Hormonal Regulation of Growth and Maturation: I. The Effect of Hormones on Fetal Growth

Itsuro Hibi and Toshiaki Tanaka

Division of Endocrinology & Metabolism, National Children's Hospital (IH), Tokyo, Department of Endocrinology & Metabolism, National Children's Medical Research Center (TT), Tokyo, Japan

Key words: fetal growth, IGF-I, insulin, GH, thyroid hormone

Fetal Growth and the Role of Thyroid Hormone

Ontogenesis of the pituitary-thyroid axis during the fetal period

Thyroid stimulating hormone (TSH) and T4 levels in the fetus gradually increase from week 20 of gestation, but the T3 level remains low until week 30, as shown in Fig. 1 by Fisher (1). On the other hand, however, rT3 remains high, because of the strong enzymatic activity of alpha ring monodeiodinase, which converts T4 to rT3. From 15% to 20% of the thyroid hormone in the fetus is thought to come from the mother via the placenta and the remaining thyroid hormone to be secreted by the fetal thyroid. A report by Vulsma et al. (2) indicating that 30% to 50% of thyroid hormone comes from the mother at term is consistent with the finding that serum levels of T4 in neonates with congenital thyroid hypoplasia range from 2.3 μg/dl to 5.4 μg/dl.

Clinical characteristics in neonates with congenital hypothyroidism

Table 1 shows clinical characteristics at birth in neonates with congenital hypothyroidism at the National Children's Hospital in Tokyo. Although gestational age is significantly higher in various conditions  

Fig. 1 Serum thyroxine (T4), reverse triiodothyronine (rT3), triiodothyronine (T3) and thyrotropin (TSH) concentrations in the fetus and after birth.
Table 1  Gestational age, birth length, birth weight, and degree of overweight in congenital hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Severe type</th>
<th>Mild type</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>40.8 ± 1.2</td>
<td>39.2 ± 1.4</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>49.3 ± 1.6</td>
<td>49.9 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Birth length SDS (L-SDS)</td>
<td>-0.4 ± 1.6</td>
<td>0.2 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3250 ± 502</td>
<td>3301 ± 600</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight SDS (W-SDS)</td>
<td>0.4 ± 0.8</td>
<td>0.6 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>W-SDS – L-SDS</td>
<td>0.6 ± 0.7</td>
<td>0.4 ± 1.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Severe than in mild congenital hypothyroidism, significant differences were not observed in height standard deviation score (SDS) at birth, either between the two types or between congenital hypothyroidism and normal neonates, demonstrating that thyroid hormone deficiency during the fetal period does not affect height at birth. But weight and weight SDS at birth were significantly greater in neonates with congenital hypothyroidism than in normal neonates.

Overweight SDS (calculated by subtracting length SDS from weight SDS: W-SDS – L-SDS in Table 1) is also significantly greater in neonates with congenital hypothyroidism than in normal neonates. Since patients with severe congenital hypothyroidism sometimes have myxedema in early infancy, overweight seems to be attributable to water retention (3, 4).

The epiphysis of the distal femur (DEF) is visible in a knee X-ray of a normal neonate at birth. An invisible or small DEF in the neonatal period is known to be an important sign of congenital hypothyroidism (5, 6). Figure 2 shows the diameter of the DEF of patients with congenital hypothyroidism: the open circles indicate mild hypothyroidism in those who were diagnosed by neonatal screening, and the closed circles indicate severe hypothyroidism in those who had been diagnosed from clinical symptoms before the screening program started. These data show clearly that DEF size reflects congenital hypothyroidism’s severity and duration. When DEF maturity in three patients with congenital hypothyroidism, diagnosed at ages ranging from 1.5 years to 2.2 years, was estimated by the Roche method (7), DEF size in these patients corresponded to less than one month (Fig. 3). DEF does not, therefore, mature under conditions of complete thyroid hormone deficiency.

Bone age is generally estimated from hand and wrist X-rays. During the neonatal period and early infancy, however, this method is useless: during these periods, bone age must be estimated from knee X-rays.
Clinical characteristics in patients with congenital hyperthyroidism

It is reported that fetuses developing under conditions of thyroid hormone excess are born small-for-date in Japan (8, 9). Table 2 shows clinical data reported at birth in 18 patients with neonatal hyperthyroidism. Thyroid hormone excess may increase linear growth slightly but produces a weight loss relative to height. In these patients, the gestational period is shorter, but the birth height is almost normal and the birth weight is low.

