Thyroid Hormone Levels in Macrosomic Fetuses: Low T3 Syndrome

MAKROZOMİK FETUSLARDA TİROİD HORMON DÜZEYLERİ: DÜŞÜK T3 SENDROMU

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Summary

Objective: The present study was undertaken to examine the role of thyroid functions at term in the development of fetal macrosomia.

Materials and Methods: This study compared the cord blood total T3, total T4, free T3, free T4 and TSH levels in macrosomic fetuses (n=40) at term with those of normal birth weight (n=18) .

Results: The total T3 (0.33+/- 0.17 ng/ml versus 0.43+/- 0.12 ng/ml), total T4 (9.37+/-3.88 micg/ml versus 11.62 +/- 2.67 micg/ml) and free T3 (0.99 +/- 0.48 pg/ml versus 2.57 +/- 1.37 pg/ml) were found to be lower in the macrosomic group; whereas there was no statistical difference in TSH and free T4 values between the two groups.

Conclusion: Laboratory findings resembling the low T3 Syndrome have been formed in macrosomic fetuses. It may be suggested that not only placenta but also the fetus itself may have a possible role in that situation.

Key Words: Macrosomia, Thyroid Hormones, Low T3 Syndrome

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Özet

Amaç: Fetal makrozominin gelişmesinde tiroid fonksiyonlarının değerlendirilmesi.

Materyal ve Metod: Toplam 40 adet makrozomik fetus ve 18 adet normal doğum ağırlıklı fetus çalışmaya alınmıştır. Ha iki gruptaki fetusların kordon kanlarından total T3, total T4, serbet T3, serbest T4 ve TSH düzeyleri bakılarak karşılaştırılmıştır

Sonuçlar: Makrozomik fetuslarda; total T3 (0.33±0.17 ng/ml vs. 0.43±0.12 ng/ml), total T4 (9.37±3.88 micg/ml vs. 11.62±2.67 micg/ml) ve serbest T3 (0.99±0.48 pg/ml vs. 2.57±1.37 pg/ml) daha düşük bulunmuşken; TSH ve serbest T4 düzeyleri açısından 2 grup arasında herhangi bir fark saptanmamıştır.

Yorum: Bu çalışmada makrozomik fetuslarda T3 düzeyinin oldukça düşük olduğunu saptadık. Bu durumdan sadece plasentanın değil fetusun kendisinin de sorumlu olabileceği akla gelmektedir.

Anahtar Kelimeler: Makrozomik fetus, Tiroid hormonları, Düşük T3 Sendromu

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Some hormones including thyroxine, cortisol, insulin-like growth factors etc. have an important role in the control of fetal growth. They act on both tissue accretion and differentiation and enable a precise and orderly pattern of growth to occur during gestation (1). Therefore, thyroid hormones, promote growth and development in utero by binding to specific receptors for altering both the metabolism and gene expression of thyroid responsive fetal tissues (2).

Thyroid hormones influence the normal rapid growth of the neonate and its individual tissues. However beyond a certain concentration the threshold of responsiveness to these hormones seem to vary between individual tissues (3). Close interrelations between the functional state of the thyroid gland and fetal mass was published by Lakovtsova and Sorokina (4).

The human placenta is not permeable to TSH and T3 but it is partially permeable to T4 and freely permeable to iodides and TRH (5). Even during the second and third trimesters, there are marked maternal to fetal serum free T4 and T3 concentration gradients (6-7). Limited but significant maternal to fetal thyroid hormone transfer throughout human pregnancy are present (8). Placenta also produces large amounts of HCG which has activity similar to TSH, and functions to inactivate much of the T4 and T3 presented from the maternal or fetal circulation (9).

Macrosomia is a condition which increases neonatal morbidity and the incidence of operative deliveries. The present study was undertaken to examine the role of thyroid functions at term in the development of fetal macrosomia.

Material - Methods

Fourty macrosomic (>4000 g) and 18 normal birth weight (2500-3999 g) fetuses at term were included in this study. Maternal age, pregnancy weeks and the socioeconomic levels were similar in the groups and none of the patients have evidence of diabetes, goiter, hypo/hyperthyroidism or any other systemic diseases. There was no family history of thyroid disorders. The mothers were not using any drugs except vitamin and iron supplementation. Because of the previous reports; in the present study we excluded fetuses with IUGR, rh/rh alloimunisation and congenital anomalies (10-12). In all of the cases the route of delivery was vaginal.

Paired sera were obtained at parturition. Cord blood samples were collected in vacuum tubes and centrifuged immediately (2000 r/min for 10 minutes). The serum was kept at -20 ^{0}C until the assays were done. Serum free T4, total T4, freeT3 and total T3 levels were determined by radioimmunoassay, using available kits (Amerlex M RIA kit) and TSH was determined by Gama BCT TSH monoclonal antibody coated tube IRMA.

