# Iodine status and thyroid function during pregnancy in a multiethnic cohort in Oslo

Results from "STORK Groruddalen Study"

Ata Ul Razzaq Khan

Supervisor: Elisabeth Qvigstad
Co-Supervisor: Sara Hammerstad
Contact Supervisor: Anne Karen Jenum

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Institute of Health and Society, Department of Community Medicine, The Faculty of Medicine, University of Oslo.

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# ABSTRACT

## Background:

According to the WHO estimates, there are approximately 2 billion people suffering from iodine deficiency. Inadequate iodine intake may result in varying degrees of adverse health outcomes ranging from mild hypothyroidism, which is associated with adverse pregnancy outcomes, to foetal iodine deficiency that impairs neurocognitive development of the growing foetus. However, the extent of ethnic differences in thyroid diseases, as well as the contributory factors in early pregnancy are still unknown. The overall aim of the present thesis is to evaluate iodine status and its effects on thyroid function during 2nd and 3rd trimesters of pregnancy and 3 months post-partum in a multi-ethnic cohort of pregnant women who participated in the STORK Groruddalen Study.

## Materials and Methods:

This thesis is based on a retrospective cohort study; the STORK Groruddalen study, which is a population-based cohort study in women attending gestational health controls at the Child Health Clinics (CHC) in the areas Bjerke, Stovner and Grorud in Oslo during 2008-2010. Groruddalen has a multi-ethnic population (40-50% with ethnic minority background) with high attendance rate at the CHC (75-85%). High quality data was collected at gestational week (GW) 14, 18 and at 3 months post-partum.
Thyroid Stimulating Hormone (TSH) and Free Thyroxine (FT4) were assayed with in-house methods at Akershus University Hospital and the Hormone Laboratory, Oslo University Hospital, respectively. Urinary iodine was assayed in spot urine by a colorimetric method at the Hormone Laboratory, Oslo University Hospital (n = 681).

## Results:

Generally, TSH levels significantly increased between 1$^{st}$ trimester (1.99 ± 1.42 mIU/L) and 2$^{nd}$ trimester (2.42 ± 1.46 mIU/L) and then decreased at 3 months post-partum (2.31 ± 3.03 mIU/L). FT4 levels showed an opposite trend with downward shift from 1$^{st}$ trimester (14.8 ± 2.29 pmol/L) to 2$^{nd}$ trimester (12.9 ± 1.70 pmol/L), and later an upward inclination at 3 months post-partum (14.7 ± 2.62 pmol/L). All ethnic groups showed similar pattern during pregnancy, however, South Asians showed increased TSH at 3 months post-partum (3.41 ± 5.38 mIU/L). The median urinary iodine concentration (UIC) was 88.8 µg/L. 78.8% of the study sample had UIC < 150 µg/L, and more 70% of the population in each ethnic group was iodine deficient. East Asian women had the highest median UIC (108 µg/L; IQR: 60, 152). Pregnant women with South Asian ethnicity had

higher and wider TSH range (0.02 ± 8.06 mIU/L) during 1st trimester with significantly increased TPO-Ab positivity.

## Conclusion:

The findings demonstrate a normal physiological pattern of TSH and FT4 levels during pregnancy and post-partum in the study population. South Asian pregnant women showed higher TSH levels which may increase the risk of developing thyroid dysfunction. Moreover, other ethnic groups also had suboptimal TSH levels with regard to the recommended TSH ranges during pregnancy. The results of median UIC also indicates that the pregnant women in the study population are iodine deficient which can incur additional risk for thyroid dysfunction.

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## Abbreviations & Acronyms

| | |
|---|---|
| BMI | Body Mass Index |
| BMR | Basal Metabolic Rate |
| CHC | Child Health Clinics |
| CV | Coefficient of Variation |
| EAR | Estimated Average Requirement |
| EA | East Asia |
| ESRR | Ethnicity-Specific Reference Ranges |
| FT4 | Free Thyroxine |
| GW | Gestational Week |
| I/Cr | Iodine-to-creatinine ratio |
| ID | Iodine Deficiency |
| IDD | Iodine Deficiency Disorders. The spectrum of clinical, social and intellectual consequences of iodine deficiency. |
| IGN | Iodine Global Network |
| IQR | Interquartile range ($25^{th}$ and $75^{th}$ percentile) |
| MEA | Middle East & Sub-Saharan Africa |
| MISA | Northern Mother-and-Child Contaminant Cohort |
| MoBa | Norwegian Mother and Child Cohort Study |
| NEW | Norway, Europe & other Western countries |
| REK | Regional Ethics Committee |
| SA | South Asia |
| Tg | Thyroglobulin |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TFTs | Thyroid Function Tests |

| | |
|---|---|
| TPRR | Total Population Reference Ranges |
| TRs | Thyroid Hormone Receptors |
| TSH | Thyroid Stimulating Hormone |
| TPO-Ab | Thyroid Peroxidase Antibodies |
| UIC | Urinary Iodine Concentration |
| UIE | Urinary Iodine Excretion |
| UiO | University of Oslo |
| WHO | World Health Organization |

# 1 Introduction

The thyroid gland produces the thyroid hormones thyroxine (T4) and triiodothyronine (T3), which contains four iodine and three iodine molecules respectively. These hormones are primarily responsible for the regulation of metabolism. A deficiency of iodine leads to decreased production of T3 and T4. Clinical and sub-clinical manifestations of iodine deficiency, termed iodine deficiency disorders (IDD), affect all stages of human life and are characterised by a variety of conditions [1,2].

## 1.1 Physiologic effects of thyroid hormones

The thyroid gland produces thyroid hormones (TH) in two forms: 3,3',5-triiodothyronine (T3) and 3',5',3,5-tetraiodo-L-thyronine (T4 or thyroxine). These hormones circulate in plasma largely bound to proteins. T4 is a prohormone with relatively low affinity for thyroid hormone receptors (TRs). In contrast, T3 which is biologically active form with high affinity for TRs is produced either by thyroid gland or intracellularly through T4 conversion into T3 by iodothyronine deiodinases [1,2]. Approximately 99.97% of T4 and 99.7% of T3 is mostly bound to thyroid hormone binding globulin (TBG) proteins, and in lesser amounts, to albumin and transthyretin. Thyroid stimulating hormone (TSH) modulates the release of thyroid hormones. Hypothalamus releases thyroid releasing hormone (TRH), which in turn stimulates anterior pituitary to secrete TSH [3].

The transcription following the hormone-receptor response then leads to a number of effects, including tissue growth, increased heat production, and oxygen consumption [4]. Furthermore, T3 increases oxygen consumption and heat production in all tissues except the brain, the spleen and testes. This causes increased basal metabolic rate (BMR: oxygen consumption by the whole body at rest) and increased sensitivity to heat in hyperthyroidism, and obverse in hypothyroidism [4].

By regulating energy expenditure, thyroid hormones play an important role in body weight regulation [4,5]. There is also a substantial evidence that thyroid dysfunction including both hypothyroidism and hyperthyroidism leads to changes in body weight. As basal metabolic rate (BMR) is elevated in hyperthyroidism, caloric requirement also increases which if not met leads

to weight loss. In hypothyroidism, BMR is decreased, and can lead to weight gain. However, massive weight gain is rarely associated with hypothyroidism [5,6].

In skeletal muscles, thyroid hormones stimulate bone turnover, leading to osteopenia in case of chronic hyperthyroidism, and mild hypercalcemia is often seen in hyperthyroidism. Although thyroid hormones stimulate synthesis of structural myoproteins, there is loss of muscle tissue or myopathy in hyperthyroidism [7]. Thyroid hormones are essential for normal development and function of central nervous system, and in adults, hyperactivity and sluggishness can be markedly striking in hyperthyroidism and hypothyroidism respectively [9].

Thyroid hormones also have effects on lipid and carbohydrate metabolism. Hyperthyroidism exacerbates diabetes mellitus as it increases hepatic gluconeogenesis, glycogenolysis and intestinal glucose absorption. Lipolysis is also increased releasing glycerol and fatty acids. Cholesterol levels decline during thyroid overactivity but are elevated in hypothyroidism [4].

Both hypothyroidism and hyperthyroidism may impair ovulation and cause infertility. However, this can be corrected by restoration to the euthyroid state [9]. Hypothyroidism also leads to a 40% increase in prolactin levels, that also reverts to normal with T4 therapy [10]. The prevalence of thyroid dysfunctions in adults is shown in **table 1.1**.

**Table 1.1. Prevalence of Thyroid Dysfunction in Adults**

| Conditions | Reported Prevalence (%) |
|---|---|
| Overt Hypothyroidism | 0.2-5.3% |
| Subclinical hypothyroidism† | 0.3-2.83% |
| Overt Hyperthyroidism | 0.2-1.3% |
| Subclinical hyperthyroidism‡ | 1-5% |

**Source Reference [11,12].*
*Estimates of prevalence varies as different diagnostic thresholds were used in different epidemiological studies.*
*†Elevated TSH concentration with a normal serum free thyroxine concentration*
*‡Serum TSH concentration< 0.1mIU/L with normal serum free thyroxine and T3 concentrations.*

## 1.2 Physiological changes of thyroid hormones during pregnancy

During pregnancy, the increased need for thyroxine (T4) production supports physiological changes in thyroid hormone production, and increases the demand for iodine [13]. Moreover, maternal renal iodine clearance also increases during gestation [14,15]. Normal physiological changes during pregnancy are shown in **table 1.2**.

During early pregnancy, thyroid stimulation starts by β-hCG (human chorionic gonadotropins), which has some structural similarities to TSH. Furthermore, sialylation and glycosylation of TBGs in the liver increases due to rise in maternal estradiol levels [16-17]. This results in decreased peripheral metabolism of TBG, consequently causing approximate 150-200% rise in serum TBG levels compared to euthyroid non-pregnant women [18-19). As T4 and T3 are mainly bound to their binding globulin proteins, an increased TBG levels causes decreased plasma T4 levels, which in turn stimulates TSH secretion from the pituitary gland, subsequently leading to an increased thyroid hormone (TH) production and secretion. This increased demand of TH is reached at about 20$^{th}$ week of gestation and persists for the entire duration of pregnancy until term [20].

**Table 1.2. Normal Physiological Changes During Pregnancy**

| **Physiological Changes** | **Impact** |
|---|---|
| ↑ Iodine distribution and Iodine Clearance (renal and transplacental) | Relative Iodine Deficiency (ID) state<br>Risk of foetal and maternal hypothyroidism |
| Placental deiodination of T4 | T4 → Reverse T3 |
| ↑ Oestrogen-stimulated hepatic production of TBG (weak TSH effect) | T3 and T4 levels ↑, FT4 and FT3 unchanged |
| 1$^{st}$ trimester β-hCG ↑ | FT4 ↑ & TSH ↓ |
| 2$^{nd}$ trimester | Maximum increase in serum T4 and T3 |
| Placental thyrotrophins (hCG, HMT, HCT) lead to placental enlargement-3$^{rd}$ trimester | FT4 ↑ & TSH ↓ |
| Post-partum increase in thyroid antibodies | Post-partum thyroiditis<br>Exacerbation of Grave's disease<br>Long-term maternal hypothyroidism |

*Source Reference [21,22].*
*TBG: Thyroid Binding Globulin proteins, HCT: Human Chorionic Thyrotrophin, HMT: Human Molar Thyrotrophin, FT4: Free Thyroxine, T3: Triiodothyronine, TSH: Thyroid Stimulating Hormone, β-hCG: Human Chorionic Gonadotropins,*

In the human foetus, the thyroid hormone and anterior pituitary TSH system start to function around 11 weeks of gestation, and the measurable TSH and Thyrotropin-releasing hormone (TRH) are present. At the same time, the foetal thyroid starts to trap iodine and the secretion of thyroid hormone begins in mid gestation (18-20 weeks). Most of maternal T3 and T4 is inactivated because of the very high placental concentration of type 3,5-deiodinase, thus very little free thyroid hormone reaches the foetal circulation. Around 20 weeks of gestation, secretion of thyroid hormones dominated by foetal pituitary TSH ensues [23]. At about 24-28 weeks, foetal TSH surges to peak levels, and T4 rises to peak levels at 35-40 weeks. However, T3 levels remains low during gestation. At the time of birth, a sudden marked elevation in TSH, T4 and T3 occurs, but the levels return to normal in the first month after birth [21].

Many questions are still unanswered regarding maternal thyroid disease and its effect on foetal and offspring outcomes. Some studies indicate detrimental effects of untreated thyroid dysfunction on the neurophysiologic development and cognitive function in offspring. Therefore, it is important to determine risk factors to prevent later disease [24-28].

## 1.3 Health consequences for the pregnant woman with a pregestational thyroidal disorder

### 1.3.1 Hypothyroidism

Both overt and subclinical hypothyroidism may have an impact on fertility. Unrecognized hypothyroidism can result in anovulatory cycles. If pregnancy does ensue, the risk of spontaneous abortions, premature delivery, pregnancy induced hypertension, and preeclampsia increases (mainly if severe hypothyroidism). In several retrospective studies, placental abruption, anaemia and postpartum haemorrhage have also been reported. [24-29]. A recent large (n = 952) double-blind, placebo-controlled trial by Dhillon-Smith et al. [30] showed that levothyroxine treated euthyroid women with positive TPO-Ab did not have higher birth rate compared to the untreated group. This might be due to an unadjusted dose of levothyroxine (50 µg) in treated group with regard to participant's body weight, TPO-Ab level, or TSH concentration. Importantly, previous contrasting studies debated on the effectiveness of treatment of thyroid disorders before

conception and in early pregnancy. An earlier systematic review by Vissenberg et al. [31] showed a non-significant reduction in miscarriage (RR: 0.58, CI: 0.32-1.06), but significant reduction in preterm birth by treatment with levothyroxine (RR: 0.31, CI: 0.11-0.90) in women with subclinical hypothyroidism and thyroid autoimmunity.

