

## ORIGINAL ARTICLE

### Reference values for thyroid hormones in the population of pregnant women in Jaen (Spain)

Piedad Santiago<sup>a,\*</sup>, María Berrio<sup>a</sup>, Pablo Olmedo<sup>b</sup>, Inés Velasco<sup>c</sup>, Baltasar Sánchez<sup>a</sup>, Eduardo García<sup>d</sup>, Julia Martínez<sup>a</sup>, Federico Soriguer<sup>d</sup>

<sup>a</sup>UGC de Endocrinología, UGC de Análisis Clínicos y Servicio de Radiología, Complejo Hospitalario de Jaén, Jaén, Spain

<sup>b</sup>Distrito Sanitario de Jaén, Jaén, Spain

<sup>c</sup>Servicio de Ginecología y Obstetricia, Hospital de Riotinto, Huelva, Spain

<sup>d</sup>Servicio de Endocrinología, Hospital Civil de Málaga, Málaga, Spain

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#### KEYWORDS

Thyroid hormones;  
Pregnancy;  
Normal ranges;  
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#### Abstract

**Objective:** To assess thyroid function in the three trimesters of pregnancy in healthy women taking iodine supplements and to define the normal reference ranges in this population.

**Design:** Descriptive study of pregnant women to define the normal ranges of thyroid hormones in this population.

**Setting:** Jaen and Osuna (Spain).

**Population:** Healthy pregnant women.

**Methods:** Thyroid hormone measurement in the three trimesters of pregnancy in healthy women taking iodine supplements.

**Results:** A total of 429 pregnant women were given iodine supplements to maintain urinary iodine levels within the normal range. FT4 levels ranged from 0.60 to 1.06 ng/dL in the first trimester, from 0.43 to 0.85 ng/dL in the second, and from 0.40 to 0.82 ng/dL in the third trimester. Reference values of thyroid stimulating hormone (TSH) ranged from 0.23 to 4.18  $\mu$ U/mL in the first trimester, from 1.78 to 3.89  $\mu$ U/mL in the second, and from 2.01 to 4.30  $\mu$ U/mL in the third trimester. FT3 levels ranged from 2.33 to 3.84 pg/mL in the first trimester, from 2.04 to 3.51 pg/mL in the second, and from 1.99 to 3.46 pg/mL in the third trimester.

**Conclusion:** Taking into account the 3rd and 97th percentiles, the reference ranges in our population were far below those recommended by our reference laboratory. In view of these results, these values should be redefined to avoid misdiagnosis of hypothyroxinemia in healthy pregnant women.

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\*Corresponding author.

E-mail address: santiago11@ono.com, piedad.santiago.sspa@juntadeandalucia.es (P. Santiago).

**PALABRAS CLAVE**  
Hormonas tiroideas;  
Embarazo;  
Rangos de  
normalidad;  
Ingesta de yodo

## Valores de referencia de hormonas tiroideas en la población de mujeres gestantes de Jaén

### Resumen

**Objetivo:** Valorar la función tiroidea en los tres trimestres de gestación en mujeres sanas suplementadas con yodo y definir los límites de referencia de la normalidad de esta población.

**Diseño:** Estudio descriptivo sobre la mujer gestante para definir los límites de normalidad de hormonas tiroideas en esta población.

**Emplazamiento:** Jaén y Osuna.

**Población:** Gestantes sanas.

**Métodos:** Determinación de hormonas tiroideas en los tres trimestres de gestación en mujeres sanas suplementadas con yodo.

**Resultados:** Cuatrocientas veintinueve gestantes fueron suplementadas con yodo para mantener nivel de yoduria en los límites de normalidad. Las concentraciones de T4-l estuvieron entre 0,60 y 1,06 para el primer trimestre, entre 0,43 y 0,85 ng/dl en el segundo trimestre y entre 0,40 y 0,82 ng/dl en el tercer trimestre. Para la TSH los valores de referencia son: 0,23 y 4,18  $\mu$ UI/ml en el primer trimestre, 1,78 y 3,89  $\mu$ UI/ml en el segundo trimestre y 2,01 y 4,30  $\mu$ UI/ml en el tercer trimestre. Para T3-l los límites en el primer trimestre son de 2,33 a 3,84 pg/ml, entre 2,04 y 3,51 pg/ml en el segundo trimestre y entre 1,99 y 3,46 pg/ml en el tercer trimestre.

**Conclusión:** Los límites de referencia para nuestra población teniendo en cuenta los percentiles 3 y 97 están muy por debajo del recomendado por nuestro laboratorio de referencia, lo que obliga a redefinir estas concentraciones para evitar diagnosticar de forma incorrecta de hipotiroxinemia a la mujer gestante sana.

