

Presumable suppression of fetal TSH lasting longer than 5-7weeks after 22weeks gestation is associated with risk of developing gestational graves' disease-related central hypothyroidism after birth

Abstract

Background/Aims: Neonates and infants whose mothers have Graves' disease (GD) may suffer from central hypothyroidism (CH) after recovery from transient hyperthyroidism. Fetal and neonatal TSH producing cells are presumably suppressed under mothers' GD in gestational GD-related CH (gG-CH). This suppression is due to thyrotoxicosis due to the transfer of TSH-receptor stimulating antibody through the placenta. However, little research has considered how long fetal TSH producing cells are suppressed by thyrotoxicosis in gG-CH. The present review was designed to identify the duration of fetal TSH suppression, which could lead to the development of gG-CH. Methods: Meta-analysis including our own case was done. Using 31 previously reported gG-CH cases, we estimated the duration of fetal hyperthyroidism, which led to TSH suppression.

Results: The shortest duration of thyrotoxicosis after 22weeks of GA was 5-7weeks and the longest one was 18weeks. Conclusion: Our results suggest that fetuses with TSH suppression duration of more than 5-7weeks from 22GA may be at risk for developing gG-CH.

Keywords: gestational graves' disease, central hypothyroidism, fetal pituitary-thyroid axis, thyrotoxicosis

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Abbreviations: GD, graves' disease; CH, central hypothyroidism; gG-CH, gestational GD-related CH; TSH, thyroid stimulating hormone

Introduction

Neonates born to mothers with Graves' disease (GD) may present with various thyroid dysfunctions, including transient hyperthyroidism and hypothyroidism.¹⁻⁸ Thyroid dysfunctions may be due to the placental transfer of thyroid stimulating hormone (TSH)-receptor stimulating antibody and anti-thyroid agents. A rare condition, gestational GD-related central hypothyroidism (gG-CH), could develop after transient hyperthyroidism, which is known to be due to the transfer of TSH-receptor stimulating antibody through the placenta.⁹ At least two factors may contribute to the development of gG-CH: 1) high TSH-receptor stimulating antibody titers (with or without high thyroid hormone levels in the mother), leading to the transfer of these antibodies through the placenta, and 2) fetal and neonatal TSH suppression, which leads to a blunted ability to establish the negative feedback system of the pituitary-thyroid axis in the fetus, neonates, and infants.¹⁰

Based on clinical knowledge, it is clear that not all neonates born to gestational mothers with GD will develop gG-CH. Therefore, we hypothesized that certain duration of fetal hyperthyroid environment and its subsequent TSH suppression may be necessary for TSH to remain suppressed, even after the remission of hyperthyroidism in the newborns. To test this hypothesis, the present study evaluated the duration of fetus hyperthyroidism in reported patients with gG-CH.

Objective

The purpose of this study was to determine the minimum duration of fetal hyperthyroidism, which could lead to fetal TSH suppression, for the development of gG-CH by examining previously reported patients.

Materials and methods

Data collection and meta-analysis

"PubMed" and "Google Scholar" databases were searched for reported cases of gG-CH. Using the keywords "maternal hyperthyroidism/GD and central hypothyroidism," or "thyrotoxicosis/GD and central hypothyroidism". This search resulted in 51 articles. Based on initial assessment, 24 of the identified 51 articles were subsequently screened for the potential cases, which were confirmed by the two authors. Cases were included if they met both of the following criteria: (1) Diagnosis of maternal GD, defined as undetectable levels of TSH with elevated fT3 and fT4 concentrations in addition to positive TSH-receptor stimulating antibody values at any time during pregnancy, (2) Diagnosis of CH after birth, defined as fT4 concentrations <1.0ng/dl in combination with TSH levels <10μIU/ml without the use of anti-hyperthyroid therapy during the neonatal period or infancy. L-thyroxine was required in the cases since fT4 levels were low. The threshold for TSH levels was used to exclude cases with primary hypothyroidism, particularly those related to anti-thyroid drug use.