Results

Fifty-eight fetuses were included in this study. Group I was consisted of 40 macrosomic fetuses that were over 4000 g at birth, and mean birth weight was 4301+/-256 g and group II was consisted of 18 normal birth weight (2500-4000 g) babies and mean birth weight was 3367+/-467 g. The difference between the groups was significant (p<0,001).

The mean TSH, T4, free T4 and free T3 concentrations are showed in Table 1. In comparison of the values between two groups, mean +/- SD of total T3 (0.33+/-0.17 ng/ml versus 0.43+/- 0.12 ng/ml), total T4 (9.37 +/- 3.88 micg/ml versus 11.62 +/- 2.67 micg/ml), and free T3 (0.99 +/- 0.48 pg/ml versus 2.57+/- 1.37 pg/ml) were found to be significantly lower in macrosomic group (p<0, 05). The levels of TSH were found to be 8.81 +/- 6.36 IU/ml in macrosomic group and 8.92 +/- 5.22 IU/ml in normal birth weight fetuses. Moreover free T4 was found to be 1.27 +/- 0.22 ng/ml in macrosomic group and 1.38+/- 0.24 ng/ml in group II. There was no significant difference in the TSH and free T4 values between the two groups.

We planned to reassess the thyroid hormone levels of our cases at the first month following the delivery. Unfortunately, the measurement of hormone levels was done in only 11 of the 40 babies. In all of the 11 babies, hormone levels were found to be in normal ranges which were compared with the results obtained at parturition.

On the other hand, glucose loading test was performed after delivery on mothers of the two groups, however there was no significant difference between the groups (p>0.05).

Discussion

Fetal growth depends on an appropriate fetal endocrine milieu and the placenta. Placenta regulates substrate supply, provides excretory functions and synthesis of various polypeptide and steroid hormones that influence aspects of maternal and fetal metabolism (13). Among the hormones fetal insulin has been implicated as the "growth hormone" of the fetus. The placenta also produces polypeptide hormones with thyrotropin like bioactivity which peak at the end of the first trimester, transiently increasing free thyroid hormone levels in maternal serum and transiently suppressing maternal TSH secretion (14), but has little influence on fetal thyroid function.

Studies in animals have shown that thyroid hormones are essential for optimal growth and development of the CNS, lung, gut and liver and the regulation of carbohydrate, protein and lipid metabolism. Reverse triiodothyronine (rT3) stimulates the adipocytes (15), amino acid uptake (16), hepatic amino transferase (17) and growth hormone secretion (18). That means that rT3 is not only an inactivation product of T4. T3 increases the transport of amino acids into the thyroid cells, bones and brain cells in animals . In the presence of insulin and adrenalin T3 stimulates sugar transport into the cells.

Fetal thyroid ontogenesis has been characterized in three phases; embryogenesis, hypothalamic maturation and development of hypothalamic-pituitary-thyroid system control (19). Embryogenesis is largely completed by 10 to 12 weeks of gestation. Hypothalamic maturation including

Table 1. Cord blood thyroid hormone levels in macrosomic and normal birth weight fetuses.

	T3	T4	free T3	free T4	TSH
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Macrosomia (n=40)	0.33±0.17	9.37±3.88	0.99±0.48	1.27±0.22	8.81±6.39
Controls (n=18)	0.43±0.12	11.62±2.67	2.57±1.39	1.38±0.24	8.92±5.22
p **	0.0262	0.0362	0.0001	0.131	0.623

* : x+/-sd

** : Student t test

the development of the pituitary portal vascular system proceeds from 6 to 7 week through 30 to 35 weeks of gestation (20). Maturation of control of thyroid hormone secretion is superimposed on a progressive increase in the fetal serum thyroxine binding globulin concentration during the period of 10 to 35 weeks of gestation. Ballabio et al employed cordocentesis to study fetal thyroid function at 18-31 weeks of gestation and demonstrated that fetal serum TSH, total and free T4 concentrations increased with gestation (21). Fetal serum TSH levels were always higher, and total T4 levels were lower than the adult values. Whereas free T4 levels reached adult levels by 28 week of pregnancy. Thorpe-Beeston also employed cordocentesis to 62 fetuses and demonstrated significant increases in concentration with gestation for fetal serum TSH, TBG, and both free and total T3 and T4 (22). No significant association were demonstrated between fetal and maternal serum thyroid hormones and TSH concentrations suggesting that in the human fetus, the pituitary thyroid axis develops independently from that of the mother (22-24). Even if fetal serum total and free T4 levels reached adult levels by 36 weeks of gestation, the fetal total and free T3 concentrations was less than half of the adult levels (22) . Since the major source of free T3 is peripheral conversion of T4 in adults, these findings suggest that in fetal life the mechanisms essential for this conversion either immature or lack of essential stimulus for being active. Another clue for late activation of the conversion mechanism was the huge increase in the capacity for hepatic conversion of T4 to T3 during labour and neonatal period (23, 25).

