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REVIEW ARTICLE

Optimal Iodine Nutrition during Pregnancy, Lactation and the Neonatal Period

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Iodine of maternal origin is required for brain development of the progeny during fetal and early postnatal life. Therefore, the iodine requirements of the mother are increased during pregnancy and lactation. This paper reevaluates the iodine requirements during pregnancy, lactation and the neonatal period and formulates original proposals for the median concentrations of urinary iodine indicating optimal iodine nutrition during these three critical periods of life. Based on an extensive and critical review of the literature on thyroid physiopathology during the perinatal period, the following proposals are made: the iodine requirements are 250-300 μg/day during pregnancy, 225-350 μg/day during lactation and 90 μg/day during the neonatal period. The median urinary iodine indicating optimal iodine nutrition during these three periods should be in the range 150-230 μg/L. These figures are higher than those recommended so far by international agencies.

Key Words: Iodine, Nutrition, Pregnancy, Lactation, Neonatal Period, Median urinary iodine

Introduction

The thyroid economy undergoes a series of metabolic changes during pregnancy and lactation.[1-4] One of the factors involved in these changes is the increased requirement of iodine in the mother due to the transfer of thyroxine (T_4) and of iodide from mother to fetus during pregnancy and to the loss of iodide in breast milk during lactation. These two processes are required in order to ensure normal brain development and prevention of mental retardation in the offspring.[5-10]

The objectives of this paper are:

1. To review the data from the literature on the iodine requirements during pregnancy, lactation and the neonatal period.
2. To offer practical recommendations regarding the median concentrations of urinary iodine indicating optimal iodine nutrition during these critical periods of life.

Requirement of Iodine During Pregnancy and Lactation

The requirement of iodine is increased during pregnancy because of at least three factors: 1) There is an increased requirement of T_4 in order to maintain a normal global metabolism in the mother. 2) There is a transfer of T_4 and iodide from the mother to the fetus and 3) There is supposed to be an increased loss of iodide through the kidney due to an increase in the renal clearance of iodide.

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Because of these three factors, the recommended dietary intake of iodine during pregnancy is higher than the value of 150 µg/day recommended for non-pregnant adults and adolescents.[11,12] Below this critical threshold of 150 µg/day, the iodine balance is negative during pregnancy.[13] WHO/UNICEF/ICCIDD recommend an iodine intake of 200 µg/day for pregnant women,[11] i.e. a percentage increase of 33% over non-pregnant women. The Institute of Medicine (IOM) of the US Academy of Sciences recommends a higher intake of 220 µg/day,[12] i.e. an increase of some 47%, and other organizations recommend 175 to 230 µg/day.[14,15]

Increase in the T_4 requirements

The daily requirement of T_4 in order to maintain euthyroidism in hypothyroid women increases by 10 to 150% during pregnancy with a median increment of 40-50%.[16-18] This represents an additional dose of 75 to 150 µg T_4/day, i.e. 50 to 100 µg iodine.

Transfer of T_4 and iodide from mother to fetus

The transfer of T_4 from mother to fetus, including before the onset of fetal thyroid function, is not quantified but it is has been estimated that up to 40% of the T_4 measured on cord at birth is still of maternal origin.[8]

The transfer of iodide is also difficult to quantify but considering that the iodine content of the fetal thyroid increases progressively from less than 2 µg at 17 weeks of gestation[19] up to 300 µg at term,[20-23] that the T_4 iodine at term probably averages 500 µg[24] and that the substitutive dose of T_4 in hypothyroid neonates is 50-75 µg/day,[25,26] it can be estimated that the transfer of iodide from mother to fetus represents some 50 µg/day. It has been estimated at 75 µg/day by the IOM.[12]

Increased renal clearance of iodide

It is often stated that the increase in iodine requirement during pregnancy is largely due to an increased loss of iodide through the kidney because of an increased renal clearance of iodide. This should decrease the serum concentration of plasma inorganic iodide, PII.[27-30] However, Liberman et al.[31] showed on the contrary that there is no significant decline in the PII during pregnancy. In addition, as shown by the data collected in Table 1 and already by Dworkin et al.,[13] almost all studies on urinary iodine during pregnancy showed that, in a given environment, the urinary excretion of iodide is almost similar in pregnant and non-pregnant women and in the general population, irrespective of the status of iodine nutrition in the population. Only the studies conducted by the group of Smyth et al.[32,33] in Ireland, the United Kingdom and Sri Lanka, by Kung et al. in Hong Kong[34] and perhaps by Hess et al. in Switzerland[35] have shown a clear-cut increase in the urinary iodine excretion during pregnancy. The results reported for Switzerland by Brander et al.[36] are difficult to interpret because of the surprisingly low value of the urinary iodine in the general population reported in this study as Switzerland is known to be iodine sufficient.[37] On the contrary, some studies showed that urinary iodine decreases during gestation.[38-40] It thus appears that the concept of systematically increased urinary loss of iodine during pregnancy is not firmly established.