Based on the inclusion criteria, 31 cases from seven references¹¹⁻¹⁹ were evaluated. Based on the timing of the mothers' diagnosis of GD, cases were divided into three groups (A, B, and C). For cases in Groups A (n=12) and B (n=9), mothers received a diagnosis of GD before and during their pregnancy, respectively. For cases in Group C (n=10), mothers were diagnosed during the postpartum period. Overall, 21 of the included 31 cases were reported in one paper,¹¹ 9 of the remaining 10 cases were reported from seven previous papers (including three Japanese journals),¹²⁻¹⁷ and one case was from our facility. The study protocol was approved by the Ethics Committee of Tokyo Metropolitan Children Medical Center.

Characteristics of included patients

Patient characteristics in Group A, B, and C are shown in Tables 1-3, respectively. CH was diagnosed for a variable length of time after birth, ranging from 2 to 425 days after birth, but the time of 425 days was exceptionally long compared to the others (Table 2).

The GA of delivery ranged across Groups A-C from 27 to 40 weeks, with an average of 35.9 weeks GA. Preterm deliveries (i.e., at less than 37 weeks) represented 91.6% (11 cases) in Group A and 77.7% (7 cases) in Group B, suggesting a tendency for premature labor under conditions reflecting poor thyroid function in these two groups.²⁰

Table 1 Summary of the patients' and their mothers' data in Group A

Case No	GA of delivery (wk)	Duration of fetal hyperthyroidism (wk)	Neonatal data			Reference
			TSH (μU/ml)	fT4 (ng/ml)	Day of Dx (day)	
1	27	5	NA	0.4	14	14
2	28	6	0.1	0.7	15	15
3	30	8	<0.05	0.3	29	13
4	32	10	4.39	0.6	14	our case
5	34	12	NA	0.65	28	14
6	34	12	1.1	0.9	61	15
7	34	12	1.1	0.8	71	15
8	36	14	0.49	0.87	7	16
9	36	14	3	7.5 (T4)	4	15
10	37	15	3	5.1 (T4)	5	15
11	37	15	0.7	0.6	50	15
12	38	16	0.09	1.05	5	16

Days of Dx, Days When Babies were Diagnosed CH; GA, gestational age In GA of delivery, the figures below the first decimal place were omitted

Table 2 Summary of the patients' and their mothers' data in Group B

Case No	GA of delivery (wk)	Duration of fetal hyperthyroidism (wk)	Maternal data	Neonatal data			Reference
			GA of GD Dx (wk)	TSH (μU/ml)	fT4 (ng/ml)	Day of Dx	
13	37	6	31	NA	0.66	2	17
14	36	6	30	0.7	0.6	96	15
15	36	6	30	0.9	0.5	40	15
16	38	7	31	4.1	0.6	2	15
17	31	8	23	NA	0.6	425	19
18	38	8	30	7.5	0.8	6	15
19	33	11	21	<0.05	0.27	58	18
20	35	13	14	0.1	0.8	NA	15
21	36	14	22	0.08	0.5	70	18

Days of Dx, days when babies were diagnosed CH; GA, gestational age In GA, the figures below the first decimal places were omitted

Table 3 Summary of the patients' and their mothers' data in Group C

Case No	GA of delivery (wk)	Duration of fetal hyperthyroidism (wk)	Neonatal data			Reference
			TSH (μU/ml)	fT4 (ng/ml)	Day of Dx	
22	36	14	1.8	0.5	11	11
23	38	16	1.2	0.4	12	11
24	38	16	2.4	0.9	16	11
25	38	16	2.8	0.3	7	11
26	38	16	3.4	0.4	18	11
27	38	16	5.9	0.5	11	11
28	38	16	2.1	0.8	17	11
29	39	17	3.3	0.6	24	11
30	40	18	3	0.8	18	11
31	40	18	1.2	0.6	NA	11

Day of Dx, days when babies were diagnosed CH; GA, gestational age

The figures below the first decimal place in GA were omitted

Definition of duration of fetal hyperthyroidism during pregnancy

The duration of fetal hyperthyroidism during pregnancy was defined for each group using the following criteria.

