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Original Article

Defective Cortisol Secretion in Response to Spontaneous Hypoglycemia but Normal Cortisol Response to ACTH stimulation in neonates with Hyperinsulinemic Hypoglycemia (HH)

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Abstract. *Introduction:* Hyperinsulinemic Hypoglycaemia (HH) is the most common cause of recurrent and persistent hypoglycemia in the neonatal period. Cortisol and GH play an important role as a counterregulatory hormone during hypoglycemia. Both antagonize the peripheral effects of insulin and directly influence glucose metabolism *Patients and Methods:* We studied cortisol and GH secretion in newborn infants with HH during spontaneous hypoglycemia. In addition, their basal ACTH level was measured and cortisol response to a standard dose ACTH test was performed. *Results:* Nine newborns with HH were studied during the first 2 weeks of life. During HH, their mean glucose concentration was 1.42 ± 0.7 mmol/L, mean beta hydroxybutyrate level was 0.08 ± 0.04 mmol/L, and mean serum insulin level was 17.78 ± 9.7 μU/mL. Their cortisol and GH levels at the time of spontaneous hypoglycemia were 94.7 ± 83.1 nmol/L and 82.4 ± 29 m IU/L respectively. They had relatively low level of ACTH (range: 14 :72 pg/ml, mean: 39.4 ± 20 pg/mL) during hypoglycemia. All infants had GH concentration > 20 mIU/L at the time of hypoglycemia. All infants underwent ACTH test. Their basal serum cortisol levels did not differ compared to cortisol levels during hypoglycemia, and all had a normal peak cortisol response (> 500 nmol/L) in response to i.v. ACTH stimulation test. *Conclusion:* Infants with HH have low cortisol response to spontaneous hypoglycemia with normal response to exogenous standard-dose ACTH. Checking hypothalamic-pituitary axis (HPA) axis later in infancy using low dose ACTH may be useful to diagnose persistent HPA abnormalities in these infants. All HH infants had appropriate elevation of GH during hypoglycemia. (www.actabiomedica.it)

Key words: Cortisol, Adrenocorticotrophic hormone, neonatal hyperinsulinemia, hypoglycemia, growth hormone, ACTH test.

Introduction

Hyperinsulinemic Hypoglycemia (HH) is the most common cause of recurrent and persistent hypoglycemia in the neonatal period (1). The aetiology may be multifactorial, including developmental immaturity of the gluconeogenic and ketogenic pathways, poor mobilisation of hepatic glycogen stores, and transient hyperinsulinism. Less common

pathological causes include persistent hyperinsulinism, hypopituitarism, adrenal disorders, and fatty acid oxidation defects (2-4). Infants from diabetic mothers (IDMs), including diabetes type 1 and 2 and gestational diabetes, represent the group with the

highest risk of developing symptomatic hypoglycemia. The overall risk of hypoglycemia episodes in IDMs is from 25 to 40% (5). Glucose levels fall to a low point in the first 1–2 h of life and then increased and stabilize gradually. Hypoglycemia may continue for 24–72 h until insulin secretion returns to normal. This metabolic risk is believed to be due to the relative fetal hyperinsulinism, manifested as a feedback mechanism for the balance of the high glucose levels induced by the maternal diabetes, and is particularly severe in those cases of poorly controlled maternal pre-existent diabetes with high levels of HbA1c (1,6).

The counterregulatory hormones, such as GH, cortisol, epinephrine, norepinephrine, and glucagon, play an essential role in the maintenance of normal blood glucose concentration. GH and cortisol have numerous effects on glucose metabolism, including increasing the rate of gluconeogenesis and antagonizing the effects of insulin. Epinephrine, norepinephrine, and glucagon, form a primary defence against hypoglycemia. It has also been shown that children with HH fail to generate an adequate serum cortisol (7) and display blunted serum glucagon release with normal epinephrine and norepinephrine responses (8). Moreover, as hypoglycemia is a potent stimulus for the release of serum growth hormone (GH), we would expect an increase of GH in response to spontaneous and insulin induced hypoglycemia. Nevertheless, contrasting results have been reported in the literature (7-11).

The aim of study attempted to assess the cortisol and GH levels during spontaneous hypoglycemia in infants with hyperinsulinemic hypoglycemia and the cortisol response to exogenous ACTH stimulation.

