

CLINICAL STUDY

Inadequate iodine nutrition of pregnant women from Extremadura (Spain)

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Abstract

Objective: To evaluate the iodine nutrition of the pregnant women of the Spanish Autonomous Community Extremadura. There are ~10 000 births per year in Extremadura, which historically contains areas with endemic goiter (Las Hurdes).

Design: Population study in which a representative sample of pregnant women of the general population was analyzed, along with another sample of pregnant women from traditionally goitrogenic areas. With the collaboration of selected health centers, an additional sample of blood and urine was obtained within the primary health care pregnancy-monitoring program; these samples were sent to a single central laboratory.

Methods: Biochemistry: determination of iodine and creatinine in urine, and serum concentrations of thyroxine, free thyroxine, tri-iodothyronine, TSH, thyroglobulin, and two anti-thyroid antibodies. Each parameter was measured by means of a single specific RIA.

Results: Changes between the first trimester and later stages of pregnancy of all biochemical variables studied corresponded with those described for other European areas with a comparable iodine nutrition. Using the urinary iodine concentration value as an indicator of iodine ingestion, it was found that in the first trimester of pregnancy six out of ten women from Extremadura ingested less than the currently recommended amount (250 µg I/day), and approximately three out of ten of these women ingested less than half of this amount.

Conclusions: It is imperative to implement in all Extremadura the generalized and controlled use of complements that contain 200–250 µg I/day throughout pregnancy and, if possible, before.

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Introduction

At a meeting of experts held on January 24 and 25, 2005, at the Headquarters of the World Health Organization in Geneva, the increasing evidence was evaluated that suggested that previous recommendations on iodine nutrition during pregnancy and breastfeeding should be reviewed (1). In this meeting, the conclusion was reached that women should ingest at least 250 µg I/day during pregnancy and breastfeeding, to prevent possible defects in fetal brain development. Present-day reality shows that we are far from accomplishing this (2), not only in Western Europe (3), but also probably in North America (4).

The present concern about insufficient iodine nutrition during pregnancy and breastfeeding is related to the increasing evidence that an insufficient iodine intake negatively and irreversibly affects the psychoneurointellectual development of the fetus (5–10), especially when there is a deficiency during the first trimester.

The present report assembles the results of an epidemiological study carried out in the Spanish

Autonomous Community of Extremadura, aimed at evaluating the state of iodine nutrition of pregnant women, with special attention to their condition during the first trimester.

Iodine deficiency in the area of Las Hurdes Altas (El Gasco, Fragosa, Martilandrán) of Extremadura was so frequent and severe that after the visit of the King of Spain, Alfonso XIII, several doctors were sent to live in the most affected villages. A successful iodine prophylaxis in the schoolchildren and in pregnant women was initiated, unfortunately interrupted with the onset of the Spanish civil war. Epidemiological studies in this area were again undertaken in the late sixties with initial results from two decades being published in 1981 (11). The prevalence of goiter in schoolchildren was initially very high, with an overall frequency of 86%; urinary iodine (UI) was <20 µg/l in 71% of the schoolchildren. Circulating thyroxine (T₄) was less than 78 nmol/l in 46% of them. Their somatic development was retarded and so was their mental development (12–14). Special prophylactic measures were undertaken in this area, and by 1993 (6) only 11%

of the schoolchildren had small goiters, the mean UI concentration was $128 \pm 45 \mu\text{g/l}$, with normal circulating T_4 ($144 \pm 45 \text{ nmol/l}$), and normal somatic growth. Because of the special prophylactic measures sustained over the decades in these villages and not enforced in the rest of Extremadura, Las Hurdes Altas was specifically left out of the present study.

In the eighties, the Health Plan for Extremadura included the distribution of iodized salt for school meals, but there has been no follow-up of its continuing implementation. Its availability in supermarkets is minimal and even less in village stores.

Subjects and methods

Study population

The study was designed as a population-based study, to obtain results that can be extrapolated to all pregnant women of Extremadura. Data of the Spanish National Statistics Institute for 2001 indicate a population of 1 058 503 inhabitants, 533 554 of which were women, and 9903 births.

Given the historical characteristics of the population of Extremadura, with areas where endemic goiter was found in the past, the sample was at the start divided into two groups: Type 1, the general population; and Type 2, those of potentially special interest because they might represent inhabitants of areas of iodine deficiency (Fig. 1).

