Fetal Loss Associated With Excess Thyroid Hormone Exposure

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Context Maternal hypothyroidism and hyperthyroidism have deleterious effects on the outcome of pregnancy. While the effects of thyroid hormone (TH) deprivation on the fetus, independently from that on the mother, can be studied in infants with congenital hypothyroidism, this is not the case in those with fetal thyrotoxicosis.

Objective To study the effects of TH excess on fetuses carried by mothers with resistance to TH (RTH) who are euthyroid despite high TH levels but who may carry normal fetuses that are exposed to high maternal hormone levels.

Design, Setting, and Participants Retrospective study of 167 members of an Azorean family with RTH. Affected individuals had the RTH phenotype (high serum concentration of free thyroxine and triiodothyronine without suppressed thyrotropin) confirmed by genotyping to identify the Arg243→Gln mutation in the TH receptor β gene.

Main Outcome Measures Pregnancy outcome of affected mothers vs that of unaffected mothers carrying fetuses conceived by affected fathers, as well as that of unaffected first-degree relatives and outcomes from the general island population. Comparison of birth weights and blood concentrations of thyrotropin (TSH) obtained during routine neonatal screening of infants born to these 3 groups.

Results Thirty-six couples with complete information belonged to 1 of 3 groups: affected mothers (n=9), affected fathers (n=9), and unaffected relatives (n=18). Mean miscarriage rates were 22.9%, 2.0%, and 4.4%, respectively (χ^2=8.66, P=.01). Affected mothers had an increased rate of miscarriage (z=3.10, P=.002, by Wilcoxon rank-sum test). They had marginally higher than expected numbers of affected offspring, ie, 20 affected and 11 unaffected children (P=.07), while affected fathers had 15 affected and 12 unaffected children (P = .35). Unaffected infants born to affected mothers were significantly smaller than affected infants, having a mean SD score for gestational age of –1.79 (SD, 0.86) vs –0.06 (SD, 1.11) to –0.22 (SD, 0.70) for all other groups (P<.001). Only unaffected infants born to affected mothers had undetectable blood levels of TSH.

Conclusion There was a higher rate of miscarriage in mothers affected by RTH that may have involved predominantly unaffected fetuses. The lower birth weight and suppressed levels of TSH in unaffected infants born to affected mothers indicates that the high maternal TH levels produce fetal thyrotoxicosis. These data indicate a direct toxic effect of TH excess on the fetus.

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THYROID HORMONE (TH) PLAYS an important role in embryogenesis and fetal maturation.[1] In rat embryos cultured in vitro, addition of serum from animals with either hypothyroidism or hyperthyroidism induced malformations.[2] Evidence of a similar effect in humans, including higher miscarriage rates, intrauterine growth retardation, and congenital malformations, however, is indirect since it comes from studies of women with autoimmune thyroid disease.[3-5] Since the presence of thyroid autoantibodies is associated with an increased rate of miscarriages,[6,7] it remains unclear whether maternal TH has a direct toxic effect on the growing fetus.

In the present study we took advantage of a disorder that circumvents the confounding factors that prevent assessment of the direct impact of maternal TH on the fetus. Indeed, individuals with resistance to TH (RTH) achieve euthyroidism by maintaining high serum levels of free TH. Furthermore, their increased thyroid gland activity is not mediated through thyroid-stimulating antibodies.[8] The disorder is caused by mutations of the TH receptor β gene (*TR*β). Mutant receptors not only have reduced function, but also interfere with the function of the normal receptor, explaining the dominant mode of inheritance.

We retrospectively examined the pregnancy outcome in a large family harboring the *TR*β mutation, Arg243→Gln (R243Q),[9] which has been previously characterized in detail.[10,11] The estimated miscarriage rate in affected and unaffected women, together with determination of the genotype of all live births, their weights, and neonatal blood thyrotropin (TSH) concentrations, allowed us to evaluate the influence of high maternal levels of TH on the fetuses.

