TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDIATRICS

Review / Derleme

Transient endocrinologic problems in the newborn period

Yenidoğan döneminde geçici endokrin sorunlar

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Cite this article as: Kurtoğlu S, Direk G, Uzan Tatlı Z, Hatipoğlu N. Transient endocrinologic problems in the newborn period. Turk Pediatri Ars 2019; 54(1): 3–12.

Abstract

Many transient endocrinologic disorders are frequently seen in newborn period. Early diagnosis and treatment is important for babies. In this article, transient endocrinopathy of newborn and relevant literature were reviewed. Blood sugar problems, especially adrenal insufficiency due to adrenal problems, thyroid problems such as transient hypotirotropinemia, are frequently encountered by physicians. Genital and urinary problems should be evaluated differently according to gender. Problems related to calcium metabolism, problems associated with water metabolism and endocrine skin problems are other problems. It is essential to know the normals of the hormones in the neonatal period in order to recognize them properly, to evaluate them properly and to interpret the tests correctly.

Keywords: Diagnosis, management, newborn, transient endocrinologic problems

Öz

Yenidoğan döneminde bir dizi geçici endokrin sorun oldukça sık görülmektedir. Olguların doğru tanınması ve uygun tedavisi önem taşımaktadır. Yazıda yenidoğanın geçici endokrin sorunlarına değinilmiş ve ilgili dizinler gözden geçirilmiştir. Kan şekeri sorunlarından geçici hipoglisemi ve hiperglisemi, sürrenal sorunlardan özellikle görece adrenal yetmezlik, geçici hipotirotropinemi gibi tiroid sorunları hekimlerin sıkça karşı karşıya geldiği sorunlardır. Genital ve üriner sorunlar cinsiyete göre farklı yorumlanmalıdır. Kalsiyum metabolizması ile ilişkili sorunlar, su metabolizması ile ilişkili sorunlar ve endokrin cilt sorunları da görülebilen diğer sorunlardır. Bunların tanınması, uygun şekilde değerlendirilmesi ve tetkiklerin doğru yorumlanabilmesi için hormonların yenidoğan dönemindeki normallerinin bilinmesi elzemdir.

Anahtar sözcükler: Geçici endokrin sorunlar, tanı, yenidoğan, yönetim

1. Blood glucose problems

Transient hypoglycemia or hyperglycemia are among the common problems observed in the neonatal period.

a) Transient neonatal hypoglycemia: Although different figures have been recommended for the definition of neonatal hypoglycemia, the American Academy of Pediatrics Committee on Fetus and Newborn defined a blood sugar level below 40 mg/dL and a level below 45 mg/dL as hypoglycemia in the first 4 hours and between the first 4th and 24th hours, respectively. If hypoglycemia persists longer than 60 minutes despite interventions, the definition of prolonged hypoglycemia is used (1). Generally, subjects who recover in the first week fall within the group of transient hypoglycemia. The causes of neonatal hypoglycemia include delayed postnatal adaptation, being a preterm and small-for-gestational-age (SGA) baby, sepsis, asphyxia, premature delivery, transient hyperinsulinemia, being an infant of a diabetic mother, glucose load in the mother during delivery, maternal use of ritodrine, erythroblastosis fetalis, perinatal asphyxia, intrauterine growth retardation, toxemia, polycythemia and increased metabolic requirements (1, 2). Tremor, jitteriness, sweating, irritability, tachypnea, and paleness related to the adrenergic system and poor suck, high-pitched cry, lethargy, coma, and hypotonia and convulsion as neuroglycopenic symptoms may be observed. In treatment, the patient is

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Received / Geliş Tarihi: 25.01.2018 **Accepted / Kabul Tarihi:** 02.04.2018

DOI: 10.14744/TurkPediatriArs.2019.04810

primarily fed orally. If improvement occurs in 30 minutes, oral feeding is continued. If no improvement occurs in 30 minutes, 10% dextrose is given by the intravenous route at a dosage of 2 mL/kg in 1 minute. If convulsions are present, it is given at a dose of 4 mL/kg. Subsequently, glucose is given by the intravenous route at a dosage of 6–8 mg/kg/minute (2).

