Effects of iodine supplementation in mild-to-moderately iodine-deficient pregnant women on thyroid function, pregnancy outcomes and newborn development in Thailand

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Thesis

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To my beloved parents

Choochart and Korbkul

and three sisters

Chutima, Chidchom, Sompong

their support always encouraged me

ABSTRACT

Background: Iodine deficiency (ID) during pregnancy has been recognized as a major cause of hypothyroidism and adverse health consequences in both mothers and children. Although urinary iodine concentration (UIC) in school-aged children is recommended as an indicator to assess ID in the general population, it may not be a good surrogate for directly assessing iodine status in pregnant women. Iodine supplementation of mildly iodine-deficient pregnant women has been recommended worldwide; however, long-term benefit and safety of iodine supplementation in this group is uncertain. Finally, pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) may negatively affect thyroid function and pregnancy outcomes.

Objectives: 1) to measure UIC in pairs of pregnant women and their school-aged children living in the same household; 2) to investigate the effects of iodine supplementation on maternal thyroid function, pregnancy and birth outcomes, and newborn development; 3) to evaluate the association between pre-pregnancy BMI and GWG with thyroid function and pregnancy outcomes.

Methods: 1) In a cross-sectional pilot study, UIC was measured in spot urine samples from pairs (n=302) of healthy pregnant mothers and their school-aged children in Bangkok; 2) A randomized controlled trial was conducted with 200 μg iodine per day or placebo given to mildly ID pregnant Thai women from <14 weeks to term. Anthropometrics, maternal thyroid function, UIC and thyroid volume were measured at baseline, 2nd and 3rd trimester, at delivery and 6-week postpartum. Birth outcomes were collected from hospital records. Neonatal thyroid function, UIC and thyroid volume were measured at delivery and 6 weeks after birth. The Neonatal Behavioral Assessment Scales (NBAS) was used to assess newborn development.

Results: 1) In the pilot study, median UIC in the pregnant women was 108 (11–558) μg/L and was lower than UIC in their school-aged children [200 (25–835) μg/L] (P<0.001); 2) In the RCT, median UIC increased significantly from baseline in both groups, and the increase was higher in the iodine group (p<0.001). At 30 weeks of gestation, only 2% of the women in the placebo group and 7% in the iodine group reported a median UIC >500 μg/L. Maternal thyroid function, thyroid volume and the prevalence of all thyroid dysfunction subtypes did not differ significantly between treatment groups during the study (p>0.05). At 6-week postpartum, the prevalence of postpartum thyroiditis (hyperthyroidism) was significantly lower in the iodine group (3%) as compared to the placebo group (9%) (OR: 95%CI, 0.17: 0.04-0.70). There were no significant differences between newborn groups in thyroid function, thyroid volume, birth characteristics, UIC and NBAS score (p>0.05); 3) Pre-pregnancy BMI was a negative predictor of free thyroxine (fT4) (β=-0.20, P<0.001) in early gestation (<14 weeks). Compared to normal weight women, the prevalence ratio (95% CI) of a low fT4 in overweight women was 3.64 (2.08–6.37) (P<0.01). In addition, secondary data analysis showed that overweight women had an 11-fold higher risk of delivering a large for gestational age infant compared to normal weight women, while women who had excessive GWG were 5.6 times more likely to deliver a macrosomic infant compared to women with normal GWG.

Conclusion: 1) UIC in school-aged children should not be used as a surrogate for monitoring iodine status in pregnancy; 2) iodine supplementation (200 μg/d) in mildly iodine-deficient pregnant Thai women was effective in increasing iodine intakes into the adequate range but had no benefit on antenatal maternal thyroid function or newborn outcomes out to 6 weeks; however, it significantly reduced the risk of maternal postpartum thyroid dysfunction; 3) excess maternal body weight both before and during pregnancy may have adverse impacts on maternal thyroid function as well

as birth weight. Therefore, maintaining normal body weight before and throughout pregnancy should be recommended.

CONTENTS

Chapter 1

Introduction

Background

Iodine deficiency (ID) is a global public health problem and it is estimated that almost two billion individuals have an insufficient iodine intake (1). Currently, severe ID is uncommon, but mild-to-moderate ID is still widespread on a global level including Europe, Africa, Latin America and Asia (1). Iodine deficiency can lead to multiple adverse effects on growth and development in all age groups especially in pregnant women who have the highest daily iodine requirement. Children born in iodine deficient areas are at risk of neurological disorders and mental retardation because of the combined effects of maternal, fetal, and neonatal hypothyroxinemia (2). For nearly all regions affected by ID, salt iodization is the most cost-effective way of delivering iodine and improving cognition. In some areas, iodization of salt may not be practical for control of ID; in those cases iodine supplementation as KI or KIO_3 tablets or oil are recommended. In 2005, 49% of mild ID and 25% of moderate ID was reported in pregnant Thai women (3). Several studies of iodine supplementation in pregnant women with mild-to-moderate ID have been published and summarized. It can be concluded that iodine supplementation improved urinary iodine concentration and lowered thyroid gland volume in the iodine supplemented group (4). However, all of these studies had small simple sizes and none of the studies reported a clear amelioration on maternal thyroid function. Therefore, the benefits and safety of iodine supplementation in pregnancy in areas of mild ID remains controversial (5,6).

The research that is described in this thesis focuses primarily on the effects of daily iodine supplementation in mild-to-moderately iodine-deficient pregnant Thai women on thyroid function, pregnancy outcomes and newborn development.

Iodine characteristics and metabolism

Iodine is an essential micronutrient that forms a vital component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3), which are crucial regulators of the metabolic rate and physical and mental development in humans. Dietary iodine is

absorbed efficiently in the gastrointestinal tract and converted mostly to iodide before absorption. In healthy adults, the absorption of iodide is greater than 90% (7). Unlike the majority of trace elements, iodide in the blood does not appear to be bound to plasma protein and is available for uptake by all the tissues of the body. The majority of the circulating iodide (~80%) is rapidly taken up by the thyroid gland, but significant amounts are also accumulated by the salivary glands, choroid plexus and the lactating mammary gland. Uptake of iodide by all of these tissues employs a similar mechanism utilizing a sodium/iodide symporter, which is stimulated by the thyroid stimulating hormone (TSH) released from the pituitary gland. Total body iodine levels are 15-20 mg in the body of healthy adults, of which 70-80% is in the thyroid (8). Once the iodine requirements for thyroid hormone production have been met, excess circulating iodide is removed from the blood by the kidney and excreted in the urine.

Iodide is taken up from the circulation by the follicle cells of the thyroid and passes into the inner colloidal space where it is rapidly oxidized to iodine (I_2), by thyroid peroxidase, and reacts with the thyrosin residues on thyroglobulin (Tg), a large glycoprotein, to produce monoiodotyrosin (MIT) and diiodotyrosin (DIT). These two precursors can condense to form the thyroid hormones triiodothyronine (T3) and thyroxine (T4) (9). These remain bound to Tg and are stored within the colloid until the thyroid is stimulated by TSH, whereupon Tg is taken up by the follicle cells and active T3 and T4 are liberated by lysosomol enzymes which are subsequently released into the circulation. The half-lives of T4 and T3 in the circulation are approximately one day for T3 and seven days for T4. Degradation of T4 and T3 in the periphery, releases iodine that enters the plasma iodine pool and can again be taken up by the thyroid or excreted by the kidney (10). The iodine pathway in the thyroid cell is presented in **Figure 1.1** (11).

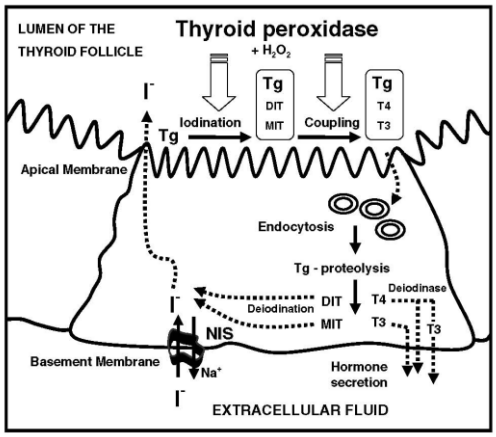


Figure 1.1 Iodine pathway in the thyroid cell

Iodine and brain development

The thyroid gland secretes mainly two iodinated products, triiodothyronine (T3) and thyroxine (T4). Triiodothyronine is the active form of thyroid hormone, and acts in the brain by binding to specific intracellular receptors which are proteins located in the cell nucleus associated to DNA. The receptors are ligand-dependent transcription factors that modulate the rate of transcription of the target genes (12). Conversion of T4 to T3 requires the action of specific cellular enzymes. In situations where the T4 supply is low,there is an increase in the efficiency of T4 to T3 conversion in the brain, together with a decrease in the periphery. This regulatory mechanism tends to increase T4 availability to the brain and T3 production from its precursor. These mechanisms are very important since ~80% of brain T3 is generated locally from T4 (13).

Human fetal thyroid ontogeny begins at 10-12 weeks of gestation and continues to develop until delivery. However, during early gestation, fetal thyroid hormone requirement is dependent on maternal supply. Timing of expression of T3 receptors during development has given some insight into when the brain becomes sensitive to thyroid hormones. In the human fetal brain the receptors are already present at the end of the first trimester of pregnancy before full development of the thyroid gland (14). During the second trimester, the human fetal brain receptors are already occupied by

the hormone, which is not the case for the receptors in other tissues, such as lung and liver. This suggests that maternally-derived T4 could reach the fetal brain and be converted locally to T3. Thus it is very likely that maternal hormone can influence fetal brain development during the second trimester of pregnancy and that therefore severe maternal hypothyroxinemia is a causative factor in the genesis of neurological cretinism (15). The role of the fetal thyroid gland is important from the third trimester of pregnancy onwards (13).

Recommended dietary allowance of iodine

The recommended dietary allowance (RDA) of iodine per age group is 50 µg/day from 0 to 6 months, 90 µg/day from 6 months to 6 years, 120 µg/day from 7 to 10 years, 150 µg/day during adolescence and adulthood, and 250-300 µg/day during pregnancy and lactation (16). The Institute of Medicine (IOM) of the US Academy of Sciences recommends a somewhat lower iodine intake of 220 µg/day for pregnant women (17).

The requirement of iodine is increased during pregnancy because of at least three factors: 1) the requirement of T4 in order to maintain a normal global iodine metabolism in the mother increases by 10 to 150% during pregnancy; 2) transfer of T4 from the mother to the fetus, before and after the onset of fetal thyroid function; it has been estimated that up to 40% of the T4 measured in cord blood at birth is still of maternal origin. The transfer of iodide is difficult to quantify but considering that the iodine content of the fetal thyroid increases progressively from less than 2 µg at 17 weeks of gestation up to 300 µg at term, it can be estimated that the transfer of iodide from mother to fetus represents some 50 µg/day; 3) an increased loss of iodide through the kidney due to an increase in the renal clearance of iodide (18).

Dietary sources of iodine

The amount of iodine found in most natural foods is typically quite small and varies depending on environmental factors such as the soil concentration of iodine, the use of

Table 1.1 Iodine content in Thai foods (µg/100 g edible portion)

Food items	Iodine content
Cereals	
Rice, unpolished	16
Glutinous rice	12
Vegetables & Fruits	
Chinese cabbage	6
Pumpkin	4
Cauliflower	3
Cabbage	4
Carrot	12
Seaweed, dried	350
Banana	7
Fig	11
Meat	
Chicken, cooked	19
Beef, meat, cooked	17
Pork, meat, cooked	16
Dwaref prawn	129
Catfish, dried	67
Giant seaperch	51
Mackerel, steamed	48
Anchovy	12
Splendid squid	15
Egg	
Egg, hen	12
Egg, duck	15
*Milk and products**	
Milk, whole, pasteurized	10
Milk, whole, UHT	7
Milk, low fat, pasteurized	6
Milk, low fat, UHT	13
Yoghurt, cream	20

** µg iodine/100 ml.*

Source: MOPH Thailand, 2001

fertilizers and livestock feed. Some of the richest food sources of iodine are often processed foods that contain iodized salt, and breads that contain iodate dough conditioners. Foods of marine origin have higher iodine content because marine plants and animals concentrate iodine from seawater. Major dietary sources of iodine in the USA and Europe are bread and dairy products (19,20). Boiling, baking, and canning of foods containing iodated salt cause only small losses (≤10%) of iodine content (21). In 2001, iodine content in Thai foods was reported in the Table for Thai Food Composition (22); some examples for frequently consumed Thai foods are shown in **Table 1.1**.

Iodine status assessments

Assessment of iodine status in populations living in areas at risk of ID is based on a number of methods. The size of the thyroid can be measured by palpation or by ultrasound; subsequently the number of goiters can be classified in accordance with WHO/UNICEF/ICCIDD guidelines. Urinary iodine concentration (UIC) can be measured by a simple colorimetric assay. Neonatal levels of TSH in the serum are used routinely in most developed countries to give an indication of congenital hypothyroidism. ID indicators and their cut-off levels are summarized in **Table 1.2**.

Table 1.2 Iodine deficiency indicators*

Iodine deficiency	None	Mild	Moderate	Severe
Iodine intake, *μg/d*	≥100	50-99	20-49	<20
Median urinary iodine, *μg/L*	>100	50-99	20-49	<20
Goiter prevalence	<5%	5-19.9%	20-29.9%	≥30%
Neonatal TSH >5 IU/mL whole blood	<3%	3-20%	20-40%	>40%
Cretinism	0	0	+	+

** Adapted from the World Health Organization (WHO) / United Nations Children's Fund (UNICEF)/ International Council for Control of Iodine Deficiency Disorders (ICCIDD).*

However, each of the indicators mentioned in **Table 1.2** have limitations. Urinary iodine is an indicator of recent iodine intake but not of thyroid function. The median UIC in school-aged children is recommended as a proxy for assessment of iodine nutrition in a population as a whole, but it still needs to be proven if UIC in school children also

reflects iodine status of pregnant women. Thyroid size decreases only slowly after iodine repletion, and therefore goiter incidence may remain high for several years after introduction of iodized salt. TSH is a sensitive measure of iodine status, but only in newborns (16).

Thyroglobulin is a thyroid-specific protein that is a precursor in the synthesis of thyroid hormone. Stimulated by TSH, transcytosis of Tg-containing endosomes across the thyrocyte results in small amounts of Tg being released into the blood (23). Tg concentrations can be measured in serum with commercially available assays, which requires venipuncture, centrifugation, and the transport of frozen samples, which may be difficult in remote IDD-affected areas (24). Therefore, measurement of Tg concentrations in dried blood spots collected on filter paper has been developed and used for many years. This method offers the following advantages: 1) sample collection is relatively painless and less invasive; 2) blood spot samples do not need to be centrifuged, separated, and immediately frozen following collection; and 3) these samples remain stable in laboratory freezers for long periods of time. Recently, international reference data of DBS-TG have become available from iodine-sufficient children (25), but such data for pregnant women in mild-to-moderately iodine-deficient populations are not available.

In 2008, Zimmermann et al (26) summarized indicators of iodine status by age group including advantages and disadvantages, as shown in **Table 1.3**.

Iodine deficiency disorders

Like other trace elements, iodine intake should be within a normal range. Either deficiency or excess will lead to metabolic disturbances. The adverse consequences of ID on growth and development are collectively known as iodine deficiency disorders (IDD) (27). ID is the leading preventable cause of brain damage and mental retardation worldwide. The most severe condition associated with ID is neurological cretinism, characterized by mental retardation, deaf mutism, and severe neurological deficits (27).

Table 1.3 Indicators of iodine status by age group

Indicators	Age group	Advantages	Disadvantages
Urinary iodine concentration (μg/L, median)	School-aged children, Adults, and pregnant women	Spot urine samples are easy to obtain Low cost External quality control program in place	Not useful for individual assessment Assess iodine intake only over the past few days Meticulous laboratory practice needed to avoid contamination Sufficiently large number of samples needed to allow for varying degrees of patient hydration
Goiter rate by palpation (%)	School-aged children	Simple and rapid screening test Needs no specialized equipment	Specificity and sensitivity are low because of a high interobserver variation Responds only slowly to changes in iodine intake
Goiter rate by ultrasound (%)	School-aged children	More precise than palpation Reference values established as a function of age, sex, and body surface areas	Need expensive equipment and electricity Operator needs special training Responds only slowly to changes in iodine intake
TSH (mU/L)	Newborn babies	Measures thyroid function at particularly susceptible age Minimum costs if congenital hypothyroidism screening program is already in place Heel-stick method to obtain sample, and storage on filter paper is simple	Not useful if iodine antiseptics used during delivery Needs standardized sensitive assay Should be taken by heel-prick at least 48 h after birth to avoid physiological newborn surge
Serum or whole blood thyroglobulin (μg/L)	School-aged children, and adults	Finger-stick approach to obtain sample, and storage on filter paper is simple International reference range available Measures improvement in thyroid function within several months after iodine repletion	Expensive immunoassay Standard reference material is available, but needs validation

However, even moderate forms of ID may lead to a certain degree of mental retardation. It has been a significant public health problem in more than 118 countries with about 1.6 billion people at risk globally. Most populations at risk of IDD are concentrated in Asia, Africa, Latin America and South America (28).

In 2008, WHO reported the number of countries, proportion of population, and estimated number of individuals with insufficient iodine intake in school-aged children and in the general population, by WHO region (**Table 1.4**) (29).

Table 1.4 Number of countries, proportion of population, and number of individuals with insufficient iodine intake in school-aged children (6-12 years) and in the general population (all age groups), by WHO region, 2007

WHO region[a]	Countries (no.)	Insufficient iodine intake (UI<100 µg/L)			
		School-aged children		General population	
		Proportion (%)	Total no. (million)[b]	Proportion (%)	Total no. (million)[b]
Africa	13	40.8	57.7	41.5	312.9
Americas	3	10.6	11.6	11.0	98.6
SE Asia	0	30.3	73.1	30.0	503.6
Europe	19	52.4	38.7	52.0	459.7
Eastern Mediterranean	7	48.8	43.3	47.2	259.3
Western Pacific	5	22.7	41.6	21.2	374.7
Total	**47**	**31.5**	**266.0**	**30.6**	**2,008.8**

a. 193 WHO Member States

b. Based on population estimates in the year 2006 (2004 revision)

Source: de Benoist, 2008

From **Table 1.4**, the iodine intake of 31.5% (266 million) of school-aged children worldwide is insufficient. Iodine intake is below requirements in 73 million children in South-East Asia and in 57.7 million children in Africa. In the European, Eastern Mediterranean, and Western Pacific regions, the figure is approximately 40 million children, whereas in the Americas, 12 million children do not have enough iodine in their diet. The greatest proportions of children with inadequate iodine intake live in the

regions of Europe (52.4%) and the Eastern Mediterranean (48.8%), and the smallest proportions are found in the Western Pacific (22.7%) and the Americas (10.6%). Extrapolating from the proportion of school-aged children to the general population, it is estimated that 2 billion people have an insufficient iodine intake (29).

Currently, in 2012, the global and regional iodine status has been updated again by Andersson et al (1). The authors concluded that the global iodine situation has markedly improved over the past decade and the number of iodine-deficient countries decreased from 54 in 2003 to 32 in 2011. However, 1.88 billion people of the world, including 241 million school-aged children, are still living with ID.

Iodine deficiency disorders (IDD) in Thailand

IDD have been recognized as one of Thailand's critical public health problems for many years. In the early 1950s, surveys in the north of Thailand showed a high prevalence of endemic goiter, identifying a defined 'goiter belt'. The goiter rate was found to be as high as 58% in the north, and a level of 15-21% was later reported in the northeast (30,31). In 1965, a pilot project on salt iodization was implemented in the endemic area (Phrae province in the north). The production capacity was 20,000 tons per year. As a result, the goiter rate declined and salt iodization was expanded to a national program in 1968.

In 1995, the Thai government and UNICEF made an agreement to accelerate activities to achieve the mid-decade goal of eradicating IDD in Thailand (32). Activities launched in each area depended upon severity mapping and targeting of households of schoolchildren, pregnant women and women of childbearing age (33). The cyclic monitoring of UIC in Thai pregnant women has been conducted since 2000 in all provinces within 5 years (15 provinces/year) except for Bangkok. A systematic random sampling method was used to collect 300 urine samples/province/year. In 2005, the Ministry of Public Health (3) reported data on ID in pregnant women from the 1st cyclic

monitoring program (**Table 1.5**). From 2000 to 2004, the percentage of mild and moderate ID increased from 34.4% to 49.4% and from 14.9% to 25.5%, respectively.
In 2011, the Ministry of Public Health (34) presented UIC data of Thai pregnant women from the 2nd cyclic monitoring program which was conducted in 2006-2010 (**Table 1.6**). Although, the positive results both of median UIC of pregnant women and percentage of ID were noted, however, the ID problem in this population still persisted.

Table 1.5 Iodine deficiency in Thai pregnant women by region (1st cyclic monitoring program)

Region	% ID									
	2000		2001		2002		2003		2004	
	<50 µg/l	<100 µg/l	<50 µg/l	<100 µg/l	<50 µg/l	<100 µg/l	<50 µg/l	<100 µg/l	<50 µg/l	<100 µg/l
North	12.9	29.7	12.5	35.9	16.6	40.3	21.6	47.2	26.4	50.0
NE	26.5	51.9	34.1	56.9	33.0	51.8	33.7	57.3	34.9	58.0
Central	11.1	32.6	20.4	49.5	22.5	46.5	16.4	43.1	23.6	51.6
South	7.9	22.4	12.6	36.7	-	-	7.5	25.3	11.0	29.4
Total	**14.9**	**34.4**	**19.7**	**45.2**	**24.4**	**47.0**	**20.9**	**44.5**	**25.5**	**49.4**

Source: MOPH Thailand, 2005

Table 1.6 UIC of Thai pregnant women by region (2nd cyclic monitoring program)

Region	Urinary iodine concentration (µg/L)*									
	2006		2007		2008		2009		2010	
	Median	< 150 (%)	Median	< 150 (%)	Median	< 150 (%)	Median	< 150 (%)	Median	< 150 (%)
North	92.5	66.5	106.5	64.1	133.4	55.3	117.7	57.0	229.5	34.6
NE	61.1	75.9	95.9	61.3	104.6	64.6	97.7	72.7	122.5	59.6
Central	84.4	73.3	88.5	71.2	118.1	61.6	117.7	58.4	196.3	38.6
South	101.0	68.0	177.4	43.3	138.4	53.5	164.0	50.0	217.2	34.7
Total	**82.5**	**71.8**	**108.2**	**61.3**	**125.5**	**58.5**	**117.8**	**59**	**178.4**	**42.6**

** percentage of median UIC<150 ug/L; if >50% indicating as ID area*
Source: MOPH Thailand, 2011

In 2013, the latest UIC information of pregnant Thai women was collected (35). The survey was conducted in 2012 and covered all provinces of the country. The report showed that there were 31 provinces out of 77 provinces in Thailand reported pregnant

women had median UIC <150 μg/L and 46.4% of this population living with mild-to-moderate ID.

Furthermore, Rajatanavin (36) reported data on the relationship between the concentration of TSH in whole blood or serum from neonates and the concentration of iodine in their mother's urine collected at birth. In 2000, paired samples of cord serum and urine were collected from 203 infants and their mothers at Ramathibodi hospital, Bangkok. In 2002-2003, 1,182 of DBS samples from a heel prick of infants and urine samples of their mothers in six rural provinces were collected. Iodine was measured in the mothers' urine and TSH was measured in blood samples. The UIC of mothers in rural Thailand was adequate, with a median of 103 μg/L but the median UIC of mothers in Bangkok was only 85 μg/L. With regard to TSH values, 31% of neonates had a TSH concentration >11.2 mIU/L, which was in the range of moderate ID. The authors concluded that the concentration of TSH in whole blood collected on filter paper from neonates was not sensitive enough to be used as a monitoring tool for iodine nutrition in the neonates, as there was no relationship with the concentration of iodine in the urine of mothers. In contrast, neonatal TSH screening using cord sera showed a significant relationship with the UIC of the mothers. Therefore, cord sera TSH can be used to assess iodine nutrition of the neonates.

It can be concluded from the information above that Thailand is still facing ID problems. Therefore, the Ministry of Public Health (MOPH) launched an IDD Elimination Program in order to combat this problem, with the following strategies:

1. Monitoring program (UIC among pregnancy): 1) during 2000-2010, cyclic monitoring program in all provinces within 5 years (15 provinces/year) except Bangkok; 2) since 2011, UIC monitoring program in all provinces yearly;
2. IDD surveillance system: 1) UIC of pregnant women and school children; 2) TSH concentration of newborns; and 3) household coverage of iodized salt;
3. Household coverage of iodized salt should be ≥90%;
4. Nutrition promotion in poverty zone (under the patronage of HRH MahaChakriSirindhorn);

5. Campaign of National Iodine Day (June 25).
   (http://nutrition.anamai.moph.go.th/temp/who/index.php?id_con=1)

In addition, in October 2010, during the intervention phase of the trial described in this thesis, MOPH launched a new iodine supplementation program for Thai pregnant women by using two types of daily prescribed iodine tablets: 1) triferdine150 (iodine, iron and folate); 2) Iodine GPO150 (only iodine) for pregnant women having thalassemia.

Iodine excess

Iodine excess is occurring more frequently during the last decade, particularly when salt iodine concentrations are too high or are poorly monitored (37). Various drugs and food preservatives contain a large quantity of iodide that is either absorbed directly or released after metabolism of the drug. High dietary iodine can also come from natural sources, such as seaweed in coastal Japan, iodine-rich drinking water in China, and iodine-rich meat and milk in Iceland from animals fed fish products. Iodophors contain large quantities of iodine and are used as udder antiseptics in the dairy industry, resulting in contamination of the milk with iodine (38).

The World Health Organization / International Council for Control of Iodine Deficiency Disorders (WHO/ICCIDD) cautioned that a median UIC >300 μg/L in school-aged children and UIC ≥500 μg/L in pregnant women are excessive (39). An increase in iodine intake in populations with chronic iodine deficiency might lead to iodine-induced hyperthyroidism (IIH). Symptoms of IIH include weight loss, tachycardia, muscle weakness, and skin warmth, without the ophthalmopathy of Graves' disease. This hyperthyroidism is nearly always transient, and the incidence reverts to baseline after 1-10 years of intervention. However, it is dangerous when superimposed on underlying heart disease, and might be lethal (40). In Thailand, there is no evidence that iodine excess is present.

Iodine nutrition and thyroid function during pregnancy

The importance of an adequate iodine status for maintenance of adequate thyroid hormone production in pregnancy has been described in the literature (41). The daily requirement of iodine for a normal adult is ~80 μg for thyroid hormone synthesis. Once the pregnancy takes place, there is a significant increase in renal iodide clearance by approximately 30-50%, and consequently the daily need for iodide increases from 80 to 120 μg in order to sustain an increase of thyroid hormone production by 50%.

