Endocrine (2019) 65:94–101
https://doi.org/10.1007/s12020-019-01882-4

ORIGINAL ARTICLE

Stable consumption of swordfish favors, whereas stable consumption of oily fish protects from, development of postpartum thyroiditis

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Received: 22 November 2018 / Accepted: 22 February 2019 / Published online: 6 March 2019

Abstract

Purpose In 236 pregnant women, we showed that selective or predominant consumption of swordfish (group A) was associated with high rates of positivity for serum thyroid autoantibodies (TPOAb and TgAb) throughout day 4 postpartum. In contrast, selective or predominant consumption of oily fish (group B) was associated with TPOAb and TgAb negativity. Rates were intermediate in group C (scanty consumption of swordfish) and group D (consumption of fish other than swordfish and oily fish). Gestational TPOAb positivity is a risk factor for postpartum thyroiditis (PPT), which evolves into permanent hypothyroidism (PH) in about 50% of cases. Purpose of this study was to verify that the different rates of thyroid autoantibodies in the four groups translated into different PPT rates.

Methods We expanded our previous cohort ($n = 412$) and duration of follow-up (month 12 postpartum), and measured frequency of PPT and PH.

Results At first timester of gestation, we confirmed the different Ab positivity rates in group A vs. group B (TPOAb = 21.7% vs. 4.7%, $P < 0.0001$; TgAb = 14.1% vs. 2.4%, $P < 0.05$). Overall, PPT prevalence was 63/412 (15.3%), but 22/92 in group A (23.9%), 4/85 in group B (4.7%; $P < 0.0001$ vs. group A), 17/108 (15.7%) in group C, and 16/117 (13.7%) in group D. Approximately half of the PPT women had PH, regardless of fish group.

Conclusions In conclusion, stable consumption of oily fish (which is enriched in polyunsaturated omega-3 fatty acids) protects from PPT, while stable consumption of swordfish (which is enriched in pollutants) favors PPT. Thus, a dietary prophylaxis of PPT is possible.

Keywords Autoimmune thyroid disease · Postpartum thyroiditis · Environmental factors · Fish consumption

Introduction

Fish consumption or supplementation with polyunsaturated omega-3 fatty acids (PUFA) was reported to cure and/or prevent autoimmune and nonautoimmune disorders, while meat consumption has often the opposite effect [1–12]. However, fish is one of the means to ingest pollutants [1, 2, 13], particularly if the fish consumed is large, like the top predators.

We took advantage of the local popularity of two varieties of seafood, the top predator swordfish and the PUFA-rich oily fish, to conduct an unprecedented study [1]. We hypothesized that, among pregnant women with stable dietary habits, the serum profile of thyroid autoantibodies (Ab) throughout gestation would have been the worst in swordfish consumers, the best in oily fish consumers and intermediate in other fish consumers. Thus, in 236 thyroid

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disease-free Caucasian women with stable dietary habits, we measured serum thyroglobulin Ab (TgAb) and thyroperoxidase Ab (TPOAb), which are markers of thyroid autoimmune disease, at each trimester of gestation and postpartum day 4. These women were stratified based on the type of fish consumed: A (swordfish selectively or predominantly, but no oily fish), B (oily fish selectively or predominantly, but no swordfish), C (swordfish not predominantly plus other fish, not necessarily oily fish), D (fish other than swordfish and oily fish). We found that the greatest in group A and the lowest in group B were positivity rates ($P < 0.001$) and serum levels ($P < 0.05$–< 0.001) of either antibody [1].

In the context of a wider study that links nutrition, pollution, autoimmunity, and women's health, we have evaluated a number of indices. One of these indices, not reported in the previous study [1], was presence of thyroid inflammation (thyroiditis) as assessed by neck ultrasound. We wished to expand the cohort and ascertain whether the worst thyroid Ab profile in group A would translate into the highest rate of postpartum thyroiditis (PPT), while the best thyroid Ab profile in group B would translate into the lowest rate. Another major interest was to check whether permanent hypothyroidism (PH), which is a complication of PPT, had the greatest occurrence in group A and the smallest in group B.

