The Influence of Gestational Stage on Urinary Iodine Excretion in Pregnancy

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Introduction: Median urinary iodine concentration (UIC) is the most commonly used indicator of population iodine nutrition. However, its validity as an indicator of dietary intake relies on a stable relationship between dietary iodine intake and urinary excretion. Physiological alterations in normal pregnancy, such as increased glomerular filtration rate, potentially invalidate UIC as an assessment tool in pregnancy.

Objective: The objective of the study was to document the impact of advancing gestation on UIC in normal pregnancy and determine whether the current reference intervals for general population iodine monitoring are appropriate for use in the context of pregnancy.

Design: Tasmania has a well-described history of mild iodine deficiency (school-age median UIC of 84 μg/liter). We assessed UIC in 759 urine samples from 431 women attending the Antenatal Clinic at the Royal Hobart Hospital, Tasmania's primary teaching hospital.

Main Outcome: The overall median UIC during pregnancy was 75 μg/liter (95% confidence interval 70.03–79.97 μg/liter) at a median gestation of 19.4 wk. Stratification by gestation, however, revealed a dynamic relationship between ioduria and gestation. Median UIC was elevated in early pregnancy and subsequently declined with advancing gestation.

Conclusion: In this mildly iodine-deficient population, current reference intervals for UIC overestimated the adequacy of iodine nutrition during the first and early second trimester of pregnancy. Gestation-specific UIC reference intervals are required to classify iodine nutrition during pregnancy. This is particularly important in populations with borderline iodine deficiency. (*J Clin Endocrinol Metab* **93: 1737–1742, 2008**)

Pregnancy is associated with substantial changes in thyroid physiology and represents a major stress on maternal iodine homeostasis (1). Adequate dietary iodine intake during pregnancy is essential to prevent adverse maternal and neonatal outcomes. In particular, mild and moderate degrees of iodine deficiency during fetal development and early childhood have been linked to reduced intellectual function (2–4). The implications of this for communities with iodine deficiency are significant given the potential for a net reduction in average population IQ.

The majority of dietary iodine (>90%) is excreted in the urine (5). Urine iodine excretion is largely a passive process dependent on glomerular filtration rate (GFR) (6). Urinary iodine concentration (UIC) in a nonpregnant individual on a stable diet represents a dynamic equilibrium between dietary intake, thyroidal iodine extraction, the total body thyroid hormone pool, and GFR. During normal pregnancy, GFR increases within the first month after conception, peaking by the end of the first trimester at approximately 40–50% above prepregnant levels (7). Hence, pregnancy can be expected to result in increased renal iodine

Abbreviations: GFR, Glomerular filtration rate; NHANES, National Health and Nutrition Studies; UIC, urinary iodine concentration.

losses, and in circumstances of borderline or overt iodine deficiency, pregnancy-related increases in GFR could deplete total body iodine reserves without the capacity for replenishment if dietary intake remains low.

The key indicator of population iodine nutrition recommended by the World Health Organization (WHO) and the International Council for Control of Iodine Deficiency Disorders is the determination of median urinary iodine concentration in a representative sample of school-aged children (8). The adequacy of iodine nutrition is defined by the following criteria: a median UIC of at least 100 μg/liter (with < 20% of the population having UIC < 50 μg/liter) represents adequate population iodine nutrition; a median UIC between 50 and 99 μg/liter represents mild iodine deficiency; and medians of 20–49 μg/liter and less than 20 μg/liter represent moderate and severe iodine deficiency, respectively (9, 10). Whereas these criteria are often generalized for use in pregnancy, changes in iodine requirements and maternal physiology with advancing gestation may invalidate the expected relationship between dietary intake and urine iodine excretion.

Recent publications including a consensus statement from the American Thyroid Association highlight the importance of higher dietary iodine intake in pregnancy, and higher pregnancy-specific UIC reference ranges, to allow for these physiological changes (11, 12). The recommendation is that a median UIC of 150–249 μg/liter might be expected in an iodine-sufficient pregnancy (5, 11, 12). Despite these considerations, there is as yet no minimum accepted median UIC that is indicative of a safe level for iodine nutrition in pregnancy or gestation-specific UIC reference intervals. Whereas it is theoretically desirable to avoid minimum targets, and in preference adopt iodine supplementation programs that achieve robust optimal population iodine nutrition, the practicalities of iodine prophylaxis will always make establishment of minimum nutritional targets an important issue.