Patients and Methods

Nine infants born to diabetic mothers (IDM's) with hyper insulinemic hypoglycemia (HH) during their neonatal period were studied during the first 2 weeks of life. Male/Female ratio (5/4), gestation was estimated at 35.3 ± 2.7 weeks. Five were delivered vaginally and the other 4 by lower-segment, caesarean section. Birth weight was between 2 and 3.9 kg, mean: 2.76 ± 0.67 kg. Placental weight was increased (mean: 784.7 ± 151.7 grams (range: 610- 884 grams; the normal placental weight in full-term babies is: 678 ± 130 grams) (12).

Seven out of the 9 infants were born to diabetic mothers (all of them had gestational Diabetes), 4 mothers were on dietary control, two were on metformin and one was on insulin therapy. The mean maternal HbA1C was 5.4 ± 0.4 % at the last trimester.

Neonates with a diagnosis of cortisol deficiency or insufficiency, and those receiving hydrocortisone or diazoxide therapy, or with evidence of a midline anatomical lesion, and history of perinatal asphyxia were excluded from the study.

Measurement of circulating concentrations of insulin, cortisol, and growth hormone (GH) during hypoglycemia (confirmed by measuring serum glucose concentration) was estimated. On another day, each infant had a standard dose of ACTH stimulation test [Cosyntropin® 62.5 μg intravenously (i.v.)]. Basal plasma ACTH level and cortisol levels at 0, 30 and 60 minutes, after stimulation test, were assessed.

The plasma glucose concentration was measured using photometric hexokinase method. Serum GH and cortisol concentrations were measured using an immunoradiometric assay (Tandem-R HGH, Hybritech, Leige, Belgium).

Data analysis

Differences between variables were analysed with t test for normally distributed variables and with the Mann-Whitney test in case of non-normality. Spearman rank correlations were used to explore relations between variables. Data are expressed as mean, standard deviation (SD) and standard error (SE). Statistical significance was accepted at p value ≤ 0.05.

Results

During spontaneous hyperinsulinemic hypoglycemia, their mean glucose concentration was 1.42 ± 0.7 mmol/L. The concomitant mean beta hydroxybutyrate level was 0.08 ± 0.04 mmol/L, and serum insulin level was 17.7± 9.7 μU/mL. Their basal ACTH levels were inappropriately low at the time of hypoglycemia

(mean: 39.4 ± 20 pg/ml, range: 14 - 72 pg/ml). Cortisol and GH levels at the time of spontaneous hypoglycemia were 94.7 ± 83.1 nmol/L and 82.4 ± 29 mIU/L, respectively (Table 1).

None of these infants had cortisol response to hypoglycemia >302 nmol/L (mean: 94.1± 83.1 nmol/L, range; 37-302 nmol/L), but a marked normal cortisol response (cortisol > 500 nmol/L) was present after ACTH stimulation test (Figure 1).

Moreover, serum cortisol level during spontaneous hypoglycemia correlated with the cortisol peak after ACTH stimulation test (r =0.5, p= 0.011) (Figure 2), but did not correlate with blood glucose level during hypoglycemia (r = 0.06, p = 0.8). GH level was correlated with blood glucose level during hypoglycemia (r = 0.45, p = 0.018) (Figure 3).

Table 1. Anthropometric and lab data of infants with hyperinsulinemic hypoglycemia.

Anthropometric and lab data	Mean ± SD
Gestational age (weeks)	35.3 ± 2.75
Weight SDS (kg)	-0.8± 1.3
Length SDS (cm)	-0.28± 0.95
Blood glucose level (mmol/L)	1.42± 0.7
Insulin level (μU/mL)	17.78 ± 9.7
Blood ketone level (mmol/L)	0.08 ± 0.04
Cortisol during hypoglycemia (nmol/L)	94.7± 83.1
Basal blood glucose before ACTH test (mmol/L)	2.7± 0.3
Basal ACTH (pg/mL)	48.9 ± 36.4
Basal cortisol (nmol/L)	107.8 ± 106.7
Cortisol at 30 min. (nmol/L)	465.9 ± 176.4
Cortisol at 60 min. (nmol/L)	767± 221.8
Growth Hormone (mIU/L)	82.4± 29