Figure 4 shows the bone age of 27 patients with hyperthyroidism diagnosed at the National Children's Hospital and 3 patients with neonatal hyperthyroidism (10, 11). The youngest patients

Table 2 Gestational age, birth length, birth weight, and degree of overweight in neonatal hypothyroidism

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>36.5 ± 2.5</td>
<td>18</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>48.0 ± 2.3</td>
<td>18</td>
</tr>
<tr>
<td>Birth length SDS (L-SDS)</td>
<td>-0.3 ± 0.8</td>
<td>18</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2617 ± 435</td>
<td>18</td>
</tr>
<tr>
<td>Birth weight SDS (W-SDS)</td>
<td>-0.05 ± 0.8</td>
<td>18</td>
</tr>
<tr>
<td>W-SDS - L-SDS</td>
<td>-0.4 ± 0.8</td>
<td>18</td>
</tr>
</tbody>
</table>

* including patients without birth length reported.
showed acceleration of bone age: this acceleration in neonatal hyperthyroidism indicates that thyroid hormone excess can accelerate bone maturation in utero, and is concordant with the observation of delayed bone maturation in congenital hypothyroidism.

**Fetal Growth and the Role of Sex Steroids**

It is well known that HCG-dependent testosterone secretion from fetal male testes increases from week 10 to week 20 of gestation (12-15). Female fetuses are exposed to high concentrations of estradiol. The effect of sex steroids on fetal growth has been assessed in patients with congenital adrenal hyperplasia.

**Clinical characteristics in patients with congenital adrenal hyperplasia (21α-hydroxylase deficiency)**

Patients with congenital adrenal hyperplasia have been exposed to higher than usual
concentrations of testosterone from the fetal development stage. Figure 5 shows birth length and weight in patients with the salt-losing type and with the simple virilizing form of congenital adrenal hyperplasia at the National Children's Hospital: their length and weight do not differ from normal neonates, allowing us to conclude that testosterone does not influence fetal growth. Nor is bone age maturation accelerated by testosterone in these patients (Fig. 6). Insensitivity of bone maturation to testosterone was examined in patients with congenital adrenal hyperplasia (CAH). Figure 7 shows bone age maturation in untreated CAH patients who were diagnosed before the start of the screening program for CAH at National Children's Hospital in Japan. Bone age acceleration begins at approximately 1.5 years in CAH (Fig. 7). Length SDS in these patients also advanced significantly, beginning from age 1.5 years (Fig. 8). We conclude from this that bone is insensitive to testosterone until 1.5 years, but a male patient with hamartoma showed an extremely advanced bone age (5.5 years) at 1.5 years, and a female patient with hamartoma showed a growth spurt at 7 months (personal communication).}

---

**Fig. 7** Bone age at diagnosis in 21-hydroxylase deficiency before screening program started.

---

**Fig. 8** Length SDS at diagnosis in untreated 21α-hydroxylase deficiency. SV: Simple virilizing type, SL: Salt losing type.
nal genitalia respond well to sex steroids; the sensitivity of bone to sex steroids requires further study.

**Clinical characteristics of patients with low sex steroid during fetal life**

There are several diseases with a 46,XY karyotype that have a low sensitivity, or none at all, to testosterone during fetal life, such as testicular regression syndrome, testicular hypoplasia, and testicular feminization syndrome. Table 4 shows clinical characteristics of neonates with these diseases. Gestational age, birth length and birth weight in these patients do not differ from those in normal neonates, allowing us to conclude that testosterone deficiency during fetal life does not influence fetal growth. The fact that birth length and weight are normal in 46,XY patients with lipoid hyperplasia corroborates the above conclusion (16). Nor does estrogen deficiency during fetal life influence fetal growth, since length and weight at birth are normal in patients with 46,XX pure gonadal dysgenesis (17), anencephaly with adrenal atrophy (18), aromatase deficiency (19-21), sulfatase deficiency in placenta (22, 23), and congenital defect of estrogen receptor (24).