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Table 1. Thyroid Function Tests in Family Members and Relatives by Marriage*

Group	Mean (SD)			
	Free T_4 Index†	Free T_3 Index†	TSH, mU/L	TG, µg/L
Affected	18.1 (2.5)‡	292 (67)‡	2.4 (2.4)	44 (32)‡
Unaffected relatives				
First-degree	8.9 (1.3)	145 (28)	2.1 (1.7)	13 (11)
Distant	8.9 (1.7)	149 (29)	2.1 (1.1)	15 (11)
By marriage	9.1 (1.5)	137 (18)	1.4 (0.6)	17 (11)
Reference range	6.0-10.5	95-190	0.4-3.8	1-30

Abbreviations: T4, thyroxine; T3, triiodothyronine; TG, thyroglobulin; TSH, thyrotropin.
*Patients who had undergone thyroid surgery were not included.
†Free T_4 and T_3 indexes were estimated from the product of the total T_4 or T_3 concentrations, respectively, and the normalized resin T_4 uptake ratio.
‡$P<.001$ vs all other groups.

METHODS

Participants

More than 200 members of an Azorean family of Portuguese ancestry with RTH were identified. They were traced to a late 19th-century founder couple, the progenitor of 61 nuclear families spanning 4 generations (generation 1, 6 families; 2, 19 families; 3, 35 families; and 4, 1 family). Of the 167 individuals available for examination, 44 were affected (23 women, 21 men) and 123 were unaffected (35 first-degree relatives [18 women, 17 men], 54 distant relatives [21 women, 33 men], and 34 relatives by marriage [14 women, 20 men]). All couples bore children and/or had pregnancies. In 23 couples, one of the spouses was affected; in 19 unaffected couples, one of the spouses was first-degree relative to an affected individual (ie, an unaffected child of an affected parent). The remaining 19 couples were distant (second-generation) relatives. Two of the affected couples were excluded because of incomplete information and another 3 because of thyroidectomy-induced hypothyroidism (TSH values of 15-75 mU/L) during all pregnancies. Information from 1 unaffected couple was incomplete.

Data Collection

A full clinical history with particular emphasis on pregnancies and miscarriages was obtained by interviewing all mothers, available spouses, and family members. The presence of pregnancy and miscarriage was made by clinical criteria (miscarriages were scored when vaginal bleeding had occurred with or without cramping and passing of clots after pregnancy had been diagnosed by a physician and confirmed by conventional pregnancy test). Records from hospital admissions, family physicians, and other relevant sources of clinical information were also obtained. The presence of RTH was not known to the participants or to the record keepers. The study was approved by the institutional review boards of the Hospital Divino Espérito Santo, Azores-Portugal, and the University of Chicago, Chicago, Ill. Informed consent (oral consent in Azores, written consent in Chicago) was obtained from all participants.

Laboratory Studies

The RTH phenotype was identified by the presence of elevated serum concentrations of free thyroxine (T_4) and triiodothyronine (T_3) in the presence of nonsuppressed TSH levels. The diagnosis was confirmed in all participants by the presence of a single nucleotide substitution in 1 allele of the *TR*β gene. This mutation, R243Q, was described in several unrelated families.[10-12]

Blood TSH values were obtained from the registry of the National Center for Neonatal Diagnosis in mainland Portugal. Of the 123 participants included in the 3 groups under analysis, 50 (41%) were born after the institution of routine screening for neonatal hypothyroidism; TSH values were recovered from 44 of these 50 (88%). Blood was collected on filter paper between the 6th and 10th day of life.

Statistical Analysis

Thyroid function test results and serum TSH levels in different groups were compared using analysis of variance.

Miscarriage rates for the groups of affected mothers, affected fathers, and unaffected first-degree relatives were first calculated as the ratio of total number of miscarriages to the total number of pregnancies (the "per pregnancy" rate). Since outcomes among multiple pregnancies in the same couple are potentially correlated, we also calculated the miscarriage rate for each couple and averaged the rates over the couples in the group (the "per couple" rate). The distribution of affected children for each couple was similarly calculated.

The per-couple miscarriage rates were analyzed using the Kruskal-Wallis test and the Wilcoxon rank-sum test. We used a 1-sided binomial test to analyze whether the observed ratio of affected to unaffected progeny in couples with an affected mother or father deviates significantly from 1. The effect of parental and infant genotype on birth weight was assessed by repeated-measures analysis of variance to account for the correlation among infants' birth weights within the same couple. Available data from the general population of San Miguel Island was used for comparison. For birth weights and neonatal TSH values, groups were compared using analysis of variance with the Tukey adjustment for multiple pairwise comparisons. Analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC); $P<.05$ was used to determine statistical significance.