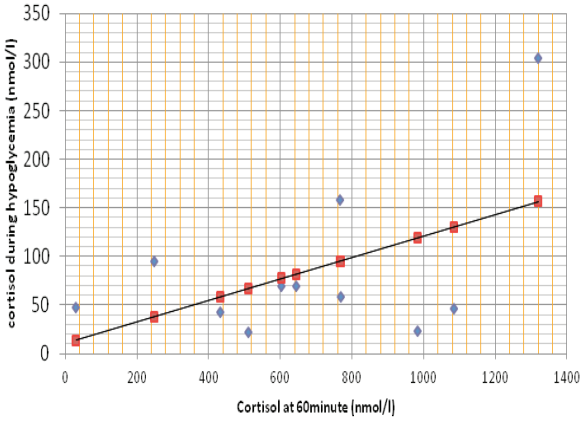

Figure 1. Correlation between cortisol level during hypoglycemia and the peak after ACTH stimulation test (r = 0.50, p = 0.011)

Discussion

Cortisol and GH play an important role as a counterregulatory hormone during hypoglycemia. Both antagonize the peripheral effects of insulin and directly influences glucose metabolism (13).

At birth, mixed cord blood cortisol concentrations are relatively high (880 nmol/L); this reflects the maternal transfer of steroids and the stress of delivery. By 24 h of age, cortisol concentrations fall rapidly to about 270 nmol/L, and by day 3 of life the normal

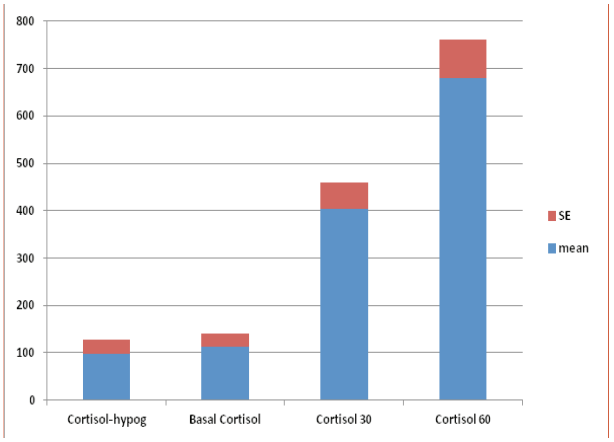

Figure 2. Cortisol secretion in response to spontaneous hypoglycemia versus values at 30 and 60 minutes after ACTH stimulation test (mean ± standard error)

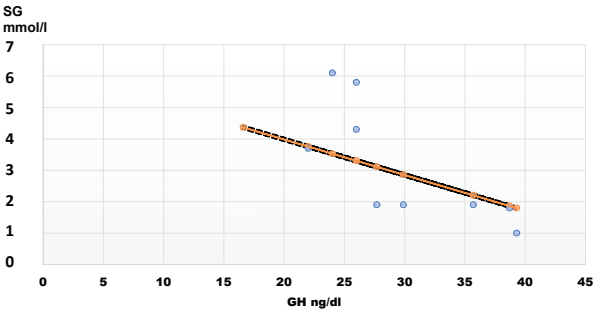

Figure 3. Correlation between SG (serum glucose) and growth hormone (GH) during hypoglycemia (r = 0.45, p = 0.018).

cortisol values range between 46.9 and 385.4 nmol/L (14-16).

The concentration of blood glucose that stimulates in adults the release of cortisol is thought to be ~ 3.5 mmol/L (17). Although cortisol is released at the glycemic threshold level, the physiological effects of cortisol on glucose metabolism generally take several hours to become manifest (9). In neonates, as in adults, a serum cortisol response to the stressful stimulus of hypoglycemia is defined as adequate if serum cortisol concentrations rise above 500 nmol/L at the time of hypoglycemia. However, data on neonates with hyperinsulinemia suggested that they may generate poor serum cortisol responses to HI (7).

Our infants, during the episodes of hypoglycemia, had a relatively low levels of ACTH (mean: 39.4 ± 20 pg/mL; range: 14-72 pg/mL) and a cortisol response considerably lower than that observed after ACTH (Cosyntropin®) stimulation test, suggesting a defective/ immature drive from the hypothalamic-pituitary (HPA) axis at the time of hypoglycemia.

It has been shown that intra-hypothalamic hyperinsulinism in newborn rats causes malformations and morphological alterations in hypothalamic nuclei, especially ventromedial (VMN) and lateral hypothalamic area (LHA) nuclei, which are thought to play an important role as glucosensors (18).

