REVIEW

Postpartum Autoimmune Thyroid Syndrome

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Introduction

PREGNANCY is associated with remarkable changes in both endocrine function and immune reaction. The fact that thyroid problems develop after pregnancy has been frequently described in old literatures; however, systematic studies have not been performed for a long time. Graves' disease was first described by Caleb H. Parry. In 1825, 3 years after Parry's death, a collection of his hitherto unpublished medical writings was assembled and published by his son. The first case of his 6 patients was seen in 1786 and had experienced palpitation, neck swelling and protrusion of eyes after delivery [1]. Thus the first patients with Graves' (Parry's) disease described in the medical literature was the case of postpartum onset. In 1840, Karl A. von Basedow reported 4 cases of Graves' (Basedow's) disease [2]. Interestingly one of his 3 female patients was also the case of postpartum onset. Reviewing these old reports, it is easily suggested that postpartum onset of Graves' disease may be frequently observed in the general population. However, little attention had been paid to the postpartum onset of Graves' disease.

Postpartum onset of hypothyroidism has long been known to occur as a result of hypopituitarism since the report by Sheehan in 1937 [3]. In 1948, on the otherhand, Robertson reported the frequent occurrence of hypothyroidism after delivery in association with endemic goiter and suggested that iodine deficiency in the postpartum period might be one

factor inducing these changes [4]. In 1955, Fraser and Garrod [5] reported four cases of primary myxoedema dating from "postpartum shock or hemorrhage." They did not discuss its possible relation to autoimmune abnormalities since the concept of autoimmune thyroiditis was unknown at that time. In 1963, Cooke reported 4 cases of "true myxoedema" developed after uncomplicated confinements [6]. All patients had positive test for anti-thyroid antibodies but he did not discuss any possible etiologies. In 1975 we reported our first case of postpartum transient hypothyroidism and possible pathogenesis of autoimmune aggravation was proposed [7]. Since then, many cases have been reported including our own earlier studies [8, 9], and currently postpartum thyroid dysfunction is well recognized in every country.

Postpartum Thyroid Dysfunction

Definition

Postpartum autoimmune thyroid syndrome is defined as any kind of thyroid dysfunction, including Graves' disease and Hashimoto's thyroiditis, that is newly occurring during the postpartum period from individuals who had experienced no previous thyroid dysfunction [10].

Various Types

Postpartum thyroid dysfunctions are classified by their clinical features (hyperthyroid and/or hypothyroid, transient or persistent) into 5 categories; (I) persistent thyrotoxicosis; (II) transient thyrotoxicosis; (III) destructive thyrotoxicosis followed by transient hypothyroidism; (IV) transient hypothy-

This review was written as a memorial article for the Miyake Prize of the Japan Thyroid Association awarded to Dr. Nobuyuki AMINO, on October 7th, 1998.

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roidism and (V) persistent hypothyroidism (Fig. 1).

Persistent thyrotoxicosis (group I) and a part of transient thyrotoxicosis (group II) revealed a high radioactive iodine uptake (RAIU), and therefore are considered as Graves' disease. In transient thyrotoxicosis with a high RAIU, the overproduction of thyroid hormones ceases spontaneously within a year. Thyrotoxicosis in postpartum Graves' disease usually occurs at 4~6 months postpartum.

Most postpartum thyroid dysfunctions occur due to an exacerbation of autoimmune thyroiditis. They often manifest themselves as transient thyrotoxicosis (destructive thyrotoxicosis). In many cases, destructive thyrotoxicosis develops at 1~3 months postpartum. Depending on the extent of the destruction, transient hypothyroidism may follow (group III) or not (group II, with a low RAIU). Occasionally, Graves' disease occurs closely after, or concomitantly with destructive thyrotoxicosis [11]. When cellular damage occurs slowly, hypothyroidism alone, rather than destructive thyrotoxicosis may be observed after delivery. In many cases, it is transient (group IV). However, it may persist in a few cases (group V).