### 1.3.2 Hyperthyroidism

Thyroid dysfunction also poses substantial challenge in the form of hyperthyroidism during pregnancy with significant implications on both the pregnant women and offspring. Both untreated or inadequately treated hyperthyroidism leads to increased risk of pre-eclampsia, low birth weight, stillbirth, preterm labour, and foetal abnormalities [32]. During pregnancy, the most common cause of overt hyperthyroidism is β-hCG-mediated hyperthyroidism, followed by Graves' disease. In Graves' diseases, presence of thyroid stimulating hormone receptor antibodies distinguishes the former from β-hCG-mediated hyperthyroidism [33]. As both of these thyroid disorders have different implications for the foetus, thus require different management approaches. Thyroiditis, toxic multinodular goiter, and toxic adenoma are other less common causes [34].

A meta-analysis by Vissenberg et al. investigated outcomes in women with diverse thyroid disorders during fecundation and early gestation. They found that women with known hyperthyroidism receiving treatment with thyrostatic drugs had a lower risk for premature birth, preeclampsia and low birth weight [31]. Prevalence of thyroid disorders during pregnancy are shown in **Table 1.3.**

**Table 1.3. Prevalence of Thyroid Disorders in Pregnancy**

| Condition | Reported Prevalence (%) |
|---|---|
| Overt hypothyroidism | 0.3–0.5% |
| Subclinical hypothyroidism | Total 2–3% |
| Overt hyperthyroidism | 0.1–0.4% |
| β-hCG-mediated hyperthyroidism | 1–3% |
| Subclinical hyperthyroidism | 2–5% |
| Thyrotoxicosis | 4% |
| Thyroid Autoimmunity | 2-17% |
| Thyroid nodules | 3–21% |
| Thyroid cancer | Varied between 12-43% in different studies |
| Postpartum Thyroiditis (PPT) | 1.1-16.7% |

*Source: Reference [35-37]*

### 1.3.3 Consequences for the offspring when the mother has gestational thyroid dysfunction

During pregnancy, the regulatory mechanisms of thyroid hormones have not yet been completely understood, however, thyroid hormones are considered to be crucial in the development and maturation of vital organs, like brain, muscle, heart, pituitary glands, reproductive system, bones, as well as in the development of hearing and vision [38].

Thyroid hormones are essential for foetal developmental, metabolic, and maturational effects during gestation and post-partum. It also impact maturation of somatic tissues necessary for survival immediately at birth [39]. Moreover, a crucial role of TH in foetal neurodevelopment has been recognized for many decades.

Severe hypothyroidism (very low thyroxine levels) can entail permanent damage to cognitive functions in the offspring in addition to other physiologic disorders. The child can develop impaired neuro-psychological function, lower IQ, and disordered or retarded growth and development. In the rare and worst cases, cerebral development can be retarded, resulting in cretinism, i.e. growth retardation, deafness and neuropsychological deficiencies [29].

An association between mild hypothyroidism during pregnancy and lower IQ-scores were reported previously [40]. In a retrospective study, infants where the mother did not receive

treatment for mild thyroid deficiency during pregnancy, had significantly lower IQ-score during testing than controls [41]. Furthermore, Pop et al. reported that marginally low FT4 in first trimester of pregnancy was associated with reduced psychomotor and mental development [42]. Moreover, a population-based cohort by Julvez et al. [43] reported lower mental score in offspring of mothers (considered iodine sufficient) who were not treated for subclinical hypothyroidism compared to the treated group (levothyroxine therapy).

Not all studies reported negative outcome of subclinical thyroid dysfunction during pregnancy. Subclinical and isolated hypothyroidism was found in 1.3% of the population, and there was no indication of distinct adverse effects or influence on perinatal outcomes [44]. In a randomized controlled study by Lazarus et al., 21846 women were randomized to screening or controls. TSH and T4 were measured in both groups in early pregnancy. In the controls, the test results were filed until birth, while the screening group was subjected to clinical follow-up and medication if needed. A TSH level above the 97.5 percentile, and FT4 level below the 2.5 percentile was considered as positive test. The group found a positive result in 4.6% in the screening group (treated with levothyroxine) vs. 5.0% in controls. However, no significant difference in the offspring's IQ at 3 years of age in offspring was found [45].

International guidelines from Endocrine Society have concluded that overt hypothyroidism is associated with foetal brain damage [29]. As hypothyroidism is a prevalent disorder and untreated hypothyroidism can have negative pregnancy outcomes, it is recommended that that women with diagnosed thyroid disease or at risk during pregnancy should have a follow up in a multidisciplinary specialist health care. Recommended indications for thyroid function screening during pregnancy are shown in **Table 1.4**.

**Table 1.4. Recommendations for Thyroid Function Screening in Pregnancy**

| |
|---|
| History of thyroid dysfunction or prior thyroid surgery |
| History of post-partum thyroiditis |
| Family history of thyroid disease |
| Symptoms of thyroid dysfunction |
| Positive for thyroid antibodies (anti-TPO antibodies) |
| History of type 1 diabetes |
| History of other autoimmune disorders |
| History of head and neck radiation |
| History of miscarriage or preterm delivery |
| History of therapeutic head or neck irradiation |
| History of infertility |
| Hyperemesis gravidarum and clinical features suggestive of hyperthyroidism |
| Residing in an area of known moderate to severe iodine deficiency |

*Source: References [35,36]*

## 1.4 Biological function of Iodine

Iodine is a trace element that is an essential component of thyroid hormones triiodothyronine (T3) and thyroxine (T4). Iodine is an essential micronutrient found in every tissue in the body. It may also play its role as an anti-oxidant, anti-inflammatory, apoptotic, antiviral, and antibacterial agent [46-48]. Additionally, by modulating BMR, thyroid hormones play a vital role in regulating energy homeostasis [49].

### 1.4.1 Iodine metabolism and functions

In a normal healthy adult, the body contains up to 15-20 mg of iodine. The ingested inorganic iodine and iodate (most extensively used in salt iodization) are nearly fully absorbed from the gastrointestinal tract [50]. It has also been estimated that more than 90% of ingested iodine is eventually excreted in the urine, mainly through the kidneys as the main route of excretion, and about 20% are being excreted in the faeces, and roughly about 5% via sweat, saliva and bile. Among lactating women, 10-15% of the daily iodine intake is excreted into breast milk [51,52].

Worldwide, iodine deficiency is the most prevalent cause of hypothyroidism [29]. According to WHO estimates, there are approximately 2 billion people suffering from iodine deficiency [53].

Inadequate iodine intake may result in varying degrees of adverse health outcomes ranging from mild hypothyroidism, associated adverse pregnancy outcomes, to foetal iodine deficiency that impairs neurocognitive development of the foetus [54,55]. However, the extent of thyroid diseases, as well as contributory factors in early pregnancy are still largely unknown.

Iodine deficiency is mostly considered to be a problem mainly in developing countries; however industrialized countries have also been exposed to the problem [53,56]. Even though Norway has been considered iodine replete for many decades, recent data suggest that mild iodine deficiency is probably prevalent in Norway [57]. In 2016, the National Council for Nutrition concluded that insufficient iodine intake is widespread in parts of the Norwegian population and that effective measures should be implemented immediately [58].

During pregnancy, iodine intake should be increased by ≥ 50%, largely due to following three reasons during early and mid-gestation [47]:

(i) to facilitate the 50% increase in thyroid hormone production,
(ii) to cover potential increased renal clearance of iodine and,
(iii) to cover the supply and demand imbalance occurring due transfer of maternal iodine and thyroid hormone to the foetus.

Theoretically, thyroidal iodine stores and potentially placental iodine stores may be utilized to meet the increasing iodine requirement of pregnancy [59]. However, this theoretical assumption might not hold true in iodine deficient areas, where thyroidal iodine stores would not have the capacity to meet the increased demand during pregnancy. Results from the Norwegian Mother and Child Cohort Study (MoBa) have shown that a high proportion of pregnant women recruited from 2002 to 2008 had suboptimal iodine intake [60].

In Norway, recent population studies have reported the re-emergence of mild iodine deficiency in some groups including pregnant and lactating women [61-62]. A recent literature review showed that the iodine intake in a large part of Norwegian population especially in young women, pregnant women and nursing mothers is insufficient [63]. A study on Somali immigrants in Norway (n = 169, 91 females and 78 males) has shown that a considerable proportion of this group has low iodine intake and sub-optimal iodine status [64]. Most of the ethnic minority

groups in Norway have emigrated from areas where iodine deficiency is endemic. Furthermore, the risk of iodine deficiency in ethnic minority groups in other European countries is also prevalent [65-68]. It has also been debated whether there is an increased iodine deficiency in Caucasian population in Norway. However, iodine status among ethnic minority groups and its associated effects are still yet to be comprehensively explored.

## 1.5 Assessment of iodine status

### 1.5.1 Adults

Different methods are used for the assessment of iodine status depending upon available resources, the age of the study subjects, dietary patterns, iodine status of the study population, and the objectives of the study [69]. A fundamental understanding of the use of biomarkers and methods for the assessment of iodine status is essential at population level as well as at individual level. Furthermore, such results should be cautiously interpreted while keeping in view the limitations of what can or cannot be inferred from such methods.

TSH is a direct biomarker of iodine status. Elevated TSH levels have been widely used to assess the iodine deficiency [70]. However, TSH is an indicator of iodine status in adults with low sensitivity as the values of TSH often remains within the normal range despite slight increase in serum TSH levels [71,72].

Serum thyroglobulin (Tg) is precursor of TH as it is produced in the thyroidal follicular cells in response to TSH. Tg is a potential biomarker in populations which seems to correlate with UIC [69,73]. Zimmermann et al. [74] examined Tg concentrations and (UIC) involving 2500 school age children from 12 different countries and concluded that Tg was a sensitive biomarker of iodine deficiency and excess. However, a high serum concentration of Tg is not a specific sign of ID and lacks diagnostic specificity [69,75,76].

Dietary assessment is not a recommended indicator for the iodine intake estimation because of the considerable variation of iodine content of the food, thus it does not accurately reflect total

iodine intake. Moreover, use of iodised salt in cooking and at the table also contributes to iodine intake, which makes the iodine intake assessment even more complicated [77].

Urinary iodine is frequently used as a biochemical indicator of iodine status as it reflects a recent dietary iodine intake (the last few days) [47]. Moreover, renal excretions of iodine also remains fairly proportional to the amount of iodine absorbed. In a healthy individual, 92% of the ingested iodine gets absorbed by the gastrointestinal tract and 90% of the absorbed iodine is secreted into the urine [78]. According to WHO, the median UIC from spot samples can indicate iodine status in populations; e.g. a median below 100 µg/L in school-aged children and adults, or below 150 µg/L in pregnant women, is suggestive of iodine deficiency in the population [79].

However, single spot UIC is not suitable indicator for individual iodine assessment, due to the fact that there is substantial intra-individual variability in daily urine output and iodine intake [47,76]. Moreover, WHO recommended cutoffs of UIC from single spot urine samples cannot be used to assess iodine status at individual level as these estimates refer to population medians. Urine volume variation might to some degree be overcome by taking into account urinary creatinine concentration, with some evidence of superiority compared to UIC if adjusted for age and sex of the individual [71,80]. In the case of malnourished subjects, the iodine-to-creatinine ratio is considered unreliable, as low protein intake lowers creatinine excretion and masks the iodine deficiency if assessed by iodine-to-creatinine ratio [47].

In countries such as Norway, where subjects generally are well nourished, the iodine-to-creatinine ratio in pregnant women is an acceptable biochemical parameter. Although, urinary iodine excretion (UIE) is the most reliable method for the assessment of nutritional iodine status of an individual that require more than one 24-h UI sample for reliable assessment. However, in epidemiological studies; such as STORK study, where a population distribution is required rather than individual UI concentrations, there is no need for the more demanding 24-h urine collections since less precision is needed provided the sample size is large [81].

### 1.5.2 Neonatal iodine assessment

In contrast to adults, neonatal TSH concentration is a sensitive indicator for the prevalence of iodine deficiency disorders (IDD) in newborn period [82-84]. Neonates have lower levels of iodine than in adults, but higher iodine turnover rate, as a result of an increased TSH stimulation when iodine supply falls [85]. Moreover, due to higher neonatal iodine turnover rate, TSH secretion is stimulated which leads to the assumption that the neonatal thyroid is extremely sensitive to iodine deficiency [86]. Thus, elevated serum TSH concentration in neonates may reflect an insufficient supply of thyroid hormones to the developing foetal brain, and is therefore considered to be the only measure that allows prediction of the risk of brain damage due to iodine deficiency [84].

In Norway, as part of the Expanded Newborn Screening Program, the program offers TSH screening to all new-borns between 48-72 hours after birth. Further testing is arranged with the consent of parents in case of a suspected disorder [65]. However, some evidence have shown that the rise in TSH levels are not sufficient for the evaluation of neonatal iodine status in mildly iodine deficient areas and re-evaluation of the present neonatal TSH threshold for the detection of iodine deficiency is required [88].

## 1.6 Health consequences of iodine deficiency

Iodine deficiency can lead to adverse clinical effects on the development and growth of the human body [50]. Collectively known as iodine deficiency (ID) disorders (IDD), are the clinical and sub-clinical manifestations of iodine deficiency that affects all stages of human life [90,91]. ID induced disorders present a significant nutritional problem worldwide that put about 2.2 billion people in 130 countries at risk [92].

The iodine deficiency has a pivotal impact on human health and development during pregnancy, lactation, and the first two years of life [75]. According to WHO, iodine deficiency is considered as “the single most important preventable cause of brain damage” [79]. Recent publications indicate that prolonged supply of iodine prior to pregnancy is associated with lower likelihood of thyroid failure during pregnancy than a sudden supply of iodine at the start of pregnancy (e.g.

through iodine supplementation); which underscores the significance of an optimum iodine intake in women of childbearing age [94].

