Change of maternal thyroid function in twin-twin transfusion syndrome

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Abstract. Human chorionic gonadotropin (hCG) has weak thyroid-stimulating activity because of its homology with thyroid stimulating hormone (TSH). In twin-twin transfusion syndrome (TTTS), which is a severe complication of monochorionic twin pregnancies, a close association between maternal serum hCG concentration and TTTS has been reported. And, TTTS can be treated by fetoscopic laser coagulation of the communicating vessels. To clarify the relationship between maternal serum hCG and maternal thyroid function in TTTS, the present study investigated the change in thyroid hormone and hCG levels after laser therapy. The protocol included collection of serial maternal blood samples in TTTS before laser therapy, and at two and four weeks after laser therapy. For 131 cases of TTTS, the following parameters were determined at each point: hCG, TSH, free triiodothyronine (fT3), and free thyroxine (fT4). The multiple of the median (MoM) of pre-operative hCG concentration in TTTS was 5.39 MoM (interquartile range, 2.83 – 8.64). There was a moderate positive correlation between hCG and fT3 in TTTS pre-operatively (R = 0.22, P = 0.030). fT4 was also positively correlated with hCG (R = 0.33, P < 0.001). Some cases showed very high concentration in fT3. When laser therapy for TTTS was effective, the hCG concentration significantly decreased, and fT3 and fT4 decreased progressively in concert with the decrease in hCG. The relationship between hCG and thyroid function in TTTS supports the finding of TTTS as a novel etiology of hCG-mediated hyperthyroidism during pregnancy.

Key words: Pregnancy, Human chorionic gonadotropin (hCG), Twin-twin transfusion syndrome (TTTS), Hyperthyroidism, Laser therapy

HUMAN CHORIONIC GONADOTROPIN (hCG) is part of the family of glycoprotein hormones, which have a common alpha-subunit and a unique beta-subunit. This family includes thyroid stimulating hormone (TSH). As a result, hCG has weak thyroid-stimulating activity [1]. In normal pregnancy, serum hCG concentrations rise soon after implantation and peak at 10 to 12 weeks of gestation, after which they decline. During the period of highest serum hCG concentrations, serum free triiodothyronine (fT3) and free thyroxine (fT4) concentrations increase, usually within the normal range, and serum TSH concentrations are correspondingly reduced. Transient subclinical hyperthyroidism occurs in 10% to 20% of normal pregnant women during the period of highest serum hCG concentrations; these women do not require treatment [2].

Twin-twin transfusion syndrome (TTTS) accounts for approximately 10% of monochorionic twin pregnancies. If left untreated, TTTS is associated with a high fetal morbidity and mortality rate [3]. A net transfusion of blood flow from one fetus (donor twin) to the other (recipient twin) via placental vascular anastomoses has been proposed as the major etiology of TTTS [4, 5]. The donor twin becomes hypovolemic and oliguric, develops oligohydramnios, and a variable degree of growth restriction also results. The recipient twin manifests polyuria, polyhydramnios, and hydrops in response to hypervolemia. TTTS can be treated by fetoscopic laser coagulation of the communicating vessels. The goal of laser therapy is to occlude vascular anastomoses, thereby interrupting inter-twin blood exchange [6, 7]. It has been reported that elevated maternal serum hCG is seen in TTTS, and that there is a close association between hCG elevation and TTTS [8]. The change in the value of hCG after laser therapy may be a marker of laser therapy efficacy [9].

There are a number of examples of hCG-mediated
hypothyroidism during pregnancy such as gestational transient thyrotoxicosis [10], hyperemesis gravidarum [11], and trophoblastic hyperthyroidism [12], including gestational trophoblastic hyperthyroidism [13]. Cases of a high serum level of hCG in TTTS have been reported, but thyroid function in TTTS has not been studied sufficiently. To clarify the relationship between hCG and thyroid function in TTTS, the present study investigated the change in thyroid hormone and hCG levels after laser therapy.