Concerning the changes of thyroid hormone concentrations during pregnancy, three phenomenons have been described (42). First, from early gestation until term, the rapid and marked rise in serum thyroxine-binding globulin (TBG) levels, under the influence of elevated estrogen concentrations, is accompanied by a reduction trend in free T4 (fT4) and free T3 (fT3) concentrations. Second, an increase of human chorionic gonadotropin (hCG) concentrations results in lower serum TSH concentrations during the first trimester. The possible explanation for this phenomenon is that hCG shares a common alpha subunit with TSH but has a unique beta subunit, so that hCG can bind to the TSH receptor on the thyroid cell membrane and acts as a TSH agonist (43,44). Third, three enzymes including type 1 monodeiodinase (MID-1), type 2 monodeiodinase (MID-2), and type 3 monodeiodinase (MID-3) catalyze the deiodination of thyroid hormones in human tissues. This enzymatic activity especially MID-3 may explain the increased T4 turnover of maternal origin and also the low T3 / high reverse-T3 pattern during pregnancy.

Maternal ID and pregnancy outcomes

Hypothyroidism is a condition in which the thyroid gland does not make enough thyroid hormone and the most common cause of hypothyroidism worldwide is iodine deficiency. Several studies have reported that maternal hypothyroidism is associated with increased risks of abortions, stillbirths, congenital malformations, pregnancy-induced hypertension, postpartum hemorrhage and fetal distress (45-48).

In 2003, Blazer et al (49) compared the results of serum TSH and fT4 levels, birth weight and head circumference between the newborns born to hypothyroid mothers (n=246) and control newborns from healthy mothers (n=139). Early neonatal serum TSH and fT4 levels were both significantly higher in a large subgroup of infants of hypothyroid mothers as compared to control neonates ($p<0.001$). The newborns of the hypothyroid study group were relatively smaller at birth and had a relatively smaller head circumference than the normal control newborns ($p<0.001$). This finding confirmed a study published in 1999, when Haddow et al (50) showed that infants of untreated hypothyroid mothers had a higher birth weight than controls, but this was not statistically significant.

The association between subclinical hypothyroidism and adverse pregnancy outcomes in 17,298 Texan women was evaluated by Casey et al (51). Thyroid function tests were performed at or before the 20th week of gestation, and women were followed prospectively to determine pregnancy outcomes. Preterm delivery, defined as gestational age less than or equal to 34 week at delivery, was almost 2-fold significantly increased in women with subclinical hypothyroidism compared with the controls ($p<0.05$). Also, a significant 3-fold increase in the incidence of placental abruption was reported in women in the subclinical hypothyroid group compared with the healthy controls ($p<0.05$). In addition, related to these findings, admission to the neonatal intensive care nursery and respiratory distress were twice as likely in infants delivered by women with subclinical hypothyroidism (RR: 1.8, 95% CI: 1.1–2.9 and 1.0–3.3, respectively). On the other hand, women who had a fT4 below 0.86 ng/dL and a TSH concentration in the normal range (isolated hypothyroxinemia), had no adverse perinatal outcome (52).

Maternal ID and infant development

Combined maternal and fetal hypothyroidism occurs mostly in regions with dietary ID. The most severely affected infants have neurologic cretinism, manifested by mental retardation (mean IQ ~29) and impaired gait and motor function (53). Whereas children from these areas may have normal school performance, impaired motor and

visual perceptive abilities have been reported (54). These abnormalities have been associated with maternal T4, but not T3 levels during pregnancy (55). In recent years the potential impact of mild to moderate ID on the fetus has been recognized. Effects on the mother and fetus include thyroid enlargement and an increase in serum Tg. Although the mother also may have relative hypothyroxinemia, the fetus maintains normal fT4 and TSH (56). However, school achievement may be impaired, and a variety of neuropsychointellectual deficits have been described (2).

Presumably, all degrees of ID affect thyroid function of the mother and the neonate as well as the mental development of the child. The damage increases with the degree of the deficiency, with overt endemic cretinism as the severest consequence (57). In a cross-sectional study in the USA (50), children of women (n=62) with high serum thyrotropin concentrations averaged 4 points lower on the Wechsler Intelligence Scale for Children than children of matched control women (n=124) (p=0.06); 15 percent of children from mothers with high thyrotropin concentration had low scores as compared with 5 percent of the matched control children.

Pop et al (58) reported a neurodevelopment assessment at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Children of women with fT4 levels below the 5th and 10th percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Development Index (PDI) scale, compared to children of mothers with higher fT4 values. After correction for confounding variables, a fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psychomotor development (RR: 5.8, 95% CI: 1.3-12.6).

In addition, in a prospective 3-year follow-up study of pregnant women and their children up to the age of 2 years (59), child development was assessed by means of the Bayley Scales of Infant Development. Children of women with hypothyroxinemia (fT4 <10th percentile) at 12 weeks' gestation had delayed mental and motor function compared to controls (children of women with fT4 between the 50th and 90th

percentile). In addition, improvement of fT4 concentrations during the 2nd and 3rd trimester of pregnancy of case mothers led to similar development scores as compared to controls.

In 2006, Kooistra et al (60) reported an examination of the neurobehavioral profile of neonates who are born to women with hypothyroxinemia by using the Neonatal Behavioral Assessment Scale (NBAS) at 3 weeks of age. Infants who were born to women with first-trimester fT4 concentrations $\leq 10^{th}$ percentile (n=108) had significantly lower scores on the NBAS orientation index than children of mothers with high fT4 values (n=96). Similarly, regression analysis showed that first-trimester maternal fT4 but not maternal TSH or fT4 later in gestation was a significant predictor of orientation scores.

Iodine supplementation trials in pregnancy

Several randomized, controlled trials of iodine supplementation in pregnancy have been published, involving a total of 596 women with mild-to-moderate ID in Europe. These studies have been reviewed by Zimmermann et al (61) (**Table 1.7**). As can be seen in **Table 1.7**, none of the trials measured long-term clinical outcomes, such as maternal goiter or infant development. Therefore, the full impact of mild-to-moderate iodine deficiency during pregnancy remains unclear.

In 2009, two randomized trials were published investigating the effect of iodine supplementation in pregnant women. Berbel et al (62) recruited three groups of pregnant women living in Spain at different gestational ages. All women received 200 μg of iodine until the end of lactation. The Brunet-Lezine scale was used to estimate the neurobehavioral development of children at 18 months of age. The development quotient of children in mothers supplemented in the first group (4-6 weeks gestation, n=13) was significantly higher than that of children whose mothers received supplements from 12-14 weeks gestation (n=12; $p<0.05$) or near term (37-40 weeks gestation, n=19; $p<0.001$). The authors also concluded that a delay in maternal

Table 1.7 Summary of trials of iodine supplementation in pregnancy with mild-to-moderate iodine deficiency

Reference/ Year	Subject characteristics	Design	Treatment	Results (In treated group vs. control group)
Romano et al 1991 (65)	Moderate ID, treated n=17 control n=18	Randomized, double blind controlled trial	120-180 μg I_2 / day (iodized salt) 1st trimester to term	- No change in TSH level - Median UI 3-fold increase vs. no change - Thyroid size: no change vs. 16% increase
Pedersen et al 1993 (66)	Mild ID, treated n=28 control n=26	Randomized, double blind controlled trial	200 μg I_2 /day (KI solution) 17 wks to term	- No differences in maternal or cord T4, T3, and TSH - Median UI: 2-fold increase vs. no change - Thyroid volume: 16% increase vs. 30% increase
Gilnoer et al 1995 (67)	Moderate ID, treated n=60 control n=60	Randomized, double blind controlled trial	100 μg I_2/day, ~14 wks to term	- No effect on maternal or cord T3, fT4, and T3/T4 ratio - Maternal and newborns UI: higher vs. lower - Maternal and newborns thyroid volume: smaller volume vs. bigger volume - Maternal and newborns TSH, Tg: lower level vs. higher level
Liesenkötter et al 1996 (68)	Moderate ID, treated n=38 control n=70	Quasi-random, double blind controlled trial	230 μg I_2 /day 11 wks to term	- No effect on maternal TSH, T3, T4, thyroid volume, or Tg - No effect on newborn TSH - Median UI 2-fold increase vs. no change - Thyroid volume in newborns: lower volume (0.7 ml) vs. higher volume (1.5 ml)

Table 1.7 Summary of trials of iodine supplementation in pregnancy with mild-to-moderate iodine deficiency (cont.)

Reference/ Year	Subject characteristics	Design	Treatment	Results (In treated group and control group)
Nohr et al 2000 (69)	Moderate ID, TPO-Ab positive, treated n=42 control n=24	Placebo-controlled, randomized, double blind trial	150 μg I_2/day, 11 wks to term	- No differences in maternal TSH, fT4, Tg - No differences in prevalence of Tg-Ab, TPO-Ab - Maternal median UI: higher vs. lower - % developed PPTD: 60% vs. 46%
Nohr et al 2000 (70)	Mild-to-moderate ID, treated n=50 control n=96	Prospective trial (not blinded, randomized)	150 μg I_2/day, during pregnancy	- No differences in T3/T4 ratios (both mothers and neonates) - Maternal TSH, Tg: lower level vs. higher level - Maternal fT4: higher level vs. lower level - Neonates TSH: higher level vs. lower level
Antonangeli et al 2002 (71)	Mild ID, treated-A n=32 treated-B n=35	Prospective, randomized, open label trial	A: 200 μg I_2/day B: 50 μg I_2/day 18-26 to 29-33 wks	- No differences in maternal fT4, fT3, TSH, Tg, thyroid volume - No differences in TPO-Ab, Tg-Ab, prevalence of PPTD - Median UI significantly higher in group A than group B

iodine supplementation at the beginning of gestation increases the risk of neurocognitive development delay in their offspring. A second Spanish study conducted in an area of mild ID by Velasco et al (63) found that children of mothers (n=133) supplemented with 300 μg of iodine daily in the first trimester had higher Bayley Psychomotor Development scores than children from mothers who did not start supplementation (n=61) until the last month of pregnancy (p=0.02).

Recently, Murcia et al (64) assessed the association between maternal iodine intake from diet and supplements during pregnancy, maternal and neonatal thyroid function and infant development. In this pre-birth cohort from Valencia, Spain, the Mental Development Index (MDI) and Psychomotor Development Index (PDI) for 691 children were obtained between 2005 and 2007 using the Bayley Scales of Infant Development at 1 year of age. The authors reported that maternal UIC, iodized salt consumption, or dietary intake of food with high iodine content was not associated with infant development. In addition, maternal intake of ≥150 μg/day of supplementary iodine was associated with a decrease in PDI of 5.2 points (95% CI: 2.2-8.1) and with a 1.8-fold increase in the odds of a PDI<85 (95% CI: 1.0-3.3). Maternal hyperthyrotropinemia (TSH > 4 mIU/L) was related to an increased risk of a PDI<85 (95% CI: 1.3-9.5) and a decrease in PDI score (95% CI: -12.3-0.0).

Maternal overweight/obesity and pregnancy outcomes

The relationship between overweight/obesity and thyroid status in adults has been described. In 2003, Sari et al (72) reported an increase of serum TSH and a decrease of serum fT3 and fT4 concentration in obese women compared to normal weight women. Similarly, a positive association between BMI and serum TSH and a negative association between BMI and serum fT4, but no association in serum fT3 levels were found in the study of Knudsen et al (73). In a recent study (74), a higher TSH and lower fT4 concentrations in overweight adults as compared to normal weight adults was reported, and this confirmed that adiposity is associated with thyroid hypofunction. In pregnant

women, a higher maternal BMI was shown to be correlated with their fT3/fT4 ratio, but not with their fT4 concentration (75).

Although information of the relationship between maternal weight and thyroid function is limited, several studies reported that maternal obesity was associated with adverse pregnancy outcomes. Mothers who are overweight or obese during pregnancy are known to be at risk of various pregnancy complications including miscarriage, pregnancy induced hypertension (PIH), gestational diabetes, pre-eclampsia, macrosomia, preterm delivery, cesarean section and neural tube defects (NTDs) in newborns (76-82).

In Thailand, the prevalence of overweight and obesity of the general population is increasing, from 18.2% and 3.5% in 1991 to 36.5% and 9.0% in 2009, respectively (83). In a study among 3,715 pregnant women who delivered at Rajavithi hospital in Bangkok (84), the percentage of maternal overweight and obesity was 13% and 4%, respectively. Furthermore, the authors stated that the overweight and obese mothers had significantly higher risk for cesarean section, pre-eclampsia, diabetes mellitus, macrosomia and postpartum hemorrhage. However, no data have been reported on the association between maternal obesity and thyroid status in Thailand.

Rationale, study objectives and outline of the thesis

Iodine deficiency remains a major public health problem in many regions of the world especially in South/Southeast Asia. Several studies confirmed that all degrees of ID affect thyroid function of the mother and the neonate as well as the neurocognitive development of the child. Therefore, an effective strategy for ID correction is needed for this population. As shown in **Table 1.7**, effects of iodine intervention on thyroid function in mild-to-moderate ID pregnant women varied considerably. These studies showed primarily that iodine supplementation increased UIC, and decreased maternal thyroid volume, TSH and Tg concentrations.

Although, three recent studies also reported on the effect of iodine supplementation in mild-to-moderate ID pregnant women on neurodevelopment in their children, these studies were not randomized, double-blind, placebo-controlled trials. It was speculated that neurodevelopment in the child may be adversely affected by mild-to-moderate ID but they were certainly not definite.

Therefore, we set up two large RCT studies in Thailand and India in 2008 with a similar study protocol, aimed to determine the effects of daily oral iodine supplementation (200 μg) or placebo in pregnant women with mild-to-moderate ID on thyroid function, pregnancy outcomes and long-term (2 years) follow up of infant development (the MITCH study). In this thesis, only the study in Thailand is described and only short-term (6 weeks) infant follow up is reported.

We started by conducting a cross-sectional study to determine the iodine status of pregnant women living in Bangkok area and confirmed that the ID problem during pregnancy still existed. We, then performed a randomized, double-blind, placebo-controlled trial, involving oral administration of iodine in pregnant women recruited from the Outpatient Department (OPD) of Obstetrics and Gynecology at Ramathibodi Hospital, Mahidol University, a large teaching hospital in Bangkok.

Inclusion and exclusion criteria were the following:

Inclusion criteria:

- Pregnant women, aged 18-40 years old
- Gestational age ≤14 weeks
- Single pregnancy
- Non-lactating
- Generally healthy
- Not taking iodine supplement

Exclusion criteria:

- Hypothyroid (TSH concentration >6.0 mIU/L)

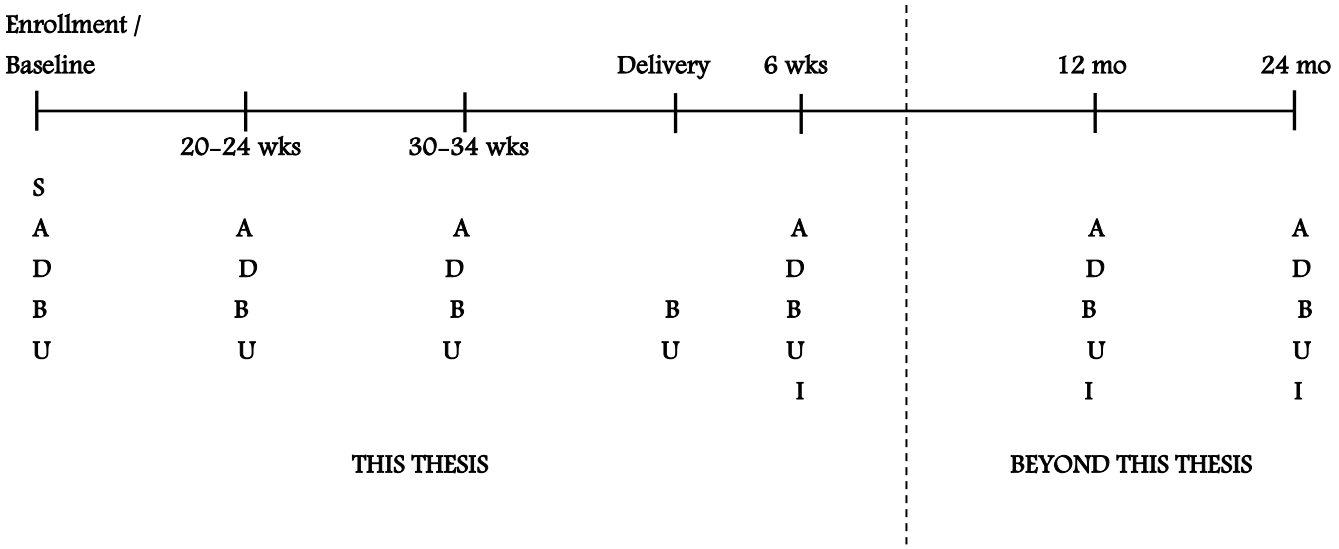
At the first hospital visit, all participants were fully informed about the aims and procedures of the study and written consent was obtained. All subjects were randomized into two treatment arms, with one treatment group receiving a daily supplement of 200 μg iodine (as potassium iodide tablets, donated by Merck KGaA, Darmstadt, Germany) until delivery, and the control group receiving an identical tablet without iodine (Merck KGaA, Darmstadt, Germany) until delivery. In addition, all pregnant women received multi-vitamin and -mineral tablets (without iodine) throughout the study.

Anthropometric measurements, blood and spot urine sample collection and thyroid gland volume measurement were performed in both mothers and newborns during the study period. For infants, the NBAS test was performed at 6-week postpartum in order to assess early infant development. A brief overview of the study design is presented in **Figure 1.2**.

Ethical approval for the study was obtained from the review committees of Ramathibodi Hospital, Mahidol University and Wageningen University. The study was registered into the clinical trials database at ClinicalTrials.gov with its identifier: NCT00791466.

In **Chapter 2**, we report on a pilot study in which the UIC of pregnant mothers is assessed and compared to the UIC of their school-aged children. In **Chapter 3**, we did a cross-sectional analysis with the baseline data of the trial to identify predictors of thyroid dysfunction in early pregnancy. In **Chapter 4**, we report the results of the MITCH study on maternal thyroid function, pregnancy outcomes and newborn development. In **Chapter 5**, we related pre-pregnancy BMI and maternal gestational weight gain to pregnancy outcomes. In the final chapter, **Chapter 6**, a summary of the main findings of the research conducted for this thesis is given, as well as a reflection on methodological considerations and opportunities for future research.

Control group (placebo tablets)
Iodine group (KI tablets, 200 μg iodine/d)



S = Socio-demographic information
A = Anthropometric measurement
D = Dietary assessment
B = Biological samples
U = Ultrasound
I = Infant development

Figure 1.2 Overview of the study protocol

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Chapter 2

Urinary iodine concentrations indicate iodine deficiency in pregnant Thai women but iodine sufficiency in their school-aged children

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Abstract

The median urinary iodine concentration (UI) in school-aged children is recommended for assessment of iodine nutrition in populations. If the median UI is adequate in school-aged children, it is usually assumed iodine intakes are also adequate in the remaining population, including pregnant women. But iodine requirements sharply increase during pregnancy.

In this study, our aim was to measure UI in pairs of pregnant women and their school-aged children from the same family, who were sharing meals, to directly assess whether a household food basket that supplies adequate iodine to school-aged children also meets the needs of pregnant women.

UI was measured in spot urine samples from pairs (n=302) of healthy pregnant mothers and their school-aged children in metropolitan Bangkok, Thailand. A dietary questionnaire was completed.

The UI [median (range)] in the pregnant women {108 (11–558) μg/L [0.85 (0.086–4.41) μmol/L]} were lower than those of their school-aged children {200 (25–835) μg/L [1.58 (0.20–6.52) μmol/L]} ($P<0.001$), indicating optimal iodine status in the children but mild-to-moderate iodine deficiency in their pregnant mothers. The estimated iodine intakes in the 2 groups were in the range of 130–170 μg/d. There was a modest positive correlation between UI in the pairs ($r=0.253$; $P<0.01$). A higher frequency of seafood meals was a significant predictor of UI in both groups, but household use of iodized salt was not.

These data suggest the median UI in school-aged children should not be used as a surrogate for monitoring iodine status in pregnancy in central Thailand; pregnant women should be directly monitored.

Introduction

Iodine deficiency causes a broad spectrum of adverse health effects that result from inadequate thyroid hormone production, termed the iodine deficiency disorders (IDD) (1,2). The fetus is particularly vulnerable and in utero iodine deficiency can cause irreversible cognitive and motor deficits (3,4). Iodine requirements sharply increase during pregnancy because of the transfer of iodine and thyroid hormone to the fetus, an increase in maternal needs for thyroid hormone, and a likely increase in maternal renal iodine clearance (4). Thus, recommended iodine intakes during pregnancy are 250 μg/d compared with 150 μg/d for nonpregnant women (1). The corresponding median urinary iodine concentration (UI) that indicates optimal iodine nutrition increases from 100–199 μg/L in nonpregnant women to 150–250 μg/L during pregnancy (1).

Although pregnancy is a critical time to optimize iodine and IDD monitoring should include pregnant women, measurements in school-aged children are often used for assessment of IDD in populations because of the vulnerability of children to iodine deficiency (5,6) and easy access in school-based surveys (1). Most national or subnational IDD surveys have been conducted in school-aged children (7) and if the median UI in school-aged children is 100–199 μg/L, it is generally assumed that all population groups, including pregnant women, have adequate iodine nutriture (1). However, recent cross-sectional surveys have suggested this assumption may not be valid (8–12).

To clarify this issue, measuring UI from pairs of pregnant women and their school-aged children from the same family would be valuable. The value of matched pairs within a family is that both groups share most meals from the same household food basket. Thus, a study of pairs can directly assess whether a diet that supplies adequate iodine to school-aged children also meets the needs of pregnant women in the household.

In Thailand, although ~66% of households use iodized salt, recent surveys have suggested iodine status in pregnancy may not be optimal (13). Therefore, our study

question was: if the median UI is adequate in school-aged children, can one assume the median UI is also adequate in pregnant women? If so, then the median UI in school-aged children could continue to be used as a surrogate for monitoring iodine status in pregnancy; if not, then pregnant women would need to be directly monitored.

Subjects and Methods

The study was carried out in Bangkok, Thailand and the surrounding metropolitan area. To recruit families with a range of socioeconomic backgrounds, pregnant women were consecutively recruited from 2 large antenatal clinics in central Bangkok (Ramathibodi Hospital and Rajavithi Hospital), a small district hospital (Putthamonthon Hospital), and in 3 factories in the city suburbs. We aimed to recruit a sample of 300 women and their children to assess iodine status in the 2 groups using spot urine samples (14). Inclusion criteria (assessed by self-report) were: 1) confirmed pregnancy; 2) in good general health without thyroid disorders, other chronic illnesses, or medications; 3) no history of iodine supplement use by the family; and 4) at least 1 child 5–14 y old living and sharing meals in the same household.

Once enrolled, the women completed a questionnaire that included: 1) age of mother and child; 2) sex of the child; 3) gestational age (at the hospital clinics, this was taken from the hospital record, based on the date of the last menstrual period; at the factories, this was by self-report from the mother); 4) parity; 5) monthly income of the family (this figure was used to estimate socioeconomic status); 6) number of meals shared with the child per day; 7) whether more salt or more fish sauce was used in the household (these 2 condiments are used widely in Thailand, but fish sauce is not iodized and only a portion of table salt is iodized); 8) estimated household consumption of salt; and 9) frequency of household seafood consumption per week: never, 1–2 times, 3–4 times, or >4 times.

A spot urine sample was collected from each woman at the clinic or the factory and from the child at the home. The samples were collected within 1–2 d of each other and

were obtained from the mothers and children at any time during the day. Data were collected from May 2007 to July 2008. Because the climate and the diet are fairly uniform in Bangkok year round, there was unlikely to be considerable seasonal variability in dietary sources of iodine. Informed written consent was obtained from all women and assent from their children. The Swiss Federal Institute of Technology Zurich, Switzerland and Mahidol University Hospital, Bangkok, Thailand reviewed and approved the study protocol.

Laboratory analyses. The urine samples were transported on ice to the Institute of Nutrition of Mahidol University, divided into aliquots, and stored at –20°C until analysis. At Mahidol, the iodine concentration in urine was measured using the Pino modification of the Sandell-Kolthoff reaction (15). The intra-assay CV at a mean UI of 72 and 242 μg/L (n=10 each) was 7.1 and 1.5%, respectively. External control was provided by the Laboratory of Human Nutrition at the Swiss Federal Institute of Technology Zurich using the same method and the inter laboratory CV (percent) at a mean UI of 100 μg/L and 212 μg/L (n=10 each) was 7.6 and 6.1%, respectively.

Data and statistical analyses. The statistical analyses were carried out using SPSS 16.0 and Microsoft Excel (XP 2002, Microsoft). The formula of the U.S. Institute of Medicine (16) was used to estimate iodine intakes from UI and body weight in the children:

UI (μg/L) x 0.0235 x body weight (kg) = daily iodine intake (μg)

Values in the text are means ± SD or, if not normally distributed, are medians (ranges). Because UI values in both women and children were skewed to the right, for both the primary and secondary outcomes, Mann-Whitney tests were used for comparisons with a Bonferroni correction, when needed. Proportions were compared using chi-square tests. We performed Spearman correlations to look for associations. In the Mann Whitney and Bonferroni tests, P-values <0.05 and <0.005, respectively, were considered significant.

Results

We recruited 302 pairs of pregnant women and their school-aged children; the refusal rate for participation in the study was <2%. The median UI, monthly income, and dietary variables comparing women recruited in the clinics to those recruited at the factories did not differ. Just over one-half of the women were in their third trimester and 77% of families reported using household salt labeled as iodized (**Table 2.1**). About 50% of the pairs shared 3 meals per day and 50% shared 1 to 2 meals per day. The median UI (range) in the pregnant women was 108 (11–558) μg/L and the median UI in their school-aged children was 200 (25–835) μg/L; these were significantly different (P<0.001). Whereas only 14.2% of the school-aged children had a UI value <100 μg/L, 69.2% of pregnant women had a UI value <150 μg/L (**Figure 2.1**). There was a modest positive correlation between the UI of pregnant women and their school-aged children (r=0.253; P<0.01) that was stronger in the 50% of women and children who shared 3 meals/d (r=0.426; P <0.001).

Using the formula of the U.S. Institute of Medicine (16) to estimate iodine intakes from UI and body weight in children 7–15 y old, a median of 200 μg/L in Thai children with a mean age of 7.7 y and a mean body weight at this age of ~26 kg (17) would correspond to a median iodine intake of ≈130 μg/d. Assuming a daily urine volume of 1.5 L and 92% dietary iodine bioavailability in the pregnant women, their median UI of 108 μg/L would correspond to a daily iodine intake of ~170 μg (16).