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## Introduction

Adequate thyroid hormone levels are essential during pregnancy to ensure adequate neurointellectual and motor development in newborn children<sup>1-3</sup>. Recent studies have shown that iodine supplementation may improve aspects of the child's neurointellectual development<sup>4,5</sup>. Iodine deficiency has been reported to be a potential cause of low thyroxine levels during pregnancy and to be associated with lower scores in neurointellectual maturation scales<sup>6,7</sup>.

Current iodine levels in Spanish pregnant women are highly variable depending on the autonomous community or region studied. In Jaen, median urinary iodine levels in pregnant women are 108  $\mu$ g/dL, lower than the minimum levels recommended by the WHO<sup>8</sup>.

Reference thyroid hormone levels in the general population cannot be superimposed on those of the pregnant population because a number of changes in thyroid hormone, transporter protein, thyroglobulin, and  $\beta$ -HCG levels occurring during the first trimester of pregnancy in response to increased estrogen levels result in different laboratory test results as compared to non-pregnant women. In clinical practice, this may lead to an erroneous interpretation of the results<sup>9,10</sup>.

Positive antiperoxidase antibodies are also related to higher TSH levels and lower FT4 levels<sup>11</sup>. In areas where iodine intake is adequate, these changes occur physiologically, with no changes in thyroglobulin levels or thyroid volume. When iodine intake is inadequate, thyroid hormone levels may be lower<sup>6</sup>. There is no agreement yet as

to what would constitute acceptable TSH limits in pregnancy. While TSH values lower than 5  $\mu$ IU/L are accepted in the general population, lower limits have been proposed for pregnant women, in whom levels less than 2.5  $\mu$ IU/mL in the first trimester and less than 3  $\mu$ IU/mL in the second and third trimesters are considered normal<sup>12</sup>. However, these levels have been questioned. Recent data have associated lower TSH levels with lower miscarriage or preterm delivery rates<sup>13</sup> and led to the suggestion that stricter limits should be established.

On the other hand, thyroid disease is common in pregnant women. From 0.2% to 1% of pregnant women experience hyperthyroidism, most commonly due to Graves-Basedow disease, while 0.2%-0.5% experience primary hypothyroidism, and 2.5% subclinical hypothyroidism; this percentage increases after delivery. Autoimmune thyroid disease is also common in pregnant women, with a prevalence of positive antiperoxidase antibodies of 9% and 4%<sup>9</sup>; this proportion is even greater in pregnant women with other autoimmune diseases such as type 1 diabetes mellitus or rheumatoid arthritis.

It is therefore important to define the values of the population of pregnant women each trimester and even in each week of pregnancy and in each laboratory and site of origin in order to diagnose clinical and subclinical diseases and to be able to assess the need for replacement or antithyroid therapy<sup>14</sup>.

The purpose of this study was to estimate, in all three trimesters of pregnancy, thyroid hormone levels in a population of pregnant women living in an area considered to be iodine-deficient.

## Materials and methods

### Materials

Healthy women from primary care health centers attending a pregnancy, delivery, and postpartum program in Jaen and the gynecology and obstetrics department of the hospital of Osuna were studied.

All women were recruited before the 10th week of pregnancy by the midwife at the health center and referred for monitoring to the endocrinology outpatient clinic of the hospital of Jaen or the gynecology clinic of the hospital of Osuna. Pregnant women did not take iodine supplements until the first laboratory tests were performed before the 10th week of pregnancy. Once the first measurement was performed, they were given a iodine dose allowing for maintenance of urinary iodine levels higher than 100 µg/L from the first trimester of pregnancy.

All pregnant women were informed about the objectives of the study and signed a standard informed consent to participate in the study. The study was approved by the ethics committee of the research board of the hospital of Jaen.

### Variables

Thyroid hormones were measured in all women, including TSH, FT4, FT3, and thyroglobulin; β-HCG and urinary iodine in the first (before the 10th week of pregnancy), second (between weeks 24 and 26 of pregnancy), and third trimesters (in the 36th of pregnancy).

### Laboratory methods

Thyroid hormones and thyroglobulin were measured using a chemiluminescent immunoassay with paramagnetic particles for the quantitative determination of TSH, FT4, FT3, and thyroglobulin levels in human serum or plasma<sup>15</sup>.

