hypoplasia. All patients underwent surgical resection within 1 month after birth. Patients treated with TA shunting underwent surgical resection at the time of delivery.

2.3. Pathologic examination

All cysts were examined macroscopically and microscopically by pathologists in the Department of Pathology at the National Center for Child Health and Development.

3. Results

Of the 14 fetuses antenatally diagnosed as having type 1 CPAM, 8 were female and 6 were male. Clinical, macroscopic, and histologic data for these 14 cases are summarized in Table 1. Thoracoamniotic shunting was used in 8 cases because of hydrops fetalis, polyhydramnios, or an increased risk of pulmonary hypoplasia (Table 1). Six cases did not undergo TA shunting. Extensive microscopic examination revealed that there existed squamous metaplasia of the cyst epithelia in 5 of 8 patients who underwent TA shunting. In contrast, squamous metaplasia was not found in patients who did not undergo TA shunting (Table 1). We did not find overt inflammation in the cases presented in this study. In some patients who underwent TA shunting, we found slight inflammation at the insertion site.

In case 8, a large complex fetal lung mass was found in the left lower lobe. Because of an increased risk of lung hypoplasia, TA shunt was placed at 26 weeks of gestation. At 1 day of life, the infant underwent lobular resection. The overall size of the mass was 7 × 5 × 1.7 cm. The mass contained several predominant macrocysts (Fig. 1A). Microscopically, the cysts were mainly lined by cuboidal, columnar, and ciliated columnar epithelia, which was consistent with the histology of type 1 CPAM (Fig. 1B). Mucinous epithelium and mucinous hyperplasia were also seen. Further examination revealed that the cyst wall was also lined by squamous metaplastic epithelium (Fig. 1C).

In case 14, a large multilocular cyst of the lung was found in the right middle lobe. The size of the resected lung lobe was 6.5 × 5 × 1.5 cm (Fig. 2A). In this case, the insertion site of the shunt tube could be identified macroscopically. Microscopically, the vernix caseosa was found at the insertion site (Fig. 2B). At the distant area from the insertion site, focal squamous metaplasia was found, suggesting that squamous metaplasia was induced by the cyst content, not by the direct contact with a shunt tube (Fig. 2C).

4. Discussion

Recent improvements in antenatal diagnosis, prenatal ultrasound, and fetal surgery have allowed us to treat fetuses
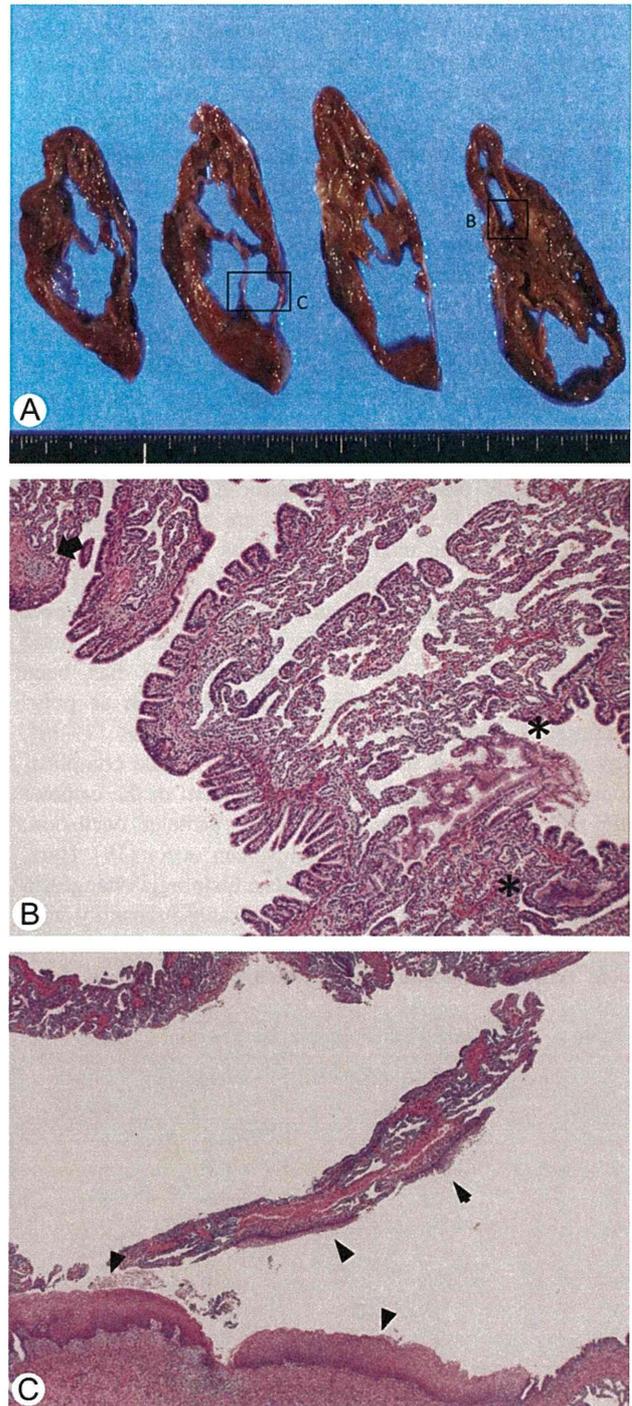