Patients and methods

Cohort

Details were provided in two previous papers [1, 14]. To enlarge the cohort from 236 [1] to 412 women [14], we were consistent in applying inclusion and exclusion criteria.

Like other previous studies on PPT (for references see ref. [15]), we enrolled women with singleton pregnancy. Avoidance of confounding variables required a homogeneous cohort of pregnant women. Entry criteria at the first gynecological visit (7–11 week of gestation) required (i) to sign the informed consent; (ii) to be a Caucasian woman stably living in the Straits of Messina area; (iii) to have no history of illicit drug/alcohol abuse except for one daily glass of wine at mealtime; (iv) to have stable dietary habits in the last 5 years, with fish consumed unfried at home; (v) to have a commensal relative who could confirm fish consumption. Final enrollment required that women had not miscarried, so that we could continue evaluation through month 12 postpartum. Exclusion criteria were (i) having already known thyroid disease, (ii) having thyroid dysfunction discovered at our initial screening, (iii) development of Graves' disease during gestation or postpartum. To avoid difficulties in estimating fish consumption, we excluded women who (i) consumed fish mixed with pasta/rice, though pasta/rice dressed with fish sauce/broth was permitted once a month maximum; (ii) went to restaurants/takeaways more than once a month. To avoid the confounding variables of toxic chemicals released from cans and decline in thyroid Ab induced pharmacologically, we excluded women who used to eat canned food and who were under immunosuppressants.

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).

Fish consumption

We applied previous methodology [1], using an Italian questionnaire [16] implemented by color photographs to show portions and type of fish, and stratifying into four fish-consuming groups (A–D), as described above in the Introduction. There were a few women who did not consume fish at all (group E). Nevertheless, we thought it was of interest enrollment of nonfish eaters for purposes of comparison with the fish eaters. The fish portion eaten by all women was the 150 g one. Because seafood was eaten as an entrée either at lunch or dinner, for statistical purposes, number of fish portions consumed each month and frequency of fish consumed each month coincided. As explained previously [1] our cohort is comparable with the Southern Italy population, except for the two-fold more frequent consumption of swordfish as a result of our local traditions. Indeed, the Straits of Messina is a major spawning area for swordfish.

Biochemical, ultrasonographic evaluation, and definition of PPT

Enrollment occurred at 7–11 weeks of gestation, when the first clinical and biochemical evaluation, and thyroid ultrasonography (US) were performed [14]. Biochemical evaluation was repeated at the second and third month of gestation, and at 6 weeks, 3, 6, and 12 months postpartum. 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. US was performed by the same ultrasonographist, who was blind to the biochemical data, using the Logiq instrument (General Electric Healthcare, UK) and a 7.5 MHz high-resolution probe. The pattern suggestive of thyroiditis was a diffuse thyroid gland hypoechogenicity with heterogeneous echotexture.

We continued to use the electrochemilumiscent kits by Roche Diagnostics (Germany) to measure serum thyrotropin (TSH), free thyroxine (FT4), free triiodothyronine (FT3), TPOAb and TgAb. 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).

Outcomes

The primary outcomes concerned the postpartum period, while the secondary outcomes concerned gestation (study entry). The primary outcome were rates of PPT and PH. PH was defined as at the end of the first postpartum year [15]. The secondary outcomes were (i) rate of positivity for either TPOAb or TgAb; (ii) rate of thyroiditis at thyroid US.

Statistics

Continuous data are presented as mean ± 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 borderline significant.

Results

Fish consumption

A complete list of fish consumed is shown in Table 1. Distribution of women among fish groups confirmed previous data [1]. For instance, the selective or prevalent swordfish consumers (group A) accounted for 22.9% of the 402 fish eaters (24.4% in the previous cohort [1]), while the overall swordfish consumers (group A+group C) accounted for 49.7% (49.1% in the previous cohort [1]).