RESULTS

All participants with RTH, except for the 3 who underwent thyroid surgery, had serum free T_4 and T_3 values above the upper limit of normal without suppressed concentrations of TSH. The latter ranged from 0.6 to 5.8 mU/L (reference range, 0.4-3.8 mU/L). Serum thyroglobulin concentrations were also high in the majority of affected participants, in agreement with the increased activity of their thyroid glands (TABLE 1). Only individuals expressing the RTH phenotype harbored the R243Q mutation, but none

manifested typical symptoms and signs of thyrotoxicosis.

The 18 affected and 18 unaffected couples used in the analysis of miscarriages had 89 and 68 pregnancies, respectively. The per pregnancy rates of miscarriage in the affected mothers, affected fathers, and unaffected first-degree relatives were 23.7%, 6.7%, and 8.8%, respectively, while the overall miscarriage rate in the general population was 8.1% (TABLE 2). The per couple mean miscarriage rates, on the other hand, were 22.9%, 2.0%, and 4.4% for the 3 groups, respectively (χ^2=8.66, P=.01). A 2-sample Wilcoxon rank-sum test showed that the miscarriage rate in the affected mothers group was significantly higher than in the combined group without affected mothers (z=3.10, P=.002).

Affected mothers delivered 20 affected and 11 unaffected children, while spouses of affected fathers delivered 15 affected and 12 unaffected children. The 56% rate of affected children in the latter group is in accordance with the expected mendelian distribution of a dominantly inherited trait. The test that the observed genotype distribution ratio of children born to affected mothers is different than 1 has a P value of .07. The per pregnancy prevalences of affected children were 64.5% and 55.6% for those born to affected mothers and affected fathers, respectively; the per couple prevalences were 77.9% and 48.1%, respectively.

Birth weight records were found for 67% to 92% of the newborns of the different groups. Unaffected infants born to affected mothers had mean SD scores for gestational age of –1.79 (SD, 0.86) vs –0.06 (SD, 1.11) for affected infants born to the same mothers (P<.001) (FIGURE 1). This was not true for infants born to affected fathers. Except for unaffected infants born to affected mothers, the mean birth weights of infants from all other groups (3.14-3.16 kg) were not different from the mean birth weight for infants born on San Miguel island (3.18 kg).

As shown in FIGURE 2, TSH values of infants born to the various groups were not significantly different except for the unaffected infants born to affected mothers, in whom TSH was undetectable (<0.1 mU/L). One of these infants had a low birth weight of 2.1 kg (–2.7 SDs). Thyroid function tests were assessed prospectively in the last born. Levels of TSH were not detectable at 1 and 7 days, and levels of free T_4 and T_3 were above the reference ranges. On day 14, levels of free T_4 had normalized and TSH level was just below reference range (0.4 mU/L); however, by day 28, TSH level had increased to 4.8 mU/L.

It is of interest to note that 1 of the affected mothers, excluded from the study because she had postablative hypothyroidism with TSH values above 15 mU/L but free T_4 levels still above reference range, delivered 2 infants with low but detectable blood TSH values (1.9 and 2.6 mU/L).

COMMENT

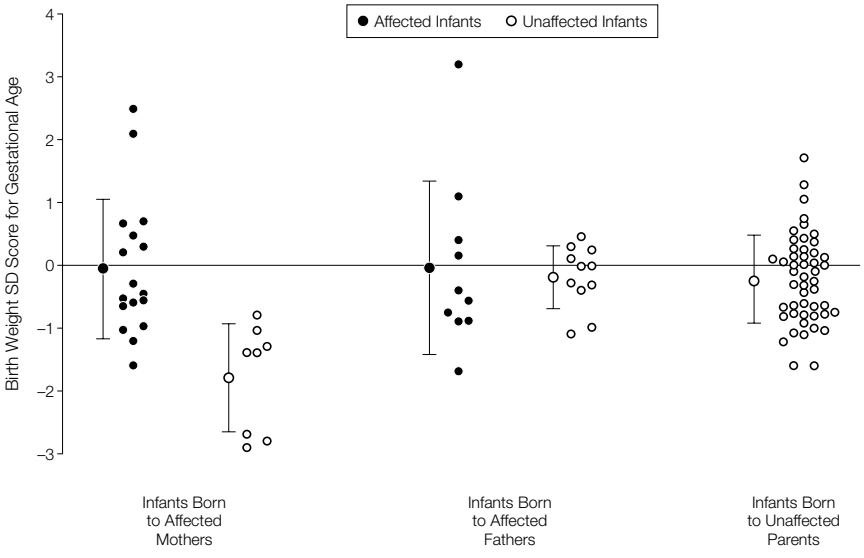
Since the first description of RTH,[13] more than 200 families have been identified.[14] Affected patients are usually heterozygous for mutations in the *TR*β