In this study, we evaluated gestational changes in UIC in Tasmania, Australia, a community with well-characterized mild iodine deficiency. The appropriateness of existing WHO criteria for classifying UIC in pregnancy was evaluated.

Subjects and Methods

Tasmania is an island state of the Commonwealth of Australia with a well-documented history of iodine nutrition (13). Before the mid-1960s, Tasmania was iodine deficient and recognized as a region with endemic goitre. Iodine prophylaxis resulted in satisfactory iodine nutrition in the 1970s and 1980s, but by 1990 iodine deficiency returned due to failure to maintain a sustained supplementation program. The current study was undertaken in Tasmania after recurrence of mild iodine deficiency. The median UIC for the indicator population of school-aged children at this time was 84 μg/liter (13).

In total, 759 random urine samples (including 73 postpartum samples) were collected from 431 consenting women attending routine antenatal clinics at the Royal Hobart Hospital during three collection phases between 1999 and 2001 (October to December 1999, February to March 2001, and July to August 2001). The 759 −73 = 686 pregnancy samples included multiple measurements from some women (232 women provided single samples, 143 women provided two samples, and 56 women provided three samples). Gestational dates at the time of collection were recorded and were later retrospectively confirmed by

correlating delivery dates and delivery gestational ages with the date of the initial sample.

Information regarding smoking status and use of vitamin supplements was not available for analysis, but patients were neither included in nor excluded from the study on the basis of these factors. Labor ward and theater staff were not informed of patients' participation in the study, and the method of delivery and exposure to iodine-based antiseptics during epidurals, episiotomies, or suturing were not specified for study participants.

Samples were assayed using the modified acid digestion method (method E) based on the Sandell Kolthoff reaction (between cerium IV and arsenic III) using a Technicon Autoanalyzer II (Pulse Instrumentation, Saskatoon, Canada). The study was approved by the human research Ethics Committee of the Royal Hobart Hospital.

The results are presented either as median values and interquartile range or as mean values and SD. To take account of the correlation between repeated measurements, we estimated robust SEs adjusted for the clustering of observations on the same women (14). Log binomial regression (log link, binomial errors), with robust SEs adjusted for the clustering of observations on the same women, was used to estimate the association between the proportion of women with UIC less than 50 μg/liter and gestation.

Results

The distribution of urinary iodine concentrations is shown in Fig. 1. The overall median UIC during pregnancy was 75 μg/liter (95% confidence interval 70.03, 79.97 μg/liter). Median UIC declined during pregnancy at an average rate of change of −0.44 mcg/liter (95% confidence interval −0.97, 0.09 mcg/liter) per week of gestation (range 4.7–41.6 wk). The relationship with
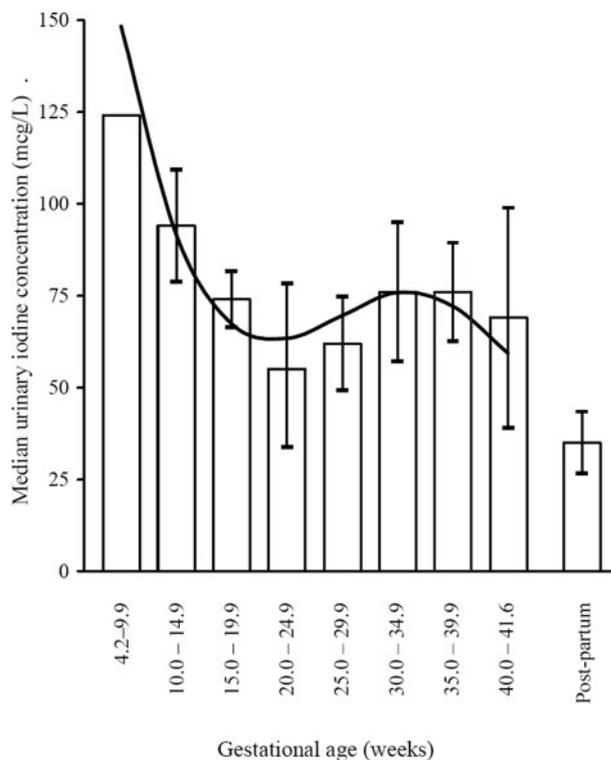