In Type 1 areas, a stratified and multi-stage sampling strategy by Health Districts was designed. In the Type 2 areas, which are sparsely populated, all women who were pregnant in 2001 were included in the study (Table 1).

Blood and spot urine samples and data of the pregnant women were collected by the health teams of the health districts selected for the study between beginning of February 2001 and mid-March 2002. This was incorporated into the activities of routine pregnancy monitoring. Activities of the health teams included recruiting pregnant women, giving information about their participation in the study, obtaining informed consent and serum and spot urine samples, freezing the samples, and subsequently shipping them to a single laboratory. Informed consent and protocol were approved by the local ethics committee. To have a normal pregnancy was the inclusion criterion for pregnant women who went for a checkup to the health center in their first trimester. Women with previous history of obstetrical complications (i.e., miscarriages, malformations, prematurity, etc.) or pathologies (i.e., diabetes, hypo- or hyperthyroidism, hypertension, etc.) were excluded, and referred immediately to the gynecologist for special care.

During their first visit, at a mean gestational age (\pm s.d.) of 10.8 ± 5.8 weeks, and after obtaining blood and urine samples, pregnant women were informed that it was advisable to take two tablets of Calcinatal daily; Calcinatal is a vitamin/mineral complex that contains $100 \mu\text{g}$ iodide per tablet. The study was done in 2001, several years before the approval of Yoduk (Recordati, Madrid, Spain) as an iodine supplement for pregnant and nursing women. It was not verified whether the women were actually taking the recommended supplement. Only in $\sim 50\%$ of the pregnant women studied during their first trimester were the biochemical analyses repeated in later stages of the pregnancy, at a mean \pm s.d. of 21.5 ± 5.8 weeks.

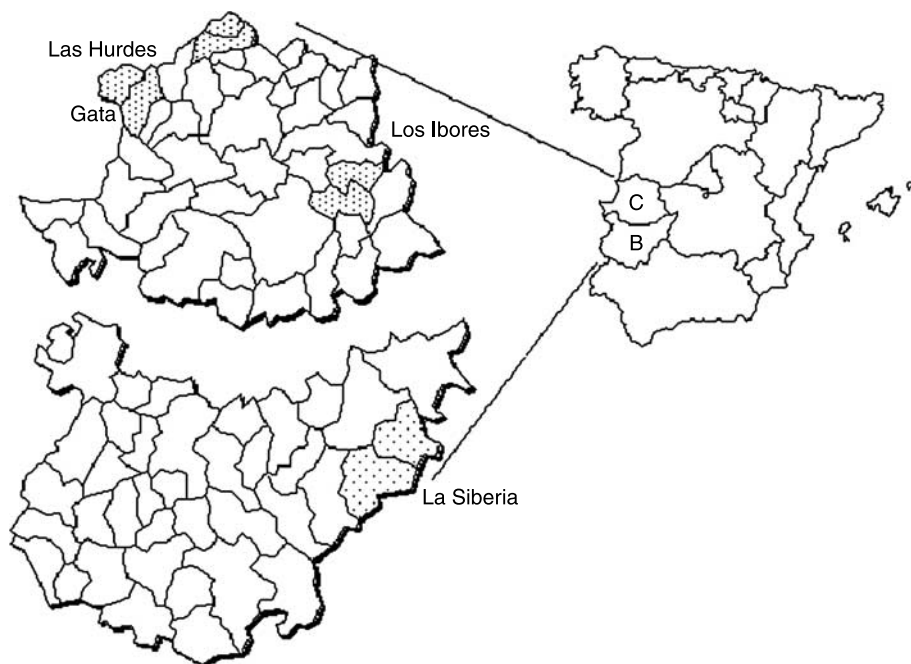


Figure 1 Map of Extremadura, in Spain, composed of two provinces: Cáceres (C) and Badajoz (B). The dotted areas correspond to the Type 2 areas, initially believed to be of special interest.

Table 1 Distribution of Type 1 and 2 pregnant women in Extremadura.

Region	Type	n	Percentage of total
General population	1	735	83.1%
Goitrogenic areas	2	150	16.9%
Total		885	

Sample selection method

To obtain a representative sample, the usual formula of sample size calculation for a single proportion was applied, with a prevalence of 50%, admitting an error E of 10%, and with a confidence level of 95%.

