REVIEW OF LITERATURE

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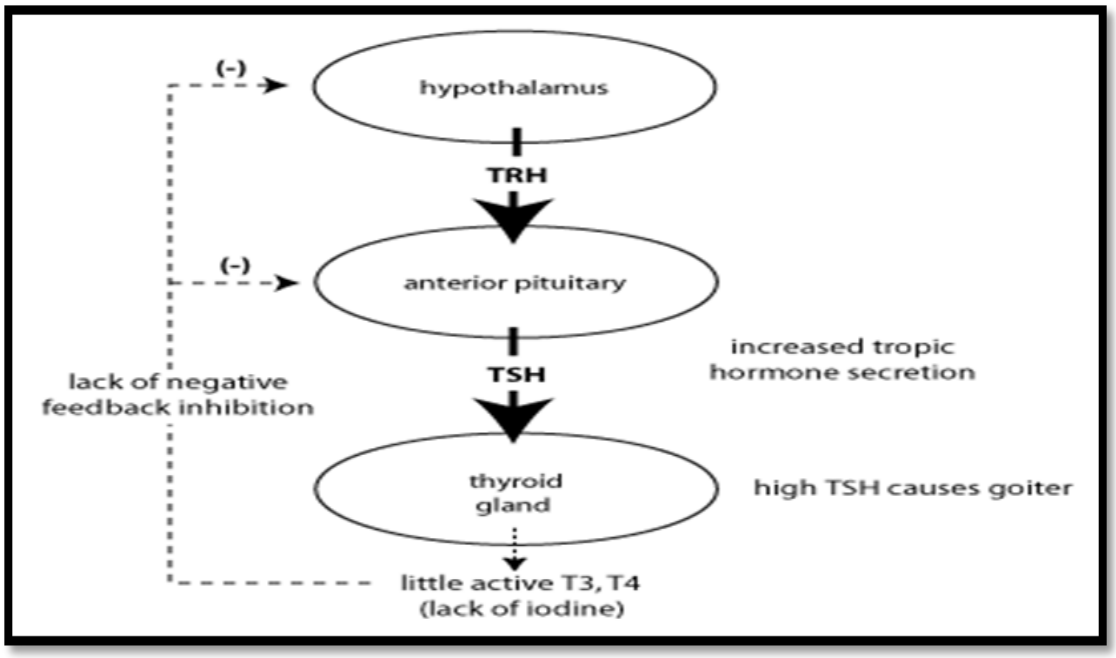
2.1 Iodine deficiency and its consequences

Iodine is one of the essential elements required for normal human growth and development. Its daily per capita requirement is 150 micrograms. Iodine is also required for the synthesis of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) (WHO, 2007). These thyroid hormones (T_4 and $T_{3)}$, are iodinated molecules of the essential amino acid tyrosine and thus regulate cellular oxidation and hence effect calorigenesis, thermoregulation and intermediary metabolism. These hormones are necessary for protein synthesis, and they promote nitrogen retention, glycogenolysis, intestinal absorption of glucose and galactose, lipolysis, and uptake of glucose by adipocytes (Hetzel et al, 1997). Synthesis and secretion of T4 and T3 are under the control of the thyroid-stimulating hormone (TSH) which is secreted from the anterior lobe of the pituitary gland. TSH stimulates iodide transport from the blood into thyroid cells, oxidation of iodide to iodine, and iodine binding to tyrosine. The synthesis of thyroid hormones is regulated by the levels of circulating free T4 and T3 as a negative feedback mechanism **(Figure 6)** (Pal, 2007).

Figure 6: Synthesis of Thyroid Hormones



Source: https://courses.washington.edu/conj/bess/thyroid/thyroid.html

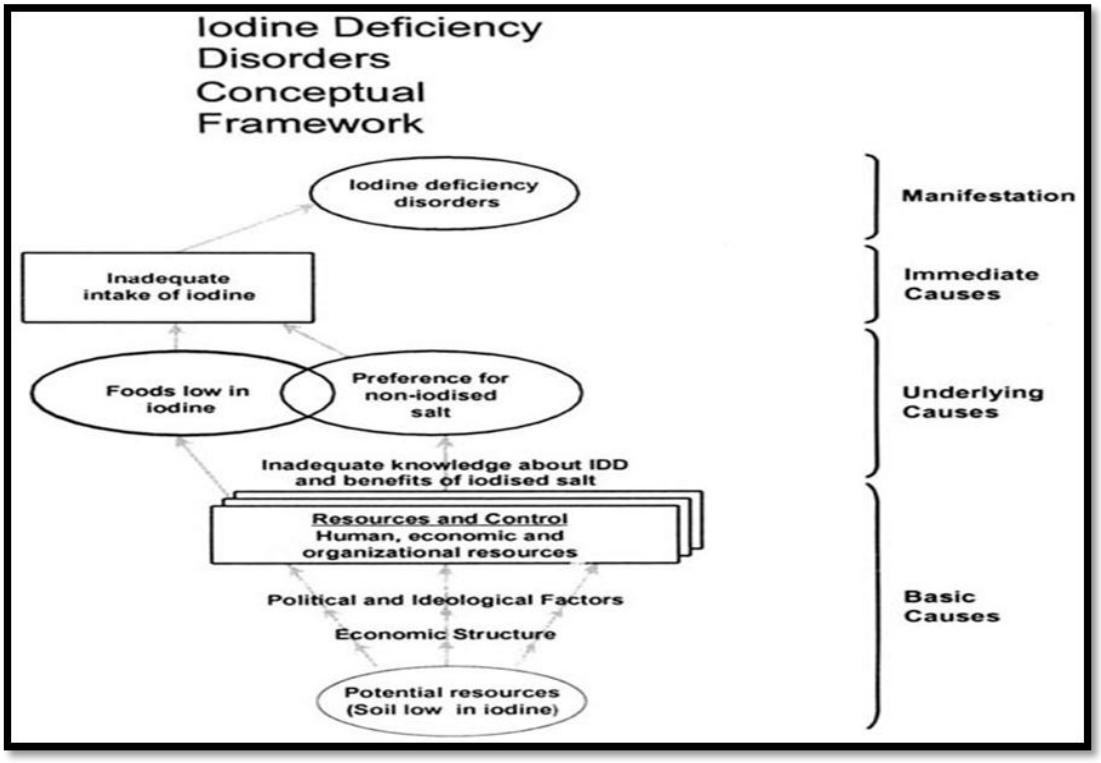
Iodine deficiency disorders refer to all of the consequences of ID in a population that can be prevented by ensuring that the population has an adequate intake of iodine. Iodine deficiency occurs when iodine intake falls below recommended levels (WHO, 2007). When iodine intake falls below recommended levels, thyroid may no longer be able to synthesize sufficient amounts of thyroid hormone. The resulting low level of thyroid hormones in the blood (hypothyroidism) is the principal factor responsible for damage to the developing brain and other harmful effects known collectively as "iodine deficiency disorders" (Hetzel et al, 1983).

Iodine is present in the superficial layers of the soil and absorbed by crops grown on it. Glaciations, heavy snow and heavy rain leach away iodine from the soil. This is further accelerated by deforestation and soil erosion. Consumption of crops and plants grown on iodine deficient soils leads to iodine deficiency in populations solely dependent on this vegetation. However, iodine cycling in many regions is slow and incomplete, and soils and ground water become deficient in iodine (WHO, 2007).

High incidence of iodine deficiency disorder has been documented from population residing in Himalayas, Andes, and Alps. Ocean water contains adequate amounts of iodine. Only people eating a specific species of sea fish and sea products like *'kelp'* are more likely to be iodine sufficient, but these are not accessible to everyone (WHO, 1995). Moreover, eating seafood does not ensure adequate dietary iodine sufficiency. Iodine deficiency in population residing at sea coast have been documented from geographical pockets of Bangkok, Manila, Goa, Bombay, Kerala, Andaman and Nicobar Islands (WHO, 1994).

Environmental factors are amongst the most common factors that interfere in thyroxin synthesis and lead to goiter formation. The most important environmental factors are (i) environmental iodine deficiency (iodine deficiency in soil, water and food) and (ii) goitrogens. The most frequent cause of goiter in India and other countries is environmental iodine deficiency (Kapil et al, 2007).

Figure 7: Iodine deficiency disorders conceptual framework



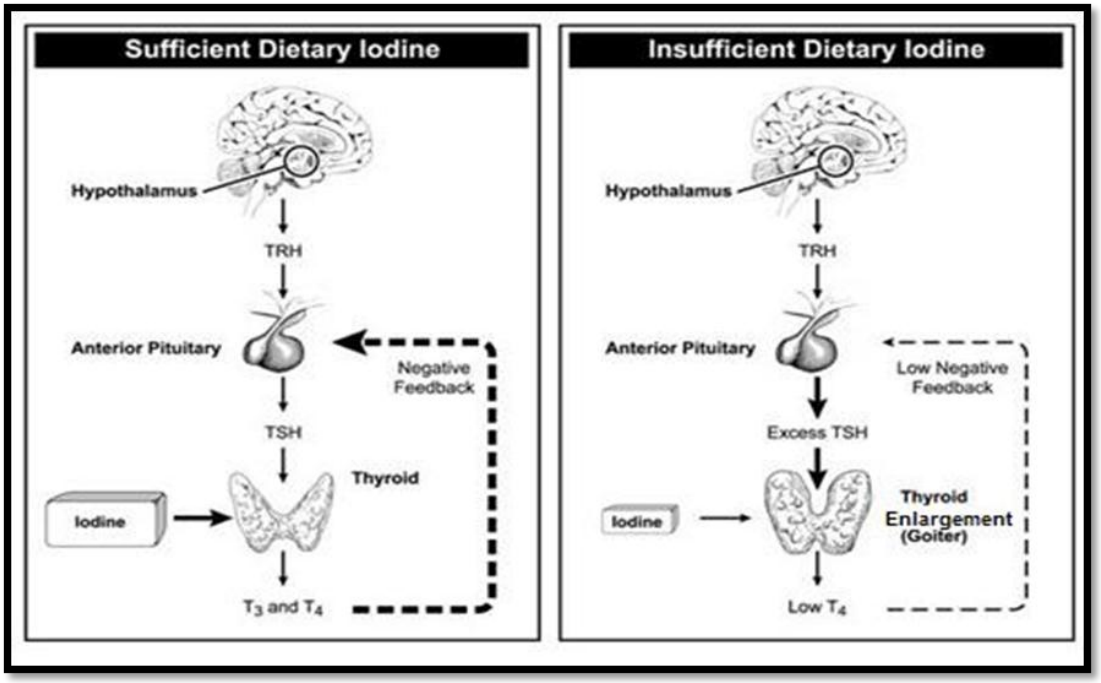
Source: UNICEF, 1990

2.1.1 Metabolism of iodine in the thyroid

Iodine enters the body in the form of iodate or iodide in the water we drink or food we consume; the iodate is converted to iodide in the stomach. The thyroid gland traps and concentrates iodide and uses it in the synthesis and storage of thyroid hormones. The minimum daily iodine intake needed to maintain normal thyroid function in adults is about 150µg/dl (Kapil, 2007).

The production of thyroxine and triiodothyronine is regulated by the thyroid-stimulating hormone (TSH), released by the anterior pituitary. TSH production is suppressed when the T4 levels are high, and vice versa. The TSH production itself is modulated by the thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus (Kapil, 2007).

Figure 8: Graphical representation of sufficient and insufficient dietary iodine intake



Source: Larsen et al, 1988

2.1.2 Health Consequences of Iodine Deficiency

Iodine deficiency affects all stages of human development starting from the fetal life. If the diet of a pregnant woman lacks iodine, the fetus is also deprived of adequate iodine and hence cannot produce enough thyroxin. This may leads to fetal growth retardation. Hypothyroid fetuses often perish in the womb, and many infants die within few weeks of birth (Menon and Skeaff, 2011). Those born with hypothyroidism have global developmental delay and remain intellectually low with low IQ compared to iodine sufficient children. They are often incapable of completing school. In areas with prevalence of mild to moderate iodine deficiency, the school children are on an average, 13.5 points of IQ below those living in iodine sufficient areas (WHO, 2007). The adverse effect of iodine deficiency in humans is depicted in **Figure 9.**

Effects on growing brain

Severe iodine deficiency during pregnancy increases the risk of stillbirths, abortions, and congenital abnormalities. Iodine supplementation to pregnant women in regions of severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive performance of the offspring. Maternal thyroxine crosses the placenta before onset of fetal thyroid function at 10–12 weeks (Sack et al, 2003). The most serious adverse affect of iodine deficiency is the brain damage to the fetus. The critical period for maximal brain growth and maturation comprises the last six months of gestation and the first year of life (Delong, 1987).

The growth and differentiation of the central nervous system is closely related to iodine and thyroid hormones and impairment of cerebral functions in the fetus is directly related to maternal thyroxinemia. Iodine induced hypothyroidism during the fetal period also leads to a decrease in the proportion and density of radial glial cells fibers of the hippocampal-formation of the brain (Ramie et al, 1988).

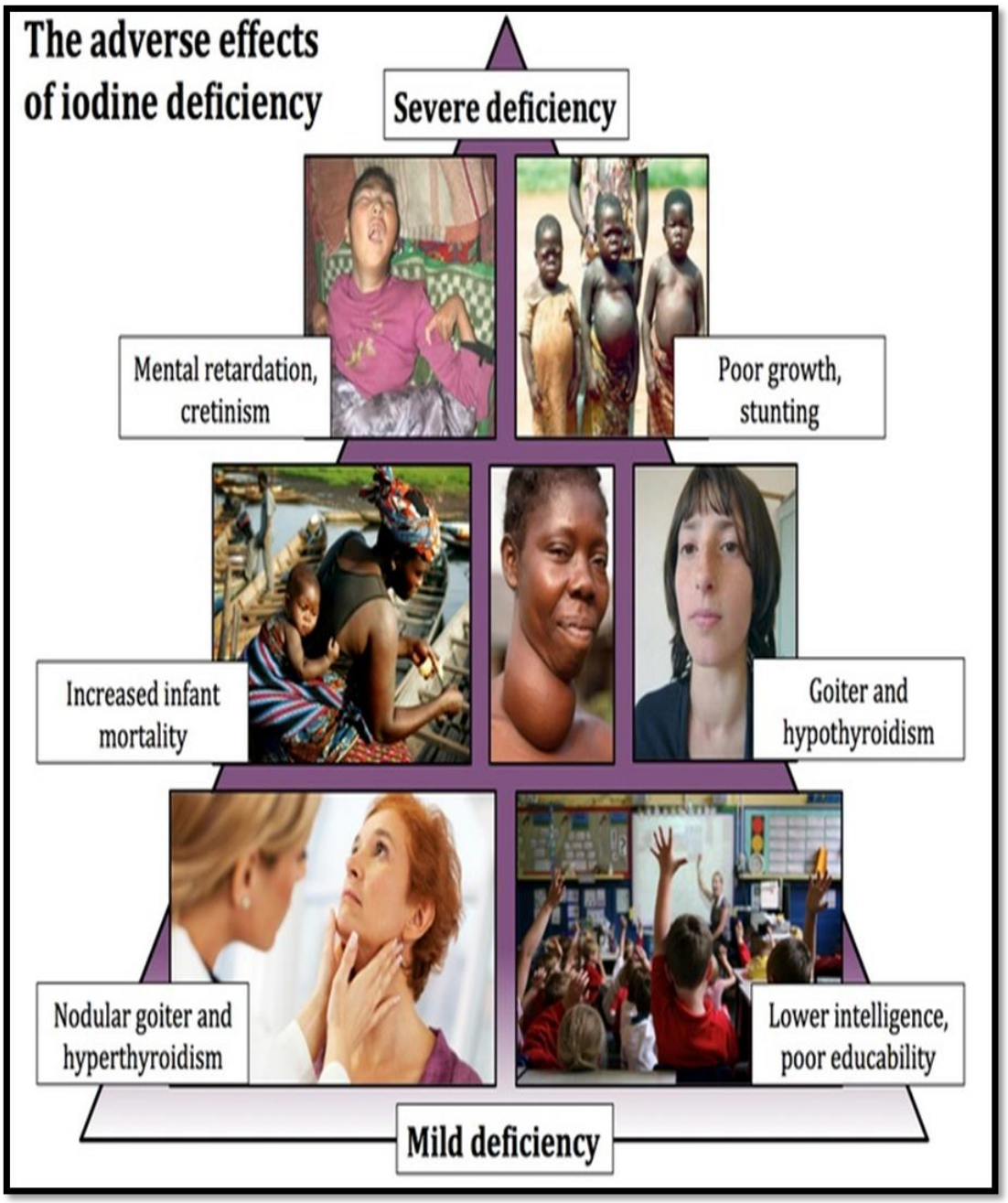
Neonates

Extensive experimental studies have been done on animals to demonstrate effect of severe iodine deficiency on the brain of neonates (Hetzel, 1989).