Confirming the 7.0–7.8 range of monthly fish consumption found in the previous study [1], the four fish groups remained comparable in terms of frequency of fish consumption (7.5–8.0 times/month or twice a week) (Table 1). Thus, any difference in outcomes needed to have a qualitative, not quantitative explanation.

Primary outcomes

Data for the primary outcomes (prevalence of PPT and PH) and data for the secondary outcomes (see next heading) are summarized in the bottom part of Table 2.

Overall, prevalence of PPT was 63/412 (15.3%), and it was the highest in the nonfish consumers (group E, 40%). Within the four groups of fish consumers, group A had the highest prevalence and group B the lowest (23.9% vs. 4.7%, $P < 0.0001$), a five-fold difference. Groups C and D had intermediate frequencies (15.7% and 13.7%), either one being statistically greater ($P < 0.05$) than frequency in group B. Of groups C and D, the latter had a borderline lower

Table 1 Subdivision of the 412 pregnant women into different fish groups, and frequency of fish consumption

Group	Frequency of fish consumption No. of times per month[a]	Type of fish consumed[b]
A ($n = 92$)	7.5	**Swordfish** (*Xiphias gladius*).
		Other fish: cod (*Gadus morhua*), European flying squid (*Todarotes sagittatus*), calamari (*Loligo vulgaris*), octopus (*Octopus vulgaris*), shrimps (*Aristeus antennatus, Penaeus kerathurus*).
B ($n = 85$)	7.5	**Any of the oily fish, alone or in combination: anchovy** (*Engraulis encrasicholus*), **sardine** (*Sardina pilchardus*), **round sardinella** (*Sardinella aurita*), **sprat** (*Sprattus sprattus*), **garfish or sea needle** (*Belone belone*), **saury** (*Scomberesox saurus*), **mackerel** (*Scomber scombrus*), **sand eel** (*Gymnammodites cicerellus*), **silver scabbardfish or beltfish** (*Lepidopidus caudatus*).
		Other fish: hake (*Merluccius merluccius*), cod (*Gadus morhua*), salmon (*Salmo salar*), sole (*Solea solea*), calamari (*Loligo vulgaris*), octopus (*Octopus vulgaris*), European flying squid (*Todarotes sagittatus*), gilthead sea bream (*Spaurus aurata*), sea bass (*Dicentrarchus labrax*), shrimps (*Aristeus antennatus, Penaeus kerathurus*), mussels (*Mytilus galloprovincialis*).
C ($n = 108$)	8.0	Swordfish + **any of**: hake (*Merluccius merluccius*), cod (*Gadus morhua*), salmon (*Salmo salar*), sole (*Solea solea*), calamari (*Loligo vulgaris*), octopus (*Octopus vulgaris*), European flying squid (*Todarotes sagittatus*), gilthead sea bream (Spaurus aurata), sea bass (*Dicentrarchus labrax*), shrimps (*Aristeus antennatus*, *Penaeus kerathurus*), mussels (*Mytilus galloprovincialis*), oily fish [for oily fish, see group B].
D ($n = 117$)	8.0	**Any of**: hake (*Merluccius merluccius*), cod (*Gadus morhua*), salmon (*Salmo salar*), sole (*Solea solea*), calamari (*Loligo vulgaris*), octopus (*Octopus vulgaris*), European flying squid (*Todarotes sagittatus*), gilthead sea bream (Spaurus aurata), sea bass (*Dicentrarchus labrax*), shrimps (*Aristeus antennatus*, *Penaeus kerathurus*), mussels (*Mytilus galloprovincialis*), clams (*Venerupis decussata*, *Venus gallina*).
E ($n = 10$)	0	No fish at all.