Group A: All 12 cases in group A had histories of either poor control or absence of treatment for GD. The hyperthyroid state had started prior to pregnancy. Pituitary negative feedback has been reported to establish in the fetus at 22weeks GA^{21,22} as discussed later. Based on this timing, we used 22weeks as the initial point at which fetal TSH was suppressed by high thyroid hormones associated with elevated TSH-receptor antibody. Duration between 22weeks GA and the GA of delivery were subsequently calculated for each patient. For example, case 1 was delivered at 27weeks. Therefore, by subtracting 22 from 27weeks, the duration of hyperthyroidism was 5weeks.

Group B: For all cases in Group B, onset of fetal hyperthyroidism was defined as the GA at which maternal GD was diagnosed for the first time. Then, we calculated the duration of fetal hyperthyroidism by subtracting the GA of Graves' disease diagnosis from the GA of delivery. For example, the GA of the delivery was at 37weeks and diagnosis of GD was given at 31weeks in case 13. Therefore, the duration of fetal hyperthyroidism was 6weeks. If GA of GD diagnosis was earlier than 22weeks of GA as in case 20, we assumed 22weeks was when suppression of fetal TSH began to occur, as explained for Group A.

Group C: Given that thyroid function was not measured during pregnancy, we could not estimate the starting point of thyrotoxicosis for patients in Group C. Based on the estimate of 22weeks as the first time when fetal TSH began to be suppressed as discussed above, we estimated duration of thyrotoxicosis during pregnancy by subtracting 22weeks from the GA of the delivery.

Results

The calculated duration of hyperthyroidism during pregnancy ranged from 5-7weeks to 18weeks among the patients. Given that TSH suppression was estimated to begin at 22(see Methods and discussed

later), earlier GA of delivery was associated with a shorter duration of hyperthyroidism in Group A. The shortest duration was observed in case 1. Across all groups, the longest duration was observed in case 30 and 31, and was 18weeks. No included cases of gG-CH were exposed to less than five weeks of hyperthyroidism. Observed exposure durations were 5-7weeks for 6 cases, 8-10weeks for 4 cases, 11-13weeks for 5 cases, and more than 14weeks for 16cases. In short, exposure to maternal thyrotoxicosis for 5-7weeks after 22weeks of GA could result in gG-CH.

Discussion

Our results suggest that thyrotoxicosis during pregnancy for 5-7weeks after 22weeks of GA might lead to gG-CH. This is the first study paper to evaluate a link between duration of thyrotoxicosis during pregnancy and risk of gG-CH. Five weeks of exposure to thyrotoxicosis was the shortest period observed in the included cases.

Excessive thyroid hormones due to high TSH-receptor stimulating antibody transferred to the fetus through the placenta are necessary for fetal TSH levels to be suppressed. The presence of high TSH-receptor stimulating antibody titers in mothers appears to be more essential for the development of gG-CH than high thyroid hormone levels in mothers. This is based on the fact that a neonate born to his/her mother with euthyroid throughout pregnancy suffered from gG-CH.⁶ Research indicates that elevated levels of maternal TSH-receptor stimulating antibody titers are a risk factor for fetal hyperthyroidism^{2,7,23,24} and are associated with the development of neonatal hyperthyroidism,²⁵ which could, in turn, result in developing gG-CH. In line with this notion, we found that high TSH-receptor stimulating antibody titers were overtly high in the mothers of all included cases (data not shown).