- TSH (range, 0.26-5.6 µIU/mL).
- Free T4. Normal range in the first trimester: 0.73-1.13 ng/dL; second trimester: 0.54-1.09 ng/dL; third trimester: 0.56-1.09 ng/dL.
- Free T3. Range, 1.80-4.6 pg/mL.
- Thyroglobulin. Range, 0-43 ng/mL.
- TPO (antiperoxidase) antibodies (enzymoimmunoassay). Range, 0-65 IU/mL. Values higher than 65 IU/mL were considered positive.
- TSI (enzymoimmunoassay for quantitative measurement of TSH receptor autoantibodies in human serum using a third generation human monoclonal thyroid-stimulating antibody). This was performed on the DYN-EX platform from the Palex company. Levels higher than 2 IU/mL are considered to be positive.
- Urinary iodine levels: 24-hour urine sample. Benotti and Benotti method<sup>16</sup>.

### Statistical analysis

Variable data were recorded in a validated computer support that allows for statistical analysis. To avoid bias in laboratory measurements, results of women with positive anti-thyroid

antibodies and TSH levels higher than 5 µIU/mL were excluded from the statistical study and analysis of the results. Descriptive statistics were performed for each individual variable and each trimester. These values are provided as the mean, median, and standard deviation, and as 3th to 97th percentiles. All continuous variables were adjusted to a normal distribution using a Shapiro test. Two-sample hypothesis testing was performed using a Student's t test or Wilcoxon or Mann-Whitney tests, considering the potential dependence between variables (e.g. during the three trimesters of pregnancy) and for classification variables of more than two levels with ANOVA and Kruskal-Wallis tests, depending on adjustment to a normal distribution. Dependence between variables was assessed using correlation coefficients (Pearson's r or Spearman's R, depending on normality adjustment). Linear regression models allowing for determining the effects of the different trimesters on hormone levels were used to assess the trend of test results during pregnancy. In all cases, the statistical decision for an H0 rejection level of  $\alpha = 0.05$ , two-tailed was taken.

## Results

A total of 429 women with a mean age of 30.9 years (range, 18-41 years) were recruited into the study. As regards autoimmunity assessment, 19 of the 305 women (6%) tested in the first trimester had positive TPO antibodies; 18 of the 239 women (7%) tested in the second trimester had positive TPO antibodies; and 7 of the 171 women (4%) tested in the third trimester had positive TPO antibodies. TSI antibodies were found in 7 women (3%) in the first trimester, in 11 women (5%) in the second trimester, and in 7 women (4%) in the third trimester. Table 1 shows the data collected.

FT4 levels significantly decreased during pregnancy, with mean values of 0.8 ng/dL, 0.61 ng/dL, and 0.59 ng/dL in the first, second, and third trimesters respectively ( $p < 0.001$ ). Table 2 shows the mean, median, and percentiles for TSH, FT4, FT3, and thyroglobulin levels.

FT4 levels in the first trimester were below the lower limit of the reference range at our laboratory (0.73 ng/dL) in 106 women (30%); in the second trimester 22% of them had FT4 levels below the lower limit of the reference range at our laboratory (0.54 ng/dL); and in the third trimester 37% had FT4 levels of 0.57 ng/dL (the lower normal limit at our laboratory) or less.

TSH levels gradually increased during pregnancy, with mean levels of 1.67 µg/dL, 1.86 µg/dL, and 2.13 µg/dL in the first, second, second, and third trimesters of pregnancy respectively ( $p < 0.005$ ) (Fig. 1). FT4 levels decreased in parallel during pregnancy, with mean values of 0.80 ng/dL, 0.61 ng/dL, and 0.59 ng/dL respectively ( $p < 0.005$ ) (Fig. 2).

A correlation existed between TSH and β-HCG levels in the first trimester ( $p < 0.001$ ); TSH levels gradually increased in the second and third trimesters in parallel to a decrease in β-HCG levels (Table 2 and Fig. 3).

FT3 levels decreased during pregnancy. The decrease was statistically significant when the first trimester was compared to the second and third trimesters, in which mean

Table 1 Prevalence of positive antibodies

	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester	3 <sup>rd</sup> trimester
Positive TPO	Tested: 305; n = 19 (6%)	Tested: 239; n = 18 (7%)	Tested: 171; n = 7 (4%)
Positive TSI	n = 7 (3%)	n = 11 (5%)	n = 7 (4%)

TPO: antiperoxidase antibodies; TSI: TSH receptor antibodies.