Finally, it has to be underlined that no data are available on the possible storage and loss of iodide in the placenta itself.

Taking all these variables into consideration, it can be speculated that the additional requirement of iodine during pregnancy is at least 100-150 µg/day, i.e. an increment of almost 100% as compared to non-pregnant adults instead of the 33% proposed by WHO/UNICEF/ICCIDD.[11] Consequently, the requirement of iodine during pregnancy is at least 250 µg/day, probably in the range of 250 to 300 µg/day. This figure is still higher than the figure of 220 µg/day proposed by the IOM,[12] which did not take into account the increased requirement of T_4 during pregnancy.

Table 1. Comparison of the median or mean (in bold) urinary iodine (µg/L) in pregnant women and in the general population or in non-pregnant controls (publications 1990-2003)

Country	General population or controls	n	S/C	Pregnant women: Trimester	Pregnant women: Urinary iodine
Countries with no iodine deficiency					
Chile[31]	-	19	S	1	594*
				2	469
				3	786
				3 months PP	459
Iran[43]	193-312†	403	C	1-3	186-338†
Sweden[77]	-	51	S	1	180*
		51	S	2	170
		51	S	3	145
Srilanka[33]	147†	-	C	1	181†
		-	C	2	136
		-	C	3	154
USA[78]	130	290	C	1-3	148
Switzerland[35] (2000)	115†	511	C	2,3	138†
Scotland[79]	**138†**	433	C	1	**137†**
Switzerland[36] (1992)	91‡	153	C	1-3	**205***
		31	C	1	**267**
		56	C	2	**206**
		66	C	3	**172**
		15	S	1	**325**
		15	S	2	**166**
		15	S	3	**183**
Iodine deficient countries					
Singapore[34,80]	98†	253	C	3	124†
		230	S	1	107†
		-		2	116
		-		3	124
		-		6 weeks PP	105
		-		3 months PP	104
Sicily (Italy)[54,81]	46*	10	S	1,2,3	33*
Turkey[82]	85*	80	S	1-3	91*
Ireland[32,33]	70†	38	S	1	135†
		38	S	2	125
		38	S	3	122
		108	C	6 weeks PP	70
UK[33]	73†	-	C	1	125†
		-	C	2	170
		-	C	3	147
France[40]	50-80*	306	S	1	50†
		224	S	3	54
Belgium[38]	50-75*	334	C	1-2	50†
		334	C	2-3	45
		136	C	1	56†
		133	C	2	50
		49	C	3	50
Denmark[83]	50*	26	S	2	51†
		26	S	3	40
		26	S	1 week PP	30
		26	S	26 weeks PP	50
		26	S	52 weeks PP	58
Denmark[84]		-	C	5 days PP	40‡
Sudan[55]	76†	47	S	3	38†
		47	S	3 months PP	51
		47	S	6 months PP	30
		47	S	9 months PP	63
New Zealand[49]	24-47*	35	S	Monthly during pregnancy and 3, 6 and 12 months PP	24-52*
Italy[85] (2002)	Marginal ID	67	C	1,2	74‡
Italy[86] (1991)	Marginal ID	18	C	3	50*
Germany[87]	Mild ID	70	S	1	55‡
		70	S	11 days PP	50
Hungary[88]	Mild ID	119	C	1,2,3	57‡

n: number of subjects; S/C: Sequential (S) or cross-sectional study(C); 1,2,3: Trimesters of pregnancy; PP: Postpartum; ID: Iodine deficiency; 100 µg/L = 0.78 µmol/L

* µg/day; † µg/L; ‡ µg/g creatinine

Table 2. Selective examples of the iodine content of breastmilk *

Countries	Medians or means (µg/L)
No iodine deficiency	
Korea	892
Japan	661
	33-385
USA	146
	168
	124
	145
	145
Sweden	93
	90
	70
Switzerland	78
Mild to moderate iodine deficiency	
Germany	93
	15-150
Belgium	95
France	82
	77
	74
	70
Spain	108
	77
United Kingdom	
Hungary	64
Guatemala	60
Philippines	57
Thailand	50
Italy (Sicily)	43
Severe iodine deficiency	
Marocco	27
Ethiopia	5-16
	64
Congo	15
	13

* Compiled from Semba-Delange 2001[41] and Dorea 2002,[42] where detailed data and references are to be found.