Prevalence

The prevalence of postpartum thyroid dysfunctions in the general population is approximately 5% (1.1~16.7%; Table 1), *i.e.* one in 20 pregnant women [10, 12-23]. The prevalence of postpartum Graves' disease (both persistent and transient) is estimated at 11% of those with postpartum thyroid

Table 1. Prevalence of postpartum thyroid dysfunction

Year	Author	Country	Prevalence (%)
1982	Amino	Japan	5.5
1982	Turney*	USA	9.0
1984	Jansson	Sweden	6.5
1985	Walfish	Canada	7.1
1986	Freeman	USA	1.9
1987	Nikolai	USA	6.7
1987	Lervang	Denmark	3.9
1988	Fung	UK	16.7
1990	Rasmussen	Denmark	3.3
1990	Rajatanavin	Thailand	1.1
1991	Roti	Italy	8.7
1991	Löbig	Germany	2.0
1992	Walfish	Canada	6.0
1992	Stagnaro-Green	USA	8.8
1992	Kannan**	India	7.0
1997	Yim***	Korea	8.0
1998	Kuijpers	Netherlands	12.4
2000	Lucas	Spain	7.8

*: Report at American Endocrine Society

**: Report at International Congress of Endocrinology

***: Report at the Asia-Oceania Thyroid Association Congress

dysfunction and 0.54% of the general population [24]. Destructive transient thyrotoxicosis (group II, with a low RAIU + group III) is the most common form of postpartum thyroid dysfunction, accounting for 50~60% of all postpartum thyroid dysfunction.

Fig. 1. Various types of postpartum thyroid dysfunction.

The rest (group IV, V) show only the hypothyroid phase, however, persistent hypothyroidism is rare (about 0.1%).

Clinical features

Thyroid dysfunction is most often subclinical, and patients can be followed without medication. Symptoms and signs in overt postpartum thyroid dysfunction are similar to those in non-postpartum cases, *i.e.* hypermetabolic and hyperdynamic symptoms are observed in thyrotoxicosis, and hypometabolic ones in hypothyroidism. The distinction between Graves' thyrotoxicosis and destructive thyrotoxicosis is clear because destructive thyrotoxicosis usually occurs at 1~3 months, whereas Graves' disease occurs at 3~6 months. The measurement of RAIU is definitive, but usually not performed in mothers who are breast-feeding. The serum total triiodothyronine (T₃) / total thyroxine (T₄) ratio (<20 ng/μg) is helpful for the diagnosis of destructive thyrotoxicosis [25]. Serial changes of serum thyroglobulin (Tg) concentration may also be helpful, because it increases before the onset of destructive thyrotoxicosis. However, because of the inter-

ference by anti-thyroglobulin antibodies with the conventional measurement system, a new sensitive multisite immuno-radiometric Tg assay should be employed for this purpose [26]. Hypothyroidism is usually transient, especially when a patient's goiter enlarges and serum thyroglobulin elevates in response to the increase in thyrotropin (TSH).

Prediction of Postpartum Thyroiditis

In postpartum thyroid dysfunction, briefly characterized as a syndrome of postpartum exacerbation of subclinical autoimmune thyroid disease, some immunological abnormalities are observed before the onset of thyroid dysfunction (and therefore, before and during pregnancy). Among these, an anti-thyroid microsomal antibody (MCAb) is the most useful marker for the prediction of the occurrence of postpartum thyroid dysfunction. In patients positive for MCAb, lymphocytic infiltration into the thyroid is always observed, and therefore these patients have "subclinical autoimmune thyroiditis" [27], which may be exacerbated after delivery. Sixty to seventy percent of women with positive MCAb in

Fig. 2. The prevalence of anti-thyroid microsomal antibody and the occurrence of postpartum thyroid dysfunction among pregnant women in the general population.

early pregnancy develop postpartum thyroid dysfunction [10]. The risk to develop postpartum thyroid dysfunction in the MCAb-negative subjects is estimated to be one-hundredth of that in MCAb-positive subjects (Fig. 2). Especially, mothers with high MCAb titer ($>5000\sim 10000\times$) always develop postpartum thyroid dysfunction. The presence of MCAb, however, does not provide any information about which type of dysfunction would occur.