Table 2 Distribution of thyroid hormone, thyroglobulin, and urinary iodine levels in the three trimesters of pregnancy

	Trimester	Mean	Median	P3	P50	P97
TSH $\mu$ IU/mL	First <sup>a</sup>	1.67	1.52	0.23	1.5	4.18
	Second <sup>b</sup>	1.86	1.78	0.36	1.78	3.89
	Third <sup>c</sup>	2.13	2.01	0.30	2.01	4.30
Free T4 ng/dL	First	0.80	0.80	0.60	0.80	1.06
	Second	0.61	0.60	0.43	0.60	0.85
	Third	0.59	0.57	0.40	0.57	0.82
Free T3 pg/mL	First	3.07	3.04	2.33	3.03	3.84
	Second	2.71	2.68	2.04	2.68	3.51
	Third	2.79	2.62	1.99	2.62	3.46
Thyroglobulin ng/dL	First	17.20	11.60	1.176	11.6	61.50
	Second	13.63	10.82	1.92	10.81	37.98
	Third	17.45	10.85	1.69	10.85	59.87
Urinary iodine $\mu$ g/L	First	129.06	109.87			
	Second	202.31	179.53			
	Third	195.64	181.78			

<sup>a</sup>First trimester: between the 7<sup>th</sup> and 10<sup>th</sup> weeks of pregnancy.

<sup>b</sup>Second trimester: 24<sup>th</sup> to 28<sup>th</sup> weeks of pregnancy.

<sup>c</sup>Third trimester: 36<sup>th</sup> to 38<sup>th</sup> weeks of pregnancy.

levels of 3.07 pg/mL, 2.71 pg/mL, and 0.79 pg/mL respectively were found.

Median and mean urinary iodine levels were 108.34  $\mu$ g/L and 128.57  $\mu$ g/L respectively. In our study, 45.5% of pregnant women had urinary iodine levels less than 100  $\mu$ IU/mL and 14% had values lower than 50  $\mu$ IU/mL. Urinary iodine levels increased during the second trimester as compared to the first trimester in all pregnant women, but decreased in the third trimester (Table 2). No significant differences were found in thyroid hormone levels in relation to urinary iodine levels either before the start of iodine supplementation, i.e. at the first measurement, or during pregnancy.

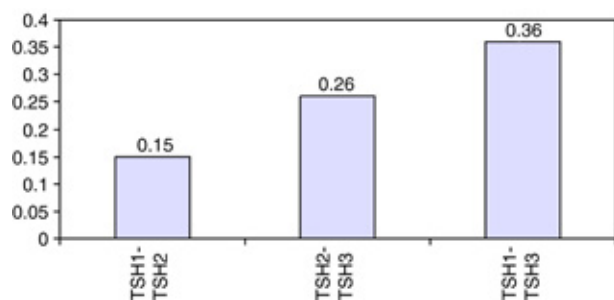
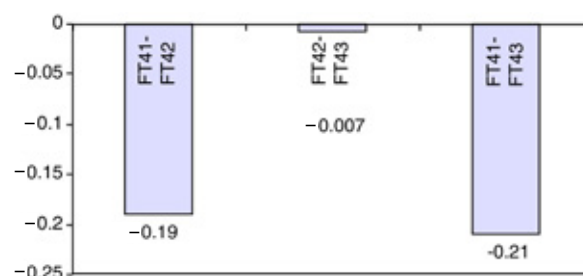


Figure 1 Percent increase in TSH levels during pregnancy.

Figure 2 Percent decrease in free T4 levels in the three trimesters of pregnancy ( $p < 0.005$ ).

## Discussion

The controversy about when to start treatment of a potential hypothyroidism during pregnancy should lead us to reconsider when this diagnosis should be made and what criteria should be used for starting treatment<sup>17</sup>. This investigation was therefore necessary, all the more so knowing, as we do, that a marked iodine deficiency exists in some areas of Spain. On the other hand, the lack of consistency in the test methods used at the different

