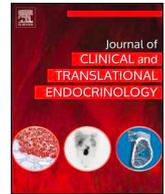




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Original research

Relatively high rate of postpartum thyroiditis in the Straits of Messina area. Predictivity of both postpartum thyroiditis and permanent hypothyroidism by performing, in the first trimester of gestation, thyroid ultrasonography and measurement of serum thyroperoxidase and thyroglobulin autoantibodies

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ABSTRACT

The prevalence of postpartum thyroiditis (PPT) averages 5%, with a range from 1% (Thailand) to 22% (Wales, UK, and Liguria, Italy), but 3.6% in another Italian region (Puglia). Evolution of PPT into permanent hypothyroidism (PH) occurs in approximately 50% of cases. Positive thyroperoxidase autoantibodies (TPOAb) in a pregnant woman is a strong predictor of PPT. Because in previous gestational cohorts we found an approximate 12% rate of TPOAb positivity, which compares with 15% in the Liguria cohort and 6% in the Puglia cohort, we hypothesized that the currently unknown prevalence of PPT in Sicily would approximate the said Liguria prevalence. We also explored the predictive value of serum thyroglobulin Ab (TgAb) positivity and ultrasonographic signs suggestive of thyroiditis (UST) at first trimester of gestation for PPT.

Of 412 pregnant women who were followed-up for 1 year after delivery, 63 (15.3%) developed PPT, and 54% of them had PH. Gestational rates of TPOAb positivity alone, TgAb positivity alone or UST were 11.4%, 7.8% or 35.0%, with associated PPT rates of 66%, 45% or 36%. TgAb assay allowed detection of 9/63 PPT women (14.3%) who were TPOAb-negative. However, TPOAb remained a better predictor compared to TgAb or UST (odds ratio = 32 vs 10 or 13). Lowering the positivity threshold for either Ab to ≥ 61 U/ml, Ab-positive were 23.8% of PPT women and 17.7% of pH women. UST was detected in 82.5% of women who developed PPT, precisely 88% of those who evolved into PH and 75.9% of those who did not.

Ours is the second study of the new millennium showing a PPT frequency > 10%. The dual Ab and lowered threshold strategy correctly predicts more cases of PPT and PH compared to the sole TPOAb strategy. We confirm that half of the PPT women will have PH.

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Introduction

A review of 21 studies from 14 countries published from 1982 through 2011, and with a number of screened women comprised between 120 and 4384 (median 571), reported a mean prevalence of postpartum thyroiditis (PPT) of 5.4%, with a range from 1.1% [Thailand] to 18.2% [Italy] [1]. However, based on women who completed the 1-yr duration follow-up after delivery, the 18.2% rate [2] increases to 22.1%, thus matching the 22.3% prevalence of Wales [3], which is the highest in the literature. Seven of the 21 studies also evaluated the rate of permanent hypothyroidism (PH) in PPT women, namely high serum levels of thyrotropin (TSH) with low or normal free thyroxine (FT4) that are detected at the end of the first year postpartum [1]. PH rate is also variable (4%–54%), with more recent rates approximating 50%; thyroid hypoechoogenicity on ultrasound (US) is considered a predictive risk factor for PH. However, thyroid US was performed in a minority of studies [1]. For some countries, more than one study on the PPT prevalence is available. Three studies were performed in Italy [2,4,5] with PPT rates from 3.9% [5] to 22.1% [2], three in Denmark [6–8] with rates from 3.9% to 8.7%, three in the United States [9–11] with rates from 1.9% [9] to 8.8% [11], and two in the Netherlands with rates of 5.2% [12] or 7.2% [13]. Thus, Italy and the United States have the greatest variability in PPT prevalence.

We were particularly struck by the almost 6-fold difference in PPT rate (22.1% vs 3.9%; $\chi^2 = 175$, $P = 6 \times 10^{-40}$) but no difference in the PH rate (49.1% vs 54.4%, respectively) reported by the two most recent Italian studies [2,5]. Both investigations were conducted in two coastal regions. The study in Liguria (northwestern Italy) was on 258 women [2], while the study in Puglia (southeastern Italy) was on 4384 women [5]. At first sight, the difference in PPT rate could have suggested a north-to-south descending prevalence of PPT. However, we noticed that the significantly greater rate of PPT in Liguria was paralleled by a significantly greater rate of positivity for serum thyroperoxidase autoantibodies (TPOAb; 15.1% vs 6.0%, $\chi^2 = 33.8$, $P = 6.0 \times 10^{-9}$). Only in one [3] of the four other cohorts with TPOAb positivity rates $\geq 10\%$ [3,8,11,13] the prevalence of PPT was high (22.3%) [3], while it ranged from 7.2% [11] to 8.8% [13] in the remaining three cohorts. Of note, in one Danish cohort [6] with a rate of TPOAb positivity (6.4%) similar to that of the Puglia cohort [5] (6.0%), the rate of PPT was identical (3.9% vs 3.9%). Very low rates of PPT (1.9% and 2.4%) were found in the two cohorts [9,14] that also had the lowest rates of TPOAb positivity (2.8% and 5.2%).