[a]Median values. Because seafood was eaten as an entrée either at lunch or dinner, number of fish portions consumed each month and frequency of fish consumed each month coincided

[b]Fish consumed most frequently (at least 50% of the time) is typed bold-face

Table 2 Rates, at the first trimester of gestation, of positivity for serum thyroid autoantibodies (TPOAb, TgAb), of thyroiditis at thyroid ultrasound, and of postpartum dysfunction (including permanent hypothyroidism) in women stratified based on pattern of fish consumption (groups A through E)

	Groups based on type of fish consumed				No fish	Whole cohort
	A ($n = 92$)	B ($n = 85$)	C ($n = 108$)	D ($n = 117$)	E ($n = 10$)	All ($n = 412$)
Pregnancy (study entry)						
Ab status						
TPOAb+ve, regardless of TgAb	20 (21.7%)	4 (4.7%)	15 (13.9%)	14 (12.0%)	3 (30%)	56 (13.6%
[vs. group A]		$\chi^2 = \mathbf{10.9}^{d}$		$\chi^2 = \mathbf{3.61}^{a}$		
[vs. group B]	$\chi^2 = \mathbf{10.9}^{d}$		$\chi^2 = \mathbf{4.52}^{b}$	$\chi^2 = \mathbf{3.20}^{a}$		
TPOAb-ve, regardless of TgAb	72 (78.3%)	81 (95.3%)	93 (86.1%)	103 (88.0%)	7 (70%)	356 (86.4%)
TgAb+ve, regardless of TPOAb	13 (14.1%)	2 (2.4%)	7 (6.5%)	5 (4.3%)	2 (20%)	29 (7.0%)
[vs. group A]		$\chi^2 = \mathbf{7.9}^{b}$	$\chi^2 = \mathbf{3.23}^{a}$	$\chi^2 = \mathbf{6.4}^{b}$		
[vs. group B]	$\chi^2 = \mathbf{7.9}^{b}$					
TgAb-ve, regardless of TPOAb	79 (85.9%)	83 (97.6%)	101 (93.5%)	112 (95.7%)	8 (80%)	383 (93.0%)
TPOAb+ve & TgAb+ve [vs. group A] [vs. group B]	2 (2.2%)	0	3 (2.8%)	3 (2.6%)	1 (10%)	9 (2.2%)
TPOAb+ve & TgAb-ve	18 (19.5%)	4 (4.7%)	12 (11.1%)	11 (9.4%)	2 (20%)	47 (11.4%)
[vs. group A]		$\chi^2 = \mathbf{8.69}^{c}$	$\chi^2 = \mathbf{2.8}^{a}$	$\chi^2 = \mathbf{4.45}^{b}$		
[vs. group B]	$\chi^2 = \mathbf{8.69}^{c}$		$\chi^2 = \mathbf{2.6}^{a}$			
TPOAb-ve & TgAb+ve	11 (12.0%)	2 (2.4%)	4 (3.7%)	2 (1.7%)	1 (10%)	20 (4.8%)
[vs. group A]		$\chi^2 = \mathbf{6.0}^{b}$	$\chi^2 = \mathbf{4.9}^{b}$	$\chi^2 = \mathbf{9.3}^{c}$		
[vs. group B]	$\chi^2 = \mathbf{6.0}^{b}$					
TPOAb-ve & TgAb-ve	61 (66.3%)	79 (92.9%)	89 (82.4%)	101 (86.3%)	6 (60%)	336 (81.6%)
[vs. group A]		$\chi^2 = \mathbf{19.0}^{d}$	$\chi^2 = \mathbf{6.9}^{c}$	$\chi^2 = \mathbf{11.8}^{d}$		
[vs. group B]	$\chi^2 = \mathbf{19.0}^{d}$		$\chi^2 = \mathbf{4.7}^{b}$			
US evidence of thyroiditis	41 (44.6%)	25 (29.4%)	37 (34.2%)	37 (31.6%)	4 (40%)	144 (34.9%)
[vs. group A]		$\chi^2 = \mathbf{4.3}^{b}$		$\chi^2 = \mathbf{3.7}^{a}$		
[vs. group B]	$\chi^2 = \mathbf{4.3}^{b}$					
Postpartum						
Thyroid dysfunction (PPT)	22 (23.9%)	4 (4.7%)	17 (15.7%)	16 (13.7%)	4 (40%)	63 (15.3%)
[vs. group A]		$\chi^2 = \mathbf{13.0}^{d}$		$\chi^2 = \mathbf{3.6}^{a}$		
[vs. group B]	$\chi^2 = \mathbf{13.0}^{d}$		$\chi^2 = \mathbf{6.0}^{b}$	$\chi^2 = \mathbf{4.4}^{b}$		
Permanent hypo in PPT [vs. group A] [vs. group B]	12/22 (54.5%)	2/4 (50%)	9/17 (52.9%)	9/16 (56.2%)	2/4 (50%)	34/63 (54%)
Permanent hypo in the whole group	12 (13.0%)	2 (2.4%)	9 (8.3%)	9 (7.7%)	2 (20%)	34 (8.2%)
[vs. group A]		$\chi^2 = \mathbf{6.9}^{c}$				
[vs. group B]	$\chi^2 = \mathbf{6.9}^{c}$		$\chi^2 = \mathbf{3.2}^{a}$	$\chi^2 = \mathbf{2.7}^{a}$		