The median (range) UI of the pregnant women in the first, second, and third trimesters was 102 (19–506) μg/L, 122 (12–482) μg/L, and 106 (11–558) μg/L, with no difference in UI between trimesters (P=0.64). Maternal age and parity were not predictors of UI (P=0.45), nor was socioeconomic level of the family (P=0.49). The median UI in pregnant women and school-aged children who ate 0, 1–2, 3–4, and >4 seafood meals/wk were 58 and 157 μg/L, 107 and 201 μg/L, 110 and 228 μg/L, and 116 and 180 μg/L, respectively. The families who ate 1 or more seafood meals/wk had higher UI values in both pregnant women and school-aged children than in families that ate none

(P<0.05). The UI values comparing families who ate between 1 and >4 seafood meals/wk did not differ (P=0.24).

Table 2.1 Characteristics and dietary intake data of the matched pairs of Thai pregnant women and their school-aged children[1]

Variable	
Age, y	
Children	7.7 ± 2.8
Pregnant women	31.7 ± 4.8
Child's sex	
Male: female, n:n	54 : 46
Trimester of pregnancy, %	
1	24.5
2	25.2
3	50.3
Parity, %	
1	63.9
2	27.5
≥3	8.6
Use of iodized salt in the household, %	
Yes	77.2
No	16.8
Don't know	6.0
Use of salt, %	
For cooking	85.9
As condiment	10.4
Both uses	3.7

[1] *Values are mean ± SD, n=302 or percentages.*

Table 2.1 Characteristics and dietary intake data of the matched pairs of Thai pregnant women and their school-aged children[1] (cont.)

Variable	
Greater household consumption of, %	
Salt	31.6
Fish sauce	63.3
No preference	5.1
Household seafood consumption per week, %	
Never	3.6
1-2 times	54.2
3-4 times	28.6
>4 times	13.6
Meals shared by mother-child pair per day, %	
1	20.8
2	27.7
3	51.5

[1] *Values are mean ± SD, n=302 or percentages.*

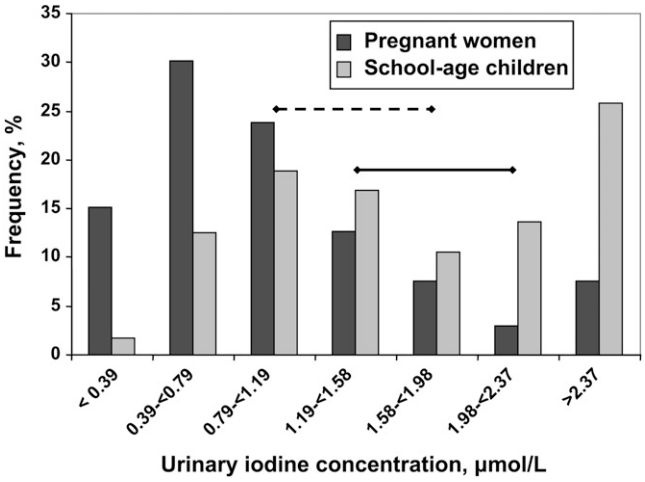

Figure 2.1 Frequency distribution of spot UI in matched pairs of Thai pregnant women and their school-aged children (n = 302).
The recommended ranges for the median UI for pregnant women and children are shown. 1 µg iodine/L = 0.0079 µmol/L.

UI concentrations did not differ between women and children from families who used iodized salt and those from families that did not (P=0.29), between women and children recruited at the hospital clinics and those recruited at factories (P=0.51), between women and children who consumed more salt and those who consumed more fish sauce (P=0.27), or between children who consumed all 3 meals at home with their mother and those who consumed 1 or 2 of their meals outside the home (P=0.38).

Discussion

Despite sharing a common household food basket, the median UI in our school-aged children was nearly double that of their pregnant mothers (P<0.001). According to the WHO criteria for assessing iodine nutrition, the median UI in our school-aged children (200 μg/L) indicated optimal iodine nutrition, at the top end of the recommended range (1). Additionally, in iodine-sufficient school-aged children, no more than 20% of UI values should be below 50 μg/L (1); in our children, only 2% had a UI value below this cut-off. Thus, both the median UI and the distribution show clear iodine sufficiency in school-aged children in the metropolitan Bangkok area. In sharp contrast, the median UI of 108 μg/L in pregnant women from the same households indicated a clear iodine deficiency (1). Approximately 1 in 6 pregnant women had a UI value <50 μg/L. These data support Thai surveys from the years 2001 to 2004, when the median UI in pregnant women declined from 150 to 110 μg/L (18).

Several recent studies have suggested suboptimal iodine status in pregnant women from areas with only partial household coverage with iodized salt, such as Italy, India, and the US (8–12). Our study confirms these previous findings and demonstrates a similar relationship within families eating from the same household food basket. In contrast, countries with long standing, successful iodized salt programs (China, Iran, and Switzerland) have reported an optimal median UI in pregnant women (19–23).

The most likely explanation for why Thai school-aged children (200 μg/L) had a sharply higher median UI than their pregnant mothers (108 μg/L) is that dietary iodine

intakes in both school-aged children and pregnant women are in the range of 130–170 μg/d. If so, the median UI concentration in primary school-aged children with smaller daily urine volumes would be higher than that of pregnant women with higher water intakes and greater urine volumes.

The median 24-h urine volume for children 7–15 y old is ~0.9mL/(h·kg) (24). Based on a mean body weight of 26 kg (17) at this age in our children, their 24-h urine volume would be ~600 mL. In contrast, the 24-h urine volume for adult women is ~1.5 L and is likely higher in pregnancy (25). Thus, dietary iodine intakes of ~130 μg/d are sufficient for the children and this will be reflected in a median UI >100 μg/L indicating adequate iodine intake (1). But their pregnant mothers would need to consume substantially more iodine-containing foods from the household food basket to attain their recommended iodine intake for pregnancy of 250 μg/d and thereby achieve the recommended median UI of >150 μg/L (1). However, we can only assume daily urine volumes varied between the women and children in this study, because we did not measure 24-h urine volumes and there are no available data from other comparative studies of children and pregnant women in Thailand.

Our findings suggest several ways that iodine intakes could be increased in Thai pregnant women. Thai iodized salt legislation recommends iodization of salt that is sold directly to the consumer, but it is not legally binding (18). The legislation could be modified to recommend iodization of salt used for food processing and specifically for fish sauce production (16,26). Regular consumption of seafood products (27), if not contaminated by heavy metals (28), should be encouraged during pregnancy. Alternatively, targeted iodine supplementation of pregnant women may be preferable in this setting.

There are several limitations to our study design. The use of iodized salt was self-reported rather than collected and directly tested by titration. The findings would be more convincing had a larger proportion of meals been shared between mothers and

their children and if additional biochemical measures of iodine status were measured in the pregnant women. Also, it would have been useful to have a nonpregnant control group to help ascertain whether lower UI concentrations during pregnancy could be attributed to pregnancy itself or to different dietary choices between adults and children in this population. Although we enrolled a sample of 300 women and their children to assess iodine status in the 2 groups using spot urine samples (14), this sample size may have not been adequate to make comparisons among subgroups of the populations, and this may have introduced a β error to some of the comparisons. Finally, this was a convenience sample and it is possible the sample was not representative of middle-income families in the region.

Our findings indicate that in this region of Thailand, the median UI in school-aged children may not be an adequate surrogate for monitoring iodine nutrition in pregnant women. These data need to be confirmed in other populations with varying dietary habits and iodine intake but suggest adequate monitoring of IDD in populations should include specific monitoring of pregnant women.

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Chapter 3

Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women

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Abstract

Hypothyroxinaemia early in pregnancy may impair fetal brain development. Increased body weight has been associated with low thyroxine concentrations in non-pregnant women. In pregnant women, morbid maternal obesity is a risk factor for thyroid dysfunction. But whether lesser degrees of overweight that are much more common could be a risk factor for hypothyroxinaemia in pregnancy is unclear.

The objective of this study was to investigate if overweight increases risk for thyroid dysfunction, and specifically hypothyroxinaemia, in iodine deficient pregnant women.

We performed a cross-sectional study at first hospital visit among healthy Thai pregnant women. We measured weight and height, urinary iodine concentration (UIC), serum thyroid hormones and thyroglobulin. Pre-pregnancy weight and relevant dietary factors were determined by questionnaire, and body mass index (BMI) was used to classify weight status.

Among 514 women (mean gestational age, 11 weeks) with a median UIC of 111 μg L^{-1}, indicating mild iodine deficiency, 12% had low free thyroxine (fT4) concentrations: 3% had overt hypothyroidism; 7% had subclinical hypothyroidism; and 8% had isolated hypothyroxinaemia. Based on pre-pregnancy BMI, 26% of women were overweight or obese. In a multiple regression model, BMI was a negative predictor of fT4 (β=-0.20, $P<0.001$). Compared to normal weight women, the prevalence ratio (95% CI) of a low fT4 in overweight women was 3.64 (2.08–6.37) ($P<0.01$).

Iodine-deficient pregnant Thai women who are overweight have a 3.6-fold higher risk of hypothyroxinaemia in the first trimester compared to normal weight women. Targeted screening should consider overweight a potential risk factor for thyroid dysfunction in pregnant women in iodine-deficient areas.

Introduction

Adequate maternal iodine status is essential during pregnancy for maternal and fetal thyroid hormone synthesis. Iodine deficiency increases risk of maternal thyroid dysfunction and hypothyroxinaemia, which can adversely affect pregnancy outcome and infant development (Wasserstrum & Anania 1995; Montoro 1997; Davis et al. 1998; Smallridge & Ladenson 2001).

Mild to moderate hypothyroxinaemia during pregnancy may impair neurodevelopment of the offspring (Haddow et al. 1999; Pop et al. 2003; Kooistra et al. 2006; Berbel et al. 2009; Costeria et al. 2011). The iodine requirement is sharply increased during pregnancy to meet increased maternal and fetal requirements. Therefore, the World Health Organization (WHO), the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the United Nations Children's Fund (UNICEF) recommends a daily iodine intake of 250 mg day^{-1} for pregnant women (WHO/ICCIDD/UNICEF 2007).

In generally iodine-sufficient Western populations, about 2–3% of pregnant women are subclinical hypothyroid and 10–15% are positive for anti-thyroid peroxidase antibodies (anti-TPO Abs) (Stagnaro-Green et al. 1990 & Allan et al. 2000). The prevalence of these thyroid disorders in iodine-deficient pregnant women has not been well defined. Mild to moderate iodine deficiency remains common in pregnant women in both high- and low-income countries (Zimmermann & Delange 2004). Globally, screening of thyroid disorders in early pregnancy is controversial, and experts generally recommend targeted high risk case finding (Abalovich et al. 2007).

Adiposity is associated with thyroid hypofunction, and overweight adults tend to have higher thyroid stimulating hormone (TSH) and lower free thyroxine (fT4) concentrations than normal weight adults (Biondi 2010). In iodine-deficient adults without overt thyroid dysfunction, higher body mass index (BMI) predicts a lower fT4 concentration (Knudsen et al. 2005), and in pregnant women at mid-gestation, high maternal BMI is positively correlated with the free triiodothyronine (fT3)/fT4 ratio

(Bassol et al. 2011). Currently, expert guidelines on screening for thyroid dysfunction in pregnancy recommend that women with morbid obesity (BMI ≥40 kg m^{-2}) be screened, but do not recommend screening for overweight women (Stagnaro-Green et al. 2011).

Although iodine status of school-aged children in Thailand is adequate, many Thai pregnant women are iodine deficient (Gowachirapant et al. 2009). In 2009, the median urinary iodine concentration in pregnant women in the Bangkok metropolitan area was 108 μg L^{-1}, and 69% of women had a UIC <150 μg L^{-1}, (the cut-off indicating iodine deficiency) (Gowachirapant et al. 2009). Therefore, our study aim was to measure iodine status and thyroid function in healthy pregnant women in the first trimester in Bangkok and to assess risk factors for thyroid dysfunction. Specifically, we determined if overweight (defined as BMI ≥23 kg m^{-2}) increases risk for hypothyroxinaemia in iodine-deficient pregnant women.

Subjects and methods

Subjects

This cross-sectional study was performed on Thai pregnant women who presented for their first prenatal visit between October 2008 and October 2010 at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand. Inclusion criteria for this study were: (1) confirmed single pregnancy; (2) age 18–40 years; (3) gestational age ≤14 weeks; (4) nonlactating; (5) apparently healthy with no history of thyroid disorders; and (6) not taking any iodine supplements. All women gave written informed consent. The ethical review boards of Wageningen University in the Netherlands and Ramathibodi Hospital in Thailand approved the study. The study was registered into the clinical trials database at http://www.clinicaltrials.gov/ with its identifier: NCT00791466.

Methods

Maternal characteristics, including dietary intakes and pre-pregnancy weight, were recorded by using a questionnaire. Four questions on seafood consumption and salt use were included in the questionnaire for assessing iodine intakes. Weight and height were

Key messages

- This study confirms that pregnant Thai women are facing mild-to-moderate iodine deficiency.
- Most of Thai pregnant women are euthyroid in the first trimester of pregnancy.
- In iodine-deficient pregnant women, overweight women have a higher risk of hypothyroxinaemia than normal-weight women.
- Not only morbidly obese women but also women who are overweight should be screened for thyroid dysfunction.

measured using standard methods. Pre-pregnancy BMI and baseline BMI were calculated. Because the association of BMI and health risk in Caucasian and Asian populations is different, women were classified by weight status using BMI reference ranges for Asian populations: <18.5 kg m^{-2} (underweight), 18.5–22.9 kg m^{-2} (normal range), 23.0–24.9 kg m^{-2} (overweight), and ≥25.0 kg m^{-2} (obese) (WHO/IASO/IOTF 2000).

A spot urine sample was collected, aliquoted, stored at -20°C and UIC was measured using the Pino modification of the Sandell–Kolthoff reaction (Pino et al. 1996) at the Institute of Nutrition, Mahidol University. This laboratory successfully participates in the EQUIP external control program for UIC analysis from the CDC in Atlanta, USA. The UIC range indicating optimal iodine nutrition in pregnancy is 150–249 μg L^{-1} (Zimmermann 2008). Salt samples from the households of a subsample of pregnant women in this study were collected (n=112) and analysed for iodine (Sullivan et al. 1995).

Whole blood samples were collected by venipuncture into vacutainer tubes without anticoagulant, centrifuged, and the serum aliquoted into cryovials and frozen at -20°C. Serum samples were analysed for TSH, total T4 (tT4), free T4 (fT4), total T3 (tT3), free T3 (fT3), thyroglobulin (Tg), and anti-TPO Abs by enzyme-labelled chemiluminescent competitive immunoassay (IMMULITE 2000, SIEMENS, Munich, Germany) at the Laboratory for Human Nutrition, ETH Zurich, Switzerland. With the exception of TSH, we used the manufacturer's reference ranges: 58–161 nmol L^{-1} for tT4, 0.89–1.76 ng

dL^{-1} for fT4, 1.3–2.6 nmol L^{-1} for tT3, 1.8–4.2 pg mL^{-1} for fT3, ≤55 ng mL^{-1} for Tg, and <35 IU mL^{-1} for anti-TPO Abs. For TSH in the first trimester of pregnancy, we used the reference range of 0.2–2.5 mIU L^{-1} (Patil-Sisodia & Mestman 2010).

Maternal thyroid gland volume measurement was performed by a portable echocamera (Aloka, Mure, Japan), using a 7.5-MHz linear transducer. Thyroid volume was calculated by using the following equation: Volume of each lobe (mL) = anteroposterior (AP) diameter (cm) x mediolateral (ML) diameter (cm) x craniocaudal (CC) diameter (cm) x 0.479, and the total lobe volumes from both sides were summed (Brunn et al. 1981). Normative thyroid volume was defined as 8.0–18.0 mL (WHO/UNICEF/ICCIDD 1993).

Results

Characteristics of the pregnant women are shown in **Table 3.1** and 514 pregnant women participated at a mean gestational age of 11 weeks. More than half of women had pre-pregnancy BMI (58%) and baseline BMI (54%) within the normal range (18.5–22.9). Prepregnancy BMI was strongly correlated with baseline BMI ($r=0.95$, $P<0.001$). Twenty-six percent of the population was overweight or obese as defined by pre-pregnancy BMI ≥23. Despite the fact that fish sauce was used more frequently (74%) as a cooking ingredient than salt (25%), 89% of the pregnant women usually bought iodised salt and 75% used salt for cooking. Sixty–nine percent of women consumed seafood once to twice a week. Salt samples obtained from a subsample of pregnant women ($n=112$) had a mean±SD iodine concentration of 60±35 ppm, indicating adequate levels of salt iodisation. There were no statistical differences in the characteristics listed in **Table 3.1** between normal weight and overweight women. With the exception for age, we used chi-square test for all variables: parity ($P=0.645$), usually buying iodised salt ($P=0.251$), salt use ($P=0.571$), use of salt and fish sauce ($P=0.246$), and weekly seafood consumption ($P=0.284$). We used independent-samples t-test for comparing mean age between normal weight and overweight women ($P=0.148$).

Table 3.1 Characteristics of pregnant women participating in the study (n=514)

Variables	n	Values[1]
Age (years)[2]	514	30 ± 5
Pre-pregnancy BMI (kg m^{-2})[3]	513	20.9 (19.1, 23.1)
<18.5	87	17
18.5-22.9	295	57.5
23.0-24.9	52	10.1
≥25.0	79	15.4
Baseline BMI (kg m^{-2})[3]	513	21.5 (19.5, 23.7)
<18.5	71	13.8
18.5-22.9	279	54.4
23.0-24.9	67	13.1
≥25.0	96	18.7
Parity		
1	224	43.6
2	177	34.4
3	87	16.9
4	20	3.9
>4	6	1.2
Usually buying iodised salt	453	88.5
Salt use		
No	5	1.0
For cooking	385	75.2
As a condiment	96	18.8
Both	26	5.0
Use of salt and fish sauce		
More salt	125	24.6
More fish sauce	377	74.1
Equal amounts	7	1.3
Weekly seafood consumption		
None	30	5.9
1-2 times	352	68.8
3-4 times	91	17.8
>4 times	39	7.5

BMI, body mass index. [1] *Values are percentages unless stated otherwise.*
[2] *Mean ± SD.* [3] *Median (first, third quartiles).*

Thyroid function tests, UICs and thyroid gland volume are shown in **Table 3.2**. In more than 80% of women, all thyroid parameters were within normal ranges. However, 12% of the women had a low fT4 concentration and 17% had elevated anti-TPO Abs. The median UIC was 111 μg L^{-1}, indicating mild ID: 23% had a UIC 100–149 μg L^{-1}, 32% had a UIC 50–99 μg L^{-1}, and 10% had a UIC <50 μg L^{-1}. None of the women had increased thyroid volume by ultrasound. The median thyroid volume of overweight women (8.50 mL) was lower than in normal weight women (8.69 mL); however, there was no statistical difference between these two values (Mann–Whitney test, P=0.903).

Based on Spearman correlation tests, there were no significant correlations between iodine intake (data from questionnaire) and TFTs (P>0.05) (data not shown).

The median of fT4 among overweight women was significantly lower than among normal weight women (P<0.001) (**Figure 3.1**).

Prevalences of thyroid dysfunctions are shown in **Table 3.3**. Three percent of women had overt hypothyroidism, 7% had subclinical hypothyroidism and 8% had isolated hypothyroxinaemia.

Table 3.4 shows the adjusted regression models for TSH, fT4, Tg and thyroid volume as dependent variables. In simple and multiple linear regression analysis, there were no significant predictors of anti-TPO Abs (data not shown). There was a significant inverse relationship between pre-pregnancy BMI and fT4 concentration (P<0.001). There was also a significant inverse relationship between baseline BMI and fT4 concentration (P<0.001). In addition, there was a significant inverse association between thyroid size and TSH concentration (P<0.01). In contrast, there was a positive relationship between pre-pregnancy BMI and Tg concentration (P<0.05). Parity was positively correlated with thyroid size (P<0.01).

Table 3.2 Thyroid hormones, urinary iodine concentration (UIC) and thyroid volume of pregnant women[1]

Indicators[2]	Normal weight (n=296)	Overweight (n=131)	All[3] (n=514)
TSH (mIU/L)[4]	1.03 (0.55, 1.60)	1.11 (0.71, 1.89)	1.07 (0.60, 1.73)
< 0.2	9.3	7.0	8.5
0.2 – 2.5	81.7	82.2	81.5
> 2.5	9.0	10.9	10.0
Total T4 (nmol/L)[4]	119.0 (102.0, 138.0)	116.0 (100.5, 138.3)	118.0 (101.0, 138.0)
< 58	0.3	0.8	0.6
58 - 161	90.4	93.1	91.7
> 161	9.2	6.2	7.7
Free T4 (ng/dL)[4]	1.08 (1.00, 1.19)	1.00 (0.88, 1.12)	1.08 (0.97, 1.19)
< 0.89	7.3	25.4	11.8
0.89 – 1.76	91.3	73.0	86.3
> 1.76	1.4	1.6	1.9
Total T3 (nmol/L)[4]	1.82 (1.51, 2.11)	2.06 (1.61, 2.40)	1.85 (1.54, 2.17)
< 1.3	8.5	10.9	8.8
1.3 – 2.6	84.7	73.6	82.2
> 2.6	6.8	15.5	9.0
Free T3 (pg/mL)[4]	3.12 (2.72, 3.60)	3.45 (2.87, 3.90)	3.16 (2.73, 3.64)
< 1.8	0.4	-	0.4
1.8 – 4.2	91.1	83.9	89.6
> 4.2	8.5	16.1	10.0
TG (ng/mL)[4]	9.11 (4.94, 16.15)	10.33 (6.78, 17.15)	9.53 (5.09, 16.7)
≤ 55	97.6	95.3	96.8
> 55	2.4	4.7	3.2
Anti-TPO Abs (IU/mL)[4]	18.6 (13.5, 26.9)	21.7 (15.6, 31.4)	19.8 (14.1, 27.4)
< 35	84.5	84.0	83.0
≥ 35	15.5	16.0	17.0
UIC (μg/L)[4]	113.20 (74.69, 172.98)	111.89 (76.25, 169.59)	111.66 (74.72, 169.79)
< 50	11.5	6.3	10.4
50 – 99	29.5	35.2	32.3
100 – 149	22.4	25.0	22.6
≥ 150	36.6	33.6	34.7
Thyroid gland volume (ml)[4]	8.69 (7.23, 10.4)	8.50 (7.53, 10.0)	8.41 (7.18, 10.2)
T3/T4 ratio[4]	0.015 (0.013, 0.017)	0.017 (0.015, 0.020)	0.016 (0.014, 0.018)

Tg, thyroglobulin; TSH, thyroid-stimulating hormone. [1]Values are percentages unless stated otherwise. [2]Cut-offs to categorise thyroid hormone concentration are based on manufacturer's reference range, except for TSH for which a pregnancy-specific cut-off range was used. [3]Including underweight women (BMI<18.5 kg m^{-2}). [4]Median (1st,3rd quartiles).

Table 3.3 Thyroid dysfunction of pregnant women (n=498) in their first trimester[1]

Thyroid dysfunction[2,3]	n	Percentages
Overt hyperthyroidism	5	1.0
Subclinical hyperthyroidism	34	6.8
Overt hypothyroidism	14	2.8
Subclinical hypothyroidism	34	6.8
Hypothyroxinaemia	42	8.4

[1]Number of pregnant women who had free T4 concentration.

[2]Cutoffs to categorise thyroid hormone concentration are based on manufacturer's reference range, except for thyroid-stimulating hormone (TSH) for which a pregnancy-specific cut-off range was used.

[3]Classified by using the definition of Helfand & Redfern (1998): overt hyperthyroidism: low TSH + high free T4; subclinical hyperthyroidism: low TSH + normal free T4; overt hypothyroidism: high TSH + low free T4; subclinical hypothyroidism: high TSH + normal free T4; hypothyroxinaemia: normal TSH + low free T4.

Table 3.4 Multiple regression model of predictors for thyroid function in pregnant women[1]

Model	Predictors	R^2	Beta (95% CI)	Sig.
TSH	Tvol	0.019	-0.137 (-0.114, -0.025)	0.002
FT4	Tvol	0.079	0.222 (0.016, 0.037)	0.000
	BMI	0.079	-0.200 (-0.019, -0.008)	0.000
TG	BMI	0,011	0.105 (0.086, 1.145)	0.023
Tvol	Parity	0.016	0.126 (0.083, 0.441)	0.004

BMI, body mass index; CI, confidence interval. [1]Stepwise regression.

As shown in **Table 3.5**, risk for a low fT4 was significantly increased in women with a pre-pregnancy BMI ≥23.0 kg m^{-2} (3.64, 95% CI: 2.08–6.37). Risk for elevated anti-TPO Abs (≥35 IU mL^{-1}) was significantly decreased in women with a smaller thyroid gland volume (0.40, 95%CI: 0.20–0.83).

Discussion

The present study confirms that pregnant women living in Bangkok are iodine deficient with median UIC of 111 μg L^{-1}. In an earlier study in pregnant women from the same area, we reported a similar median UIC of 108 μg L^{-1} (Gowachirapant et al. 2009). Other studies have found suboptimal iodine status among pregnant women in Thailand. In 2007, Rajatanavin (2007) reported the median UICs of mothers in Bangkok and six

rural provinces in Thailand were 85 and 103 μg L^{-1}, respectively. In southern Thailand, the median maternal UIC ranges from 51 to 106 μg L^{-1} (Jaruratanasirikul et al. 2009).