Children

Children living in iodine deficient areas have an intelligence quotient (IQ) of 13.5 points lower than children living in iodine sufficient areas. The chronic iodine deficiency is likely to have widespread effects on cognitive performance and development due to the broad impact of hypothyroidism on neuronal development, structure, and function (Hetzel, 1983).

Figure 9: The adverse effects of iodine deficiency



Source: From IDD Newsletter (http://www.ign.org/p142000263.html)

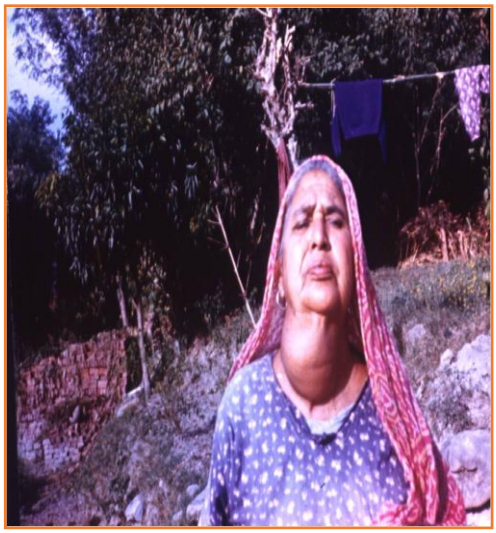
2.1.3 Clinical features of Iodine Deficiency Disorder

The simple goiter is the clinical manifestations of iodine deficiency that arise solely from enlargement of the thyroid. Goitrous enlargement may also be associated with varying degrees of hypothyroidism (Zimmermann et al, 2008). Cretinism, both goitrous and non-goitrous occurs with increased frequency in the children of goitrous parents in many countries where goiter is common.

In severe endemic goiter, an abnormally high number of patients exhibit irreversible anomalies of intellectual and physical development. These anomalies are extremely polymorphous and have been grouped under the endemic cretinism. The prevalence of the cretinism may be 5-15% of the population in severely iodine deficient regions. It is a serious complication of iodine deficiency (Delange, 1985; Hetzel, 1983; Pharoah et al, 1980).

Figure 10: Goiter in school age child

Figure 11: Goiter in an adult female



2.2 Prevalence of Iodine Deficiency

2.2.1 Global Scenario

Using the median UIC level in school-age children as proxy for iodine status in the general population between 2012 and 2014, 19 countries have changed their iodine status. Eight countries previously classified as mildly or moderately deficient have now reached sufficient iodine nutrition at the national level (these include

Afghanistan, Australia, Ghana, Guatemala, Hungary, Mongolia, New Zealand, and Papua New Guinea). At the same time, Denmark slipped and is now mildly deficient. This means that in 2015 only 25 countries remained iodine deficient, compared to 32 in 2011. This remarkable progress reflects a growing global awareness of iodine deficiency disorder and the tremendous success of iodization programs. Overall, global iodine status continues to improve. According to the available data, Haiti is the only country which changed status from mildly to moderately deficient. Remarkably, there have been no countries in the "severely deficient" category for more than a decade (Global Iodine Score card, 2015; IDD Newsletter, 2015; UNICEF; Andersson et al, 2012; Zimmermann and Andersson, 2012).

In 2014, the urinary iodine concentration level data cover approximately 97.8% of the world's population of school-age children, compared to 96% in 2012. Countries that previously had no data that have new urinary iodine concentration level estimates include South Sudan (a new WHO state), Sierra Leone, North Korea, South Korea, and Thailand. The proportion of the global population covered by national-level surveys has also increased, now at 71% compared to 60% in 2012 (Global Iodine Score card, 2015, IDD Newsletter, 2015; UNICEF; Andersson et al, 2012; Zimmermann and Andersson, 2012).

The number of countries, proportion of population, and number of individuals with insufficient iodine intake in school age children and the general population, by WHO region, 2011 is depicted in **Table 4**.

Table 4: Countries, proportion of population, and number of individuals with insufficient iodine intake in school age children and the general population, by WHO region, 2011

WHO region[3]	Countries (n)	Insufficient iodine intake[2]			
		School		General population	
		Proportion (%)	Total n (millions)[4]	Proportion (%)	Total n (millions)[3]
Africa	10	39.3 (38.8, 39.9)	57.9 (57.1, 58.7)	40.0 (39.4, 40.6)	321.1 (316.3, 325.9)
Americas	2	13.7 (12.6, 14.7)	14.6 (13.5, 15.7)	13.7 (12.5, 14.8)	125.7 (114.8, 136.5)
Eastern Mediterranea	4	38.6 (37.0, 40.3)	30.7 (29.4, 32.0)	37.4 (35.8, 38.9)	199.2 (191.0, 207.5)
Europe	11	43.9 (43.1, 44.7)	30.5 (29.0, 31.1)	44.2 (43.5, 45.0)	393.3 (386.8, 399.8)
Southeast Asia	0	31.8 (31.0, 32.7)	76.0 (74.0, 78.0)	31.6 (30.7, 32.5)	541.3 (526.5, 556.0)
Western Pacific	5	18.6 (17.9, 19.3)	31.2 (30.0, 32.4)	17.3 (16.6, 18.1)	300.8 (288.0, 313.5)
Global total	32	29.8 (29.4, 30.1)	240.9 (237.8, 243.9)	28.5 (28.2, 28.9)	1881.2 (1856.2, 1906.4)

[1] Values are means (95% CI). School age children defined as children 6–12 y old; general population defined as all age groups. UIC, urinary iodine concentration. [2] UIC <100 g/L. [3]A total of 193 WHO member states. [4] Based on United Nations population estimates in the year 2010 Source: UNICEF; Andersson et al, 2012; Zimmermann and Andersson, 2012

Proportion of households using iodized salt

Globally, only three out of four households are consuming adequately iodized salt, putting far too many children at risk **(Figure 12)**.

And globally, more than 35 million newborns were at risk of iodine deficiency disorders in 2013 **(Figure 13)**.

Figure 12: Percentage of households consuming adequately iodized salt, 2009–2013

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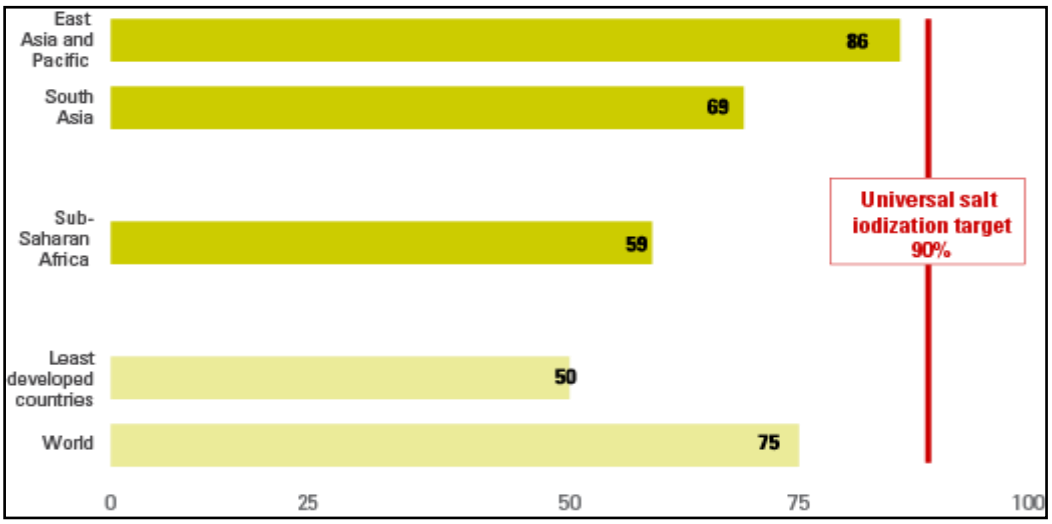
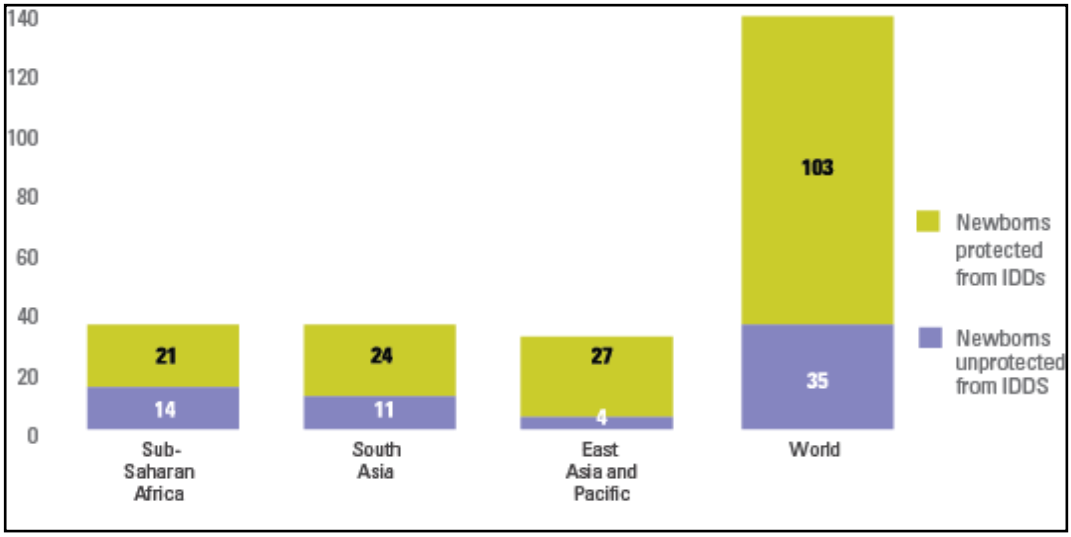


Source: UNICEF global nutrition database, 2014, based on Multiple Indicator Cluster Surveys (MICS), Demographic and Health Surveys (DHS) and other nationally representative household surveys, 2009–2013

Figure 13: Number of newborns unprotected and protected from iodine deficiency disorders (IDDs) as assessed through household consumption of adequately iodized salt (millions), 2013



Source: UNICEF global nutrition database, 2014, based on MICS, DHS and other nationally representative household surveys, 2009–2013

Iodine deficiency status in South East Asia is depicted in **Table 5**. It was found that amongst the school age children all 8 countries were iodine sufficient. And amongst the pregnant mothers all South East Asia countries were iodine deficient except Maldives.

Table 5: Iodine deficiency status in South East Asia

Country	Year	Iodized salt coverage %	Median UIC School Aged Children (µg/l)	Median UIC pregnant women (µg/l)
Afghanistan	2013	66	171	107
Bangladesh	2011	57	145	122
Bhutan	2007	95	298	-
India	2009	71	154	<150
Maldives	2007	96	176	159
Nepal	2011	80	202.8	114
Pakistan	2011	69	126	105
Sri Lanka	2011	68	163	113

Source: Global Iodine Score card, 2015; IDD Newsletter, 2015; UNICEF; Andersson et al, 2012; Zimmermann and Andersson, 2012

2.2.2 Indian Scenario

In India, the classical endemic belt of iodine deficiency disorder extends from the State of Jammu and Kashmir in the west, though parts of Punjab, Haryana, Himachal Pradesh, Uttarakhand, Uttar Pradesh, Northern part of Bihar, and West Bengal to northeastern states (ICMR, 1989; Pandav, 1982). After the results of the Kangra valley project on iodized salt supplementation, Government of India (GOI), in the year 1962, launched National Goitre Control Programme (NGCP).

In 1981: Nutrition Foundation of India, evaluated National Goitre Control Programme (Gopalan, 1981).

In 1983: India adopted a policy of Universal Salt Iodization (USI) to ensure that all edible salt for human and animal consumption is iodized.

In 1984: Government of India, launched the programme of Universal Iodization of salt, with an objective to iodize entire edible salt in the country in a phased manner, by 1990.

In 1988: Protection from Food Adulteration Act was amended to specify that iodized salt should have iodine in the concentration of at least 30 ppm at production level and at least 15 ppm at consumer level.

In 1989: the Indian Council of Medical Research (ICMR) carried out a multi-centric study on the prevalence of iodine deficiency disorder. Nine States outside the "traditional goitre-belt" were studied for the prevalence of goitre and cretinism. Goitre prevalence observed was 21.1% and the overall cretinism prevalence was 0.7% (ICMR, 1989).

In 1998-1999: Data from NFHS II (1998-99) reported that while 70 percent of the population in India consumed salt with some amount of iodine, only 49 percent used adequately iodised salt. A total of 28% of households were using non-iodised salt (NFHS-2).

In 2003; A country-wide study was carried out in 40 districts of India to assess the impact of universal salt iodization on the prevalence of iodine deficiency disorder, particularly in the districts with higher levels of endemicity before universal iodization was introduced. Overall the prevalence of total goitre declined from 14% to 69% during 1984-94 to 2% to 40% in 2003, The median urinary iodine concentration levels among 6-11 year children was observed to be <100 μg/dl only in 9 out of 40 districts (NIN, 2003).

In 2004: The survey conducted by the central and state health directorates, Indian Council of Medical Research and medical colleges have demonstrated that not even a single state is free from the problem of IDD. Out of 582 districts in the country, district level surveys conducted in 324 districts have revealed that IDD is a major public health problem in 263 districts, i.e. a total goiter prevalence rate of 10% and more in the population (MOHFW, 2004-05).

In 2005: The Salt department, under its Monitoring Information system receives reports from State Health Authorities. The reports received from 12 states revealed

that 73.7% of iodized salt were adequately iodized (15 ppm and more iodine) (Annual Report of Salt Department, 2008-2009).

In 2005-2006: A countrywide evaluation conducted under NFHS-3, in 2005–2006 measured the iodine content of cooking salt. Overall, 49% of the households used salt that was iodized at the recommended level of 15 ppm or more. About 22% salt was inadequately iodized i.e. less than 15 ppm. It was found that the use of iodized salt varied dramatically from one state to another (NFHS-3).

In 2009: A Coverage Evaluation Survey was conducted in 2009 and reported that 91.0% of households had access to iodized salt, of which 71.0% consumed adequately iodized salt. Another 9.0% consumed salt with no iodine (UNICEF, 2010).

In 2015: National Iodine and Salt Intake Survey (NISI) reported household coverage with iodized salt was 92%, and 78% with adequately iodized salt (≥15 ppm). Only 14% of households were still consuming inadequately iodized salt (iodized at 5–14.9 ppm), and 8% were using salt with no detectable amounts of iodine (90% household access to adequately iodized salt). Median urinary iodine concentration (MUIC) at the national level was 158µg/L among women of reproductive age (non pregnant), reflecting optimal iodine nutrition in India. The median varied significantly between the rural (148.5 µg/L) and urban (167.9 µg/L) areas. The Central zone reported the lowest median (128.6 µg/L) and the North zone reported the highest (204.0 µg/L), both well within the adequate range (ICCIDD, Jagriti, 2015).

Proportion of Households consuming adequately iodised salt should be more than 90% but the current status reported that in India only 78% of the households were consuming adequately iodized salt. The school age children had adequate iodine status but the pregnant mothers are still iodine deficient **(Table 6)**.

Table 6: Status of Iodine Deficiency Disorder in India

Indicator	**Goal**	**Status**
Salt iodisation Proportion of Households consuming adequately iodised salt	>90%	78% (NISI, 2015)
Urinary Iodine Median in the general population Median in pregnant women Median in women of reproductive age group	 100-199 µg/L 150-249 µg/L 100-199 µg/L	 154 µg/L <150 µg/L 158 µg/L
Programmatic Indicators Attainment of indicators	At least 8 of 10	7/10

Source: ICCIDD, 2015

2.3 Iodine Deficiency in Pregnant Mothers

Iodine deficiency is the world's single most significant cause of preventable brain damage and mental retardation. Iodine deficiency during pregnancy leads to still births, spontaneous abortions, preterm delivery, and fetal wastage and cretinism (WHO, 2001). The maternal thyroid hormones crosses the placenta and if mother is deficient in iodine during pregnancy, then the less transfer of maternal thyroid hormones to fetus leads to morphological, physiological and biochemical abnormalities in developing embryo (Contempre et al, 2003).

Iodine uptake by the thyroid is higher during pregnancy and the iodine reserve in the thyroid can decrease to approximately 40% of preconception levels. The increased clearance rate can lead to an increase in thyroid volume in pregnant women in iodine deficient areas. There is no or little change in thyroid volume observed in pregnant women in areas with sufficient dietary iodine intake (Glioner et al, 1997, Perez-Lopez et al, 2007, Zimmerman et al, 2009).