b) Transient neonatal hyperglycemia: In newborns, a complete blood glucose level above 125 mg/dL and a plasma glucose level above 150 mg/dL is defined as hyperglycemia (3). It is observed more commonly in preterm babies and hyperglycemia occurs following hypoglycemia in the first week in these babies; the most common cause is glucose and lipid infusion. In preterm babies, insulin level is low and the receptors are not fully mature. In very preterm babies, the proinsulin level is higher and the levels of insulin-like growth factor (IGF-1), which increases peripheral glucose use, are low. Sepsis, necrotizing enterocolitis, cerebral bleeding, convulsion, hypernatremia, therapeutic premature delivery, and surgical interventions, which cause stress, increase the blood glucose level (3, 4). Fungal infections occur more commonly, if hyperglycemia is present. In addition, they cause hyperglycemia. Maternal use of diazoxide and administration of theophylline, steroids, phenytoin, and vasoactive drugs to the baby may cause hyperglycemia. Babies with starvation, isovaleric acidemia, propionic acidemia, and beta-ketotiolase deficiency may rarely present with a picture of hyperglycemia. In addition, it has been proposed that 46 XXDq 13 deletion may cause neonatal hyperglycemia and low phosphate level may increase hyperglycemia. Hyperglycemia predisposes to infections, increased oxidative stress, and may be a risk factor for bronchopulmonary dysplasia, prolonged hospitalization, mortality, and retinopathy in preterm babies.

There are different approaches in the diagnosis and treatment. It is thought that the level of hyperglycemia that increases the risk of osmotic diuresis, electrolyte imbalance, and intraventricular hemorrhage in newborns is 360 mg/dL. In treatment, the speed of administration of glucose is reduced in the primary step, but it is not reduced below 4–5 mg/kg/min. Different figures have been proposed for insulin treatment. Administration of bolus insulin may lead to a rapid reduction in the blood glucose levels. Insulin treatment is initiated at a dose of 0.01–0.02 U/kg/h; it is incremented by 0.01 U, and the maximum dosage is 0.1 U/kg/h. The objective is to adjust the infusion speed such that the plasma glucose level is kept between 150 and 200 mg/dL. If the plasma glucose level is 180–200 mg/dL, the infusion is reduced by 50%. If it decreases below 180 mg/dL, the infusion is stopped. If it is below 150 mg/dL, the dosage of glucose may be increased by 2 mg/kg/min. The infusion dose is adjusted by measuring the plasma glucose level with intervals of 30–60 min. If 25 U/kg insulin is added to a solution of 50 mL and this fluid is administered at a dosage of 0.2 mL/h, this corresponds to a dosage of 0.1 U/kg/h (5).

2. Adrenal gland problems

Transient adrenal gland insufficiency and pseudohypoaldosteronism may be observed in newborns.

a) Relative adrenal insufficiency: This is a condition in which newborn babies cannot produce a sufficient adrenal response against stress. The adrenal axis is not fully functional until the 30th gestational week. Therefore, a sufficient cortisol response against acute stress cannot be obtained in preterm babies. In the event of acute stress, adrenocorticotropic hormone (ACTH) and cortisol synthesis is suppressed with cytokines, tissue resistance develops against cortisol, and relative adrenal insufficiency occurs with a reduction in adrenal blood flow in both preterm and term babies. When corticosteroids are used prenatally, a picture of adrenal insufficiency occurs in 3–10 days (6). In recent years, the term 'critical illness-related corticosteroid insufficiency (CIRCI)' has been recommended instead of relative adrenal insufficiency (7, 8). The most important sign is cardiovascular problems, and persistence of hypotension, oliguria, and hyponatremia despite fluid and inotropic support is a significant finding.

The diagnostic criteria include a cortisol level below 10 micrograms in a blood sample obtained randomly and a less than 9 microgram/dL increment in the cortisol level after stimulation with 250 microgram ACTH. It is known that hydrocortisone treatment is beneficial in relative adrenal insufficiency. While waiting for the result of cortisol levels in a randomly obtained blood sample, hydrocortisone at a dose of 1 mg/kg is initiated. If the blood pressure improves in 2–6 hours, it is continued at a dosage of 0.5 mg/kg every 12 hours (8–10 mg/m^2/day). If the cortisol level is above 15–20 microgram/dL in a random blood sample, the drug is discontinued and other cardiac and vascular supportive therapies are continued (8).

b) Transient pseudohypoaldosteronism: Congenital adrenal hyperplasia (CAH) is considered primarily in newborns in the presence of a picture of hyponatremia, natriuresis, hyperpotassemia, thrombocytosis, hypotension, and dehydration. Pseudohypoaldosteronism is considered if the aldosterone level is found to be considerably high. However, aldosterone may be found to be low because of the hook effect in some cases (9). Other than genetic eti-

ology, unresponsiveness in aldosterone receptors occurs due to pressure and cytokines in cases of hydronephrosis, hydroureter or pyelonephritis. Therefore, renal and adrenal ultrasonography is performed primarily for the diagnosis. The picture improves with treatment of infection and interventions directed to hydronephrosis-hydroureter (10).