Biochemical methods

Serum and spot urine samples were kept frozen and sent to Laboratory B-16 of the Institute of Biomedical Investigations 'Alberto Sols' in Madrid.

Urine samples were thawed and iodine concentrations were estimated using digestion with chloric acid following the method of Benotti and Benotti (15); creatinine concentrations were determined using picric acid (16).

In serum samples, the following parameters were measured: free T₄ (FT₄), T₄, tri-iodothyronine (T₃), thyrotropic hormone (TSH), thyroglobulin (Tg), and anti-thyroid peroxidase (anti-TPO) and anti-Tg antibodies using the DYNtest RIA reagents from Brahms Diagnostica GmbH (Berlin, Germany); DYNtest FT₄ (SPART);

DYNtest T₄; DYNtest T₃; DYNtest TSH; DYNtest TgS; DYNtest anti-TPO; and DYNtest anti-Tgn.

Reference ranges: 10–25 pmol/l for FT₄; 58–154 nmol/l for T₄; 1.23–3.08 nmol/l for T₃; 0.3–4.0 mU/l for TSH; <70 ng Tg/ml for Tg; <100 U/ml for anti-TPO and anti-Tg antibodies. UI concentrations for pregnant women should be >150 µg I/l (13).

Statistical analysis

For comparison of the averages of the quantitative variables included in this study between women of Types 1 and 2 and between those considered Ab+ and Ab-, during and after the first trimester of pregnancy, Student's *t*-test for independent samples was used. Differences were considered statistically significant when the *P* values were not greater than 0.05. To determine the degree of linear association between FT₄ levels and iodine intake, Pearson's linear correlation coefficient was calculated. The SPSS 13.0.0 program (Chicago, IL, USA) was used for the statistical analysis of the data.

Results

Concentrations of circulating FT₄, T₄, and T₃, obtained in samples of the first trimester, did not show statistically significant differences between Types 1 and 2. UI data did not indicate a greater iodine deficiency in Type 2 samples, which had served as the criterion to divide the samples

Table 2 Biochemical data in the first trimester of pregnancy, at 10.8 ± 5.8 weeks of gestational age.

Variable	n	Mean	± s.d.	± s.e.m.	P
Urinary iodine (µg/l) ^a					
Ab-	761	160	119	4	NS
Ab+	86	156	129	14	
Creatininuria (g/l)					
Ab-	764	0.85	0.38	0.01	NS
Ab+	87	0.86	0.36	0.04	
Iodine/creatinine (µg/g)					
Ab-	759	210	152	6	NS
Ab+	87	208	166	18	
FT ₄ (pmol/l)					
Ab-	768	17.3	3.7	0.1	NS
Ab+	89	17.6	4.6	0.5	
T ₄ (nmol/l)					
Ab-	769	135	33	1	NS
Ab+	90	127	43	5	
T ₃ (nmol/l)					
Ab-	766	2.79	0.78	0.03	NS
Ab+	90	2.87	0.03	0.12	
TSH (mU/l)					
Ab-	769	1.36	0.95	0.03	0.000
Ab+	90	2.31	2.03	0.21	
Tg (ng/ml)					
Ab-	766	8.47	14.78	0.53	NS
Ab+	90	6.68	8.87	0.94	

^aThe median UI value for the antibody-positive women: 123 µg/l with a minimum of 20 µg/l and maximum of 800 µg/l. This corresponds to an insufficient WHO (1) category of I intake.

The median UI value for the antibody-negative women: 125 µg/l with a minimum of 20 µg/l and maximum of 820 µg/l. This corresponds to an insufficient WHO (1) category of I intake.

into two types. Consequently, the results obtained in Types 1 and 2 areas were evaluated together as coming from a single population.

The biochemical data obtained in the first trimester of pregnancy are summarized in Table 2. Data are separated according to negativity or positivity for anti-TPO and/or anti-Tg antibodies; data are considered antibody positive when serum concentrations of one or both antibodies are above 100 U/ml.

We found that ~10% of the pregnant women included in this study had anti-thyroid antibodies. This only had an effect on the levels of circulating TSH, which were somewhat higher in Ab+ women, but not on the other biochemical variables studied.

