**Topic:** THYROID MORPHOLOGY AND FUNCTION IN THE OFFSPRING OF MOTHERS WITH GRAVES’ DISEASE

**Title:** Loss of integrity of thyroid morphology and function in children born to mothers with inadequately treated Graves’ disease.

**Authors:** Kempers MJ, van Trotsenburg AS, van Rijn RR, Smets AM, Smit BJ, de Vijlder JJ, & Vulsma T (Amsterdam & Rotterdam, The Netherlands)

**Reference:** Journal of Clinical Endocrinology & Metabolism 92: 2984-2991, 2007

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**SUMMARY**

**Context:** Central congenital hypothyroidism (CH-C) in neonates born to mothers with inadequately treated Graves' disease usually needs l-T4 supplementation. The thyroid and its regulatory system have not yet been extensively studied after l-T4 withdrawal, until the authors observed disintegrated thyroid glands in some patients.

**Objective:** The aim was to study the occurrence and pathogenesis of disintegrated thyroid glands in patients with CH-C.

**Design, setting, patients, participants:** Thyroid function was measured and thyroid ultrasound imaging performed in 13 children with CH-C due to inadequately treated maternal Graves' disease (GD) after withdrawal of l-T4 supplementation (group “Aa”). In addition, thyroid ultrasound imaging was performed in 6 children with CH-C born to inadequately treated mothers with GD, in whom l-T4 supplementation was not withdrawn yet (group “Ab”) or never initiated (group “Ac”), in 6 euthyroid children born to adequately treated mothers with GD (group “B”), and finally in 10 l-T4-supplemented children with CH-C as part of multiple pituitary hormone deficiency (group “C”).

**Main outcome measures:** Thyroid function and anatomical aspect (volume, echogenicity and echostructure) were measured.

**Results:** In group “A”, five children developed thyroidal hypothyroidism characterized by persistently elevated TSH concentrations and exaggerated TSH responses after TRH stimulation. In the majority of patients in groups “A” and “C”, thyroid echogenicity and volume were decreased, and the echostructure was inhomogeneous. Thyroid ultrasound imaging was normal in group “B” children.

**Conclusions:** Inadequately treated maternal Graves' disease not only may lead to CH-C but also carries an, until now, unrecognized risk of thyroid disintegration in the offspring as well. The authors speculate that insufficient TSH secretion due to excessive maternal-fetal thyroid hormone transfer inhibits physiological growth and development of the child's thyroid.

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**COMMENT**

Central congenital hypothyroidism (CH-C) is a rare condition only described a few years ago. When not a part of congenital multiple pituitary hormone deficiencies, CH-C is characterized by neonatal hypopituitary hypothyroidism associated with maternal thyrotoxicosis, and it is considered to result from fetal pituitary suppression due to elevated thyroid hormone levels in the mother. The infants are diagnosed by their low serum T4 levels – at neonatal screening for CH – and are treated with l-T4. CH-C is considered to be transient, and these infants are usually
withdrawn from l-T4 supplementation after
a few months. The present study was
initiated after the authors had observed
(after l-T4 withdrawal) persistent thyroid
dysfunction in some of them.

Group “A” comprised 19 infants born to
mothers with inadequately treated Graves’
disease with elevated serum free T4 (>2.5
ng/dl) and a suppressed TSH. Before
initiating l-T4 supplementation, neonatal
free T4 levels were low (< 0.93 ng/dl) and
serum TSH also – inappropriately – low
(0.1-7.5 µU/ml). After withdrawal of l-T4
supplementation, 5 infants had persistent
TSH elevation, 4 infants had transient TSH
elevation and finally 4 infants had normal
serum TSH. Group “B” comprised 6
infants born to mothers with “adequately”
treated Graves’ disease (either cured or
 treated with ATD); neonatal thyroid
function was normal in all 6 children. One
of the interesting – and novel – features of
present study was to show the presence of
frequent abnormalities (probably irrever-
sible) in the ultrasound pattern in infants
of group “A”, with a reduced echogenicity
and inhomogeneous echostructure, at ages
between 1.1 & 8.5 years.

The main message of this extensive
follow-up study of children born with CH-
C, due to inadequately treated maternal
Graves’ disease, was to show that there is a
risk of persistent thyroid function abnor-
malities in the offspring. While the
neonatal pituitary dysfunction improved
after birth, 5 of these infants developed
primary hypothyroidism during childhood,
with persisting hyperthyrotropinemia,
exaggerated TSH response to TRH
stimulation, and thyroid glands with small
volume and inhomogeneous echostructure.
The authors attribute this disease entity to
the consequences of CH-C, although they
cannot rule out the possibility of a
detrimental role of maternal antibodies
during pregnancy on the development of
the fetal thyroid gland (for instance
blocking TSH-receptor auto-antibodies
could lead to an abnormal thyroidal
development). Long term follow-up is
needed to evaluate the incidence and
further consequences of this novel
pathological entity, and to define the most
appropriate diagnostic and therapeutic
approach. In the mean time, careful
monitoring of maternal thyroid function is
highly recommended in mothers with
active Graves’ disease, as well as a careful
follow-up of children born to such
mothers, including thyroid function
determination and imaging by ultrasound.
(Daniel Glinoer, M.D.; Ph.D.)

See Table below

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Echogenicity</th>
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<th>Estimated volume (ml)</th>
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</table>

Inhomog, Inhomogeneous.
* Reference values are obtained from patients with sufficient iodine supply.
* Range is presented [3–6 yr (females) (16)].
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* Range is presented [0–2 yr (females) (16)].
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* Mean ± sd is presented [9 yr (17)].

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