FIG. 1. UIC. The *columns* represent median UIC with 95% confidence intervals (the interval for the small group of n = 18 measurements made at less than 10 wk was −358 to 638 μg/liter). The *curved line* represents predicted values from the regression of median UIC on gestational age.
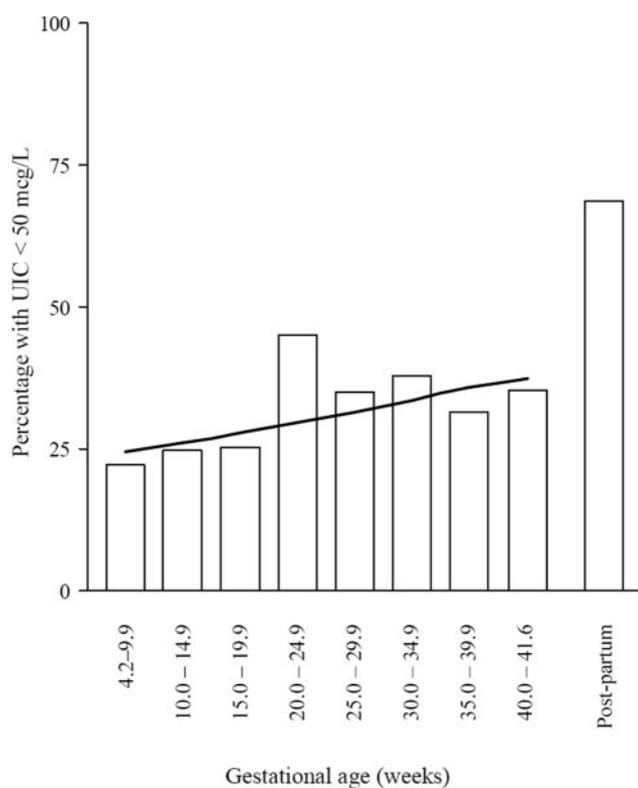
TABLE 1.　UIC by gestational age

Category of gestational age	n^a	Gestation (wk)	Maternal age (yr)	UIC (μg/liter)	UIC less than 50 μg/liter (%)
		Mean (SD)	Mean (SD)	Median (IQR)	
4.7–9.9 wk	18	8.68 (1.23)	26.48 (2.72)	124 (63, 920)	22.2
10.0–14.9 wk	178	12.64 (1.25)	27.42 (5.15)	94 (48, 240)	25.3
15.0–19.9 wk	171	17.89 (1.37)	27.51 (5.79)	74 (49, 102)	25.2
20.0–24.9 wk	54	22.18 (1.54)	27.29 (5.34)	55 (28, 145)	46.3
25.0–29.9 wk	48	27.84 (1.26)	29.49 (6.61)	62 (46, 99)	33.3
30.0–34.9 wk	63	32.60 (1.44)	29.88 (5.86)	76 (42, 138)	33.3
35.0–39.9 wk	134	36.76 (1.18)	28.98 (5.17)	76 (46, 190)	28.4
40.0–41.6 wk	20	40.67 (0.56)	28.69 (5.18)	69 (38, 104)	40.0
Postpartum^b	73	n.a.	27.94 (5.83)	35 (22, 55)	68.5

IQR, Interquartile range

^{a} Number of samples.

^{b} All postpartum samples taken within 5 d of birth.

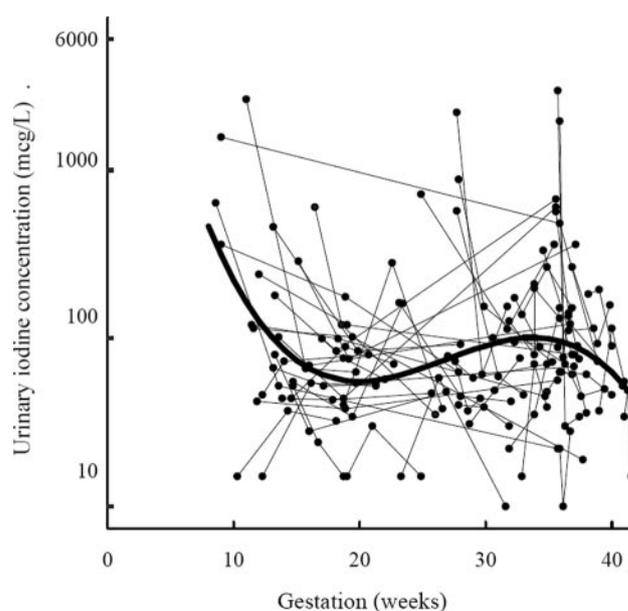gestation was nonlinear, however ($P < 0.001$) (Table 1 and Fig. 1). The decline was most marked before wk 22 of gestation; during that interval, the average rate of change was -4.20 μg/liter (95% confidence interval -6.37, -2.03 μg/liter) per week of gestation, and median UIC was estimated to fall below the reference value for the nonpregnant population of 84 μg/liter after 15.4 wk. This was followed by a modest increase of 0.88 μg/liter·wk (95% confidence interval -2.60, 4.35 μg/liter·wk) between wk 22 and 34 and a subsequent decline at an average rate of change of -5.07 μg/liter·wk (95% confidence interval -10.47, 0.34 μg/liter·wk) thereafter to term.