Figure 2 illustrates differences in UI, creatininuria, and iodine/creatinine ratios between the first trimester and later stages of the pregnancy. In the three panels at the left, the percentage of women having the indicated values of UI, creatininuria, and iodine/creatinine ratios are shown, whereas the panels at the right show the

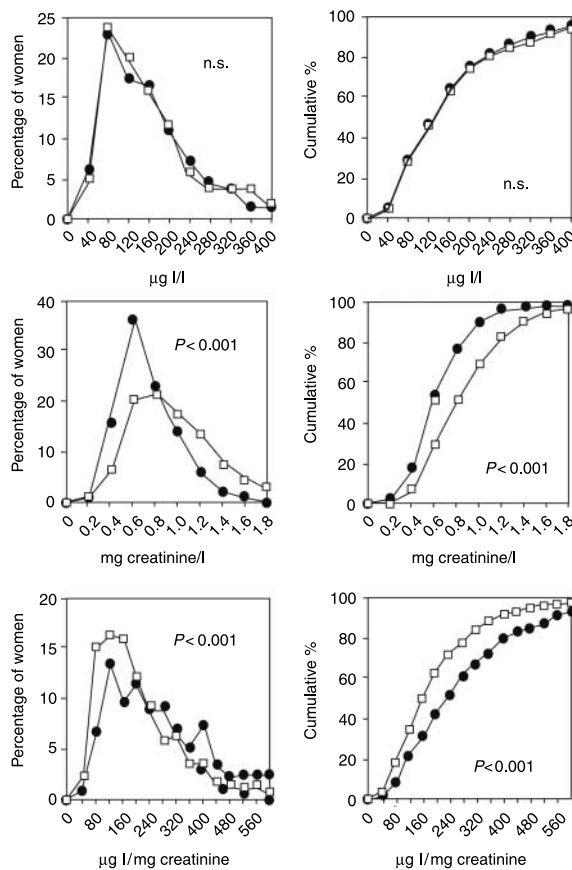


Figure 2 Three panels at the left: percentage (%) of women with data collected in the first trimester (\square , $n=863$, 10.8 ± 5.8 weeks gestational age) and in later stages (\bullet , $n=424$, 21.5 ± 5.8 weeks gestational age) of the pregnancy with the indicated values of urinary iodine concentrations (UI), creatininurias, and iodine/creatinine ratios. Three panels at the right: cumulative percentage of the corresponding panel at the left. NS, not statistically significantly different.

cumulative percentage. The UI values were not statistically significantly different, but creatininurias and iodine/creatinine ratios were. These ratios were higher in samples taken after the first trimester; thus depletion of intrathyroidal iodine stores as pregnancy progressed in the Type 2 groups appeared unlikely.

Figure 3 illustrates the differences in FT_4 , T_4 , T_3 , and TSH between the first trimester and later stages of pregnancy. There are statistically significant differences in FT_4 , T_3 , and TSH, but not in T_4 , during both stages of