**Fetal Growth and the Role of Growth Hormone**

It has been shown that maternal GH does not cross the placenta to the fetus in maternal acromegaly, maternal hypophysectomy, etc. (25, 27). Whether GH influences fetal growth is still controversial. Reports of normal length and weight at birth in patients with anencephaly (18, 28, 29) and congenital panhypopituitarism (30-32) suggest that GH does not influence fetal growth. On the other hand, however, short birth length in Laron syndrome (27, 33, 34), type IA GHD (35, 36), Pit-1 abnormality (36), congenital GH deficiency (37), and GH deficiency with cleft lip (38) demonstrates that GH does have an in-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Gestational age, birth length, birth weight, and degree of overweight in 21α-hydroxylase deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>SL (Salt losing type) 19 (M:9, F:10)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.8 ± 1.6</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>50.1 ± 2.1</td>
</tr>
<tr>
<td>Birth length SDS (L-SDS)</td>
<td>0.3 ± 1.2</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3311 ± 503</td>
</tr>
<tr>
<td>Birth weight SDS (W-SDS)</td>
<td>0.6 ± 1.4</td>
</tr>
<tr>
<td>W-SDS – L-SDS</td>
<td>0.4 ± 0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Testicular feminization and birth weight in boys without testosterone effect during fetal life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Testicular feminization Complete type Incomplete type Sub total Testicular hypoplasia or regression Total</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>5</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>39.8 ± 1.6</td>
</tr>
<tr>
<td>Birth length SDS</td>
<td>49.2 ± 1.8</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3205 ± 546</td>
</tr>
</tbody>
</table>
fluence on the fetus (Fig. 9). It is reported that birth length is normal in patients with GH deficiency related septo-optic dysplasia. Although Laron claims that the lower IQ in Laron syndrome may be an effect of GH on brain maturation (39), no mental deficiency has been recognized in GH insensitivity syndrome in Ecuador (40, 41). Since congenital GH deficiency and Laron syndrome are associated with severe hypoglycemia during the neonatal period, it is questionable whether mental deficiency in these diseases is attributable solely to a GH deficiency. The frequency of hypoglycemia in Laron syndrome differs little among reports from Israel (33), Ecuador (41), and Europe (34, 42), but reported IQ does differ. Some factor other than GH and hypoglycemia may influence IQ, and the influence of GH on the fetus is therefore still unclear. Even if GH does affect the fetus, its effect may be marginal. Some speculate that IGF-I and IGF-II are more important than GH for fetal growth and that GH seems not to have major effects on IGFs in the fetus.

### Fetal Growth and the Role of Insulin

It is well known that Langerhans’ islets in the fetal pancreas begin to secrete insulin at week 20 of gestation (1). The insulin concentration in umbilical cord is reported to show a weak but significant positive correlation with birth weight (1, 43, 44). In healthy premature babies, however, insulin concentrations in umbilical cord do not correlate with gestational age from week 27 to week 35 (45).

### Fetal growth in patients with pancreatic agenesis or hypoplasia

Canadian doctors (46, 47) have demonstrated that siblings with pancreatic agenesis born from consanguineous parents showed severe intra-uterine growth retardation (below the 3rd percentile in length, weight, head circumference, and brain weight, as well as decreased DNA in all tissues). Several reports have confirmed this observation (48-50). Patients with pancreatic agenesis usually develop insulin-dependent diabetes mellitus before malabsorption due to...
Table 5 Gestational age, birth length, birth weight, and degree of overweight in infantile-onset IDDM

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Birth length (cm)</th>
<th>Birth length SDS (L-SDS)</th>
<th>Birth weight (g)</th>
<th>Birth weight SDS (W-SDS)</th>
<th>W-SDS – L-SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=6</td>
<td>39.5 ± 1.5</td>
<td>(38–42)</td>
<td>N=7</td>
<td>45.0 ± 2.8</td>
<td>(39.5–48)</td>
</tr>
<tr>
<td>N=5</td>
<td>-2.9 ± 1.1</td>
<td>(-4.8–2.1)</td>
<td>N=10</td>
<td>2371 ± 424</td>
<td>(1330–2800)</td>
</tr>
<tr>
<td>N=5</td>
<td>-2.3 ± 1.1</td>
<td>(-4.0–1.2)</td>
<td>N=5</td>
<td>+0.5 ± 0.8</td>
<td>(-0.9–1.0)</td>
</tr>
</tbody>
</table>

★ Comparison with normal children.