The serum thyroid Ab that are typically measured to screen for PPT are TPOAb only, as done in the Puglia study [5], rather than both TPOAb and thyroglobulin Ab (TgAb), as done in the Liguria study [2]. Assay of serum TPOAb in the first trimester of gestation is considered the optimal screening tool [1], with 33 to 50% of TPOAb +ve women destined to develop PPT [1]. Other predictors of PPT are nonhumoral indices, including personal history positive for autoimmune nonthyroid diseases (AINTD, particularly type 1 diabetes mellitus (DM-1), family history positive for AINTD, and family history positive for autoimmune thyroid diseases (Graves' diseases [GD], Hashimoto's thyroiditis [HT]) [1].

No data on PPT are available for our island, which is the southernmost Italian region. Because on cohorts of women sampled at around delivery for other purposes we had found rates of thyroid Ab positivity of approximately 12% [15; S. Benvenega, unpublished], we hypothesized that in a further cohort of pregnant women, we would have found a PPT rate closer to that of Liguria [2] than that of Puglia [5], and a PH rate of approximately 50%, which is similar to that of both Liguria and Puglia. Because assessed only in one Brazilian study employing TPOAb solely [16], we wished to assess the predictive value of upper-normal levels of both TPOAb and TgAb in addition to elevated Ab levels. We also wished to evaluate the predictivity of nonhumoral, noninstrumental risk factors for PPT.

Patients and methods

Cohort

Of the approximately 10,000 women who deliver each year in the province of Messina (Sicily) and province of Reggio Calabria (Calabria) combined, which are the two provinces separated by the Straits of Messina, most of those forming our cohort delivered at the Division of Obstetrics & Gynecology of the two major hospitals in the metropolitan cities. These were the University hospital of Messina and the metropolitan hospital of Reggio Calabria.

Similar to other studies on PPT [1], upon informed consent we enrolled women with singleton pregnancy within the first 11 weeks of gestation and who had no known thyroid disease. Excluded from the study were all women who had thyroid dysfunction discovered at our initial screening. Also excluded were women who developed Graves' disease during gestation or postpartum. Levothyroxine (L-T4) treatment was initiated if serum TSH concentration was above the trimester-specific reference interval (> 2.5 mU/L, first trimester, and > 3.0 mU/L in the other two trimesters) with a decreased FT4, or if TSH concentration was > 10.0 mU/L irrespective of FT4 [17]. L-T4 dose was titrated to maintain serum TSH below the said trimester-specific upper normal limit, and serum FT4 at or above the mid-value of the range. After delivery, L-T4 administration was stopped, and substitutive treatment, in case of hypothyroidism, was initiated based on the conditions specified in the following section.

The women who completed this study (first trimester of gestation to end of the 12th month postpartum) were 412. Age at enrollment was 31.6 ± 4.3 years (range 19–43).

A questionnaire was administered to investigate on smoking status, family and personal history for thyroid disease, and AINTD. If necessary, and upon consent, clinical records of either the pregnant woman or consanguineous relatives were examined.

Biochemical, ultrasound evaluation and definition of postpartum thyroid dysfunction

Enrollment occurred between week 7 and 11 of gestation, when the first clinical, biochemical and instrumental evaluation was performed. Subsequent biochemical evaluation was performed at the second and third month of gestation, and at 6th week, 3rd, 6th and 12th month postpartum. Thyroid function tests were also performed at any time point during the first year postpartum if signs or symptoms of thyroid dysfunction had appeared. Thyroid US was repeated at 6 weeks and 12 months postpartum, and at 3 and 6 months in women who developed thyroid dysfunction at either time point.

In the context of postpartum dysfunction, hyperthyroidism was defined as subnormal TSH levels (< 0.27 mU/L), and hypothyroidism as elevated TSH levels (> 4.2 mU/L) [5]. Hyperthyroidism was treated with beta-blockers (propranolol) if disturbing symptoms existed and/or FT4 levels were > 33 pmol/L, namely > 1.5 -fold greater than the upper normal limit of 22 pmol/L [5,17]. Unless TSH was > 4.2 mU/L and coexisting with FT4 < 12 pmol/L, or > 10 mU/L and coexisting with normal FT4 levels, or disturbing symptoms of increasing intensity were present, hypothyroidism was not treated [5]. If treated, L-T4 replacement was withdrawn by the end of 11th month postpartum, in order to reassess TSH at the end of the 12th month postpartum and permit diagnosis of pH if TSH was > 4.2 mU/L. In the very few women in whom hypothyroidism started to be detected at month 12 postpartum, serum TSH was reassessed 8 weeks later. Because TSH elevation (> 4.2 mU/L) at the end of the 14th month was confirmed, throughout the paper we will refer to PH as TSH > 4.2 mU/L that existed at the end of 12th month postpartum.