Table 2 summarizes our screening study in early pregnancy [24]. In the 3405 consecutive pregnant women, the 208 subjects had already been diagnosed to have thyroid disease and 262 subjects were found with positive MCAb results. They were newly diagnosed to have subclinical autoimmune thyroiditis and thus the prevalence of positive MCAb titers among pregnant women in the general population is estimated to be 7.7%. Among these, 71 subjects were

successfully followed up until 6 months postpartum, and we found that 44 cases (62.0%) developed various types of postpartum thyroid dysfunction (Table 3) [24].

Although the measurement of MCAb with semi-quantitative particle agglutination tests (MCPA) is simple and inexpensive, the significance of the screening for postpartum autoimmune thyroid syndrome is not established and will likely vary by country [28]. Anti-thyroid peroxidase antibody (TPOAb) is not better than MCPA for predicting postpartum thyroid dysfunction [29].

Prediction of Postpartum Graves' Disease: Recurrence and Onset

Graves' disease is aggravated in early pregnancy, ameliorates in the latter half of pregnancy, and often relapses postpartum [30]. Human chorionic gonadotropin (hCG) plays a crucial role in the aggravation of Graves' thyrotoxicosis in early pregnancy [31]. The relapse of Graves' thyrotoxicosis after parturition may occur even in the patient in remission before pregnancy. In the patient whose thyroid function in early pregnancy is accelerated above the normal range, wherein thyroid is naturally stimulated by hCG, recurrence of Graves' thyrotoxicosis after delivery is probable [32].

Among the groups of postpartum thyroid dysfunction, the new onset of Graves' disease is of most interest in clinical practice, because early diagnosis and therapy just at the onset of the disease can lead

Table 2. Screening of anti-thyroid microsomal antibodies in early pregnancy

	Case No.	%
MCAb Positive	470	13.8
Prediagnosed Graves' disease	160	4.7
Prediagnosed Hashimoto's disease	47	1.4
Hypothyroidism	1	0.03
Newly found positive cases	262	7.7
MCAb Negative	2935	86.2
Total	3405	100

Anti-thyroid microsomal antibodies were measured by agglutination assay.

Table 3. Postpartum development of thyroid dysfunction in patients with positive anti-thyroid microsomal antibodies

Post-partum thyroid function	Number of cases	%
Normal (euthyroid)	27	38.0
Dysfunction	44	62.0
(I) Persistent Graves' thyrotoxicosis	2	2.8
(II) Transient Graves' thyrotoxicosis	3	4.2
(III) Destructive thyrotoxicosis followed by transient hypothyroidism	23	32.4
(IV) Transient thyrotoxicosis alone	7	9.9
(V) Transient hypothyroidism alone	9	12.7
Total	71	100

7.0

55.0

to early remission [24]. Postpartum period is an important time in terms of Graves' onset, because 40% of Graves' patients who have had one or more deliveries, developed their disease in the postpartum period [33]. Stimulating type of the anti-TSH receptor antibody (thyroid stimulating antibody; TSAb) would be a useful marker to monitor postpartum development of Graves' disease, because TSAb has already been positive before the onset of Graves' disease [34] when measured with a sensitive bioassay [35]. Our prospective study [24] revealed that the pregnant women with positive TSAb in early pregnancy had a high-risk of developing postpartum Graves' disease. Seventy-one pregnant women with positive MCAb in early pregnancy were prospectively observed from early pregnancy to the postpartum period (Table 3). Among these 71 women, 7 showed positive TSAb, and 5 (70%) of them developed postpartum Graves' disease (Fig. 3). Thyrotoxicosis in 3 of those 5 was transient and spontaneously improved within a year. Graves' disease did not occur in the TSAb-negative subjects. On the other hand, the conventional radio receptor assay for anti-TSHR antibodies, namely thyrotropin-binding inhibitory

immunoglobulins (TBII) was not able to discriminate postpartum Graves' disease (Fig. 3).