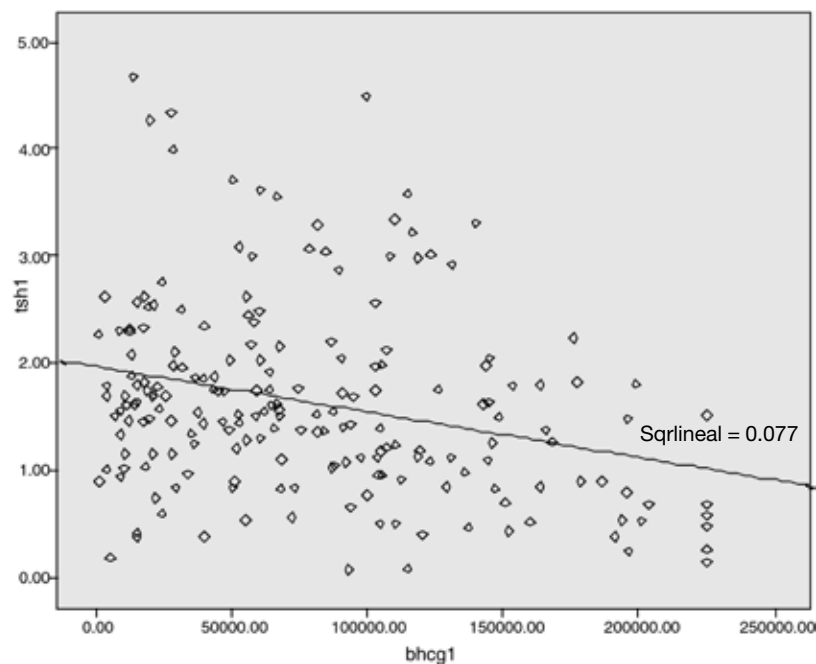


Figure 3 Correlation between TSH and b-HCG in the first trimester ( $p < 0.001$ ).

reference laboratories and even the use of different measurement units obliges physicians to make their own “local” measurements in routine practice so as to be able to take action if needed in a pregnant woman in whom low thyroxine levels are detected.

This study was intended to define the normal levels of thyroid hormones in healthy pregnant women from an iodine-deficient population for a given test method and for a specific reference hospital, knowing that thyroid hormone levels are highly variable depending on the trimester of pregnancy analyzed<sup>18,19</sup>.

A significant advantage in our study was the homogeneity of our sample in terms of race, as some studies have reported race-dependent variability in hormone levels<sup>20,21</sup>. All pregnant women in our sample were Caucasian, and almost all of them had a similar educational level. Not quite 30% of all women surveyed used iodinated salt. Iodine consumption may also be influenced by the use of multivitamin complexes containing iodine<sup>22</sup>, but all of our pregnant women received iodine supplementation.

The reliability of the test data collected is ensured by quality controls of measurements regularly performed at our reference laboratory.

A first significant finding was that pregnant women in our area had very low FT4 levels before the 10th week of pregnancy, with mean values coinciding with the lower normal limit of the reference laboratory. This means that half the pregnant women studied had hypothyroxinemia in the first trimester, with the resultant potential compromise for brain development at a crucial stage for the embryo.

On the other hand, FT4 levels gradually decreased with pregnancy, but mean FT4 levels continued to be in the lower normal limit for our reference laboratory. This contrasts

with other studies recently performed in Spain on pregnant women with the same clinical profile as our sample, in whom levels found during the first trimester of pregnancy agreed with their reference values<sup>23</sup>. We wonder whether the FT4 levels found in our sample are related to the median urinary iodine levels in our population, much lower than those recommended by the WHO<sup>8</sup>, as was concluded in a prior study conducted in Andalusia<sup>24</sup>. However, statistical data analysis showed no significant differences in FT4 levels with regard to the urinary iodine levels of the pregnant women studied.

TSH levels significantly decreased during the first trimester concomitantly with an elevation in  $\beta$ -HCG levels, and gradually increased concomitantly with a decrease in FT4 levels in the second and third trimesters.

Thyroid physiology thus behaved in our pregnant women as reported in previously published studies<sup>9,10</sup>.

Unlike in other studies, positive TPO antibodies were only found in 5.4% of our sample.

Since subjects who showed positive TPO antibodies were excluded from statistical analysis, we are led to believe that there is no reason why thyroid function should have been compromised in our pregnant women, and that all the thyroid tissue of the women included in statistical analysis therefore functioned adequately. TSH levels were also slightly higher in pregnant women with positive TPO antibodies, in agreement with findings by other authors such as Pearce et al<sup>11</sup>.

## Conclusion

We may conclude that the reference limits for FT4 in pregnant women in our area, considering that the 3th and

97<sup>th</sup> percentiles are below those provided by the reference laboratory, range from 0.60 and 1.06 ng/dL in the first trimester, from 0.43 and 0.85 ng/dL in the second trimester, and from 0.40 and 0.82 ng/dL in the third trimester. The reference values for TSH range from 0.23 to 4.18  $\mu$ U/mL in the first trimester, from 1.78 to 3.89  $\mu$ U/mL in the second trimester, and from 2.01 to 4.30  $\mu$ U/mL in the third trimester. FT3 reference levels range from 2.33 to 3.84 pg/mL in the first trimester, from 2.04 to 3.51 pg/mL in the second trimester, and from 1.99 to 3.46 pg/mL in the third trimester.

These results demonstrate the need to recommend and promote the consumption of iodinated salt by the entire population and to ensure iodine supplementation throughout pregnancy.

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## Conflict of interest

The authors state that they have no conflict of interest.

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