Several other studies have measured cortisol responses to stress in young infants. These investigations, while diverse in their findings, on average suggest that infants exposed to higher levels of prenatal stress may present with greater HPA axis hypoactivity and a decreased infant cortisol reactivity (19-21). Moreover, newborns born to diabetic mothers have an increased oxidative stress and DNA damage compared to those born to mothers with euglycemia (21). Therefore, their perinatal stress may explain their HPA axis hypoactivity.

A previous report supported our observations. Hussein et al. (7) studied serum cortisol concentrations in 7 IDM neonates at 10, 20, 30, 40, and 50 min. at the time of hypoglycemia. Their serum cortisol levels were 213 ± 44, 223 ± 48, 209 ± 49, 228 ± 46, and 252 ± 30 nmol/L, respectively. None of their infants had level equal or > 520 nmol/L. In six neonates, who had plasma ACTH levels inappropriately low at the time of hypoglycemia (mean plasma ACTH concentration: 13.2 pg/mL), the cortisol response was assessed after an 62.5 μg i.v. bolus injection of Synacthen®. Serum cortisol concentrations at 0, 10, 20, 30, 40, and 50 minutes were 208 ± 39; 219 ± 46, 378 ± 139; 664 ± 57; 905 ± 121; 1048 ± 247, and 1192 ± 105 nmol/L, respectively (5).

It has been also postulated that specialized glucose-sensing neurons in the ventromedial hypothalamus (VMH) are able to detect falling blood glucose and trigger the release of counterregulatory hormones during hypoglycemia. The molecular mechanisms used by glucose-sensing neurons are uncertain but may involve cell surface ATP-sensitive K(+) channels (K(ATP) channels) analogous to those of the pancreatic beta-cell. Data reported by Evans et al. (23) suggest that closing of K (ATP) channels in the VMH (much like the beta-cell) impairs defense mechanisms against glucose deprivation and therefore could contribute to defects in glucose counter regulation. As KATP plays a key role as the glucose sensor in VMN and LHA, further studies are needed to determine whether patients with defects in pancreatic KATP channels have impaired counterregulatory hormonal responses.

The finding of good cortisol response to an i.v. bolus injection of ACTH proves a normal adrenal cortical secretion. However, the dose used for the test (62.5 ug) was extremely higher compared to the physiological ACTH release during stress. It has been shown that in adults the peak plasma ACTH level, after insulin-induced hypoglycemia, was significantly lower than that induced after the injection of 1.0 μg of ACTH given i.v. (low dose ACTH test) (69.6 ± 9.3 vs. 120.2 ± 15.5 pmol/L; p= < 0.0002) (24).

However, in children the cortisol response to spontaneous hypoglycemia is highly age dependent. Young normal infants may present a poor cortisol response (immature axis) compared with older infants and children (mature axis) (24). Crofton et al. (25) reported that in 21 hypoglycemic infants (<3 months of age) the median cortisol level was 205 nmol/L (range: 50–584 nmol/L). Only half the infants had cortisol concentrations greater than 200 nmol/L during hypoglycemia and five had levels below 100 nmol/l. These levels in infants < 3 months of age were markedly lower than those observed in 15 older (age >6 months) hypoglycemic infants (median: 1370 nmol/L,

range:142–3190 nmol/L).

The negative effects of HH on the HPA axis may be prolonged. It has been shown that gestational diabetes (GDM) exposed children had reduced cortical excitability and a reduced salivary cortisol when compared with control children. In addition, recent data have reported a lower morning cortisol secretion in adolescents born to women with GDM (26-28). Therefore, it appears that checking HPA axis later in infancy using low dose ACTH may be useful to diagnose HPA abnormalities in these infants.

In our study six out of nine newborns had normal/elevated GH levels at time of HH (GH: 82.4 ± 29 mU/L, range: 36.6-118 m U/L). For pediatric population, the cut-off for defining an appropriate GH response to the insulin induced hypoglycemia test is 15 mU/L. Consensus guidelines for the diagnosis of GH deficiency in neonates suggests a cut-off of twice that in the older pediatric population (20-30 mU/L) (29).