Table 6 Gestational age, birth length, birth weight, and degree of overweight in neonatal transient diabetes mellitus

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Birth length (cm)</th>
<th>Birth length SDS (L-SDS)</th>
<th>Birth weight (g)</th>
<th>Birth weight SDS (W-SDS)</th>
<th>W-SDS – L-SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=11</td>
<td>32.7 ± 7.2</td>
<td>(24–42)</td>
<td>N=11</td>
<td>40.3 ± 5.4</td>
<td>(30.5–50)</td>
</tr>
<tr>
<td>N=9</td>
<td>-1.5 ± 1.7</td>
<td>(-2.7–0.0)</td>
<td>N=11</td>
<td>1591 ± 705</td>
<td>(514–2938)</td>
</tr>
<tr>
<td>N=9</td>
<td>-2.0 ± 1.8</td>
<td>(-4.3–0.1)</td>
<td>N=9</td>
<td>-0.5 ± 1.9</td>
<td>(-4.3–2.3)</td>
</tr>
</tbody>
</table>

★ Comparison with normal children.

Pancreatic enzyme deficiency in childhood (51-53). Pancreatic enzyme deficiency can sometimes be detected by testing after the onset of diabetes. Some patients with pancreatic hypoplasia also develop diabetes and malabsorption in adult life (54). The occurrence of symptoms depends on the severity of the pancreatic defects.

**Clinical characteristics in patients with IDDM before 3 months of age**

Table 5 shows the clinical characteristics at birth in ten insulin-dependent diabetes mellitus (IDDM) patients whose diabetes developed before they were 3 months old; the data are from the 1981 Japanese national survey (55). These patients were light-for-date and short-for-date despite their normal gestational age, as previously reported (47, 57, 58). Weight SDS for length SDS (W-SDS – L-SDS), however, was within the normal range (56).

Table 6 shows clinical characteristics at birth in 11 patients with neonatal transient diabetes mellitus. Birth weight was light for gestational age and birth length was also short for date despite the early gestational age. Weight SDS for length SDS, however, was within the normal range. It can be concluded that insulin deficiencies during fetal life, such as pancreatic agenesis, pancreatic hypoplasia, IDDM, and neonatal transient IDDM, induce growth failure but are not related to low adiposity.

Table 7 shows clinical characteristics at birth in 12 patients with nesidioblastosis, which is characterized by fetal hyperinsulinism. Birth length in these patients was not significantly shorter than normal, but birth weight for date and weight SDS for length were significantly increased.

Figure 10 shows the birth length SDS in infantile IDDM, neonatal transient IDDM, and nesidioblastosis. It has been demonstrated that insulin deficiency during fetal life — as seen in pancreatic agenesis or hypoplasia, infantile IDDM, and neonatal transient IDDM — disturbs linear
growth, but hyperinsulinism during fetal life, seen in nesidioblastosis, does not affect linear growth. Figure 11 shows the birth weight SDS for birth length SDS in these diseases. The insulin-deficient state does not decrease the weight gain for length, but hyperinsulinism increases weight for length as shown in nesidioblastosis. It has been suggested that this weight gain for length gain is attributable to fat gain (57, 59).

Mechanism of growth by insulin during fetal life

Umbilical cord insulin concentrations do not correlate with gestational age from week 27 to week 35 and show only a weak correlation with birth weight (45), conflicting with the clinical data shown above. Insulin, however, must bind to an insulin receptor before it exerts its action. Insulin receptors appear from week 15 of gestation in parallel with IGF-I receptor and increase
in number until week 25, after which receptor affinity increases (60).

Insulin receptors of monocytes from umbilical blood are reported to have five times the binding capacity of insulin receptors of monocytes from adult blood (61). It is speculated that the mechanism of insulin's growth promotion is as follows. First, insulin binds to its receptor on a fetal cell and promotes the intake of nutrients. It is reported that insulin promotes growth by stimulating IGF-I secretion as well as inhibiting IGFBP-1 secretion by the liver postnatally (62). Second, it is speculated that the same mechanism functions during the fetal stage. Though it is difficult to differentiate insulin's direct action from its indirect action via IGF-I, we speculate, based on evidence provided in the next section, that the indirect action is more important than the direct action.