Whereas the prevalence of samples with UIC less than 50 μg/liter in the reference population (of school-age children) was 20%, 29.2% (200 of 686) of the samples from the pregnant women in this study were within that range, and 36.9% (159 of 431) of the pregnant women provided at least one sample with UIC less than 50 μg/liter. The proportion of women with UIC less than 50 μg/liter increased ($P = 0.038$) with advancing pregnancy (Fig. 2). Additionally, 68.5% (50 of 73) of the postpartum samples taken within 5 d of birth were less than 50 μg/liter.

Summary data on the age of the mother at the time of the first UIC measurement are shown in Table 1. Once account was taken of gestation (by including terms for gestation in the regression models), maternal age was not a significant predictor of median UIC ($P = 0.69$) or the proportion with UIC less than 50 μg/liter ($P = 0.91$), and adjusting for it had minor or negligible impact on the coefficient estimates for gestation.

FIG. 2. Percentage of subjects with UIC less than 50 μg/liter. The *columns* represent the percentages. The *line* represents predicted values from the regression of the logarithm of the proportion of women with UIC less than 50 μg/liter on gestational age.

FIG. 3. Repeated measurements of UIC. *Lines* connect *points* representing measurements made on the same individuals for women (n = 56) with three measurements. The *heavier line* represents predicted values from the regression of mean UIC on gestational age for those women.

Figure 3 shows the repeated UIC measurements from women who provided three serial samples. The predicted values are from the regression of mean UIC on gestation. The nonlinear shape of this relationship was modeled by including the square of gestation and the cube of gestation as covariates in the regression (a cubic polynomial in gestation), and the UIC measurements were log transformed to reduce the influence of extremely large values in the right-skewed distribution of UIC.

Discussion

Our data suggest that use of the standard reference criteria for assessment of population iodine nutrition based on the median UIC of school-aged children is inappropriate for assessment of the adequacy of iodine nutrition during pregnancy. Thus, despite the well-documented existence of iodine deficiency in Tasmania based on childhood UIC measures, the current study shows that the median UIC during the first trimester of pregnancy would be misclassified as borderline adequate based on the conventional WHO reference criteria. Increased ioduria during early pregnancy, resulting from increased GFR is likely to be the explanation for the potential overestimation of iodine nutrition. This has the capacity to conceal the degree of iodine deficiency, which became fully evident in these study patients only in the latter stages of pregnancy.

Whereas more recent publications have proposed specific UIC ranges for use in pregnancy, our data indicate that gestation-appropriate reference ranges for UIC in pregnancy are required. These could be determined using data from iodine sufficient communities, preferably after iodine sufficiency is validated in nonpregnant women of reproductive age. Moreover, confirmation of adequate maternal iodine nutrition by exclusion of pregnancies associated with neonatal and maternal goiter, in conjunction with evaluation of childhood neurocognitive function would be appropriate.

However, in the absence of clearly defined reference intervals for iodine excretion in pregnancy, studies from populations with both adequate iodine nutrition and iodine deficiency provide insight into changes expected in normal pregnancy. The most comprehensive population data derive from the National Health and Nutrition Studies (NHANES) in the United States (15, 16) (Table 2). The NHANES studies were undertaken between 1971 and 2002 and show that in comparison with the nonpregnant

female population of reproductive age, median urine iodine excretion is increased in pregnancy. This is observed both in NHANES I in which median UIC was 327 µg/liter during pregnancy, compared with 293 µg/liter in the nonpregnant female population, and in the NHANES III in which median UIC was 141 µg/liter in pregnancy, compared with 127 µg/liter in the nonpregnant female population. The percentages of pregnant women with UIC less than 50 µg/liter were less than 1 and 6.9% in the two studies, respectively, which is lower than the 4 and 15.3%, respectively, of the nonpregnant females of reproductive age studied. Similarly urinary iodine to creatinine ratios demonstrate an increase in ioduria for pregnant compared with nonpregnant women.