During lactation, considering that the iodine content of breastmilk in conditions of iodine sufficiency is in the range of 150-180 µg/L[41,42] (Table 2) and that the milk production is from 0.5 to 1.1 liter per day up to the age of 6 months, the daily loss of iodine in human milk is estimated at some 75 to 200 µg/day. Consequently, the iodine requirement during lactation is estimated at 225 to 350 µg/day. The slight difference, if any, as compared to the figure of 290 µg/day recommended by IOM[12] results from more recent data on the iodine content of breast milk.[41,42]

Level of Urinary Iodine Indicating Optimal Iodine Nutrition During Pregnancy and Lactation

Considering that most (above 90%) of the iodine absorbed in the body eventually appears in the urine, urinary iodine excretion is a good marker of a very recent dietary iodine intake.[11] Therefore, a median urinary iodine in the general population varying from 100 to 199 µg/L is considered as an indicator of an adequate iodine intake and an optimal status of iodine nutrition.[11] As the iodine requirement is increased during pregnancy, the median urinary iodine during pregnancy indicating optimal iodine nutrition needs to be higher than 100 µg/L. Table 1 compares the data available in the literature on urinary iodine in pregnant women and in the general population. In this Table, the countries are arbitrarily listed on the basis of roughly decreasing iodine intake of the general population, starting with Chile[31] which is exposed to iodine excess based on the WHO/UNICEF/ICCIDD criteria,[11] down to countries where different degrees of mild to moderate iodine deficiency have been documented. As indicated earlier, there is a striking similarity between the urinary iodine in pregnant women and in the global population except in the reports published by Smyth et al.[32,33] in which the values during pregnancy are systematically markedly higher than in non-pregnant controls. Therefore, it appears difficult to derive a reference value for urinary iodine during pregnancy and lactation from the data collected in countries with no iodine deficiency as this value varies from 800 µg/L in Chile[31] to 138 µg/L in Switzerland, where the median urinary iodine in the general population is barely above the lower limit of normal.[35] In Iran, where iodine deficiency has been successfully eliminated,[43] the median urinary iodine in pregnant women in four different cities varies from 186 to 403 µg/L and is almost entirely similar to the values found in the general population in the same cities.[44] The values during pregnancy are of the same order of magnitude as the 250-300 µg/day recommended as intake based on metabolic studies. And yet, in spite of these relatively elevated values, Azizi et al.[44] underline that with such medians, some 8% of the values are still below the critical threshold of 100 µg/L for non-pregnant adults. They suggest that the recommended dietary intake of iodine during pregnancy should be still higher. It has to be recognized however, that this figure of 8% corresponds almost exactly to the percentage of values (7.2%) below the cut-off point of 50 µg/L indicating at least moderate iodine deficiency in a general population when the median is between 100 and 200 µg/L.[45] This percentage is considered as acceptable[45] considering the well documented day to day variability of urinary iodine, including during pregnancy.[46-49]

From these different considerations, it can be concluded that the recommended median value for urinary iodine during pregnancy and lactation has to be based on theoretical grounds. If, as in non-pregnant adults, the recommended median (100 to 200 µg/L) corresponds to the recommended intake (150 µg/day), the median urinary iodine during pregnancy and lactation should be in the range 225-350 µg/L. If, on the contrary, this recommended median was based on a recommended intake of 225-350 µg/day and a mean daily urinary volume of 1.5 L/day, it should be in the range of 150-230 µg/L, i.e. only slightly higher than the value recommended for non-pregnant adults.

It has to be recognized that thyroid function and volume remained perfectly normal during pregnancy in Iran[44] as well as in Chile[31] for values still twice higher, which strongly suggests that these values are not excessive and potential sources of side effects.[50,51] On the contrary, in all countries submitted to some degree of iodine deficiency where the point has been investigated, thyroid function is critically impaired during pregnancy and in the neonate even when it remains normal in the general population.[52-56] The anomalies include progressive decrease in free T_4 and increase in serum Tg and thyroid volume. The alterations are usually still more marked in the neonates than in the mothers.[52] They are at least partly corrected by iodine supplementation during pregnancy and lactation.[57,58] In summary, it appears that the recommended dietary intake of iodine during pregnancy (250-300 µg/L) and lactation (225-350 µg/L) should be higher than what has been proposed earlier, especially by WHO/UNICEF/ICCIDD,[11] and that a median urinary iodine indicating optimal iodine nutrition during pregnancy and lactation could be in the range 150-230 µg/L.