Severe iodine deficiency (median UIC of school-age children <20 μg/L) have a wide array of adverse health outcomes including, neonatal hypothyroidism, mental retardation, cretinism, loss of pregnancy, and infant mortality [46]. The role of thyroid hormones in foetal neurodevelopment and during infancy is critically important, and maternal and foetal hypothyroidism may have serious neurological and cognitive deficits [95].

There is a higher risk of goiter in general population and in pregnant women due to rise in thyroid volume as a result of mild to moderate iodine deficiency [96]. However, changes in thyroid function during pregnancy are generally not associated with mild iodine deficiency. A systematic review by Taylor et al. 2014 [97] concluded that iodine supplementation during pregnancy has an overall effect in improving maternal thyroid indices, even in marginally iodine deficient areas. Excessive iodine supplementation (>200 μg I/d) also suggests a negative impact on thyroid function in pregnancy.

The recommended iodine intake in the Nordic countries is 150 g/day from ten years of age [99,103] and 175 μg/day during pregnancy [23], while the estimated average requirement (EAR) is 95 μg/day [100]. The WHO recommends a daily iodine intake of 250 μg/day during pregnancy and 150 μg/day for non-pregnant women of reproductive age [98] (**Table 1.5**). A median Urinary Iodine Concentration (UIC) of at least 100 μg/L is assumed to prevent IDD in the general population [101].

**Table 1.5. WHO Recommended daily Iodine Intake**

| Population Group | Recommended intake, Nordic, µg/day | Recommended intake, WHO, µg/day | WHO recommendation for median concentration of iodine in urine at sufficient intake, µg/L |
|---|---|---|---|
| Children | | | |
| 12−23 months | 70 | 70 | ≥ 100−199 |
| 2−5 years | 90 | 90 | ≥ 100−199 |
| 6−9 years | 120 | 120 | ≥ 100−199 |
| Children from 10 years and young | 150 | 150 | ≥ 100−199 |
| adults | 150 | 150 | ≥ 100−199 |
| pregnant | 175 | 250 | ≥ 150−299[1] |
| breastfeeding | 200 | 250 | - |

*Adapted from Henjum et al. [63]*
*Source: Reference [72, 99-101]*

## 1.7 STORK Groruddalen Study

The STORK Groruddalen study is a population-based cohort study in women attending gestational health controls at the community health centers in the areas of Bjerke, Stovner and Grorud in Oslo. Groruddalen in Oslo has a multi-ethnic population (40-50% with ethnic minority background), which has increased with more than 10% during the last 5 years. This increase challenges health personnel to reflect on and adapt to current health information for these pregnant women. The project was initiated by Professor Anne Karen Jenum, a former general practitioner and district medical responsible Johan Torper in 2007 [81].

The ultimate goal of this project is to contribute to a better health for mother and child by characterizing the extent of putative ethnic differences in iodine status and thyroid dysfunction during pregnancy and puerperium, and possible effects on the neonatal outcomes. This multi-ethnic population-based study can give us valuable information regarding normal and pathological pregnancies, and can provide a better understanding of short and long-term consequences of inappropriate iodine levels for these women.

Results from the STORK Groruddalen-study has demonstrated an increased prevalence of gestational diabetes and several other health problems, and more frequent sick leave in ethnic minority women compared to women of Caucasian origin. Many women have a different diet (mainly low fibre-high simple carbohydrate) and low levels of physical activity, and this was found to be strongly related to ethnicity and gestational diabetes [104,105]. Furthermore, the neonates of women with a minority background have a body composition that are associated with overweight, type 2 diabetes and development of cardiovascular disease later in life [105].

A report on iodine status in Norway highlighted the need for new studies on iodine status among pregnant women [58]. The present study serve to assess iodine status during pregnancy and the effect of ethnic differences in relation to thyroid dysfunction during gestation and post-partum.

## 1.8 Aims of the study

The overall aim of the present thesis is to evaluate iodine status and its effects on thyroid function in a multi-ethnic cohort of pregnant women who participated in STORK Groruddalen Study, during 2nd and 3rd trimesters of pregnancy and postpartum.

The specific study objectives were:

1. To determinate the iodine status of the pregnant women belonging to different ethnicities based on UIC from a spot urine sample; adjusted for creatinine using the epidemiological criteria from the WHO.
2. To estimate the prevalence of iodine deficiency in early pregnancy [GW 12-14, or first visit], and test for correlations between iodine levels and TSH/FT4 in early and late pregnancy and 3 months post-partum.
3. To investigate the associations between ethnicity and iodine status during pregnancy and its subsequent effects on thyroid functions.

# 2 Methodology

## 2.1 Study design

This thesis is based on a retrospective cohort study; a part of STORK Groruddalen study, which is a population based cohort study in women attending gestational health controls at the community health centers in the areas of Bjerke, Stovner and Grorud in Oslo, aiming to 1) gather population-based data on health challenges at population levels, i.e. obesity, low physical activity, gestational diabetes and other pregnancy related health problems in different ethnic groups, including pregnancy outcomes and growth trajectories in the fetus and offspring, and 2) to improve health care during pregnancy and puerperium and develop culturally sensitive health services adapted to different ethnical groups.

Inclusion of the participants was conducted during May 2008 to May 2011. Groruddalen covers affluent as well as more deprived residential areas. A local information campaign was conducted prior to the recruitment of pregnant women, and all general practitioners in the area were asked to refer pregnant women as early as possible to child health clinics. Midwives recruited women in early pregnancy in three child health clinics, covering three out of four districts in Groruddalen. Participant recruitment was made based on the eligibility criteria if they; 1) lived in the study district, 2) planned to give birth at one of two study hospitals, 3) were in <20 week's gestation, 4) could be able to communicate in Norwegian or any of the eight translated languages, 5) were able to give an informed consent. However, pregnant women who had known diabetes or in need extensive medical follow-up during pregnancy were excluded from study population [81]. The attendance of STORK Groruddalen Study is given in **Figure 1.1**.

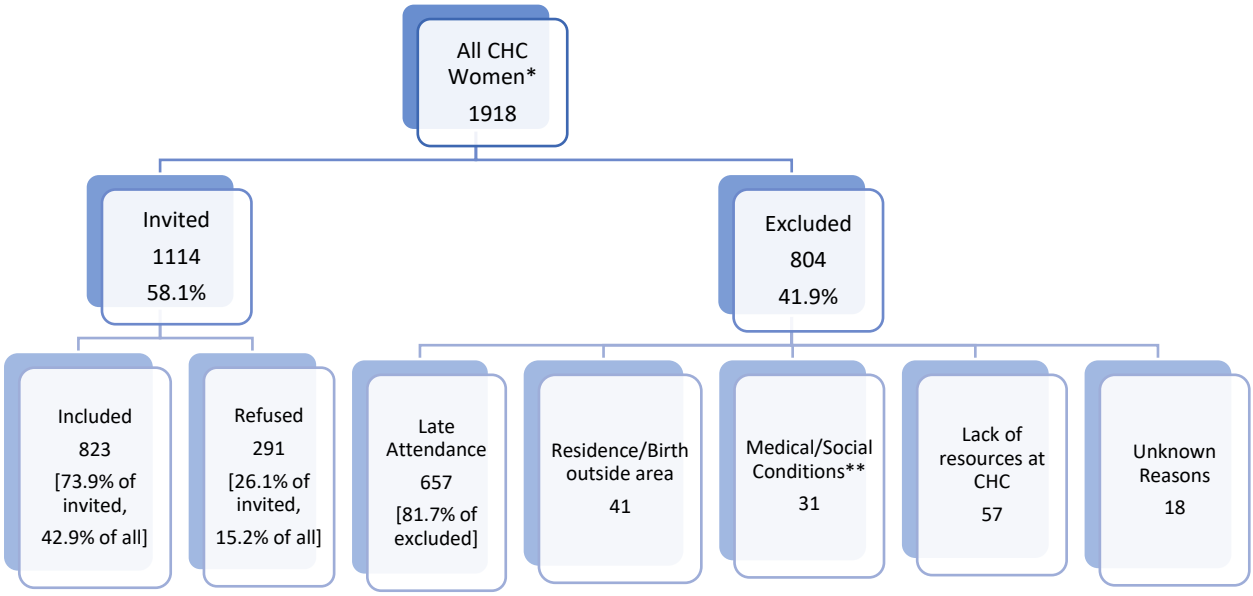


**Figure 1.1.** Reprint from Jenum et al. 2010 [81].
*Attendance of STORK Groruddalen Cohort, at the Child Health Center (CHC) from 6th May 2008 to 15th May 2010, based on invited, excluded and refused participation. *Represents number of pregnancies of women attending the CHC during this period, 42 women represented two pregnancies (1876 unique pregnancies). **Includes nine women excluded in one pregnancy as they were already included in the study.*

## 2.2 Population

The STORK Groruddalen study is a population-based cohort study in women attending gestational health controls at the community health centers in the areas Bjerke, Stovner and Grorud in Oslo. A total of 823 pregnant women participated in the study. Of the study population, 59% had ethnic minority background and the participants were representative for the major ethnic minorities in Norway. UIC values were available for 681 pregnant women. Therefore, in the current study, statistical analysis were applied for 681 pregnant women. The final study sample were divided into 4 ethnic groups; 298 (43.7%) ethnic Europeans, 173 (25.4%) ethnic South Asians, 38 (5.6%) ethnic East Asian and 172 (25.3%) with Middle East/Sub-Saharan African ethnicity.

## 2.3 Analytical procedures

Venous blood samples were collected after an overnight fast, transferred to Matrix tubes and then frozen on site, or sent for routine analyses or further handling before freezing at the Akershus University Hospital and the Hormone Laboratory, Oslo University Hospital, Aker. Morning urine after an overnight fast was sampled and transferred to Nunc tubes and frozen on site. Biological materials frozen at the CHC were transported on ice and biobanked at -80$^{o}$ C. TSH and FT4 were assayed with in-house methods at Akershus University Hospital and the Hormone Laboratory, Oslo University Hospital, respectively. Urinary iodine was assayed in spot urine by a colorimetric method at the hormone Laboratory, Oslo University Hospital. Reference interval for iodine is 17.76 – 635.78 µg/L and intraassay percentage coefficient of variation (% CV) is 8% at UIC 63.45 µg/L, 5% at 114.21 µg/L, and 4% at 279.18 µg/L. The reference interval for FT4 is: 8-21 pmol/l and CV is 4% at 12.1 pmol/L, 18.5 pmol/L, and 33.0 pmol/L. The refence interval for TSH is 0,3-4,2 mIU/L, and CV is 9% at TSH concentration 0.05 mIU/L, 2% at 3.8 mIU/L and 2% at 24.7 mIU/L. For TPO-Ab the CV is 10% at TPO-Ab concentration 40 kIU/L, 65 kIU/L and 537 kIU/L.

## 2.4 Data & variables

Six hundred and eighty-one pregnant women with available urine were included in our analysis. The data include a broad range of health associated factors including thyroid function tests (FT4, TSH, TPO-Ab) from GW 14 and 28, and at 3 months postpartum for 80% of the participants. Collected data in GW 14, 28 and 3 months after delivery shown in **table 2.1**.

**Table 2.1.** Main data collection in relation to gestational weeks/postpartum period.

| | Gestational weeks | | | | 0–28 days after birth | 10–14 weeks postpartum |
|---|---|---|---|---|---|---|
| | 8–20 | 21–29 | 30–34 | 35–42 | | |
| Mother | V1 | V2 | | | | V3 |
| *Questionnaire data* | | | | | | |
| Demographic factors, family, medical and obstetric history | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| Physical activity and related psychosocial factors | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| Diet | | 28 ± 2 | | | | 12 ± 2 |
| Pregnancy complications | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| Delivery complications | | | | | | 12 ± 2 |
| *Measurements* | | | | | | |
| Blood pressure | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| Anthropometry | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| Physical activity, intensity, duration objectively measured[a] | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| *Blood and urine samples* | | | | | | |
| Fasting EDTA blood, serum/plasma[b] | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| Oral glucose tolerance test[c] | | 28 ± 2 | | | | 12 ± 2 |
| Urine[b] | 8–20 | 28 ± 2 | | | | 12 ± 2 |
| *Electronic medical records* | | | | | | |
| Pregnancy and delivery complications | | | | | Pregnancy + 0–28 | |
| Father | | | | | | |
| *Questionnaire data* | | | | | | |
| Demographic factors, family, and medical history | | 28 ± 2 | | | | |
| Fetus/offspring | | | | | | |
| *Fetal ultrasound visits* | UR | U1 | U2 | U3 | | |
| Fetal weight, cardiovascular, and haemodynamic system | 17–19 | 22–24 | 30–32 | 36–38 | | |
| *Offspring measurements* | | | | | | |
| Body weight, HC, and length | | | | | 0 | 12 ± 2 |
| Anthropometry, skin folds | | | | | 0–3 | |
| *Offspring blood samples* | | | | | | |
| Umbilical cord venous plasma (EDTA)[c] | | | | | 0 | |
| *Placenta* | | | | | | |
| Macro- + microscopic examination[c] | | | | | 0 | |
| *Electronic medical records* | | | | | | |
| Neonatal adverse outcomes | | | | | 0–28 | 12 ± 2 |
| Questionnaire data | | | | | | |
| Breastfeeding, nutrition, and health | | | | | | 12 ± 2 |

*Reprint from Jenum et al. 2010 [81].*

[a] Sensewear Armband [107].

[b] Bio-banked and stored at -80°C.

[c] Oral glucose tolerance test performed in all women at V2 and at V3 only in women with gestational diabetes mellitus. HC, head circumference; UR, routine ultrasound at maternity unit; U1-3, ultrasound visits at the child health clinics; V1-3, mothers' visits at the child health clinics.

### 2.4.1 Exposure variable

Blood and urine samples were collected at the routine antenatal care visits during visit 1 (GW 8-20), visit 2 (GW 21-29), and visit 3 (10-14 weeks post-partum). UIC was explored both as a crude measure (µg/L) and adjusted for urinary creatinine (µg/g).

