

Short Communication

Amniotic fluid iodine concentrations do not vary in pregnant women with varying iodine intake

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Iodine deficiency is an important clinical and public health problem. Its prevention begins with an adequate intake of iodine during pregnancy. International agencies recommend at least 200 µg iodine per d for pregnant women. We assessed whether iodine concentrations in the amniotic fluid of healthy pregnant women are independent of iodine intake. This cross-sectional, non-interventional study included 365 consecutive women who underwent amniocentesis to determine the fetal karyotype. The amniocentesis was performed with abdominal antisepsis using chlorhexidine. The iodine concentration was measured in urine and amniotic fluid. The study variables were the intake of iodized salt and multivitamin supplements or the prescription of a KI supplement. The mean level of urinary iodine was 139.0 (SD 94.5) µg/l and of amniotic fluid 15.81 (SD 7.09) µg/l. The women who consumed iodized salt and those who took a KI supplement had significantly higher levels of urinary iodine than those who did not ($P=0.01$ and $P=0.004$, respectively). The urinary iodine levels were not significantly different in the women who took a multivitamin supplement compared with those who did not take this supplement, independently of iodine concentration or multivitamin supplement. The concentrations of iodine in the amniotic fluid were similar, independent of the dietary iodine intake. Urine and amniotic fluid iodine concentrations were weakly correlated, although the amniotic fluid values were no higher in those women taking a KI supplement. KI prescription at recommended doses increases the iodine levels in the mother without influencing the iodine levels in the amniotic fluid.

Iodine: Amniotic fluid: Pregnancy

Although marked physiological differences exist between the maternal and fetal thyroids, both systems interact through the placenta and the amniotic fluid, modulating the transfer of iodine and small but biologically important amounts of thyroid hormones from the mother to the fetus⁽¹⁾. Prior to the end of the first trimester, when the fetal thyroid gland and the pituitary-thyroid axis become functional, the thyroid hormones required by the fetus are all obtained from the maternal circulation⁽²⁾.

The volume and content of amniotic fluid is the result of a balance between the urine and the fetal pulmonary fluids, the amount of fluid that is reabsorbed or swallowed by the fetus⁽³⁾ and transfer of water and solutes across the fetal membranes.

Animal studies have demonstrated a rapid exchange between the mother and fetus and between the fetus and the amniotic fluid, suggesting that the amniotic fluid could act as an iodine

reservoir for the fetus⁽⁴⁾. Etling *et al.*⁽⁵⁾ found high levels of iodine in the amniotic fluid of women who had undergone urographic examinations with iodized contrast materials or who had been exposed to iodized agents vaginally. However, few studies have investigated the iodine concentration in the amniotic fluid of human subjects and these only examined the influence of the overload of high iodine concentrations. Nevertheless, the effect of physiological amounts of iodine intake in healthy pregnant women has not been studied sufficiently.

The aim of the present study was to determine the iodine concentrations in urine and amniotic fluid during the 14th–22nd weeks of pregnancy in a series of pregnant women and compare the results with those of previous observations suggesting that iodine concentrations in amniotic fluid are influenced by the amount of iodine intake⁽⁵⁾.

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Materials and methods

The present study, conducted during the first half of 2006, included 365 Caucasian women seen consecutively at the Foetal Medicine Office of the Department of Obstetrics and Gynaecology of Carlos Haya University Hospital, Malaga, Spain. The sample size was calculated from the urinary iodine levels in pregnant women in previous studies by us⁽⁶⁾, giving a final sample error of <1%.

The women were referred to this prenatal diagnosis office from both primary care and the High-Risk Obstetrics Office to undergo genetic amniocentesis to determine the fetal karyotype. The amniocentesis was undertaken during gestation week 16.1 (SD 1.4) (range 14.0–22.2). Those women with an abnormal fetal karyotype were excluded from the study. All the women gave informed consent to the study, which was approved by the Ethics and Clinical Research Committee of Carlos Haya University Hospital.

The variables, collected from the clinical and obstetrical history, included age of the mother, gestational age, intake of iodized salt, multivitamin supplements and KI supplements. No woman took herbal products, had used iodized disinfectants recently (iodized povidone) or had undergone medical examinations involving radiological contrast material. The women had a normal renal and thyroid function. Gestational age was calculated as the time between the first day of the last menstrual period and the date on which the measurement took place.