In support of our data, Kelly et al. (30) reported that most of IDM had GH levels greater than 30 mU/L during hypoglycemia. The two infants who had lower GH levels of 6.6 mU/L and 17.3 mU/L, during hypoglycemia, achieved levels of 28.4 mU/L and 34.1 mU/L on other occasions.

In order to prevent long-term neurological lesions, a glucose treatment should be immediately initiated for all neonates who show symptoms of hypoglycemia. Although evidences for the use of corticosteroid in the management of HH is limited.

Hydrocortisone can also be used as an adjuvant in very severe and resistant cases. Physiologically glucocorticoids reduce insulin secretion and increase insulin resistance as well as enhancing both gluconeogenesis and glycogenolysis. In theory these effects should induce an increase in serum glucose concentrations (31,32).

However, due to the potential side effects of glucocorticoid administration, its use has been restricted to a short course (1 to 2 days), unless a patient has documented adrenal insufficiency (33,34).

Common side effects associated with glucocorticoid therapy include growth suppression, feed intolerance, and hypertension. Preterm, very-low-birth weight infants treated with hydrocortisone have an increased risk of spontaneous perforation of the gastrointestinal tract (35,36).

More debates concern the newborn with asymptomatic hypoglycemia. In these cases, the most important is the initiation of enteral feeding immediately after birth, during the first hour of life, breastfeeding or with assistance (33).

In conclusion, our infants with HH had low cortisol response to spontaneous hypoglycemia with normal response to exogenous standard -dose ACTH suggesting defective central HPA response to hypoglycemia. Checking HPA axis later in infancy using low dose ACTH may be useful to diagnose HPA abnormalities. All HH infants had appropriate elevation of GH during hypoglycemia.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Nold JL,Georgieff MK. Infants of diabetic mothers. Pediatr Clin North Am. 2004;51,619-637.
2. Stanley CA, Baker L. The causes of neonatal hypoglycemia. N Engl J Med. 1999;340:1200–1201.
3. Artavia-Loria E, Chaussain JL, Bougneres PF, et al. Frequency of hypoglycemia in children with adrenal insufficiency. Acta Endocrinol Suppl (Copenh). 1986;279:275–278.
4. LaFranchi S. Hypoglycemia of infancy and childhood. Pediatr Clin North Am. 1987;34:961–982.
5. Barnes-Powell LL. Infants of diabetic mothers: the effects of hyperglycemia on the fetus and neonate. Neonatal Netw. 2007; 26:283-290.
6. Ward Platt M, Deshpande S. Metabolic adaptation at birth. Semin Fetal Neonatal Med. 2005;10:341-350.
7. Hussain K, Hindmarsh P, Aynsley-Green A. Neonates with symptomatic hyperinsulinemic hypoglycemia generate inappropriately low serum cortisol counterregulatory hormonal responses. J Clin Endocrinol Metab. 2003;88:4342-4347.
8. Hussain K, Bryan J, Christesen HT, Brusgaard K, Aguilar-Bryan L. Serum glucagon counterregulatory hormonal response to hypoglycemia is blunted in congenital hyperinsulinism. Diabetes. 2005;54:2946-2951.
9. Mitrakou A, Ryan C, Veneman T, et al . Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol. 1991;260:E67–E74.
10. Kenny FM, Preeyasombat C, Spaulding JS, Migeon CJ. Cortisol production rate. IV. Infants born of steroid-treated