Table 2. Rates of Miscarriage

	Affected		Unaffected (First-Degree Relatives)	Unrelated*
	Mothers	Fathers		
No. of couples	9	9	18	1804
No. of pregnancies	59	30	68	3765
No. of miscarriages	14	2	6	305
Miscarriage rate, %				
Per pregnancy	23.7	6.7	8.8	8.1
Per couple†	22.9‡	2.0	4.4	

*General population of San Miguel Island.
†Average of the miscarriage rates of each couple in the group.
‡χ^2_2 = 8.66 and P = .01 by Kruskal-Wallis test; unrelated individuals are not included in this comparison.

Figure 1. Birth Weights in the Different Groups and According to Genotype



Data are expressed as mean SD score for gestational age using a chart obtained for singleton infants born to the Portuguese population and adjusted for the sex of the infant. A highly significant reduction in birth weight was found only in unaffected infants born to affected mothers. In addition, 3 of the infants in this group are of low birth weight, according to World Health Organization criteria. Groups were compared using analysis of variance with the Tukey adjustment for multiple pairwise comparisons. P<.001 for affected vs unaffected infants born to affected mothers; P=.99 for affected vs unaffected infants born to affected fathers; P=.001 for unaffected infants born to affected fathers vs those born to affected mothers; and P<.001 for infants born to unaffected parents vs unaffected infants born to affected mothers.

gene, as was also the case in the large Azorean family described herein. Screening was extended to 74 descendants of siblings of the founding mother and 108 descendants of the founding father and no RTH was identified, indicating that the R243Q mutation occurred de novo in 1 of the founders. This is not surprising considering that the mutation involves a CpG mutational hot spot.[15]

The study was undertaken to assess the effect of TH excess on the fetus without the concomitant effect of hormone excess on the mother and without the possible effect of antibodies associated with autoimmune thyrotoxicosis. This occurs rarely in congenital thyrotoxicosis due to gain-of-function mutations in the TSH receptor gene.[16] However, even in these rare occurrences, thyrotoxicosis does not occur before the full development of the fetal thyroid gland. The study of women with RTH provided a unique opportunity to evaluate the direct effect of maternal TH excess on the fetus without producing hypermetabolism in the mother. In these women that carry both unaffected and affected fetuses, only the former should experience the metabolic effects of excess maternal hormone. Fetuses harboring the same mutation as the mother would be exposed to appropriate levels of the hormone. Furthermore, couples made up of affected fathers and unaffected mothers carrying unaffected and affected fetuses serve as invaluable controls for any other unknown effect of the mutant allele harbored by the fetus.

Our data show a 3- to 4-fold increase in the rate of miscarriage in affected mothers compared with that of spouses of affected fathers or unaffected first-degree relatives, as well as with the overall miscarriage rate in the population of San Miguel Island. The latter was similar to that found in other regions of the world.[17] This difference held true to an even greater extent when rates were calculated per couple.

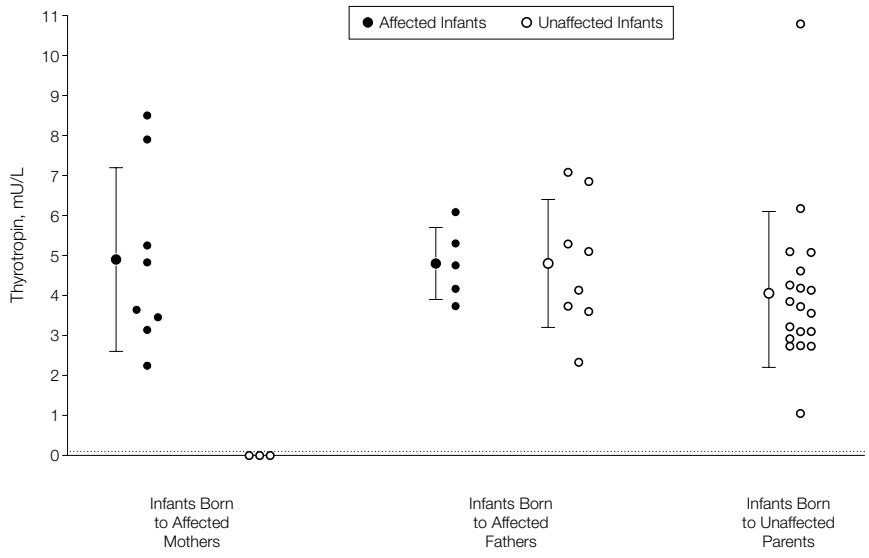
Fertility was not impaired in affected couples, regardless of whether women or men harbored the mutant *TR*β gene. The greater number of pregnancies among affected mothers compared with those among spouses of affected fathers was not significant ($z=1.39$, $P=.16$, by Wilcoxon rank-sum test). Furthermore, the higher rate of miscarriage was not related to increased maternal age and/or greater parity, both of which are known risk factors for spontaneous abortion.[18] Indeed, the age span of parity in women from both groups was not different and there was no correlation between parity and rate of miscarriage.