### 2.4.2 Outcome variables

TSH, free T4 (FT4), and thyroid peroxidase antibodies (TPO-Ab), were measured in plasma samples at GW 14, GW28, and at 3 months post-partum. For TSH and FT4, the cutoffs for defining low and high values were set to the 2.5th and 97.5th percentiles in a subsample of TPO-Ab negative (TPO-Ab <34 kIU/L) women.

## 2.5 Data handling

TSD – Services for Sensitive Data; a platform provided by the University of Oslo has been used to collect and store data, and analysis. TSD is developed and operated by the University of Oslo (UiO) and is a part of NorStore; the national infrastructure for handling and storage of scientific data.

## 2.6 Definitions and recommendations of iodine status and iodine intake

In this study, we used the WHO recommended epidemiological criteria for the assessment of iodine status [98]. According to WHO, for a population, the median UIC is the recommended indicator for the evaluation of iodine status, and median UIC < 150 µg/L reflects iodine insufficiency, while median UIC between 150-299 µg/L is considered to reflect adequate iodine status in pregnant women (**table 1.5**).

## 2.7 Statistical methods & analysis

The current results are mainly based on descriptive statistics. Descriptive statistics were applied to thyroid functions tests, iodine levels and other cohort characteristics, using parametric or non-parametric methods as appropriate.

Non-parametric tests were applied to test differences of UIC and iodine-to-creatinine ratio between different ethnic groups. Similarly, non-parametric tests were used to determine the differences in TSH and FT4 levels among different ethnicities.

*p*-Values were reported for overall association between continuous exposures and outcomes. A *p*-value < 0.05 was considered statistically significant. Subsequently, pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons, where adjusted p-values were presented. All statistical analyses were performed using Statistical Package for Social Science, version 25 (IBM statistic software, 2017, NY; USA).

The main explanatory variable in this project is urinary iodine level in the various ethnic groups, additionally adjusted for urinary solute concentration/volumes by urinary creatinine. The effect of degree of iodine repletion was tested on the main outcomes: FT4 and TSH during pregnancy and post-partum was tested first by Spearman's rank correlation analysis and scatterplots. Two-tailed cut-offs used with *P* value < 0.05 being considered statistically significant. Later, multiple regression was used to model associations with continuous outcomes. Adjusted models included the following covariates: age, prepregnancy BMI, 1$^{st}$ trimester BMI, ethnicity, education, parity, and gestational week at the time of inclusion in the study. Values are reported as adjusted $R^2$.

## 2.8 Ethics

The study protocol was approved by The Regional Committee for Medical and Health Research Ethics for South Eastern Norway (REK 18.10.07, 2007/894), and The Norwegian Data Inspectorate. Written consents were obtained from each pregnant woman, also on behalf of her offspring. An example of a written consent form is added to this protocol as appendix 1. The Regional Ethics Committee and Norwegian Directorate of Health approved the study and the

storage of biological material. Data was handled anonymously and stored according to standards of Norwegian Data Inspectorate.

## 2.9 Literature search strategy

Since August 2018, to be updated on relevant scientific literature, I subscribed to weekly e-mail updates from PubMed on new literature matching the following search criteria: MESH terms were used: «pregnancy» AND «iodine status/urinary iodine concentration» AND «thyroid function».

The searches were broad, and all titles/abstracts were read to identify relevant papers. Later, these relevant references were imported to EndNote library. I also found some relevant papers and reports from reference lists, in Iodine Global Network (IGN) (http://www.ign.org/), American Thyroid Association (https://www.thyroid.org/), and newsletters from the WHO.

# 3 Results

## 3.1 Descriptive characteristics of the study population

A total of 823 pregnant women were recruited to the Stork Groruddalen. Urine iodine samples were collected and analysed for 681 pregnant women. The descriptive characteristics of 681 pregnant women included in our study are shown in **Table 3.1**.

The study population was divided into 4 ethnic groups; NEW (Norway, Europe and other western countries, n = 298), SA (South Asia, n = 173), EA (East Asia, n = 38), and MEA (Middle East and Sub-Saharan Africa, n = 172). The mean age of the study participants was 29.8 ± 4.9 (SD) years. The mean age was statistically significantly higher in the "NEW" group (30.5 ± 4.5 years) compared to "SA" (28.9 ± 4.5 years, p = 0.003) and "MEA" (29.1 ± 5.6 years, p = 0.009) groups. 50.6% of the study participants had normal BMI (18.5-24.9 Kg/$m^2$) during 1$^{st}$ trimester (GW ≤ 12), while 29.6% and 16.3% were overweight (25-29.9 Kg/$m^2$) and obese (>30 Kg/$m^2$) respectively. The majority of the cohort was multiparous (54.8%). Pregnant women with greater proportion of higher education (District College/High School/University Education) were mainly from Norway, Europe and other western countries (42.5%).

**Table 3.1. Cohort characteristics for participants with available urinary iodine levels (n = 681 pregnant women)**

| | |
|---|---|
| **Age, years (Mean (SD)) *** | 29,8 (4,9) |
| NEW (*n=298*) | 30,5 (4,5) |
| SA (*n=173*) | 28,9 (4,5) |
| EA (*n=38*) | 30,8 (4,8) |
| MEA (*n=172*) | 29,1 (5,6) |
| **1st Trimester† BMI, Kg/m$^2$ (Mean (SD))** | 25,4 (5) |
| Less than 18.5 | 24 (3,5) |
| 18.5-24.9 | 344 (50,6) |
| 25-29.9 | 201 (29,6) |
| Greater than 30 | 111 (16,3) |
| **Country of Birth, *n (%)*** | |
| Born in Norway, Norwegian parents | 230 (33,8%) |
| Born in Norway, one Norwegian parent | 15 (2,2%) |
| Born in Norway, Foreign parents | 43 (6,3%) |
| Born abroad | 393 (57,7%) |
| **Ethnicity, *n (%)*** | |
| NEW | 298 (43,3%) |
| SA | 173 (25,4%) |
| EA | 38 (5,6%) |
| MEA | 172 (25,3%) |
| **Parity, *n (%)*** | |
| Primiparous | 308 (45.2%) |
| Multiparous | 373 (54.8%) |
| **Civil Status, *n (%)*** | |
| Married/Cohabitant | 643 (94,4%) |
| Other | 38 (5,6%) |
| **Education, *n (%)*** | |
| <10 years primary school | 109 (16,1%) |
| 10-12 years high school | 281 (41,4%) |
| District College/High School/University Education | 288 (42,5%) |

*Values are given in Mean, Standard Deviations and Percentages*
**The mean differences of age (years) between groups is significant at the level of p<0.001(One-Way ANOVA)*
*†Gestational week ≤ 12*
*NEW (*Norway, Europe & other western countries*), SA (South Asia), EA (East Asia), MEA (Middle East & Sub-Saharan Africa), SD (standard deviation).*

## 3.2 Thyroid function tests & thyroid peroxidase antibody levels during 1st, 2nd trimester and 3 months post-partum in different ethnic groups

The descriptive analysis of TSH, FT4 and TPO-Ab levels among different ethnic groups during 1st trimester, 2nd trimester and 3 months post-partum in the study population are shown in **Table 3.2**. TSH levels were found to be higher than usual in the study population during 1st trimester (1.1-5.7 mIU/L), 2nd trimester (1.4-5.9 mIU/L), and at 3 months post-partum (0.3-6.2 mIU/L). TSH levels increased slightly during 2nd trimester and returned to normal at 3 months post-partum. Subsequent post hoc analysis also revealed significant differences in TSH levels during 1st trimester between the "EA" and "SA" ethnic groups ($p < 0.001$), and "NEW" and "SA" ($p = 0.001$) ethnic groups, but not between any other group combination ($p > 0.05$). During 2nd trimester, post hoc analysis revealed significant differences in TSH levels between the "EA" and "SA" groups ($p < 0.001$), "NEW" and "SA" groups ($p < 0.001$), and "MEA" and "SA" ($p = 0.004$) ethnic groups, but not between any other group combination.

At 3 months post-partum, post hoc analysis revealed significant differences in TSH levels between the "EA" and "SA" groups ($p = 0.009$), "NEW" and "SA" ($p < 0.001$), and "MEA" and "SA" ($p < 0.001$) ethnic groups, but not between any other ethnic groups.

In the current study, mean FT4 levels during 1st trimester (13.3±2.02 pmol/L), 2nd trimester (12.6±1.58 pmol/L), and at 3 months post-partum (14.0±3.77 pmol/L) were all within the reference range. In all ethnicities, FT4 levels showed a downward trend during 2nd trimester, which returned to baseline during post-partum. Moreover, FT4 levels were significantly different among different ethnic groups at 3 months post-partum ($p = 0.012$). However, no significant differences in FT4 levels were found between different ethnic groups during 1st trimester and 2nd trimester. Median TPO-Ab positivity did not differ significantly between different ethnicities throughout the course of pregnancy and 3 months post-partum.

**Table 3.2. TSH, FT4 & TPO-Ab positive levels among different ethnicities during 1st, 2nd trimester & 3 months post-partum**

| Thyroid Stimulating hormone (mIU/L) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ethnic Groups** | **Ist Trimester (n= 665)** | | | **2nd Trimester (n= 621)** | | | **3 months postpartum (n= 494)** | | |
| | **N** | **Mean† (SD)** | **2.5th-97.5th** | **N** | **Mean† (SD)** | **2.5th-97.5th** | **N** | **Mean† (SD)** | **2.5th-97.5th** |
| All Ethnicities | 665 | 1.99 (1.42) | 1.1-5.7 | 621 | 2.42 (1.46) | 1.4-5.9 | 494 | 2.31 (3.03) | 0.3-6.2 |
| NEW | 285 | 1.86 (1.12) | 0.14-5.01 | 275 | 2.16 (1.08) | 0.57-5.11 | 206 | 1.85 (1.0) | 0.22-4.40 |
| SA | 171 | 2.51 (1.90) | 0.02-8.06 | 160 | 3.01 (1.81) | 0.35-7.71 | 135 | 3.41 (5.38) | 0.64-12.4 |
| EA | 38 | 1.28 (0.91) | 0.001-* | 34 | 1.63 (0.93) | 0.001-* | 30 | 1.84 (1.16) | 0.09-* |
| MEA | 171 | 1.93 (1.26) | 0.02-5.04 | 152 | 2.46 (1.52) | 0.34-5.90 | 123 | 2.01 (1.25) | 0.15-5.50 |

| Free Thyroxine (pmol/L) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ethnic Groups** | **Ist Trimester (n= 668)** | | | **2nd Trimester (n= 621)** | | | **3 months postpartum (n= 494)** | | |
| | **N** | **Mean‡ (SD)** | **2.5th-97.5th** | **N** | **Mean‡ (SD)** | **2.5th-97.5th** | **N** | **Mean‡ (SD)** | **2.5th-97.5th** |
| All Ethnicities | 668 | 14.8 (2.29) | 11.0-20.0 | 621 | 12.9 (1.70) | 9.9-17.0 | 494 | 14.7 (2.62) | 10.3-19.0 |
| NEW | 288 | 14.7 (1.99) | 10.9-19.0 | 275 | 12.7 (1.60) | 9.3-16.0 | 206 | 15.0 (2.81) | 11.9-19.0 |
| SA | 171 | 14.8 (2.59) | 11.0-21.0 | 160 | 13.0 (1.86) | 9.7-17.0 | 135 | 14.1 (2.42) | 8.4-18.7 |
| EA | 38 | 15.1 (3.03) | 10.0-* | 34 | 13.0 (1.79) | 8.9-* | 30 | 14.7 (2.39) | 9.1-* |
| MEA | 171 | 14.7 (2.24) | 11-19 | 152 | 15.0 (2.81) | 9.9-17.0 | 123 | 14.6 (2.64) | 9.8-21.2 |

| Thyroid Peroxidase Antibodies Positives (>34 kU/L) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ethnic Groups** | **Ist Trimester (n= 37)** | | | **2nd Trimester (n= 25)** | | | **3 months post-partum (n= 30)** | | |
| | **N** | **Median‾** | **2.5th-97.5th** | **N** | **Median‾** | **2.5th-97.5th** | **N** | **Median‾** | **2.5th-97.5th** |
| All Ethnicities | 37 | 265 | 60-800 | 25 | 105 | 38-600 | 30 | 420 | 70-1000 |
| NEW | 13 | 175 | 36.0-* | 6 | 85 | 38.0-* | 11 | 450 | 38.0-* |
| SA | 19 | 355 | 34.0-* | 16 | 115 | 40.0-* | 14 | 380 | 60.0-* |
| EA | 0 | - | - | 0 | - | - | 0 | - | - |
| MEA | 5 | 180 | 42.0-* | 3 | 120 | 70.0-* | 5 | 365 | 100.0-* |

*NEW (*Norway, Europe & other western countries*), SA (South Asia), EA (East Asia), MEA (Middle East & Sub-Saharan Africa).*

*†Mean TSH was statistically significantly different between groups during 1st, 2nd trimesters & at 3 months post-partum (p < 0.001).*

*‡Mean FT4 was statistically significantly different between groups at 3 months post-partum (p = 0.012), but not statistically significantly different between groups during 1st (p = 0.436), 2nd Trimester (p = 0.182).*

*‾Median TPO-Ab positivity was not statistically significantly different between during 1st trimester (p = 0.072), 2nd trimester (p = 0.451) & at 3 months post-partum (p = 0.874).*

** SPSS did not produce 97.5th percentile due to small sample population size.*

The trends of mean TSH and mean FT4 along with their respective standard error of means (SEM) during pregnancy (GW 15, GW28) and 3 months post-partum among different ethnicities are shown in **Figure 3.1**. TSH levels increased during 2nd trimester in all ethnic groups and returned to baseline at 3 months post-partum in all ethnic groups except "SA" and "EA" ethnic groups. In case of FT4, "MEA" group demonstrated an opposite trend compared to all other ethnicities where the levels rose during 2nd trimester and declined to baseline at 3 months post-partum.