Serum TSH, FT4, FT3, TPOAb and TgAb were assayed using electrochemiluminescent kits (Roche, Mannheim, Germany). Reference values are 0.27–4.2 mU/L (TSH), 12–22 pmol/L or 9.3–17.1 pg/ml (FT4),

3.1–6.8 pmol/L or 2.0–4.4 pg/ml (FT3), > 100 U/ml (TPOAb and TgAb).

Thyroid US was performed by the same ultrasonographer, who was blind to the biochemical data, using the Logiq instrument (General Electric Healthcare, UK) and a high-resolution probe of 7.5 MHz. The pattern suggestive of thyroiditis was a diffuse thyroid gland hypoechogenicity with heterogeneous echotexture.

Statistics

Continuous data are presented as mean \pm SD, median and range. Comparisons between proportions of categorical variables was performed using the χ^2 test or Fisher's exact test, as appropriate. The level of statistical significance was always set at $P < 0.05$. P values between 0.10 and 0.05 were considered to be borderline significant.

Results

Of the 412 women who completed the study, 63 (15.3%) developed PPT.

Thyroid dysfunction appeared in the classical biphasic form (hyperthyroidism, followed by hypothyroidism) in 30% of women. At the end of the 12th month of postpartum follow-up, 34 PPT women (54%) were hypothyroid, while the remaining 29 (46%) regained euthyroidism.

Prevalence of PPT and risk factors evaluated in the first trimester of gestation

Risk factors other than TgAb, TPOAb and ultrasound

Smoking status or previous miscarriage(s) were not risk factors for PPT (Table 1).

As said above, the overall prevalence of PPT was 15.3%, but it was greater upon stratifying based on other risk factors. Positive personal history for AINTD was present in 109 women (26.4%), of whom 29 (26.6%) developed PPT (Table 1). Particularly, 4/412 women (1.0%) had DM-1, 3 of whom (75%) developed PPT. Family history was positive for AINTD in 191 women (46.3%) (Table 1), in 12 of whom (6.3%) the AINTD being DM-1. Of these 191 or 12 women, 43 (22.5%) or 6 (50%) developed PPT.

Family history was positive for AITD (namely, GD, HT or both) in 28 women (6.8%), of whom 16 (57.1%) developed PPT (Table 1). Hence, among the 63 PPT women, the rates of personal history positive for AINTD, family history positive for AINTD or family history positive for AITD were 46.0%, 68.2% or 25.4%, respectively. Family history positive for AITD separated the PPT group from the nonPPT group with an odds ratio (OR) of approximately 10 (Table 1).

Serum TgAb, TPOAb and thyroid ultrasound

In the entire cohort, 20 women tested positive for TgAb only (4.8%; TgAb +ve/TPOAb -ve), 47 for TPOAb only (11.4%; TgAb -ve/TPOAb +ve), and 9 for both TgAb and TPOAb (2.2%; TgAb +ve/TPOAb +ve). Thus, 29 women (7%) were TgAb +ve and 56 (13.6%) were TPOAb +ve.

Of the 29 women who were TgAb +ve regardless of TPOAb status, 17 (58.6%) developed PPT; however, the rate declined to 9/20 (45.0%) considering women positive for TgAb solely (Table 1). Of the 56 women who were TPOAb +ve regardless of TgAb status, 39 (69.6%) developed PPT (Table 1); however, this rate declined slightly to 31/47 (66.0%) upon considering women positive for TPOAb solely. Of the 9 women who were TgAb +ve/TPOAb +ve, 8 (88.9%) developed PPT. Thus, the hierarchical order of predictivity was positivity for both TPOAb and TgAb (89%) > positivity for TPOAb solely (66%) > positivity for TgAb solely (45%). Of the 336 women who tested negative for both TgAb and TPOAb (TgAb -ve/TPOAb -ve), only 15 (4.5%) developed PPT. Hence, of the 63 PPT women, only these 15 (23.8%) were TgAb

-ve/TPOAb -ve, while the other 48 (76.2%) were positive for at least one Ab.