The thyroid stores iodine from the diet. However, maternal iodine status is not entirely dependent on the current dietary intake during gestation. If preconception iodine nutrition is adequate there, then there will be sufficient stored thyroid hormone to support the mother and fetus, at least in the first trimester of pregnancy. However, if preconception dietary intake is deficient the increasing demands of later pregnancy may produce a deficit iodine status which if left untreated can result in a hypothyroxinaemic state (Smyth et al, 2006). Evidence suggests that in areas of mild to moderate iodine deficiency, the maternal thyroid is able to adapt to meet the increased thyroid hormone requirements of pregnancy (Zimmerman et al, 2009). Although, during the first two trimesters of pregnancy the foetus is entirely dependent on the maternal thyroid hormone supply as the foetal thyroid does not develop until 13-15 weeks of gestation (Smyth et al, 2006, Glioner et al, 1997). As it progresses into the third trimester, it develops the ability to produce its own thyroid hormones but it is still dependent on maternal iodine for hormone synthesis (Burrow et al, 1994).

According to WHO, the median UIC level of <150µg/l amongst pregnant mothers indicates iodine deficiency in the community (WHO, 2007). Pregnant women with normal thyroid stimulating hormone (TSH) levels often have low free T4 levels, even

in areas in which iodine intake is sufficient within the general population. This condition is termed as hypothyroxinemia. Recent findings suggest that the hypothyroxinemia can negatively affect child health outcomes, including neonatal behavior and infant cognitive functioning (Wang et al, 2012; Melse-Boonstra et al, 2012).

Studies conducted in various regions of the world with varying iodine status have assessed the impact of maternal iodine status on that of neonates and on thyroid function and neuropsychiatric development of neonates (Arrobas-Velilla et al, 2011; Wong et al, 2011). A study conducted on overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome reported significant adverse effects on maternal and fetal outcome. Thus, emphasizing the importance of routine antenatal thyroid screening during pregnancy for early detection of iodine deficiency (Sahu et al, 2010).

2.3.1 Metabolism of iodine during pregnancy

After being reduced to iodide, dietary iodine is rapidly absorbed from the gut. Iodide of dietary origin then mixes rapidly with iodide derived from the peripheral catabolism of iodothyronines and together they constitute the extrathyroid pool of plasma inorganic iodide (PII), which exists in a dynamic equilibrium with two organs, the thyroid gland and the kidneys (Lazarus, 2014).

A normal adult uses approximately 80mg iodide a day to produce thyroid hormones. When the iodine intake by non-pregnant women is adequate (150mg/day), a kinetic balance is achieved by thyroid uptake of 35% of the available iodine. Of the 80mg hormonal iodide produced daily by thyroid hormone catabolism, 15mg iodide is lost in the faeces, leaving 65 mg to be redistributed between the thyroid gland and irreversible urinary losses. In these conditions, the metabolic balance remains in equilibrium and the body is able to maintain a plentiful store of iodine in the thyroid ranging from 10 to 20 mg (Glinoer, 2007).

In contrast, when iodine intake is restricted before the onset of a pregnancy to approximately 70mg day or less, the body must increase iodide trapping through the pituitary–thyroid feedback mechanism in order to maintain the necessary absolute iodine intake. In such conditions, there is a shortfall of iodine of approximately 10mg

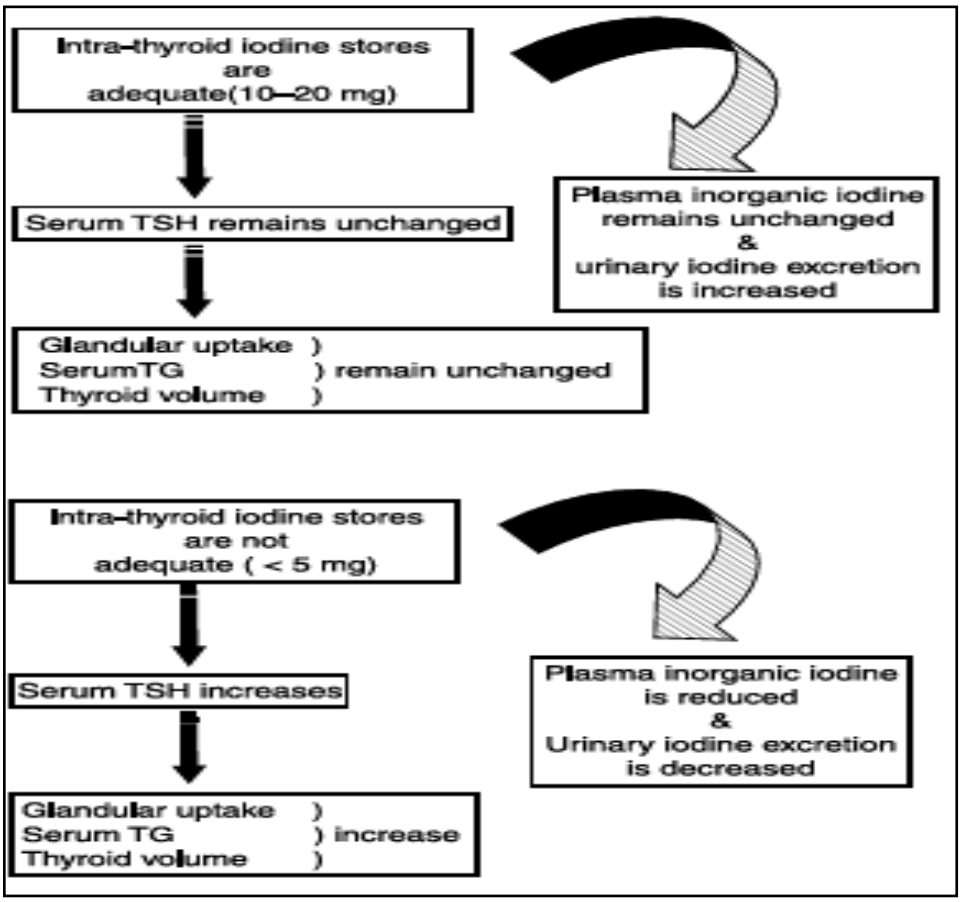
day and the thyroid gland uses stored iodine, which is therefore progressively depleted to low amounts of 2–5 mg stable iodine. Over time, if the nutritional situation remains unchanged, the metabolic balance of iodine becomes negative (Glinoer, 2007).

There are two fundamental changes that take place during pregnancy. They are: i) There is a significant increase in renal iodide clearance by approximately 30–50% and, ii) a sustained increase in thyroid hormone production by 50%, from 80 to 120mg hormonal iodide a day. Since the renal iodide clearance already increases in the first weeks of gestation and persists thereafter, this constitutes an obligatory iodine leakage' which tends to lower the circulating PII concentration and, in turn, induces a compensatory increase in the thyroidal clearance of iodide. These mechanisms underscore the increased physiological activity of the thyroid gland during the first half of pregnancy. It has been observed that in such conditions, there is a shortfall of about 20mg iodine a day (Glinoer, 1997; Glinoer, 2007).

In order to sustain an increased production of thyroid hormones, the glandular machinery must draw iodine from already depleted thyroid stores. This is the rationale for the excessive stimulation of the thyroid gland observed during a pregnancy that takes place in iodine-deficient conditions. The consequences of this are relative hypothyroxinaemia, preferential secretion of tri-iodothyronine, an increased concentration of serum thyroid-stimulating hormone as well as serum thyroglobulin and, finally, increase in thyroid volume leading to goitre (Glinoer D, 1997).

The conceptual model of iodine nutrition and thyroid function when iodine store are adequate and not adequate is depicted in **Figure 14.**

Figure 14: Conceptual model of iodine nutrition and thyroid function when iodine store are adequate (upper diagram) and not adequate (lower diagram)



Source: Adapted from Glinoer, 2007

2.3.2 Prevalence of Iodine Deficiency in Pregnant Mothers

2.3.2.1 Global Scenario

Various researchers have carried out studies to assess the iodine nutrition status of pregnant women globally at different point of gestation **(Table 7)**. Globally the prevalence of iodine deficiency during pregnancy was and still is the area of concern from most of the developing countries and few of the developed countries. In developed and developing countries the prevalence of iodine deficiency from last few decades was reported by many researchers using thyroid volume as an indicator.

The relationship between iodine deficiency and still birth was first documented in 1939 in Canada. The supplementation of prophylactic potassium iodide to pregnant women reduced the incidence of abortion and stillbirth (Kemp et al, 1939). De Long et al. have reported the effects of iodine deficiency at different trimesters of

pregnancy. Correction of iodine deficiency during the second trimester reduced neurological abnormalities, increased head growth, and improved the development quotient in a severely iodine-deficient area of western China. However, the correction of iodine deficiency during the third trimester did not improve occurrence of neurological development (DeLong et al, 1998; Chan et al, 2000; Koibuchi et al, 2000).

A study conducted to assess the association between iodine status and reproductive failure in West African women revealed that reproductive failure was associated with low iodine status. The risk of reproductive failure increased when women had severe iodine deficiency. It was found that women with severe iodine deficiency had stillbirth rate of 15/1000 live births whereas women who were not iodine deficient had a stillbirth rate of 8.7/1000 live births. Also, approximately 30% of iodine deficient women had more than 3 abortions as compared to 16% in non deficient women (Dillon et al, 2000). A study conducted in Zaire revealed a strong association between reproductive failure and cretinism. The rate of stillbirth reduced from 18/1000 live births to 9/1000 live births after the supplementation of iodine to the women (Thilly et al, 1980). A study conducted in Papua New Guinea revealed that mothers who were given iodized oil injection before conception had a prevalence of live births of 42.2/1000 compared with 61.0/1000 in mothers who did not receive iodized oil injection before conception (Pharoah et al, 1994). A study was conducted by Shamim et al, 2012 in Bangladesh among pregnant women in early (≤16 weeks, n=1376) and late (≥32 weeks, n=1114) pregnancy. It was found that median urinary iodine concentrations were 66 and 55µg/L in early and late pregnancy, respectively; urinary iodine <150 µg/ L was found in >80% of women at both times in pregnancy indicating iodine deficiency at both times. Further studies on iodine nutritional status amongst pregnant mothers worldwide is depicted in **Table 7**.

Table 7: Iodine nutritional status amongst pregnant women worldwide

Author; Year	Study Area	N	Trimester	Median UIC (µg/L)
Glinoer et al, 1990	Belgium	230	1,	58
		265	2,	58
		370	3,	53
Pedersen et al, 1993	Denmark	26	2	51
		26	3	40
Mocan et al, 1995	Turkey	90	1,2,3	91
Caron et al, 1997	France	306	1	50
		224	3	54
Mezosi et al, 2000	Hungary	119	1,2,3	57
Hess et al, 2001	Switzerland	511	2,3	138
Antonangeli et al, 2002	Italy	67	1,2	74
Rajatanvani et al, 2007	Thailand	125	3	103
Mehdi et al, 2009	Bangladesh	60	1	143
		60	2	132
		60	3	120
Shamim et al, 2012	Bangladesh	1376	1	66
		1114	3	55
Lombamo, et al, 2014	Ethiopia	172	1,2,3	15

2.3.2.2 Indian Scenario

Iodine deficiency in pregnant women poses additional reproductive risks, including overt hypothyroidism, infertility and increased abortions in pregnant women. Iodine deficiency induced hypothyroidism causes infertility, gestational hypertension, increased first trimester abortions and stillbirths (Dunn et al, 2011).

A recent study conducted by Kapil et al, in three districts (Kangra, Kullu and Solan) of Himachal Pradesh amongst pregnant mothers reported the Total Goiter Rate as 42.2 % (Kangra), 42.0 % (Kullu) and 19.9 % (Solan), respectively and the median urinary iodine concentration level as 200µg/l (Kangra), 149µg/l (Kullu) and 130µg/l (Solan). The percentage of pregnant mothers consuming adequately iodized salt

(iodine content of 15 ppm and more) was found to be 68.3% (Kangra), 60.3% (Kullu) and 48.5% (Solan). It was found that pregnant mothers in Kullu and Solan districts had iodine deficiency as indicated by a median urinary iodine concentration of less than 150µg/l (Kapil et al, 2014).

Another recent departmental study by Joshi et al, 2014 conducted in Vadodara district of Gujarat reported the median urinary iodine concentration amongst pregnant mothers as 297.1µg/l indicating adequate iodine nutritional status amongst pregnant mothers of Vadodara district, Gujarat. Similar findings i.e adequate iodine status (median urinary iodine concentration: 172µg/l) amongst pregnant mothers were also reported from Bangalore (Jaiswa et al, 2015).

A study by Kapil et al, 1999 reported that 22.9% of the pregnant women in Delhi had urinary iodine excretion levels of less than 150µg/L. Another study found iodine deficiency in 9.5% of the pregnant women as revealed by urinary iodine concentration levels of less than 150µg/L indicating iodine deficiency (Kapil et al, 1997). High incidence of neonatal hypothyroidism has been reported in iodine deficient endemic regions due to iodine deficiency amongst pregnant women (Kochupillai et al, 1986).

A hospital based study conducted in Delhi amongst pregnant mothers reported the median urinary iodine concentration level as 304µg/l indicating adequate nutritional status amongst the pregnant mothers studied (Grewal et al, 2013). Another hospital based study from West Bengal amongst full term pregnant women reported the median UIC as 144µg/dl indicating mild iodine deficiency (Chakraborty et al, 2006).

A community based study was conducted amongst pregnant mothers in Udham Singh Nagar, Uttaranchal reported the TGR as 14.6%. The median UIC was found to be 95µg/l (Pathak et al, 2003). Another study conducted in Bombay amongst 429 pregnant mothers reported the TGR as 45% and median UIC level as <100µg/l (Dodd et al, 1993). Another community based study conducted in Jodhpur district; Rajasthan reported the median UIC level as 117µg/l. The 77.3% of the families were consuming salt with iodine content of <15 ppm (Singh et al, 2009). Another study from Rajasthan amongst pregnant mothers documented the median UIC level as 127µg/l indicating iodine deficiency amongst pregnant mothers in Rajasthan (Ategbo et al, 2008).

2.3.2.3 Comparison of iodine deficiency status amongst Pregnant Mothers in Uttarakhand and Gujarat

There is very limited data available on status of iodine deficiency amongst pregnant mothers from Uttarakhand and Gujarat state. **Table 8** depicts the status of iodine nutrition among pregnant mothers of Uttarakhand and Gujarat state.

Table 8: Comparison of iodine deficiency in pregnant mothers of Gujarat and Uttarakhand

States	Author/ Year	Place	TGR (%)	Median UIC (µg/l)	Percentage of Iodine content of salt with less than 15ppm
Uttarakhand	Pathak et al, 2003	Uttaranchal	14.6	95	-
Gujarat	Joshi et al, 2014	Vadodara		297.14	

2.3.3 Effect of Iodine deficiency in Pregnancy

2.3.3.1 Effect of Severe Iodine Deficiency

Severe iodine deficiency in pregnancy has the potential to cause both maternal and fetal hypothyroidism. Severe iodine deficiency is also associated with poor obstetric outcomes including spontaneous abortion, prematurity, and stillbirth (WHO, 2007). Thyroid hormone plays an essential role in neuronal migration, myelination, and synaptic transmission and plasticity (Escobar et al, 2007; Rapozo et al, 2006). Animal models have demonstrated that even mild and transient maternal hypothyroxinemia during pregnancy can disrupt neuronal migration in the fetus (E. Aus´ et al, 2004). Therefore, iodine deficiency is associated with adverse effects on the fetus (WHO, 2007). Despite global public health efforts, iodine deficiency still remains the leading preventable cause of mental retardation worldwide (Pearce et al, 2009).

Several studies have also documented that severe iodine deficiency is also linked to intellectual development in early childhood in the absence of overt mental retardation (Qian et al, 2005; Zimmerman et al, 2009).

2.3.3.2 Effects of Mild-to-Moderate Iodine Deficiency

A study by Pop et al. examined Bayley Scales of Infant Development scores among 10- month-old infants of women with fT4 levels below the tenth percentile in the first trimester of pregnancy compared to infants of women with higher fT4 levels at that gestational age (Pop et al, 1999). The infants with lower maternal fT4 had significantly lower psychomotor scores.

Henrich et al. studied expressive vocabulary at the age of 18 and 30 months in 3659 children of women with normal TSH but varying fT4. They found that lower maternal fT4 was associated with an increased risk of expressive language delay (Henrichs et al, 2010). Haddow et al. assessed the IQ of 7 to 9 year-old children of women with subclinical hypothyroidism in pregnancy, identified by elevated TSH in the second trimester, and found that IQ scores in these children averaged 7 points lower than children of matched women with normal thyroid function in the second trimester (Haddow et al, 1999).

A small study conducted by Vermiglio et al, found a significantly greater prevalence of attention deficit hyperactivity disorder (ADHD) among the offspring of mothers from an area of mild-to-moderate iodine deficiency in comparison to those of mothers in a "marginally" iodine-sufficient area (Vermiglio et al, 2004).