3. Thyroid problems

A picture of transient hypothyroidism or hyperthyroidism may be observed in the neonatal period.

a) Transient hyperthyroidism: Presence of Graves' disease, Hashimoto's disease, use of high-dose thyroxine and antiseptics containing iodine in the mother may cause a picture of transient thyrotoxicosis. In addition, thyroid hormone levels may be found to be high because of interaction with the measurement methods in babies who receive biotin treatment, though clinical findings are absent.

The most common cause is maternal Graves' disease. An increase in antibodies during pregnancy is also observed in mothers who have undergone thyroidectomy or received radioactive iodine treatment before pregnancy. Thyroid-stimulating hormone receptor (TSHR) antibodies, which are produced in the mother, cross the placenta after the 17th gestational week. Fetal hyperthyroidism becomes prominent in the 26–28th weeks with the response of fetal TSH receptors. The picture of hyperthyroidism in the postnatal period occurs in 7–10 days with a reduction in TSHR-blocking antibodies and subsides through the effect of anti-thyroid drug use by the mother. In babies with blocking and stimulating antibodies in serum, the blocking antibodies, which have a half-life of 12 days, decrease, whereas a picture of late hyperthyroidism due to blocking antibodies occurs on the 21st day at the earliest. Intrauterine growth retardation, hepatosplenomegaly, lymphadenopathy, prolonged acrocyanosis, craniocynocytosis, microcephaly, periorbital edema, and goiter are found in the baby. Other signs and symptoms include vivacious look, exophthalmos, exaggerated Moro and other reflexes, increased appetite, inability to gain weight, frequent stools, vomiting, fever, tachycardia, sweating, systolic hypertension, supraventricular tachycardia, heart failure, pulmonary hypertension, and chylothorax (11).

In the diagnosis, free T3 (fT3), free T4 (fT4) are found to be increased and TSH is found to be inhibited. Polycythemia, thrombocytopenia, hypoglycemia, and increased levels of aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin are observed. On radiography, enlarged thymus, chylothorax, and advanced bone age are found. Increased TSHR antibodies in the cord blood and newborn confirm the diagnosis.

Table 1. Causes of transient hypothyroidism in newborns (13, 14)

a. Primary hypothyroidism
Iodine deficiency
Iodine load
Maternal hypothyroidism
Maternal use of methimazole, propylthiouracil, lithium and D-penicillamine
Small-for-gestational-age baby, intrauterine growth retardation
b. Central hypothyroidism
Use of dopamine, octreotide, corticosteroids, and morphine products
A picture of critical illness
Following cardiopulmonary by-pass
Application of deep hypothermia
Babies of mothers with untreatable Graves' disease

In the differential diagnosis, viral infections, sepsis, congenital heart diseases, and the picture of narcotic withdrawal syndrome should be considered. Cases may be confused with the picture of infantile colic.

Treatment: propylthiouracil is not recommended because of hepatotoxicity. Methimazole is initiated at a dosage of 0.2–0.5 mg/kg/day in 2 doses and it is adjusted according to the levels of fT4 and TSH. Propranolol is imitated at a dosage of 2 mg/kg/day in 2 doses for sympathetic hyperactivity. If hemodynamic disruption is present, lugol solution is initiated (3x1 drops/day). Lugol should be given at least one hour after methimazole so that the thyroid gland does not retain iodine (11, 12).

b) Transient hypothyroidism: An increase in the number of the cases of hypothyroidism is being observed with the initiation of congenital hypothyroidism screening programs in many countries of the world. A portion of the cases diagnosed with screening or hormone measurements are transient (Table 1).