Amniocentesis was performed with the usual technique in our hospital, with abdominal antisepsis using chlorhexidine (in no case was iodized povidone used) and ultrasound-guided amniotic cavity puncture, extracting 20 ml amniotic fluid. During the office visit but prior to the amniocentesis, all the women provided a urine sample. The iodine concentration in the urine was measured by the modified Benotti and Benotti technique⁽⁷⁾ and in the amniotic fluid with a modification of this method: amniotic fluid samples (0.1 ml) and standards ranging from 0 to 40 µg/l (0.1 ml) were digested with 0.6 ml chloric acid solution at 110°C for 90 min. After heating, 0.4 ml water, a solution of arsenious acid (0.2 ml)

and ceric ammonium sulphate solution (0.2 ml) were added to each tube. The absorbance of each sample was measured 20 min later at 420 nm with a spectrophotometer. In urine samples the intra- and inter-assay CV was 3.2% and 3.5%, respectively, and in the amniotic fluid samples the intra- and inter-assay CV was 11.9% and 14.8%, respectively.

The continuous variables are shown as means and standard deviations and the discrete variables as percentages. Comparisons between means were made with the Mann–Whitney test. Values were considered to be statistically significant when $P \leq 0.05$. The Pearson correlation coefficient was calculated to estimate the linear correlation between iodine in urine and amniotic fluid.

Results

The mean age of the women was 37.8 (SD 3.1) years (range 25.1–45.0). The mean urinary iodine concentration was 139.0 (SD 94.5) µg/l (range 10.6–546.2), the median concentration being 117.6 µg/l. Of the women, 40% had urinary iodine concentrations below 100 µg/l. The mean iodine concentration in the amniotic fluid was 15.81 (SD 7.09) µg/l (range 2.50–42.50). The iodine concentration in the urine was ten-fold that of the concentration in the amniotic fluid (iodine in urine/iodine in amniotic fluid: 10.66 (SD 9.13); range 0.16–79.08). The CV were 68% for iodine in urine and 44% for iodine in the amniotic fluid, indicating a greater variability in the concentration of iodine in the urine than in the amniotic fluid. A weak but significant linear correlation was found between the iodine concentrations in urine and amniotic fluid (r 0.11, $P=0.03$).

The women who consumed iodized salt or those who had a KI supplement had significantly higher urinary iodine concentrations than those who did not ($P=0.01$ and $P=0.004$, respectively) (Table 1). As expected, the urinary iodine concentrations were significantly higher in those women who took iodized salt and a KI supplement ($P<0.001$) (Table 1). A total of ninety-eight women took various multivitamin supplements. In twenty of those women, the

Table 1. Levels of iodine in urine iodine, in amniotic fluid and iodine in urine/iodine in amniotic fluid according to the intake of multivitamin supplements, iodized salt and potassium iodine**

(Means and standard deviations)

		<i>n</i>	%	Urinary iodine (µg/l)		Iodine in amniotic fluid (µg/l)		Iodine in urine/iodine in amniotic fluid	
				Mean	SD	Mean	SD	Mean	SD
Multivitamin supplements	No	267	73.2	132.9	95.8	15.64	7.04	10.11	8.36
	Yes	98	26.8	145.4	90.6	16.20	6.62	10.62	8.15
Multivitamin supplements with iodine	No	345	94.5	135.8	94.4	15.78	6.86	10.23	8.35
	Yes	20	5.5	145.9	93.7	17.08	8.29	10.41	7.46
Iodized salt	No	220	60.3	127.1	85.7	15.50	7.28	9.86	8.03
	Yes	145	39.7	154.4*	105.7	16.05	6.78	11.55§	9.06
KI	No	290	79.5	128.5	81.7	15.71	7.05	9.80	7.88
	Yes	75	20.5	174.8†	127.4	15.80	6.88	12.88*	9.79
Iodized salt +KI	No	189¶	51.8	122.6	80.8	15.61	7.23	9.49	8.11
	Yes	44	12.1	195.4‡	136.5	16.59	6.30	14.00*	11.08

* $P=0.01$; † $P=0.004$; ‡ $P<0.001$; § $P=0.008$.

|| 100–200 µg/d.

¶ Women who only took one of the two (iodized salt or KI) are not included in this group.