Table 3.5 Prevalence ratios of predictors in relation to iodine status and thyroid function in first trimester pregnant women

Independent variables	Prevalence ratios (95% CI)			
	UIC < 150 μg/L	TSH > 2.5 mIU/L	Free T4 < 0.89 ng/dL	Anti-TPO Abs ≥ 35 IU/mL
Age (yrs)				
< 25	Ref.	Ref.	Ref.	Ref.
25-30	0.87 (0.64-1.19)	1.15 (0.49-2.70)	0.83 (0.39-1.75)	1.21 (0.55-2.68)
> 30	0.87 (0.64-1.18)	1.08 (0.46-2.52)	0.90 (0.44-1.87)	1.88 (0.89-4.00)
BMI (kg/m^2)				
< 18.5	1.11 (0.83-1.48)	1.30 (0.63-2.70)	1.03 (0.41-2.55)	0.74 (0.37-1.46)
18.5-22.9	Ref.	Ref.	Ref.	Ref.
≥ 23.0	1.04 (0.81-1.35)	1.20 (0.63-2.30)	3.64 (2.08-6.37)**	1.03 (0.61-1.72)
Parity				
1	Ref.	Ref.	Ref.	Ref.
2	0.99 (0.78-1.27)	1.09 (0.59-2.01)	1.60 (0.89-2.87)	1.10 (0.66-1.85)
> 2	0.92 (0.69-1.23)	0.83 (0.38-1.81)	1.24 (0.62-2.49)	1.22 (0.69-2.15)
Tvol (ml)[1]				
< 7.18	1.08 (0.83-1.40)	0.96 (0.51-1.82)	1.09 (0.62-1.91)	0.40 (0.20-0.83)*
7.18-10.20	Ref.	Ref.	Ref.	Ref.
> 10.20	1.11 (0.85-1.43)	0.50 (0.22-1.13)	0.36 (0.15-0.85)*	1.03 (0.62-1.70)
Seafood (times/wk)				
None	Ref.	Ref.	Ref.	Ref.
1 – 2	1.02 (0.64-1.62)	1.43 (0.34-5.98)	1.86 (0.45-7.68)	0.78 (0.31-1.97)
3 – 4	0.98 (0.59-1.65)	2.02 (0.45-9.04)	2.33 (0.53-10.27)	1.39 (0.52-3.67)
> 4	0.82 (0.44-1.53)	1.21 (0.20-7.28)	0.41 (0.04-4.47)	0.77 (0.22-2.66)
Iodized salt use				
Yes	Ref.	Ref.	Ref.	Ref.
No	1.13 (0.79-1.62)	0.90 (0.32-2.49	1.37 (0.62-3.01)	1.07 (0.49-2.33)

*CI, confidence interval; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration; *P < 0.05, **P < 0.01 (compared with reference group). [1]Categorised by percentiles.*

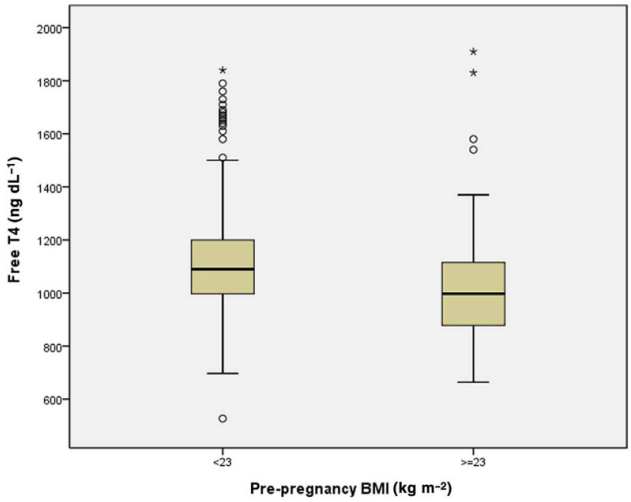

Figure 3.1 Box plot of free T4 concentration (ng dL^{-1}) and pre-pregnancy body mass index (BMI) (kgm^{-2}).
Outliers are indicated by *

There may be several reasons why iodine intakes are low in Thai pregnant women. The salt iodisation program in Thailand, begun in 1995, currently covers only 60–70% of Thai households with adequately iodised salt, below the national goal of at least 90% coverage (World Health Organization, Regional Office for South-East Asia 2004; Division of Nutrition, Ministry of Public Health 2005; UNICEF & National Statistical Office, Thailand 2006; Jaruratanasirikul et al. 2009). In many rural areas, salt from local small producers is often not iodised. Moreover, in Thailand and throughout Southeast Asia, fish sauce is a more popular household seasoning than salt, reducing the contribution of iodised salt to dietary iodine intakes. In the present study, three of four women used mainly fish sauce for household seasoning, whereas only one in four used mainly salt. In the urban households of the women in this study, all salt samples analysed were adequately iodised (≥15 ppm) (Keetman 2010). Thus, use of iodised salt in the production of fish sauce, or, alternatively, direct iodisation of fish sauce, are likely to be the effective dietary interventions to increase intakes in this population. Iodine supplementation during pregnancy could also increase iodine intakes, but most Thai women present for prenatal care near the end of the first trimester. Therefore, prenatal supplementation would likely not be effective in increasing intakes during the first trimester, the period during which the fetus is most vulnerable to ID.

However, despite their low iodine intakes, most pregnant women in this study were euthyroid and all had normal thyroid volume. Glinoer et al. (1995) suggested an increased T3/T4 ratio >0.025 reflects excessive thyroid stimulation during pregnancy due to iodine deficiency. In our sample, the median T3/T4 ratio was 0.016, evidence that thyroid function was normal in many of these women. Spot UIC is a useful indicator for assessing recent iodine intake of this population because about 90% of daily ingested iodine is excreted in the urine. But this method has large day-to-day variation and should not be used to classify an individual's iodine status. Therefore, a 24-h urine sample collection or repeated spot urine samples may be more useful for categorizing individual status. A combination of UIC and thyroid function tests may provide the most accurate assessment of iodine status of pregnant women.

Because iodine intakes in the general Thai population are adequate, many of these women likely entered pregnancy with ample stores of intrathyroidal iodine, enough to support increased needs for iodine in the early stages of pregnancy. Although none of the women had evidence of increased thyroid volume, thyroid volume was inversely correlated with TSH and positively correlated with fT4. This pattern, in the first trimester of pregnancy, is thought to be due to high circulating human chorionic gonadotropin that stimulates thyroid hormone production and TSH (Haddow et al. 2008). In addition, we found that higher parity was associated with greater thyroid volume, as has been previously reported in iodine deficient European populations (Rotondi et al. 2000; Knudsen et al. 2002). Thus, repeated pregnancy maybe a risk factor for goitre, particularly in iodine deficient areas.

Although most women in our study were euthyroid, 12% of women had low fT4 concentration: 3% had overt hypothyroidism; 7% had subclinical hypothyroidism; and 8% had isolated hypothyroxinaemia. These prevalences are about three fold higher than those reported for iodine sufficient Western populations, where generally 2–3% of pregnant women are hypothyroid, of whom 0.3–0.5% have overt hypothyroidism and 2–2.5% have subclinical hypothyroidism. In a recent study in iodine-sufficient Asian women early in pregnancy (n=2899) (Wang et al. 2011), the prevalence of overt or

subclinical hypothyroidism was 7.5% and the prevalence of hypothyroxinaemia was only 0.9%. Thus, our results suggest that low iodine intakes in Thai pregnant women increase risk for hypothyroxinaemia, and thus improving iodine intakes should be a public health priority.

The novel finding in this study is the clear inverse relationship between body weight and fT4 in mildly iodine-deficient pregnant women. In general, overweight adults tend to have slightly higher TSH and, in some studies, lower fT4 concentrations than normal weight adults (Lindeman et al. 2003; Biondi 2010). Greater subcutaneous fat is associated with lower fT4 in overweight adults, independent of age, gender and smoking (Alevazaki et al. 2009). The link between body weight and thyroid function is less well studied in areas of iodine deficiency. In iodine-deficient Danish adults without overt thyroid dysfunction, higher BMI was associated with lower fT4, but not fT3 (Knudsen et al. 2005). In pregnant Spanish women at mid-gestation, higher maternal BMI was directly correlated with the fT3/fT4 ratio, but not with fT4 alone (Bassol et al. 2011).

Several mechanisms may contribute to a higher prevalence of thyroid hypofunction in overweight pregnant women who are iodine deficient. Obese adults may be more likely to develop autoimmune hypothyroidism leading to mild thyroid failure (Marzullo et al. 2010). However, in our subjects, there was no correlation between anti-TPO Abs and either BMI or fT4. Inflammatory cytokines released by adipose tissue may impair the hypothalamic–pituitary–thyroid axis (Toni et al. 2004) but this should result in negative associations between BMI and serum TSH as well as fT4, a pattern not visible in our subjects. Circulating oestrogen metabolites maybe increased in pregnant women who are overweight, and 2-methoxyestradiol has been shown to have detrimental effects on thyroid cells in culture (Wang et al. 2000). A leptin-induced increase in TSH secretion may occur in obesity via hypothalamic effects (Zimmermann-Belsing et al. 2003), but this would increase TSH and thyroid hormone secretion, a pattern not found in our subjects. Finally, there may be a higher peripheral conversion of T4 to T3 in obesity due to increased deiodinase activity as a compensatory mechanism to improve energy

expenditure (Biondi 2010). This could accentuate the preferential thyroidal secretion of T3 over T4 in iodine deficiency and lead to lower fT4 levels. However, in our subjects the median T3/T4 ratio was not increased compared to previous reports in iodine-deficient pregnant women (Glinoer et al. 1995), and there was no correlation between BMI and the T3/T4 ratio.

Because thyroid dysfunction during early pregnancy is associated with poor offspring development, many expert groups, including the Endocrine Society (Abalovich et al. 2007), recommend a case-finding approach where women at high risk for thyroid disorders are screened. But this approach has been questioned. In a recent large Chinese study (Wang et al. 2011), despite using a recommended case finding screening strategy, 82% of pregnant women with hypothyroidism were missed. Thus, the optimal screening criteria to identify women with hypothyroidism in early pregnancy remain uncertain. Current guidelines (Stagnaro-Green et al. 2011) recommend targeted screening based on weight status only in morbidly obese women (BMI ≥40 kg m^{-2}). However, our data suggest milder degree of maternal adiposity (BMI ≥23 kg m^{-2} in Asian populations) should be considered a potential risk factor for thyroid dysfunction, particularly in iodine-deficient areas.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

All the authors contributed to the study design and article writing. SG performed data collection, laboratory work, data entry and analysis under supervision of AMB, PW and MBZ.

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Chapter 4

A randomized controlled trial of iodine supplementation in mildly iodine-deficient pregnant Thai women

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Will be submitted for publication together with results from Indian trial

Abstract

Background: Severe iodine deficiency (ID) during pregnancy causes many adverse effects both in the mother and newborn. Although iodine supplementation in mildly deficient pregnant women is widely recommended, long-term effects and safety of supplementation remain uncertain.

Objectives: To evaluate the effects of iodine supplementation on maternal thyroid function, pregnancy and birth outcomes, and newborn development.

Methods: An RCT with 200 μg iodine/d or placebo given to 511 mildly iodine-deficient pregnant Thai women from 11 weeks to term. Maternal thyroid function, urinary iodine concentration (UIC) and thyroid volume were measured at baseline, 2nd and 3rd trimester, at delivery and 6-week postpartum. Birth outcomes were collected from hospital records. Neonatal thyroid function, UIC and thyroid volume were measured at delivery and 6 weeks after birth. At 6 weeks, the Neonatal Behavioral Assessment Scales (NBAS) was used to assess newborn development.

Results: Median UIC increased significantly from baseline in both groups, and the increase was higher in the iodine group ($p<0.001$). At 30 weeks of gestation, only 2% of the women in the placebo group and 7% in the iodine group reported a median UIC >500 μg/L. Maternal thyroid function, thyroid volume and the prevalence of all thyroid dysfunction subtypes did not differ significantly between treatment groups ($p>0.05$). At 6-week postpartum, the prevalence of postpartum thyroiditis (hyperthyroidism) was significantly lower in the iodine group (3%) as compared to the placebo group (9%) (OR: 95%CI, 0.17: 0.04-0.70). There were no significant differences between newborn groups in thyroid function, thyroid volume, birth characteristics, UIC and NBAS score ($p>0.05$).

Conclusion: Supplementation with 200 μg iodine/day in mildly iodine-deficient pregnant Thai women was effective in increasing iodine intakes into the adequate range and was safe. However, it had no benefit on antenatal maternal thyroid function or

newborn outcomes out to 6 weeks. Iodine supplementation significantly reduced the risk of maternal postpartum thyroid dysfunction.

Introduction

According to WHO/UNICEF/ICCIDD, an optimal daily iodine intake for pregnant women should be at least 250 μg/day and a spot urinary iodine concentration (UIC) of less than 150 μg/L indicates iodine deficiency (ID) in the population (WHO/UNICEF/ICCIDD 2007). Currently, severe ID is rare on the national level (Benoist, McLean et al. 2008), but mild-to-moderate ID continues to affect many countries in Europe, Asia and Africa and has recently recurred in Australia and in the UK (Caldwell 2005; Li 2006; Haddaw 2007; Vanderpump 2011). In Thailand, pregnant women are at risk for mild to moderate ID (Rajatanavin 2007; WHO/UNICEF/ICCIDD 2007; Jaruratanasirikul 2009; Gowachirapant 2014). Globally, iodine deficiency during pregnancy is thought to be one of the leading preventable causes of hypothyroidism in both mothers and neonates, and when severe, its adverse consequences on growth and neurodevelopment of the child are well recognized (Hetzel 1979; Hetzel 1987; Delange 1994; Delange 2001; Pop 2003; Escobar 2007). The fetal thyroid begins to concentrate iodine at 10-12 weeks of gestation, and the synthesis and secretion of thyroid hormone ensues at ca. 20 weeks of gestation (Brown 2004). The fetus is therefore fully dependent on maternal iodine stores and thyroid hormone supply across the placenta until mid-gestation. It has been suggested that not only severe ID but also mild to moderate ID in pregnancy may impair the cognitive ability of offspring (Zimmermann 2007; Zimmermann 2008; Bath 2013). However, this hypothesis has not been tested in a randomized controlled trial of maternal iodine supplementation.

Several iodine supplementation trials in pregnant women with mild-to-moderate ID reported an increase in maternal UIC and a decrease in thyroid size and/or serum thyroglobulin (Tg) in the treated group, but none found a clear improvement in maternal thyroid function (Zimmermann 2009). It may be that pregnant women are able to draw sufficient iodine from intrathyroidal stores to maintain adequate thyroid hormone production, even when they have mildly deficient intakes. However, these studies had small sample sizes, and therefore the effects and safety of iodine supplementation on maternal thyroid function remain uncertain. Recommendations on

iodine supplementation during pregnancy are still under debate: WHO does not recommend maternal supplementation if the general population is iodine sufficient (WHO/UNICEF 2007); in contrast, many expert medical groups advise maternal supplementation with 150 to 250 μg/day. There is a clear lack of data on the effects of iodine supplementation in pregnancy on long-term outcomes such as postpartum maternal thyroid function, birth outcomes, growth and infant development. A recent systematic review of randomized controlled trials of iodine supplementation in pregnancy (Zhou 2013) confirmed the lack of quality evidence of the effect of prenatal iodine supplementation on cognitive function of the offspring. Therefore, in the present study, we aimed to assess the effect of oral iodine supplementation in mildly iodine-deficient pregnant women on maternal thyroid stimulating hormone (TSH), free thyroxine (fT4) and thyroglobulin (Tg) concentrations as the primary outcomes. In addition, we determined effects on other thyroid function indicators, pregnancy and birth outcomes, and newborn development as secondary endpoints.

Subjects and methods

Subjects

This randomized double blind controlled trial was conducted in pregnant Thai women who registered at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand between October 2008 and August 2011. Further follow up continued until June 2013, but those results are not reported here. Inclusion criteria were: 1) singleton pregnancy; 2) age 18 to 40 y; 3) gestational age ≤14 weeks; 4) non-lactating; 5) generally healthy with no history of thyroid disorders; and 6) not taking any iodine supplements. Women who had thyroid stimulating hormone (TSH) concentration >6.0 mIU/L at screening were excluded from the study. All women gave signed informed consent. The study was approved by the ethical review committees of Ramathibodi Hospital in Thailand and by Wageningen University in the Netherlands, and supervised by an external data safety and monitoring board (DSMB). It was registered at http://www.clinicaltrials.gov/ with its identifier: NCT00791466.

Methods

After eligibility screening, pregnant women were allocated to two treatment groups by simple randomization; half of the women received a daily supplement of 200 μg iodine (as potassium iodide tablets, Merck, Darmstadt, Germany) until delivery. Another half received an identical tablet without iodine (Merck, Darmstadt, Germany) until delivery. All of the women received a multi-vitamin and -mineral (without iodine) tablet until delivery.

At the beginning of the study, maternal characteristics including pre-pregnancy weight, salt usage patterns and seafood consumption were recorded by using a questionnaire. Weight and height were measured by using standard methods. Pre-pregnancy body mass index (BMI) was calculated, and women were classified by weight status using international BMI reference ranges: <18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal range), 25.0-29.9 kg/m^2 (overweight), and ≥ 30.0 kg/m^2 (obese) (WHO 2004).

During the study, maternal thyroid function, UIC and thyroid gland volume were measured at baseline, 2nd and 3rd trimester, at delivery and post-delivery (6 weeks after delivery). For infants, birth characteristics from hospital records and thyroid gland volume were measured at delivery and 6 weeks after birth, and a spot UIC was measured at 6 weeks after birth.

For UIC, spot urine samples were collected, aliquoted, stored at -20°C and UIC was measured using the Pino modification of the Sandell-Kolthoff reaction (Pino, Fang et al. 1996) at the Institute of Nutrition, Mahidol University. This laboratory successfully participates in the EQUIP external control program for UIC analysis from the CDC in Atlanta, USA (http://www.cdc.gov/labstandards/equip.html). The UIC reference ranges for pregnant women during pregnancy and post-delivery are 150-249 μg/L and 100-199 μg/L, respectively (WHO/UNICEF/ICCIDD 2007). For infants, UIC ≥100 μg/L was used to indicate optimal iodine nutrition (WHO/UNICEF/ICCIDD 2007).

Whole blood samples were collected from pregnant women by venipuncture into tubes without anticoagulant, and at delivery cord blood samples were collected. Blood samples were centrifuged, and the serum aliquoted and frozen at -20°C. Serum samples were analyzed for TSH, total T4 (TT4), free T4 (fT4), total T3 (TT3), free T3 (fT3), thyroglobulin (Tg), and anti-TPO Abs (TPO-Abs) by enzyme-labeled chemiluminescent competitive immunoassay (IMMULITE 2000, SIEMENS, Germany) at the Laboratory for Human Nutrition, ETH Zurich, Switzerland. With the exception of TSH and TT4 during pregnancy, we used the manufacturer's reference ranges: 0.4-4.0 mIU/L for TSH, 58-161 nmol/L for TT4, 0.89-1.76 ng/dL for fT4, 1.3-2.6 nmol/L for TT3, 1.8-4.2 pg/mL for fT3, ≤ 55 ng/mL for Tg, and < 35 IU/mL for TPO-Abs (SIEMENS, Germany). For TSH, during pregnancy, we used trimester specific reference ranges: 0.1-2.5 mIU/L for 1st trimester, 0.2-3.0 mIU/L for 2nd trimester, and 0.3-3.0 mIU/L for 3rd trimester (Stagnaro-Green 2011). For TT4, we multiplied the non-pregnancy reference range by 1.5 and used the resulting range of 87-241.5 nmol/L as a reference (Mandel 2005).

From infants, a heel-prick blood sample was collected within 72 hours after birth, spotted onto filter paper and dried at room temperature. Dried blood spots (DBS) were stored in low gas permeable plastic bags and frozen at -20°C and transported to the Laboratory of Human Nutrition, ETH, Zurich, Switzerland. DBS-TSH was analyzed using Delfia Neonatal hTSH Kits and the Genetic Screening Processor (GSP) machine (PerkinElmer, Wallac, Turku, Finland) at the Protein and Hormone Laboratory, Children's Hospital Zurich, Switzerland.

Maternal thyroid gland volume was measured by using a portable echocamera (Aloka, Mure, Japan), using a 7.5-MHz linear transducer. Neonatal thyroid size measurement was performed by an iU22 ultrasound system (Philips, Bothell, WA) using 17-5 MHz probe. Measurements were done under supervision of an experienced radiologist at Ramathibodi hospital. Thyroid volume was calculated by using the following equation: volume of each lobe (ml) = AP diameter (cm) x ML diameter (cm) x CC diameter (cm) x 0.479, and the total lobe volumes from both sides were summed. Normative thyroid volume of healthy adults was defined as 8.0-12.0 ml (WHO/UNICEF/ICCIDD 2007).

At 6 weeks postpartum, the Neonatal Behavioral Assessment Scales (NBAS) test was carried out by a trained nurse in order to assess newborn development. The NBAS contains 28 behavioral items, 18 neurologic reflex items, and 7 supplementary items that measure the quality of responsiveness and the amount of input that the infant needs from the examiner to show their best performance. Scores on the NBAS were reduced to the following 7 clusters: 1) habituation; 2) orientation; 3) motor; 4) range of state; 5) regulation of state; 6) autonomic stability; and 7) reflexes, including supplementary items (Brazelton and Nugent 1995).

Low birth weight (LBW) was defined as weight at birth of <2,500 grams (WHO 2013) and preterm birth was defined as babies born alive before 37 weeks of pregnancy (WHO 2013). Small-for-gestational age (SGA) was defined as birth weight less than the 10^{th} percentile for a given gestational age and sex using the Alexander reference (Alexander 1996). Ponderal index (PI) was calculated as birth weight (kg)/length(m)^3 and defined as less than the 10^{th} percentile using gestational age-specific percentiles for PI (Landmann, Reiss et al. 2006). Compliance with supplement use was measured by counting tablets returned after delivery; good compliance was defined as 80% of protocol prescribed treatment taken. All serious adverse events (SAE) during pregnancy were recorded and reported to the DSMB.

Data analyses

Samples size was calculated based on an anticipated decrease in the prevalence of elevated newborn TSH (>10 mIU/L at postnatal days 2-4) with treatment. The study need to have 80% power to detect a decrease of 0.8 (from an anticipated incidence of 10% in the control to 2% with treatment) in the proportion of elevated newborn TSH values with a significance level of 0.05. The calculation indicates a sample size of 250 pregnant women (125 women in each treatment arms). In addition, when 10% loss to follow-up was considered, a total of 275 pregnant women were enrolled.

All data were double-entered, cross-checked for entry mistakes and stored in a central database in Excel (2007; Microsoft). Data analyses were done with SPSS 21.0 (IBM, USA). Distributions of variables were checked for normality by using the Kolmogorov-Smirnoff test. Variables with non-normal distribution were log-transformed before analysis. Variables were expressed as means ± SD for normally distributed data and medians (1^{st}, 3^{rd} quartiles) for non-normally distributed data. Primary analysis was per protocol, and included the effect on repeated follow-up measures of the primary endpoints (fT4, Tg and TSH) up till week 30 of gestation. Differences in effects between groups were tested by using Linear Mixed Models (LMM). In these models, treatment and gestational age (in months) at each time point were modeled as fixed effects. Other potentially explanatory co-variables including age, parity and pre-pregnancy BMI were added to the model as random effects and evaluated for significant effects on the model and its goodness of fit by using the -2 log likelihood. LMM analysis was conducted as well for all continuous secondary parameters. Generalized Linear Mixed Models (GLMM) analysis was used for binary secondary endpoints, as described for the primary analysis. For data from women 6 weeks postpartum, linear regression and logistic regression were used for continuous and binary data, respectively. Models were adjusted for possible co-variables including maternal age, parity, gestational age at delivery, BMI at 6-week, duration from delivery to 6-week appointment, and baseline values of each dependent variable. For neonatal data analysis, linear regression and logistic regression were used for continuous and binary data, respectively. Models were adjusted for possible co-variables including age, parity, pre-pregnancy BMI, gestational age at delivery, and baseline values of each dependent variable for thyroid function data. A value of $p<0.05$ was considered statistically significant.

Results

Five hundred and eleven pregnant women were enrolled in the study and randomly assigned to the intervention groups. Loss to follow up was similar in both intervention groups, and reasons for declining participation were not notably different (**Figure 4.1**).

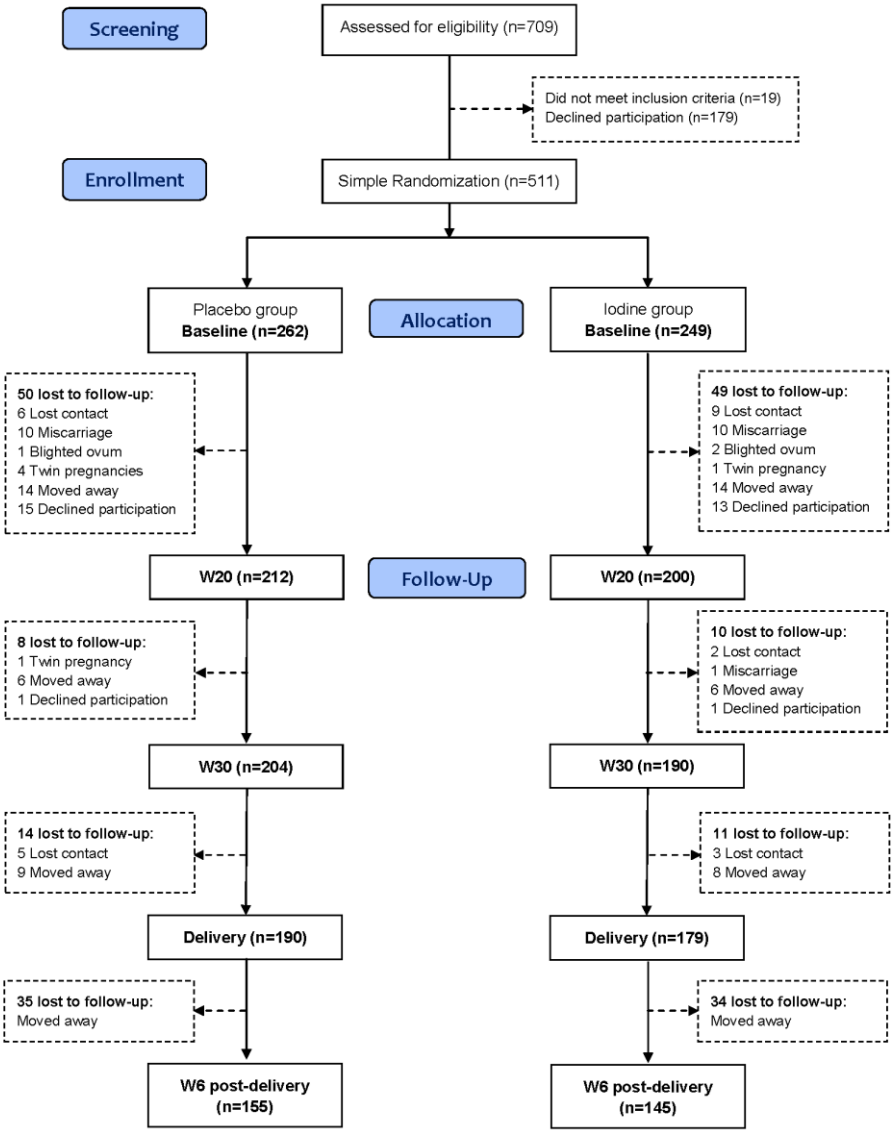

Figure 4.1 Flow diagram of the MITCH Thailand study

At baseline, 40% of women in the placebo group and 47% in the iodine group were uniparous. The prevalence of overweight and obesity in the groups did not differ significantly (13% and 3.8% in the placebo group, 10% and 3.6% in the iodine group, respectively). Most of the women were purchasing iodized salt for their households (88% in the placebo group and 89% in the iodine group) and were using salt for cooking (73% in the placebo group and 78% in the iodine group).