History is taken and fT3, fT4, TSH, thyroglobulin, and urine iodine are measured to elucidate the etiology. Thyroid ultrasonography and thyroid scintigraphy are performed. If the venous blood TSH is < 6 mU/L, it is considered normal. If TSH is between 6 and 20 mU/L, it is followed up and checked 2 weeks later; treatment is initiated if it is >20 mU/L (15).

c) Transient neonatal hyperthyrotropinemia: In this condition, the TSH level is increased, although the total or free thyroxine levels are normal in the newborn. Iodine deficiency, iodine load, hypoplasia, pseudo hypoparathyroidism, exposure to low-dose radiation after the 11st week during pregnancy, Down syndrome, maternal blocking antibodies, anti-thyroid drugs, inactivating mutations in the TSH receptor, gestational diabetes, Kabuli make-up syndrome, partial TTF-1 deficiency, interaction in TSH measurements ('human anti-mouse' antibodies), macro-TSH (increased TSK also in the mother) and idiopathic causes are involved in the etiology. Diagnostic tests are performed as in cases of transient hypothyroidism. Free T4 and TSH are measured again at the end of the first month. If the TSH level decreases below 6 mU/L, it is considered transient neonatal hyperthyrotropinemia. Low-dose thyroxine treatment is recommended in patients whose increased TSH levels persist or whose TSH levels increase above 35 mU/L at the 30th minute with the TRH test (16).

d) Hypothyroxinemia of prematurity: In this condition, fT4 levels are below the reference values, although the TSH levels are normal in preterm babies. The diagnostic criteria include a fT4 level below 0.8 ng/dL and a TSH level below 10 mU/L in the postnatal 2–4 weeks (17). Preterm deliveries occur with a rate of 12% in the community and hypothyroxinemia develops in 35–50% of the babies. In a study conducted by van Wassenaer et al., (18) in which all thyroid functions of 100 preterm babies whose gestational ages were less than 30 weeks were monitored for 8 weeks, it was found that hypothyroxinemia of prematurity became prominent as the gestational age decreased, the disease did not cause statistically significant difference, and the fT4 level reached the lowest level on the 7th day and started to increase afterwards. In the same study, it was found that the "reverse" T3 (rT3) level did not change in ill preterm babies.

There is insufficient evidence to show that thyroid hormone treatment has a positive effect on hypothyroxinemia of prematurity. In a randomized controlled study conducted by van Wassenaer et al., (17) no evidence could be found to indicate that thyroid hormone treatment improved the prognosis. However, a second examination, which was not included in the study design, revealed evidence indicating that babies younger than 27–28 weeks could benefit from treatment.

It should be kept in mind that thyroxine treatment aimed at correcting hypothyroxinemia in preterm babies may also have adverse effects. Late-onset circulatory impairment was reported a few days after thyroxine treatment in a preterm baby with low birth weight (19).

4. Genital and urinary problems

A) Problems observed in female babies

Genital and urinary problems are observed more commonly in girls.

a. Cervical discharge and menstruation: Increased cervical secretion with the action of estrogen is observed as vaginal discharge. Uterine bleeding is observed immediately after birth. In the fetal period, the endometrial layer becomes thick with the action of estrogen and uterine bleeding occurs with the stimulus of progesterone. Another important point is the fact that uterine bleeding in the neonatal period is associated with the clinical picture of endometriosis in adolescence (20). Menstrual bleeding may also be observed in preterm babies with ovarian hyperstimulation (21). It has been emphasized that menstrual bleeding is a finding of mini-puberty in preterm babies and may generally be observed at about the adjusted postnatal age of 2.5 months (22).

b. Hydrocolpos and hydrometrocolpos: This is a problem observed in 0.006% of newborn babies. Accumulation of fluid in the vagina with cervical secretion in the presence of vaginal obstructions caused by factors including imperforated hymen and complete transverse vaginal agenesis is called hydrocolpos, and accumulation of fluid in the uterine cavity is called hydrometra. If menstrual blood is added, a diagnosis of hydrometrocolpos is made. Infected cases are known as pyometrocolpos or pyometra (23, 24). Abdominal swelling is observed prenatally and at the time of delivery. Pelvic cystic structure, mass, and obstructive uropathy are found on ultrasonography. Magnetic resonance imaging (MRI) may be performed, when necessary. In treatment, hymen perforation and vaginal interventions are performed besides draining the cystic structure. McKusick-Kaufman and Bardet-Biedl syndromes should be considered if other findings are present in patients presenting with a picture of hydrometrocolpos in the neonatal period (25).

c. Cliteromegaly: The newborn is placed in the supine frog-leg position, the hips and knees are kept in flexion, slight pressure is applied on the abdomen, the labia major are spread, and the height and width of the clitoris are measured by separating the clitoral prepicium. In addition, the cavernous structure is examined by palpation. If the corpus cavernosum is prominent, androgenic action with maternal or fetal origin is considered and its causes are investigated. If the corpus cavernosum is normal on physical examination, transient causes including difficult labor, edema, ecchymosis, SGA, prematurity, and normal variation should be considered.

