thyroid state than maternal TSH. However, recent analysis in the Generation R cohort showed that maternal TSH was associated with brain imaging by MRI, which is an objective reproducible measure of brain development [9].

While non-verbal IQ is a language- and culture-free measure of cognitive ability which is less dependent on the learning stimulus received by the child during the first years of life, it is somewhat surprising that maternal iodine status was not associated with child non-verbal IQ, considering that low FT4 was associated with lower child non-verbal IQ. Our results show an association of lower maternal UI/Creat with lower child verbal IQ instead, suggesting that maternal iodine status potentially affects child neurodevelopment in a specific manner. Why this would be the case, requires further investigation regarding the underlying mechanisms. We speculate that the association between maternal iodine status and child verbal IQ may be explained through effects of mild iodine deficiency, via thyroid hormone, on the auditory system [10,11], but this requires further study.

Methodological considerations

Exposure assessment

As a proxy measurement for thyroidal iodine availability, we have used one to four measurements of urinary iodine concentration in pregnant women, which we divided by the creatinine concentration to take urine dilution into account. The urinary iodine concentration in a single spot urine sample is known to fluctuate based on diet, and reaches a peak concentration ap-

proximately 4-5 hours after meals [12]. In large populations, this day-to-day variation in iodine intake, and thus the random measurement error, is balanced out in a median value of spot urinary iodine concentration [13]. The precision by which the iodine status of a population can be determined, increases with the number of individuals included. For instance, a study showed that the mean iodine excretion in a population can be estimated with a 5% or 2% precision range if from 489 or 3054 individuals a spot urine sample is collected, respectively [14]. Because the number of individuals included in the birth cohort studies in this thesis is large, it seems safe to say that we have estimated the iodine status of these populations with high precision. Another important factor in determining individual iodine status, is timing of urine collection. For example, early morning urine void tends to underestimate daily iodine excretion [15]. In SELMA, early morning urine void was collected in all women, and in INMA (i.e., INMA Valencia) fasting urine samples were collected [16], but it is unsure whether these were overnight fasting samples. In Generation R and ALSPAC, urine was obtained at random moments during the day. It remains unsure whether potential timing of sampling significantly affected the population status, and whether this error was random or more common in subgroups of women that gave birth to children with lower IQ scores or neurodevelopmental problems.

In general, random measurement error in the exposure flattens the slope of the regression line, resulting in a regression coefficient biased towards the null [17]. To minimize random measurement error in the exposure variable, one could obtain repeated measurements or use a biomarker, if available, that better reflects the exposure. For individual iodine status, more research should be performed into thyroglobulin, which is a protein from which thyroid hormones are formed [18], as a biomarker for individual iodine status. In children, reference ranges of blood spot thyroglobulin have been made available in iodine-sufficient children, and a median blood spot thyroglobulin concentration above 40 Ig/L has been suggested to reflect adequate iodine status [19]. In pregnant women, thyroglobulin may be a sensitive biomarker of individual iodine status [20], but references ranges have yet to be defined. Alternatively, individual iodine status can be determined by repeated measurements. Research suggests that if 10 or 55 urine spot samples were obtained from each individual over a period of time, we could calculate the mean iodine excretion for this individual with a 25% or 10% precision range (e.g., if the mean iodine excretion was 200 µg/L, then the true iodine excretion with a 25% precision range would be between 150-250 µg/L) [14]. Determining individual iodine status by a limited number of repeated measurements is unlikely to be very precise (i.e., 1 to 4 samples were obtained from mothers from the cohorts included in this thesis; the precision range would be approximately 40 to 50%).

Next, as a proxy of the fetal exposure to maternal thyroid hormone we used maternal serum TSH or FT4 concentrations measured before mid-gestation. FT4 was measured using immunoassays and may potentially have under- or overestimated the true concentration due to immunoassay interference [21–23]. Owing to the use of different assays and reference ranges

between the cohorts, the absolute value of the thyroid function tests could not be compared across cohorts and standardization of both the TSH and FT4 concentration was necessary.