Several lines of evidence support the notion that TSH levels can be suppressed as late as 22weeks of GA in the fetus of gestational GD. First, IgG transfer from mother to fetus begins as early as 13weeks.²⁶ In particular, transplacental passage of TSH-receptor antibody was confirmed as early as 21weeks of GA.^{17,27,28} Second, fetal Graves' disease presented with undetectable TSH and remarkably elevated thyroid hormones in a patient of 20weeks of GA.²⁹ Finally, an intra-

amniotic thyroxine treatment for fetal hypothyroidism was successful with fetal TSH suppression at 22weeks of GA.^{30,31} If fetal negative feedback was instead established at 20weeks GA, our results estimating the duration of hyperthyroidism during pregnancy would be extended by 2weeks.

It is reasonable to speculate that a certain minimum duration is needed to lead to the development of gG-CH. However, babies affected by this disorder could have a shorter duration of the exposure of fetal hyperthyroidism than that reported here. Unreported gG-CH cases in which thyrotoxicosis duration was less than 5weeks might exist.

Other limitations of this study warrant mention. First, this study was based on the assumption that fetal TSH negative feedback is established in 22weeks of GA as discussed above. Second, some cases with gG-CH that received treatment to combat hyperthyroidism may have been missed, given that neonates with this condition could recover spontaneously while tapering the dose of anti-thyroid drugs. This form of gG-CH is presumably self-limiting. On the other hand, we could emphasize that we have succeeded in answering to our initial clinical question raised, or how long fetal TSH producing cells are suppressed in gG-CH, by scrutinizing previous cases reported to have that condition.