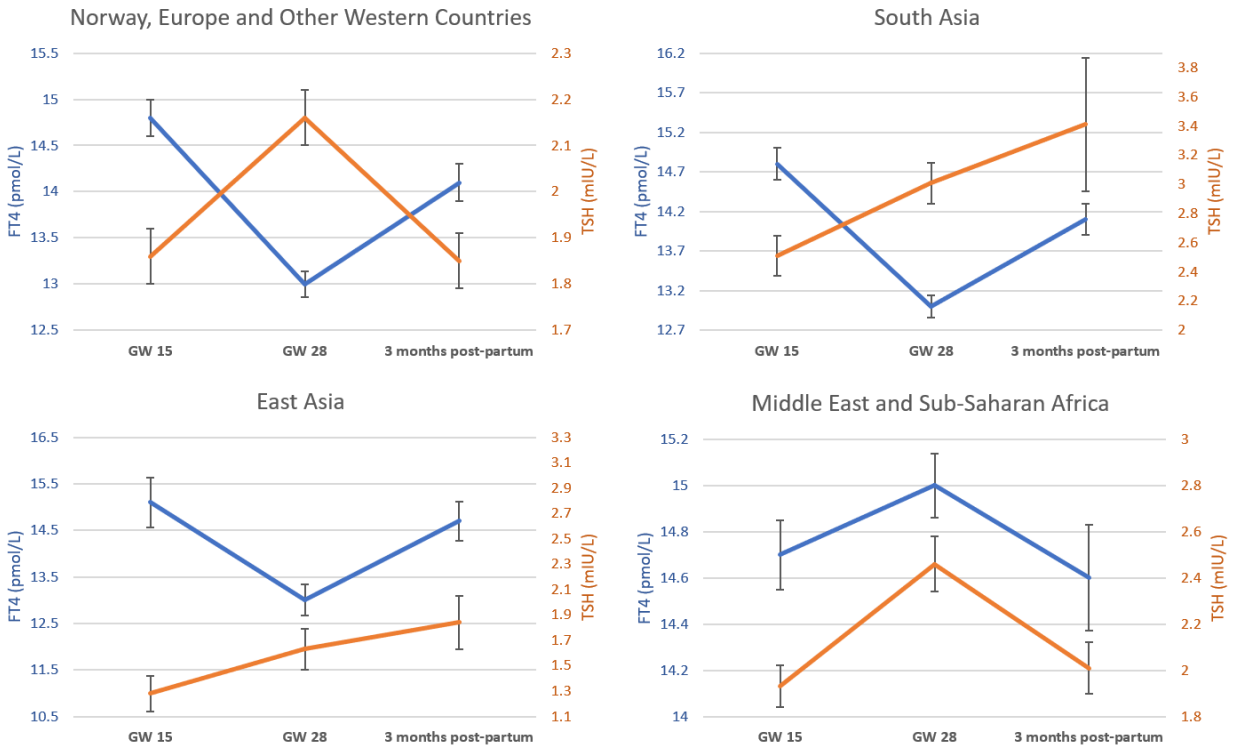


**Figure 3.1.** Line graph illustrating trends of mean TSH and mean FT4 along with their respective standard error of means (SEM) during pregnancy (GW 15, GW28) and 3 months post-partum among different ethnicities in STORK Groruddalen Cohort.

## 3.3 Iodine status and thyroid function tests/thyroid peroxidase antibody positivity

The pregnant women in the study population were categorized as iodine deficient (UIC = <150 µg/L) and iodine sufficient (UIC = <150-249 µg/L) and are shown in **Table 3.3**. We found no

significant differences in TSH levels based on iodine status groups during 1st trimester, 2nd trimester and post-pregnancy. The concentrations of FT4 according to iodine status groups at each trimester did not differ significantly either.

TPO-Ab positivity (>34 kU/L) during 1st trimester in iodine "deficient" group was significantly higher than for iodine "sufficient" group ($p = 0.031$). However, TPO-Ab positivity between the two groups were not significantly different during 2nd trimester or at 3 months post-partum. Moreover, we found that an increase in TSH levels during early pregnancy was significantly associated with increased TPO-Ab positivity ($r_s = 0.368$, $p = 0.025$).

**Table 3.3. Thyroid function tests, thyroid peroxidase antibody positivity & relationship with iodine status**

| | | 1st Trimester | | | 2nd Trimester | | | 3 months post-partum | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Thyroid Parameters** | **Iodine Status** | ***N*** | **Mean ± SD** | ***P-value*** | ***N*** | **Mean ± SD** | ***P-value*** | ***N*** | **Mean ± SD** | ***P-value*** |
| FT4 (pmol/l) | *Adequate* | 537 | 14.9 ± 2.3 | 0.483 | 537 | 13.0 ± 1.7 | 0.455 | 537 | 14.7 ± 2.4 | 0.143 |
| | *Insufficient* | 89 | 14.8 ± 2.4 | | 89 | 12.8 ± 1.7 | | 89 | 14.6 ± 3.7 | |
| TSH (mIU/L) | *Adequate* | 537 | 2.0 ± 1.4 | 0.825 | 537 | 2.4 ± 1.4 | 0.829 | 537 | 2.2 ± 1.9 | 0.503 |
| | *Insufficient* | 89 | 2.0 ± 1.5 | | 89 | 2.3 ± 1.2 | | 89 | 2.9 ± 6.8 | |
| TPO-Ab positive (kU/L) | *Adequate* | 537 | 209.8 ± 214.5 | 0.031 | 537 | 143.5 ± 131.6 | 0.254 | 537 | 316.1 ± 270.0 | 0.197 |
| | *Insufficient* | 89 | 363.4 ± 287.4 | | 89 | 224.0 ± 88.5 | | 89 | 582.5 ± 431.9 | |

*Epidemiological criteria for assessing iodine status in pregnant women according to World Health Organization (WHO); Iodine deficiency UIC < 150 µg/L and Iodine adequate 150-249 µg/L. Values are expressed as mean ± SD. P-value for the comparison between iodine sufficiency and adequate status in each trimester using Kruskal-Wallis H test. FT4; Free Thyroxine, TSH; Thyroid Stimulating Hormone, TPO-Ab positive; Thyroid Peroxidase Antibody > 34 kU/L.*

## 3.4 Thyroid function tests and gestational age

Early or late inclusion (including blood samples) in the study was used to group the pregnant women into two groups; i.e. inclusion “before GW12” and inclusion “after GW12”, and is presented in the **table 3.4**. While testing to determine differences in FT4 levels between the two groups, mean FT4 levels were found to be significantly different between groups during 1st trimester ($p < 0.001$), but there were no significant differences between groups during 2nd trimester and postpregnancy. A post-hoc analysis revealed that FT4 levels during 1st trimester were significantly higher in “before GW12” group than in “after GW12” group (15.5 ± 2.60 vs. 14.6 ± 2.21 pmol/l, $p< 0.001$).

Contrary to this, post-pregnancy TSH levels between the two groups were significantly different ($p = 0.046$), but not during 1$^{st}$ trimester and 2$^{nd}$ trimester. A subsequent post-hoc analysis showed that postpregnancy TSH levels were significantly higher in “before GW12” group than in “after GW12” group (2.9 ± 6.32 vs. 2.1 ± 1.94, $p = 0.046$).

**Table 3.4. Thyroid function tests and gestational week at inclusion**

| | | 1st Trimester | | | 2nd Trimester | | | 3 months post-partum | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Thyroid Parameters** | **Gestational Week at Inclusion** | ***N*** | **Mean ± SD** | ***P-value*** | ***N*** | **Mean ± SD** | ***P-value*** | ***N*** | **Mean ± SD** | ***P-value*** |
| FT4 (pmol/l) | Before GW12 | 110 | 15.5 ± 2.60 | <0.001 | 103 | 12.9 ± 1.78 | 0.739 | 80 | 14.9 ± 2.89 | 0.599 |
| | After GW12 | 558 | 14.6 ± 2.21 | | 518 | 12.9 ± 1.75 | | 414 | 14.6 ± 2.61 | |
| TSH (mIU/L) | Before GW12 | 109 | 2.1 ± 1.72 | 0.402 | 103 | 2.6 ± 1.90 | 0.469 | 80 | 2.9 ± 6.32 | 0.046 |
| | After GW12 | 556 | 2.0 ± 1.45 | | 518 | 2.4 ± 1.38 | | 414 | 2.1 ± 1.94 | |

*Mean TSH/FT4 levels among two groups of pregnant women based on GW at the time of inclusion in the study; i.e. inclusion "before GW12" and inclusion "after GW12.*

## 3.5 Iodine status and urinary iodine concentration

Median iodine based on UIC was 88.8 µg/L, while median iodine-to-creatinine ratio was 77.9 µg/g. (**Table 3.5**)**.** The overall UIC varied from 12.6-1167.4 µg/L and only 13.1% of the total cohort had an iodine sufficiency (UIC = 150-249 µg/L). The overall iodine-to-creatinine ratio varied from 5.1-1043.3 µg/g and only 77 participants (11.3%) of the total cohort had an adequate iodine status (I/Cr = 150-249 µg/g) (**Figure 3.2**).

**Table 3.5. Urinary Iodine Concentration in pregnant women in Stork Groruddalen Cohort**

| | ***N*** | **Median (IQR)*** | **2.5$^{th}$-97.5$^{th}$** | **Range** |
|---|---|---|---|---|
| UIC (µg/L) | 681 | 88.8 (76.1) | 24.9-401.1 | 1154.8 |
| Iodine-to-creatinine ratio (µg/g) | 669 | 77.9 (72.5) | 22.8-367.9 | 1038.2 |

**Interquartile range*

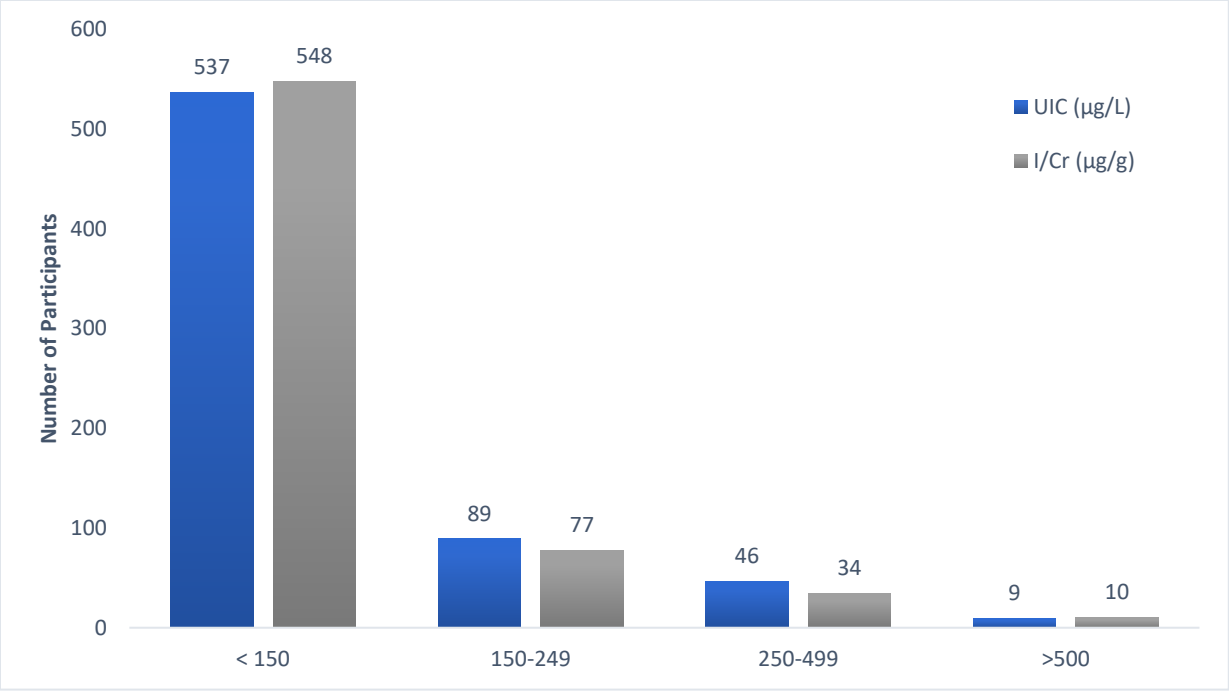


**Figure 3.2.** Distribution of Urinary Iodine Concentration (UIC, blue bars) and Urinary Iodine-to-creatinine ratio (I/Cr, grey bars) in the STORK Groruddalen Cohort (*n* = 681) according to WHO epidemiological criteria [5]. Y-axis: number of pregnant women, X-axis: UIC cutoffs ranges (<150 µg/L: Insufficient, 150-249 µg/L: Adequate, 250-499 µg/L: Above requirement, >500 µg/L: Excessive)

The median UIC, median I/Cr, and their respective upper quartiles are below the WHO recommended level (150 µg/L) in the study cohort (**Figure 3.3**).