Fig. 1 Gross (A) and microscopic (B, C) appearance of case 8. A, The specimen displays several predominant macrocysts. Histologic sections were made from 2 areas and shown in images B and C. B, The cysts are lined by columnar to pseudostratified columnar epithelia. Mucinous epithelia are seen in the right lower area (asterisks). A small cartilaginous tissue can be found in the left upper area (arrow). C, A histologic section shows focal squamous metaplasia (arrow heads).
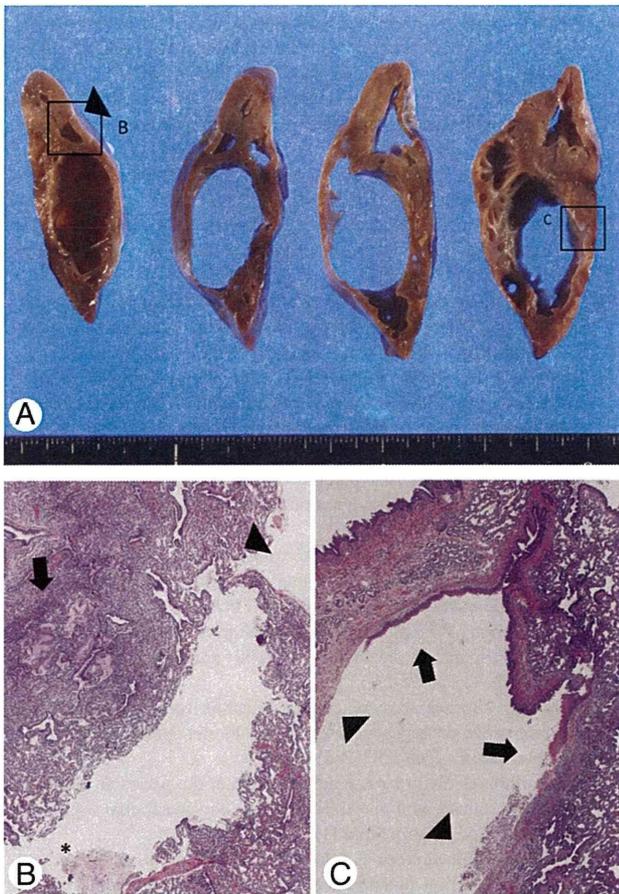
Fig. 2 Gross (A) and microscopic (B, C) appearance of case 14. A, The specimen shows a multilocular large cyst. The shunt insertion site can be identified and pointed by an arrowhead. Histologic sections were made from 2 areas and shown in images B and C. B, The insertion site of the TA shunt tube (arrowhead) shows cyst wall disruption and vernix caseosa (asterisk). Mucinous hyperplasia is also seen (arrow). C, The section shows focal squamous metaplasia (arrows) and epithelial cell detachment (arrowheads).

with type 1 CPAM. Fetal interventions for type1 CPAM includes amnioreduction, thoracocentesis, administration of steroid, CPAM resection, and TA shunt placement [14]. Although these treatments decrease the risk of pulmonary hypoplasia and fetal death, caution is needed because of possible complications.