Mechanism in Postpartum Thyroid Disease

The immune rebound hypothesis explains the enhancement of immune activities after parturition as the rebound from the suppressed immune state. During pregnancy, maternal immune activities are suppressed so as not to reject the developing fetus. Sudden release from the immune suppression at the moment of delivery intensifies immune activities above the normal level, just as the sudden cessation of immuno-suppressive drugs gives rise to the exacerbation of autoimmune diseases [36]. The antibody titers of MCAb and anti-thyroglobulin antibodies decrease as pregnancy progressed and increase after delivery in pregnant women with Graves' disease and Hashimoto's disease. These changes support above concept [37]. The immune rebound seems to be rather a general phenomenon observed in the postpartum period, because serum levels of immunoglobulins [38], and counts of lymphocytes and

Fig. 3. Relations between thyroid stimulating antibodies (TSAb) or thyrotropin binding inhibitory immunoglobulin (TBII) in early pregnancy and postpartum thyroid dysfunctions.

natural killer (NK) / K cell activity [39] decrease in late pregnancy and increase after delivery even in the normal pregnant women. Because immunological situations after abortion are similar to those during the postpartum period, post-abortional thyroid dysfunction may also occur in some cases [9, 40].

The postpartum rebound of immune activities consists of two phases (Fig. 4). Cytotoxic T cells and

NK cells increase from 1 to 4 months postpartum (Fig. 5) [41]. The enhancement of cellular immunity may exacerbate tissue injury in Hashimoto's thyroiditis. In contrast, CD5⁺ cells, which produce autoantibodies, increase from 7 to 10 months postpartum (Fig. 5) [41]. The enhancement of humoral immunity may cause postpartum Graves' disease, which is caused by anti-TSH receptor autoantibodies.

Fig. 4. Immune rebound hypothesis of postpartum autoimmune thyroid diseases.

Fig. 5. Changes in absolute numbers of peripheral cytotoxic T cells, helper T cells, suppressor T cells, CD5⁻ B cells, CD5⁺ B cells, and NK cell subsets during and after pregnancy.

Indeed, Hashimoto's thyroiditis is frequently aggravated from 1 to 4 months postpartum and Graves' disease frequently develops or relapses from 4 to 12 months postpartum (Fig. 4). Recent study on the production of cytokines revealed that Th1-type and Th2-type cytokines decreased during pregnancy, Th1-type cytokines increased during early postpartum period and Th2-type cytokines increased during later postpartum period (Fig. 6) [42]. These data also strongly support the immune rebound hypothesis [36].

Postpartum Autoimmune Syndrome

Postpartum aggravation or onset of autoimmune thyroid diseases through the immune rebound mechanism has become an established clinical entity, wherein thyroid dysfunction can clearly be demonstrated in thyroid function tests, and autoimmune abnormalities are detected by thyroid autoantibodies to predict the onset of dysfunction. However, we believe that autoimmune disease is not an all-or-nothing phenomenon, but normal subjects proceed into subclinical autoimmune state after the initiation of autoimmunity (Fig. 7). After additional events that activate immune system, patients may develop clinical autoimmune disease, which may initially be reversible or transient. Postpartum immune rebound is a phenomenon generally observed after parturition, and easily assumed to be the event that activates not only autoimmune thyroid disease but

Fig. 6. Changes in the levels of Th1-type cytokine (IFN- γ and IL-2) and Th2-type cytokines (IL-4 and IL-10) during and after pregnancy. The data are mean $\pm$ SEM. Significantly different from non-pregnant controls at $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***).

Fig. 7. Proposed time-course of developing autoimmune disease.

also many other autoimmune diseases in postpartum women. To investigate other postpartum autoimmune diseases, the strategy similar to that in postpartum autoimmune thyroid disease may be applied.

Rheumatoid arthritis is one of the autoimmune diseases that have long been documented to be ameliorated during pregnancy and aggravated after delivery [43]. The onset of rheumatoid arthritis is suppressed during pregnancy but increased after delivery, especially the first 3 months postpartum [44]. Actually onset of rheumatoid arthritis during postpartum period is 6 times more frequent than the other period [45]. Postpartum onset of rheumatoid arthritis was found in 0.08% of women in the general population and could be partially predicted by measuring rheumatoid factors in early pregnancy [46].