Requirement of Iodine in Neonates

As underlined by the IOM,[12] no functional criteria of iodine status have been demonstrated that reflect response to dietary intake in infants. Consequently, the recommended intake of iodine in neonates reflects the observed mean iodine intake of young infants exclusively fed human milk in iodine replete areas. Up to the late sixties, the iodine content of breast milk in such areas was usually around 50 µg/L.[41,42,59] Considering a daily intake of breast milk of some 0.6 to 1 liter in the neonate and young infant, the assumption was that an infant may get 30 to 50 µg/day iodine in milk from an adequately fed mother.[60] However, it is well established that the iodine content of breastmilk is critically influenced by the dietary intake of the pregnant and lactating mother and of the general population and that much higher figures have been recorded more recently.[41,42] Thus, again on theoretical grounds, the requirement of io dine in neonates was evaluated from metabolic studies by determining the value which

Table 3. Median or mean (in bold) urinary iodine (UI) concentrations (µg/L) in neonates in iodine sufficiency and iodine deficiency

Countries and location	n	Gestational age	Urinary iodine (µg/L)*	Range	Reference
Japan	118	FT Breastfed	736		Harada et al. 1994[63]
Hokkaido	182	FT Bottlefed	521		
United States					
Boston	?	PT≤ 36 weeks	148	16-510	Brown et al. 1997[89]
Torrance	50	FT	921		Delange et al. 1984[90]
Canada					
Toronto	81	FT	148		Delange et al. 1986[72]
The Netherlands					
Rotterdam	64	FT	162		Delange et al. 1986[72]
Amesterdam	36	FT	**150**		Bakker et al. 1999[91]
Sweden					
Stockholm	39	FT	112		Delange et al. 1986[72]
Stockholm	61	FT	96		Heidemann et al. 1984[65]
Mild to moderate iodine deficiency					
Germany					
Nine towns 1983	461	FT	12-29		Heidemann et al. 1984[65]
Berlin West 1985	87	FT	28		Delange et al. 1986[72]
Kiel 1992	50	FT	33		Grebe et al 1993[92]
Frankfurt 1992	21	FT	37		Bohles et al. 1993[93]
Berlin West 1994	177	FT	31		Grüters et al. 1995[94]
Berlin East 1994	213	FT	44		Grüters et al. 1995[94]
Gottingen 2000	22	FT	50		Roth et al. 2001[95]
Heidelberg 1999	32	FT	**95**		Klett et al. 1999[96]
Belgium					
Brussels 1983	103	PT+FT	35	10-150	Delange et al. 1984[90]
Brussels 1985	196	FT	48		Delange et al. 1986[72]
Brussels 2000	90	FT	86		Ciardelli et al. 2001[97]
Italy					
Rome 1985	114	FT	47		Delange et al. 1986[72]
Catania 1985	14	FT	71		Delange et al. 1986[72]
?towns 1995	195	FT	56	10-950	Rapa er al. 1996[98]
Milano 1995	18	PT 30 weeks	**123**		Parravicini et al. 1996[99]
Torino	9	FT	67	10-162	Bono et al 1998[100]
France					
Lille 1985	82	FT	58		Delange et al. 1986[72]
Toulouse 1985	37	FT	29		Delange et al. 1986[72]
Ireland					
Belfast 1993	?	FT	**100**		Barakat et al. 1994[101]
Israel					
Tel Aviv 1996	55	PT 30-31 wks		55-100	Linder et al. 1997[102]
Czech Republic					
Prague 1998	50	FT	79		Hnikova et al. 1999[70]
Prisbram 1998	50	PT	78		
Hungary					
Budapest 2002	55	FT	35		Peter et al. 2003[103]
Gyor 2002	65	FT	57		
Miskole 2002	54	FT	59		
Nyiregyhaza	35	FT	75		
Severe iodine deficiency					
Gottingen 1985	81	FT	15		Delange et al. 1986[72]
Heidelberg 1985	39	FT	13		Delange et al. 1986[72]
Freiburg 1985	39	FT	11		Delange et al. 1986[72]

n: number; FT: Full-term, PT: Pre-term
* Values are medians or means (bold).

resulted in a situation of positive iodine balance, which is required in order to insure a progressively increased intrathyroidal iodine pool in the growing young infant. Such iodine balance studies were conducted in healthy preterm and in fullterm infants aged approximately one month in Belgium, a country with mild iodine deficiency.[61] These studies, reported extensively elsewhere,[60] indicate that the iodine intake required in order to achieve a positive iodine balance is at least 15 µg/kg/day in fullterms and 30 µg/kg/day in preterms. This corresponds approximately to 90 µg/day and is consequently twice higher than the 1989 US recommendations of 40-50 µg/day[62] but is still a bit lower than the present recommendation of 110 µg/day by the IOM.[12]