mothers and of diabetic mothers. Infants with trisomy syndrome and with anencephaly. Pediatrics. 1966;37:960-966.
11. Senniappan S, Hussain K. An Evaluation of Growth Hormone and IGF-1 Responses in Neonates with Hyperinsulinaemic Hypoglycaemia. Int J Endocrinol. 2013; 2013: 638257 doi: 10.1155/2013/638257.
12. Soliman AT, Eldabbagh M, Saleem W, Zahredin K, Shatla E, Adel A. Placental weight: relation to maternal weight and growth parameters of full-term babies at birth and during childhood. J Trop Pediatr. 2013;59:358-364.
13. Hussain K, Aynsley-Green. Management of hyperinsulinism in infancy and childhood . Ann Med. 2000; 32:544–551.
14. Stevens JF.Plasma cortisol levels in the neonatal period. Arch Dis Child.1970;45: 592–592.
15. Weiner DJ, Smith J, Dahlan S, Berg G, Moshang T 1987 Serum adrenal steroid levels in healthy full-term 3 day old infants. J Pediat.1987; 110:122–124.
16. De Feo P, Perriello G, Torlone E, et al. Contribution of cortisol to glucose counterregulation in humans. Am J Physiol. 1989;257:E35-E42.
17. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest. 1987; 79: 777-781.
18. Plagemann A, Harder T, Rake A, et al. Perinatal elevation of hypothalamic insulin, acquired malformation of hypothalamic galaninergic neurons, and syndrome x-like alterations in adulthood of neonatally overfed rats. Brain Res.1999; 836:146–155.
19. Mitanchez D, Yzydorczyk C, Siddeek B, Boubred F, Benahmed M, Simeoni U. The offspring of the diabetic mother--short- and long-term implications. Best Pract Res Clin Obstet Gynaecol. 2015;29:256-269.
20. Howland MA, Sandman CA, Glynn LM. Developmental origins of the human hypothalamic-pituitary-adrenal axis. Expert Rev Endocrinol Metab. 2017;12:321-339.
21. Tollenaar MS, Beijers R, Jansen J, Riksen-Walraven JM, de Weerth C. et al. Maternal prenatal stress and cortisol reactivity to stressors in human infants. Stress. 2011;14:53–65.
22. Durga KD, Adhisivam B, Vidya G, Vishnu Bhat B, Bobby Z, Chand P. Oxidative stress and DNA damage in newborns born to mothers with hyperglycemia - a prospective cohort study. J Matern Fetal Neonatal Med. 2018;31:2396-2401.
23. Evans ML, McCrimmon RJ, Flanagan DE, et al. Hypothalamic ATP-sensitive K + channels play a key role in sensing hypoglycemia and triggering counterregulatory epinephrine and glucagon responses. Diabetes. 2004;53:2542-2551.
24. Nye EJ, Grice JE, Hockings GI, Strakosch CR, Crosbie GV, Walters MM, Jackson RV. Comparison of adrenocorticotropin (ACTH) stimulation tests and insulin hypoglycemia in normal humans: low dose, standard high dose, and 8-hour ACTH-(1-24) infusion tests. J Clin Endocrinol Metab. 1999;84:3648-3655.
25. Crofton PM, Midgley PC. Cortisol and growth hormone responses to spontaneous hypoglycaemia in infants and children. Arch Dis Child. 2004;89:472-478.
26. Van Dam JM, Garrett AJ, Schneider LA, et al. Reduced Cortical Excitability, Neuroplasticity, and Salivary Cortisol in 11-13-Year-Old Children Born to Women with Gestational Diabetes Mellitus. EBioMedicine. 2018; 31:143-149.
27. Van Dam JM, Goldsworthy MR, HagueWM, et al. Lower Morning Cortisol Secretion in Adolescents Born to Women with Gestational Diabetes Mellitus. Lancet. 2020 (preprint) https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3516135.
28. Simsek Y, Karaca Z, Tanriverdi F, Unluhizarci K, Selcuklu A, Kelestimur F. A comparison of low-dose ACTH, glucagon stimulation and insulin tolerance test in patients with pituitary disorders. Clin Endocrinol (Oxf). 2015;82:45-52.
29. Crofton PM, Midgley PC. Cortisol and growth hormone responses to spontaneous hypoglycaemia in infants and children. Arch Dis Child. 2004;89:472-478.
30. Kelly A, Tang R, Becker S, Stanley CA. Poor specificity of low growth hormone and cortisol levels during fasting hypoglycemia for the diagnoses of growth hormone deficiency and adrenal insufficiency. Pediatrics. 2008;122: e522-528.
31. Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. J Pediatr Pharmacol Ther. 2013;18:199-208.
32. Jane E. McGowan. Neonatal Hypoglycemia. Pediatr Rev. 1999;20: e6-e15.
33. Mehta A. Prevention and management of neonatal hypoglcaemia. Arch Dis Child. 1994;70:F54–F65.
34. Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. J Pediatr Pharmacol Ther. 2013; 18:199-208.
35. Watterburg KL, Gerdes JS, Cole CH. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004;114:1649–1657.
36. American Academy of Pediatrics, Committee on Fetus and Newborn and Canadian Paediatric Society, Fetus and Newborn Committee. Post-natal corticosteroids to treat or prevent chronic lung disease in pre-term infants. Pediatrics. 2002;109:330–338.

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