As reviewed recently [1], very few studies have addressed the value of an US pattern suggestive of thyroiditis (UST) as a risk factor for subsequent PPT. UST was recorded in 144 women (34.9%), of whom 52 (36.1%) developed PPT (Table 1). Hence, most PPT women (52/63 [82.5%]) had an UST already in the first trimester of gestation. Considering the 336 women negative for both TPOAb and TgAb, an UST was detected more frequently in women who developed PPT (9/15 [60.0%]) than in women who did not (68/321 [21.2%], $\chi^2 = 12.2$, $P = 0.0005$, OR = 5.58 [95% CI: 1.9–16.2] (data not shown).

Value in predicting PPT based on lowering the threshold of thyroid Ab positivity in the first trimester of gestation

As said in the Introduction, only one Brazilian study [16] evaluated this issue, and for the sole Ab that was measured, TPOAb. Serum TPOAb had a reference range of 0–100 U/ml [16], the same as ours for both TPOAb and TgAb. Like Barca et al. [16] did for TPOAb, we ascertained whether the 61–100 U/ml range for either Ab contained women who subsequently developed PPT (Table 1).

As it can be deduced from Table 1, there were 12 (2.9%) or 13 (3.1%) women with TPOAb or TgAb within this range regardless of status for the other Ab, with the corresponding rates of PPT being 3/12 (25.0%) or 9/13 (69.2%). Considering selective positivity for TPOAb or TgAb at between 61 and 100 U/ml, there were 11 TPOAb +ve/TgAb -ve women (2.7%) and 6 TPOAb -ve/TgAb +ve women (1.5%), with corresponding PPT rates of 2/11 (18.2%) and 4/6 (66.7%). Thus, considering as abnormal the approximately upper half (61–100 U/ml) of the 0–100 U/ml reference range provided a payoff for TgAb, because it permitted “to catch” an additional 14% women (9/63) who developed PPT and who were missed by the threshold positivity set at ≥ 101 U/ml.

When these data are pooled with those in the previous heading, where threshold of abnormality for either Ab was > 101 U/ml, the resulting picture is the following upon setting the threshold for either Ab at ≥ 61 U/ml. Regardless of status for the other Ab, the rate of PPT was 42/68 (61.8%) in TPOAb +ve women, and 26/42 (61.9%) in TgAb +ve women (Table 1). These two rates compare with the corresponding aforementioned rates of 39/56 (69.6%) and 17/29 (58.6%) resulting from threshold set at ≥ 101 U/ml (Table 1). Considering selective Ab positivity, in the entire cohort there were 58 women who were TPOAb +ve/TgAb -ve (14.1%), and another 26 who were TPOAb -ve/TgAb +ve (6.3%). The corresponding rates of PPT were 33/58 (56.9%) and 13/26 (50%). These two rates compare with the corresponding aforementioned rates of 31/47 (66%) and 9/20 (45%), based on abnormal levels of Ab set at ≥ 101 U/ml.

In summary, only a few additional PPT cases are captured by lowering the cut-off point for abnormal levels of either Ab at ≥ 61 U/ml, but relatively more are so when the threshold is lowered for TgAb compared to TPOAb (9 additional cases vs 3).

Prevalence of permanent hypothyroidism (PH) and its risk factors, evaluated in the first trimester of gestation

Of the 63 women who developed PPT, 34 (54.0%) were hypothyroid at the end of the 12th month of follow-up after delivery (Table 2). Rates of risk factors were consistently greater in the PH group compared to the euthyroid group, but only for two predictors statistical significance was reached: family history positive for AITD, and family history positive for AINTD (Table 2). Statistical significance was borderline ($P = 0.09$, OR = 2.2) for personal history positive for AINTD (Table 2). Considering the TPOAb -ve/TgAb -ve PPT women, a sonographic pattern suggestive of thyroiditis had been present in 5/6 (83.3%) of those who developed PH compared to 4/9 (44.4%) of those who did not (data not shown). The gap between these two PPT groups widened on

Table 1
Risk factors for postpartum thyroiditis (PPT) in a cohort of 412 pregnant women.*