For details about type of fish consumed, see Patients and methods. Group E women consumed no fish at all, but consumed meat. Symbols for statistical significance: ^{a}P between 0.10 and 0.05 (borderline significant); $^{b}P < 0.05$; $^{c}P < 0.001$, $^{d}P < 0.0001$. When lines for statistical comparisons are void, it means a level of $P > 0.10$. Distribution of the four types of Ab (TPOAb+ve & TgAb+ve, TPOAb+ve & TgAb–ve, TPOAb–ve & TgAb+ve, and TPOAb–ve & TgAb–ve) among the four fish groups was statistically different ($\chi^2 = 29.5$, $P = 0.0005$)

The boldface print for χ^2 means that the difference between proportions is statistically significant, as indicate by the superscript letters

prevalence of PPT compared to group A ($P < 0.10$). All 63 PPT women had ultrasound evidence of thyroiditis at 6 and 12 months postpartum (data not shown).

The rate of PH in women with PPT was similar across groups (~55%). However, because of the said differences in PPT rates, the frequency of PH in the whole fish group (that is, PPT women and non-PPT women) was the highest in group A and the lowest in group B (13.0% vs. 2.4%, $P < 0.001$), with intermediate frequencies in the other two fish groups.

Secondary outcomes

The secondary outcomes concerned the first trimester of gestation (study entry).

(i) *Rate of positivity for thyroid Ab*: Thyroid Ab status was considered in a multifold manner: (i) positivity (or negativity) of one Ab regardless of the status for the other thyroid Ab positivity; (ii) positivity (or negativity) for one Ab taking into account positivity (or negativity) for the other Ab.

Paralleling the pattern described above for PPT, the frequency of either TPOAb or TgAb positivity was the highest in group A (21.7% or 14.1%) and the lowest in group B (4.7% or 2.4%), these rates between the two groups differing statistically ($P < 0.0001$ or $P < 0.05$) (Table 2). Intermediate were the frequencies of either Ab in the other two groups, with an at least borderline significant difference compared to group A and/or group B. There was a fair overlap with previous data [1], as illustratively shown by TPOAb positivity in groups A, B, C and D (25%, 0%, 14.7%, and 8.8% in that study, vs. 21.7%, 0%, 13.9%, and 12.0% in this study). Nonfish eaters had high rates of positivity for either thyroid Ab (30% or 20%) (Table 2).