2.3.3.3 Effect of Maternal Iodine deficiency on newborns

a) **Central Nervous System and Fetal Brain**

The development of nervous system occurs in the first trimester of pregnancy, which depends on the availability of thyroid hormones. After 12 weeks of pregnancy, the fetal thyroid glands start secreting thyroid hormones (Kochupillai et al, 1984) which help in tissue metabolism, growth and brain development of the fetus and the neonate, which in turn influences physical and intellectual growth and development of the growing child (Delange, 1995; Sinha et al, 1992; Mussa et al, 1990). The severe iodine deficiency during first trimester of pregnancy adversely affects the fetal thyroid function, which leads to cretinism, a severe form of mental retardation (Lindsay and Stuart, 2001). Iodine deficiency during pregnancy causes both maternal and fetal

hypo-thyroxinaemia, leading to irreversible impairment of fetal brain development (Hollingsworth et al, 1985).

b) **Perinatal Mortality**

Iodine deficiency during pregnancy is associated with an increased risk of stillbirths, abortions and congenital abnormalities. Prevalence of perinatal mortality has been found to be twice in pregnant women who had low serum thyroxine concentrations than those with higher serum thyroxine concentrations (Pharoah et al, 1976).

2.3.3.4 Effect of Maternal Iodine Deficiency on IQ of the children

Severe iodine deficiency in pregnancy results in significant impairment in cognition of the child. It has been suggested that cretinism is at the far end of a spectrum of effects that iodine deficiency can have on the central nervous system, and that varying degrees of intellectual impairment can occur across this spectrum concordant with the degree of iodine deficiency (Skeaff, 2011).

A number of studies published on pregnant women living in moderate to mild iodine deficiency and correlation with the mental development of their children. A study conducted in United States to compare IQ scores of seven to nine year old children of mothers with subclinical hypothyroidism during pregnancy found IQ scores of seven points lower than controls (Zimmerman et al, 2009). A meta-analysis of 37 studies of IQ in iodine deficient regions in China found a reduction of 12.45 IQ points when compared to iodine sufficient regions. Thus it was reported that iodine supplementation before and during pregnancy to women in iodine deficient areas could prevent their child from intellectual deficit (Qian et al, 2005).

A study by Berbel et al, 2009 reported that the development quotient of children in mothers supplemented in the first group (i.e., 4–6 weeks) was significantly higher than that of children whose mothers received supplements from 12–14 weeks gestation and near term. Similarly another Spanish study conducted in an area of moderate iodine deficiency (i.e., UIC of pregnant women in this area was <100μg/L) by Velasco et al, (2009) found that children of mothers supplemented with 300μg of iodine in the first trimester had higher psychomotor development scores than children from mothers who did not start supplementation until the last month of pregnancy. A

study conducted by Haddow et al, (1999) reported that maternal hypothyroidism has adverse effects on the child's development even without immediate clinical manifestation. As thyroid hormones are transferred from mother to fetus, both before and probably even after the onset of fetal thyroid function (Glinoer & Delange, 2000), maternal thyroid sufficiency might therefore be most important in early pregnancy. A case-control study in Bangladesh, comparing mental retardation according to maternal history of goiter, found an increased risk of reduced intelligent scores in children of goitrous mothers (Durkin et al, 2000).

2.3.4 Effect of Iodine supplementation during pregnancy

A review of six randomized control trials (RCTs) (Zimmerman and Delange, 2004) found a significant increase in urinary iodine concentration level with iodine supplementation. These studies also found that supplements are generally effective at minimizing increases in thyroid volume during pregnancy (Zimmerman et al, 2009). However, there was no clear effect on total or free thyroid hormone concentrations (Zimmerman and Delange, 2004; Zimmerman, 2009). Iodine supplementation was considered efficacious for both maternal and newborn iodine status.

The review of iodine status of pregnant women in Europe concluded that, supplements appear to be generally safe and recommends that pregnant and lactating women and women planning to become pregnant could take an iodine supplement of 150 g/d (Zimmerman and Delange, 2004). Iodine supplementation, at the recommended doses of 50 to 250 g/d, will not lead to an iodine intake in excess of the UL of 1100 g/d. Currently, recommendations for iodine supplementation in areas of mild to moderate deficiency vary from 50 to 250 g/d. (Perez-Lopez, 2007; WHO, 2007; Zimmerman and Delange, 2004). The most widely utilized method for iodine supplementation is salt iodisation. Another strategy is injection of iodised oil, which is advocated for isolated regions where there is limited access to iodised salt (Lindsay and Stuart, 2001). After the supplementation of iodised oil to pregnant women, a significant reduction in the mortality of infants and young children has been documented. Iodine supplementation also reduces the prevalence of endemic cretinism (Thilly, 1983; Glinoer, 1997). Perinatal mortality can be reduced by iodine supplementation to mother before or during pregnancy.

2.3.5 Maternal iodine status and gestational age

Thyroid status is known to have an important bearing on the ability of women to conceive and to bring a normal infant to term. Both maternal hyper and hypothyroidism have deleterious effect on pregnancy outcome and thyroid hormone excess has direct toxic effect on fetus (Anseimo et al, 2004; Potter et al, 1979).

Gestational hyperthyroidism although uncommon, may lead to prematurity, intrauterine growth retardation (IUGR), fetal or neonatal thyrotoxicosis etc. (Lazarus et al, 2005; Karabinas et al, 1998). Gestational hypothyroidism is relatively common leading to fetal & maternal morbidities; like maternal obstetrical complications, impaired neuropsychological developments of neonates with low IQ levels. (Lazarus et al, 2005; Karabinas et al, 1998; Rodien et al, 2005). Adequate supply of iodine is essential to maintain the normal thyroid function. It is especially important particularly during pregnancy where the iodine requirement is increased due to enhanced renal clearance of iodine, transfer of iodine from mother to fetus as well as greater need of iodine to make more thyroid hormones to support the increased metabolic demand in pregnancy (Lazarus et al, 2000; Glinoer et al, 1997).

A study conducted by Tahrim et al, 2009 reported that the thyroid hormones (serum FT 3, FT 4) was decreased and serum TSH was increased significantly in 3rd trimester of pregnancy compared to 1st trimester. Various other studies have also documented that pregnant women was found to be iodine deficient progressively with advancing gestational age probably because of the failure of adequate dietary iodine intake particularly in advanced pregnancy. This could also be due the non appetizing and anorexic problems incident to the pathophysiological changes during pregnancy (Azizi et al, 2002; Eltom et al, 2000; Glinoer et al, 1995; Pathak et al, 2003; Caron et al, 1997; Dunn et al, 1998; Pedersen et al, 1993).

2.4 Iodine Deficiency in Neonates

Iodine deficiency among neonates is one of the most common preventable causes of mental retardation. The complications of ID amongst neonates results in intellectual impairment and neurodevelopment delay present later in life when it is too late to be treated or reversed. Timely treatment is very important to effect adequate neurocognitive development during the critical first 3 years of life. The earlier the treatment is started, the higher the IQ levels are achieved later in life (WHO, 2007).

The neonatal brain is only a third of the size of the adult's brain, if ID and neonatal thyroid failure continue for about 3months, this condition can lead to irreversible brain damage. Based on scientific data available, it is estimated that about 10% or more of newborns in severe goiter endemic areas are at risk of neonatal hypothyroidism and resultant compromised physical and mental development (Ramji et al, 1994). Infants born to mothers, who have thyroxin concentration below the 10^{th} percentile before the 13th week of gestation, have impaired neuropsychological development and maturation of the central nervous system (Kochupillai et al, 1983). The recognized role of thyroid hormones in brain development and the irreparable nature of brain damage is caused by untreated hypothyroidism early in life (Fisher et al, 1979).

Because serum TSH is determined mainly by the level of circulating thyroid hormone, which in turn reflects iodine intake, TSH can be used as an indicator of iodine nutrition. TSH is a sensitive indicator of iodine status in the newborn period (Delange et al, 1997). Compared to the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. Particularly when iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation. Serum TSH concentrations are therefore increased in iodine-deficient infants for the first few weeks of life, a condition termed transient newborn hypothyroidism (Zimmermann et al, 2003; WHO, 1994). TSH is used in many countries for routine newborn screening to detect congenital hypothyroidism. If already in place, such screening offers a sensitive indicator of iodine nutrition (WHO, 2007).

2.4.1 Prevalence of Iodine Deficiency in Neonates

2.4.1.1 Global Scenario

Research studies conducted in different countries have reported the TSH level of more than 5mlU/l in Western Uganda (20-32%), Estonia (18.1%), Italy (14.4%), Spain (9.0%), Thailand (8.9%), Australia (6.8%), Poland (3-5%) and Iran (3.6%), respectively (Ehrenkranz et al, 2011; Mikelsaar et al,1999; Costante et al,1997; Peris Roig et al, 2009; Jaruratanasirikul et al, 2009; Rahman et al, 2010; Ołtarzewski et al, 2003; Najafi et al, 2008).

2.4.1.2 Indian Scenario

Iodine deficiency increases the risk of neonatal mortality. Neonates are more sensitive than children and adults to the effect of iodine deficiency because their brain develops up to 3 years of age (WHO, 2007).

Iodine deficiency in neonates leads to cretinism including mental deficiency with a mixture of mutism, spastic diplegia, squint, hypothyroidism and short stature. Neonates are the most vulnerable group for ID. According to WHO, raised TSH in neonates at birth is an indicator for ID. WHO (2007) reported that a >3% frequency of TSH concentrations above 5mIU/L in samples collected 3-4 days after birth indicates iodine deficiency in a population.

Recent studies conducted in the neighboring state (Himachal Pradesh) reported TSH level of >5mlU/l in 73.4% (Kangra) and 63.2% (Solan) of the neonates indicating presence of iodine deficiency in the districts studied (Kapil et al, 2014). Another study conducted in West Bengal has reported the TSH level of more than 5mlU/l in 2.95 % of the neonates (Chakraborty et al, 2006).

2.4.1.3 Comparison of iodine deficiency status amongst Neonates in Uttarakhand and Gujarat

Uttarakhand: No data is available from Uttarakhand state.

Gujarat: A departmental study conducted by Rana et al, 2012 in Vadodara, Gujarat reported that TSH levels amongst neonates was found to be 36.2% (<10uIU/ml), 31.2% (10-20uIU/ml) and 12.6% (>20uIU/ml), respectively. Another departmental study conducted by Joshi et al, 2012 reported that 26.6 % of the neonates were observed having TSH level of >10μIU/ml which indicates moderate iodine deficiency.

There is very limited data available on the status of iodine nutrition amongst neonates of India.

2.4.2 Neonatal Hypothyroidism

Neonatal hypothyroidism is due to inadequate thyroid hormone production in newborns and its exact incidence in India is unknown. Universal neonatal screening (NS) is still not practiced in few developing countries.

The worldwide incidence of Congenital Hypothyroidism (CH) is 1:3000–1:4000 (Klett et al, 1997). The incidence has racial and global topographic differences, being highest in Europe 1:3300 and as low as 1:5700 live births infants in Japan with an average of 1:4500 live births in most other parts of the globe (Kochupillai et al, 1993).

Neonatal thyroid screening in the United Kingdom has shown a significantly higher incidence of neonatal hypothyroidism in Asian families in comparison with non-Asians (1/918 in Asians compared 1/3391 within non-Asians) (Rosenthal et al, 1998). The incidence is lower among African American newborns and higher among Hispanic newborns compared with the rate among white newborns (Olney et al, 2010).

Incidence of neonatal hypothyroidism in several countries has been well documented. Earlier studies reported an incidence of neonatal hypothyroidism as 3:1207 (Ethiopia), 1:1446 (Italy), 1:1667 and 1:3670 (Latin America), and 1:4000 (United States), respectively (Mekonnen et al, 2003; Corbetta et al, 2009; Borrajo et al, 2007; Harris et al, 2007). Newborn screening in Brazil had revealed consistent lowering in the

incidence of neonatal hypothyroidism in 3 consecutive years (1:3616 in 2005, 1:1369 in 2006 and 1:1030 in 2007) (Botler et al, 2012). Thus, this high prevalence of neonatal hypothyroidism is indicative of widespread IDD throughout the globe at different intensities.

High incidences of neonatal hypothyroidism in iodine deficient areas with endemic goiter and/or cretinism have been documented from other countries. Thilly et al. reported 10% incidence of neonatal hypothyroidism in Zaire, as reflected in cord blood hormone levels during birth (Thilly et al, 1978). One of the studies conducted on 20107 newborns in Tehran and Damavand showed the estimated incidence of NH as one in every 914 births (Ordookhani et al, 2003).

One of the studies conducted in Saki (Nigeria), reported the incidence of neonatal chemical hypothyroidism as 14.7/1000 birth in the cord blood samples obtained from the babies at the time of delivery for thyroid function tests (Ojule et al, 1998).

A recent study conducted by Kapil et al, 2014 in district Kangra, Himachal Pradesh have documented that 4.4% of neonates were suffering from neonatal hypothyroidism (Kapil et al, 2014).

In early 80s by screening the cord blood of over 20,000 newborns, reported the incidence of neonatal hypothyroidism as 133, 85 and 75, respectively in the three endemic districts of Uttar Pradesh, much higher than in Delhi and in coastal Kerala/1000 births (Kochupillai et al, 1993). The incidence of neonatal hypothyroidism, as reflected in cord blood thyroxin and thyrotropin levels, varied from 0.6% to 13.3% in iodine deficient and normal regions of India, depending on the degree of ID as assessed by the pattern of urinary iodine excretion in the affected population (Klett et al, 1997).

Earlier studies conducted in India reported the incidence of congenital hypothyroidism (CH) as 1:476, 1:1700, 1:2481 and 1:2804, respectively (Rama Devi et al, 2004; Desai et al, 1987; Desai et al, 1994; Mathew et al, 2008).

One of the studies conducted in Mumbai in which 12,407 neonates were screened over 26 months for their cord blood thyrotrophin level TSH, reveled a higher incidence (1:2481) of neonatal hypothyroidism (Desai et al, 1987). Data on Neonatal Screening for neonatal hypothyroidism with cord blood T4 studies on more than

25,000 newborns in the same area of Mumbai have shown the incidence of 1 in 2,804 (Desai et al, 1994).

2.4.2.1 Neonatal Hypothyroidism Screening

Neonatal hypothyroidism screening has been identified as a potential method for early detection and prevention of the adverse effects of thyroid deprivation on the brain development of neonates, thus promoting an early intervention (Sareen and Pradhan, 2015).

Newborn screening for neonatal hypothyroidism has been implemented in the United States, Canada, Western Europe, Japan, Australia, New Zealand, Taiwan, parts of China, Mexico and Israel (Salim et al, 2014). Neonatal Hypothyroidism screening programs have been instituted to allow its early detection and initiation of therapy (Corbetta et al, 2009). It resulted in bringing down worldwide incidences of neonatal hypothyroidism from 1:7000 to 1:3000 to 4000 (ACP, 2006). Under this, the newborns are subjected to screen for hypothyroidism by estimation of serum thyrotrophic TSH levels. TSH level of more than 20μl/dl in neonates indicates insufficient supply of thyroid hormones to the developing brain.

Newborn screening is ultimately a public health program. Currently, there are no national programs for neonatal hypothyroidism screening in India (Mathew et al, 2008).

2.4.3 Effect of other factors on TSH levels of the neonates

Various studies have shown correlation between CB TSH levels and other factors such as neonate gender, birth weight, mode of delivery, maternal age etc (Rashmi et al, 2007; Kim et al, 2005; Chan et al, 2001; Chan et al, 2006).

2.4.3.1 Maternal Factor

Maternal age and other diseases

A recent study conducted by Raj et al, 2014 found that there was a correlation between maternal age and CBTSH with babies of mothers of older age groups having higher CBTSH levels. Another study conducted by Ingrida et al, reported that older

maternal age in pregnancy and newborn gestational age were associated with elevated newborn bloodspot TSH levels on the third day of life (Ingrida et al, 2010).

A study by Herbstman, et al 2008 reported that umbilical cord serum level of TSH and total and free T4 were not associated with maternal age or weight gain during pregnancy (Herbstman et al, 2008).

A number of maternal conditions, including hypertension, preeclampsia, cardiac, renal, hepatic, respiratory, immuno- logic conditions, and HIV have not been found to be associated with neonatal thyroid hormone status either in this or in prior studies (Franklin et al, 1985; Chan et al, 2003; Ward et al, 2000; Low et al, 1986).

Many studies have examined the impact of maternal diabetes or gestational diabetes on neonatal thyroid status. Most of these studies found no association (Erenberg et al, 1978; Franklin et al, 1985; Ward et al, 2000; Wilker et al, 1984). However, few have controlled for other potentially confounding factors that may distort the observed association. Chan et al, 2003 found that babies of diabetic mothers had higher cord blood TSH levels in multivariate but not univariate models. Studies that specifically examined gestational diabetes reported associations with higher TSH levels in cord blood (Low et al, 1986; Lao et al, 2002). There was speculation that this elevation might be a function of increased stress among newborns of mothers with gestational diabetes (Lao et al, 2002).