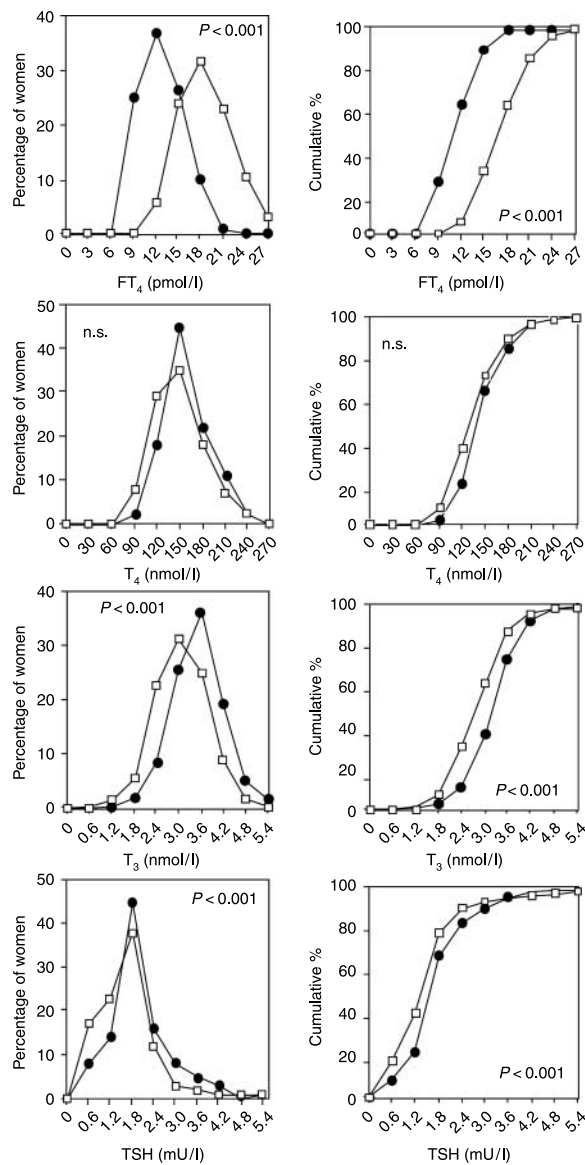


Figure 3 Four panels at the left: percentage (%) of women with data collected in the first trimester (\square , $n=863$, 10.8 ± 5.8 weeks gestational age) and in later stages of the pregnancy (\bullet , $n=424$, 21.5 ± 5.8 weeks gestational age) with the indicated values for circulating FT_4 , T_4 , T_3 , and TSH. Four panels at the right: cumulative percentage of the corresponding panels at the left. NS, not statistically significantly different.

pregnancy. FT₄ decreased after the first trimester, whereas serum concentrations of T₃ and TSH increased.

Of the 424 women for whom data were obtained in the second half of pregnancy (Table 3), there were 4 (0.94%) continuing to have TSH above normal, 2 of them (0.47%) being antibody positive. There were only 2 women out of 863 (0.23%) with low FT₄ at baseline, but no data were available for them later in gestation.

Figure 4 shows the cumulative percentage of pregnant women as a function of their UI concentrations during the first trimester ($n=863$). An UI of 150 µg/l is compatible with the minimum sufficient iodine ingestion during pregnancy (1, 17). Six out of ten pregnant women ingested less than this amount, and almost three out of ten women ingested less than half the necessary minimum amount.

Average FT₄ during the first trimester was 17.3 ± 3.7 pmol/l, significantly less ($P < 0.001$) than the 19.9 ± 4.5 pmol/l of the 120 women of the Autonomous Community of Madrid supplemented with Calcinal, advised to take two tablets daily (6).

Discussion

The results obtained for the pregnant women from Extremadura, both in the first trimester and in later phases of pregnancy, are in agreement with what was described in other studies done in Europe in areas with a similar degree of iodine deficiency (18–23).

Thus, for example, in a series of 984 Caucasian women, it was found that 11.7% were anti-thyroid antibodies positive (18), which is very similar to the value described in the present study. As in our study, their serum TSH was higher than that of antibody-negative pregnant women. Given the higher incidence of obstetric complications in these women, a systematic screening for anti-thyroid antibodies and a more exhaustive monitoring of these pregnancies has been proposed (20–23).

The changes in the different variables illustrated in Figs 3 and 4 between the first trimester and later phases of pregnancy also agree with those observed in other European studies (21). Thus, for example, FT₄ decreases, T₄ does not change, and T₃ and TSH tend to increase. During the first trimester, human chorionic gonadotropin (hCG) plays a very important role in determining maternal circulating thyroid hormone concentrations: although its TSH-like activity is very low compared with that of TSH, the extremely high concentrations reached during the first trimester of pregnancy stimulate thyroid secretion of the iodinated hormones to the point that TSH secretion is inhibited. As a result, maternal circulating concentration of both FT₄ and FT₃ are very high, especially during the first trimester, later decreasing with diminishing hCG stimulation. This increase in FT₄ and FT₃ concentrations requires an increased availability of iodine. When iodine is insufficient, the maternal thyroid responds immediately with auto-regulatory mechanisms, among which are increased synthesis and secretion of T₃

Table 3 Biochemical data after the first trimester of pregnancy, at 21.5 ± 5.8 weeks gestational age.

Variable	<i>n</i>	Mean	± s.d.	± s.e.m.	<i>P</i>
Urinary iodine (µg/l) ^a					
Ab–	362	164	125	7	NS
Ab+	45	178	170	25	
Creatininuria (g/l)					
Ab–	365	0.87	0.37	0.02	NS
Ab+	46	0.87	0.31	0.05	
Iodine/creatinine (µg/g)					
Ab–	362	210	160	8	NS
Ab+	46	234	213	31	
FT ₄ (pmol/l)					
Ab–	368	17.5	3.8	0.2	NS
Ab+	46	16.7	2.7	0.4	
T ₄ (nmol/l)					
Ab–	369	137	33	2	NS
Ab+	46	125	37	6	
T ₃ (nmol/l)					
Ab–	367	2.79	0.78	0.04	NS
Ab+	46	2.64	0.59	0.09	
TSH (mU/l)					
Ab–	369	1.30	0.90	0.05	0.000
Ab+	46	2.35	2.07	0.31	
Tg (ng/ml)					
Ab–	367	8.21	8.62	0.45	NS
Ab+	46	6.70	7.20	1.06	