Although different values are found in different countries, the criteria for cliteromegaly in term babies are generally as follows: height >10 mm and/or width >7 mm (26). In a study conducted in our country, the 3rd percentile value was found as 2 mm, the 10th percentile value was 2.76 mm, the 50th percentile value was 5.03 mm, the 90th percentile value was 6.84 mm, and the 97th percentile value was found as 8.04 mm for the clitoral height in term babies (27). In India, the 95th percentile value in preterm babies was reported as 6 mm (28). The reason for transient cliteromegaly in preterm babies is increased level of dehydroepiandrosterone (DHEA) because of the persistence of fetal zone activity and maintenance of increased dehydroepiandrosterone sulphate (DHEA-S), which is formed as sulphate in the liver. It may be confused clinically with CAH (29). Absence of labial fusion and pigmentation and a normal 17-OH progesterone level are important in babies. The DHEA-S level decreases in 3–6 months or when babies reach term and cliteromegaly regresses (29). In addition, frequent blood transfusions with adult male blood may cause cliteromegaly in very preterm babies (30). Transient cliteromegaly related to androgen-secreting ovarian cyst was reported in two very preterm babies (31).

d. Ovarian cyst: These patients are generally diagnosed in the 3rd trimester in the prenatal period. Cysts form with the mutual contribution of maternal estrogen, placental human chorionic gonadotropin (hCG), and fetal gonadotropins (32). Ovarian cysts are observed in cases of CAH and hypothyroidism (33, 34). Small follicular cysts are found in 90–98% of cases. Larger follicular cysts have been reported with varying rates. On physical examination, abdominal mass is found and it may be palpated as a moving mass if the cyst undergoes autoamputation. The diagnosis is made with ultrasonography in the prenatal and postnatal period (35). The cyst may be simple or complex. A finding that suggests that the cyst originates from the ovary is the presence of small daughter cysts on the cyst wall or in the region where the cyst is found (36). If the cyst's pedicle is twisted, an appearance of a snail shell emerges. In complex cysts, the fluid-debris level supports intracystic hemorrhage if peripheral septation is present (34). Magnetic resonance imaging is performed when necessary. In the differential diagnosis, enteric duplication cyst, cystic lymphangioma, meconium pseudocyst, hydrometrocolpos, ovarian tumors (cystadenoma, cystic teratoma, granulosa cell tumor), and urachal cyst should be considered. Ovarian tumors are generally solid, tend to enlarge, and are associated with ascites (36).

Cysts are monitored if their height is 2 cm. If its diameter is 5–6 cm, there is a risk for torsion, intracystic hemorrhage, and intestinal and urinary stenosis. If the cyst's diameter is 3–5 cm in the prenatal period, there is a risk for rupture, peritonitis, chorioamnionitis, and fetal injury, though aspiration is recommended (36). If distension and pressure effects are present, which could hinder vaginal delivery, aspiration may be performed (34). Close monitoring is appropriate in the postnatal period. Most cysts reduce and disappear in 6–7 months (37).

e. Ovarian hyperstimulation syndrome: This picture, which is observed in preterm babies, was reported for the first time by Sedin et al. (38). In these patients, unilateral or bilateral ovarian cysts and edema in the labia and upper thigh, sometimes involving the hypogastric region, are observed together with increased gonadotropin and estradiol levels. Some babies may be diagnosed through vaginal bleeding (21). Excessive gonadotropin response to reduction in placental steroids because of immature hypothalamopituitary-gonadal axis is blamed in preterm babies. It is thought that vascular endothelial growth factor (VEGF) secreted from the granulosa and theca cells in the stimulated ovary causes edema (39). Spontaneous recovery is observed in 5–6 weeks together with ovarian cysts. In severe cases, medroxyprogesterone acetate may be given with the objective of reducing steroid synthesis (40).