There also have been inconsistent results regarding the impact of diabetes on T4 measurements, such that Wilker et al. found lower T4 levels measured at various points during the postnatal period (cord blood, 2 hours, 12 hours, and 72 hours after delivery) among infants of diabetics (Wilker et al, 1984). An early study by Erenberg found no difference between T4 measured in cord blood among infants of diabetic and nondiabetic mothers (Erenberg et al, 1978).

Iodine intake is among the most important nutritional factors influencing thyroid hormone level, as it is required for thyroid hormone synthesis (Glinoer et al, 2001). When dietary iodine is insufficient, compensatory mechanisms enable the thyroid gland to hoard more of the available iodine and more efficiently reuse iodide that is released when T4 is converted to triiodothyronine (T3). In spite of this compensation, thyroid hormone concentrations are affected by iodine deficiency, such that total and

free T4 are decreased and both T3 and TSH are normal or increased (Boyages et al, 1993). During pregnancy, iodine availability is especially important due to the increased demand placed on the maternal thyroid system (Glinoer et al, 2001). It has been shown that maternal iodine deficiency is related to higher TSH concentrations in the newborn, such that, at a population level, the cumulative TSH shifts to the right as the severity of iodine deficiency increases (McElduff et al, 2002; Sullivan et al, 1997).

Several studies have reported no relationship between smoking during pregnancy and TSH, total T4, or free T4 as measured in either cord blood or neonatal bloodspots (Williams et al, 2005; Ericsson et al, 1987; Hannigan et al, 1995). A study examining the effect of drug abuse (marijuana and=or cocaine) during pregnancy on neonatal thyroid parameters found no associations (Hernandez et al, 1992). An additional study found no relationship with alcohol use and neonatal T4 measured in bloodspots (Hannigan et al, 1995). The possible relationship between TSH and alcohol intake is potentially important to the design of environmental studies since alcohol can affect metabolism, and therefore levels of exposure to many xenobiotic substances (Herbstman, 2007).

2.4.3.2 Delivery Factor

It is possible that factors such as delivery mode, labor, augmentation of labor, and labor duration are potential confounding factors for thyroid hormone status and environmental exposures.

A study by Armanian et al, 2013, reported that cord blood TSH level was higher in newborns with vaginal delivery compared with cesarean delivery. It could be explained by stress events during pregnancy and labour. Another study by Fuse et al., on healthy neonates with different types of delivery, including cesarean section, normal vaginal delivery and by vacuum extractor found that there was no statistically significant difference in cord blood TSH among neonates in study groups (Fuse et al, 1991).

On the other hand, Kim et al., showed that cord blood TSH was affected by perinatal stress events and is significantly higher in infants born vaginally than of cesarean section (Kim et al, 2005). A study by Herbstman et al, 2008 reported that umbilical cord serum level of TSH and total and free T4 were not associated with most delivery

factors that were examined, including, duration of labor, detection of intrapartum fever. However, babies born via vaginal delivery had higher levels of TSH in cord blood.

The majority of studies have found that vaginal deliveries result in higher average TSH cord levels (Franklin et al, 1985; Lao et al, 2002; Miyamoto et al, 1991; Chan et al, 2001). This may be related to the observation that stress during delivery seems to be associated with elevated TSH in cord blood (Tehrani et al, 2003; Copeland et al, 2002). However, few research studies have reported that TSH in cord blood is not influenced by mode of delivery (Erenberg et al, 1978; Ericsson et al, 1987; Fuse et al, 1991) and one concluded that deliveries via cesarean section result in higher TSH measured in neonatal bloodspots (McElduff et al, 2005).

A study by Tehrani et al, reported that babies born via elective C-sections had higher average cord TSH levels (Tehrani et al, 2003). Two other studies reported that instrumental vaginal deliveries had higher cord blood TSH values than spontaneous vaginal deliveries (Miyamoto et al, 1991; Chan et al, 2001). Other studies have found that cesarean sections with and without labor have similar cord TSH levels (Chan et al, 2003; Lao et al, 1989).

The only study to explicitly study labor augmentation found that oxytocin use was not associated with either TSH or T4 levels measured in cord blood (Fuse et al, 1991). Prior studies examining the duration of labor have reported inconsistent results; one found no association between labor duration and cord TSH or free T4 (Fuse et al, 1991) and others found that longer duration of labor (particularly the second stage) was associated with increased cord TSH levels (Miyamoto and Lao, 1991). Other factors marking a stressful delivery have been linked to higher cord TSH levels, including malpresentation (Chan et al, 2001) and intrapartum fever (Chan et al, 2003).

2.4.3.3 Infant Factor

Gestational age

Studies conducted reported that gestational age were independently related to neonatal TSH levels in newborns without CH in the region of mild iodine deficiency (Ingrida et al, 2010; Bėrontienė et al, 2002).

A study by Korada et al observed that gestational age was associated with increased bloodspot TSH levels in multivariate but not univariate models, but multiple regression analysis confirmed that this was a reflection of the close link between gestational age and birth weight (Korada et al, 2009). On the contrary, Herbstman et al. concluded that gestational age was independently associated with lower cord TSH, higher cord total T4, and higher neonatal and subsequent bloodspot total T4 (Herbstman et al, 2008).

In the study by Miyamoto et al. TSH levels varied widely and had no correlation with gestational age because they were affected by the mode of delivery (Miyamoto et al, 1991). It is known however, that as gestational age increases, the fetus elevates the synthesis of both T4 and TSH (Burrow et al¸ 1994). That statement was confirmed in the study by McElduf et al., where higher TSH values had been associated with older gestational age (McElduf et al ¸2005). Studies of fetal and neonatal thyroid function show that thyroid hormone levels rise as pregnancy advances (Murphy et al, 2004; LaFranchi et al, 1999) with levels of TSH in cord blood and neonatal blood spot samples positively related to gestational age (Herbstman et al, 2008).

A study conducted by Raj et al, reported that the CBTSH levels were also found to increase with increasing gestational age, unlike authors who found a negative correlation between gestational age and CBTSH levels (Raj et al, 2014).

It is known that as gestational age increases, the fetus increases the synthesis of both T4 and TSH (Burrow et al, 1994). A study by Klein et al. found a constant positive relationship between TSH and T4 until approximately 34 weeks gestation, at which time, none of the thyroid parameters varied with increasing age (Klein et al, 1982). Among infants who are born preterm, the hypothalamic–pituitary axis development is attenuated and therefore the TSH surge for preterm births is smaller and later (Murphy et al, 2004; LaFranchi et al, 1999). At birth, term newborns typically experience a surge in TSH, peaking at around 30 minutes after delivery and followed by a gradual rise in T4 over the first 24 hours of life (Fisher et al, 1981). It is known that there is a negative change in TSH and a positive change in T4 levels going from cord blood levels to neonatal heel prick bloodspot measurements (Wilker et al, 1984).

Birth Weight

A study by Herbstman et al, reported that infants born preterm had higher levels of TSH and lower total T4 (as measured both in cord blood and bloodspots). Likewise, infants who were born with low birth weight (<2500 g) also had higher TSH and lower total T4 values a both time points. When birth weight was adjusted for gestational age, it was not independently related to TSH but was associated with a smaller increase in total T4 in cord blood. Birth weight is so highly correlated with gestational age, it is not surprising that birth weight is also positively correlated with TSH and thyroid hormone measures in univariate analyses (Herbstman et al, 2008). Other studies have reported an association between birth weight and TSH levels (Frank et al, 1996); but not independently of gestational age (Chan et al, 2003).

Gender

Most studies have reported that male infants generally have higher TSH levels, as measured in either cord blood or bloodspots as compared to females, a trend that is consistent with our analyses (Sullivan et al, 1997; Chan et al, 2001). Additionally, the Apgar score at 1 and 5 minutes have been reported to be inversely associated with cord blood and bloodspot TSH (Sullivan et al, 1997; Lao et al, 2002).

A study by Kirsten 2000 reported that TSH is highly variable among healthy newborns; this is one of the factors contributing to the false positive rate for this test when used in newborn screening programs. Additionally, TSH varies greatly by gestational age and birth weight and shows lower levels in premature or low birth weight newborns (Kirsten et al, 2000).

2.5 Iodine Deficiency in School Age Children

School age children are the most preferred group as they are easily accessible, vulnerable to iodine deficiency and respond to salt iodization program. According to WHO/UNICEF/ ICCIDD, if more than 5% of school age children (6–12 years) are suffering from goiter, region should be classified as endemic to iodine deficiency (WHO, 2007).

A study conducted have reported that, physical growth and cognitive development in children are faster during early years of life, and that by the age of four years, 50% of the adult intellectual capacity has been attained and before thirteen years, 92% of adult intellectual capacity is attained (Vernon et al, 1976).

2.5.1 Prevalence of Iodine Deficiency in children

2.5.1.1 Global Scenario

Globally the prevalence of iodine deficiency has been observed affecting millions of school age children in both developing and developed countries equally.

According to nationally representative surveys conducted between 1993 and 2011, 148 countries were estimated for status of iodine nutrition among school age children using urinary iodine concentration level. It was reported that the iodine intake of 29.8% of school age children worldwide is insufficient. Over one-half of the children with low iodine intakes are basically from 2 regions: Southeast Asia (76 million children) and Africa (58 million children) (Andersson et al, 2012).

The global prevalence in school age children of inadequate iodine intakes has fallen over the past 8 years from 36.5% in 2003 to 31.5% in 2007 and to 29.8% in 2011. Large decreases in prevalence between 2003 and 2011 occurred in Europe, the Eastern Mediterranean, Southeast Asia, and the Western Pacific (Andersson et al, 2012).

In 2011, iodine intake was inadequate in 32 countries, adequate in 69, more than adequate in 36, and excessive in 11 countries. Of the 32 countries with iodine deficiency, 9 are classified as moderately deficient and 23 countries as mildly deficient. No country was categorized as severely deficient. Since 2003 and 2007, the number of countries with insufficient iodine intake has decreased; at the same time, the number of countries

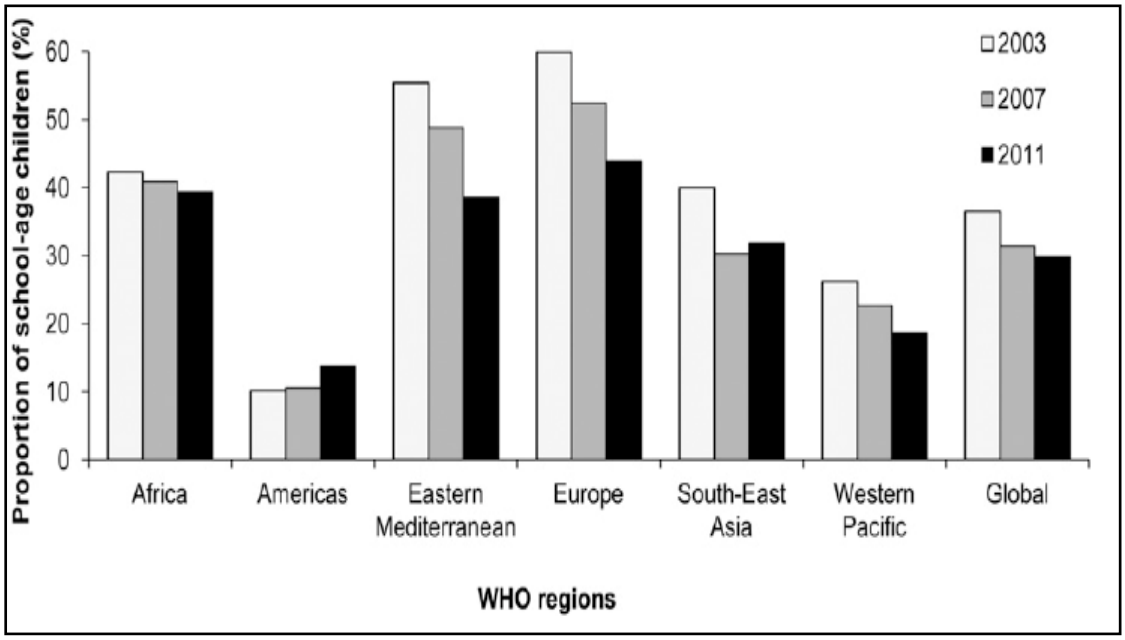
with intake increased and countries with more-than-adequate and excessive iodine intake increased (Andersson et al, 2012).

Various other studies conducted on school age children worldwide is depicted in **Table 9**.

The proportion of school age children with insufficient iodine intake by WHO regions is depicted in **Figure 15.**

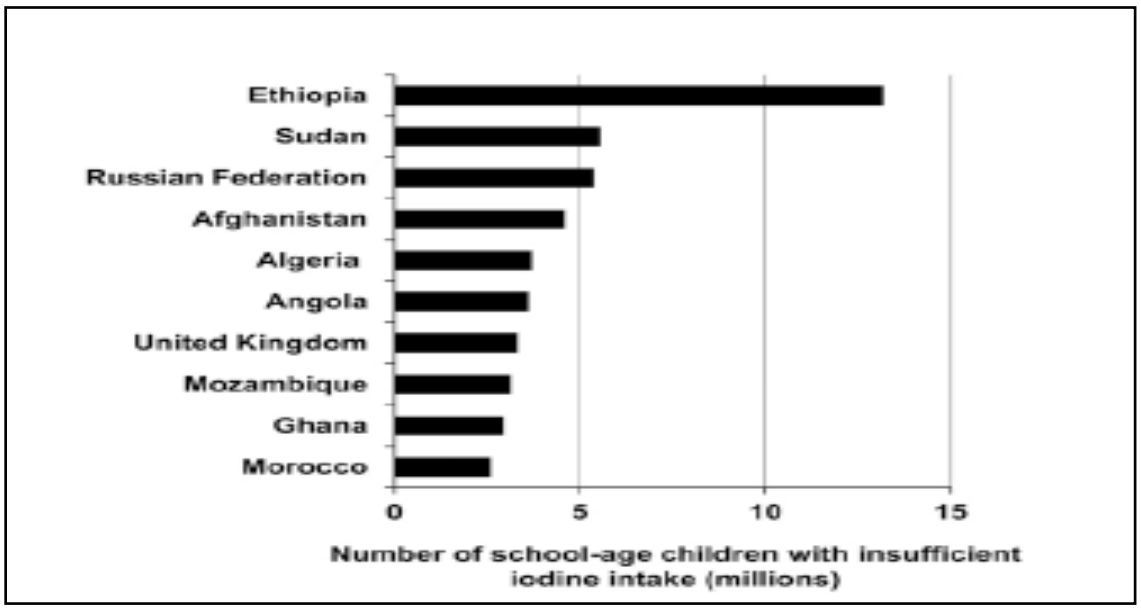
The top 10 iodine deficient countries (based on national median UIC level <100µ g/L) with the greatest number of school age children with insufficient iodine intake in 2011 is depicted in **Figure 16.**

Figure 15: Proportion of school age children with insufficient iodine intake (UIC <100µg/L), by WHO regions in 2003, 2007 and 2011.



Source: Andersson et al, 2012

Figure 16: Top 10 iodine deficient countries (based on national median UIC level <100µ g/L) with the greatest number of school age children with insufficient iodine intake in 2011



Source: Andersson et al, 2012

Table 9: Studies on iodine deficiency in children worldwide

Author; Year	Study Area	Age Group (yrs)	TGR (%)	Median UIC (µg/L)	<100 MUIC (µg/L) (%)	% of population consuming adequately iodized salt consumption	Conclusion
Kibatu et al, 2014	Ethiopia	6-18	39.5	39.9	-	-	Deficient
Tessema M et al, 2014	Ethiopia	6-12	54	-	-	-	Deficient
Dube W et al, 2014	Zimbabwe	6-12	-	185	15.5	94.0	None
Anderson et al, 2012	Europe	6-12	_	_	29.8	_	
De Benoist et al, 2008	WHO regions (47 countries)	6-12	_	_	31.5	_	Deficient
Abuye et al, 2007	Ethiopia	6-12	39.9	24.5	83.0	4.20	Deficient
Andersson et al, 2005	WHO regions (UNPD)	6-12	15.8	_	36.5	_	Deficient
Zimmerman et al, 2004	WHO regions (UNPD)	6-12	_	_	36.4	_	Severe Deficiency
Biswas et al, 2002	India	8-10	11.3	150	14.7	85.1	Transition phase of ID
Copeland et al, 2002	Bangladesh	6-10	27.0	73	_	_	Deficient
Copeland et al, 2002	Guatemala	6-16	15.0	181	_	_	Deficient

2.5.1.2 Indian Scenario

Iodine deficiency is a public health problem in India. Recent studies conducted by Kapil et al, amongst school age children (6-12 years) in three districts of Himachal Pradesh documented the TGR as 15.8% (Kangra), 23.4% (Kullu) and 15.4% (Solan), respectively. Median UIC level was 200µg/l (Kangra), 175µg/l (Kullu) and 62.5µg/l (Solan). Thus according to the UIC levels district Solan has ID. Whereas, according to the TGR, all the three districts were suffering from iodine deficiency (Kapil et al, 2013a, 2013b, 2013c). Another study from Kashmir documented the TGR as 3.8% and median UIC level as 104µg/L indicating adequate iodine nutritional status amongst the population studied (Masoodi et al, 2014).