In this study, we report that TA shunt placement causes histologic changes in the cyst epithelia. Squamous metaplasia in the cyst epithelia was found in fetuses treated prenatally with TA shunting, but not in untreated fetuses, suggesting that TA shunting may change the nature of the cyst epithelium as a consequence of long-term exposure to the intrauterine environment. Supporting this idea is our finding that the increase in mucinous hyperplasia seen in TA shunt population was statistically significant. The Mann-Whitney U test was used to test if there was a difference in mucinous hyperplasia between TA shunt population and non−TA shunt population (P =.073). This raises the

possibility that residual lung parenchyma could be also affected by the intrauterine environment. Because mucinous hyperplasia has been implicated in the occurrence of bronchioloalveolar carcinoma, this also raises the possibility that there is potential for seeding the thoracic cavity and amniotic cavity with malignant cells through TA shunting. Collectively, squamous metaplasia in the cyst epithelia may be a useful "biomarker" for predicting potential complications and occurrence of bronchioloalveolar carcinoma.

Although TA shunting has lower risks to the fetus and mother as compared to lobectomy, it has been recently reported that fetuses treated with TA shunting could develop postnatal chest wall deformities, suggesting that TA shunt may affect the rib development of patients [21]. Other known risks and complications for TA shunting include catheter displacement, improper function of the catheter, catheter occlusion from thrombus or effusion material, fatal fetal hemorrhage, procedure-related placental abruption, premature rupture of membrane, and preterm labor. These procedure-related complications should be carefully taken into consideration before TA shunting is chosen as a treatment option. In this study, we discovered that TA shunting causes squamous metaplasia of the cyst epithelium. Our findings suggest that histologic changes also should be carefully examined to identify other procedure-related complications.

The cause of squamous metaplasia seen in the cyst epithelium is not clear. It is also possible that long-term exposure to the intrauterine environment led to the change in the nature of cyst epithelium and squamous metaplasia. It has been shown that proinflammatory mediators and meconium in amniotic fluid can cause local inflammation and apoptosis of the lung epithelial cells [22-24]. It has been also reported that the nature of fetal tissue can be changed when it is exposed to the intrauterine environment in long term [25]. Collectively, it is possible that long-term exposure to the intrauterine environment led to the change in the nature of cyst epithelium and consequent columnar to squamous metaplasia.

Our findings raise the possibility that TA shunt placement could cause unexpected changes in the cyst environment, leading to histologic changes in the cyst epithelium. Careful pathologic examination of the cyst is crucial for further understanding of the possible biological effects of TA shunting and prevention of unexpected complications.

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ORIGINAL ARTICLE

Levothyroxine replacement therapy and refractory hypotension out of transitional period in preterm infants

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Summary

Background Recent studies suggest that refractory hypotension from causes other than septicaemia or cardiac failure is common in extremely preterm infants even out of the transitional period. Marked response to low-dose cortisol suggests underlying adrenal insufficiency, although the exact mechanism remains unknown.

Methods To investigate potential triggers for and related short-term outcomes of early-onset (<Day 7) and late-onset (≥Day 7) refractory hypotension, clinical data for 70 infants <30 weeks gestation were assessed.

Results The incidence of early-onset refractory hypotension ($n = 7$) was correlated with younger gestational ages <26 weeks ($P < 0.05$), whereas the incidence of late-onset refractory hypotension ($n = 14$) was correlated with younger gestational ages and levothyroxine supplementation ($P < 0.05$ and 0.01, respectively). The incidence of both early- and late-onset refractory hypotension was correlated with risks of short-term adverse outcomes such as prolonged mechanical ventilation and hospital stay.

Conclusions Levothyroxine supplementation was identified as an independent variable correlated with an increased incidence of refractory hypotension out of the transitional period; as seen in hypothyroidism with Addison's disease, the immature hypothalamic-pituitary-adrenal axis may not respond properly to the increased demand for cortisol, which may precipitate premature infants into refractory hypotension. Following the administration of levothyroxine, preterm infants may have to be carefully monitored for early signs of refractory hypotension.