Outcome assessment

The assessment of the outcome is likely subject to measurement error. We have used IQ scores and child behavioral problems as outcomes related to fetal brain development. These outcomes were assessed with validated tests or questionnaires. While each child was administered an IQ test, their behavior, i.e., ADHD symptoms and autistic traits, was assessed through questionnaires filled in by parents and/or teachers. The assessment of child behavior may be a more subjective dimension of health than IQ, because every informant may have different perspectives on behavior. This may be influenced by the behavior required in a particular setting. With regards to ADHD, the international DSM-IV criteria require that attention and/or hyperactivity symptoms cause some impairment in at least two settings, e.g., at home, work, or school [24]. Due to low-to-moderate agreement between teacher and parental observations, multi-informant assessment has been recommended in order to understand the behavior of a child more completely [25,26]. However, ADHD symptoms were assessed by a single informant in the cohorts included in this thesis, with exception of a proportion of children in ALSPAC. Potentially, random error in the assessment of ADHD may therefore have been higher in INMA and Generation R than in ALSPAC. In general, random error in the outcome measurements may lead to wider confidence ranges as a result of higher standard error, and as such, there is a higher chance to obtain statistically non-significant associations. By increasing the sample size, precision of the estimates can be retained. Again, bias can only be introduced if the degree of random measurement error is uneven between the cases [i.e., those with ADHD or autistic traits above the (validated) cut-off] and the controls [i.e., those without ADHD or autistic traits below the (validated) cut-off]. However, due to the natural course of cohort studies, it is unlikely that the misclassification of children depended on the exposure status during pregnancy, since the exposure status was unknown to the assessors.

The accuracy of a meta-analysis

With the growing number of individual studies, meta-analyses are useful to summarize the existing evidence from often small studies into an overall pooled estimate. This may enhance evidence-based policy decisions, a re-evaluation of clinical practice guidelines, or be an incentive for further research. The individual studies that are used for a meta-analysis will, to some extent, be heterogeneous. The pregnant populations of INMA, Generation R, and ALSPAC differed in maternal and child characteristics, maternal iodine status, the assays that were used to measure iodine status and thyroid function, and in the outcome assessment. Heterogeneity across studies can be minimized by using individual participant data, so that similar in- and exclusion criteria can be applied and the data and analyses can be harmonized. But even then, there will be some degree of heterogeneity. In this thesis, we

have performed random-effects meta-analyses instead of fixed-effects meta-analyses, because a random-effects meta-analysis does not assume that differences in effect estimates across cohorts is due to chance only. There are three types of heterogeneity: clinical (e.g., differences related to the population characteristics, interventions, and outcomes), methodological (e.g., differences in how the study was conducted and the risk of bias), and statistical. There are currently no criteria to check the degree of clinical and methodological heterogeneity [27]. In contrast, statistical heterogeneity can be assessed by the I^2 statistic, which indicates the percentage of variability across studies due to heterogeneity rather than chance[28]. If the degree of heterogeneity is unknown, a high percentage of I^2 (i.e., ≥75%) indicates that studies are highly heterogeneous and in the absence of strict criteria, it is up to the meta-analysist to decide whether the meta-analysis is meaningful or if it is better to present the cohort-specific effect estimates only[27]. While several meta-analyses included in this thesis showed moderate statistical heterogeneity (i.e., $I^2 \sim 50\%$), the only meta-analysis which showed a high I^2 of 77.7% was of the association of maternal UI/Creat with child autistic traits in those with at least one measure of UI/Creat in the first 14 weeks of pregnancy (chapter 4.2). This finding should therefore be interpreted with caution.

Clinical implications

Should we be concerned about mild-to-moderate iodine deficiency during pregnancy?