There were no differences in median UIC between the two groups at baseline ($p>0.05$) **(Table 4.1)**. Median UIC increased significantly from baseline in both groups (from 110.1 µg/L to 154.6 µg/L in the placebo group and from 112.0 µg/L to 233.3 µg/L in the iodine group), and the increase was greater in the iodine group ($p<0.001$). At 30 weeks of gestation, 44% of the women in the placebo group and 29% in the iodine group had a median UIC 50-149 µg/L, 4% of the women in the placebo group and 2% in the iodine group had a median UIC < 50 µg/L. In addition, at 30 weeks, only 2% of the women in the placebo group and 7% in the iodine group reported a median UIC > 500 µg/L.

Table 4.1 Urinary iodine concentrations (µg/L) of Thai pregnant women given 200 µg iodine daily or placebo[1]

	Baseline (Week 11)		Week 20		Week 30	
	Placebo	Iodine	Placebo	Iodine	Placebo	Iodine
	(n=260)	(n=248)	(n=152)	(n=167)	(n=185)	(n=171)
Median	110.1	112.0	143.8	223.9	154.6	233.3
(IQR)[2]	(69.2, 172.2)	(75.2, 165.0)	(86.3, 237.3)	(132.3, 345.7)	(107.9, 212.4)	(140.0, 314.8)
> 500	2 (0.8)	2 (0.8)	0 (0.0)	13 (7.8)	3 (1.6)	12 (7.0)
150- 500	92 (35.0)	80 (32.3)	70 (46.1)	106 (63.5)	94 (50.8)	105 (61.4)
100- 149	51 (19.6)	64 (25.8)	34 (22.4)	24 (14.4)	47 (25.4)	35 (20.5)
50 -99	87 (33.5)	77 (31.0)	39 (25.7)	20 (12.0)	34 (18.4)	15 (8.8)
< 50	28 (10.8)	25 (10.1)	9 (5.9)	4 (2.4)	7 (3.8)	4 (2.3)

[1]n(%), [2]per intention-to-treat, using linear mixed models (p=0.000)

Maternal thyroid function tests, TPO-Abs and thyroid volume are summarized in **Table 4.2a and 4.2b**, for both the per protocol and intention-to-treat LMM analysis. There were no significant differences between groups in any of the measured variables during the study using either of the analytic approaches. Within both groups, there was no

Table 4.2a Thyroid function and thyroid volume of Thai pregnant women given 200 µg iodine daily or placebo[1]

	Baseline (Week 11)		Week 20		Week 30		p value[3]
	Placebo	Iodine	Placebo	Iodine	Placebo	Iodine	
	(n=101)	(n=105)	(n=86)	(n=101)	(n=99)	(n=101)	
TSH (mIU/L)	1.24 (0.78, 1.66)	0.95 (0.46, 1.48)	1.27 (0.83, 1.70)	1.17 (0.79, 1.71)	1.24 (0.85, 1.72)	1.17 (0.72, 1.81)	0.349
Elevated[2]	9 (9.3)	9 (8.7)	3 (3.6)	6 (6.5)	3 (3.3)	4 (4.4)	0.328
Low[2]	3 (3.1)	5 (4.9)	1 (1.2)	2 (2.2)	2 (2.2)	4 (4.4)	-
fT4 (ng/dL)	1.11 (1.02, 1.18)	1.09 (0.99, 1.20)	0.82 (0.79, 0.89)	0.78 (0.71, 0.88)	0.81 (0.71, 0.88)	0.77 (0.68, 0.83)	0.062
< 0.89	6 (6.3)	6 (5.9)	64 (75.3)	73 (78.5)	72 (76.6)	81 (85.3)	0.402
> 1.76	0 (0.0)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
TT4 (nmol/L)	118.0 (102.0, 134.0)	116.0 (98.3, 138.0)	119.0 (105.0, 133.0)	114.0 (101.8, 128.0)	119.0 (102.0, 134.5)	113.0 (100.3, 129.0)	0.853
< 87	8 (8.0)	7 (6.8)	5 (5.9)	12 (12.8)	10 (10.8)	11 (11.5)	0.927
> 241.5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
fT3 (pg/mL)	3.00 (2.60, 3.72)	3.06 (2.65, 3.52)	3.24 (2.72, 3.76)	3.27 (2.79, 3.82)	3.38 (2.89, 3.75)	3.33 (2.99, 3.86)	0.732
< 1.8	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.1)	0 (0.0)	-
> 4.2	10 (10.5)	7 (6.9)	8 (10.1)	10 (11.9)	13 (14.8)	10 (11.2)	0.864
TT3 (nmol/L)	1.77 (1.50, 2.08)	1.82 (1.57, 2.13)	2.34 (1.99, 2.68)	2.39 (2.03, 2.71)	2.36 (2.13, 2.71)	2.46 (2.11, 2.70)	0.932
< 1.3	9 (9.0)	9 (8.6)	1 (1.2)	1 (1.0)	0 (0.0)	1 (1.0)	-
> 2.6	5 (5.0)	9 (8.6)	28 (33.3)	29 (29.9)	37 (40.2)	36 (37.5)	0.467
Tg (ng/mL)	9.76 (5.46, 17.25)	9.41 (4.56, 17.80)	10.15 (5.66, 16.10)	8.93 (4.65, 15.70)	11.50 (6.28, 22.20)	9.85 (5.26, 16.22)	0.532
> 38.5	6 (6.4)	6 (6.2)	6 (7.7)	5 (5.7)	8 (8.8)	5 (5.7)	0.928
TPO-Abs (IU/mL)	17.1 (12.4, 24.2)	16.7 (10.9, 25.7)	14.2 (10.1, 21.2)	12.8 (10.0, 23.3)	11.6 (10.0, 18.9)	14.8 (10.0, 20.3)	NA[4]
≥ 35	11 (10.9)	13 (12.4)	4 (4.6)	12 (12.2)	3 (3.0)	7 (7.0)	0.078
TT3/TT4 ratio	0.0150	0.0156	0.0191	0.0206	0.0202	0.0213	0.609
	(0.0137, 0.0166)	(0.0134, 0.0180)	(0.0171, 0.0224)	(0.0175, 0.0230)	(0.0177, 0.0244)	(0.0179, 0.0249)	
fT3/fT4 ratio	2.6720	2.7710	3.9763	4.0488	4.1578	4.4050	0.372
	(2.3398, 3.4177)	(2.3907, 3.2337)	(3.1884, 4.4622)	(3.3960, 5.1250)	(3.6408, 5.1237)	(3.8490, 5.2224)	
Tvol (ml)	8.7 (7.2, 10.4)	8.3 (7.5, 10.3)	8.5 (7.2, 9.5)	8.2 (7.0, 9.7)	8.0 (6.7, 9.6)	8.1 (7.2, 9.1)	0.480
> 12	8 (7.9)	3 (2.9)	3 (3.5)	3 (3.0)	2 (2.0)	3 (3.0)	0.545

[1]median (IQR) or n(%), [2]trimester-specific reference ranges (1st=0.1-2.5 mIU/L, 2nd=0.2-3.0 mIU/L, 3rd=0.3-3.0 mIU/L), [3]per protocol, using linear mixed models for continuous data; generalized linear mixed models for binary data, [4]Not available, data could not be normalized

Table 4.2b Thyroid function and thyroid volume of Thai pregnant women given 200 µg iodine daily or placebo[1]

	Baseline (Week 11)		Week 20		Week 30		p value[3]
	Placebo	Iodine	Placebo	Iodine	Placebo	Iodine	
	(n=262)	(n=249)	(n=171)	(n=185)	(n=190)	(n=176)	
TSH (mIU/L)	1.11 (0.67, 1.72)	1.00 (0.56, 1.75)	1.24 (0.78, 1.71)	1.22 (0.78, 1.79)	1.30 (0.84, 1.80)	1.13 (0.71, 1.72)	0.952
Elevated[2]	26 (10.1)	24 (9.8)	7 (4.2)	13 (7.5)	4 (2.3)	7 (4.5)	0.375
Low[2]	13 (9.9)	13 (5.2)	4 (1.5)	5 (2.0)	4 (1.5)	7 (2.8)	0.416
fT4 (ng/dL)	1.07 (0.95, 1.18)	1.08 (0.98, 1.20)	0.81 (0.74, 0.88)	0.78 (0.72, 0.88)	0.79 (0.71, 0.87)	0.77 (0.68, 0.84)	0.490
< 0.89	35 (13.6)	24 (10.0)	128 (79.0)	137 (78.3)	147 (79.5)	138 (85.7)	0.376
> 1.76	2 (0.8)	7 (2.8)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	-
TT4 (nmol/L)	117.0 (102.0, 135.0)	118.0 (101.0, 138.0)	116.0 (102.0, 131.0)	114.0 (102.0, 129.0)	116.5 (101.0, 131.0)	113.0 (99.7, 129.0)	0.564
< 87	19 (7.3)	19 (7.7)	11 (6.6)	21 (12.0)	15 (8.2)	15 (9.3)	0.305
> 241.5	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
fT3 (pg/mL)	3.21 (2.77, 3.69)	3.13 (2.70, 3.58)	3.22 (2.87, 3.74)	3.35 (2.82, 3.99)	3.38 (2.90, 3.85)	3.32 (2.96, 3.85)	0.519
< 1.8	1 (0.4)	1 (0.4)	1 (0.7)	2 (1.2)	1 (0.6)	1(0.7)	-
> 4.2	27 (10.3)	21 (8.4)	18 (6.8)	20 (8.0)	28 (10.6)	17 (6.8)	0.323
TT3 (nmol/L)	1.85 (1.54, 2.19)	1.85 (1.56, 2.16)	2.34 (2.00, 2.68)	2.38 (2.03, 2.77)	2.42 (2.13, 2.86)	2.44 (2.12, 2.74)	0.923
< 1.3	22 (8.4)	23 (9.3)	2 (1.2)	2 (1.1)	1 (0.5)	1 (0.6)	-
> 2.6	20 (7.6)	25 (10.0)	52 (19.8)	59 (23.5)	75 (28.5)	62 (24.7)	0.877
Tg (ng/mL)	9.57 (6.35, 17.00)	9.38 (4.63, 16.58)	10.40 (5.58, 15.90)	8.60 (4.63, 15.50)	11.90 (6.35, 22.30)	9.78 (5.46, 18.10)	0.269
> 38.5	11 (4.6)	11 (4.7)	10 (6.6)	7 (4.2)	18 (10.3)	9 (6.0)	0.184
TPO-Ab (IU/mL)	16.2 (11.0, 26.2)	17.7 (11.5, 24.7)	14.2 (10.0, 21.8)	13.7 (10.0, 21.7)	11.7 (10.0, 18.9)	12.8 (10.0, 19.6)	NA[4]
≥ 35	40 (15.2)	37 (14.7)	15 (8.8)	21 (11.5)	13 (6.8)	11 (6.5)	0.828
TT3/TT4 ratio	0.0155	0.0155	0.0198	0.0207	0.0211	0.0216	0.766
	(0.0139, 0.0145)	(0.0135, 0.0179)	(0.0176, 0.0228)	(0.0176, 0.0234)	(0.0181, 0.0251)	(0.0179, 0.0253)	
fT3/fT4 ratio	2.9274	2.8325	4.0044	4.2073	4.2285	4.3709	0.159
	(2.4951, 3.5984)	(2.4390, 3.4800)	(3.4522, 4.7820)	(3.4171, 5.1010)	(3.6561, 5.1296)	(3.7534, 5.3018)	
Tvol (ml)	8.5 (7.1, 10.2)	8.3 (7.3, 10.1)	8.5 (7.3, 9.6)	8.4 (7.0, 9.7)	8.1 (7.1, 9.4)	8.0 (7.0, 9.1)	0.113
> 12	15 (5.7)	5 (2.0)	5 (2.9)	7 (3.8)	4 (2.1)	7 (4.0)	0.523

[1]median (IQR) or n(%), [2]trimester-specific reference ranges (1st=0.1-2.5 mIU/L, 2nd=0.2-3.0 mIU/L, 3rd=0.3-3.0 mIU/L), [3]per intention-to-treat, using linear mixed models for continuous data; generalized linear mixed models for binary data, [4]Not available, data could not be normalized

significant change in TSH but a significant decrease in fT4 from baseline to 30 weeks. Median Tg concentration increased significantly in the placebo group during the intervention ($p<0.05$).

At baseline, 4.7% of women had subclinical hyperthyroidism and 8.6% of women had subclinical hypothyroidism (**Table 4.3**). The prevalence of all subtypes of thyroid dysfunction did not differ significantly during the study ($p>0.05$).

Table 4.3 Prevalence of thyroid dysfunction among Thai pregnant women given 200 µg iodine daily or placebo[1]

Thyroid dysfunction[2]	Baseline (Week 11)		Week 20		Week 30		p
	Placebo	Iodine	Placebo	Iodine	Placebo	Iodine	value[3]
Hyperthyroidism	12 (4.6)	13 (5.2)	4 (2.4)	4 (2.1)	4 (2.1)	7 (4.0)	0.715
Overt hyperthyroidism	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Subclinical hyperthyroidism	12 (4.6)	12 (4.8)	4 (2.4)	4 (2.1)	4 (2.1)	7 (4.0)	-
Hypothyroidism	26 (9.9)	24 (9.6)	6 (3.6)	13 (7.2)	4 (2.1)	7 (4.0)	0.708
Overt hypothyroidism	4 (1.5)	2 (0.8)	0 (0.0)	2 (1.1)	0 (0.0)	1 (0.6)	-
Subclinical hypothyroidism	22 (8.4)	22 (8.8)	6 (3.6)	11 (6.1)	4 (2.1)	6 (3.4)	-
Isolated hypothyroxinemia	15 (5.7)	17 (6.8)	11 (6.4)	19 (10.4)	14 (7.3)	13 (7.4)	0.609

[1]n(%), [2]overt hyperthyroidism: low TSH + high TT4; subclinical hyperthyroidism: low TSH + normal TT4; overt hypothyroidism: high TSH + low TT4; subclinical hypothyroidism: high TSH + normal TT4; isolated hypothyroxinemia: normal TSH + low TT4. [3]per intention-to-treat, using generalized linear mixed models.

At 6-week postpartum (**Table 4.4**), median Tg, TT4 and TT3 concentrations were significantly higher in the placebo group than in the iodine group ($p=0.043$, 0.010, and 0.003, respectively). There were no significant differences in other thyroid functions, thyroid volume or the prevalence of TPO-Abs ($p>0.05$). The prevalence of hyperthyroidism was significantly lower in the iodine group (3%) as compared to the placebo group (9%) (OR: 95%CI, 0.17: 0.04-0.70). Of the women who were hypothyroid in the postpartum, six women had elevated TPO-Abs. The percentage of women with a TT3 concentration less than 1.3 nmol/L was significantly greater in the iodine group (23%) as compared to the placebo group (11%) (OR: 95%CI, 2.77: 1.27-6.05). Sixty-one percent of women in the placebo group and 73% in the iodine group had a UIC value greater than 100 µg/L ($p>0.05$).

Table 4.4 Thyroid function, thyroid volume and urinary iodine concentration of Thai women at 6 weeks postpartum after being given 200 µg iodine daily or placebo during pregnancy[1]

	Placebo (n=135)	Iodine (n=129)	Beta	p value[2]	R square
Thyroid function					
TSH (mIU/L)	1.26 (0.87, 1.73)	1.21 (0.74, 1.65)	0.093	0.147	0.135
< 0.4	13 (9.6)	6 (4.6)			
> 4.0	1 (0.8)	1 (0.9)			
Free T4, ng/dL	1.01 (0.93, 1.13)	1.02 (0.92, 1.09)	-0.078	0.225	0.181
< 0.89	19 (17.3)	23 (21.1)			
> 1.76	3 (2.2)	2 (1.5)			
Total T4, nmol/L	85.6 (74.3, 97.8)	81.3 (69.5, 94.4)	-0.154	0.010	0.253
< 58	6 (5.0)	8 (7.0)			
> 161	1 (0.7)	2 (1.5)			
Free T3, pg/mL	3.01 (2.64, 3.41)	2.85 (2.53, 3.21)	-0.116	0.079	0.155
< 1.8	0 (0)	0 (0)			
> 4.2	6 (4.4)	3 (2.3)			
Total T3, nmol/L	1.56 (1.40, 1.80)	1.50 (1.31, 1.65)	-0.183	0.003	0.210
< 1.3	12 (10.5)	26 (22.5)			
> 2.6	2 (1.5)	1 (0.8)			
Tg (ng/mL)	9.51 (4.79, 15.90)	7.94 (4.89, 15.30)	-0.105	0.043	0.471
> 38.5	6 (4.4)	5 (3.8)			
TPO-Abs, IU/mL	34.3 (23.7, 47.1)	34.4 (25.1, 52.2)	0.036	0.470	0.446
≥ 35	58 (48.3)	57 (49.6)			
TT3/TT4 ratio	0.0186	0.0187			
	(0.0161, 0.0224)	(0.0157, 0.2161)			
fT3/fT4 ratio	2.9630	2.7700			
	(2.5086, 3.3952)	(2.4420, 3.2877)			
Thyroid volume, ml	7.2 (6.1, 8.4)	7.3 (5.8, 9.0)	-0.002	0.975	0.295
> 12	4 (3.0)	8 (6.2)			
Thyroid dysfunction[3]					
Hyperthyroidism	12 (9.1)	4 (3.2)			
Overt hyperthyroidism	3 (2.3)	2 (1.6)			
Subclinical hyperthyroidism	9 (6.8)	2 (1.6)			
Hypothyroidism	1 (0.8)	1 (0.8)			
Overt hypothyroidism	0 (0.0)	1 (0.8)			
Subclinical hypothyroidism	1 (0.8)	0 (0.0)			
Isolated hypothyroxinemia	18 (13.5)	20 (15.5)			
Urinary iodine concentration, µg/L	93.6 (60.3, 159.8)	115.5 (73.0, 155.3)	0.063	0.305	0.122
≥ 100	61 (48.4)	73 (58.9)			
50 – 99	47 (37.3)	38 (30.6)			
20 – 49	17 (13.5)	13 (10.5)			
< 20	1 (0.8)	0 (0)			

[1]median (IQR) or n(%), [2]linear regression (adjusted for age, gestational age at delivery, BMI at 6wk, parity, baseline value of each dependent variable and duration from delivery to w6).
[3]classified by using the definition of Helfand & Redfern (1998): overt hyperthyroidism: low TSH + high free T4; subclinical hyperthyroidism: low TSH + normal free T4; overt hypothyroidism: high TSH + low free T4; subclinical hypothyroidism: high TSH + normal free T4; isolated hypothyroxinemia: normal TSH + low free T4.
***OR(95% CI)** using logistic regression for the prevalences. 1.08(0.07-17.43) for TSH>4.0mIU/L; 1.55(0.76-3.17) for fT4<0.89ng/dL; 1.99(0.61-6.55) for TT4<58nmol/L; error for fT3<1.8 pg/mL; 2.77(1.27-6.05) for TT3<1.3nmol/L; 0.94(0.21-4.20) for Tg>38.5ng/mL; 1.00(0.55-1.83) for TPO-Ab≥35IU/mL; 2.29(0.65-8.06) for thyroid volume>12ml; 0.17(0.04-0.70) for hyperthyroidism; error for hypothyroidism; 1.19(0.57-2.51) for isolated hypothyroxinemia.*

Newborn thyroid function, thyroid volume and birth characteristics, as well as UIC and NBAS score at 6 weeks postpartum are shown in **Table 4.5**. The percentage of low birth weight and preterm birth were higher in the placebo group (8.8% and 10.6%, respectively) than in the iodine group (5.4% and 5.4%, respectively), but these differences were not statistically significant. Length of gestation also did not differ significantly between groups (placebo 268.7 ± 11.9 days, iodine 270.5 ± 8.9; p=0.143). There were no significant differences between newborn groups in any of the other variables measured. After the newborns who were born at gestational age <35 weeks were excluded, no significant differences were seen in median NBAS scores between the groups (p>0.05).

Discussion

This study is the largest randomized controlled trial of iodine supplementation in mildly ID pregnant women that has been done to date. The iodine supplementation regimen was well tolerated by the women and significantly increased iodine intakes into the adequate range as judged by a median UIC >150 μg/L at 20 and 30 weeks. In the intention-to-treat analysis, there were no significant differences in maternal thyroid functions, thyroid disorders or thyroid volume during the study. However, at 6 weeks postpartum, thyroid hormone concentrations and Tg were higher in women in the placebo group and there was a significantly increased risk of postpartum hyperthyroidism, most of it mild and subclinical. Among the newborns, there were no significant differences in thyroid functions, thyroid volume, or in development scores and UICs at 6 weeks postpartum. There was tendency for reduced risk of low birth

Table 4.5 Neonatal characteristics, thyroid function, thyroid volume, urinary iodine concentration and Neonatal Behavioral Assessment Scales score in Thai newborns born to women who were given 200 µg iodine daily or placebo during pregnancy (N=324)[1]

	Placebo	n	Iodine	n	Beta	p value[3]	R square
At delivery							
Characteristics							
Sex; female:male	87 : 83		80 : 69				
Birth weight, gram[2]	3092 ± 478	170	3120 ± 392	149	0.010	0.831	0.326
< 2500, n(%)	15 (8.8)		8 (5.4)				
Preterm, n(%)	18 (10.6)		8 (5.4)				
Head circumference, cm	34.0 (33.0, 35.0)	164	34.0 (33.0, 35.0)	147	-0.062	0.256	0.185
Ponderal index[2]	25.0 ± 2.2	166	25.4 ± 2.0	147	0.085	0.142	0.066
< 10th percentile, n(%)	5 (3.0)		1 (0.7)				
Small-for-gestational age, n(%)	24 (14.1)		26 (17.4)				
Thyroid function (cord blood)							
TSH (mIU/L)	5.630 (3.545, 8.320)	165	5.240 (3.290, 8.490)	147	-0.010	0.866	0.017
fT4 (ng/dL)	1.09 (0.96, 1.18)	162	1.06 (0.95, 1.17)	141	-0.037	0.547	0.024
TT4 (nmol/L)	119.0 (103.0, 138.0)	167	114.0 (96.7, 138.5)	146	-0.041	0.492	0.018
fT3 (pg/mL)	1.76 (1.42, 2.32)	139	1.72 (1.39, 2.40)	114	0.062	0.364	0.070
TT3 (nmol/L)	0.86 (0.72, 1.49)	88	0.86 (0.71, 1.71)	79	0.137	0.108	0.039
Tg (ng/mL)	53.0 (31.2, 84.1)	165	41.6 (18.3, 81.5)	145	-0.059	0.337	0.029
TPO-Abs (IU/mL)	11.5 (10.0, 17.0)	173	11.2 (10.0, 17.1)	151	0.014	0.716	0.543
Thyroid volume, ml[2]	0.72 ± 0.2	67	0.63 ± 0.3	64	-0.095	0.274	0.142
Post-delivery							
Within 72 hrs after delivery							
DBS-TSH, mIU/L	1.4 (0.9, 2.2)	118	1.4 (0.9, 2.5)	101	0.008	0.927	0.026
> 5, n(%)	4 (3.4)		2 (2.0)				
Week 6 postpartum							
Urinary iodine concentration, µg/L	193.3 (136.7, 303.5)	76	168.7 (97.3, 305.7)	83	0.039	0.660	0.040
< 100, n(%)	9 (11.8)		21 (25.3)				
NBAS score							
Habituation	7.6 (6.8, 8.1)	18	7.0 (5.4, 8.3)	22	-0.321	0.109	0.213
Social-interactive	6.9 (6.0, 8.1)	68	7.4 (6.4, 8.0)	66	0.091	0.343	0.062
Motor system	5.8 (5.2, 6.4)	72	6.0 (5.3, 6.6)	73	0.051	0.584	0.026
State organization	3.8 (3.0, 4.1)	53	3.8 (2.8, 4.0)	48	-0.059	0.606	0.071
State regulation	4.0 (2.6, 4.7)	40	4.0 (3.3, 4.5)	38	-0.041	0.747	0.164
Autonomic system	6.7 (5.3, 7.3)	71	6.7 (6.0, 7.3)	61	0.105	0.288	0.056
Reflexes	3.0 (2.0, 4.0)	75	3.0 (1.8, 4.0)	74	0.005	0.959	0.012
Supplementary items	6.3 (5.1, 8.1)	55	6.7 (5.3, 8.3)	48	0.040	0.714	0.101

[1]median (IQR), [2]mean ± SD, [3]linear regression (adjusted for age, pre-pregnancy BMI, parity, gestational age at baseline, gestational age at delivery, UIC at w30,and baseline value of each dependent variables for thyroid function).
***OR(95% CI)** using logistic regression for the prevalence: 0.92(0.31-2.75) for low birth weight; 0.48(0.19-1.19) for preterm; 0.22(0.03-1.92) for PI<10th percentile; 1.06(0.56-2.01) for SGA; 0.30(0.03-2.69) for DBS-TSH>5mIU/L; 1.69(0.68-4.19) for UIC<100μg/L.*

weight and preterm birth in the iodine group, but this did not reach statistical significance. Therefore, in summary, although iodine supplementation was safe and effective in normalizing iodine intakes, it had no measured benefit for the mother during pregnancy and no benefit on newborn variables out to 6 weeks. However, it did reduce the risk of postpartum thyroid dysfunction in the mothers.

Similar to our study, previous iodine supplementation studies in pregnant women, also showed a 2- to 3-fold increase of UIC in the treated group (Romano 1991; Pedersen 1993; Liesenkotter 1996). However, in our study, an increment of UIC was also found in the placebo group, which may be caused by an increase of renal clearance over pregnancy (Delange 2004). However, we did not find such a difference in UIC between trimesters in an earlier cross-sectional study in women from the same area (Gowachirapant 2009). It may be due to increased awareness of the importance of iodine intake during pregnancy, women in the study may have changed their habits. Nevertheless, there was a distinct difference in UIC between groups in the 2nd and 3rd trimester of pregnancy. When a median UIC of >500 μg/L was used for indicating iodine excess, only a few women in this population reported a median UIC above the cut-off. It can be concluded that supplementation with 200 μg iodine per day appears to be a good dose for this mild-to-moderate ID pregnant women, effective at increasing intakes into the recommended range of UIC without causing excess iodine intakes.