Conclusion

Our results suggest that fetal TSH suppression for 5-7weeks after 22weeks GA could lead to the development of central hypothyroidism in babies born to mothers with uncontrolled gestational Graves' disease during pregnancy.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Van der Kaay DC, Wasserman JD, et al. Management of neonates born to mothers with Graves' disease. *Pediatrics*. 2016;137(4):e20151878.
2. Besancon A, Beltrand J, Le Gac I, et al. Management of neonates born to women with Graves' disease: a cohort study. *Eur J Endocrinol*. 2014;170(6):855-862.
3. Brown RS, Bellisario RL, Botero D, et al. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. *J Clin Endocrinol Metab*. 1996;81(3):1147-1151.
4. Brand F, Liegeois P, Langer B. One case of fetal and neonatal variable thyroid dysfunction in the context of Graves' disease. *Fetal Diagn Ther*. 2005;20(1):12-15.
5. O'Connor MJ, Paget-Brown AO, Clarke W. Premature twins of a mother with Graves' disease with discordant thyroid function: a case report. *J Perinatol*. 2007;27(6):388-389.
6. Zwaveling-Soonawala N, van Trotsenburg P, Vulmsa T. Central hypothyroidism in an infant born to an adequately treated mother with Graves' disease: an effect of maternally derived thyrotrophin receptor antibodies? *Thyroid*. 2009;19(6):661-662.
7. Papendieck P, Chiesa A, Prieto L, et al. Thyroid disorders of neonates born to mothers with Graves' disease. *J Pediatr Endocrinol Metab*. 2009;22(6):547553.
8. Levy-Shraga Y, Tamir-Hostovsky L, Boyko V, et al. Follow-up newborns of mothers with Graves' disease. *Thyroid*. 2014;24(6):1032-1039.
9. Matsuura N, Konishi J, Fujieda K, et al. TSH-receptor antibodies in mothers with Graves' disease and outcome in their offspring. *Lancet*. 1988;1(8575-6):14-17.
10. Matsuura N, Harada S, Ohyama Y, et al. The mechanisms of transient hypothyroxinemia in infants born to mothers with Graves' disease. *Pediatr Res*. 1997;42(2):214-218.
11. Kempers MJ, van Trotsenburg AS, van Rij RR, et al. Loss of integrity of thyroid morphology and function in children born to mothers with inadequately treated Graves' disease. *J Clin Endocrinol Metab*. 2007;92(8):2984-2991.
12. Tamaki H, Amino N, Takeoka K, et al. Prediction of later development of thyrotoxicosis or central hypothyroidism from the cord serum thyroid-stimulating hormone level in neonates born to mothers with Grave's disease. *J Pediatr*. 1989;115(2):318-321.
13. Hashimoto H, Maruyama H, Koshida R, et al. Central hypothyroidism resulting from pituitary suppression and peripheral thyrotoxicosis in a premature infant born to a mother with Graves' disease. *J Pediatr*. 1995;127(5):809-811.
14. Higuchi R, Kumagai T, Kobayashi M, et al. Short-term hyperthyroidism followed by transient pituitary hypothyroidism in a very low birth weight infant born to a mother with uncontrolled Graves' disease. *Pediatrics*. 2001;107(4):e57.
15. Kemper MJ, van Tijn DA, van Trotsenburg AS, et al. Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. *J Clin Endocrinol Metab*. 2003;88(12):5851-5857.
16. Lee Y, Loke KY, Ng S, et al. Maternal thyrotoxicosis causing central hypothyroidism in infants. *J Paediatr Child Health*. 2002;38(2):206-208.
17. Higuchi R, Miyawaki M, Kumagai T, et al. Central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks gestation: 3 cases. *Pediatrics*. 2005;115(5):e623-e625.
18. Onigata K, Nako Y, Nagashima K, et al. Thyroid hormone disorders in neonates born to mothers with Basedow' disease. *The KITAKANTO Medical Journal (In Japanese)*. 1996;46:239-247.
19. Nishizawa K, Hosaka A, Ymashiro Y. A case of transient pituitary hypothyroidism secondary to poor controlled maternal Graves' disease. *Journal of Japan Society for Premature and Newborn Medicine (In Japanese)*. 2004;16:23-28.
20. Mannisto T, Mendola P, Grewal J, et al. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *J Clin Endocrinol Metab*. 2013;98(7):2725-2733.
21. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid*. 1992;2(2):155-159.
22. Zwaveling-Soonawala N, van Trotsenburg P, Vulmsa T. Central hypothyroidism in an infant born to an adequately treated mother with Graves' disease: thyrotrophin receptor antibodies? *Thyroid*. 2009;19(6):661-662.
23. Skuza KA, Sills IN, Stene M, et al. Prediction of neonatal hyperthyroidism in infants born to mothers with Graves' disease. *J Pediatr*. 1996;128(2):264-268.
24. Mortimer RH, Tyack SA, Galligan JP, et al. Graves' disease in pregnancy TSH receptor binding inhibiting immunoglobulins and maternal and neonatal thyroid function. *Clin Endocrinol (Oxf)*. 1990;32(2):141-152.

25. Barbesino G, Tomer Y. Clinical utility of TSH receptor antibodies. *J Clin Endocrinol Metab.* 2013;98(6):2247–2255.
26. Palmeira P, Quinello C, Silveira-Lessa AL, et al. Carneiro-Sampaio M: IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immun.* 2012;2012:985646.
27. Pitcher-Wilmott RW, Hindocha P, Wood CB. The placental transfer of IgG subclasses in human pregnancy. *Clin Exp Immunol.* 1980;41(2):303–308.
28. Radetti G, Persani L, Moroder W, et al. Transplacental passage of anti-thyroid auto-antibodies in a pregnant woman with auto-immune thyroid disease. *Prenatal Diagn.* 1999;19(5):468–471.
29. Rakover Y, Weinert E, Mosh N, et al. Fetal pituitary negative feedback at early gestational age. *Clin Endocrinol.* 1999;50(6):809–814.
30. Hanono A, Shah B, David R, et al. Antenatal treatment of fetal goiter: A therapeutic challenge. *J Matern Fetal Neonatal Med.* 2009;22(1):76–78.
31. Ribault V, Castanet M, Bertrand AM, et al. Experience with intraamniotic thyroxine treatment in nonimmune fetal goitrous hypothyroidism in 12 cases. *J Clin Endocrinol Metab.* 2009;94(10):3731–3739.