There has been increased international support for the elimination of iodine deficiency disorders since 1990, which led to the endorsement of universal salt iodization as the most cost-effective preventive measure in 1994. Although great improvement has been made in the last 2-3 decades, iodine deficiency is still common among pregnant women, even in countries with a mandatory or voluntary iodine fortification program [29–31]. According to the global iodine status in 2017, 39 out of 72 countries (54.2%) reported insufficient iodine intake in pregnant women (i.e., median UIC < 150 µg/L) [31,32]. Because this public health problem remains to exist, the EUthyroid consortium, and other signatories of the Krakow Declaration on Iodine, have called on governments, public health authorities, the food industry, scientists, and health professionals for what they think is needed towards the elimination of iodine deficiency disorders: obligatory universal salt iodization, harmonized monitoring and evaluation of fortification programs across countries, and public information campaigns [33].

The results of this thesis indicate that mild-to-moderate iodine deficiency during pregnancy is associated with a higher risk of TPOAb positivity, but not with meaningful alterations in other thyroid function tests. Lower iodine status in the first 14 weeks of gestation was associated with lower mean child verbal IQ scores. Our research therefore suggests that adequate iodine intake in early pregnancy is important for fetal brain development. One of the means

of achieving adequate iodine intake in pregnancy, is iodine supplementation. In the United Kingdom, a country without an iodine fortification program or supplementation recommendation, universal iodine supplementation before, during, and right after pregnancy has been estimated to hypothetically increase child IQ with 1.2 IQ points [34]. However, randomized controlled trials have thus far failed to show any benefit of daily iodine supplementation during pregnancy for child IQ. The most recent randomized, placebo-controlled trial conducted in Thailand and India, showed no statistical difference in child non-verbal or verbal IQ scores at a mean age of 5.4 years of daily supplementation with 200 µg iodine as potassium iodide of mildly iodine-deficient women [35]. It should be noted however that pregnant women from India included in this trial were not iodine deficient at baseline (i.e., median UIC of 188 µg/L) and that treatment only started at a mean gestational age of 10.7 weeks [36]. Two other randomized trials also showed no benefit of treatment, but these were underpowered [37,38]. Several non-randomized trials in mild-to-moderate iodine deficient regions showed mixed results for benefits of iodine supplementation for neurodevelopment [39–41]. Two of the studies suggest benefits of a maternal intake of 200 or 300 µg of iodine supplements for child neurodevelopment up to 2 years of age [39,40]. Another study, without placebo group, found no difference in child neurodevelopmental outcomes if the mother used iodized salt or took iodine containing supplements of either 150 µg or 230 µg per day [41].

If a future randomized placebo controlled trial were to be designed, then our results indicate that supplementation should not start later than the first trimester. Iodine supplementation may even need to be started before conception, as there is evidence that a late start of iodine supplementation (i.e., between week 13-20 of gestation) is associated with a lower FT4 concentration than when supplementation is initiated preconceptionally [42], and pre-pregnancy iodine status has been associated with child IQ [43]. A future randomized placebo controlled trial should be performed in a country which has not yet introduced iodine supplementation recommendations.

Should mild maternal thyroid dysfunction be treated?

Our results clearly indicate that mild maternal thyroid dysfunction, particularly low FT4, is associated with lower IQ scores in the offspring. From an individual point of view, lower IQ may lead to poorer academic achievements. From a public health perspective, IQ loss in a population may have economic implications. A loss of 5 IQ points has been estimated to cost $30 billion per year in Canada and $275 billion to $326 billion per year in the United States [44]. In clinical practice, TSH, but not FT4, is used as the first line parameter to screen maternal thyroid status at the first prenatal consultation. Even though our results suggest that screening for FT4 may need to be considered, evidence is first needed from randomized controlled trials on the benefits of screening and subsequent levothyroxine treatment of women with mild thyroid dysfunction during pregnancy for child neurodevelopment.