More recently NHANES 2001–2002 (16) showed that in pregnancy the median UIC was 172.6 µg/liter, with 7.3% of women less than 50 µg/liter. This is again higher than nonpregnant females of child-bearing age who exhibited a median UIC of 132 µg/liter with 16.8% less than 50 µg/liter. Similarly, when comparing the urine iodine-creatinine ratios, there was an increased ratio in the pregnant state, compared with nonpregnant women. Again, it is evident that in the iodine-sufficient U.S. population, UIC in pregnancy is elevated relative to that found in nonpregnant women, and thus, the proportion of individuals with iodine excretion values less than 50 µg/liter is lower during pregnancy than in the background nonpregnant female population; in absolute terms affecting less than 10% of the pregnant population. The median pregnancy UIC is, however, lower than the median childhood UIC, which is the standard reference for overall population iodine nutrition used by the WHO.

Studies in populations with mild iodine deficiency from communities in Switzerland (17), the United Kingdom (18, 19), and Hong Kong (20), which provide gestation-specific data, also show an overall increase in ioduria in pregnancy, compared with nonpregnant women of reproductive age (Table 3). However, stratification of the data by gestation show conflicting changes; the Swiss and United Kingdom studies show a decrease with advancing gestation as found in our study population: the data from Hong Kong reveal an increasing level of ioduria with advancing gestation. The explanation for these differences is unclear, but ethnic variation in diet structure or degree of overall iodine deficiency may play a role. In all of these studies, however, the median UIC for pregnancy was higher than the nonpregnant female control population.

Another Australian study by Gunton *et al.* (21) examined

TABLE 2. Published data on UIC in pregnancy from iodine-replete populations

		Nonpregnant women	Pregnant women	Children younger than 12 yr	Total population
NHANES I 1971–1974, USA (15)	Median UIC (µg/liter)	293	327	421	320
	Percent less than 50 µg/liter	4.0	1.0		2.6
	Iodine to creatinine ratio (µg/g)	284.1	373.0		287.3
NHANES III 1988–1994, USA (15)	Median UIC (µg/liter)	127	141	237	145
	Percent less than 50 µg/liter	15.3	6.9		11.7
	Iodine to creatinine ratio (µg/g)	111.9	132.2		113.1
NHANES 2001–2002, USA (16)	Median UIC (µg/liter)	132	172.6	221	167.8
	Percent less than 50 µg/liter	16.8	7.3	7.0	11.1
	Iodine to creatinine ratio (µg/g)	126.9	166.2		128.6

TABLE 3. Published data on UIC in pregnancy from areas of mild iodine deficiency (median population UIC 50–99 μg/liter)

	Median UIC (μg/liter)			
Author and country of origin	Nonpregnant women	First trimester	Second trimester	Third trimester
Brander et al. (17), Switzerland	91 (91)[a]	267 (236)[a]	206 (213)[a]	172 (183)[a]
Smyth (18, 19), United Kingdom	70[b]	135[b]	124[b]	122[b]
	73[c]		170[c]	147[c]
Kung et al. (20), Hong Kong	97.7[d]	106.6[d]	115.5[d]	124.4[d]
Gunton et al. (21), Australia	64[e] (108)[f]		104[g] (159)[f]	

[a] Data were also provided as urine iodine to creatinine ratio (micrograms per gram creatinine). Control population was healthy, nonpregnant women from the same regions of Switzerland as study participants.

[b] Data were from Ireland. Nonpregnant control population was premenopausal women.

[c] Data were from Cardiff, Wales. Controls were nonpregnant, not specified as women of reproductive age.

[d] Urinary iodine units were converted from micromoles per liter to micrograms per liter. Control population was age-matched nonpregnant healthy women.

[e] Nonpregnant women samples were taken from healthy nonpregnant volunteers but not specified as females of reproductive age.

[f] Data were also provided as urine iodine-creatinine ratio (micrograms per gram creatinine).