Although of borderline significance, the difference in genotype frequency among descendants of affected mothers (20 affected vs 11 unaffected offspring), when combined with a significantly higher miscarriage rate, suggests that these women tend to miscarry more unaffected than affected fetuses. The difference in genotype frequency was not found in the progeny of affected fathers who had, as expected, almost equal numbers of affected and unaffected offspring. Since the mothers were not thyrotoxic and had no thyroid autoantibodies, it may be concluded that miscarriages were the consequence of the fetal exposure to the high levels of TH. This is further supported by the improved survival of the affected fetuses, for whom high TH levels were physiological, just as they were for their affected mothers. Contrary to findings in women with uncontrolled hyperthyroidism,[19] women with RTH had no increased frequency of premature labor, preeclampsia, stillbirths, and perinatal loss, further indicating that mothers with RTH are not thyrotoxic despite their high circulating levels of TH.

Unaffected infants born to affected mothers showed a significantly lower birth weight than their affected siblings. This suggests that the high maternal TH level was able to induce a catabolic state during fetal life, similar to what happens in children and adults with uncontrolled hyperthyroidism.[20] That these infants were thyrotoxic is supported by their suppressed blood levels of TSH at birth.

Taken together, these findings represent the first evidence in humans that TH

Figure 2. Neonatal Blood Thyrotropin Concentrations in the Different Groups and According to Genotype



Only unaffected infants born to mothers with resistance to thyroid hormone had undetectable blood thyrotropin values (<0.1 mU/L; dotted line) on routine screening. Groups were compared using analysis of variance with the Tukey adjustment for multiple pairwise comparisons. $P=.003$ for affected vs unaffected infants born to affected mothers; $P>.99$ for affected vs unaffected infants born to affected fathers; $P=.005$ for unaffected infants born to affected fathers vs those born to affected mothers; and $P=.01$ for infants born to unaffected parents vs unaffected infants born to affected mothers.

excess can, by itself, impair embryogenesis of growing fetuses through transplacental passage of maternal TH. Until now, greater attention has been given to the deleterious effect of insufficient TH passage from mother to fetus.[21,22] Yet, indirect evidence for the potentially toxic effect of TH excess is contained in the recent finding of high levels of iodothyronine deiodinase 3 in the uterine lumen surrounding the fetal cavity.[23] This enzyme inactivates the potential biological effect of T_4 and T_3 by converting them into the inactive forms 3,3′,5-triiodothyronine (reverse T_3) and 3,3′-diiodothyronine, respectively. In this respect, it is interesting to note that the relative deficiency in TH levels occurring in affected fetuses carried by unaffected mothers (spouses of affected fathers) did not increase fetal attrition.

The data presented herein show, for the first time in humans, that high levels of TH can exert a direct toxic effect on fetal development. This is manifested by an increased rate of miscarriages and a lower birth weight of unaffected infants born to euthyroid mothers with high levels of TH. As expected, fetuses harboring a mutation that reduces the sensitivity to TH are protected from this toxic effect of TH excess. Given the established importance of providing TH replacement to even mildly hypothyroid pregnant women, it is important to recognize that overreplacement appears to be equally detrimental.

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Study concept and design: Anselmo, Weiss, Refetoff.
Acquisition of data: Anselmo, Weiss, Refetoff.
Analysis and interpretation of data: Cao, Karrison.
Drafting of the manuscript: Anselmo, Refetoff.
Critical revision of the manuscript for important intellectual content: Anselmo, Cao, Karrison, Weiss, Refetoff.
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Statistical analysis: Cao, Karrison.
Administrative, technical, or material support: Weiss, Refetoff.
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