** For details of subjects and procedures, see Materials and methods.

multivitamin supplements contained amounts of iodine ranging from 20 to 200 µg. The urinary iodine concentrations in the women who took multivitamin supplements were not significantly different to those in the other women, independent of the iodine concentration in the multivitamin supplement (Table 1). The iodine concentrations in the amniotic fluid were also independent of the dietary intake of iodine (Table 1).

Finally, the ratio of iodine in urine:iodine in amniotic fluid followed a similar pattern to the iodine concentrations in urine, although the intake of iodized salt failed to divide the study population into two significantly distinct sub-samples ($P=0.08$) (Table 1).

Discussion

The most important finding in the present study was that the concentration of iodine in the amniotic fluid during the 14th–22nd weeks of pregnancy was not influenced by the amount of iodine consumed in the diet or by the doses of KI supplements.

Iodine deficiency is one of the most important public health problems in the world⁽⁸⁾ and in Europe⁽⁹⁾, including Spain⁽¹⁰⁾. The median concentration of urinary iodine in the pregnant women in this study was 117.6 µg/l, with 40% of them having urinary iodine concentrations below 100 µg/l. Previous studies by our group have shown that the dietary intake of iodine by pregnant women from Malaga during 2002 and 2003 was deficient, with a median urinary iodine concentration of about 90 µg/l⁽⁶⁾.

Pregnancy results in increased iodine requirements. It is therefore necessary to supplement iodine intake with iodized salt or a preparation containing a convenient amount of KI, especially in those populations where iodine intake is low⁽¹¹⁾. Until 2004, supplementary iodine was administered in Spain in the form of multivitamin preparations that either contained an insufficient amount of iodine or, in order to achieve an adequate intake, required the additional consumption of unnecessarily high amounts of many other compounds, such as vitamin A, which has potential toxic effects during pregnancy⁽¹²⁾. In 2004 a KI supplement was placed on the market, enabling individualized prescription of the recommended amount of iodine. Since then, the practice of prescribing a 200 µg supplement of iodine and potassium has become general. This has resulted in the finding in the present study of a slight rise in the urinary iodine concentrations in pregnant women as compared with the previous study⁽⁶⁾. Notwithstanding this, only 21.6% of the women in the current study took this supplement.

As expected, the urinary iodine concentrations in the pregnant women were clearly dependent on the dietary intake of iodine. The concentrations were higher in the women who took a KI supplement and significantly higher, too, in those who consumed iodized salt. Those women who had taken multivitamin supplements, however, showed no change in their urinary iodine concentrations, even though many of these preparations contain variable amounts of iodine. These results support the recommendation that, if we wish to achieve the objectives of an adequate iodine intake during pregnancy, an active prescription of an iodine preparation that can be administered independently is preferable.

The results of the present study are rather unexpected, as the few studies examining the iodine concentration in amniotic

fluid found that it was influenced by environmental iodine. Animal studies using a double tracer with I^{131} and I^{125} showed a rapid exchange between the mother and the fetus and between the fetus and the amniotic fluid, suggesting that amniotic fluid could act as an iodine reservoir for the fetus⁽⁴⁾. Etling *et al.*⁽⁵⁾ examined 218 samples of amniotic fluid collected at varying times during pregnancy and found high levels of iodine in women who had undergone urographic studies with iodized contrast material or who had been exposed to iodized agents intravaginally. Iodized agents used as disinfectants or as contrast agents are known to have an amount of iodine that may even be thousands of times greater than that obtained from the diet⁽¹³⁾. Vaginal douching with povidone-iodine during pregnancy results in maternal iodine overload and increases the iodine content of amniotic fluid⁽¹⁴⁾. However, none of these studies examined the influence of iodine from the diet or from iodine supplements.

The iodine required for the functioning of the fetal thyroid gland comes from the circulating iodine in the mother and the deiodination of iodothyronines in the placenta^(1,11,15). We found a weak linear correlation between the iodine in the urine and that in the amniotic fluid. However, this appears to be just a statistical association rather than a relevant biological association, as the iodine concentration in the amniotic fluid was not associated with dietary variation of iodine, as occurs in the urine of the mother. On the other hand, iodine levels in the amniotic fluid are relatively constant between women and the iodine concentration was some ten times less in the amniotic fluid than in the maternal urine. This finding could suggest that the mother has a regulatory mechanism for maintaining amniotic fluid levels of iodine⁽¹⁶⁾, irrespective of dietary levels.