A study conducted by P V S et al, 2014 amongst school children of 6-15 years of age, from southern part of India reported that the goitre prevalence in the study to be 0.12%. Moreover, UIC level of ≥100mcg/l was found in 90.2% and <100mcg/l in 9.75% of children. Estimation of iodine content of the salt samples revealed that 90.7% consumed adequately iodised salt (>15ppm). Thus concluding that the Bellur Hobli is not an endemic area for goitre and there is no biochemical iodine deficiency in this population due to effective implementation of Universal iodization programme (UIP) (P V S et al, 2014).

A recent study conducted by Ravesh et al, 2015 (MCHWS 2014) among 6-12 years school age children in Gulbarga city found that the TGR was 4.32% and 51.1% of the children were consuming salt with iodine intake of 15ppm and more. A study from West Bengal amongst 3,490 school age children revealed the TGR as 9% (Arlappa et al, 2011). A study from Orissa amongst 1200 school age children reported the TGR as 8%, median UIC level as 85.4µg/l, and 55% of the households were consuming salt with iodine content of less than 15ppm thus indicating presence of ID in the subjects studied (Moorthy et al, 2007). A study from Manipur documented the TGR as 34.9% (Chandra et al, 2006). A multicentric study conducted in 15 districts of India by Indian Council of Medical Research reported the TGR as 4.78% and median UIC levels <100µg/l. It was also found that 44.6% of the households were consuming salt of iodine content <15ppm (Toteja et al, 2004).

A study carried out in Bharatpur district, Rajasthan reported the TGR as 7.2% and the median UIC level as >100µg/l. It was also reported that 44% of the families were consuming salt with iodine content of <15ppm (Kapil et al, 2003). Another study from Udaipur district, Rajasthan reported the TGR as 8.4% and the median UIC level as >100µg/l. Fifteen percent of the families were consuming salt with iodine content of <15ppm (Pradhan et al, 2002).

Earlier studies conducted from India reported the median UIC of <100µg/l amongst school age children in Solan, Himachal Pradesh (62.5µg/l), Uttar Pradesh (60µg/l), Jammu (96.5µg/l), Panchamahal, Gujarat (70µg/l), Bihar (85.6µg/l), West Bengal (92.5 µg/l), respectively indicating iodine deficiency amongst pregnant mothers (Kapil et al, 2013; Chandra et al, 2009; Bhat et al, 2008; Misra et al, 2007; Sankar et al, 2006; Biswas et al, 2006).

2.5.1.3 Comparison of iodine deficiency status in Uttarakhand and Gujarat

In Gujarat: In Gujarat State, the IDD control program was first introduced in Bharuch District in 1982 followed by Valsad and some talukas of Vadodara districts in 1988. In 1994, the entire State was covered under NIDDCP (NRHM Gujarat). In 2009, to assess the magnitude of IDD a survey was carried out by the Government Medical Colleges- Surat, Vadodara, Bhavnagar, Rajkot, Ahmedabad and Jamnagar in all the districts of the state as per the national guidelines. The survey reported that 16 districts are IDD endemic in the state. According to NFHS-III adequately iodized salt (≥ 15 ppm) consumption in Gujarat is 56% and non-iodized/ nil iodized (0 ppm) salt consumption is 28% (NRHM Gujarat). The severe TGR was found in Bhavnagar district (34.2%) followed by Surat (33.1%) and Dang (31.2%) districts. These districts require special intervention to minimize deficiency of goiter. Gujarat had moderate goiter prevalence rate i.e. 16.5% (NRHM Gujarat).

In Uttarakhand: In Uttarakhand the use of adequately iodized salt by the population has decreased from 60% in NFHS-2 (1989-99) to 46% in NFHS-3 (2005-06).

The comparison of iodine deficiency amongst school age children in both Gujarat and Uttarakhand state is depicted in **Table 10**.

Table 10: Comparison of iodine deficiency in school age children (6-12 years) of Gujarat and Uttarakhand

States	Author/ Year	Study area	TGR (%)	Median UIC (µg/l)	Percentage of Iodine content of salt with <15ppm
Uttarakhand	NGCP,2004	Nainital	6.9	-	-
	WHO, 2003	Nainital	-	110	-
	NIN, 2003	Nainital	-	-	55.2
	Mittal, 2000	Terai region	38.1		
	Kapil et al, 1999	Udham Singh Nagar	-	175	-
	NIN, 2003	Nainital	-	110	
Gujarat					
	Chandwani et al, 2012	Bharuch, Gujarat	23.2	110	7.0
	Chudasama et al,2011	Kutch, Gujarat	11.2	110	7.7
	Misra et al, 2007	Panchmahal, Gujarat	20.5	70.0	45.7

2.5.2 Effect of iodine deficiency on the cognition of the children

Iodine deficiency has widespread implications because iodine is a key component of the thyroid hormones, which are crucial for brain and neurological development and severe iodine deficiency in pregnancy result in adverse childhood outcomes, such as cretinism and mental retardation (Zimmermann et al, 2009).

A meta-analysis was conducted which included 21 observational and experimental studies including a control group, on the effect of iodine deficiency on mental development. The study reported that the IQs of non-iodine deficient groups on average 13.5 points higher than those of the iodine-deficient groups. This clearly suggests the detrimental effect of iodine deficiency on IQ of the children (Bleichrodt and Born, 1994).

Similarly, another meta-analysis of Chinese studies by Qian et al, 2005 reported an approximate difference of 10 IQ points between moderate to severely iodine-deficient and iodine-sufficient or iodine-supplemented populations.

A study conducted by Bath et al, 2013 published in lancet assessed an association between maternal iodine status and child IQ at 8 years of age and reading ability at 9

years of age. It was found that after adjustment for confounders, children of women with an iodine-to-creatinine ratio of less than 150µg/g were more likely to have scores in the lowest quartile for verbal IQ, reading accuracy, and reading comprehension than were those of mothers with ratios of 150µg/g or more.

A study conducted by Stagnaro-Green et al, reported that poor neuro-developmental outcomes have been noted in children of pregnant women with mild thyroid hormone deficiency (Stagnaro-Green et al, 2011). A study conducted by Gordon et al in New Zealand on children aged 10-13 taking a 50mg/d iodine supplement vs. placebo for 28 weeks found significant improvement in UIC and Tg levels. It was also reported that mild ID prevents children from attaining their full intellectual potential and that iodine supplementation improves UIC, Tg and cognitive performance (Gordon et al, 2009). Another cross-sectional study conducted by Santiago-Fernandez, on mildly iodine-deficient Spanish schoolchildren observed an increased likelihood of children with a lower IQ with poorer iodine status (Santiago-Fernandez et al, 2004).

An eleven-year follow-up study conducted by Haddow et al, has established the relationship between maternal hypothyroxinemia and low IQ in offspring. The study reported that **i)** untreated hypothyroidism in mothers causes a reduction in IQ of their children and treatment probably prevents it. **ii)** hypothyroidism in mother affects the neurological and psychomotor development of the offspring **iii)** treatment is beneficial to the offspring and **iv)** it takes long for subclinical hypothyroidism to manifest clinically (Haddow et al, 1999). A study by Tiwari et al, also reported that severely iodine deficient (SID) children were slow learners (Tiwari et al, 1996).

A study was conducted by Bhowal et al, 2014, in three Government schools in the district of 24 Parganas, West Bengal, found that 12.3%, 15.6% & 24.3% of the children were in the severe, moderate & mild range of ID in terms of urinary iodine excretion and 85.6% & 14.3% of the children were consumed iodated salt ≥15 ppm & < 15 ppm of iodine level. Iodine status of the children has significant positive correlation ($P<0.01$) with IQ grades and academic achievement of the subjects studied. Also academic achievement of the children has significant positive correlation ($P<0.05$) with their intelligence level.

2.5.3 Effect on Somatic growth

The effects of subclinical IDD are less known than those of the severe syndrome. Intellectual abilities are known to be affected by development damage in utero, which is largely irreversible and by ID in early childhood or later life, with lower thyroixine levels leading to reduced intellectual and physical development, which further can be improved by iodine supplementation (Bleichroft et al, 1996; Delange, 1994; Lofti and Mason, 1993).

A study was conducted by Mansourian and Ahemdi reported that there is an inverse age correlation ($p<0.05$) between thyroxin concentrations among children and adolescents. This in turn indirectly suggested that, in normal condition growth is regulated by thyroid hormone, indicated by increased TSH with age. However, during iodine deficiency, increased TSH at early stage compared to standard age may lead to insufficient growth of the children (Mansourian and Ahmedi, 2010).

Another study conducted by Boas et al, assessed 859 prepubertal euthyroid Danish children (4–9 yr) for clinical investigation, including anthropometrical measurements and determination of TSH, thyroid hormones, autoantibodies, urinary iodine excretion, and thyroid volume (TV) by ultrasound. It was found that Growth hormone/ Insulin like growth factor -I-axis was positively correlated with thyroid size, suggesting a role in the regulation of thyroid growth. Moreover, anthropometric measurements, in particular body surface area, were the best predictors of TV (Boas et al, 2009).

A study by Azizi et al,1995; Lal et al,1996 among children in iodine deficient areas in Iran and India showed retarded height and bone maturation; in Iran, impaired growth was inversely correlated with TSH. Mason et al. 2002, reviewed studies from Sri Lanka, Nepal, Bangladesh, India and the Philippines, found use of iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in children less than 3 years of age. Similarly, a study in Kenya conducted by Neumann et al, 1994 reported that household use of iodized salt was directly correlated with height in preschool children in Kenya. Another study conducted by Thurlow et al, 2006 amongst 6–12-year-old children of Thailand children found an inverse correlation between urinary iodine concentration and height for age z- score.

In order to detect somatic and psychomotor disturbances in children and adolescents residing in areas of iodine deficiency, a study was conducted by Azizi et al on schoolchildren and reported the occurrence of physical and psychomotor disturbances in apparently normal schoolchildren from areas of ID. Thus, the study concluded that the alteration in psychomotor development may occur in children with normal physical growth, due to ID (Azizi et al, 1993).

A cross-sectional studies conducted on iodine deficiency and child growth have reported mixed results. A study by Koutras et al, 1973 in Greece, reported that school age children in areas of endemic goiter had decreased height and weight and delayed bone maturation compared to children in nonendemic areas, but there was no correlation of goiter with somatic growth. Goiter was also not associated with growth in children in Bolivia (Bautista et al, 1977) and Malaysia (Ali et al, 1994).

There are few intervention studies which examined the effect of iodine repletion on growth of school age children. A study conducted by Zimmerman, to assess whether iodine repletion improves growth in school age children and to investigate the role of Insulin like growth factor (IGF-I) and Insulin like growth factor binding protein (IGFBP-3) in this effect. Three prospective, double-blind intervention studies were done in areas of varying ID: in Moroccon children (severely iodine deficient); in Albanian children (moderately iodine-deficient) and in South African children (mildly iodine deficient). In all three studies, iodine treatment increased median UIC and in the controls remained unchanged. In South African children, iodine repletion modestly improved IGF-I but did not have a significant impact on IGFBP-3, total T4 or growth. In Albenian and Moroccon children, iodine repletion significantly increased total T4, IGF-I, IGFBP-3, weight-for-age Z scores, and height-for-age Z scores. These controlled studies clearly demonstrate that, iodine repletion in improves somatic growth (Zimmerman et al, 2009).

A study conducted by Ren et al, 2002 in China amongst 5-year-old children, reported that the median UIC levels increased from <10 to 176µg/L after iodine addition to irrigation water, and this reduced the childhood stunting.

Studies conducted in Asian countries, reported that household access to IS was correlated with increased weight-for-age and mid-upper-arm circumference in infancy (Mason et al, 2002). However, other intervention studies reported no significant

difference was observed on child growth who were given iodine with other micronutrients and alone. (Bautista et al, 1982; Shreshtha et al, 1994) (Van Stuijvenberg et al, 1999; Rivera et al, 2001; Moreno-Rayes et al, 2003).

A study conducted by Huda et al, 2001 in moderately iodine-deficient Bangladeshi schoolchildren reported that a 4- month controlled trial of 400 mg of iodine as oral iodized oil did not affect weight gain, but the treated children remained iodine deficient.

Improved growth in iodine deficient children receiving iodine is likely due to improved thyroid function. Both thyroid hormone and growth hormone (GH) are essential for normal growth and development (Shapiro et al, 1978; Robson et al, 2002), even during fetal life (Shields et al, 2011). Thyroid hormone is required for normal GH expression in vitro (Ceda et al, 1992; Ezzat et al, 1991) and in vivo (Samuels et al, 1989) and in animal studies, promotes GH secretion and modulates the effects of GH at its receptor (Hochberg et al, 1990; Nilsson et al, 1994). Thyroid hormone also directly affects epiphyseal growth, bone maturation and stature (Robson et al, 2002; Nilsson et al, 1994).

Many research studies have documented positive correlation between iodine and growth (Bautista et al, 1977; Ali et al, 1994; Lal et al, 1996). Iodine status may influence growth through its effects on the thyroid axis. Administration of T4 to hypothyroid children increases their growth (Hernandez et al, 1995). Thyroid hormone promotes GH secretion and modulates the effects of GH at its receptor (Crew et al, 1986; Samuels et al, 1989; Hochberg et al, 1990). IGF-I and IGF binding protein (IGFBP) – 3 are also dependent on thyroid status (Burstein et al, 1979). In human, hypothyroidism decreases circulating IGF-I and IGFBP- 3 levels, and thyroid hormone replacement increases them (Miell et al, 1994; Iglesias et al, 2001). In iodine-deficient children, impaired thyroid function and goitre are inversely correlated wd with IGF-I and IGFBP-3 concentrations (Wan Nazaimoon et al, 1996; Aydin et al, 2002; Alikapifoolu et al, 2002). However, in an uncontrolled trial, oral iodized oil paradoxically decreased IGF-I and IGFBP-3 concentrations in Turkish Children and many of the children remained ID after treatment (Ozon et al, 2004).

2.6 Iodine Deficiency in Adolescent Girls

Iodine deficiency is a main nutrition problem affecting adolescent population. As adolescent girls are the future mothers, ID in them will affect the newborns, resulting in neonatal hypothyroidism. Further, ID in pregnancy increases the risk of still birth, abortions, increased perinatal deaths, infant mortality, and congenital anomalies (WHO, 2007). The adolescents remain a largely neglected, difficult to measure, and hard-to-reach population, in which the needs of adolescent girls in particular are often ignored.

Inadequacy of iodine may put adolescent girls at risk for developing IDD, as sensitivity to iodine deficiency is increased as the thyroid gland metabolism is enhanced during sexual maturation (Als et al, 2000b). Puberty is a crucial period for hormonal interactions in the human life cycle (Hanna and Lafanchi, 2002). Marked changes in thyroid occur during puberty as an adaptation to both body and sexual development (Flueury et al, 2001). Thyroid hormones are one of the major growth regulators along with growth hormone (GH) and the insulin growth factor (IGFs) (Morkou et al, 2008). They influence almost all aspects of child development and thus play a crucial role as a regulator of nervous system, myelination, dental and skeletal development, metabolism, organ function, growth and puberty (Larsen et al, 1998). Thyroid disorders in adolescent girls may present as goiter or as general cluster of abnormal symptoms and physical findings (Betendorff, 2002).

Adolescent girls as well as young women are likely to become pregnant in the near future. Before pregnancy, women ideally should have an average daily intake of iodine as 150ug, to ensure that their intra-thyroidal iodine stores are replenished before pregnancy (Glinoer et al, 1995). According to WHO (2007), the median UIC level of <100µg/L amongst adolescent girls indicates iodine deficiency in the population studied.

2.6.1 Prevalence of Iodine Deficiency in Adolescent girls

2.6.1.1 Global Scenario

Iodine plays a major role in proper functioning of almost all cells of the human body. Iodine deficiency disorders have been recognized as one of the major public health problems.

A recent study published in lancet conducted amongst 14-15 years school girls reported that United Kingdom is still iodine deficient. Urinary iodine measurement indicative of mild iodine deficiency were present in 51% of subjects, moderate deficiency in 16% and severe deficiency in 1% of the subjects studied (Vanderpump et al, 2011).

A study conducted amongst adolescent girls aged 10-15 years in Mali, West Africa reported the iodine deficiency as 66.6% in the subjects and out of this 31.7% of the subjects reported moderate to mild risk for iodine deficiency (Pawloski et al, 2004). Another study conducted by Ara et al, 2010 in Bangladesh reported median UIC level of 135µg/l amongst Bangladeshi adolescent girls.