There have been several controlled trials of iodine treatment in mild-to-moderately iodine deficient pregnant women in Europe that have measured maternal and newborn thyroid function. Romano et al (Romano 1991) gave 120-180 μg iodine as iodized salt or control daily beginning in the 1st trimester to healthy pregnant Italian women (n=35; median UIC 31-37 μg/L). Iodine supplementation increased median UIC 3-fold and

maternal thyroid volume was lower, but there was no effect on maternal TSH. Pedersen et al (Pedersen 1993) randomized pregnant Danish women (n=54) to receive either 200 μg iodine/day as KI solution or no supplement from 17 weeks to term. Median UIC increased from 55 μg/L to 90-110 μg/L in the treated group. Maternal thyroid volume increased 16% in the treated group vs. 30% in controls. Maternal Tg and TSH, and cord Tg were significantly lower in the treated group, but there were no significant group differences on maternal or cord T4, T3, and fT4. In a double-blind, placebo-controlled trial, Glinoer et al (Glinoer 1995) supplemented pregnant Belgian women with biochemical criteria of excess thyroid stimulation (n=120; median UIC 36 μg/L) with 100 μg iodine/day or control from ~14 weeks to term. Treatment had no significant effect on maternal or cord T3, fT4, and T3/T4 ratio. Iodine treatment resulted in significantly higher maternal UIC, and lower thyroid volume, TSH and Tg concentrations. Newborns of the treated group also had significantly higher UIC, lower thyroid volume and Tg concentrations. Liesenkotter et al (Liesenkotter 1996) gave 230 μg iodine/day or control from 11 weeks to term in pregnant German women (n=108; median UIC 53 μg/g creatinine; goiter rate 42.5%). In the iodine group, median UIC increased to 104 μg/g creatinine and newborn thyroid volume was significantly lower, but there were no significant group differences in maternal TSH, Tg, T3, T4, or thyroid volume, or newborn TSH. In a placebo-controlled, double-blind trial, Nohr et al (Nohr 2000) gave a multinutrient supplement containing 150 μg iodine/day or control to pregnant Danish women positive for antithyroid peroxidase antibodies (n=66) from 11 week to term, and found no differences in maternal TSH, fT4 or Tg between groups. Finally, Antonangeli et al (Antonangeli 2002) supplemented pregnant Italian women (n=67; median UIC 74 μg/g creatinine) with 50 μg or 200 μg iodine/day from 18-26 week to near term but found no significant differences in maternal fT4, fT3, TSH, Tg or thyroid volume between groups.

Our study population with a baseline median UIC of ca. 110 μg/L, was less iodine deficient than these European populations and our sample size was much larger. Our findings that maternal and newborn thyroid functions did not differ between groups confirm the previous European studies in that none of those studies showed a significant

impact of supplementation on maternal and newborn total or free thyroid hormone concentrations. In the European studies, although iodine supplementation generally reduced thyroid size compared to controls, only two of six studies reported that maternal TSH or Tg was lower with supplementation. In contrast, in our study, there were no group differences in maternal or newborn TSH, Tg or thyroid volume. Taken together, these studies suggest that when maternal iodine deficiency is moderate (baseline median UIC <100 μg/L), the maternal thyroid is able to adapt to meet the increased need for thyroid hormone by a small increase in thyroid stimulation manifest as a small increases in thyroid volume and, in some instances, a modest increase in TSH or Tg. In more mild iodine deficiency (median maternal UIC 100-150 μg/L), the thyroid is able to adapt without a measurable increase in thyroid stimulation. Iodine intake in the general Thai population is adequate (Gowachirapant 2009; Gowachirapant 2014) and many of the women in our study are likely to have entered pregnancy with abundant stores of intrathyroidal iodine. Once pregnant, although their daily iodine requirement increases and their iodine intakes are mildly deficient, the thyroid is able to draw on iodine from the thyroidal iodine pool (which can be 10-20 mg in healthy adults) in order to meet needs for thyroid hormone synthesis and maintain euthyroidism (Zimmermann 2009).

Postpartum thyroiditis (PPT) is the occurrence of thyroid dysfunction in the first postpartum year in women who prior to pregnancy were euthyroid (Stagnaro-Green 2011). Its overall prevalence is approximately 5%, but PPT develops in 33-50% of women who are TPO-positive in the first trimester (Smallridge 2000; Stagnaro-Green 2012). In the classic form (ca. 25% of cases), transient hyperthyroidism is followed by hypothyroidism, which may be permanent in 10-50% of cases; another 32% of cases present with isolated hyperthyroidism (Stagnaro-Green 2011; Stagnaro-Green 2012). In our study, at 6 weeks postpartum, there was significantly more PPT in the placebo group than in the iodine group (9.9% vs. 4.0%, respectively) and nearly all of the PPT was mild hyperthyroidism without clinical symptoms. The OR (95% CI) for hyperthyroidism in the iodine group was 0.17 (0.04-0.70), and TT3 and TT4 concentrations were also significantly higher in the placebo group than in the iodine

group. The prevalence of TPO-positivity in the women with PPT was 49% but positivity rates and median TPO-Abs concentrations did not differ significantly between groups (Table 4.4). Whether iodine intake during pregnancy and the postpartum period is a risk factor for PPT remains unclear. Three randomized studies have examined the effects of iodine supplementation on PPT. In a mildly iodine-deficient German population, women with no previous thyroid disease (n=70) received either 50 or 250 μg/day iodine postpartum; there were no differences in PPT prevalence over 8 months postpartum between groups (Reinhardt 1998). In an iodine sufficient Swedish population, TPO-positive women (n=58) received 150 μg/day iodine or control postpartum, and the iodine exacerbated the hypothyroid phase of PPT (Kampe 1990). In the third study, moderately iodine deficient TPO-positive Danish pregnant women (n=66) were given 150 μg/day iodine (as a part of a multivitamin -mineral containing 50 μg/day of selenium) or the same supplement without iodine; the supplement was given during pregnancy only or during pregnancy and the postpartum. There were no significant differences in frequency or severity of PPT over 9 months postpartum between groups (Nohr 2000). In contrast to these previous studies that suggested iodine has no effect or may aggravate PPT, our data suggest iodine supplementation during pregnancy reduces risk of PPT in mildly iodine deficient women.

In this study, we saw a trend toward a beneficial effect of iodine supplementation on prevalence of low birth weight and preterm delivery. Severe ID during pregnancy is known to cause stillbirths, congenital cretinism and dwarfism (WHO/UNICEF/ICCIDD 2001). Because thyroid hormone stimulates growth hormone secretion and modulates the effects of growth hormone receptor (Crews 1989; Samuels 1989; Hochberg 1990), which may explain effects of iodine on growth. Furthermore, insulin-like growth factor (IGF)-1 and insulin-like growth factor-binding protein (IGFBP)-3 are also dependent on thyroid hormone status (Burstein 1979; Geary 1989; Angerva 1993; Miell 1993; Nanto-Salonen 1993). Our modest findings are supported by an Algerian study where 0.5 ml of oral iodized oil given to moderately ID pregnant women before or during the first trimester of pregnancy increased birth weight (Chaouki 1994). More data from controlled studies on the effects of iodine supplementation on fetal growth and

gestational length are needed to draw firm conclusions. Of interest, and confirming findings of previous studies linking maternal thyroid autoimmunity to preterm birth (Negro 2006), 11 of 16 preterm babies were born to mothers who were TPO positive in the first trimester.

The Neonatal Behavioral Assessment Scales (NBAS) has been used in several studies to examine the effects of pre- and perinatal risk factors (Ferrari 1986; Anderson 1989; Rizzo 1991; Oyemade 1994), obstetric medication and mode of delivery on neonatal behavior (Gathwala 1990; Steinberg 1992). Results of a study among 209 low birth weight and/or premature Japanese infants confirmed the usefulness of the NBAS for predicting the risk of later developmental disabilities (Ohgia 2003). In the present study, we did not see any differences in NBAS scores between newborns born to mothers from either group. This may be a logical consequence of the fact that the intervention did not provide an explicit improvement of thyroid function both in mothers and their newborns. However, when concerning low birth weight infants, the NBAS cluster scores of state regulation and supplementary items were significantly lower in low birth weight infants compared to normal weight infants (data not shown).

The high percentage of loss to follow up in the study is a limitation of this trial. Loss to follow up can bias the results and may lead to erroneous interpretation. Despite the fact that all women were asked for their intention to stay in the same area of residence for the duration of the study, most of the loss-to-follow up was caused by women or their newborns moving back to their hometown. In Thailand, it is common that infants born in an urban area will grow up with relatives in a rural area, sometimes far away from their parents. However, in our study, loss to follow up was similar in both intervention groups, and reasons for decline were not different. Therefore, we are confident that the loss to follow up was not caused by the study treatment itself, and therefore inferences still can be made.

In conclusion, supplementation of 200 μg iodine/day in mildly iodine deficient pregnant Thai women beginning at the end of the first trimester was safe and well-tolerated.

Iodine supplementation increased maternal iodine intakes into the adequate range but did not significantly improve maternal or newborn thyroid function, birth outcomes, or newborn development at 6 weeks postpartum. However, it modestly but significantly reduced the risk of postpartum thyroiditis. Further data analysis in the mothers and infants over the first two years postpartum will reveal whether iodine supplementation has led to any maternal benefits or improvement in child development at later ages. Furthermore, results from a second study site in India are currently being analyzed to see if they support the findings of this study.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Chapter 5

Pre-pregnancy body mass index and gestational weight gain in Thai pregnant women and associations with pregnancy outcomes

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Abstract

Maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) have been reported to be associated with pregnancy outcomes, especially with birth weight. Due to the nutritional transition in Thailand, the double burden of malnutrition is increasing and this may have negative consequences on birth outcomes.

This study aimed to investigate the relationship between pre-pregnancy BMI and GWG with pregnancy outcomes.

We performed a secondary analysis of data obtained from an RCT of iodine supplementation in mildly iodine deficiency (ID) pregnant Thai women. Pre-pregnancy BMI was classified using the WHO classification. GWG was categorized using the IOM recommendation. Binary and multinomial logistic regressions were used to investigate the relationship between pre-pregnancy BMI and GWG with pregnancy outcomes.

Among 378 pregnant women, the prevalence of pre-pregnancy underweight (BMI <18.5 kg/m^2) and overweight (BMI ≥ 25 kg/m^2) were 17.2% and 14.3%, respectively. Normal weight women had the highest median GWG [15.0 (12.0, 19.0)] when compared to underweight [13.7 (11.4, 18.5)] and overweight women [13.2 (9.0, 16.3)]. Forty one percent of women had excessive GWG, while 23% of women gained weight inadequately. Women with a high pre-pregnancy BMI had an 11-fold higher risk of having a large for gestational age infant. Women who had excessive GWG were 5.6 times more likely to deliver a newborn with macrosomia.

In conclusion, both high pre-pregnancy maternal weight and excessive weight gain during pregnancy increase risk of infant macrosomia. Therefore, maintaining normal body weight before and throughout pregnancy should be recommended in order to reduce the risk of excessive infant birth weight and its associated complications.

Introduction

Despite a rising trend in overnutrition in young children and in non-communicable diseases among adults,[1,2] the prevalence of low birth weight (LBW) in Thailand has remained at a constant level of 8-10% over the last 10 years.[3]

Undernutrition, both before and during pregnancy, results in poor fetal growth, LBW, and preterm birth.[4,5] In contrast, overnutrition is associated with higher risk of macrosomia, cesarean delivery, and other pregnancy complications such as gestational diabetes and preeclampsia.[4-6] Maternal nutrition may not only affect the immediate pregnancy outcomes. Since fetal and early postnatal life is a period of rapid growth and development, nutritional perturbations during this period may predispose to health and diseases later in life.[7-9]

The relationship between pre-pregnancy nutritional status and gestational weight gain (GWG) with birth weight has been investigated in many studies in Thailand.[10-14] The evidence showed that low pre-pregnancy BMI and less GWG was one of the determinants of LBW in Thai population.[11,14] On the other hand, high GWG was associated with high birth weight.[10,12,13] The evidence of the relationship between maternal nutritional status on timing of delivery was also documented. High pre-pregnancy BMI increased risk of preterm delivery.[15,16] Among high pre-pregnancy BMI women, low GWG was associated with an increased risk of preterm delivery.[17]

In order to obtain collective evidence on these associations, studies are needed to assess the risk for both LBW and macrosomia related to maternal body weight in populations presently undergoing the nutrition transition, such as Thailand. This knowledge can guide us to more appropriate recommendations in Thailand and other countries in the region that are also facing the double burden of malnutrition. Therefore, this study aimed to investigate the association between pre-pregnancy BMI and GWG with pregnancy outcomes.

Participants and Methods

Participants

This study is a secondary analysis of data obtained from a randomized double blind controlled trial on the effect of iodine supplementation in mild-to-moderately iodine-deficient pregnant women on thyroid function, pregnancy outcomes and early infant development in Thailand. The intervention study was conducted among pregnant Thai women who had attended antenatal clinic at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand between October 2008 and June 2013. Inclusion and exclusion criteria were explained in previous publication.[18] Pregnant women were followed-up until delivery. The analyses were limited to 380 women who had birth outcome data.

The ethical review boards of Wageningen University, the Netherlands and Ramathibodi Hospital, Thailand approved the study protocol. The study was registered into the clinical trials database at http://www.clinicaltrials.gov/ and its identifier number is NCT00791466.

Methods

At enrolment, maternal characteristics of the women including age, parity, education and occupation were recorded using a questionnaire. Data on birth weight and date of delivery were obtained from the hospital records. Self-reported pre-pregnancy weight and measured height at the enrolment were used for pre-pregnancy BMI (kg/m^2) calculation. Weight at the first antenatal visit (4%) or at the enrolment (1%) was used in women whom pre-pregnancy weight was not available. Pre-pregnancy BMI was classified using the international cut-off points proposed by WHO; underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2).[19] Due to small number of obese women (n=15, 4%), women with BMI ≥25.0 kg/m^2 were considered as overweight.

GWG was estimated as the difference in kilograms between the delivery weight and pre-pregnancy weight. GWG was categorized as inadequate, adequate, and excessive, according to the IOM recommendations.[20] Adequate GWG was defined as 12.5–18, 11.5–16, 7–11.5, and 5–9 kg for underweight, normal weight, overweight, and obese women, respectively.

Low birth weight was defined as weight at birth of <2500 grams, while macrosomia was defined as weight at birth ≥4000 grams. Preterm was defined as babies born alive before 37 weeks of pregnancy.

Maternal blood sample was collected at baseline, 2nd and 3rd trimester, and at delivery for hemoglobin (Hb) concentration measurement. Hb concentration was analysed using flow cytometry method (automated blood count analyzer, Sysmex, USA) at Ramathibodi Hospital.

Statistical analyses

Participant's characteristics are presented as means±SD, medians (first, third quartiles), or percentages, where appropriate. Participant's characteristics were compared by pre-pregnancy BMI and GWG categories using Chi-square test for discrete variables and analysis of variance (ANOVA) with Tukey's post hoc or Kruskal-Wallis test with Mann-Whitney *U* test for continuous data. Binary and multinomial logistic regressions were used to assess the relationship between pre-pregnancy BMI and GWG with pregnancy outcomes including birth weight and preterm delivery. The models were adjusted for parity, pre-pregnancy BMI or GWG, Hb at 3rd trimester, sex of baby, gestational diabetes mellitus, preeclampsia, treatment group, and preterm delivery (for birth weight outcome only). All statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL).

Results

Of 380 pregnant women, 2 women were excluded from data analyses because of the uncertainty in GWG (GWG less than 0.5 kg). Hence, the data of 378 pregnant women were analyzed. Maternal characteristics presented by pre-pregnancy BMI are shown in **Table 5.1**. The prevalence of underweight and overweight were 17.2% and 14.3%, respectively. Underweight women tended to be younger than normal and overweight women ($p<0.01$). Median GWG in normal weight women [15.0 (12.0, 19.0) kg] was higher than in underweight [13.7 (11.4, 18.5) kg] and overweight women [13.2 (9.0, 16.3) kg] ($p<0.01$). According to the IOM recommendation for GWG, 22.8 %, 36.2 %, and 41.0 % of women had inadequate, adequate, and excessive weight gain, respectively (**Table 5.2**). Median Hb concentrations were not different by both pre-pregnancy BMI and GWG categories ($p>0.05$) (**Table 5.1, 5.2**).

The average birth weight of infants born to underweight women was lower than that of infants born to overweight women ($2988_{\pm}478$ g vs. $3224_{\pm}579$ g, $p<0.05$). However, the average birth weight of infants born to normal weight women did not differ from that of infants born to underweight and overweight women (**Table 5.3**). Similarly, the average birth weight of infants born to inadequate GWG women was lower than that of those born to excessive GWG women ($3021_{\pm}407$ g vs. $3189_{\pm}495$ g, $p<0.05$) but it was similar to that of infants born to adequate GWG women ($p>0.05$).

The relationships between pre-pregnancy BMI and birth weight and preterm delivery are shown in **Table 5.4**. In unadjusted multinomial logistic regression model, women who were underweight before pregnancy were 2.7 times (crude OR: 2.65, 95%CI: 1.08-6.53) as likely to have LBW infants compared to normal weight women. However, this significant relationship disappeared in the adjusted model. In addition, women who were overweight before pregnancy were 6.1 times (crude OR: 6.12, 95%CI: 1.83-20.41) as likely to have macrosomic infants compared to normal weight women. The relationship was stronger after adjusting for possible confounders (adjusted OR: 11.48,

Table 5.1 Characteristics of participants classified by pre-pregnancy body mass index (BMI)

Characteristics	Pre-pregnancy BMI[1]			
	Underweight	Normal weight	Overweight	p-value[2,3]
No. of participants (%)	65 (17.2)	259 (68.5)	54 (14.3)	-
Maternal age[4], y	27.0 ± 4.8[a]	30.0 ± 4.8[b]	30.0 ± 5.2[b]	0.000
Pre-pregnancy BMI[5], kg m^{-2}	17.7[a] (17.1, 18.1)	21.0[b] (19.7, 22.3)	27.9[c] (26.4, 30.5)	0.000
Gestational weight gain, kg	13.7[a,b] (11.4, 18.5)	15.0[a] (12.0, 19.0)	13.2[b] (9.0, 16.3)	0.036
Gestational weight gain, %				
Inadequate	35.4	22.4	9.3	0.000
Adequate	40.0	37.8	24.1	
Excessive	24.6	39.8	66.7	
Parity, %				
Primiparous	55.4	39.0	35.2	0.035
Multiparous	44.6	61.0	64.8	
Education, %				
<12 yr	4.6	8.1	13.0	0.411
12 yr	30.8	36.3	35.2	
>12 yr	64.6	55.6	51.9	
Occupation, %				
Officer workers	52.3	50.2	46.3	0.193
Owned business	12.3	17.4	9.3	
General employee	10.8	15.1	25.9	
Others	24.6	17.4	18.5	
Hemoglobin at baseline, g/L	117 112 (124)	120 (113, 127)	120 (116, 127)	0.136
Hemoglobin at 3rd trimester, g/L	114 (110, 122)	116 (110, 122)	119 (111, 123)	0.289

[1]BMI (kg m^{-2}): underweight (<18.5), normal weight (18.5–24.9), and overweight (≥25.0)

[2]Chi-square test for discrete data

[3]ANOVA or Kruskal-Wallis test for continuous data; values in a row without a common letter differs

[4]Mean ± SD (all such values)

[5]Median (first, third quartiles) (all such values)

Table 5.2 Characteristics of participants classified by gestational weight gain (GWG)

Characteristics	IOM gestational weight gain[1]			
	Inadequate	Adequate	Excessive	p-value[2,3]
No. of participants (%)	86 (22.8)	137 (36.2)	155 (41.0)	-
Maternal age[4], y	29.0 ± 5.9	30.0 ± 4.9	29.0 ± 4.5	0.139
Pre-pregnancy BMI[5], kg m^{-2}	20.6[a] (18.3, 22.3)	20.4[a] (18.8, 22.5)	21.3[b] (19.8, 24.3)	0.001
Gestational weight gain, kg	10.0[a] (7.6, 11.0)	13.7[b] (12.6, 15.0)	19.0[c] (17.0, 22.0)	0.000
Parity, %				
Primiparous	38.4	37.2	46.5	0.230
Multiparous	61.6	62.8	53.5	
Education, %				
<12 yr	10.5	9.5	5.8	0.535
12 yr	38.4	32.1	36.1	
>12 yr	51.2	58.4	58.1	
Occupation, %				
Officer workers	43.0	50.4	53.5	0.566
Owned business	17.4	16.1	13.5	
General employee	17.4	18.2	15.9	
Others	22.1	15.3	20.0	
Hemoglobin at baseline, g/L	120 (113, 125)	120 (113, 126)	120 (114, 126)	0.974
Hemoglobin at 3rd trimester, g/L	114 (108, 122)	118 (111, 123)	115 (110, 123)	0.252

[1]Adequate gestational weight gain: 12.5–18, 11.5–16, 7–11.5, and 5–9 kg for underweight, normal weight, overweight, and obese women

[2]Chi-square test for discrete data

[3]ANOVA or Kruskal-Wallis test for continuous data; values in a row without a common letter differs

[4]Mean ± SD (all such values), [5]Median (first, third quartiles) (all such values)

Table 5.3 Pregnancy outcomes classified by pre-pregnancy BMI and gestational weight gain

Pregnancy outcomes	Pre-pregnancy BMI				Gestational weight gain			
	Underweight	Normal weight	Overweight	p-value[1,2]	Inadequate	Adequate	Excessive	p-value[1,2]
No. of participants	65	259	54	-	86	137	155	-
Birth weight[3], g	2988 ± 478[a]	3116 ± 405[a,b]	3224 ± 579[b]	0.016	3021 ± 407[a]	3074 ± 409[a,b]	3189 ± 495[b]	0.011
Birth weight, %								
< 2500 g	13.8	5.8	7.4	0.009	10.5	7.3	5.8	0.189
2500-2999 g	29.2	30.5	33.3		31.4	31.4	29.7	
3000-3999 g	55.4	61.4	48.1		57.0	59.9	58.1	
≥4000g	1.5	2.3	11.1		1.2	1.5	6.5	
Gestational age at delivery[4],wk	39 (38, 40)	39 (38, 40)	38.5 (38, 39)	0.719	39 (38, 40)	39 (38, 39)	39 (38, 40)	0.908
Preterm delivery, %	10.8	6.6	7.9	0.345	11.6	5.8	7.7	0.296

[1]Chi-square test for discrete data

[2]ANOVA or Kruskal-Wallis test for continuous data; values in a row without a common letter differs

[3]Mean ± SD (all such values)

[4]Median (first, third quartiles) (all such values)

Table 5.4 Crude and adjusted odds ratios (OR) for pregnancy outcomes classified by pre-pregnancy BMI

	Crude OR			Adjusted OR[1]		
	Pre-pregnancy BMI (kg/m^2)			Pre-pregnancy BMI (kg/m^2)		
	< 18.5	18.5 – 24.9	≥ 25.0	< 18.5	18.5 – 24.9	≥ 25.0
Birth weight (g)						
< 2500	2.65	Referent	1.63	2.36	Referent	1.42
	(1.08-6.53)*		(0.50-5.30)	(0.76-7.35)		(0.32-6.37)
2500-2999	1.06	Referent	1.39	0.76	Referent	1.47
	(0.57-1.97)		(0.72-2.69)	(0.38-1.53)		(0.67-3.25)
3000-3999	Referent	Referent	Referent	Referent	Referent	Referent
≥ 4000	0.74	Referent	6.12	0.76	Referent	11.48
	(0.09-6.31)		(1.83-20.41)**	(0.12-4.87)		(3.17-41.63)**
Preterm	1.72	Referent	1.78	1.13	Referent	1.09
delivery	(0.68-4.34)		(0.67-4.75)	(0.37-3.46)		(0.32-3.65)

*$p < 0.05$, **$p < 0.01$, multinomial logistic regression for birth weight and binary logistic regression for preterm

[1]adjusted for parity, gestational weight gain, hemoglobin at 3rd trimester, baby sex, gestational diabetes mellitus, preeclampsia, treatment group (and preterm for birth weight model only)

Table 5.5 Crude and adjusted odds ratios (OR) for pregnancy outcomes classified by gestational weight gain

	Crude OR			Adjusted OR[1]		
	Gestational weight gain			Gestational weight gain		
	Inadequate	Adequate	Excessive	Inadequate	Adequate	Excessive
Birth weight (g)						
< 2500	1.51	Referent	0.82	0.84	Referent	0.53
	(0.57-3.96)		(0.32-2.12)	(0.25-2.88)		(0.16-1.77)
2500-2999	1.05	Referent	0.98	0.81	Referent	0.76
	(0.58-1.91)		(0.58-1.63)	(0.41-1.61)		(0.41-1.41)
3000-3999	Referent	Referent	Referent	Referent	Referent	Referent
≥ 4000	0.84	Referent	4.56	1.59	Referent	5.62
	(0.07-9.47)		(0.97-21.41)	(0.18-13.80)		(1.09-29.06)*
Preterm	2.12	Referent	1.35	2.36	Referent	1.18
delivery	(0.80-5.61)		(0.54-3.42)	(0.75-7.43)		(0.38-3.65)

*$p < 0.05$, multinomial logistic regression for birth weight and binary logistic regression for preterm

[1]adjusted for parity, pre-pregnancy BMI, hemoglobin at 3rd trimester, baby sex, gestational diabetes mellitus, preeclampsia, treatment group (and preterm for birth weight model only)

95%CI: 3.17-41.63). There was no significant relationship between pre-pregnancy BMI and preterm delivery (p>0.05).

The relationships between GWG and birth weight and preterm delivery are summarized in **Table 5.5**. There was no relationship between inadequate GWG and having low or high birth weight (p>0.05). Nevertheless, the adjusted model showed that women who had excessive GWG were 5.6 times (adjusted OR: 5.62, 95%CI: 1.09-29.06) as likely to have macrosomic infants compared to women with normal GWG. GWG was not related to preterm delivery (p>0.05).

Discussion

Several publications reported the association between maternal pre-pregnancy BMI and GWG and pregnancy outcomes especially birth weight. Our findings from this secondary data analysis strengthened those results. Mothers who are underweight before pregnancy or gained weight inadequately tended to have a higher risk of having LBW infants when compared to overweight mothers or gained excessive weight. From the unadjusted multinomial logistic regression, underweight women had a 2.7-fold higher risk of having LBW infants, while overweight women had a 6-fold higher risk of having macrosomic infants compared to normal weight women. The relationship was stronger after adjusting for possible confounders, and overweight women had an 11-fold higher risk of having macrosomic infants. In addition, women who had excessive GWG were 5.6 times as likely to have macrosomic infants compared to women with normal GWG. These findings confirmed that maternal body weight both before and during pregnancy influence birth weight.