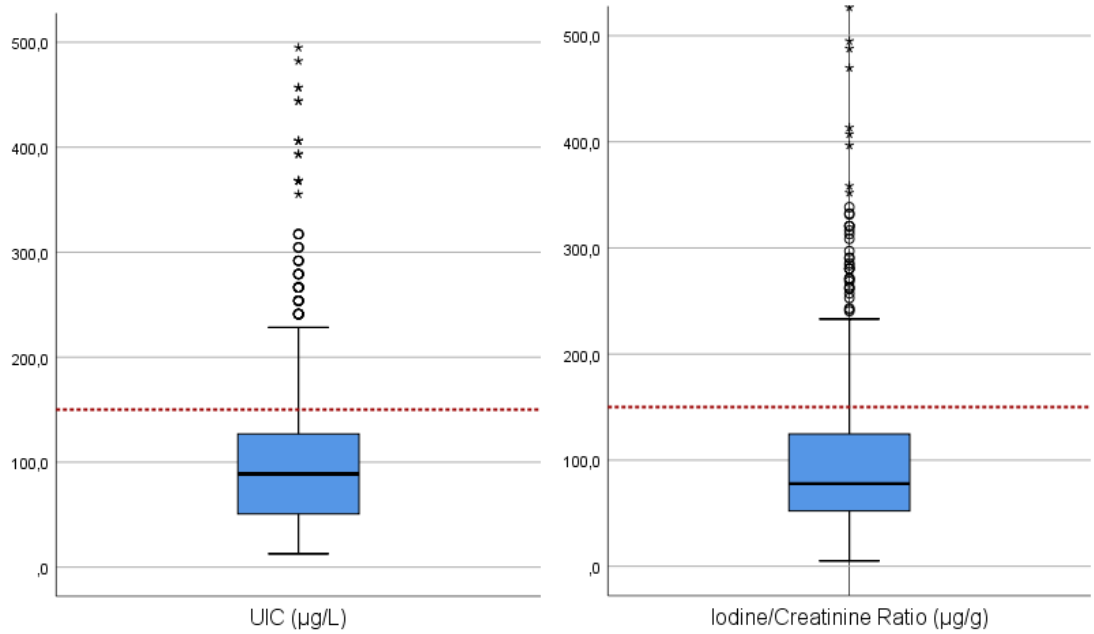


**Figure 2.3.** Urinary Iodine Concentration (n = 681) and Iodine-to-creatinine ratio (n = 669) from the STORK Groruddalen Study. The stippled horizontal line marks the epidemiological criteria for assessing adequate Iodine status based on median UIC (≥ 150 µg/L) by the WHO.

The descriptive analysis for UIC (µg/L) and I/Cr (µg/g) between different ethnic groups in the study population was carried out (**Table 3.6**). Pregnant women in "EA" ethnic group had the highest median UIC (107.8 µg/L) compared to other ethnic groups, while "MEA" ethnic group had the lowest median UIC (76.1 µg/L). Median UIC was not significantly different between any ethnic group (p = 0.672). In the current study, reference ranges (i.e. 2.5p-97.5p) for UIC and I/Cr ratio for the pregnant women in STORK cohort were 24.9-401.1 µg/L and 22.8-367.9 µg/g respectively (**Table 3.6**).

**Table 3.6- Urinary iodine concentration and iodine-to-creatinine ratio among different ethnicities**

| UIC (µg/L), n= 681 | | | |
|---|---|---|---|
| **Ethnic Groups** | **Median† (IQR)*** | **2.5th-97.5th** | **Range** |
| All Ethnicities (*n*=681) | 88.8 (76.1) | 24.9-401.1 | 1154.8 |
| NEW (*n*=298) | 88.8 (76.1) | 25.3-309 | 875.6 |
| SA (*n*=173) | 88.8 (76.1) | 25.3-428.9 | 748.7 |
| EA (*n*=38) | 107.8 (92) | -* | 444.2 |
| MEA (*n*=172) | 76.1 (88.8) | 15.5-593.5 | 1154.8 |

| I/Cr (µg/g), n= 669 | | | |
|---|---|---|---|
| **Ethnic Groups** | **Median† (IQR)*** | **2.5th-97.5th** | **Range** |
| All Ethnicities (*n*=681) | 77.9 (72.5) | 22.8-367.9 | 1038.2 |
| NEW (*n*=298) | 79 (61.1) | 22.2-316.6 | 964.5 |
| SA (*n*=173) | 78.2 (78.2) | 20.9-377.4 | 796.5 |
| EA (*n*=38) | 81.8 (82.4) | -* | 452.7 |
| MEA (*n*=172) | 75 (82.3) | 24-545.9 | 1025.2 |

**Interquartile range*

*†p-value = 0.672 for the comparison of median UIC between different ethnic groups suggests non-statistical significant difference.*

*‡p-value = 0.695 for the comparison of median I/Cr ratio between different ethnic groups suggests non-statistical significant difference.*

** SPSS did not produce 97.5th percentile due to small sample population size.*

*NEW (*Norway, Europe & other western countries*), SA (South Asia), EA (East Asia), MEA (Middle East & Sub-Saharan Africa),*

## 3.6 Urinary iodine distribution in relation to median UIC cut-offs

In the present study, the distribution of median UIC was explored based on ethnicity of the pregnant women participated in the STORK Groruddalen Study (**Figure 3.4**). Pregnant women in "NEW" ethnic group had the highest proportion of iodine deficiency (82.5%), followed by "SA" (76.9%), "MEA" (75%), and "EA" (70.6%). Overall, more than 70% of the study participants in each ethnic group had an insufficient iodine status (UIC < 150 µg/L). `Among all the ethnicities, pregnant women in "EA" group had the highest proportion of iodine sufficiency (20.6%), followed by "SA" (15%), "MEA" (13.2%), and "NEW" (11.9%). 2.6% and 1.3% of the pregnant women belonging to "MEA" group and "SA" group had an iodine excess respectively.

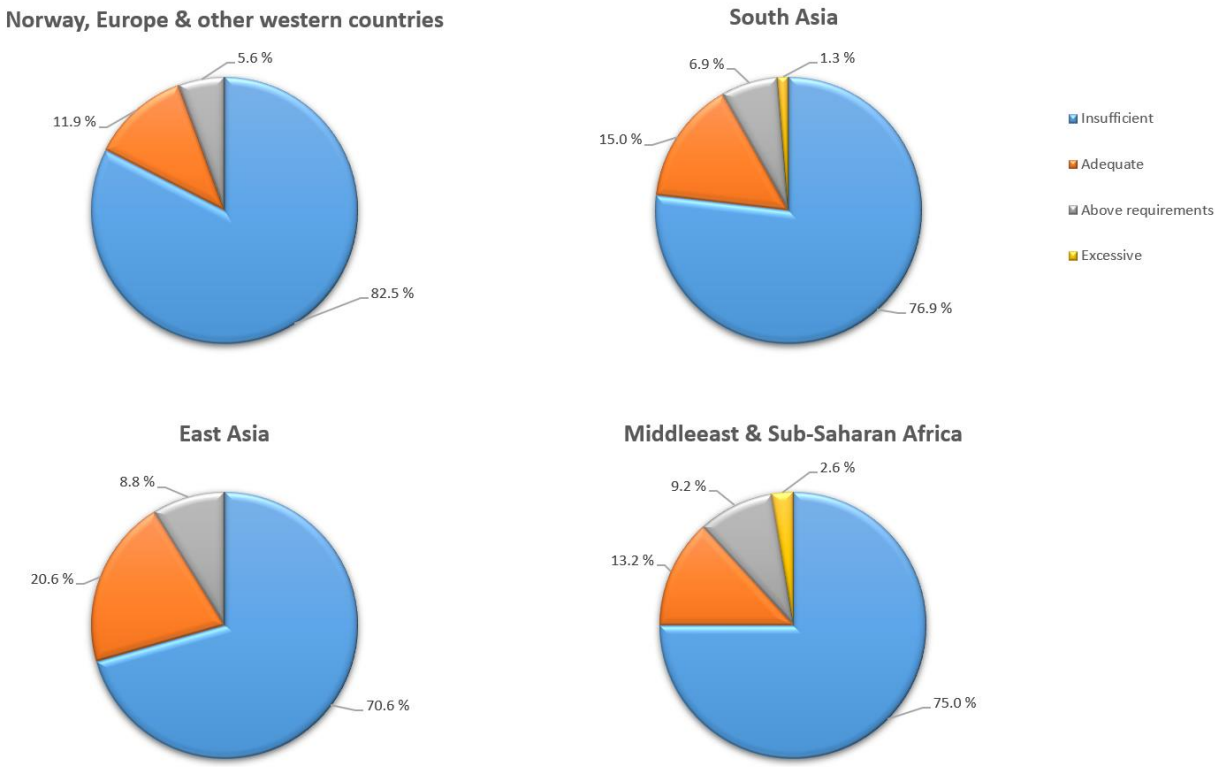


**Figure 3.4.** Pie-charts showing distribution of WHO recommended cut-offs of median UIC among different ethnic groups in STORK Groruddalen Cohort: Insufficient (<150 µg/L), Adequate (150-249 µg/L), Above requirement (250-499 µg/L), Excessive (>500 µg/L).

## 3.7 Associations between UIC and thyroid function

There was no significant correlation between UIC and TSH during 1st trimester ($r_s$ = 0.018, p = 0.643), 2nd trimester ($r_s$ = 0.023, p = 0.563) or at 3 months post-pregnancy ($r_s$ = -0.027 p = 0.551).

A similar correlation model using UIC and FT4 was carried out, which also did not show any significant correlation during 1st trimester ($r_s$ = -0.025 p = 0.524), 2nd trimester ($r_s$ = -0.060, p = 0.134) or at post-pregnancy ($r_s$ = -0.084 p = 0.063).

Multiple regression was run to model predictors of thyroxin levels (FT4). High prepregnancy BMI, GW, Iodine-to-creatinine ratio, and age were associated with decreased FT4, while education was associated with increased FT4. These predictors explained 8.1% of the variance in FT4 (p < 0.001). However, the regression model did not significantly predict the covariates for TSH (p > 0.05). Regression coefficients and standard errors of the regression model can be found in **Table 3.7**.

**Table 3.7. Summary of the multiple regression analysis**

| Variable | *β* | *$SE_B$* | *CI* | *p-value* |
|---|---|---|---|---|
| Intercept | | 0.796 | 17.83-20.69 | <0.001 |
| Iodine-to-creatinine ratio | -0.116 | 0.001 | -0.003-0.000 | 0.038 |
| Age | -0.214 | 0.020 | -0.137-0.063 | <0.001 |
| Education | 0.128 | 0.141 | 0.130-0.620 | 0.004 |
| Gestational Week | -0.141 | 0.240 | -1.361-0.427 | <0.001 |
| Prepregnancy BMI | -0.081 | 0.096 | -0.378-0.003 | 0.037 |

***Dependent variable: FT4 (pmol/L)), Inclusion Gestational Week (Before GW12, After GW12), Prepregnancy BMI (underweight, normal, overweight, obese), Education (<10 years primary school, 10-12 years high school, District College/High School/ University Education), $SE_B$ = Standard error of the coefficient, β = Standardized regression coefficient, CI = 95% Confidence Interval (Lower and Upper limit).***

## 3.8 Population-specific reference ranges for TSH and FT4

**Table 2.5** shows the 2.5th and 97.5th percentiles for plasma TSH and FT4 levels for the study population belonging to different ethnicities. Pregnant women belonging to "SA" ethnic group had higher TSH levels during 1st trimester compared to "NEW" and "MEA" ethnic groups (0.02-

8.06 vs. 0.14-5.01 and 0.02-5.04 respectively). A similar trend among these ethnic groups was observed during 2nd trimester and at 3 months post-partum. Based on the reference ranges determined in the subgroup of the study population after excluding TPOAb-positive subjects, 3.7% of the total study population had subclinical hypothyroidism (high TSH and normal FT4), 1% had overt hypothyroidism (high TSH and low FT4), 11% had isolated hypothyroxinemia (normal TSH and low FT4), 4.6% had subclinical hyperthyroidism (low TSH and normal FT4), and 2.4% had overt hyperthyroidism (low TSH and high FT4) as shown in **Table 2.8**. Based on the ethnicities, "NEW" group had the highest prevalence of euthyroidism (84.2%), followed by "MEA" (73.5%), "SA" (70.4%), and "EA" group has the lowest prevalence of the euthyroidism at 55.3%.

**Table 2.8. Thyroid status in STORK Groruddalen study population**

| **Diagnosis** | ***N* (%)** |
|---|---|
| Euthyroidism | 479 (76.3%) |
| Subclinical Hypothyroidism | 23 (3.7%) |
| Overt Hypothyroidism | 6 (1%) |
| Subclinical Hypothyroxinemia | 69 (11%) |
| Subclinical Hyperthyroidism | 29 (4.6%) |
| Overt Hyperthyroidism | 15 (2.4%) |

*Data from subgroup of the study cohort: patients with TPO-Ab positive (TPO-Ab > 34kU/L) were excluded.*

# 4 Discussion

## 4.1 Methodological Considerations

### 4.1.1 Data Collection

A total of 823 mothers were enrolled in STORK Groruddalen study, but only those with urinary iodine data available (n = 681) were included for analysis in this study. Data was collected in collaboration with Child Health Clinics (CHC) in Groruddalen, Oslo. The objective of STORK Groruddalen study was to collect unique information from a representative group of multi-ethnic women in order to address important public health problems and mechanisms of disease. Participation rates were high in all ethnic groups.

### 4.1.2 Exclusion Criteria

Participants whose urinary iodine data was not available were excluded in this study. Moreover, as in The Avon Longitudinal Study of Parents and Children (108), spot urine samples with UIC > 500 µg/ L were not excluded in this study. This is because the it is not uncommon to observe such high levels in routine urine samples, though they may be statistical outliers.

### 4.1.3 Urinary Creatinine

As daily creatinine excretion rate in urine is relatively constant, we used urinary creatinine concentration to adjust UIC for intra-individual variations within the study population and to approximate iodine status in the whole group (109).

Another reason to use urinary creatinine concentration was to determine if the spot urinary sampling was valid or not. According to WHO, if a spot urinary sample has a creatinine concentration of less than 30 mg/ dl or > 300 mg/dl, another urine sample should be collected (110). As morning urine after an overnight fast were sampled and analysed, and concentrated urine might had exceeded the recommended WHO range. Thus, it could be one limitation of this

study and urine samples should have been discarded if the creatinine concentration had exceeded the analytical cut-off.

## 4.2 Descriptive characteristics

The mean age of the pregnant women in the study population is within the range of the Norwegian national average age (29.5 years) of women at giving their first birth to children [111]. The mean age reported in other Norwegian studies [112-114] and in studies conducted in other European countries [115,116] also includes women within the same age range.