A study conducted amongst adolescent girls in Rawalpindi reported the Total Goiter Rate as 57%, which was quite high may be because of the fact that Rawalpindi is surrounded by hills of Himalayans range and soil may have reduced the iodine content (Shahid et al, 2009).

A recent study conducted by Watutantrige Fernando et al, 2015 in Italy amongst childhood to adulthood females reported that median UIC decreased from childhood to adulthood (median UIC 107, 77 and 55µg/l in the young girls, females at puberty and fertile women, respectively). Though using iodized salt improved iodine status in all groups, a significantly higher UIC was only noted in females at puberty. And concluded that, dietary iodine status declines from childhood to adulthood in females due to different eating habits. A mild iodine deficiency emerged in women of child-bearing age that could have consequences during pregnancy and lactation.

2.6.1.2 Indian Scenario

We have limited data available on the status of iodine deficiency amongst adolescent girls from India.

However a recent national study National Iodine and Salt Intake Survey (NISI) conducted amongst women of reproductive age groups reported that the median urinary iodine concentration (MUIC) at the national level was 158µg/L, reflecting optimal iodine nutrition in India. The median varied significantly between the rural (148.5µg/L) and urban (167.9µg/L) areas. Sub-nationally, iodine intake was found to be adequate across all zones and in both urban and rural areas. The Central zone reported the lowest median (128.6µg/L) and the North zone reported the highest (204.0µg/L), both well within the adequate range. There was a positive correlation between UIC level and iodine content of household salt: the median UIC was 112.4µg/L in the households with non-iodized salt, 123.4µg/L in the households with poorly iodized salt, and 168.4µg/L in those with adequately iodized salt. Access to adequately iodized salt has been increasing steadily, and by as much as 7% since 2009 (ICCIDD, 2015).

A study conducted by Goyle and Prakash, 2011 amongst 10-16 adolescent girls of Punjab reported that 21.6% of the subjects had mild iodine deficiency. Another study conducted by Ray et al, 2009 amongst women of reproductive age group in West Bengal reported that 76.3% are suffering from iodine deficiency.

A study conducted amongst adolescent boys and girls in Bombay reported the high prevalence of goitre as 56% in both boys and girls visible goiter in girls was 10.6% (Dodd et al, 1993). Another similar study conducted in Bombay reported the total goiter rate of 65.2% among boys and 69.6% among girls indicating a high prevalence of mild and moderate IDD among the adolescents studied (Dodd et al, 1992).

2.6.1.3 Comparison of status of iodine deficiency amongst Adolescent girls in Uttarakhand and Gujarat

There is no data available on the iodine status amongst adolescent girls from Uttarakhand and Gujarat state.

2.6.2 Effect of Iodine Deficiency on the cognition of the Adolescent girls

Iodine deficiency also appears to have adverse effects on growth and development in the postnatal period. Adolescents in regions of ID are at risk for some degree of intellectual disability. A meta-analysis of studies relating iodine deficiency to cognitive development suggested that iodine deficiency alone caused an average loss of 13.5 intelligence quotient (IQ) points in affected subjects (Bleichrodt et al, 1994).

Intellectual disability resulting from the effects of iodine deficiency on the central nervous system during fetal development is not reversible. In contrast, the additional impairment caused by continuing postnatal hypothyroidism and/or iodine deficiency may improve with appropriate thyroid hormone replacement and/or iodine supplementation (van den Briel, 2000).

2.7 Other Factors Affecting iodine status

2.7.1 Environmental influences

Iodine deficiency has multiple adverse outcomes on growth and development in animals and humans lives. The main cause of iodine deficiency in soils is leaching by glaciation, floods or high rainfall. Mountainous regions have some of the highest prevalence of iodine deficiency (WHO, 2007).

Iodine deficiency also occurs due to flooding, rain, deforestation which leads to lower iodine content of the vegetation and crops cultivated in the land. Unclean drinking water may contain humic substances that block thyroidal iodination, and industrial pollutants, including resorcinol and phthalic acid, may also be goitrogenic (Gaiten et al, 1989). Perchlorate is a competitive inhibitor of thyroidal iodine uptake (Blount et al, 2006). It appears that most of these goitrogenic substances do not have a major clinical effect unless there is coexisting iodine deficiency.

Food and water are considered the major sources of iodine to meet the daily metabolic requirement. The iodine content of the diet is considered critical to compensate for the metabolic losses (Koutras et al, 1970). Less priority is given to quantitative factors, such as absorption and the balance of iodine resulting from important sources like water and food.

Data on the iodine contents of foods and water from the goitre-endemic northeast region of India are scanty (Tulpule et al, 1969; Sharma et al, 1994). Despite the widespread occurrence of IDD, very few studies provide comprehensive information on the iodine content of water and food samples.

2.7.1.1 Iodine content of Water

WHO reported that the mean concentration of total iodine in drinking-water in the USA is 4µg/litre, and the maximum concentration is 18µg/litre. This is presumably predominantly iodide (WHO, 2005).

In general, iodine deficient areas have water iodine levels below 2µg/l (Hetzel et al, 1989).

A recent study conducted by Longvah et al, 2012 in 22 states of India reported that the mean iodine content of drinking water was found to be 9.0±7.78 µg/l. It was further reported that the mean iodine content in water samples from the goitre-endemic states of northeast India ranged from 6.65±1.8 µg/l in Sikkim to 8.89±4.98µg/l in Assam. The water iodine content from northeast India varied from 3.0 to 31.5µg/l. However, values below 3µg/l in Gelecky PHC, Assam, have been reported (RMRC Dibrugarh; Annual Report 1991-1992).

Several studies conducted by Chandra et al in different regions reported that the iodine content of water ranges from 22-119µg/l in West Bengal (Chandra et al, 2005), 7.5-10.7 µg/L in Siddharth Nagar, Uttar Pradesh (Chandra et al, 2008), 21 to 119µg/L in Sunderban, West Bengal (Chandra et al, 2007), 1.8-2.6microg/l in Imphal, Manipur (Chandra et al, 2006), 48.9 ± 30.7microg/l in West Bengal (Chandra et al, 2006), 82µg/l in Howrah (Chandra et al, 2004) and 2.92 +/- 1.75µg/l in Manipur (Chandra et al, 2008).

In Arunachal Pradesh, water iodine content ranged from 3.5 to 14.5µg/l, whereas Tulpule et al, 1969 reported a higher iodine content of 13± 26µg/l in water samples from Arunachal Pradesh. This could be due to seasonal fluctuations (Broadhead et al, 1965) and differences in the method of estimation. Such a conclusion was also drawn in other studies by Koutras et al, 1970 and Fischer and Carr, 1974.

A study conducted by Ramalingaswamy, 1973 reported that iodine contents of water samples to be less than 3.0µg/l in the goitre-endemic areas of India, Nepal and Sri Lanka. However, Krishnamachari, 1974 reported 9±36µg/l of iodine content from the goitre belt of the Aurangabad district, Maharashtra. High water iodine contents have been reported by Mahesh et al. 1989 from other nonendemic areas such as Hyderabad.

A study by Caughey and Follis, 1965 reported a high incidence of goitre in areas where iodine concentration in drinking water was from 3 to 7µg/l as compared with non-endemic regions with water iodine contents of 20µg/l or more. The lowest range of iodine content in water (3±12.6µg/l) was encountered in Sikkim, where the incidence of goitre was reported to be 54% (Pulger et al, 1992).

According to various studies, the goitre rates in northeast India ranged from 25 to 54% (Health Information of India, 1993; ICMR task force study, 1989; Pulger et al, 1992). In the Gilghit district of Pakistan, the iodine content of water ranges from 1.2 to 13.0µg/l with goitre rates of 25.2±76.5% (Siraj-ul-Haq Mahmud, 1986). The low iodine content of water and high incidence of goitre, prevalent in the sub-Himalayan belt, can be observed in the Gilghit district of Pakistan as well as in northeast India. Weak but significant negative correlations have been reported between drinking water iodine concentration and goitre prevalence (Das et al, 1989). The distribution of environmental iodine deficiency in northeast India is more or less similar. The water iodine content of all the states varied within a narrow range with 82% of the samples from 5.0 to 10µg/l and a pooled mean of 7.38±2.7µg/l.

2.7.1.2 Iodine content of Food

Crops grown on iodine deficient soil will be iodine deficient. As a result human and animal populations which are totally dependent on food grown in such soil become iodine deficient. The iodine content of plants grown in iodine deficient soil may be as low as 10 µg/kg compared to 100 µg/kg dry weight in plants in a non-iodine deficient soil (Hetzel, 1989).

The main natural sources of dietary iodide are seafood (200–1000 µg/kg) and seaweed (0.1– 0.2% iodide by weight). Iodide is also found in cow's milk (20–70 µg/litre) and may be added to table salt (100 µg of potassium iodide per gram of sodium chloride) to ensure an adequate intake of iodine (WHO, 2003). The estimated dietary iodine requirement for adults ranges from 80 to 150 µg/day (WHO, 2007).

A recent study conducted by Longvah, et al, 2012 in 22 states of India reported that in cereals the mean iodine content of rice from the goitre-endemic states of northeast India was lowest in Sikkim (8.8±3.0 µg/100g) and highest in Assam (12.9±2.6 µg/100g). The iodine content of rice in northeast India with a pooled mean of sample was 10.4±2.9 µg/100g in contrast to samples from non-endemic areas such as Hyderabad (40.0±3.36 µg/100g). Similarly, pooled mean iodine contents of other cereals were 8.0±2.9 µg/100g (maize), 7.3±2.6 µg/100g (millet) and 8.25±1.3µg/100g (Job's tears) from the goitre-endemic states of northeast India were around 25% of the values reported from non-endemic areas such as Hyderabad. Similarly, a low iodine

content of cereals was also reported from other goitre-endemic areas such as Baiga Chak, Madhya Pradesh by Mahesh et al, 1993.

It was also found that among the legumes analyzed red gram contained relatively high iodine content (18.0±21.7 µg/100g). The pooled mean iodine content of individual legumes from the states of northeast India was 17.6±5.0 µg/100g (soyabeans), 9.1±2.9 µg/100g (rice beans), 20.1±5.6 µg/100g (field beans), 11.8±3.9 µg/100g (Green gram), 16.3±4.1µg/100g (cowpea), 14.8±5.5 µg/100g (Black gram), and 19.6±2.9 µg/100g (Red gram). It was concluded that all the foods analyzed from northeast India showed that the area is highly deficient in iodine with 45% of the foods falling below 10µg/100g sample and 100% below 30µg/100g sample. It is clear that the foods from endemic areas such as northeast India have much lower iodine contents compared with non-endemic areas, thus reflecting the genuine differences in the iodine content of the environment (Longvah et al, 2012).

2.7.2 Role of Goitrogens

Dietary substances that interfere with thyroid metabolism can aggravate the effect of iodine deficiency; and they are termed as goitrogens (Gaitan et al, 1989). Goitrogens are substances that suppress the function of the thyroid gland by interfering with iodine uptake, which can cause an enlargement of the thyroid, i.e., a goiter.

Presence of goitrogens which adversely influence the utilization of iodine in staple foods is also recognized as one of the etiological factor for IDD. They are generally present as thioglucosides or glucosinolates; the glucan portion of which is responsible for its goitrogenicity. Other chemical substances such as thiocyanates, thio-oxazazolidone, flavanoids, disulphides, phenols, phthalates, biphenyls and lithium, found in environment are also included in goitrogens category. These goitrogens are known to interfere with iodine metabolism at various stages or levels. Some of these substances are found in abundance in certain tubers and vegetables like tapioca, cabbage and cauliflower (Zimmermann, 2012).

Many vegetables and staple foods consumed in developing countries contain cyanogenic glucosides that can liberate cyanide. Cyanide is converted to thiocynate in the body. This is a goitrogen, as it blocks the uptake of iodine by the thyroid. With the

exception of cassava, cyanogenic glucosides are located in the inedible portion of plants. Cruciferous vegetables, including cabbage, kale, cauliflower, broccoli, turnips etc. contain glucosinolates. Similarly cassava, lima beans, linseed, sorghum and sweet potato contains cyanogenic glucosides; both these contents can be converted to thiocynate. Cassava, contains linamarin- a thioglycoside. Thus, it must be soaked before mconsumption, if not soaked adequately or cooked to remove the linamarin, it is hydrolyzed in the gut to release cyanide, which is metabolized to thiocynate (Ermas et al, 1972). The adverse effects can also be overcome by increasing iodine intake. The goitrogens present in various food is depicted in **Table 11**. Soy and millet contain flavanoids that may impair TPO (Thyroid Peroxidase) activity. Soy-based formula without added iodine has been observed to affect infants, but in healthy adults, soy-based products appear to have negligible effects on thyroid function (Messina and Redmond, 2006).

Table 11: Dietary Goitrogens

Goitrogen	**Mechanism**
Foods	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides; they are metabolized to thiocyanates that compete with iodine for thyroidal uptake
Cruciferous vegetables: cabbage, kale, cauliflower, broccoli, turnips, rapeseed	Contains glucosinolates; metabolites compete with iodine for thyroidal uptake
Soy, millet	Flavonoids impair thyroid peroxidase activity
Nutrients	
Selenium deficiency	Accumulated peroxides may damage the thyroid, and deiodinase deficiency impairs thyroid hormone synthesis
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and may blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A-mediated suppression of the pituitary TSHβ gene

2.8 Interactions of iodine with other micronutrients

2.8.1 Iron and Iodine Metabolism

Deficiencies of iron and iodine are the major public health problems in India, and many children are at high risk of both goiter and iron deficiency anemia. Iron deficiency with or without anemia can have adverse effects on thyroid metabolism. If iron deficiency anemia is a nutritional factor that influences the pathogenesis of IDD, it may have a greater impact on IDD than previously described goitrogens because of its high prevalence in vulnerable groups (Zimmermann, 2002).

Iron deficiency anemia can also reduce thyroid hormone concentration in humans. Although, Lukaski et al, (1990) observed no differences in thyroid hormone and TSH concentrations between iron depleted and iron repleted women. Studies have also demonstrated a relationship between anemia and hypothyroidism; anemia was found in 25-50% of hypothyroid patients (Das et al, 1975; Horton et al, 1976). Hematological findings were diverse and anemia was due to iron deficiency only in a few cases.

Evidence from cross-sectional studies has investigated the correlation between iodine deficiency disorder and iron deficiency anemia is equivocal. A survey in Ethiopian children found no correlation in goiter rate or thyroid hormone levels and iron status (Wolde-Gebriel et al, 1993b). Also no significant difference was found in the prevalence of anemia between goitrous and non-goitrous subjects in the Philippines (Florentino et al, 1996).

A study by Azizi et al, 2002 in Iran reported a highly significant difference in goiter rates by palpation between children with low and normal serum ferritin levels. Zimmermann et al, 2000c assessed iron status and goiter rate by palpation in 419 children aged 6-15 years in two villages in western Côte d'Ivoire and found a relative risk of 1.9 for goiter for children with IDA.

The first intervention trial was conducted by Zimmermann et al. 2000 in western Co ˆte d'Ivoire, in which the effect of a 200-mg oral dose of iodine, as iodised oil, in goitrous school-age children with (n=53) or without iron deficiency anemia (n=51) was investigated. A relation between iron deficiency anemia and iodine metabolism

was found and they also found that non-anaemic children responded more rapidly to iodine with regard to thyroid size and TSH concentration, and children with iron deficiency anemia responded mainly after co-administration of iron (Zimmermann, 2000).

Another similar study conducted in iron deficient goitrous school children in western Co ˆte d'Ivoire, who received either placebo or iron supplementation (60 mg per day 4 times per week) in addition to iodised salt consumed at home reported that iron supplementation improves the efficacy of iodised salt in goitrous children with iron deficiency (Hess et al, 2002).

In a double-blind, controlled intervention trial conducted on 6- to 15-year-old children who were randomly assigned at the household level to receive either iodised salt (IS) or dual-fortified salt (DFS) for 9 months. It was found that in the DFS group, the haemoglobin and iron status improved significantly compared with that in the IS group ($P < 0.05$) (Zimmermann et al, 2002; Zimmermann et al, 2003).

Zimmermann et al. conducted a second study using a different iron compound, micronized ferric pyrophosphate, to fortify the dual-fortified salt at w2 mg iron per gram of salt. After 10 months of salt consumption during family meals, the iron status of school-age children in the DFS group was significantly improved compared with those in the Iodized salt group (Zimmermann et al, 2004). To test the concept of DFS to control iron and iodine deficiency in various populations, three additional trials evaluated the impact of DFS on iron and iodine status of school-age children in Co ˆte d'Ivoire (Wegmuller et al, 2006) and India (Andersson et al, 2008) and of families in India (Vinodkumar et al, 2007). The studies found a significant increase of iron status and reduction of anaemia prevalence in the DFS groups compared with the IS group.