B) Problems observed in male babies

a. Priapism: This is a prolonged and persistent erection of the penis. It is observed with a rate of 0.15/1000 and has two types. The first type is veno-occlusive or ischemic type and considerably painful. Priapism due to sickle cell anemia is not observed in the newborn because of fetal hemoglobin. The second type, non-ischemic priapism, derives from the arteries, is not painful, and may be observed with polycythemia and after blood transfusions. The idiopathic form is observed most commonly; it may occur spontaneously and is not associated with catheterization and rectal stimulation. Secondary priapism is related to congenital syphilis, phosphodiesterase inhibitors, strained cord, malignancy or perineal trauma. Priapism generally lasts for 2–12 days and may prolong up to 20 days in cases of pyocavernositis. In the diagnosis, complete blood count, penile Doppler ultrasonography, bladder imaging, and cavernous blood gases are obtained. In non-ischemic cases, treatment is generally not needed and spontaneous recovery is expected. However, treatment is required against the risk for fibrosis and erectile dysfunction in ischemic priapism (41). In the presence of increased blood flow, cavernous blood is emptied and adrenaline or phenylephrine is injected. Another therapy is the administration of intravenous ketamine at a dose of 0.5 mg/kg. Phlebotomy is recommended in cases of polycythemia (41, 42).

b. Scrotal hair: Isolated scrotal hair is a condition in which physical examination findings and androgen levels are normal. In these subjects, the penile length is normal (3.5±0.4 cm) and pigmentation in the genital area and nipples is absent. It may be a finding of minipuberty. In addition, it is thought that sensitivity of the scrotal hair follicles to testosterone or increased regional 5-alpha reductase activity may be involved in the etiology. Scrotal hair disappears at about the age of one year (43).

5. Breast problems

Enlarged breasts may be observed in both sexes; the term neonatal breast enlargement is used instead of thelarche or gynecomastia. If the breasts are very large, the term 'neonatal mastauxe' is used. This finding is observed in 60–90% of babies. It may be present at birth or emerge in the first week. Maternal estrogens and prolactin and kisspeptin, which are increased in the newborn, are involved in the etiology (44, 45). Estrogen enlarges lactotropic cells and increases prolactin secretion by suppressing dopamine. In addition, handling the breasts causes the release of prolactin. In cases of severe congenital hypothyroidism, galactorrhea may be observed with increased prolactin levels. Increased prolactin levels continue until the postnatal 6th month. Galactorrhea due to increased prolactin is observed in 5–20% of cases. The fluid secreted by squeezing the breasts is named 'witch's milk;' it resembles breastmilk and contains IgA, IgG, lactoferrin, lysozyme, and lactalbumin. In male babies, estrogen increases with aromatization of androgens in the liver and adipose tissue. Hormones used by the mother or given to the baby, metronidazole, ketoconazole, diazepam, tricyclic antidepressants, alcohol, heroine, methadone, amphetamine, omeprazole, ranitidine, captopril, nifedipine, methyldopa, spironolactone, metoclopramide, domperidone, and fennel tea are among the other factors (44). Lavender and tea tree oils may cause breast enlargement. Galactocele, mastitis, and abscesses may also cause breast enlargement.

The breast diameter is generally measured to be 1–2 cm. However, the breasts may be considerably enlarged in some cases. The term 'neonatal mastauxe' is used for physiologic breast enlargement when the breast diameter is smaller than 3 cm and the term 'giant mastauxe' is used when the breast diameter is larger than 3 cm. If there is cystic accumulation in the mammary ducts (> 0.5 mL), this is called galactocele. If >1.5 mL milk is secreted daily and this condition continues for longer than 12 weeks, the term 'neonatal galactorrhea' is used (46). Although it is a benign condition, mastitis and abscess may develop as a result of squeezing the breasts. It is bilateral in 10% of cases. The most common causative agent is staphylococci. Sepsis and brain abscess may develop. Subclinical mastitis causes restlessness, and a misdiagnosis of infantile colic may be made (47). On breast ultrasonography, increased vascularity and hyperechoic breast tissue are found. However, very little vascularity and heterogeneous hypoechoic breast tissue are observed in physiologic breast enlargement (48). Intravenous antibiotics and abscess drainage, if necessary, are applied in treatment.

Hyperpigmentation in the newborn is observed in the presence of CAH, cortisol deficiency, and adenosine deaminase deficiency. Transient pigmentation may occur in babies who experience intrauterine stress. Inverted nipples are observed in cases of Turner syndrome. However, this may be a transient finding in healthy newborns.