There is also substantial scientific evidence that iodine has an influence on physical development as well [117]. Current BMI showed that 29.6% of the women were overweight and 16.3% were obese. Research have shown that overweight and morbid obesity may be a risk factor for thyroid dysfunction in pregnant women in iodine-deficient areas [118]. This is because that changes in thyroid-stimulating hormone could well be secondary to obesity [119]. Data have also disclosed a significant relation between obesity and thyroid autoimmunity suggesting obesity to be a risk factor for acquired thyroid failure [120]. However, there was no association between UIC and obesity in this study.

The education level was higher than in MoBa study [121], Norkost 3 [122], and in the general Norwegian female population of age 16 years and older [123]. No associations were found between UIC and maternal education in our study. However, in a large longitudinal study conducted by Bath and Steer et al. 2013 [124], maternal education was found to be positively associated with maternal iodine status.

The majority of pregnant women were multiparous (54.8%) in this study and no association was found between parity and UIC. This is in accordance with results of a large community-based study by Walsh et al. [125] that showed that parity is not a risk factor for thyroid autoimmunity or thyroid dysfunction. However, a study conducted by Abdelsalam K. [126] suggests that the risk of pregnancy related complications secondary to thyroid dysfunction increases with grand multiparity (woman who has had ≥5 births (live or stillborn) at ≥20 weeks of gestation).

## 4.3 Thyroid function tests and thyroid autoimmunity

In the present study, we observed a decrease in TSH and increase in FT4 levels during the first trimester of pregnancy, consistent with physiological changes secondary to β-hCG stimulus [127-129]. To determine the ethnicity-specific references ranges (ESRR) of thyroid function tests in pregnancy, we measured the concentrations of TSH, FT4, and TPO-Ab during first trimester, second trimester and at 3 months post-partum (**Table 3.2**). We observed that pregnant women with South Asian ethnic background had the highest upper and lower reference limits of TSH compared to all other ethnicities during the course of pregnancy ($1^{st}$ trimester = 0.02-8.06 pmol/L, $2^{nd}$ trimester = 0.35-7.71 pmol/L) and at 3 months post-partum (0.64-12.4pmol/L). Moreover, TSH levels were higher than the recommended range in the study population. This is important because an increased risk of gestational thyrotoxicosis has been observed in Asian women [130]. Therefore, there is a need for further studies on exploring thyroid reference intervals in Asian women during early pregnancy.

Compared to our findings, a large multi-ethnic population-based cohort study from the Netherlands [131] involving pregnant women from Dutch, Turkish, Moroccan, and Surinamese ethnic background showed lower TSH levels in their study population (0.11–4.18 vs. 1.10–5.70 mIU/l). Evidence from literature suggests a higher TSH concentration level in the Middle Eastern and Asian pregnant women compared to the European and South American pregnant women which also corresponds to our findings [132,133].

Only a few studies have investigated the differences in TFTs in pregnant women of different ethnicities [134-137], and no data are currently available on the possible ethnic differences in thyroid function in pregnant women in Norway. Results from a study on pregnant women from different parts of the US have shown ethnic differences on TSH levels, but no effects on FT4 (134-136). A study involving 589 pregnant women (134) found that African American had a lower median TSH compared to white women (1.1 mU/L vs. 1.5 mU/L). The same authors conducted a study on pregnant women during second trimester (135) and showed a similar trend in median TSH between two ethnic groups (0.97 mU/L in African American vs. 1.21 mU/L in white pregnant

women). In our study the TSH levels were slightly higher overall, which may be explained by different assays used to determine TSH and FT4 levels.

Data on ethnic differences in FT4 levels during pregnancy are sparse. We observed significant differences in FT4 levels between different ethnic groups during 1st trimester. However, FT4 levels for all ethnic groups were within their respective reference ranges. A study by Pearce et al. [133] at on pregnant women (n = 668) during 1st trimester showed that ethnicity was not associated to T4 levels. In the current study, we found that pregnant women with East Asian ethnic background had significantly higher FT4 levels compared to all other ethnic groups during 1st trimester. However, ethnic differences in binding proteins such as thyroid hormone–binding globulin, and albumin could explain the discrepancy between T4 and FT4 levels in the two studies.

In the current study, we found that 37 (5.4 %) pregnant women were TPO-Ab positive, which is in accordance with the results in other studies conducted in different pregnant populations (138,139). South Asian women in our cohort had the highest prevalence of TPO-Ab positivity (51.3%). However, we did not observe any significant differences in TPO-Ab positivity among different ethnic groups in our study. Ethnic differences in TPO-Ab positivity have been found in large American studies in men and non-pregnant women [140], as well as in pregnant women [134,135]. There is an increased risk of postpartum thyroiditis, miscarriage, and foetal death due to TPO-Ab positivity in pregnancy [143,144]. Therefore, it is still to be established whether South Asian women in particular and pregnant women in general are more susceptible to these pregnancy adversities in Norway.

Furthermore, we found that TSH levels were higher in TPO-Ab positive pregnant women. Similar results were found in other studies [133,145,146]. But, a literature review by Stagnaro-Green et al [1147] reported a non-significant association between TSH levels and TPO-Ab positivity. This increase in TSH in euthyroid TPO-Ab positive pregnant women could be explained by the reduction in functional reserve of thyroid gland that occur as a result of autoimmune-mediated inflammation [148].

## 4.4 Urinary iodine concentration and iodine status

The median UIC (88.8 µg/ L) classifies the pregnant women in this study as iodine deficient. The median iodine-to-creatinine ratio is also low (78.9 µg/ L) (**Table 3.5**). According to literature, considering that 90% of iodine is excreted in urine, a UIC of minimum 150 µg/L reflects iodine sufficiency (78). However, we found that only 89 (13%) of the study population have a UIC above 150 µg/L (**Figure 3.2**). Furthermore, more than 70% of study participants in each ethnic group had an insufficient iodine status. It is also worth noticing that pregnant women in our study with ethnic background from Norway, Europe and other western countries had the highest iodine insufficiency (82.5%). An Australian study [149] on pregnant women who participated in Down's Syndrome screening study showed that the median UIC of Caucasian women (52 µg/L) was significantly lower than that of Vietnamese women (58 µg/L, P< 0.01) and Indian/Sri Lankan women (61 µg/L, P = 0.03). A study in the US from a sample of pregnant women in National Health and Nutrition Examination Survey (NHANES) and the National Children's Study (NCS) Vanguard Study reported significant differences in median UIC among non-Hispanic blacks; 131 µg/L, non-Hispanic whites;147 µg/L and Hispanics; 148 µg/L respectively [150].

The median UIC obtained in the present study are in accord with other studies reporting a high prevalence of iodine deficiency in pregnant women in Norway [15-153]. The results from MoBa [154] and MISA [155] studies showed that 80 % and 89% of the pregnant women had UIC < 150 µg/L, respectively. Insufficient iodine status has also been reported in other Nordic regions. A cross-sectional study in Sweden [156] involving 459 pregnant women showed a median UIC 98 µg/L. The median UIC in a Danish cross-sectional study in 158 pregnant women was 119 µg/L [157]. The situation is similar in some other European countries like, Austria [158], Poland [159], Belgium [160], Spain [161], UK [124,162], Italy [163], Portugal [164], Latvia [165], with UIC ranging from 57 µg/L in the UK to 140 µg/L in Spain. In contrast to this, a study involving more than 1000 pregnant women in Rotterdam, Netherlands have shown UIC of 230 µg/L [166], while a median UIC of 200 µg/L and 205 µg/L was reported in Iceland [167] and Switzerland [168] respectively. This comparison of iodine status between our study and other studies indicate that Norway is a part of European region with inadequate iodine nutrition during pregnancy [169].

**Table 4.1. Iodine status based on UIC reported in Nordic region and Europe.**

| Author(s)/ Year | Study Design/ Country | Number of Subjects | Urinary Iodine Concentration (Median, IQR) |
|---|---|---|---|
| Henjum / 2017-18 (185) | Cross-sectional/ Norway | 403 women (age 19–29 years) in Oslo & Bergen | Spot urine: All: 75 (42, 130)<br>Non-vegetarians (n = 367): 80 (45, 130)<br>Vegetarians (n = 36): 38 (27, 55) |
| Granfors/ 2017 (94) | Cross-sectional/ Sweden | 459 pregnant women | 98 (57, 148) |
| Henjum / 2016 (77) | Cross-sectional/ Norway | 804 pregnant women in the Oslo area (average age 31 years). | Spot urine: 92 (59, 140) |
| Henjum / 2016 (13) | Cross-sectional/ Norway | 175 nursing women (average age 32 years) | Spot urine: 64 (39, 95) |
| Madar / 2015-16 (61) | Cross-sectional/ Norway | 169 Norwegian Somalis (men and women 20–73 years) in Oslo area | Spot urine: 63 (38, 100) |
| Lindorfer / 2014 (93) | Cross-sectional/ Austria | 246 pregnant women | All: median UIC (IQR not specified): 87<br>Supplements not taken: 80.1<br>Supplement taken: 97.3 |
| Konrade/ 2013 (102) | Country wide cluster survey/ Latvia | 550 pregnant women | UI/Cr: 80·8 (46·1, 130·6)<br>Median UIC: 69·4 (53·9, 92·6) |
| Andersen/ 2012 (95) | Cross-sectional/ Denmark | 245 pregnant women (median age: 30.5 years) | Supplements taken: 109 (66, 191)<br>Supplements not taken: 68 (35, 93) |
| Dahl / 2011-12 (76) | Cross-sectional population-based prospective cohort/ Norway | 954 pregnant women in the LiN study (age 17-43 years) | Spot urine (IQR not specified): 85 |

| | | | |
|---|---|---|---|
| Moreno-Reyes/ 2010-11 (97) | Country wide cluster survey/ Belgium | 1311 pregnant women (mean age 28.5 years) | Ist trimester, n = 550: 117 (70–189)<br>3rd trimesters, n = 616: 131 (74–239) |
| Carlsen / 2010-11 (186) | Cross-sectional study 2x24h, diet interview/ Norway | 1787 adults (18–70 years) | Estimated intake (IQR not specified):<br>Women (18–70 years): 130<br>Men (18–70 years): 176<br>Young women (18–29 years): 110 |
| Bath/ 2009-11 (99) | double-blind, placebo-controlled, randomized trial/ UK | 230 pregnant women (mean age 30.73 years) | (IQR not specified)<br>Median UIC: 56.8<br>UI/Cr: 116 |
| Zygmunt/ 2010 (96) | Cross-sectional/ Poland | 115 pregnant women (mean age 29.2 years) | UIC (IQR not specified):<br>79.6 |
| Berg / 2007-09 (109) | Cohort Study/ Norway | 197 pregnant women in MISA study | Spot urine (median, 2.5 & 97.5 percentile):<br>2nd trimester: 75 (12, 316)<br>3 days postpartum: 32 (4, 127)<br>6 weeks postpartum: 47 (7, 179) |
| Abel / 2002–08 (187) | Cohort study; Norwegian mother and child cohort study (MoBa)/ Norway | 77,164 pregnant women. UIC measured in spot urine in 2,938 subjects. | Spot urine:<br>Supplements not taken (n = 1,950): 61 (32, 104)<br>(n = 988): 86 (43, 140) |
| Molin / 2006 (188) | Intervention study/ Norway | 38 (28 women) healthy students at OsloMet (20–40 years) | Spot urine before intervention: 90 (70, 128) |
| Limbert/ 2005-07 (101) | Cohort Study/ Portugal | 3631 pregnant women (mean 29.2 years) | Median UIC: 84.9 (67.6, 124.1) |

| | | | |
|---|---|---|---|
| Aguayo/ 2002-04 (98) | Prospective Observational Study/ Spain | 2104 pregnant women in 1st trimester, 1322 pregnant women in 2nd trimester (mean age 32.6 years) | Mean UIC: 1st trimester: 88.5 (range: 16–875), 2nd trimester: 140 (range: 21–880) |
| Ghassabian/ 2002-06 (103) | Generation R Study, population-based birth cohort/ Netherlands | 2375 pregnant women (UIC samples taken) | Median UIC: 229.6<br>UI/Cr: 296.5 |

*Different studies describing iodine status in different population groups in Norway, and Europe presented by time for data collection (latest first). The results in the last column are median (IQR; 25- and 75-percentile)*

In 2014, the Global Iodine Nutrition Scorecard was published by the IGN that assumed Norway an iodine sufficient country [169]. The results from MoBa study have shown that there is an inadequate iodine status in pregnant women even though the general population has an adequate iodine intake [154]. Our study results correspond to these findings and necessitates the need to investigate and update current knowledge of consequences of ID in pregnant women. So that, an optimized and sustainable iodine status can be achieved.

In our study, we reported both urinary iodine (UIC) in μg/L, and urinary iodine corrected for urinary creatinine (μg/g) to facilitate comparison with other studies. However, it is well established that the glomerular filtration rate and renal plasma flow increases by 40-65% and 50-85% during pregnancy [170], respectively, and that tubular function of processing water and electrolytes are also altered; which in turn may impact UIC results [171]. Therefore, to minimize the variation due to dilution and urine volume during pregnancy, UIC should be standardized to urinary creatinine and reported in μg/g creatinine units in order to facilitate more accurate assessment of iodine status in pregnancy. Moreover, UIC can be subjected to hydration status and mirror short-term iodine intake only, and it might be more accurate measure of iodine status to calculate the probability of iodine intake [141,142]. The results from a study in the US

concluded that using method of probability of adequate iodine intake might provide a better and complete understanding of prevalence of iodine sufficiency and inadequacy at a population level compared to consideration of UIC alone [172].