Various mechanisms have been suggested for the interaction between iron and iodine deficiencies. Results from animal studies suggest that IDA may influence thyroid metabolism by altering the central nervous system control (Beard et al, 1998) , decreasing T3 binding to hepatic nuclear receptors (Smith et al, 1993) and reducing thyroid peroxidase activity (Hess et al, 2002), an enzyme essential for thyroid hormone synthesis. Iron deficiency anemia could also impair thyroid metabolism through lowered oxygen transport (Surks et al, 1969). It is likely that these

mechanisms jointly contribute to the impairment of thyroid function in iron deficiency.

Thus it could be observed that a series of randomised controlled trials consistently found a significant reduction in thyroid volume in iron-deficient school-age children when iron was provided along with iodised salt either as iron supplement (Hess et al,2002) or included into DFS (Zimmermann et al,2003; Zimmermann et al, 2004). Thus it was observed that a high prevalence of iron deficiency among children in areas of endemic goitre may reduce the effectiveness of iodised salt programmes. Thus, the prevention of iron deficiency is not only beneficial for iron-related outcomes, but also to improve the response to iodised salt.

In 1980s, National Institute of Nutrition (NIN), Hyderabad, India developed Iron fortified salt (IFS). The efficacy cum effectiveness trials of IFS were conducted in a multi-centric study. It was found that there was an increase in Hemoglobin levels (Nadiger et al, 1980). In 1986, adoption of Universal Salt Iodization (USI) policy was done in the country. Under this policy, all edible salt in the country was to be iodised. It was decided by MOHFW, Government of India that two types of salt i.e. IFS and Iodized Salt would create an operational difficulty in monitoring of iodine content of salt under PFA act and hence IFS was given low priority.

A community based effectiveness study was conducted in tribal area of East Godavari District in Andhra Pradesh, India. This study was initiated in 1989 and concluded in 1992. A population of about 5000 was included in the study. The prevalence of Goitre decreased significantly; however, there was no significant impact of DFS on the prevalence of anaemia (Ranganathan et al, 2006).

In 1996, a randomized double blind study was carried out for a period of two years among children belonging to backward communities in four Residential Schools in and around Hyderabad, India. Hemoglobin (Hb) status, urinary iodine excretion and calcium-phosphorus homeostasis of the beneficiaries were evaluated. The children were followed up after 6 months, 1 year and 2 years after commencement of the study. No improvement in the Hemoglobin levels of the children receiving DFS was reported. The increments in hemoglobin at 2 years showed negative correlation with initial hemoglobin level in the children however when the increments in hemoglobin levels between IS and DFS groups were adjusted for the effects of age, sex and initial

hemoglobin by ANOVA, there was a significant difference ($p < 0.001$) between the adjusted means, indicating an overall improvement of iron status in DFS group. When all the school children in both the treatment groups were categorized as (i) those who showed no change ($\leq \pm 10$g/L), ii) those who improved ($\geq +10$g/L), and iii) those who deteriorated (≥ -10g/L). There was a significant association between the desirable shift in hemoglobin and consumption of DFS ($P<0.01$). The data obtained from this study raised the concerns about stability of iodine in the DFS (Sivakumar et al, 2001).

To date, only one multi-micronutrient fortified edible salt (MMNS) has been produced in India. This was produced by Sundar Chemicals Pvt Ltd., a private sector undertaking, in 1990s. Edible Salt is fortified with 10 micronutrients, namely, iron, iodine, vitamin A, vitamins B1, B2, B6, B12, folic acid, niacin and calcium. A positive impact has been documented on the micronutrient status of the beneficiaries consuming such fortified salt.

2.8.2 Selenium and Iodine Metabolism

Selenium content in foods is determined by the soil content, the use of selenium-containing fertilizers and agricultural practices, as soil pH and moisture determine the selenium uptake by the plant (Combs Jr, 2001). Absorption of selenium in humans is efficient and not regulated (US Institute of Medicine, 2000). Thus, selenium deficiency occurs mainly in regions where selenium soil content is low.

Selenium functions largely through an association with proteins, known as selenoproteins. It is an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defense systems, and immune function (Rayman et al, 2002). Its role in thyroid hormone metabolism is crucial, and therefore selenium has the potential to play a major part in the outcome of Iodine deficiency disorder.

These effects of selenium derive from two aspects of its biological function: 1) three selenium containing deiodinases regulate the synthesis and degradation of the biologically active thyroid hormone T3, and 2) selenoperoxidases and possibly thioredoxin reductase protect the thyroid gland from H_2O_2 produced during the synthesis of thyroid hormones (Arthur et al, 1999).

Epidemiological surveys suggest that concomitant iodine and selenium deficiencies are present in settings where myxedematous cretinism is highly prevalent in Central Africa (Goyens et al, 1987; Vanderpas et al, 1990), leading to the hypothesis that selenium deficiency exposes the thyroid gland to free radical damage of hydrogen peroxide produced during thyroid hormone synthesis (Arthur et al, 1999). However, a similar association of iodine and selenium deficiencies in Tibet and in China does not lead to myxedematous cretinism, indicating that a number of other risk factors must play a role (Kohrle et al, 2005).

However, some studies have failed to provide convincing support for the hypothesis that selenium deficiency is the only compounding factor responsible for endemic cretinism seen in some iodine-deficient areas (Arthur et al, 1999). A study by Ngo et al, 1997 found in an area in Zaire, where cretinism had not been reported, the same degree of combined selenium and iodine deficiency as in northern Zaire, an area of endemic cretinism. Similarly the distribution of myxedematous cretinism is not related to selenium deficiency in China (Ma et al, 1993).

Only a few studies investigated the association between selenium and iodine status in humans. A study by Giray et al, 2001 investigated the association of selenium deficiency and goiter prevalence in school children in Turkey and found an association between low enzymatic antioxidants (glutathione peroxidase, catalase, and superoxide dismutase) and low selenium status and goiter (Giray et al, 2001), whereas the other study conducted by Erdogan et al, 2001 reported that low serum selenium had little or no impact on goiter endemics (Erdogan et al, 2001). Whereas a study conducted by Zagrodzki et al, 2000 in Poland, found no association between selenium status and free T4 and TSH concentrations in goitrous and non-goitrous children (Zagrodzki et al, 2000).

The first selenium supplementation trial was done in school children in the Democratic Republic of the Congo (formerly known as Zaire) (Contempre et al, 1992). Mean serum total T4, free T4 and reverse T3 concentration fell significantly to 66%, 71% and 73% of the initial value with selenium supplementation without a concomitant rise in serum TSH concentration (Contempre et al, 1991; Contempre et al, 1992).

Several other studies investigated the impact of selenium supplementation on thyroid function in different population groups in industrialised countries. In apparently healthy adults, daily selenium supplementation with doses ranging from 10 to 300 µg per day were provided for a duration of 1, 5, and 12 months (Hawkes et al, 2008). The four studies that included the analysis of serum or plasma selenium concentration found a significant increase in the selenium-supplemented groups compared with the placebo group. However, four out of five studies found no difference in thyroid hormone or TSH concentrations between groups (Arthur et al, 1997; Thomson et al, 2005; Hawkes et al, 2008).

In summary, iodine and selenium interact in multiple ways in thyroid metabolism (Kohrle et al, 2005). Although there is some indication from animal studies and cross-sectional studies in humans that selenium deficiency can adversely affect thyroid function (Arthur et al, 1999), randomised controlled trials investigating the impact of selenium supplementation on thyroid metabolism in various population groups found inconsistent results, but generally failed to confirm the hypothesis. The expected interaction may be too modest to be detected in randomised intervention trials, subjects were not sufficiently iodine and/or selenium deficient and/or adaptation of the thyroid metabolism may be able to sufficiently adapt to mild-to moderate selenium deficiency. Interactions between selenium and thyroid metabolism may be a concern in areas of severe selenium deficiency (Contempre et al, 1992) and high-risk population groups (Negro et al, 2007).

2.8.3 Vitamin A and Iodine Metabolism

Vitamin A deficiency is the leading cause of childhood blindness and a major nutritional determinant of severe infection and mortality among children in low-income countries (Sommer et al, 1996). Although the health consequences of vitamin A deficiency are not well described beyond early childhood, data from several intervention trials indicate that vitamin A deficiency in women of reproductive age may increase morbidity and mortality during pregnancy and the early postpartum period (West et al, 2002).

Vitamin A in food is present in various forms, of which the pre-formed retinol from animal source foods such as liver, eggs and dairy products is the most bioavailable

dietary source of vitamin A. The absorption of pro-vitamin A carotenoids from plants is influenced by various factors (West & Castenmiller, 1998). Thus, populations relying mainly on plant-based foods are at increased risk of vitamin A deficiency.

A study by Zimmermann, was conducted in an area of severe iodine deficiency in northern Morocco. School children with low vitamin A status were randomly assigned to receive placebo or a high dose vitamin A capsule at 0 and 5 months. All children received iodised salt (25mg per gram salt) for 10 months. It was concluded that in areas of concurrent iodine and vitamin A deficiencies, vitamin A supplementation along with iodised salt improves the efficacy of iodised salt (Zimmermann, 2004)

Another study conducted by Zimmermann et al. reported that vitamin A supplementation alone in iodine deficient children with mild vitamin A deficiency reduced circulating TSH, serum thyroglobulin and thyroid size without significantly affecting thyroid hormone concentrations (Zimmermann et al, 2007).

Also some studies have documented some association between thyroid function and vitamin A metabolism. Wolde-Gebriel et al, 1993a reported that in an area of severe vitamin A deficiency, total T3 was significantly correlated with retinol, transthyretin, and albumin in children, while T4 was associated with none of these biochemical parameters. In a total of 14740 school children in Ethiopia, those children with visible goiters had significantly lower serum retinol levels than children without or only small palpable goiters (Wolde-Gebriel et al, 1993b).

A study conducted by Goswami & Choudhury, 1999 in India, reported that hypothyroid women had increased retinol concentrations and hyperthyroid women had decreased retinol levels compared to controls. Further research is necessary to evaluate the association between thyroid and vitamin A metabolism and its public health significance.

2.8.4 Zinc and Iodine Metabolism

Adequate zinc nutrition is essential for human health because of zinc's critical structural and functional roles in multiple enzymes that are involved in gene expression, cell division and growth, and immunological and reproductive functions.

As a consequence, zinc deficiency affects children's physical growth, and the risk and severity of a variety of infections (Brown et al, 2004).

There are implications that zinc is also important for normal thyroid homeostasis. Zinc's role is complex and may include effects on both the synthesis and mode of action of the thyroid hormones (Arthur & Beckett, 1999).

Cross-sectional studies investigated whether hypothyroid or hyperthyroid patients have abnormally low or abnormally high serum zinc concentrations, and found inconsistent results (Hess & Zimmermann, 2004; Ganapathy & Volpe, 1999).

In a study conducted by Dabbaghmanesh in Iranian school children (n=1188), no differences in thyroid hormone concentration and goitre rate were found in children with low and high serum zinc concentration (Dabbaghmanesh et al, 2008). But, a study conducted by Ozata M in Turkey found that goitrous men had significantly lower plasma zinc concentrations than a comparison group of 140 non-goitrous men. However, the statistical analysis did not control for potential confounding factors (Ozata et al, 1999). No correlation was observed between zinc intake or serum zinc concentration and thyroid hormone concentrations in middle-aged and older European men and women (n = 387) (Meunier et al, 2005). A cross-sectional study by Ozata et al, 1999 in Turkey, reported that plasma zinc concentration in goitrous male adults was significantly lower than in the control group. In summary, existing studies found inconclusive evidence for interactions between zinc deficiency and thyroid metabolism.

2.9 Tackling dual problem of iodine deficiency and Hypertension (WHO, 2014)

Recently a regional workshop was help on sodium intake and iodized salt in the Member States for South-East Asia Region sodium intake and iodized salt in the Member States for South-East Asia Region.

Recommendations of the workshop were:

- To develop policies and strong legislation to regulate the reduction of dietary salt intake.
- Baseline values of dietary sodium intake should be established at country level by the '24-hour urine' method in different population groups.
- Dietary surveys to identify sources of high salt in the diet of populations.
- Public education and behaviour change communication regarding salt reduction is the main strategy in reduction of salt intake to be implemented across all the Member States.
- Capacity building of health workers and other workers should be enhanced with regard to reduction of dietary salt intake.
- It may be beneficial to take a combined approach to the food industry to achieve both salt reduction while promoting use of only iodized salt.
- Public health messages on dietary salt reduction should be clear and simple and not contradict or confuse the messages regarding promoting consumption of iodized salt.
- A national-level committee should be set up to monitor and regulate dietary salt reduction and salt iodization programmes and ensure cooperation and safeguard optimization of both salt reduction and salt iodization and should be planned from the initiation of salt reduction programmes.
- Iodine content in salt should be adjusted based on regular monitoring of both salt consumption and assessment of urinary iodine to minimize problems that may ensue with reduction of dietary salt and delivery of iodine to populations through salt iodization.

2.10 Program to eliminate or control iodine deficiency disorders: National Iodine Deficiency Disorders Control Programme (NIDDCP) in India

(Source:http://nrhm.gov.in/nrhm-components/national-disease-control-programmes-ndcps/iodine-deficiency-disorders.html)

2.10.1 Objectives

Realizing the magnitude of the problem the Government of India launched a hundred percent centrally assisted National Goitre Control Programme (NGCP) in 1962 with the following objectives:

i. Initial surveys to assess the magnitude of the Iodine Deficiency Disorders.
ii. Supply of iodized salt in place of common salt.
iii. Resurveys to assess the impact of iodized salt after every 5 years.
iv. Health Education & Publicity.
v. Laboratory monitoring of iodated salt and urinary iodine excretion.

In August 1992, the National Goitre Control Programme (NGCP) was renamed as National Iodine Deficiency Disorders Control Program (NIDDCP).

2.10.2 Evaluation

The status of salt iodization and urinary iodine excretion levels in different states has been extensively assessed by various research studies in recent years. The available data shows that the strategy of salt iodization has been successful in the country in prevention of iodine deficiency disorders. More than 70% of population has been found to be consuming iodized salt.

A countrywide evaluation was conducted under NFHS-3, in 2005-06 measured the iodine content of cooking salt in each interviewed household using a rapid-test kit. Table 3 shows the extent of salt iodization at the household level. Overall, 51 percent of households use cooking salt that is iodized at the recommended level of 15 ppm or

more. Only 23.9 percent used salt that is not iodized at all and 25.0 percent use salt that is inadequately iodized (less than 15 ppm).

The use of iodized salt varies dramatically from one state to another. The variations are due to a number of factors, including the scale of salt production, transportation requirements, enforcement efforts, the pricing structure, and storage patterns.

The use of adequately iodised salt is uniformly high (72 percent or higher) throughout the north east region, in most states in the north region, and in Kerala, reaching a high of 94 percent in Manipur. The use of adequately iodised salt is lowest (less than 40 percent) in Andhra Pradesh, Madhya Pradesh, Uttar Pradesh and Orissa. Despite the fact that the overall use of iodized salt has not changed since NFHS-2, several states have made substantial improvements over time but the situation has deteriorated in other states. The largest gains have been made in Kerala (from 39 percent in NFHS-2 to 74 percent in NFHS-3), Goa (from 42 percent to 65 percent), Jammu and Kashmir (from 53 percent to 76 percent), Tamil Nadu (from 21 percent to 41 percent), Meghalaya (from 63 percent to 82 percent) and Nagaland (from 67 percent to 83 percent). The states in which the use of adequately iodised salt has deteriorated substantially are Haryana (from 71 percent to 55 percent), Himachal Pradesh (from 91 percent to 83 percent), and Assam (from 80 percent to 72 percent).

2.10.3 Areas Requiring Strengthening

The research studies conducted have identified following areas which require strengthening in NIDDCP.

i. A low priority is accorded to the NIDDCP by the state governments leading to irregular distribution of iodised salt for varying periods
ii. Lack of monitoring of the quality of iodised salt procured and distributed by road transport.
iii. Failure of lifting of allotted quotas of iodised salt by wholesale agents for further distribution to retailers.
iv. Inadequate coordination between salt traders and food inspectors (the implementers of PFA Act) causing disruption in procurement, distribution and sale of iodised salt.

v. Poor coordination between various departments like food and civil supply, health, Industry, Railways.

vi. Incomplete ban notification in the selected States/UTs for the sale of non-iodised salt.

vii. Non Establishment of IDD Control Cell in selected States/UTs.

viii. IDD Monitoring Laboratories are yet to be set up in all the States.

ix. Inadequate enforcement of PFA act by the State/UT Governments to ensure the quality of iodised salt is available to the consumer

x. Regular IDD surveys and resurveys are not conducted by the State/UT governments to monitor the progress or to identify new areas of endemicity.