6. Endocrine skin problems

a) Pigmentation: Extensive pigmentation may be present in the genital region and nipples. Although the most important factors include CAH, adrenal hypoplasia and cortisol deficiency, transient pigmentation related to intrauterine stress may be observed. The signs and symptoms of CAH should be investigated and a definite diagnosis should be made (49).

b) Acne neonatorum: This condition is observed in 20% of babies, especially in male babies. It may be present at the time of birth or emerge 4–6 weeks after birth. It is observed as closed comedones on the forehead, nose, and cheeks (50). It may sometimes extend in the form of erythematous papules and scarring cysts on the neck and upper trunk. Maternal virilizing tumors or increased secretion of fat as a result of stimulation of the skin adipose glands with neonatal androgens (especially increased DHEA-S levels) and colonization of Malessezia species in some cases lead to acne. Increase in testicular androgens with minipuberty leads to a more increased rate of acne in male babies (51). These cases may be confused with toxic erythema, neonatal cephalic pustulosis, milia, pustular miliaria, and eruptions related to bromur, iodure, phenobarbital, and lithium.

In newborns, acne spontaneously recovers in 1–3 months. In some cases, azelaic acid or tretionin cream, erythromycin or benzoyl peroxide cream-gels may be needed. In severe and persistent cases, CAH and virilizing tumors should be investigated (51).

7. Calcium metabolism

Transient hypocalcemia and transient hypercalcemia are among the frequently observed problems in newborns.

Table 2. Weekly levels of growth hormone and growth factors in newborns

Parameter	0–7 days	8–14 days	15–21 days	22–30 days
GH ng/mL	13,65±5,68	9,85±4,06	8,735±3,19	7,91±5,57
IGF-1 (ng/mL)	55,4±49,6	69,6±46,6	82,30±70	89,5±47,6
IGFBP-3 (ng/mL)	2 043±572	2 352±777	3 002±856	3 133±1 150

GH: Growth hormone; IGF-1: Insulin-like growth factor; IGFBP-3: Insulin-like growth factor binding protein

The serum calcium level is 7.6–11.3 mg/dL in the first week after birth and it reaches 8.6–11.8 mg/dL in the first month.

a) Transient hypocalcemia: Preterm delivery, low birth weight, SGA, asphyxia, gestational toxemias, maternal diabetes, maternal hyperparathyroidism, maternal vitamin D deficiency, excessive calcium load in pregnancy, nutrition with cow's milk, blood exchange, phototherapy, aminoglycoside antibiotics, anticonvulsant drugs, osteoporosis, use of bicarbonate in treatment of acidosis, rotavirus infection, and hypomagnesemia are known as factors that lead to transient hypocalcemia. The clinical picture occurs when the calcium level is below 7 mg/dL in preterm babies and below 7.5 mg/dL in term babies. The signs and symptoms include apnea, tachycardia, cyanosis, feeding difficulty, vomiting (because of pyloric spasm), irritability, facial-laryngospasm, tetany, hyperacusia, startle attacks, and focal or generalized epilepsy (52, 53). In the diagnosis, serum calcium, phosphorus, alkaline phosphatase, magnesium, parathormone, vitamin D, blood urea nitrogen (BUN), creatinine, urinary calcium/creatinine ratio, and serum albumin levels are measured. In some cases of vitamin D deficiency, a picture of pseudo-hypoparathyroidism may be observed (54). In treatment, calcium is not given by rapid IV push; 10% calcium gluconate (2.5 mL/kg, 5 mL/kg or 7.5 mL/kg) is added to daily fluid according to the degree of hypocalcemia (52). In cases of vitamin D deficiency, 1000–1500 U vitamin D is given daily for 6–8 weeks. If the magnesium level is low, 15% magnesium sulphate is infused at a dose of 0.4 mL/kg and the infusion is repeated if necessary (52).