In accordance with our study, many investigators reported similar associations between pre-pregnancy BMI and birth weight. Fleten et al[21] reported a direct association between BMI and birth weight among 43,705 Norwegian mothers. The authors concluded that a one-unit increase in BMI resulted in a 20.3 gram increase in birth weight. Moreover, a study among 292,568 singleton term Chinese pregnancies,

pre-pregnancy underweight was associated with an increased risk of delivering a LBW infant (OR 1.9, 95%CI 1.3-1.6), while overweight and obese women had a 2.5- and 3.5-fold of giving birth to a macrosomic infant, respectively.[5] The association between BMI and birth weight can be related to several explanations: 1) protein-energy availability; 2) micronutrient intakes; and 3) plasma volume. Fetuses of low pre-pregnancy weight women may receive inadequate nutrients from the mothers and hence the growth of the fetus is restricted.[22] Previous evidence showed that micronutrient deficiencies which are common in developing countries contributed to intrauterine growth restriction (IUGR). Increased micronutrient intakes leads to an increase in infant birth size and a reduction of IUGR in low pre-pregnancy BMI women.[23] Moreover, underweight women have smaller plasma volume compared to normal or overweight women. A low plasma volume leads to a low cardiac output. Consequently, a low cardiac output may result in a low utero-placental blood flow and thus a decrease in nutrient transfer from the mothers to the fetuses in underweight women.[24] However, in the present study, a significant relationship between pre-pregnancy BMI and LBW disappeared in the adjusted regression model. This might be due to the reason that other pregnancy complications, such as preeclampsia, play a stronger role in explaining LBW in this population.

Consistent with other reports, when GWG was taken into consideration, women who gained weight excessively during pregnancy showed a higher risk of having macrosomic babies when compared to women with normal GWG. In addition, a systematic review of the effect of maternal weigh gain during pregnancy on birth weight confirmed our findings that excessive GWG increased risk of high birth weight in normal and obese pregnant women.[25] However, due to limited sample size, we were not able to categorize our population by both pre-pregnancy weight and GWG simultaneously.

Although the international BMI cut-off points have been recommended and widely used as a tool for assessing individual nutritional status,[26] an appropriate cut-off points for Asian population is still controversial. Some evidence showed that Asians generally have

a higher percentage of body fat than Europeans and the risks of type 2 diabetes and cardiovascular disease is substantial among Asians at BMI lower than the WHO cut-off point of 25 kg/m^2. Therefore, this information calls for redefining a different BMI classification for a different ethnic population. Unfortunately, there is not sufficient data to date to support this hypothesis and indicate an explicit BMI cut-off for Asian population. Therefore, the WHO expert consultation recommended to continue using an international BMI cut-off.[19]

Despite the fact that a lot of studies investigated the determinants of birth weight, a few studies assessed the effect of macro and micronutrient status simultaneously. Micronutrient deficiencies such as iron deficiencies have been known to be related to LBW.[27,28] In this study, we were able to consider the effects of both macro and micronutrient status on birth weight by adjusting for anemia (Hb concentrations) in the data analysis models. In addition, since this is a secondary analysis of data obtained from an RCT with iodine supplementation, treatment group was also included as a co-variate in both binary and multinomial logistic regression models.

In conclusion, our findings from the present study confirmed the strong association between pre-pregnancy BMI and GWG, and adverse birth outcomes. Therefore, women should be advised to maintain appropriate body weight before and during pregnancy in order to prevent any detrimental effects on pregnancy outcomes.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Chapter 6

General discussion

Mild-to-moderate iodine deficiency (ID) in pregnant women still remains a public health problem in many regions of the world including Thailand. The latest report on urinary iodine concentration (UIC) monitoring among pregnant Thai women displays the current situation, showing that pregnant women in 31 out of 77 provinces have a median UIC <150 μg/L, and 46.4% of pregnant women are estimated to live with mild-to-moderate ID (MOPH 2013). Globally, the health consequences of all degrees of ID in pregnancy have been acknowledged, ranging from increased risk of stillbirths, thyroid dysfunction of the mothers and neonates, as well as compromised neurocognitive development of the child (Hetzel 1983). These severe health consequences call for an effective strategy to correct and prevent ID in pregnant women, and iodine supplementation could be an effective solution. Currently, iodine supplementation is widely recommended in order to control ID in areas where salt iodization cannot adequately be implemented (WHO/UNICEF 2007). However, although several randomized trials with maternal iodine supplementation studies have been conducted in mildly ID areas, the efficacy and safety of iodine supplementation during pregnancy remains uncertain (Zimmermann 2004).

In order to get clarity on the efficacy and safety of iodine supplementation in pregnancy in areas where low iodine intake is of mild to moderate health concern, we undertook the largest randomized controlled trial (RCT) to date. In this trial, we have evaluated the effects of daily intake of a 200 μg iodine supplement in mild-to-moderate ID pregnant Thai women on safety and long-term outcomes including newborn development at early stage of life.

In the next sections, the main findings of this thesis are summarized, methodological issues and results are discussed in a broader perspective. Furthermore, implications for public health and future research are given.

6.1 Main findings

The main findings of this thesis are summarized in **Table 6.1**.

In a pilot study comprising 302 pairs of pregnant mothers and their school-aged children, we found that pregnant Thai women in the Bangkok area are indeed facing mild ID with a median UIC of 108 μg/L. In contrast, median UIC of their school-aged children living in the same household was 200 μg/L, indicating optimal iodine status. According to the recommendation of WHO/UNICEF/ICCIDD (WHO/UNICEF/ICCIDD 2007), median UIC in school-aged children is commonly used as an indicator of iodine status of the general population in surveys. Therefore, we concluded that the median UIC in school-aged children does not reflect iodine status in pregnant women and pregnant women should be monitored seperately in iodine status surveys (**chapter 2**).

As in most emerging economies, overweight and obesity is on the rise in Thailand. In a cross-sectional analysis of data collected at baseline for the RCT, we found that 26% of the participating pregnant women had entered their pregnancy either with overweight or being obese. In addition, maternal body mass index (BMI) was negatively associated with free thyroxine (fT4), and overweight pregnant women had a 3.6-fold higher risk of hypothyroxinemia in the first trimester when compared to normal weight women. This finding calls for attention to achieving appropriate maternal weight in preparation for pregnancy (**chapter 3**).

As compared to placebo, iodine supplementation during pregnancy did not significantly improve maternal thyroid function and newborn development in our study population of 511 mild-to-moderate iodine-deficient pregnant women. However, the iodine supplementation modestly improved the percentage of newborns with low birth weight and preterm birth, and significnatly reduced risk of maternal postpartum thyroiditis. Moreover, only a few women in the iodine supplementation group had excessive intake as indicated by a median UIC >500 μg/L, and there were no detrimental effects on

maternal or newborn thyroid function. Therefore, daily iodine supplementation with 200 μg of iodine during pregnancy can be considered to be safe (**chapter 4**).

Pre-pregnancy body mass index (BMI) and weight gain during pregnancy were previously shown to be associated with pregnancy outcomes (Doherty 2006, Kiel 2007), and our results from a secondary data analysis confirmed this phenomenon. Overweight/obese (BMI≥25 kg/m^2) mothers had an 11-fold higher risk of having newborn with macrosomia. Pregnant women who had excessive GWG were 5.6 times as likely to deliver babies with macrosomia. These findings stress the importance of maintaining normal body weight before and throughout pregnancy (**chapter 5**).

Table 6.1 Main findings of the studies described in this thesis

Chapter	Study design	Population	Objectives	Main findings
2	Cross-sectional	302 pairs of pregnant Thai mothers and their school-aged children	To assess if UIC in school-aged children is indicative for iodine status of pregnant women.	UIC was 108 μg/L in pregnant women and 200 μg/L in their children. Measurement of UIC in school-aged children should not be uesd for monitoring iodine status in pregnancy.
3	Cross-sectional	514 pregnant Thai women in the first trimester of preganacy	To assess determinants of maternal thyroid dysfunction.	Overweight pregnant women have a 3.6-fold higher risk of hypothyroxinemia in the first trimester compared to normal weight women.
4	Randomized , double-blind, placebo-controlled	511 pregnant Thai women with mild-to-moderate ID at baseline	To evaluate the effects of daily iodine (200 μg KI) supplementation in pregnant women on thyroid function, pregnancy outcomes and newborn development.	No effects on maternal thyroid function and infant performance, but women in the iodine group were less likely to develop postpartum thyroiditis. Supplementation of 200 μg iodine daily in mildly ID pregnant women was safe.
5	Secondary data analysis	378 pairs of Thai mothers and their newborns	To investigate the relationship between pre-pregnancy BMI, weight gain during pregnancy with pregnancy outcomes.	Overweight/obese mothers had an 11-fold higher risk of having macrosomic infant. Women who had excessive GWG were 5.6 times as likely to deliver babies with macrosomia.

6.2 Overall methodological considerations

In this part of the thesis, methodological aspects that may influence the results and interpretation of the study are critically discussed.

6.2.1 Pilot study

To verify iodine deficiency (ID) situation among pregnant Thai women, a cross-sectional study was conducted as a pilot project in Bangkok and in a nearby province. In addition to assessing the median UIC of pregnant women in the target population for our later RCT, we also aimed to investigate whether the presence of ID in school-aged children assessed with a cutoff of median UIC <100 μg/L is indicative for ID in pregnant women. Because ~50% of iodine requirement increased during pregnancy, a median UIC cutoff for school-aged children seems to be an inappropriate value for pregnant women. For this, we recruited pregnant women who registered at the antenatal clinic in three hospitals (Ramathibodi and Rajavithi Hospital in Bangkok, and Putthamonthon Hospital in Nakhon Pathom) and three factories in the city suburbs with their school-aged children living in the same household.

Our findings in **Chapter 2** show that, although the mothers and their school-aged children lived in the same household and share meals together, median UIC of school-aged children was twice that of pregnant mothers. This strengthens the idea that using median UIC in school-aged children is inappropriate to assess iodine status of pregnant women. Some children participating in the pilot study took part in a school feeding program and this may have introduced iodine in their meals outside the home. UIC measurements were performed with the greatest care in the laboratory of INMU, which is participating in the EQUIP quality control program of the CDC, Atlanta, USA.

Since the study population consisted of a convenience sample from the Bangkok area, median UIC in mothers and children in this study cannot be extrapolated to the total Thai population. Moreover, our findings could have been strengthened if other

biochemical indicators such as thyroid function would also have been measured. Taking all these points into consideration, we can conclude that our pilot study does not provide definite evidence for the inadequacy of using UIC in school-aged children as a means to monitor iodine status of pregnant women. Our findings should be corroborated with studies in other settings and in nationally representative ID monitoring surveys.

6.2.2 Randomized controlled trial (RCT)

6.2.2.1 Sample size

At the time of writing the study protocol, we did not have a good estimate of concentrations of thyroid function indicators in pregnant women in Thailand, or of what magnitude of change to expect with iodine supplementation. Therefore, sample size was first calculated based on an anticipated decrease from 10% in the control to 2% with treatment in the prevalence of elevated newborn TSH (>10 mIU/L at postnatal days 2-4) with treatment. During recruitment, the sample size was increased arbitrarily to over 250 women per treatment group in view of the anticipated high dropout rate at first follow-up. It can therefore be argued that the sample size has not been appropriate in view of the primary objective of the study. However, the present study is by far the largest iodine supplementation trial in mild-to-moderate iodine deficient pregnant population to date, and when effects have been missed these will likely have been small.

6.2.2.2 Participants

In view of the large number of pregnant women that had to be enrolled into the study, as well as the multitude of data and indicators to collect from both mothers and their children, we decided to conduct the study in the large hospital (Ramathibodi hospital) of Mahidol University in Bangkok. In this hospital, we would be able to recruit the required number of participants and also had confidence that all participants would be under the capable supervision of medical doctors and nursing staff. We had previously

confirmed in the pilot study that iodine status of pregnant women attending the antenatal clinic in this hospital was in the mild deficient range (Gowachirapant 2009). However, women in our study were for instance relatively high educated and are not representative for pregnant women in Thailand in general. Outcomes of the study may have shown a different picture in case the study would have been conducted in a more deprived area.

6.2.2.3 Randomization and blinding

Randomization

To avoid any imbalance in baseline study population characteristics in our randomized controlled trial (RCT), participants were randomly divided into two treatment arms (iodine and placebo group). A simple randomization method was used, implying that each day of recruitment when the exact number of eligible pregnant women was known, an equivalent number of lots with alphabet "A" or "B" were prepared. By picking the lots, pregnant women were assigned to the two intervention groups. We can conclude that the randomization had been successful, since indicators at baseline did not differ between the two intervention groups. Furthermore, randomization was sustained throughout the study since we did not see any selective dropout at any timepoint of data collection.

Blinding

The study was conducted in a double-blind manner, with all subjects and field staff being blinded to study treatment. Also those involved in biochemical and data analysis up to the primary investigator was blinded to study treatment.

6.2.2.4 Dosage

Various doses of iodine (ranged 50–230 μg/day) have been used in iodine supplementation studies among European pregnant women. In 1991, Romano et al (Romano 1991) gave 120-180 μg iodine daily to healthy pregnant Italian women. Two

years later, in 1993, Pedersen et al (Pedersen 1993) used the dose of 200 μg iodine in their study. Half the dose used by Pedersen (100 μg iodine) was supplemented to Belgian pregnant women in 1995 (Glinoer 1995), while, in 1996, a high dose of iodine (230 μg) was used in the study of Liesenkotter et al (Liesenkotter 1996). In 2000, Nohr et al (Nohr 2000) gave a multinutrient supplement containing 150 μg iodine to pregnant Danish women who had positive TPO-Abs. Finally, among Italian pregnant women, a dose of 50 μg or 200 μg iodine was selected for supplementation in the study of Antonangeli et al (Antonangeli 2002). However, from all these intervention studies, the safe dose of iodine supplementation in pregnant women remains unclear.

We based our treatment dose of 200 μg of iodine per day on the recommendation of WHO/UNICEF/ICCIDD that optimal daily iodine intake in pregnant women is 250 μg/day (WHO/UNICEF/ICCIDD 2007) and assumed that participants could cover the remaining need of iodine (50 μg) from their food. Although we did not estimate iodine intake of pregnant women in this study, based on UIC in the iodine supplemented group we calculated that their intake at the end of the supplementation period was ~380 μg/day, hence was in the adequate iodine intake range. In addition, we did not detect any adverse effects of the supplementation dose of 200 μg of iodine per day during pregnancy in our study.

6.2.2.5 Ethics

In 2008, the year when this RCT started, iodine supplementation in pregnancy was not a policy in Thailand and depended on decision of the obstetricians/gynecologists. In general, pregnant women who were at risk of ID, were indicated by interview on thyroid disease history, before being supplemented with iodine. For this reason, the study protocol was approved by the ethical committee both at Ramathibodi hospital in Thailand and at Wageningen University in the Netherlands. However, in order to ensure that all pregnant women would receive an adequate amount of iron and folate, we decided to give them a multi-vitamin and -mineral (without iodine) until delivery.

6.2.2.6 Outcomes

(1) Urinary iodine concentration (UIC)

Since median UIC in the iodine group increased significantly into the adequate range in our study, we can conclude that the intervention has been successful. The increase was larger in the iodine group when compared to placebo. However, a rise of UIC was also found in the placebo group, which may either have been caused by an increase of renal clearance over pregnancy (Delange 2004), or by increased awareness about the importance of iodine in the entire study population. We have not monitored iodized salt use habits throughout the study, and dietary intake data have not yet been analyzed.

(2) Thyroid function

Iodine is an important precursor for thyroid hormone production in the thyroid gland, such as thyroxine (T4) and triiodothyronine (T3), which are crucial regulators of the metabolic rate and physical and mental development in humans. In the present study, seven thyroid function parameters were measured including total and free thyroid hormones (TT4, fT4, TT3, fT3), thyroid-stimulating hormone (TSH), thyroglobulin (Tg) and anti-thyroid peroxidase antibodies (TPO-Abs). Free T4 is an effective thyroid hormone which influences the brain development of newborn, while TT4, TT3 and fT3 are indirect indicator of iodine status. TSH and Tg are effective indicator of thyroid stimulation. In addition, TPO-Abs was also measured because it can be used as indicator of iodine supplementation safety. With this, we have covered all relevant thyroid status indicators.

However, since there are no (trimester) specific cutoffs of these parameters for pregnant women, except for TSH and TT4, we have used the reference ranges provided by the assay manufacturer (IMMULITE 2000, SIEMENS, Germany) for all other parameters. Although this was the best we could do with current knowledge, this may have led to some misclassification.

For defining thyroid dysfunction, usually TSH and fT4 concentrations of individuals are considered (Helfand 1998). Since no reference fT4 cutoff for pregnant women has been defined to date, we sought the advice of an expert in thyroid disease who suggested using TSH and TT4 concentrations for assessing the prevalence of thyroid dysfunction in pregnancy accurately. At post-delivery, we have applied the usual TSH and fT4 cutoffs for non-pregnant women.

(3) Thyroid volume

Although normative values of thyroid volume in healthy adults and school-aged children have been formulated, thyroid volume is only a proper indicator for long-term ID and responds slowly to changes in iodine intake. Therefore, we did not see any changes in thyroid size of our participants during the study. Furthermore, according to the normative value of healthy adults' thyroid volume (8.0-18.0 ml) provided by WHO/UNICEF/ICCIDD since 1993 (WHO/UNICEF/ICCIDD 1993), none of the participants in our study had an enlarged thyroid gland. However, when the upper value is reduced from 18.0 to 12.0 ml (WHO/UNICEF/ICCIDD 2007), only 4%, 3.3% and 3% of the women with thyroid volume above the cutoff was reported at baseline, 2nd and 3rd trimester, respectively.

Measuring infants' thyroid volume was challenging, since it required expensive equipment and electricity. In addition, it has to be done under supervision of an experienced radiologist. Therefore, we had quite some missing data for this indicator. However, little data on infant's thyroid volume have been published to date, and normative thyroid volume for healthy infants are still lacking. Our data can add to defining such normative values.

(4) Newborn development

Several studies have reported that ID during pregnancy induces irreversible impairment of newborn development (Pharoah 1984, Pop 1999, Delange 2001, Pop 2003, Kooistra

2006). Therefore, in this study, we also aimed to investigate the effects of iodine supplementation on newborn development at 6 weeks after birth and during the follow-up period (1 and 2 years). In order to get that information, two child development test tools were applied. For 6-week old newborns, the Neonatal Behavioral Assessment Scales (NBAS) was used, while the Bayley Scales of Infant Development (BSID) was tested at 1 and 2 years (results not reported in this thesis).

The *Neonatal Behavioral Assessment Scale (NBAS)* focuses on the newborn's capacity to control levels of stimulation using states of consciousness when adapted to the environment. The NBAS scores were reduced to the following 7 clusters: 1) habituation; 2) orientation; 3) motor; 4) range of state; 5) regulation of state; 6) autonomic stability; 7) reflexes, and include extra supplementary items. However, although this test seems to be an easy tool and has even been conducted in small babies, it was often quite challenging to collect complete scores because infants were often out of control. For instance, one set of the test (habituation) had to be done while the infant was sleeping but we could not force the newborns to sleep at the time of testing. This has led to a substantial number of missing data in the newborn development assessment.

6.2.2.7 Dropout and compliance

Dropout

In general, dropout was rather high in the study (41% until 6 weeks post-delivery). There are two important reasons for this. First, a high number of dropouts occurred between delivery and the appointment at 6 weeks after delivery. Although all participating pregnant women were requested to reside in the area for the duration of the study (~3 years) since at the beginning of the study, most of the women originally came from other provinces in Thailand, once they give birth, they moved back to their hometown to leave the children with their grandparents, according to Thai tradition with infants born in an urban area. Second, due to the women have their own health insurance at the hospital that is closest to their house, therefore, it is more convenient for them to re-register at those hospital for delivery. However, the number of dropouts

in the study was similar in both intervention groups. Therefore, we are confident that the dropout was not caused by the study treatment itself, and therefore inferences still can be made.

Compliance

One of the important issues in (biomedical) human studies is compliance assessment since it can refer to an awareness of participants and a success of the intervention study. Although there are many techniques for assessing compliance during an intervention study, two simple techniques were selected to use in this RTC. First, we directly measured the compliance by counting tablets returned after delivery. However, this method is limited by dependency on the women to return the exact number of unused tablets to us. Moreover, due to the high dropout rate, this measure does not provide us with a reliable estimate of compliance. Second, we used UIC measurement to assess compliance indirectly. Although this measure cannot be used as an individual tool, it reflects recent iodine intake of the study population groups. In the present study, we found a clear increase in UIC in the iodine group, indicating that iodine supplements were taken in by study participants.

6.2.2.8 Data analysis (per protocol / per intention-to-treat)

Although our trial was well planned and carefully conducted, as with any RCT many unexpected problems occurred during the study. In our data analysis plan, we planned to analyze the data *per protocol*.

For this, we compared both treatment groups including only those participants that met all inclusion and exclusion criteria and with known adherence to treatment (Shah 2011). This would reflect the maximal potential benefits to be expected from iodine supplementation. However, *per protocol* analysis can be biased due to exclusion of participants threatening the original comparability of the treatment groups at baseline characteristics, which may result in confounding (Sedgwick 2013). Due to the large number of women without known compliance data, *per protocol* analysis led to

exclusion of a large number of women. Therefore, sticking to the original plan of *per protocol* analysis would threaten the internal validity of the study.

Intention-to-treat (ITT) analysis is a comparison of the treatment groups that includes all patients as originally allocated after randomization (Shah 2011). ITT analysis ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization and maintains prognostic balance generated from the original random treatment allocation (Gupta 2011). However, missing data is a limitation of this method, which can be solved using imputation techniques when appropriate.

In our study, both *per protocol* and ITT analysis were used (**Table 4.2a and 4.2b**) to compare the effects of iodine supplementation on maternal thyroid function. The results of data analysis did not differ between the two analysis methods except for fT4. In the *per protocol* analysis (**Table 4.2a**), a marginal significant difference in fT4 concentration between the treatment groups was detected, which disappeared in the ITT analysis (**Table 4.2b**). In *per protocol* analysis, a significantly larger number of women in the iodine group were found to have high TPO-Abs after delivery as compared to the placebo group. This difference also disappeared fully in ITT analysis. A higher number of participants in the ITT analysis when compared to *per protocol* analysis could be one possible explanation for this consequence. In retrospect, in view of the limitation regarding high dropout and lack of compliance data, we consider ITT as the preferred analysis method for our study. Therefore, we have based our conclusions on ITT analysis in order to avoid any bias of the results.

6.3 Implications for public health

Although our pilot study had a small sample size (302 pairs of mother and their school-aged children) and was not representative for the nation as a whole, publication of the results of our study has led to several other studies investigating the association between UIC in pregnant women and school-aged children. In 2012, Vandevijvere et el (Vandevijvere 2012) conducted a cross-sectional study and aimed to investigate

whether the median UIC among Belgian school-aged children reflects the iodine status of their nonpregnant mothers. They found a low median UIC in both school-aged children (113.1 μg/L) and their mothers (84.4 μg/L). The authors also concluded that the median UIC in children may not be an adequate surrogate measure of adults' iodine status and the monitoring iodine status should not be limited to children, but should be extended to women of child-bearing age. A study of Wong et al (Wong 2011) among 8,622 pregnant Chinese women and 16,844 school-aged children also confirmed this: median UIC of school-aged children indicated adequate iodine intake, while inadequate iodine status in pregnant women was reported. In addition to our study, these reports led to wider attention to the direct monitoring of iodine status in pregnancy.

Our findings from the RCT confirm that iodine supplementation with 200 μg/day in mildly iodine-deficient pregnant women is safe because only a few women had UIC >500 μg/L, indicating iodine excess, after the intervention from ~11 weeks to term. Moreover, the intervention could also reduce postpartum thyroiditis of the women in the iodine supplemented group. This finding is important, since iodine supplementation in pregnancy is common practice in some countries for many years. In Thailand, for example, the Ministry of Public Health (MOPH) launched an iodine supplementation program for Thai pregnant women in October 2010, recommending two types of daily iodine tablets: 1) triferdine150 (iodine, iron and folate); 2) Iodine GPO150 (only iodine) for pregnant women having thalassemia. Based on the research described in this thesis, the recommendation of iodine supplementation in mild-to-moderate ID pregnant women living in areas where salt iodization is not adequately covered can be sustained.

6.4 Future research

As presented in **Chapter 1**, two large RCT of iodine supplementation studies in Thailand and India with a similar protocol and objectives were started in 2008. Therefore, we expect that further data analysis in the mothers and their children over the first two years will provide more additional information of iodine supplementation on maternal benefits or improvement in child development at later ages. Furthermore, the results

from another study site in India, where the mothers have adequate iodine intake indicated by median UIC >150 μg/L at the beginning of the study, are currently being analysed to determine the effects of daily iodine supplementation and to see whether those results support the findings of this study. Moreover, until now, information on the coverage of iodine tablets use during pregnancy in Thailand is still lacking. Monitoring of this program among pregnant Thai women including assessment of thyroid function can provide further evidence for future iodine supplementation planning.

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Summary

Iodine deficiency (ID) during pregnancy remains a major global public health concern. WHO recommends that monitoring of iodine status in populations be done by assessing urinary iodine concentrations (UIC) of school-aged children and it is often assumed this will also reflect iodine status of pregnant women.

Mild-to-moderate ID is not only of concern in developing countries such as Thailand, but mild ID has also reoccurred in several industrialized countries. In order to address adverse health effects of ID during pregnancy both for the mother and their children including offsprings' neurocognitive development, daily iodine supplementation in pregnancy is widely recommended. However, the long-term benefits and safety of routine iodine supplementation in mild-to-moderate ID pregnant women is uncertain.

Due to economic growth and changes in lifestyle of people, overweight and obesity is increasing in Thailand. In pregnancy, adiposity may have a negative impact on thyroid function, pregnancy and birth outcomes.

In order to investigate these issues, a pilot study was carried out in which UIC of pregnant women and their school-aged children were assessed. Subsequently, an RCT was conducted with 200 μg iodine per day in mildly ID pregnant Thai women between October 2008 and June 2013. The overall aim was to evaluate the effects of iodine supplementation during pregnancy on maternal thyroid function, birth outcomes and newborn development up till 6 weeks postpartum. In addition, effect of pre-pregnancy weight and weight gain during pregnancy on maternal thyroid function and pregnancy outcomes was assessed.

In **Chapter 2**, a cross-sectional study of UIC measurement among 302 pairs of pregnant mothers and their school-aged children in Bangkok and nearby provinces is described. It showed that although the school-aged children lived in the same household with the mothers, their median UIC (200 μg/L) was adequate and almost twice as high as compared to their mothers' median UIC (108 μg/L) indicating mild ID. This finding confirms that UIC in school-aged children was not indicative for iodine status of their

pregnant mothers. Hence, iodine status in pregnant women should be monitored separately.

Overweight during pregnancy can have various adverse health consequences. In **Chapter 3**, we used the baseline data of our RCT and determined the relationship between pre-pregnancy body mass index (BMI) and thyroid dysfunction in early pregnancy. In this cross-sectional study, we used the Asian BMI classification by which overweight was defined as BMI ≥23 kg/m^2, which is lower when compared to international BMI cutoff for overweight (≥25 kg/m^2). We found that overweight pregnant women with mild-to-moderate ID had a 3.6-fold higher risk of hypothyroxinemia in the first trimester. These findings suggest that not only morbidly obese women (BMI ≥40 kg/m^2), but also overweight women in ID areas should be screened for thyroid dysfunction.