In the other modality of categorization of thyroid Ab, four sets of TPOAb and TgAb status were possible, from both TPOAb and TgAb being positive to both TPOAb and TgAb being negative (Table 2). Overall, this distribution in four categories was statistically different ($P < 0.001$). The first category (both TPOAb and TgAb positive) was the one least represented, with overlapping rates in the four fish groups. The second and third category (TPOAb+ve/TgAb–ve and TPOAb–ve/TgAb+ve) were overrepresend in group A and under-represented in group B, with intermediate representation (especially for TPOAb positivity) in the other two groups. As a result, the fourth category (TPOAb–ve/TgAb–ve) had the lowest frequency in group A and the greatest in group B ($P < 0.0001$), with intermediate frequencies in the other two fish groups. Ab distribution in group E mimicked that in group A.

It could be of interest to quantify the rates of thyroid Ab positivity and Ab categorization in the subgroup of women who developed PPT upon maintaining stratification based on the type of fish consumed (Table 3). Because of the relatively small number of PPT women, particularly in the PPT-protected group B ($n = 4$), differences were statistically insignificant. However, the apparent trend is a 2.5-fold greater of TPOAb positivity regardless of TgAb (68% vs. 25%) and TPOAb plus TgAb positivity (9.1% vs. 0%) in group A compared to group B.

(ii) *Rate of thyroiditis at neck ultrasound*: Ultrasound-detected thyroiditis displayed the intergroup pattern described above for thyroid Ab, namely overrepresentation in group A (44.6%) and underrepresentation in group B (29.4%), with intermediate representation in the other two groups (Table 2).

It could be of interest to quantify the frequency of thyroiditis in the subgroup of women who developed PPT upon maintaining stratification based on type of fish consumed (Table 3). However, the relatively small number of women in fish groups, especially in group A ($n = 4$) and the high rates of thyroiditis across groups (80% or above) preclude statistical significance of differences.

Discussion

As mentioned in the Results section, our present data on 412 women agree nicely with those we have reported for a smaller cohort of women ($n = 242$) [1]. In the previous paper [1], we had inferred that the greatest rate of gestational positivity for thyroid Ab in the women who consume solely or preferentially swordfish (group A) would have translated into the greatest rate of PPT, while the lowest rate of gestational thyroid Ab positivity in the women who do not consume swordfish at all but consume small oily fish either solely or preferentially (group B) would have translated into the lowest rate of PPT. This inference was verified here. Indeed, the 4.6-fold and 5.9-fold greater rate of TPOAb positivity in group A compared to group B corresponds to a 5.1-fold greater rate of PPT in group A compared to group B. The rate of PPT was also expected to be high in the nonfish eaters (group E), and this expectation was also met, the PPT rate being even higher than that in group A.

Furthermore, we found a 5.4-fold greater rate of PH in group A women compared to group B women. Women of group A who developed PPT had the same odds of

Table 3 Rates, at the first trimester of gestation, of positivity for serum thyroid autoantibodies (TPOAb, TgAb), and of thyroiditis at thyroid ultrasound, in women who developed PPT and who were stratified based on pattern of fish consumption