^aThe median UI value for the antibody-positive women: 160 µg/l with a minimum of 40 µg/l and maximum of 432 µg/l. This corresponds to a barely adequate WHO (1) category of I intake (150–249 µg/l).

The median UI value for the antibody-negative women: 125 µg/l with a minimum of 25 µg/l and maximum of 640 µg/l. This corresponds to an insufficient WHO (1) category of I intake.

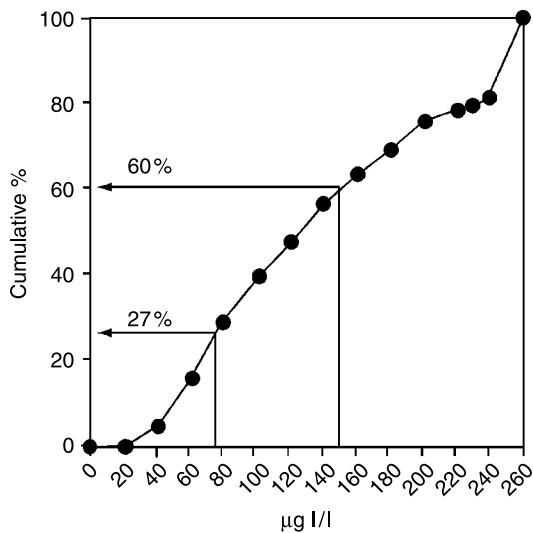


Figure 4 Cumulative percentage of pregnant women as a function of urinary iodine concentrations (UI) during the first trimester ($n=863$, 10.8 ± 5.8 weeks gestational age). The minimum WHO (1) median UI compatible with an adequate iodine ingestion during pregnancy is $150 \mu\text{g/l}$ (1, 14). Six out of ten pregnant women ingest less than this amount, and almost three out of ten women ingest less than half of the necessary minimum.

at the expense of T_4 . Consequently, maternal circulating T_4 and FT_4 decrease, but T_3 and FT_3 remain the same or even increase, thus avoiding an increase in circulating TSH. The mother remains euthyroid, as both clinical and subclinical hypothyroidism require an increase in circulating TSH, but the T_4 available to the fetus may be insufficient for neurodevelopment (7–9).

In the present study, we did not observe a correlation between FT_4 and iodine intake as measured by UI in pregnant women from Extremadura, although other studies show an increase in FT_4 when deficient iodine nutrition is corrected (6, 22, 23).

We want to lay emphasis on the result that a very important proportion of the pregnant women of Extremadura do not ingest the currently recommended minimum amounts of iodine, with the consequent increased risk for deficits in the psychoneurointellectual development of the child (2, 5, 7–9, 24).

It is urgent to make the population and the health personnel, especially those attending to pregnant women, aware of the need to take appropriate iodine supplements during pregnancy and breastfeeding. This has been facilitated through very active measures taken by the Spanish Ministry of Health, including a signed agreement between the Ministry and UNICEF-España, which included active promotion of the special measures to be taken to ensure the increased iodine intake needed during pregnancy and lactation, under the direct responsibility of the Maternal-Infant Health Section at the Ministry. The first preparation of a supplement containing $200 \mu\text{g I/tablet}$ ($261.6 \mu\text{g KI/tablet}$) that was approved was Yoduk[®] 200 (Recordati-España), at a cost of 0.079

€/per tablet, further halved to 0.04 €/day through the National Public Health System. Other similar preparations from other firms were later also approved, at similar low prices. Recently, a new preparation of Recordati-España is being subsidized, Yoduk-Complex, which contains, per tablet, KI ($200 \mu\text{g I}$), folic acid (400 mg), and vitamin B12 ($2 \mu\text{g}$). The recommendation is to start one month prior to onset of pregnancy (when planned) and to take it for the first 3 months, to then be stopped and Yoduk 200 started until the end of lactation. The cost for the pregnant woman is again quite low (0.08 €/tablet).

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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