There are only limited studies that have investigated other autoimmune diseases in relation to pregnancy and parturition. Lymphocytic autoimmune hypophysitis is a rare disease but interestingly 30% of the cases developed during the postpartum period in female patients [47]. The pituitary may also be a subject of autoimmune damage during the postpartum period. There are case reports of some autoimmune diseases developed after delivery possibly through the immune rebound mechanism including postpartum renal failure [48] or post-delivery hemolytic-uremic syndrome [49], postpartum idiopathic polymyositis [50], postpartum syndrome with antiphospholipid antibodies [51], and postpartum autoimmune myocarditis [52]. It is likely that many other possible postpartum autoimmune diseases are as yet unexplored. We would like to propose the new term, postpartum autoimmune syndrome that includes many postpartum autoimmune diseases as shown in Table 4. Detection of subclinical autoimmune diseases in early pregnancy by screening autoantibodies using sophisticated laboratory tests [53, 54], is important to establish the prediction of many postpartum autoimmune diseases. Puerperal diseases should be carefully examined in relation to autoimmune abnormalities in the affected organs. We believe that onset of these autoimmune diseases could be prevented by immunomodulating therapy in the near future [55].

Table 4. Various types of postpartum autoimmune disease

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1. Postpartum Thyroiditis
 2. Postpartum Graves' disease
 3. Postpartum Autoimmune Hypophysitis
 4. Postpartum Rheumatoid Arthritis
 5. Postpartum Autoimmune Myocarditis
 6. Postpartum Autoimmune Hepatitis
 7. Postpartum Autoimmune Diabetes Mellitus
 8. Postpartum Systemic Lupus Erythematosus
 9. Postpartum Autoimmune Gastritis
 10. Postpartum Autoimmune Thrombosis
 11. Postpartum Autoimmune Hemophilia
 12. Postpartum Autoimmune Aortitis
 13. Postpartum Polymyositis
 14. Postpartum Autoimmune Nephritis
 15. Postpartum Autoimmune Psychosis
 16. Postpartum Cerebral Angiopathy
 17. Herpes Gestationis, Pemphigoid Gestationis
 18. Postpartum Autoimmune Osteoporosis
 19. Postpartum Ovarian Failure
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Summary

Postpartum thyroid dysfunction is rather a common problem during postpartum period, found in approximately 5% of mothers in the general population. It occurs from subclinical autoimmune thyroiditis that is aggravated after parturition and causes various types of thyroid dysfunction. Immune activity is physiologically suppressed during pregnancy so that the fetus is not rejected, and rebounds above the normal level after parturition. Graves' disease and Hashimoto's thyroiditis spontaneously ameliorate during pregnancy, and are often aggravated after parturition. The high-risk mothers for postpartum thyroid dysfunction can be well screened by anti-thyroid microsomal antibody (MCAb) and 60% to 70% of MCAb-positive mothers develop postpartum thyroid dysfunction, which is transient in most cases. New onset of Graves' disease may be screened by thyroid stimulating antibody (TSAb) and 70% of TSAb-positive mothers develop either transient or persistent postpartum Graves' disease that usually occurs at 3~6 months postpartum. Immune rebound after parturition may not cause only autoimmune thyroid diseases but other autoimmune

diseases, which may be investigated with the similar strategies to those in postpartum autoimmune thyroid disease. Thus, we found that postpartum onset of rheumatoid arthritis occurred in 0.08% of women in the general population and could be partially predicted by measuring rheumatoid factors in early pregnancy. There are several case reports of other autoimmune diseases developed after delivery; postpartum renal failure or post-delivery hemolytic-uremic syndrome, postpartum idiopathic polymyositis, postpartum syndrome with antiphospholipid antibodies, postpartum autoimmune myocarditis. Many other possible postpartum autoimmune diseases are still unexplored. Postpartum autoimmune

thyroid syndrome is a good model for understanding the mechanism of onset and aggravation of other autoimmune diseases. Prediction and prevention of postpartum onset of many autoimmune diseases could be established in the near future.

Acknowledgments

This study was supported by Grants-in-Aid for Scientific Research to N.A. (No. 09307055, No. 11357021 and No. 12877388) from the Ministry of Education, Science, and Culture, Japan.

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