	Groups based on type of fish consumed				No fish	Whole cohort
	A ($n = 22$)	B ($n = 4$)	C ($n = 17$)	D ($n = 16$)	E ($n = 4$)	All ($n = 63$)
Pregnancy						
Ab status						
TPOAb+ve, regardless of TgAb	15 (68.2%)	1 (25%)	11 (64.7%)	9 (56.3%)	3 (75%)	39 (61.9%)
TPOAb-ve, regardless of TgAb	7 (31.8%)	3 (75%)	6 (35.3%)	7 (43.7%)	1 (25%)	24 (38.1%)
	$P = 0.26$ (Fisher's exact test)					
	Df = 3, $\chi^2 = 2.91$, $P = 0.406$					
TgAb+ve, regardless of TPOAb	6 (27.3%)	2 (50%)	3 (17.6%)	4 (25%)	3 (75%)	18 (28.6%)
TgAb-ve, regardless of TPOAb	16 (72.7%)	2 (50%)	14 (82.3%)	12 (75%)	1 (25%)	45 (71.4%)
	$P = 0.56$ (Fisher's exact test)					
	Df = 3, $\chi^2 = 1.86$, $P = 0.60$					
TPOAb+ve & TgAb+ve	2 (9.1%)	0	2 (11.8%)	3 (18.8%)	1 (25%)	8 (12.7%)
TPOAb+ve & TgAb-ve	13 (59.1%)	1 (25%)	9 (52.9%)	6 (37.5%)	2 (50%)	31 (49.2%)
TPOAb-ve & TgAb+ve	4 (18.2%)	2 (50%)	1 (5.9%)	1 (6.2%)	1 (25%)	9 (14.3%)
TPOAb-ve & TgAb-ve	3 (13.6%)	1 (25%)	5 (29.4%)	6 (37.5%)	0	15 (23.8%)
	Df = 3, $\chi^2 = 2.86$, $P = 0.41$					
	Df = 9, $\chi^2 = 10.53$, $P = 0.31$					
Thyroid echography						
US evidence of thyroiditis	18 (81.8%)	4 (100%)	14 (82.4%)	13 (81.2%)	3 (75%)	52 (82.5%)

developing PH compared to women of group B or other groups. However, because of the scanty number of PPT women in group B ($n = 4$), this data needs to be confirmed.

Concerning the content of PUFA (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA], we had found [1] that the estimated median monthly ingestion of DHA + EPA was the greatest in group B (12.7 g), significantly greater ($P < 0.001$) than in the other three fish groups (A = 6.3, C = 5.7, D = 4.1). However, concerning another beneficial substance, selenium, the highest estimated median monthly ingestion (495 µg) was in group A; values B were 411 µg in group B (P = 0.06 vs. A), 361 µg in group C ($P <$ 0.01 vs. A or B), and 342 µg in group D ($P < 0.001$ vs. A or B) (1). Importantly, concerning the immunotoxicant mercury, its estimated median monthly ingestion was enormously different in group A compared to group B (1063 vs. 25 µg, $P < 0.001$), with values of 251 µg in group C ($P <$ 0.001 vs. both A and B), and 30 µg in group D ($P < 0.001$ vs. A, not significant vs. B) [1]. Because increased iodination of thyroglobulin may trigger thyroid autoimmunity, one could attribute the greatest or the lowest frequency of PPT to increased ingestion of iodine-enriched fish or iodine-poor fish, respectively. This is not the case, because swordfish, anchovy and sardine have very similar iodine content (24–29 mcg iodine/100 g) [17], and because groups of women did not differ for the frequency of fish consumption (see Table 1).

PPT is an autoimmune disease that shares thyroid lymphocytic infiltration and HLA haplotypes with Hashimoto's thyroiditis [18]. Based on the present study, PPT should be added to the list of autoimmune disease that can be prevented/ameliorated by fish consumption (or supplementation with fish oil/PUFA) and favored by no consumption of fish or by high consumption of meat [1–12].

There are strengths in our study. First, we have enrolled an homogeneous cohort of women, excluding a number of counfounding factors. Particularly important is that our women had stable dietary habits. Second, we have taken advantage of local opportunities. Indeed, the Straits of Messina is a major spawning area for swordfish, so that this top predator is a fish consumed frequently. Thus, we could form subgroups of women where swordfish consumers were contrasted with other seafood consumers, particularly the oily fish consumers. Third, we have found a potential environmental risk factor for PPT, namely consumption of predator fish. As a corollary, different studies conducted worldwide have reported a wide range of PPT prevalence (1–22%), sometimes within the same country, because

cohorts may have differed for their dietary habits, particularly fish consumption. Environmental pollution is being increasingly appreciated as an exogenous trigger of thyroid autoimmunity, including our geographical area [19–21].