b) Transient hypercalcemia: If the total calcium level is above 11 mg/dL or ionized calcium level is above 5.6 mg/dL, a diagnosis of hypercalcemia is made in the neonatal period. Besides persistent and genetic causes, factors that lead to transient hypercalcemia include phosphate deficiency, high-dose vitamin A and D intake by the mother and the newborn, maternal hypoparathyroidism, development of maternal hyperparathyroidism as a result of pseudo-hypoparathyroidism, subcutaneous adipose tissue necrosis, lactase deficiency, severe hypothyroidism, thyrotoxicosis, primary adrenal insufficiency, Down syndrome, IMAGe syndrome, indomethacin, addition of excessive calcium into parenteral nutrition solutions, use of prostaglandin-E, and immobilization (55). The clinical picture is generally indistinct. Most patients are diagnosed during laboratory investigations. Serum calcium, phosphorus, alkaline phosphatase, parathormone, vitamin A and D, BUN, creatinine, albumin, acid-base balance, urinary calcium/creatinine ratio, and lung, wrist, and long bone radiographs are evaluated as diagnostic tests. In addition, maternal calcium, phosphorus, alkaline phosphatase, parathormone, vitamin A and D levels are measured. It should be kept in mind that transient normocalcemic hyperparathyroidism may occur in babies whose mothers have hypoparathyroidism (55). In treatment, intake of calcium and vitamin D is discontinued and phosphate support is given. Diuresis and steroid treatment is initiated and oral or intravenous bisphosphonates are given in severe cases (56).

8. Water metabolism

The picture of central or nephrogenic diabetes insipidus may be permanent or transient. A picture of urine output above 4–6 mL/kg/hour, hypernatremia, dehydration and fever is noted in the newborn (57). Periventricular-intraventricular hemorrhage, Listeria meningitis, and asphyxia are involved in the etiology of transient central diabetes insipidus (58, 59). Transient nephrogenic diabetes insipidus has been reported following fetal exposure to haloperidol in newborn babies (60). Hypercalcemia, hypopotassemia, and use of lithium, gentamycin, rifampicin, amphotericin-B, and methicillin are among the other factors (57).

9. Hormone levels

Hormone levels show variance in the cord blood and in the postnatal weeks. This should be noted when interpreting the hormone results.

a) Prolactin: During pregnancy, the prolactin level in the maternal and fetal blood increases. Its level in cord blood has been measured as 246±88 ng/mL in term babies and 172±88 ng/mL in preterm babies (61). A sex difference is not observed in term babies in the first postnatal week. In preterm babies, it has been found as 190±17 ng/mL in

boys and 104±10 ng/mL in girls. The levels are similar in the postnatal 6th week in term and preterm babies. In another study, the mean value was found as 96.44 ng/mL in the postnatal 0–30 days, independent of sex difference (97.5 percentile, 236.6 ng/mL) (62).

b) Growth hormone and growth factors: The levels of growth hormone, cortisol, thyroid hormones, and adrenergic hormones increase after birth for metabolic adaptation and decrease to normal levels subsequently. In the postnatal period, the levels of growth hormone decrease, whereas the levels of growth factors increase gradually. Therefore, growth hormone and growth factor levels should be interpreted weekly in newborns (63) (Table 2).

c) Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormones: Gonadotropins, which have a high level in fetal life, are inhibited by placental hormones near delivery. The hypothalamo-pituitary-gonadal axis is activated with birth and mini-puberty occurs with hormonal changes. The testosterone level increases to a level of 60–400 ng/dL in boys and the estradiol level increases to a level of 5–50 pg/mL in girls in 20–60 days. The levels of sex hormone are high until the 6th month in boys and until the 12nd month in girls, and begin to decrease subsequently. In the postnatal 11–15th days, LH is measured as 1.8 IU/L in girls and 3.55 IU/L in boys, and FSH is measured as 8.16 IU/L in girls and 3.71 IU/L in boys. Mini-puberty starts later in preterm babies. A diagnosis of Turner syndrome can be made if the FSH value is found to be above 40 IU/L when evaluating mini-puberty (64). A diagnosis of hypogonadotropic hypogonadism is made if the LH level is <0.8 IU/L and the testosterone level is below 30 ng/dL in boys between the 15th day and 6th month, and if the FSH level is below 1.0 IU/L in girls between the 15th day and 2 years (65).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K.; Design - G.D.; Supervision - S.K., N.H.; Data Collection and/or Processing - S.K., G.D.; Analysis and/or Interpretation - S.K.; Literature Review - Z.U.T.; Writing - S.K., G.D.; Critical Review - S.K., N.H.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - S.K; Tasarım - G.D.; Denetleme - S.K., N.H.; Veri Toplanması ve/veya İşlemesi - S.K., G.D.; Analiz ve/veya Yorum - S.K.; Literatür Taraması - Z.U.T.; Yazıyı Yazan - S.K., G.D.; Eleştirel İnceleme - S.K., N.H.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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