[g] Gestation of pregnancy samples was not specified.

variations in UIC during pregnancy and 3 months postpartum, comparing these results with those from a nonpregnant reference population of adults. Whereas the pregnancy samples were sourced from a high-risk rather than routine obstetric clinic and the nonpregnant samples derived from patients attending a diabetes clinic or other healthy volunteers, the study produced comparable findings with those described in our current report (Table 3).

Therefore, based on available epidemiological studies relating to UIC in pregnancy from populations that are both iodine sufficient as well as mildly iodine deficient, it should be expected that median UIC will be higher in pregnant than the nonpregnant female population. Correspondingly, the proportion of women with UIC less than 50 μg/liter should be less in the pregnant population than the nonpregnant female population. Failure of UIC to rise in pregnancy relative to the nonpregnant median may therefore represent a subtle manifestation of iodine deficiency, unmasked by pregnancy.

In each of these studies (including the borderline iodine populations from Switzerland, the United Kingdom, and Hong Kong, and iodine replete NHANES populations from the United States), the median UIC in pregnancy is higher than the median UIC for nonpregnant women of reproductive age. It should be noted, however, that in the NHANES data, the median UIC in pregnancy is lower than that of school-aged children, which is the value taken by the WHO as representative of population iodine nutrition. The school-age median UICs for the corresponding periods in the United Kingdom, Swiss, Hong Kong, or Gunton papers are not provided.

Our study data also show a lower overall median UIC in pregnancy of 75 μg/liter (compared with the reference childhood median of 84 μg/liter), with 29.2% of samples in the iodine-deficient range and 36.9% of pregnant women returning at least one sample with UIC less than 50 μg/liter. When analyzed by gestation, however, the median maternal UIC was initially higher than in the control childhood population. It subsequently declined at an average rate of 0.44 μg/liter per week of gestation, although more quickly in the earlier stages. By the 16th week, the

median pregnancy UIC had fallen below the control childhood population median UIC.

The low median UIC in this study and the decreasing level with advancing gestation, appear to represent depletion of total body iodine stores due to fetoplacental use, increased GFR-related losses, and inadequate dietary compensation. Thus, multiple factors interact in pregnancy to aggravate imbalanced iodine homeostasis when iodine nutrition is inadequate.

Socioeconomic status and educational level of patients were not recorded and could potentially have influenced time of initial presentation for clinic review. The patients enrolled in the study, however, were representative of the majority of the general population using the public health system in Tasmania in terms of socioeconomic status, educational level, and ethnicity. Furthermore, another study of the Tasmanian population has shown no association between socioeconomic status and UIC (22). Alterations in dietary habits during pregnancy are also unlikely to fully explain the lower median pregnancy UIC observed in our study (22).

Iodine-based antiseptic exposure during and after delivery was not recorded in the study but if significant would be expected to raise the postpartum UIC values, rather than lower them. The postpartum UIC median measured in this study was 35 μg/liter; the lower concentration would be consistent with sequestration of iodine in breast milk.

Thus, because UIC is normally used as the surrogate indicator of dietary iodine intake, in borderline-deficient populations, higher UIC in early pregnancy relative to nonpregnant women of reproductive age may be misinterpreted as indicative of more adequate iodine nutrition than is the case in reality. Comparison of pregnancy UICs to school age UICs is also misleading because there appears to be such a significant difference between levels, as seen in the NHANES data. Unless gestation-specific normative reference ranges are used for assessment of the pregnant population, erroneous conclusions about iodine nutrition in pregnancy may be reached. Furthermore, failure to achieve a sustained elevation in UIC in pregnancy relative to nonpregnant female controls appears indicative of significant compromise to

total body iodine stores with consequent fetomaternal iodine depletion.

The importance of iodine nutrition in pregnancy and lactation is ultimately to prevent any detrimental effect to both the mother and child. Further research to determine whether the low UIC in this study population has caused altered thyroid function or size in the mothers or children, or more significantly, any neurocognitive or behavioral differences in the children is required.

Conclusion

Reference intervals for UIC specific to each trimester of pregnancy need to be established. This would permit accurate assessment of the dietary adequacy of pregnant populations residing in regions of marginal iodine sufficiency. Based on available epidemiological studies from populations that are both mildly iodine deficient as well as iodine sufficient, it should be expected that: 1) median UIC will be at least as high in pregnancy as in nonpregnant women of reproductive age, 2) the proportion of pregnant women with UIC less than 50 μg/liter should be less than 10%, and 3) median UIC should not decline with advancing gestation.

Acknowledgments

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