Risk factor	PPT, Yes [n = 63]		PPT, No [n = 349]		Statistics
	Yes	No	Yes	No	
<i>Smoking status</i>					
Currently, n = 18 (4.4%)	2 [3.2%]		16 [4.6%]		$\chi^2 = 0.26, P = 0.88$ OR = 1.13 (0.56–2.30)
Formerly, n = 79 (19.2%)	12 [19.0%]		67 [19.2%]		
Never, n = 315 (76.4%)	49 [77.8%]		266 [76.2%]		
<i>Previous miscarriage</i>					
Yes (59/412 = 14.3%)	10/63 = 15.9%		49/349 = 14.0%		$\chi^2 = 0.15, P = 0.70$ OR = 1.15 (0.55–2.42)
No (353/412 = 85.7%)	53/63 = 84.1%		300/349 = 86.0%		
<i>Personal history (autoimm. nonthyroid diseases)</i>					
Positive, n = 109 (26.5%)	29 [46.0%]		80 [22.9%]		$\chi^2 = 14.65, P = 0.0001$ OR = 2.87 (1.64–5.0)
Negative, n = 303 (73.5%)	34 [54.0%]		269 [77.1%]		
<i>Family history (thyroid diseases)</i>					
Positive, n = 127 (30.8%) [§]	27 [42.9%]		100 [28.7%]		$\chi^2 = 5.05, P = 0.025$ OR = 1.87 (1.08–3.24)
Negative, n = 285 (69.2%)	36 [57.1%]		249 [71.3%]		
+ve for Hashimoto's thyroiditis, n = 25 (6.1%) [§]	15 [23.8%]		10 [2.9%]		$\chi^2 = 41.1, P = 6 \times 10^{-10}$ OR = 10.6 (4.5–24.92) P = 0.027
Graves' disease, n = 5 (1.2%) [§]	3 [4.8%]		2 [0.6%]		
Hashimoto's t. and/or Graves' d., n = 28 (6.8%) [§]	16 [25.4%]		12 [3.4%]		$\chi^2 = 40.6, P = 8 \times 10^{-10}$ OR = 9.6 (4.26–21.50)
Thyroid nodules, n = 66 (16.0%) [§]	11 [17.5%]		55 [15.8%]		
No further specified, n = 45 (10.9%) [§]	6 [9.3%]		39 [11.2%]		$\chi^2 = 0.11, P = 0.73$ OR = 1.13 (0.56–2.30) $\chi^2 = 0.15, P = 0.70$ OR = 0.84 (0.34–2.07)
<i>Family history (autoimm. nonthyroid diseases)</i>					
Positive, n = 191 (46.4%)	43 [68.2%]		148 [42.4%]		$\chi^2 = 14.34, P = 0.0002$ OR = 2.92 (1.65–5.17)
Negative, n = 221 (53.6%)	20 [31.7%]		201 [57.6%]		
<i>TPOAb status, regardless of TgAb</i>					
TPOAb, positive at ≥ 101 U/ml, n = 56 (13.6%)	39 [61.9%]		17 [4.9%]		$\chi^2 = 148, P = 5 \times 10^{-34}$ OR = 31.7 (15.7–64.2)
, negative at ≤ 100 U/ml, n = 356 (86.4%)	24 [38.1%]		332 [95.1%]		
, positive at ≥ 61 U/ml, n = 68 (16.5%)	42 [66.7%]		26 [7.4%]		$\chi^2 = 136, P = 2 \times 10^{-31}$ OR = 24.8 (12.8–48.0)
, negative at ≤ 60 U/ml, n = 344 (83.5%)	21 [33.3%]		323 [92.6%]		
<i>TgAb status, regardless of TPOAb</i>					
TgAb, positive at ≥ 101 U/ml, n = 29 (7.0%)	17 [27.0%]		12 [3.4%]		$\chi^2 = 45.2, P = 1.8 \times 10^{-11}$ OR = 10.4 (4.66–23.12)
, negative at ≤ 100 U/ml, n = 383 (93.0%)	46 [73.0%]		337 [96.6%]		
, positive at ≥ 61 U/ml, n = 42 (10.2%)	26 [41.3%]		16 [4.6%]		$\chi^2 = 78.4, P = 8 \times 10^{-19}$ OR = 14.6 (7.19–29.73)
, negative at ≤ 60 U/ml, n = 370 (89.8%)	37 [58.7%]		333 [95.5%]		
<i>Thyroiditis at ultrasound</i>					
Present, n = 144 (35.0%)	52 [82.5%]		92 [26.4%]		$\chi^2 = 74.1, P = 7.5 \times 10^{-18}$ OR = 13.2 (6.60–26.40)
Absent, n = 268 (65.0%)	11 [17.5%]		257 [73.6%]		

* The denominator to calculate percentages in the column "Risk factor" is 412, and in the columns "PPT, Yes" or "PPT, No" is 63 or 349, respectively. Statistically significant differences are highlighted by the bold print. Lack of a χ^2 value in the last column indicates that statistical analysis was by the Fisher's exact test.

[§] In the breakdown of positivity, numbers do not add up to 127 because a given woman may have more than one consanguineous with thyroid disease.

Table 2
Risk factors for permanent hypothyroidism.