**Materials and Methods**

This study included 131 pregnant women diagnosed with TTTS, referred to National Center for Child Health and Development between 2007 and 2010. The diagnostic criteria of TTTS included polyuric polyhydramnios in the recipient twin, the deepest vertical pool measuring at least 8 cm, and oliguric oligohydramnios in the donor twin, with the deepest vertical pool measuring at most 2 cm. The Quintero staging system was used to describe the fetuses [14]. The protocol included collection of serial blood samples before and at two and four weeks after laser therapy. The study was prospective in its design and the following parameters were determined at each point: maternal serum hCG, TSH, fT3, and fT4. All hormones were measured with an appropriate chemiluminescent enzyme immunoassay (CLEIA): IMMULITE HCG (LKCG), IMMULITE Third Generation TSH (LKTS), IMMULITE Free T3 (LKF3), or IMMULITE Free T4 (LKF4) (Diagnostic Products Corporation, Los Angeles, CA). Hyperthyroidism was defined as follows: increased fT3 or fT4 levels with decreased or suppression of TSH. Laser therapy was undertaken for Quintero stage I to IV TTTS between 16 and 26 weeks of gestation. The laser therapy was performed as described in a previous report [15]. We excluded the some cases in which a single or double fetal death occurred after laser therapy, and recurrent cases of TTTS with polyhydramnios/oligohydramnios, because fetal death itself can lead to a decrease in hCG, and the recurrence of TTTS did not cause a decrease in hCG, as has been previously reported [9].

All patients provided written informed consent to undergo fetoscopic laser surgery and to participate in this study, which was approved by the ethics committee of our institution.

**Statistical analysis**

Pre- and post-operative changes were assessed with the Wilcoxon signed-rank test, and correlations among the parameters were evaluated with the use of Spearman’s rank correlation (R). All P values were two-tailed. Multiplicity due to the assessment of changes over time was controlled for with the Bonferroni correction.

**Results**

(a) The median pre-operative concentration of maternal serum hCG in TTTS cases was 96,952 mIU/mL (interquartile range (IQR), 50,964 – 155,472). This value converted to 5.39 multiples of the median (MoM) (IQR, 2.83 – 8.64 MoM) based on the median hCG value (18,000 mIU/mL=1 MoM) of singleton pregnancies in our institution examined at the same gestational age, significantly higher than in normal twin pregnancies, which have been reported to be almost 2 MoM (Fig. 1-A) [16, 17].

(b) The pre-operative correlation between maternal serum hCG and fT3 in TTTS evaluated pre-operatively was assessed. There was a moderate positive correlation between hCG and fT3 in TTTS pre-operatively (R = 0.22, P = 0.030). Some cases showed very high concentration in fT3. Also, fT4 was positively correlated with hCG (R = 0.33, P < 0.001). These findings illustrate the classic relationship between hCG and both fT3 and fT4.

When laser therapy for TTTS was effective, the concentration of hCG significantly decreased (Fig. 1-A). As shown in Fig. 1, fT3 and fT4 decreased progressively in correspondence with the decrease of hCG (Fig. 1-B, 1-C). On the other hand TSH remained suppressed during four weeks.

**Discussion**

The present study showed the change of maternal thyroid function in TTTS, pre and post laser therapy. There was positive correlation between hCG and both fT3 and fT4 pre-operatively, and some cases showed very high concentration especially in fT3. When laser therapy for TTTS was effective, the concentration of hCG significantly decreased, and the change in thyroid function was concomitant with the decrease in hCG. The present study suggests that TTTS represents a novel but predictable aetiology of hCG-medi-
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fT3 and fT4 values before and after laser therapy

Concomitant with hCG levels, the fT3 and fT4 values significantly decreased after fetal surgery. Median (IQR) and P-values were compared with the pre-operative measurements.

Fig. 1 Changes in maternal serum hCG, fT3 and fT4 values before and after laser therapy

One limitation of this study was that thyroid hormone control values were not absolutely studied in twin pregnancies. Another limitation is that thyroid hormone levels may change throughout pregnancy. Further study on this topic is needed.

In conclusion, the present study showed the change of maternal thyroid function in TTTS, pre and post...
laser therapy. The relationship between hCG and thyroid function in TTTS supports the finding of TTTS as a novel etiology of hCG-mediated hyperthyroidism during pregnancy. In pregnancies complicated by TTTS, it is important to evaluate thyroid function, especially in fT3, and to carefully manage associated hyperthyroidism.

### References


### Disclosure

Conflicts of interest: The authors report that they have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.