Alternative explanation for the mechanism of low serum T3 levels could be rapid deoiodination by the placenta (26).

The secretion of TSH and thyroid hormones is minimal until midgestation (13). At this time fetal thyroid gland iodine uptake and serum T4 concentrations begin to increase (19, 27). TSH is also present in the 12 week old fetus and rapidly rises thereafter, paralleling the increasing levels of FT4. T4 is detectable in the fetal serum by the twelfth week of gestation. Thereafter, both the total T4 and FT4 increase linearly in relation to the gestational age. At term the T4 reaches a level of 12.0 +/- 4.0 micg/dl in the umbilical cord serum.

Thyroid hormones undergo biochemical transformation in tissues (28). These include deiodination, side chain metabolism and conjugation with sulphate or glucronide. Monodeiodination of the thyroid hormones is the most important pathway of thyroid hormone metabolism. Several enzyme activities are involved in this monodeiodination; two types of monodeiodinase (type I and II) activity and innerring iodothyronine monodeiodinase (type III). Type I deiodinase predominantly expressed in liver and kidney is inhibited by propilthiouracile (PTU), and stimulated by thyroid hormone. Type II deiodinase activity, predominantly located in brain, pituitary, and brown adipose tissues is insensitive to PTU and inhibited by thyroid hormone. Type I activity in liver, kidney and perhaps muscle probably accounts for most of the peripheral deiodination of T4. The type II deiodinase probably plays an important role in providing intracellular T3 to those tissues that are dependent on t3 during fetal life , whereas the activity of the type I enzyme which provides increased serum T3 levels, increases only during the final weeks of gestation and during postnatal life. Type III deiodinase is present in fetal liver, brain, skin and placenta. This enzyme catalyzes the conversion of T4 to rT3 and to 3, 3'-diiodothyronine. Studies of the ontogenesis of this enzyme system in rodents and sheep have shown a predominance of type III enzyme activity in the fetal period (13).

In the fetus T4 is metabolized predominantly to reverse T3, rather than to T3. Fetal serum T3 concentration is low throughout gestation. Fetal thyroidal T3 and rT3 are low; suggesting secretion of these hormones is minimal in utero. The low fetal blood T3 production rate is due to low levels of hepatic outer ring iodothyroninedeiodinase activity in fetal liver. However hepatic T4 to rT3 conversion is quite active and probably accounts for most of the fetal rT3 production. Placental T4 to rT3 conversion may also contribute. We found that T3 levels in macrosomic fetuses were significantly lower than in normal birth weight infants ($p<0.05$). Unfortunately in the present study rT3 levels were not measured.

Placental size seems to be a determinant of fetal growth (29). Placentas of macrosomic fetuses tend to be larger in size than the normal population. Besides this anatomic status, placentas of the macrosomic fetuses thought to have some enzymatic and physiologic differences. An increase in placental deiodinase activity in macrosomic fetus may lead to low thyroid hormone levels.

Features of the low T3 Syndrome in the premature infant are similar to those in older children or adults. These include a low serum T3 concentration due to a decreased rate of conversion of T4 to T3 in nonthyroidal tissues, variable serum rT3 levels with values equal to or lower than concentrations in "healthy" premature infants, and normal or low total serum T4 concentrations with free T4 levels usually in the range of values for healthy premature infants of matched gestational age and weight.

There may be differences in the efficacy of thyroid hormones in tissues between macrosomic and normal birth weight fetuses. In the present study laboratory findings resembling the low T3 Syndrome have been formed in macrosomic fetuses. It may be suggested that not only placenta but also the fetus itself may have a possible role in this situations. The Low T3 Syndrome in macrosomic fetuses is a transient situation as we found the thyroid

hormone levels in normal ranges one month after the first assessment in eleven macrosomic infants.

A controlled clinicomorphological study of 170 big fetuses versus 70 medium body mass fetuses was performed with a special emphasis on the endocrine regulation in the functional system mother-placenta-fetus. Even if clinically there was no evidence of mother's endocrine system pathology, through morphological studies significant morphofunctional peculiarities of thyroid gland was found in macrosomic fetuses in comparison to controls. (30) In a morphological study of thyroid gland and adrenal cortex of macrosomic fetuses compared to the controls, it also had been found that the thyroid gland functional activity, as well as of glomerular and fascicular zones of adrenal cortex were significantly increased. (4)

In conclusion thyroid hormones appear to have both generalized actions on RNA and protein synthesis and specific actions on the transcription of particular proteins.

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