Risk factors recorded at the first trimester of gestation	PPT, permanent hypo		Statistics
	Yes [n = 34]	No [n = 29]	
TPOAb, ≥ 101 /U ml (n = 56)	23 [67.6%] (41.1%)	16 [55.2%] (28.6%)	$\chi^2 = 1.03, P = 0.31$ OR = 1.70 (0.61–4.74)
, ≥ 61 U/ml (n = 68)	24 [70.6%] (35.3%)	18 [62.1%] (26.5%)	
TgAb, ≥ 100 U/ml (n = 29)	11 [32.4%] (37.9%)	6 [20.7%] (20.7%)	$\chi^2 = 0.51, P = 0.48$ OR = 1.47 (0.51–4.20)
, ≥ 61 U/ml (n = 42)	14 [41.2%] (33.3%)	12 [41.4%] (28.6%)	
Thyroiditis at ultrasound (n = 144)	30 [88.2%] (20.8%)	22 [75.9%] (15.3%)	$\chi^2 = 1.08, P = 0.30$ OR = 1.83 (0.58–5.79)
Personal history +ve for AINTD (n = 109)	17 [50.0%] (15.6%)	12 [41.4%] (11.0%)	
Family history +ve for AINTD (n = 191)	27 [79.4%] (14.1%)	16 [55.2%] (8.4%)	$\chi^2 = 0.0003, P = 0.99$ OR = 0.99 (0.36–2.71) P = 0.32 OR = 2.39 (0.62–9.17)
Family history +ve for AITD (n = 28)	14 [41.2%] (50.0%)	2 [6.9%] (7.1%)	
			$\chi^2 = 2.80, P = 0.09$ OR = 2.25 (0.86–5.86)
			$\chi^2 = 4.24, P = 0.039$ OR = 3.13 (1.03–9.49) P = 0.0029 OR = 9.45 (1.93–46.4)

Abbreviations: AINTD = autoimmune nonthyroid disease; AITD = Autoimmune thyroid disease.

Statistical comparison refers to rates in brackets. Lack of a χ^2 value in the last column indicates that statistical analysis was by the Fisher's exact test. Statistically significant P values (i.e. < 0.05) have been boldfaced, whereas borderline significant P values (i.e. between 0.05 and 0.10) have been boldfaced and italicized.

Table 3

Comparison between our study and the other two Italian studies on postpartum thyroiditis that were conducted in the new millennium and that concern cohorts of women followed-up from pregnancy through month 12 postpartum.^{*,§}