Randomized controlled trials have yet to show benefit of treatment. The CATS trial was the first to investigate the treatment effect of levothyroxine (LT4) administration in pregnant women with subclinical hypothyroidism or hypothyroxinemia on child neurodevelopment [45]. Women with these mild types of thyroid dysfunction were randomized to either standard care (control group) or treatment with 150 µg of levothyroxine per day, which was initiated at a median gestational age of 13 weeks and 3 days. The offspring of these women underwent neuropsychological testing when they were 3 and 9.5 years of age [45,46]. This trial found no statistical significant difference in IQ score between the control and treatment group at both time points in childhood. One of the explanations for the absence of effect may be that the dose of levothyroxine was not optimal. During the course of pregnancy, the dose had to be lowered or increased in 10% and 5% of women due to signs of side-effects, respectively. In two other randomized controlled trials, women with subclinical hypothyroidism were randomized to placebo or instructed to take 100 µg of levothyroxine daily, while women with hypothyroxinemia were randomized to placebo or treatment with a dose of 50 µg of levothyroxine per day [47]. The primary outcome was the child IQ score at the age of 3 or 5 years. Though a 3-point difference in IQ was observed in both trials between the treatment and the placebo group, this difference did not reach statistical significance. The absence of a statistical difference may have to do with the fact that these trials were only powered to detect a difference of 5 IQ points; an expected effect size which was based on the 7 IQ point difference between children born to treated or untreated women with overt hypothyroidism [48]. Another concern was that treatment was started relatively late - week 16 and 4 days of gestation for subclinical hypothyroidism and week 18 for hypothyroxinemia. This may have been too late to result in a beneficial effect because adequate maternal thyroid hormone transfer to the fetus is especially important for fetal brain development during the period when the fetal thyroid is not functionally mature yet (i.e., before mid-gestation).

How could observational studies help to design future randomized clinical trials?

Observational studies can inform on what is a realistic IQ difference between the treated and untreated group. A realistic expected effect size is essential for adequate power calculations. The study in chapter 5.1 showed that hypothyroxinemia during pregnancy is associated with a 2 to 4 point IQ difference, depending on the cut-off values used and the type of IQ score. As a consequence, a marked difference of 5 IQ points or higher may not be a realistic aim for studies that investigate the effect of treatment of mild gestational thyroid dysfunction. In addition, observational studies can help to identify vulnerable periods for exposure to inadequate thyroid hormone concentrations. This can provide more insight into the optimal timing of treatment. The most vulnerable periods could be investigated by testing for differential effects by gestational age. If thyroid function tests are performed repeatedly during pregnancy, observational studies can also provide a better understanding of how the duration of thyroid

dysfunction is associated with offspring neurodevelopmental outcomes. Unfortunately, most cohorts only have a single measurement available. To our knowledge, a study with repeated thyroid function measurements in relation to child neurocognitive outcomes has only been performed once and showed that low a FT4 concentration at week 12, but which increased during pregnancy, was associated with better mental and motor function scores at the age of 2 years than when FT4 remained low at week 24 and week 32 of gestation [49].

Future research

The urinary iodine concentration is commonly used as a marker for iodine status of populations. However, due to high day-to-day variability of urinary iodine concentrations [14,50,51], a reliable marker of individual iodine status is currently missing. Future studies should investigate whether thyroglobulin (and possible other new potential biomarkers) could be used during pregnancy as a marker for individual iodine status. Studies need to examine the dose-dependent effects of iodine or levothyroxine supplementation on thyroid function to investigate the optimal dose for treatment and examine if treatment during pregnancy, well before the fetal thyroid is fully functional (i.e., at mid-gestation), would be beneficial for child neurodevelopment.

Conclusion

The results of this thesis suggest:

- that public-health interventions focusing on improving the dietary iodine intake of pregnant women need to follow a country-specific approach, taking into account differences in dietary habits.
- that mild-to-moderate deficiency are not associated with meaningful variation in clinical reference ranges of thyroid function tests.
- that mild-to-moderate iodine deficiency may not be severe enough to evoke adaptive mechanisms to chronic low iodine intake (e.g., preferential production of T3).
- that maternal iodine status in particularly the first 14 weeks of gestation constitute a vulnerable period for fetal exposure to maternal iodine deficiency.
- that there is consistent evidence for a role of maternal thyroid hormone in normal brain development.

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