Ethnicity is often a powerful predictor and an explanatory factor of behaviours and health conditions in a multicultural society, that when added as an explanatory variable can increase our comprehension of the causes of iodine deficiency and disease development [173]. It is worth noticing here that ethnicity itself is not suggested to be responsible for health status, rather it might be explained by the differences in exposures and particular behaviours among different ethnic groups. For example, dietary behaviours typically differs between different ethnic groups. In view of the large and diverse ethnic population, especially in Oslo, targeted group strategies could be made in order to address specific dietary health issues. The employment of culturally sensitive approaches can be more effective in ensuring adequate dietary intake among all population groups than a single solution for the whole population.

## 4.5 Iodine status and thyroid function

In the present study, we did not observe any association between iodine status based on UIC and thyroid functions (TSH/FT4), as reported by other authors [174-178]. This lack of correlation could be attributed to pregnancy changes and to previous amount of iodine storage in the thyroid gland in a population which does not have persistent iodine deficiency, so that the gestational thyroid hormone synthesis would be guaranteed [129,179,180]. However, results from MoBa eTox (n=2999); a large substudy of MoBa cohort [181], demonstrated an inverse association between UIC and FT4 levels in pregnant women with mild iodine deficiency (UIC = 68 µg/L, IQR: 35, 116). The authors hypothesize that this might be due to inhibition of thyroid hormone production due to higher iodine availability during pregnancy (as a result of iodine supplementation). The results from MISA study also reported higher median concentration of TSH, T3, T4, FT3 and FT4 in pregnant women with UIC < 150 µg/L [155]. Several other studies reported no associations between maternal UIC and thyroid function [182-185]. However, the study population in some of these studies were reported iodine sufficient, and the disparity between the study findings

might be explained by the severity and timing of iodine deficiency and its influence on thyroid function in different populations.

However, we found that the pregnant women with insufficient iodine status had significantly higher TPO-Ab positivity compared to pregnant women with adequate iodine status (209.8 ± 214.5 vs. 363.4 ± 287.4 kU/L, p = 0.031). There is a limited and inconclusive evidence regarding the association between iodine status and thyroid autoimmunity. However, the prevalence of thyroid autoantibodies increases with age and is more common in women [186], which has also been demonstrated in two population-based studies in older people aged 75–80 years that thyroid autoantibodies occur more frequently if iodine deficiency is present. The increase in antibodies might partly be explained by the old age and immune capability of the study subjects in these studies [187,188]. We also observed significant association between age and TPO-Ab positivity at 3 months post-partum. Similar observations had been reported from some other studies as well [188,189]. We did not find any association between parity and TPO-Ab positivity during pregnancy and postpartum. The results from the historic Danish cohort study of pregnant women participated for the assessment of Down's Syndrome showed that TPO-Ab positive pregnant women had significantly more previous pregnancies and births but found no association between the parity and TPO-Ab positivity. Moreover, neither thyroid dysfunction nor antibody positivity were found to be associated with negative obstetric outcomes [191]. Other studies also concluded similar findings [192,193]. Moreover, the fact that either insufficient or excess iodine status may lead to thyroid disease is well acknowledged, and therefore, must be considered in further investigating the association between iodine intake and thyroid autoimmunity [194,195].

## 4.6 Thyroid function and gestational age

During pregnancy, a rise in β-hCG leads to rise in thyroid hormone levels, thus maternal thyroid status changes with gestational age. Moreover, an altered iodine clearance and placental metabolism of thyroid hormones, as well as oestrogen-induced increase in thyroxine binding globulin proteins also affects maternal thyroid status [196]. These unambiguous variations in

thyroid status during pregnancy necessitate the need for gestational age specific reference ranges. In our study, we observed higher FT4 and TSH levels in pregnant women included in the cohort before GW 12 compared to those pregnant women included after GW 12 during 1st trimester and at 3 months post-partum (**Table 3.4**). In recent years, several other studies have published gestational-age-specific reference ranges for use in pregnant women [197-200]. A comparative study of two large prospective longitudinal cohorts of Danish pregnant women showed that despite belonging to same area, the use of gestational-age-specific reference ranges from different laboratories led to misclassification of maternal thyroid status [201]. Incorrect interpretation of maternal thyroid can pose a great risk in the care of pregnant women. Although, universal thyroid function screening during pregnancy has been officially endorsed by members of the Endocrine Society [202], prior establishment of method and region-specific gestational age-related reference ranges of thyroid function is necessary for the proper implementation of screening programs [201].

## 4.7 Strengths and limitations

The closed cohort study design enabled us to estimate a risk or an incidence rate to measure the occurrence of iodine deficiency in our study cohort. Because of a retrospective cohort design of this study, it relied on existing records and collected data from the STORK Groruddalen study. One of the major strengths of our study is the multiethnicity which allows generalizability of the findings and ethnic comparisons. The study design in our case was quite feasible and offered the advantage of providing the information that was much less costly than that from a prospective cohort study. As there was no need to wait for the effect (iodine deficiency) to occur, it produced results much sooner. The sample size was large enough to define iodine status in a population.

Potential problems with the retrospective cohort approach included selection bias and misclassification bias because of the retrospective nature of the study. However, in STORK cohort, pregnant women attending the child health clinics for antenatal care in Groruddalen, Oslo were included in the study. However, we did not have repeated measurements of UIC over the course of pregnancy, rather a single UIC measurement of different pregnant women in early

pregnancy, therefore, a temporal relationship cannot be confirmed. The sample size in our study was also a limitation compared to other studies (e.g. MoBa eTox, MISA study) that found an association between iodine status and thyroid function in pregnant women in Norway.

## 4.8 Conclusion

The findings of the current study add to the evidence that a large proportion of pregnant women in Norway are iodine deficient. There were significant differences in TFTs among different ethnicities, but the levels were in their reference ranges. We also found that iodine deficiency is associated with higher TPO-Ab positivity during 1$^{st}$ trimester of pregnancy and higher TSH levels were observed in TPO-Ab positive pregnant women. Furthermore, pregnant women with South Asian ethnic background are at higher risk of developing thyroid dysfunction.

## 4.9 Future Perspectives

The findings of this study have potential public health implications and indicates a need for public health strategies with emphasis on vulnerable population subgroups to improve adequate iodine nutrition during pregnancy as well as adds to the debate on screening for thyroid dysfunction in pregnant women.

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# 6 Appendix-Patient Consent Form

[engelsk samtykke mor ]

# To you who are pregnant and live in Stovner, Grorud or Bjerke districts

# Requesting your participation in the "STORK Groruddalen" research project

## Purpose of the study

The purpose is to develop pregnancy and natal care and the health clinic services so that we are better equipped to prevent and treat new health problems due to overweight, lack of physical activity and diabetes. Women with diabetes and their children have a somewhat higher risk of complications during pregnancy. Sometimes diabetes arises during pregnancy. Even if the condition normally passes after giving birth, there is a greater risk of developing type-2 diabetes later.

Staff at the health clinics in the city districts of Stovner, Grorud and Bjerke are working with the university hospitals in the Oslo area to study these problems to find out how they impact the health of mother and child in the long and short term and why pregnancy diabetes and type-2 diabetes are increasing. Aker University Hospital is responsible for the study.

## What does the study entail?

At the health clinic you will receive one extra and one expanded check-up during your pregnancy and an extra examination after giving birth. We will take some extra blood and urine tests and readings, and ask you questions about your health, physical activity and diet. You will also be given extra ultrasound examinations during your pregnancy. Blood tests will be taken from the baby's umbilical cord and the placenta after you give birth, and some examinations and blood tests of the baby will be undertaken later.

## What happens to the tests and the information about you?

The tests and information will only be used as described under the section "purpose of the study". All the information and tests will be processed without using names or dates of birth or other information that could be tied directly to you. A coded list that connects the study results and the participants' names is only available to authorised health personnel who are involved in the study, and this list will be deleted when the study is concluded in 2030. It will of course not be possible to identify the participants when the results and findings from the study are published. To find out how many people might get diabetes and/or cardio-vascular disease in the future we want to have access to this information from your regular GP, from the hospital where you are being treated and from the Norwegian Diabetes Register for Adults, the Norwegian Patient Register, the Prescription Register, Causes of Mortality Register and the Medical Register of Births.

## Voluntary participation

Participation in the study is voluntary and everyone has the right to take time to consider this before making a decision. Those who do not wish to participate do not need to state a reason and this will not have any consequences for their further treatment. If you want to participate, sign the declaration of consent on the last page. You can later choose to withdraw your consent, without this having any effect on your treatment, by contacting the head of the project Anne Karen Jenum, Dr. med. (telephone 91 18 14 16).

**More information on the study is provided in *Chapter A***
**More information about the biobank, personal-data security, financing and insurance is provided in *Chapter B***

# Chapter A – detailed explanation of the study

All pregnant women attending pregnancy check-ups in the city districts of Stovner, Grorud and Bjerke will be invited to take part in the study. If you agree to participate, we will ask you to come to an extra examination at the health clinic around the 12th week, to an expanded examination around the 28th week and to an extra examination around 12 weeks after you give birth.

Each time we will ask you questions about your health and interview you about your diet and physical activity. We will also measure your physical activity with an armband that you strap to your upper arm. In addition, we will ask some questions about your health and any illnesses in the family, weigh you with a special scale that indicates fat-content, and measure the thickness of your skin using a simple external measuring method.

Before each of these three appointments you will have to fast due to the extra blood tests that will be taken together with the regular pregnancy tests. This means that you cannot eat, drink or smoke after midnight the night before your appointments. You will be told the results of the regular tests and some of the other blood tests at the next appointment. Other samples from the tests will be sent to the hospital to be frozen for later analysis. This also applies to the urine samples.

Around the 28th week we will take a blood-sugar (glucose) test as follows: After taking the blood tests that you have fasted for you will drink 75 gram glucose. After two hours we will take a new blood test. It is a good idea to bring a packed lunch with you so you can eat afterwards. The tests will be analysed at the health clinic. You will be told immediately if you have pregnancy diabetes. Then you will receive extra follow-up/treatment.

You will also be offered three extra ultrasound examinations to check your baby's growth. After the birth we will cooperate with the hospital where you gave birth and collect information from your medical records about your pregnancy and the results form the ultrasound examinations, and about the course of the birth, your health and your baby's height, weight, head circumference, distribution of body fat and general health condition. Blood tests will also be taken from the baby's umbilical cord and the placenta when you give birth.

After the birth we want to chart how long the baby is breastfed and how the child grows (height and weight) during its early years. This is done during the normal check-ups of the child at the health clinic. We would like to carry out some additional examinations of your child at six and ten years of age (diet, physical activity and blood tests). ***Women who have indicated pregnancy diabetes*** will undergo another blood-sugar examination approximately three months after giving birth. We will also call them in for an appointment once a year for five years, and then every fifth year for new tests to find out whether they have developed type-2 diabetes.

With follow-up studies we will ask again for your consent to participate.

### *Possible advantages and discomfort/disadvantages*

- We will gain more knowledge about physical activity, healthy diet and health
- You get extra careful follow-up if pregnancy diabetes is indicated
- The blood-sugar test (week 28 and the third month after the birth) can cause nausea
- None of the other examinations have discomforts or risks beyond what is normal when taking blood tests

- When taking blood tests of children at six and ten years of age, they can have a local anaesthetic salve applied to their skin

# Chapter B – Personal data security, biobank, financing and insurance

## Personal data security

Information that will be registered about you includes medical-record information from the health card for pregnant women, from the hospital medical records for the mother and child in connection with the pregnancy and birth, collected by authorised health personnel, from the interview about diet and physical activity and results from all collected readings and blood and urine tests. For the child, this will be information from the hospital concerning the birth and the immediate post-natal period, and health clinic data on breastfeeding, increase in weight and supplemental examinations on diet, physical activity and blood tests at six and ten years of age. To find out more about the health consequences of physical inactivity, being overweight and diabetes and the later health of mother and child, especially why some develop diabetes and cardio-vascular disease, we want to compile information about these diagnoses from your medical records from your regular GP and the hospital where you are being treated, and to connect the information from the "STORK Groruddalen" project with data from the Norwegian Patient Register, the Norwegian Diabetes Register for Adults, the Prescription Register, the Causes of Mortality Register and the Medical Register of Births. Anyone who is allowed access to this information is bound by the duty of confidentiality. Information about the father's health and any prevalence of cardio-vascular disease and diabetes in the family will also be collected. To be able to follow you and your child's medical development over a long period of time, the information and test results will not be deleted until 2030. The managing director at Aker University Hospital is responsible for the data processing in the study.

## Material and information given to other institutions etc.

If you agree to participate in the study, you are also consenting to the possibility that the information and test results, which have been made anonymous, can be stored and processed by various researchers and cooperation partners connected to the project, in Norway and abroad. This is necessary if we are to fulfil the purpose of the study. We will place the same strict requirements for protection of information on our cooperation partners, including those in countries which do not have as strong legal protection of personal information as Norway.

## Biobank

The blood and urine tests and tissue from the placenta and information derived from this material will be stored in a research biobank at Aker University Hospital. If you agree to participate in the study, you are also consenting to putting the biological material and the results of the analyses in the biobank. Kåre Birkeland, Prof. dr. med., is responsible for the biobank. The plan is to maintain the biobank until 2030. After this, the material and the information will be destroyed in accordance with internal guidelines.

## Right of access to and deleting of information about you and deleting test results

If you agree to participate in the study, you have the right to see which information has been registered about you. You also have the right to correct any mistakes in the registered information. If you choose to withdraw from the study, you can demand that the collected test results and information be deleted, unless the information has already been used in the analyses or used in scientific publications.

## Financing, the role of the head of the project and insurance

The study and the biobank are financed by research funds from the Research Council for the South-east Health Region. Later we will be able to apply for other funds from the pharmaceutical industry. The head of the project has no personal financial interests in the project. The Norwegian System of Compensation to Patients applies to participation in the study.

## Consent to participate in the study

I am willing to participate in the study

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(Signed by the project participant, date)

I confirm that I have informed the person in question about the study

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(Signed, role in the study, date)