In the RCT (**Chapter 4**), 200 μg of iodine (KI tablets) or placebo was supplemented daily to 511 mildly ID pregnant women from <14 weeks of gestation until delivery. In this study, iodine supplementation did not benefit thyroid function, thyroid volume, birth outcomes or NBAS score of newborns, but it did significantly increase UIC and reduce the prevalence of postpartum thyroid dysfunction in mothers. Moreover, since only a few women in the study population had a UIC >500 μg/L indicating iodine excess, and there were no detrimental effects on thyroid function of the mother or newborn, we can conclude that supplementation with 200 μg iodine per day in mildly ID pregnant women is safe.

In **Chapter 5**, in a secondary analysis of data from the above RCT, pre-pregnancy BMI and weight gain during pregnancy were considered as possible predictors of negative pregnancy outcomes. We found that newborns born to overweight/obese (BMI≥25 kg/m^2) mothers had an 11-fold higher risk for macrosomia. Moreover, pregnant women with excessive GWG were 5.6 times more likely to deliver babies with macrosomia. These findings underline the importance of maintaining normal body weight before and during pregnancy should be recommended.

Finally, the main findings of the research described in this thesis are summarized and overall methodological considerations are discussed in **Chapter 6**. This also includes the implications for public health and future research are also presented.

In conclusion, this study is the largest RCT of iodine supplementation in mildly ID pregnant women that has been done to date. The results indicate that maternal iodine supplementation is safe and effective in normalizing iodine intake of the mothers, but this findings should not be generalized to all Thai regions due to the differences of iodine status in rural and urban areas. Our findings suggest that routine iodine supplementation may not be necessary in mildly iodine-deficient pregnant women from areas with well-functioning, effective iodized salt program. This may be because adequate thyroidal iodine stores accumulated pre-pregnancy can contribute to iodine requirements during pregnancy. Furthermore, body weight of pregnant women (especially overweight) should be monitored, since this associated with thyroid dysfunction and unfavourable birth outcomes.

Samenvatting

Jodiumtekort (ID) tijdens de zwangerschap is nog steeds een belangrijk wereldwijd volksgezondheidsprobleem. De WHO adviseert om de jodiumstatus in populaties te monitoren door middel van het bepalen van het jodiumgehalte in de urine (UIC) bij schoolgaande kinderen. Er wordt vaak aangenomen dat dit ook de jodiumstatus van zwangere vrouwen weerspiegelt.

Mild tot matig jodiumtekort is niet alleen zorgwekkend in ontwikkelingslanden zoals Thailand, maar mild jodiumtekort komt ook voor in verschillende geïndustrialiseerde landen. Om de nadelige gezondheidseffecten van jodiumtekort tijdens de zwangerschap voor moeder en kind, als ook de neurocognitieve ontwikkeling van de nakomeling aan te pakken, wordt dagelijkse suppletie tijdens de zwangerschap algemeen aanbevolen. Echter, de voordelen op lange termijn en de veiligheid van routinematige jodium suppletie bij zwangere vrouwen met mild tot matig jodiumtekort zijn onduidelijk.

Door de economische groei en leefstijlveranderingen zijn overgewicht en obesitas toegenomen in Thailand. Tijdens de zwangerschap zou adipositas in combinatie met jodiumtekort een negatieve invloed kunnen hebben op de schildklierfunctie, de zwangerschap zelf en de geboorte uitkomsten.

Om deze kwesties te onderzoeken, werd een pilotstudie uitgevoerd waarbij UIC van zwangere vrouwen en hun schoolgaande kinderen werd onderzocht. Vervolgens werd tussen oktober 2008 en juni 2013 een gerandomiseerde, gecontroleerde trial (RCT) uitgevoerd met 200 μg jodium per dag bij zwangere Thaise vrouwen met mild jodiumtekort. Het hoofddoel van deze trial was het evalueren van de effecten van jodium suppletie tijdens de zwangerschap op maternale schildklierfunctie, geboorte uitkomsten en de ontwikkeling van de pasgeborene tot zes weken na de bevalling. Daarnaast werd het effect van het gewicht voor aanvang van de zwangerschap en gewichtstoename tijdens de zwangerschap op maternale schildklierfunctie en zwangerschapsuitkomsten onderzocht.

In **Hoofdstuk 2,** wordt een cross-sectionele studie beschreven waarin UIC is gemeten bij 302 paren van zwangere moeders en hun schoolgaande kinderen in Bangkok en omliggende provincies. Het bleek dat, hoewel de schoolgaande kinderen in hetzelfde huishouden met de moeders woonden, hun mediane UIC (200 μg/L) voldoende en bijna twee keer zo hoog was in vergelijking met het mediane UIC van hun moeders (108 μg/L), wat wijst op mild jodiumtekort. Deze bevinding bevestigt dat UIC van schoolgaande kinderen niet indicatief was voor jodiumstatus van hun zwangere moeders. Daarom moet jodiumstatus bij zwangere vrouwen apart onderzocht worden.

Overgewicht tijdens de zwangerschap kan verschillende nadelige gevolgen voor de gezondheid hebben. In **Hoofdstuk 3,** hebben we de baseline gegevens van onze RCT gebruikt om de relatie te bepalen tussen body mass index (BMI) voor aanvang van de zwangerschap en schildklierafwijkingen in het begin van de zwangerschap. In deze cross-sectionele studie gebruikten we de Aziatische BMI-indeling waarbij overgewicht werd gedefinieerd als BMI $\geq$ 23 kg/m^2, wat lager is in vergelijking met het internationale BMI-afkappunt voor overgewicht ($\geq$ 25 kg/m^2). Wij vonden dat zwangere vrouwen met overgewicht en mild tot matig jodiumtekort een 3,6-maal hoger risico hadden op hypothyroxinemie in het eerste trimester. Deze bevindingen suggereren dat niet alleen vrouwen met morbide obesitas (BMI $\geq$ 40 kg/m^2), maar ook vrouwen met overgewicht in gebieden waar jodiumtekorten voorkomen, gescreend moeten worden op schildklierafwijkingen.

In de RCT (**Hoofdstuk 4**), werden vanaf <14 weken zwangerschap tot aan de bevalling dagelijks supplementen met 200 μg jodium (KI tabletten) of placebo gegeven aan 511 zwangere vrouwen met mild tot matig jodiumtekort. Uit deze studie bleek dat jodium suppletie niet de schildklierfunctie, het schildkliervolume, geboorte uitkomsten of NBAS score van pasgeborenen heeft bevorderd, maar dat het wel de UIC significant heeft verhoogd en de prevalentie van postpartum schildklierafwijkingen bij moeders heeft verlaagd. Aangezien slechts enkele vrouwen in de studiepopulatie een UIC > 500 μg/L

hadden, wat wijst op een teveel aan jodium, en er geen schadelijke gevolgen voor de schildklierfunctie van de moeder en de pasgeborene waren, kunnen we bovendien concluderen dat suppletie met 200 µg jodium per dag voor vrouwen met mild jodiumtekort veilig is.

In **Hoofdstuk 5**, in een secundaire analyse van gegevens uit bovenstaande RCT, werden BMI voor aanvang van de zwangerschap en gewichtstoename tijdens de zwangerschap beschouwd als mogelijke voorspellers van negatieve zwangerschapsuitkomsten. We vonden dat pasgeborenen, geboren bij moeders met overgewicht of obesitas (BMI $\geq$ 25 kg/m^2), een 11-maal hoger risico op macrosomie hadden. Bovendien hadden zwangere vrouwen met overmatige gewichtstoename tijdens de zwangerschap 5,6 keer meer kans op baby's met macrosomie. Deze bevindingen onderstrepen het belang van het handhaven van een normaal lichaamsgewicht voor en tijdens de zwangerschap.

Tenslotte zijn in **Hoofdstuk 6** de belangrijkste bevindingen van het onderzoek uit dit proefschrift samengevat en worden algemene methodologische overwegingen besproken. Dit hoofdstuk omvat ook de implicaties voor de volksgezondheid en toekomstig onderzoek.

Tot besluit, deze studie is de grootste RCT van jodium suppletie bij zwangere vrouwen met mild jodiumtekort die tot nu toe is gedaan. De resultaten geven aan dat maternale jodium suppletie veilig en effectief is in het normaliseren van de jodiuminname van de moeders, maar deze bevindingen moeten niet gegeneraliseerd worden naar alle regio's in Thailand vanwege de verschillen in jodiumstatus tussen rurale en stedelijke gebieden. Onze bevindingen suggereren dat routinematige jodium suppletie wellicht niet nodig is in zwangere vrouwen met mild jodiumtekort in gebieden met een goed functionerend, effectief gejodeerd zout programma. De reden hiervoor kan zijn dat adequate jodium voorraden in de schildklier, opgestapeld voor aanvang van de zwangerschap, kunnen bijdragen aan de jodiumbehoefte tijdens de zwangerschap. Bovendien dient het

lichaamsgewicht van zwangere vrouwen (vooral vrouwen met overgewicht) gecontroleerd te worden, omdat dit geassocieerd is met schildklierafwijkingen en ongunstige geboorte uitkomsten.

บทสรุป

การขาดธาตุไอโอดีนในระหว่างตั้งครรภ์ยังคงเป็นปัญหาสาธารณสุขที่สำคัญระดับโลก ด้วยเหตุนี้ องค์การอนามัยโลก (World Health Organization, WHO) จึงแนะนำให้ตรวจติดตามภาวะไอโอดีนของกลุ่มประชากรทั่วไปโดยการตรวจวัดปริมาณไอโอดีนในปัสสาวะของเด็กวัยเรียน และคาดการณ์ว่าวิธีการดังกล่าวจะสามารถสะท้อนถึงภาวะไอโอดีนของหญิงตั้งครรภ์ได้

การขาดธาตุไอโอดีนระดับไม่รุนแรงถึงปานกลาง (mild-to-moderate iodine deficiency) ไม่เพียงแต่เป็นปัญหาในประเทศกำลังพัฒนาอย่างประเทศไทย แต่กำลังย้อนกลับมากลายเป็นปัญหาในประเทศอุตสาหกรรมหลายๆประเทศในปัจจุบัน ทั้งนี้เพื่อเป็นการป้องกันปัญหาสุขภาพต่างๆจากการขาดธาตุไอโอดีนในระหว่างตั้งครรภ์ที่อาจเกิดขึ้นกับทั้งมารดาและบุตร รวมไปถึงพัฒนาการทางสติปัญญาของลูกหลานรุ่นต่อไป จึงมีคำแนะนำอย่างแพร่หลายในการให้ยาเม็ดไอโอดีนเสริมสำหรับหญิงตั้งครรภ์ อย่างไรก็ตาม ประโยชน์และความปลอดภัยจากการได้รับยาเม็ดไอโอดีนเสริมในหญิงตั้งครรภ์ที่มีภาวะการขาดธาตุไอโอดีนระดับไม่รุนแรงถึงปานกลางยังขาดความชัดเจน

เนื่องด้วยภาวะทางเศรษฐกิจที่เติบโตอย่างรวดเร็ว ประกอบกับรูปแบบการดำเนินชีวิตที่เปลี่ยนแปลงไป ส่งผลให้ประเทศไทยกำลังประสบกับปัญหาประชากรที่มีน้ำหนักเกินและอ้วนเพิ่มมากขึ้น โดยเฉพาะภาวะไขมันในร่างกายสูงในหญิงตั้งครรภ์ซึ่งอาจส่งผลกระทบเชิงลบต่อการทำงานของระบบต่อมไทรอยด์ รวมไปถึงผลของการตั้งครรภ์ต่างๆและสุขภาพของบุตรด้วย

ดังนั้น เพื่อเป็นการตรวจสอบประเด็นปัญหาต่างๆข้างต้น จึงดำเนินงานการวิจัยนำร่องเพื่อตรวจวัดปริมาณไอโอดีนในปัสสาวะของทั้งมารดาที่กำลังตั้งครรภ์และบุตรที่อยู่ในวัยเรียน หลังจากนั้น จึงทำการวิจัยหลักซึ่งเป็นการวิจัยเชิงทดลองแบบสุ่มและมีกลุ่มควบคุม (randomized controlled trial, RCT) ด้วยการให้ยาเม็ดไอโอดีนเสริมในปริมาณ 200 ไมโครกรัมต่อวัน สำหรับหญิงตั้งครรภ์ชาวไทยที่มีภาวะการขาดธาตุไอโอดีนระดับไม่รุนแรง ระหว่างเดือนตุลาคม 2552 ถึงเดือนมิถุนายน 2557 โดยมีวัตถุประสงค์เพื่อประเมินผลของการได้รับยาเม็ดไอโอดีนเสริมในระหว่างตั้งครรภ์ ต่อระบบการทำงานของต่อมไทรอยด์ ผลของการตั้งครรภ์ของมารดา รวมถึงการคลอดบุตร และพัฒนาการของบุตรเมื่ออายุครบ 6 สัปดาห์ นอกจากนั้น ยังศึกษาผลของน้ำหนักตัวก่อนตั้งครรภ์และการเพิ่มน้ำหนักตัวระหว่างตั้งครรภ์ของมารดาต่อระบบการทำงานของต่อมไทรอยด์ และการตั้งครรภ์ของมารดาด้วย

บทที่ 2 เป็นรายงานผลจากการศึกษาแบบภาคตัดขวาง (cross-sectional study) โดยทำการตรวจวัดปริมาณไอโอดีนในปัสสาวะของคู่มารดาที่กำลังตั้งครรภ์และบุตรวัยเรียน จำนวน 302 คู่ ในพื้นที่กรุงเทพมหานครและจังหวัดใกล้เคียง ผลการศึกษาแสดงให้เห็นว่า แม้ว่าบุตรวัยเรียนจะอาศัยอยู่ในบ้าน

เดียวกันกับมารดาที่กำลังตั้งครรภ์ แต่ค่ามัธยฐานของปริมาณไอโอดีนในปัสสาวะ (200 ไมโครกรัมต่อลิตร) บ่งชี้ว่ามีระดับไอโอดีนในร่างกายที่เพียงพอ และสูงกว่ามารดาเป็นสองเท่า (108 ไมโครกรัมต่อลิตร) ซึ่งบ่งชี้ถึงภาวะการขาดธาตุไอโอดีนระดับไม่รุนแรงของมารดา ผลการศึกษานี้ยืนยันว่า การตรวจวัดปริมาณไอโอดีนในปัสสาวะของเด็กวัยเรียน ไม่สามารถบ่งชี้ถึงภาวะไอโอดีนของมารดาที่กำลังตั้งครรภ์ได้ ดังนั้น หญิงตั้งครรภ์จึงควรได้รับการตรวจติดตามภาวะไอโอดีนในระหว่างตั้งครรภ์แยกเป็นการเฉพาะ

ปัญหาน้ำหนักเกินในระหว่างตั้งครรภ์อาจส่งผลกระทบอันไม่พึงประสงค์ต่อสุขภาพของทั้งมารดาและบุตร บทที่ 3 เป็นการวิเคราะห์ข้อมูลโดยใช้ข้อมูลเบื้องต้นของการวิจัยหลัก เพื่อตรวจสอบความสัมพันธ์ระหว่างดัชนีมวลกายก่อนตั้งครรภ์ (pre-pregnancy body mass index) ของมารดากับปัญหาความผิดปกติของการทำงานของต่อมไทรอยด์ (thyroid dysfunction) โดยการศึกษาแบบภาคตัดขวางนี้อ้างอิงค่าดัชนีมวลกาย 23 กิโลกรัมต่อตารางเมตร ที่ใช้บ่งชี้ภาวะน้ำหนักเกินสำหรับประชากรชาวเอเชีย ซึ่งมีค่าต่ำกว่าค่าอ้างอิงดัชนีมวลกายสากล (25 กิโลกรัมต่อตารางเมตร) ผลการศึกษาพบว่าหญิงตั้งครรภ์ที่มีภาวะขาดธาตุไอโอดีนระดับไม่รุนแรงถึงปานกลาง และมีปัญหาน้ำหนักเกินร่วมด้วย มีความเสี่ยงต่อปัญหาภาวะระดับไทรอยด์ฮอร์โมนในเลือดต่ำ (hypothyroxinemia) ในช่วงการตั้งครรภ์ไตรมาสแรก มากกว่าหญิงตั้งครรภ์ที่มีน้ำหนักปกติถึง 3.6 เท่า ผลการศึกษานี้บ่งชี้ว่า ไม่เพียงแต่หญิงตั้งครรภ์ที่เป็นโรคอ้วน (ดัชนีมวลกาย ≥ 40 กิโลกรัมต่อตารางเมตร) เท่านั้น ที่ควรได้รับการตรวจคัดกรองเพื่อป้องกันการเกิดปัญหาความผิดปกติของการทำงานของต่อมไทรอยด์ แต่หญิงตั้งครรภ์ที่มีน้ำหนักเกินและอาศัยอยู่ในพื้นที่ที่มีการขาดไอโอดีนด้วย ก็ควรได้รับการตรวจคัดกรองดังกล่าวด้วย

การวิจัยหลักซึ่งเป็นการวิจัยเชิงทดลองแบบสุ่มและมีกลุ่มควบคุม (บทที่ 4) เป็นการให้ไอโอดีนเสริมในรูปของยาเม็ดโพแทสเซียมไอโอไดด์ปริมาณ 200 ไมโครกรัมต่อวัน หรือยาเม็ดหลอก ในหญิงตั้งครรภ์ที่มีภาวะการขาดธาตุไอโอดีนระดับไม่รุนแรงจำนวน 511 ราย ตั้งแต่อายุครรภ์ < 14 สัปดาห์ จนกระทั่งคลอด พบว่า การได้รับไอโอดีนเสริมนี้ ไม่ทำให้ระบบการทำงานของต่อมไทรอยด์ ขนาดของต่อมไทรอยด์ การคลอดบุตร และคะแนนการทดสอบพัฒนาการของทารกดีขึ้น แต่ทำให้ปริมาณไอโอดีนในปัสสาวะของมารดาเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ อีกทั้งยังช่วยลดความชุกของปัญหาความผิดปกติของการทำงานของต่อมไทรอยด์หลังคลอดของมารดาด้วย ยิ่งไปกว่านั้น ยังสามารถสรุปได้ว่า การให้ไอโอดีนเสริมปริมาณ 200 ไมโครกรัมต่อวัน ในหญิงตั้งครรภ์ที่มีภาวะการขาดธาตุไอโอดีนระดับไม่รุนแรงนี้ มีความปลอดภัย เนื่องจากพบหญิงตั้งครรภ์จำนวนน้อย ที่มีปริมาณไอโอดีนในปัสสาวะ > 500 ไมโครกรัมต่อลิตร ซึ่งบ่งชี้ถึงภาวะการได้รับไอโอดีนเกิน และไม่พบว่าเกิดอันตรายใดๆต่อผลการทำงานของระบบไทรอยด์ทั้งกับมารดาและบุตร

บทที่ 5 เป็นการวิเคราะห์ข้อมูลทุติยภูมิที่ได้จากการวิจัยหลัก เพื่อศึกษาความสัมพันธ์ระหว่างดัชนีมวลกายก่อนการตั้งครรภ์และการเพิ่มน้ำหนักตัวระหว่างตั้งครรภ์ ซึ่งอาจเป็นปัจจัยสำคัญที่สามารถทำนายผลอันไม่พึงประสงค์ต่อการตั้งครรภ์ของมารดาได้ จากการศึกษาพบว่า ทารกที่เกิดจากมารดาที่มีปัญหาน้ำหนักเกินหรืออ้วนก่อนตั้งครรภ์ (ดัชนีมวลกาย ≥ 25 กิโลกรัมต่อตารางเมตร) มีความเสี่ยงต่อการมีขนาดตัวโตกว่าปกติ (macrosomia) มากกว่าทารกปกติทั่วไป 11 เท่า นอกจากนั้นยังพบอีกว่า หญิงตั้งครรภ์ที่มีการเพิ่มน้ำหนักตัวขณะตั้งครรภ์มากกว่าเกณฑ์ที่กำหนด จะมีความเสี่ยงเป็น 5.6 เท่า ในการให้กำเนิดทารกที่มีขนาดตัวโตกว่าปกติ เมื่อเทียบกับหญิงตั้งครรภ์ที่มีการเพิ่มน้ำหนักอยู่ในเกณฑ์ที่แนะนำ จากผลการศึกษานี้ ชี้ให้เห็นถึงความสำคัญของการให้คำแนะนำในการดูแลน้ำหนักตัวของมารดาทั้งก่อนและระหว่างตั้งครรภ์ให้เหมาะสม เพื่อป้องกันปัญหาดังกล่าว

บทที่ 6 รวบรวมผลการศึกษาทั้งหมดที่ได้จากการวิจัยนี้ รวมถึงประเด็นข้อจำกัดและปัญหาอุปสรรคต่าง ๆของการวิจัย ทั้งในแง่ของขั้นตอนกระบวนการการทำวิจัย ปัญหาที่เกี่ยวข้องกับการวิเคราะห์ตัวอย่างชีวภาพ และอื่นๆที่เกี่ยวข้องกับการวิเคราะห์ข้อมูลทางสถิติ นอกจากนั้น ยังได้ให้ข้อเสนอแนะในการนำผลการศึกษาไปประยุกต์ใช้และประเด็นการศึกษาที่น่าสนใจและควรทำการศึกษาเพิ่มเติมในอนาคตอีกด้วย

โดยสรุป การศึกษานี้เป็นการวิจัยเชิงทดลองแบบสุ่มและมีกลุ่มควบคุม ที่ทำการศึกษาผลของการให้ไอโอดีนเสริมในหญิงตั้งครรภ์ที่มีภาวะขาดธาตุไอโอดีนระดับไม่รุนแรงที่มีขนาดใหญ่ที่สุดเท่าที่เคยมีการศึกษามาจนถึงปัจจุบัน ผลการศึกษาบ่งชี้ว่า การได้รับไอโอดีนในระหว่างตั้งครรภ์มีความปลอดภัยและมีประสิทธิผลในการช่วยรักษาระดับของไอโอดีนที่ได้รับเข้าสู่ร่างกายของมารดาได้ แต่อย่างไรก็ตาม ผลจากการศึกษานี้ไม่สามารถนำไปขยายผลในวงกว้างสำหรับประชากรไทยทั่วทั้งประเทศได้ ทั้งนี้เนื่องจากมีความแตกต่างของภาวะไอโอดีนในประชากรที่อาศัยอยู่ในเขตเมืองและชนบท ผลการศึกษานี้ชี้ให้เห็นว่า การให้ไอโอดีนเสริมอาจไม่มีความจำเป็นสำหรับหญิงตั้งครรภ์ที่มีภาวะขาดไอโอดีนระดับไม่รุนแรงซึ่งอาศัยอยู่ในพื้นที่ที่มีการดำเนินงานเรื่องเกลือเสริมไอโอดีนอย่างมีประสิทธิภาพ ทั้งนี้อาจเนื่องมาจากระดับของไอโอดีนที่สะสมในร่างกายก่อนการตั้งครรภ์มีปริมาณที่เพียงพอและยังสามารถช่วยเติมเต็มความต้องการของไอโอดีนที่เพิ่มขึ้นในระหว่างตั้งครรภ์ได้ นอกจากนั้น ประเด็นเรื่องน้ำหนักตัวของหญิงตั้งครรภ์โดยเฉพาะผู้ที่มีปัญหาน้ำหนักเกินควรได้รับการดูแล เพราะมีความสัมพันธ์กับความผิดปกติของการทำงานของต่อมไทรอยด์และอาจส่งผลกระทบอันไม่พึงประสงค์ต่อการตั้งครรภ์และการคลอดบุตรด้วย

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Sueppong Gowachirapant

About the author

Curriculum Vitae

Sueppong Gowachirapant was born on the 22th of January, 1976 in Phetchaburi province, Thailand. In 1993, he completed high school at Prommanusorn School Phetchaburi. In 1997, he graduated with a Bachelor degree of Science from the Department of Food Technology, Faculty of Engineering and Industrial Technology, Silpakorn University, Nakhon Pathom and his senior project was entitled "Stability of lycopene and non-enzymatic browning reaction in low-sugar chilli tomato sauce product". In 2002, he completed his Master degree of Science in Food and Nutrition for Development from the Institute of Nutrition, Mahidol University (INMU), Nakhon Pathom and his research was entitled "Effect of carrot consumption on plasma carotenoids and lymphocyte subpopulations in healthy subjects".

After obtaining his Master degree in 2002, he started working as a researcher in several community-based projects at the Institute of Nutrition, Mahidol University. The research subjects focused on micronutrient deficiencies especially iron deficiency in various vulnerable groups such as school-aged children, reproductive age women and thalassemia patients. All of the projects were collaborative research between INMU and other research institutions including the University of Otago, New Zealand and the Swiss Federal Institute of Technology (ETH) Zurich, Switzerland. In September 2007, he was admitted for a sandwich PhD program at the Division of Human Nutrition, Wageningen University supervised by Prof. Michael Zimmermann (Switzerland), Assist. Prof. Alida Melse-Boonstra (the Netherlands) and Assoc. Prof. Pattanee Winichagoon (Thailand). That year, he finished his PhD research proposal and one year after that (2008), a large RCT of iodine supplementation in mildly iodine-deficient pregnant women was conducted at Ramathibodi Hospital, Bangkok, Thailand. After almost five years, October 2008 – June 2013, his research was completed.

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Overview of completed training activities

With the educational activities listed below the PhD candidate has complied with the educational requirements set by the Graduate School VLAG (Food Technology, Agrobiotechnology, Nutrition and Health Sciences)

Discipline specific activities	Organiser and location	Year
Courses, workshops, conferences		
Methodology nutrition research	Division of Human Nutrition, Wageningen	2007
Nutrition & lifestyle epidemiology	VLAG, Wageningen	2011
19th ICN	NAT, Thailand	2009
Micronutrient Forum	Micronutrient Initiative, China	2010
Public Health Nutrition 2010	WPHN association, Portugal	2010
Nutrition & Cognition	ILSI, Malaysia	2010
Stable isotope training	IAEA, India	2011
Laboratory training	ETH, Switzerland	2011
General courses		
Information literacy for PhD	WUR Library, Wageningen	2007
Endnote 9 advanced	WUR Library, Wageningen	2007
Erasmus summer programme	NIHES, Rotterdam	2011
English study (IELTS preparation)	St.Nicholas College, UK	2011
VLAG PhD week	VLAG, Wageningen	2007
Optional courses and activities		
Research proposal preparation	VLAG, Wageningen	2007
PhD retreat and seminar	VLAG, Wageningen	2007
PhD excursion (Scandinavia)	Division of Human Nutrition, Wageningen	2009
PhD excursion (USA)	Division of Human Nutrition, Wageningen	2011

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