Level of Urinary Iodine Indicating Optimal Iodine Nutrition in Neonates

Table 3 summarizes the data from the literature on the median urinary iodine in neonates in countries or areas with iodine sufficiency and with different degrees of iodine deficiency. There is a large variability in the results even in iodine sufficient countries, where they vary from 736 µg/L in Hokkaido, Japan,[63] which is submitted to an extremely high iodine intake[64] to 96 µg/L in Stockholm.[65]

Therefore, again, the data from the literature do not help substantially in identifying the optimal urinary iodine level and this level has also to be defined on the basis of theoretical considerations. Based on an iodine requirement of 90 µg/day and a volume of urines in neonates of some 0.4 to 0.5 liter/day,[66] the median urinary iodine indicating optimal iodine nutrition in neonates can be evaluated at some 180 to 225 µg/L when ignoring the fact that the iodine balance of the neonate should also be positive in order to constitute the iodine stores of the thyroid. This level, which is higher than the one recommended for schoolchildren and adults, is indeed observed when healthy young infants are supplemented with a daily physiological dose of 90 µg/day.[67] It is also the value reported in some parts of the United States supposed to be iodine sufficient.[68,69] On the other hand, studies reported in the literature in which urinary iodine has been determined simultaneously in mothers at delivery and in neonates during the first days of life[39,70,71] indicate that these levels are almost similar in mothers and neonates. Therefore, based on the considerations on optimal urinary iodine in pregnant mothers, it can be extrapolated that the level in neonates should be around 150 to 230 µg/L, which is almost similar to the figure derived from the iodine requirements of the neonates.

The data reported from neonates in conditions of mild, moderate and severe iodine deficiency are indeed much lower than normal, down to less than 20 µg/L in Germany[72] before the partly successful implementation of a program of voluntary salt iodization.[73] It is particularly interesting to observe that this level progressively increased with time in Germany and in Belgium for example following the implementation of programs of iodine supplementation[73,74] and silent iodine prophylaxis, respectively.[75]

In summary, the recommended dietary intake of iodine in neonates is 90 µg/day and the median urinary iodine to be expected when this requirement is met is 180 to 225 µg/L, a value almost similar to the one recommended for pregnant women.

Conclusion

Pregnant and lactating women and neonates are the main targets to the effects of iodine deficiency because of the impact of maternal, fetal and neonatal hypothyroxinemia on brain development of the progeny.[5-10] Therefore, any program of salt iodization in a population should pay special attention to these particular groups. And yet, no firm recommendations are presently available on the level of urinary iodine indicating optimal iodine nutrition in these groups. This paper constitutes an attempt to propose such normative values. It appears that an extensive review of the literature based in particular on the evaluation of urinary iodine in these groups in iodine replete populations does not offer clear answers to the questions because of the variability of individual results even in iodine sufficient countries. One first conclusion of this paper is thus that more accurate data should be collected in iodine sufficient countries, comparing systematically and at the same time the urinary iodine in the general population, in non-pregnant adults, schoolchildren, pregnant and lactating women and in neonates.

However, based on the data from the literature and on metabolic considerations, it is proposed that the recommended dietary intake of iodine is 250-300 µg/day for pregnant women, 225-350 µg/day for lactating women and 90 µg/day for neonates and young infants. It is proposed that the median level of urinary iodine indicating optimal iodine nutrition during pregnancy and lactation is in the range 150-230 µg/L. Recommendations for neonates are still more difficult not only because of the lack of accurate data but also because the neonate is not in a steady state regarding iodine metabolism and that urinary iodine probably represents a relatively imprecise estimation of the iodine intake. However, based on the data from the literature and on theoretical considerations, it can be concluded that the median urinary iodine indicating optimal iodine nutrition in the neonate should be in the same range of 180-225 µg/L, almost similar to the value recommended for their mothers.

It has to be emphasized again that these levels are higher than the ones recommended for the general population and are supposed to be potentially responsible for side effects in adolescents and non-pregnant adults.[11] Therefore, special attention should be focused on iodine supplementation and monitoring urinary iodine during pregnancy and possibly during the neonatal period in addition to programs of Universal Salt Iodization in countries with iodine deficiency.[58] This recommendation is particularly relevant considering that pregnant and lactating women and neonates have usually a limited access to salt in general and, consequently, to iodized salt, and that even in the United States, where the status of iodine nutrition is adequate in the general population (median urinary iodine of 145 µg/L), 6.7% of the pregnant women are still affected by moderate to severe iodine deficiency (urinary iodine below 50 µg/L).[76]

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