Limitations of the study are possible difficulties of replication in some countries for objective reasons. The consumption at home, in the context of the Mediterranean diet, of local, wild, fresh fish that is purchased mostly in outdoor markets and is cooked unfried, contrasts with consumption of imported, aquacultured, frozen, storecooked (often fried) fish in the context of unhealthy diets. The U.S. FDA and the Environmental Protection Agency advise pregnant women and children (i) to avoid eating those fish with the potential for the highest level of mercury contamination (e.g., shark, swordfish, king mackerel, or tilefish from the Gulf of Mexico) and (ii) to eat 8–12 oz [(=227–340 g), two average meals] per week of a variety of fish and shellfish that are lower in mercury (e.g., salmon, shrimp, pollock, canned light tuna, tilapia, catfish, and cod) [13]. Due to the protection given by oily fish, another limitation is the low number of women who developed PPT in this fish group, which precludes sound conclusions on additional protection towards PPT evolution into PH. However, the number of women in the whole cohort ($n =$ 412) is not small, because it is within the range of 120–4384 (median 571) reported in previous studies from 14 countries on PPT [15]. In 7 of the 21 studied covered by that review [15], the size of the cohort is 120–368, and in another 6/21 it is 460–643.

In summary, stable consumption of the omega-3-rich oily fish, namely a consumption that had started years before gestation and continues through gestation and postpartum, protects towards PPT development. The value of such protection can be appreciated when both oily fish and swordfish are consumed, in that oily fish attenuates the PPT risk conferred by consumption of swordfish. The PPT risk is maximum in women who do not to consume any fish at all (meat eaters). The PPT protection conferred by regular oily fish consumption is reflected by low rates of humoral and instrumental marker of thyroid autoimmunity, namely thyroid antibodies and sonographic evidence of thyroiditis. Pending confirmation of our data, the translational implication of our results is dietary prophilaxys of a frequent disorder in the context of women's health. A dietary approach of thyroid autoimmune disorders seems even better than a nutraceutical approach [22–26], with oily fish bringing additional benefits on both gestational and neonatal outcomes other than autoimmunity-related [27].

Acknowledgements We thank Prof. Luigi Manasseri, physiologist and nutritionist at the University of Messina, for having reviewed the seafood consumption analysis. We thank the following obstetricians/gynecologists/endocrinologists and family physicians for help in carrying-out this study: Professor Domenico Granese, former Director of the Division of Obstetrics and Gynecology and Director of the School of Midwifery at our University hospital; professor Rosario D'Anna and professor Francesco Corrado, who succeeded as the Director of the School of Midwifery; Doctors Angela Scilipoti, Carmela Lo Re, Antonello Ardizzone, Silvia Russo, Pietro Rizzo, Emanuela Raffone, Angelo Santamaria, and Filippo Genovesi; Doctors Lorella Li Calzi, Taddeo Pappa, Salvatore Seminara, and Domenico Tromba; Doctors Umberto Alecci, Dr. Antonio Alibrando, Angelo Crescenti, Emanuele Crescenti, Santi Inferrera, Sebastiano Marino, Francesco Peditto, Riccardo Scoglio, Salvatore Totaro, Giuseppe Pantano, Giuseppe Simone and Carmen Simone. We also gratefully acknowledge midwives and nurses, particularly drs. Rita Laccoto and Franco Previte.

Funding This work was partly supported by a grant from the Regional Department of Health (Assessorato Regionale alla Sanità, Programma per lo sviluppo del Servizio Sanitario Regionale, bando 2007, Prot. no. 3/Dip/1097) awarded to S.B.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments. Approval for this study was given from the ad hoc committee of the Regional Department of Health (protocol no. 3/1097).

Informed consent Informed consent was obtained from all individual participants included in the study.

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