Descriptor	This study	Filippi et al. (2)	Stagnaro-Green et al. (5)
Location (city/cities [and region])	Straits of Messina [Sicily, Calabria]	Genova [Liguria]	Lecce & Brindisi [Puglia]
No. of women	412	258	4384
Ab status at pregnancy			
TPOAb +ve, regardless of TgAb	56 (13.6%)	39 (15.1%)	261 (6.0%) $\chi^2 = 35.6$, P = 2.4×10^{-9} OR = 2.48 (1.83–3.38)
TPOAb –ve, regardless of TgAb	356 (86.4%)	219 (84.9%)	4123 (94.0%)
TgAb +ve, regardless of TPOAb	29 (7.0%)	21 (8.1%)	N/A
TgAb –ve, regardless of TPOAb	383 (93.0%)	237 (91.9%)	N/A
TPOAb +ve & TgAb +ve	9 (2.2%)	17 (6.6%) $\chi^2 = 8.61$, P = 0.003 OR = 0.31 (0.13–0.71)	N/A
TPOAb +ve & TgAb –ve	47 (11.4%)	22 (8.5%)	N/A
TPOAb –ve & TgAb +ve	20 (7.8%)	4 (1.6%) $\chi^2 = 5.0$, P = 0.025 OR = 3.24 (1.1–9.6)	N/A
TPOAb –ve & TgAb –ve	336 (81.6%)	215 (83.3%)	N/A
Postpartum			
Thyroid dysfunction (PPT)	63 (15.3%)	57 (22.1%) $\chi^2 = 5.0$, P = 0.025 OR = 0.64 (0.43–0.95)	169 (3.9%) $\chi^2 = 107$, P = 4.4×10^{-25} OR = 4.50 (3.30–6.13)
Permanent hypothyroidism in PPT	34/63 (54.0%)	28/57 (49.1%)	92/169 (54.4%)
Permanent hypo in the cohort	34/412 (8.3%)	28/258 (10.9%)	92/4384 (2.1%)
Ab status (pregnancy) in PPT			
TPOAb +ve, regardless of TgAb	39/63 (61.9%)	27/57 (47.4%)	97/169 (57.4%)
TPOAb –ve, regardless of TgAb	24/63 (38.1%)	30/57 (52.6%)	72/169 (42.6%)
TgAb +ve, regardless of TPOAb	17/63 (27.0%)	12/57 (21.1%)	N/A
TgAb –ve, regardless of TPOAb	46/63 (73.0%)	45/57 (78.9%)	N/A
TPOAb +ve & TgAb +ve	8/63 (12.7%)	11/57 (19.3%)	N/A
TPOAb +ve & TgAb –ve	31/63 (49.2%)	16/57 (28.1%) $\chi^2 = 5.61$, P = 0.018 OR = 2.48 (1.16–5.31)	N/A
TPOAb –ve & TgAb +ve	9/63 (14.3%)	1/57 (1.7%) P = 0.003 OR = 17.50 (2.2–137)	N/A
TPOAb –ve & TgAb –ve	15/63 (23.8%)	29/57 (50.9%) $\chi^2 = 9.44$, P = 0.002 OR = 0.30 (0.14–0.66)	N/A
Women with this Ab status (pregnancy) who developed PPT			
TPOAb +ve, regardless of TgAb	39/56 (69.6%)	27/39 (69.2%)	97/261 (37.2%) $\chi^2 = 19.8$, P = 8.4×10^{-6} OR = 3.88 (2.08–7.23)
TPOAb –ve, regardless of TgAb	24/356 (6.7%)	30/219 (13.7%) $\chi^2 = 7.71$, P = 0.0055 OR = 0.45 (0.26–0.80)	72/4123 (1.8%) $\chi^2 = 39.0$, P = 4.3×10^{-10} OR = 4.07 (2.53–6.54)
TgAb +ve, regardless of TPOAb	17/29 (58.6%)	12/21 (57.1%)	N/A
TgAb –ve, regardless of TPOAb	46/383 (12.0%)	45/237 (20.0%) $\chi^2 = 5.69$, P = 0.017 OR = 0.58 (0.37–0.91)	N/A
TPOAb +ve & TgAb +ve	8/9 (88.9%)	11/17 (64.7%)	N/A
TPOAb +ve & TgAb –ve	31/47 (66.0%)	16/22 (72.7%)	N/A
TPOAb –ve & TgAb +ve	9/20 (45.0%)	1/4 (25.0%)	N/A
TPOAb –ve & TgAb –ve	15/336 (4.5%)	27/215 (12.6%) $\chi^2 = 14.20$, P = 0.0005 OR = 0.32 (0.17–0.63)	N/A

* Not listed here is a relatively old Italian study [4] on 219 women (rate of PPT = 8.7%) in whom thyroid autoantibodies started to be measured at delivery. Similar to us, the Liguria study [2] found that “No differences between women with and without PPT were observed as regards age, parity, smoking habits, gestational age, history of previous miscarriages”, and the Puglia study [5] found that “previous pregnancy, age, smoking status, were not significantly associated with PPT.”

§ Not to overload the table, only for significant differences statistical details are shown, with P values highlighted by the bold print. Lack of a χ^2 value in the last column indicates that statistical analysis was by the Fisher's exact test. N/A = Not applicable.

lowering the threshold of positivity to > 60 U/ml, as the corresponding rates were 4/5 (80.0%) and 1/4 (25.0%) (data not shown).

Summary

The dual Ab and lowered threshold strategy, with the predictor

being positivity for at least one thyroid Ab at levels ≥ 61 U/ml, allows to detect additional cases of PPT or PH compared with the classical, single TPOAb strategy at a positivity threshold of ≥ 101 U/ml. The additional proportion of PPT identified is 23.8% (54/63 [85.7%] vs 39/63 [61.9%], $\chi^2 = 9.24$, **P = 0.002**, OR = 3.7, 95% CI = 1.5–8.8), while the additional proportion of pH detected is 17.7% (29/34 [85.3%] vs 23/34 [67.6%], $\chi^2 = 2.94$, **P = 0.086**, OR = 2.77, 95% CI = 0.8–9.1).

Discussion

Here we have shown that, among pregnant women living in the Straits of Messina area, the rate of PPT is 15.3%. This rate is comprised between 3.9% of Puglia, another region of southern Italy [5], and 22.1% of Liguria, a region in northwestern Italy [2], but it is closer to the latter. These three studies are summarized and contrasted in Table 3.