**Fetal growth and growth factors**

Much evidence is accumulating to show that IGF-I is the most important growth factor for fetal growth. Changes in fetal length parallel changes in the IGF-I concentration, and birth weight shows a significant positive correlation with IGF-I concentrations in umbilical cord blood (63-65). Fujieda et al. (66) have demonstrated that IGF-I increases and IGFBP-1 decreases with gestational age and that birth weight correlates positively with IGF-I and negatively with IGFBP-1. Intra-uterine growth retardation and postnatal growth disturbance have been clearly demonstrated in IGF-I knock-out mice (67-69).

It is well known that IGF-I is GH-dependent and GH is of fundamental importance for growth in postnatal life, but whether IGF-I is GH-dependent or IGF-I secretion is regulated by other factors in fetal life, is unclear. Fetal GH concentrations peak at week 25 of gestation, whereas IGF-I concentrations peak at birth and do not parallel GH concentrations. Newborns with anencephaly show normal IGF-I for date and normal birth weight. Other evidence for non-GH dependency during fetal life is offered by the normal birth weight and length of newborns with congenital hypopituitarism.

What then regulates IGF-I secretion? Evidence suggests that maternal nutrition is the most important factor. Maternal malnutrition decreases both maternal and fetal IGF-I concentrations, and injection of glucose or insulin into the fetus restores the fetal IGF-I concentration to the level before deprivation; amino acid injection, however, does not effectively influence IGF-I secretion (70). We infer that the fetus has an independent system that either secretes IGF-I when insulin is injected or, as a second mechanism, synthesizes insulin when glucose is injected (70-72). Fetal insulin also increases the intake of glucose and amino acids from the placenta. The removal of the pancreas from the sheep fetus decreases the IGF-I level (72), indicating that insulin plays an important role in IGF-I secretion. Insulin also promotes growth in postnatal life: though it does not influence bone directly, insulin contributes to growth by stimulating the liver to synthesize IGF-I and decrease IGFBP-1 secretion (70-74).

Two mechanisms regulate IGF-I metabolism: the GH - IGF-I - IGFBP-3 system and the insulin - IGF-I - IGFBP-1 system. In fetal life, the latter system is dominant; postnatally, both systems become important.

It is still not clear why low concentrations of IGF-I play such an important role in the fetus, but studies on IGFBPs are producing some answers: i) a low IGFBP-1 concentration increases the availability of IGF-I in the tissues; ii) a high concentration of IGFBP-2 binds mainly to IGF-II and increases the availability of IGF-I; and iii) although both IGF-I and IGFBP-3 concentrations are low in the fetus, the molar ratio of IGF-I to IGFBP-3 is relatively high (75). Fetal growth is influenced not by genetic factors but mainly by nutrition (76). Thus, in order to utilize nutrients, maternal nutrition, placental function, and fetal metabolism are all equally important. Fig-
Figure 12 schematizes fetal growth and the role of hormones (76, 77). Placenta lactogen secreted by the placenta increases the mother's appetite and the intake of nutrients. Placental growth hormone, also secreted by the placenta, increases the IGF-I concentration in the mother. Maternal IGF-I regulated by pituitary GH, placental GH, and insulin increases glucose and amino acid transport from the placenta to the fetus (1). Fetal IGF-I is regulated by pituitary GH and pancreatic insulin, whose secretion is stimulated by glucose transported from the placenta. Insulin increases IGF-I availability by stimulating IGF-I secretion and inhibiting IGFBP-1 secretion by the liver. Fetal IGF-I also increases glucose transport from the placenta. Pituitary GH increases IGFBP-3 secretion, which is thought to deliver IGF-I to peripheral tissues. But in the fetus, the main mechanism is IGF-I regulation by insulin.

IGF-II is also thought to play an important role in fetal growth, but its mechanism is still unclear.

Acknowledgements

The authors thank Dr. Sachiko Kitanaka, Dr. Norio Ishikawa, Dr. Naoya Koda, Dr. Shigeo Nagafuchi, Dr. Reiko Horikawa and Dr. Ayako Tanae for their generous help, discussion and comments.

References

52. Winter WE, Macaren NK, Riley WI, Toskesw PP, Andres J, Rosenbloom AL. Congenital pancreatic hypoplasia: a syndrome of exocrine and


75. Bang P, Giudice LC, Rosenfeld RG. Insulin-like growth factors (IGFS) and IGF binding proteins as endocrine growth factors in the human fetus.