In conclusion, the present study shows that the concentration of iodine in the amniotic fluid of pregnant women during the 14th–22nd weeks of pregnancy is not influenced by the amount of dietary iodine. This may have certain implications in clinical practice. A reasonably generalized consensus exists about the convenience of prescribing at least 200 µg of KI for all pregnant women in populations with a mild iodine deficiency, as occurs in most European countries⁽¹⁷⁾. Nevertheless, before prescribing, many clinicians still require an individualized approach to the iodine deficiency, which is not very realistic, or type A evidence of its benefit in older children, about which few studies have been undertaken, or else clinical guarantees that are difficult to satisfy about the iatrogenic potential that a supplementary iodine dose has in some women. The results of this study show that increasing the amount of dietary iodine raises the iodine pool in the mother with no increase of iodine in the amniotic fluid. This will help to achieve adequate levels of thyroxine in the mother and, consequently, adequate transfer of thyroxine to the fetus during the early period of development⁽²⁾, at the same time avoiding the risk of an excessive increase of iodine in the fetal economy.

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References

- Burrow GN, Fisher DA & Larsen PR (1994) Maternal and foetal thyroid function. *N Engl J Med* **331**, 1072–1078.
- Morreale de Escobar G, Obregón MJ & Escobar del Rey F (2004) Role of thyroid hormone during early brain development. *Eur J Endocrinol* **151**, U25–U37.
- Tomoda S, Brace RA & Longo LD (1985) Amniotic fluid volume and foetal swallowing rate in sheep. *Am J Physiol* **249**, R133–R138.
- Book SA, Wolf HG, Parker HR & Bustad LK (1974) The exchange of radioiodine in pregnant and foetal sheep. *Health Physics* **26**, 533–539.
- Etling N & Vielh JP (1979) Iodine overloads in amniotic fluids. *Nouv Presse Med* **8**, 1647–1648.
- Dominguez I, Reviriego S, Rojo-Martinez G, *et al.* (2004) Iodine deficiency and thyroid function in healthy pregnant women. *Med Clin (Barc)* **122**, 449–453.
- Benotti J & Benotti N (1963) Protein bound iodine, total iodine and protein and butanol extractable iodine by partial automation. *Clin Chem* **9**, 408–416.
- World Health Organization (2001) *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination*. Geneva: Department of Nutrition, WHO.
- Delange F (2002) Iodine deficiency in Europe and its consequences: an update. *Eur J Nucl Med Mol Imaging* **29**, Suppl. 2, S404–S416.
- Foz M (2004) Iodine deficiency in Spain: an unsolved problem. *Med Clin (Barc)* **122**, 459–460.
- Glinoe D (1997) The regulation of thyroid function in pregnancy; pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* **18**, 404–433.
- International Vitamin A Consultative Group (1998) *Safe Doses of Vitamin A During Pregnancy and Lactation*. IVACG Statement. Washington, DC: International Vitamin A Consultative Group.
- Morreale de Escobar G & Escobar del Rey F (2000) El yodo durante la gestación, lactancia y primera infancia. Cantidades mínimas y máximas: de microgramos a gramos (Iodine during pregnancy, infancy and early childhood. Minimum and maximum quantities: micrograms of a gram). *An Esp Pediatr* **53**, 1–5.
- Mahillon I, Peers W, Bourdoux P, Ermans AM & Delange F (1989) Effect of vaginal douching with povidone-iodine during early pregnancy on the iodine supply to mother and foetus. *Biol Neonate* **56**, 210–217.
- Raiti S, Holzman GB, Scott RL & Blizzard RM (1967) Evidence for the placental transfer of tri-iodothyronine in human beings. *N Engl J Med* **277**, 456–459.
- Schroder-van der Elst JP, van der Heide D, Kastelijn J, Rousset B & Obregon MJ (2001) The expression of the sodium/iodide symporter is up-regulated in the thyroid of fetuses of iodine-deficient rats. *Endocrinology* **142**, 3736–3741.
- Delange F, Dunn JT & Glinoe D (1993) Specific recommendation on iodine nutrition for mothers and infants in Europe. In *Iodine Deficiency in Europe*, pp. 478–479 [F Delange, JT Dunn and D Glinoe, editors]. New York: Plenum Press.