Such differences in PPT rate paralleled the differences in TPOAb positivity during pregnancy, with our rate (13.6%) being closer to that of Liguria (15.1%) [2] rather than that of Puglia (6.0%) [5]. The rate of TgAb positivity can be compared only with the Liguria study [2], and again it was very close (7.0% vs 8.1%). However, while our rate of women who developed PPT and had tested TgAb +ve during pregnancy was similar to that in the Liguria cohort [2] (27.0% vs 21.1%), the corresponding rate for TPOAb differed (61.9% vs 47.4%) and it was closer to that of the Puglia cohort (57.4%) [5]. Noteworthy, in our cohort and Liguria cohort [2] remarkably similar were the abilities of the TgAb +ve status in pregnancy to predict subsequent PPT (58.6% [17/29] and 57.1% [12/21]). This similarity in predictivity also applied to the TPOAb +ve status (69.6% [39/56] and 69.2% [27/39]), in sharp contrast with the Puglia cohort [5] (37.2% [97/261]). In a Welsh study [3] with a PPT rate (22.3% [49/220]) matching that of the Liguria study [2], the rate of gestational positivity for thyroid microsome Ab (which are a proxy of TPOAb) was 24.5% (54/220), and the predictivity of thyroid microsome Ab +ve status for the development of PPT was 50% (27/54). Concerning PH, its rate among PPT women does not differ in the three Italian studies, with one in two PPT women failing to regain euthyroidism (Table 3).

We complemented our study with an evaluation of the possible value of the following predictors of PPT and/or PH: 1) “high-normal” levels of thyroid Ab; 2) thyroid inflammation detected at ultrasound. We found that, indeed, cases of PPT and/or PH were “hidden” within the range of 61–100 U/ml of either thyroid Ab, a range that still indicates normality (negativity) based on the formal upper normal limit of 100 U/ml. However, these cases were relatively few (3 for TPOAb, but 9 for TgAb), accounting for 4.8% and 14.3% of the 63 PPT cases. Concerning permanent PH, such cases were 1 (TPOAb) and 3 (TgAb), thus accounting for 2.9% and 8.8% of the 34 cases of PPT complicated by permanent thyroid failure. We found that the risk for TPOAb levels at 61–100 U/ml in the first trimester of gestation being predictive of PPT or PH was 25% or 8.3%; the corresponding risk for TgAb levels was 69.2% or 23.1%. In brief, and as summarized at the end of Results, a screening for both PPT and PH that is based on the two Ab assays and on consideration of upper-normal values is more rewarding than one based on TPOAb only and with positive values defined as those above the upper normal limit. To the best of our knowledge, only one study [16] showed the value of upper normal levels of TPOAb (60–100 U/ml) during pregnancy, with an OR of 3.0 for predicting PPT. TgAb were not measured [16].

Formal evidence of correlation between sonographically-evaluated thyroiditis and cytologically-evaluated lymphocytic infiltration of the thyroid in PPT women had been provided by others [18]. We found that presence of thyroiditis at ultrasound in the first trimester of gestation confers a significant risk for PPT (OR = 13.2) compared to its absence, and that this risk is similar to that of TgAb positivity (Table 1). Previously, a Brazilian study on 368 women [16] reported an OR of 6.4 for the sonographic evidence of thyroiditis being predictive of PPT. In a study from Puglia on 74 women who were TPOAb +ve in the first trimester of gestation, the rate of sonographic thyroiditis at 10-week gestation was 86.5% [19], which compares with ours 85.7%. Of those 74 women, 36 (49%) developed PPT [19], which compares with ours 60.7%. No sonographic data were given for the control group of 81 women who were TPOAb-ve at enrollment in the first trimester of pregnancy, and in whom the PPT was 3.7% [19]. In our cohort, of 356 TPOAb-ve women, 76 (21.3%) had thyroiditis in the first trimester of

gestation, with 24 developing PPT (31.6% of 76, and 6.7% of 356). Considering the already very high prevalence of gestational thyroiditis in women who developed PPT, it is not surprising that an ultrasound picture of thyroiditis was a statistically insignificant predictor of pH in our cohort.

In summary, ours is the second study in the English-language literature performed in the new millennium showing that PPT has a frequency greater than 10%. This frequency ranks third after a Welsh study (22.3%) [3] and another Italian study (22.1%) [2]. Also, we and another Italian group [2] found that, based on positivity for the classical biochemical risk factor of PPT (TPOAb), the development of PPT can be predicted in two-thirds of the TPOAb +ve pregnant women, a rate that is greater than the one-third to one-half reported in the literature [1]. However, detection of PPT women is maximized by adding the assay of TgAb, as almost 15% of our PPT women were TgAb +ve but TPOAb –ve in the first trimester of gestation. Moreover, we confirm the few studies showing that US evidence of thyroiditis during gestation is a predictor of PPT. However, because of its high frequency in the entire gestational cohort (35%) and very high frequency in the group that developed PPT (> 80%), the value of sonographically-detected thyroiditis as a predictor of pH was insignificant. Finally, we confirm recent data showing that approximately half of PPT women will have PH.

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