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Background

Systemic hypotension associated with hypovolaemia, myocardial dysfunction and deficient vascular tone is a common complication of sick preterm infants.[1,2] Prompt treatment of hypotension is essential because persistent hypotension is associated with increased risks of intraventricular haemorrhage, periventricular leucomalacia and long-term neurodevelopmental sequelae in this vulnerable group of patients.[3–5] Shortly after birth, a significant proportion of very-low-birth-weight infants experience refractory hypotension, which is resistant to intravenous volume expanders and inotropes but responds dramatically to exogenous cortisol.[6–8] Refractory hypotension has been recognized even out of the transitional period,[1,8–10] which is characterized by emerging hypotension and oliguria after the first week of life with an otherwise stable general condition. A recent nationwide survey in Japan revealed that approximately 4% of very-low-birth-weight infants were given intravenous hydrocortisone for late-onset refractory hypotension.[11] Although most cases are responsive to hydrocortisone, a delay in treatment may result in unfavourable outcomes.[10,12] However, currently, the outcome associated with late-onset refractory hypotension is unknown.

For the development of late-onset refractory hypotension, insufficient cortisol secretion relative to systemic demands is suspected as an important underlying condition, based on the marked response to low-dose hydrocortisone.[10–12] However, to precipitate once-stabilized infants into refractory hypotension, triggers specific to this postnatal period might be required. At present, various therapeutics and clinical conditions have been proposed as potential causatives, including inotropes, narcotics, diuretics, xanthine analogues, inappropriate sodium/water intake, levothyroxine and antenatal corticosteroids.[13,14]

Given the recent increase in reports of late-onset refractory hypotension, we speculated that the principal trigger is related to newly introduced treatments. Of these, levothyroxine is increasingly prescribed for transient hypothyroxinaemia of prematurity (THOP), which is characterized by low serum thyroxine levels without a corresponding increase in TSH concentrations.[15,16] Thyroid hormones are essential for the normal development of the central nervous system,[17,18] supporting the benefit of levothyroxine

supplementation. Indeed, in 2001, nearly a third of neonatologists in the United States had already given thyroid hormone to treat THOP.[19] However, hormonal supplementation for THOP is still controversial, because THOP might be the consequence of a teleological adaptation to a poor nutritional status, as observed in patients with euthyroid sickness;[20,21] as seen in adult[22] and adolescent[23] patients with insufficient adrenal function, monotherapy with levothyroxine may induce acute adrenal crisis via an increase in metabolism and cortisol demand. Thus far, except for a recent case report, no study has addressed the relationship between thyroid hormone supplementation and late-onset refractory hypotension.[24]

We performed a retrospective observational study in preterm infants to investigate potential causes of and the short-term outcome associated with the development of refractory hypotension observed at different timings.

Methods

This study was conducted with the approval of the local Ethics Committee of Kurume University School of Medicine (Fukuoka, Japan).

Study population and clinical information

Of 689 infants who were cared for at a tertiary NICU (Maternal and Perinatal Medical Centre, Kurume University School of Medicine) between January 2006 and August 2009, 77 infants were born at less than 30 weeks gestation, who were retrospectively enrolled in the study. Of these, seven infants with either severe foetal hydrops ($n = 2$) or major congenital anomalies ($n = 5$) were excluded from the population. Antenatal information was collected from clinical records of remaining 70 infants regarding maternal steroids, preterm rupture of membranes, histopathologically confirmed chorioamnionitis, tocolysis (ritodrine hydrochloride and/or magnesium sulphate) and mode of delivery. Postnatal variables included multiple pregnancies, gender, gestational age (GA), birth weight, Apgar scores (1/5 min), cord-blood pH and base-excess, intraventricular haemorrhage ($\geq$Grade 3 on Papile's scale),[25] patent ductus arteriosus (assessed using ultrasound) after Day 6, severe systemic infection (confirmed with either positive blood culture, elevated c-reactive protein >40 mg/l or postmortem findings), delayed establishment (>Day 13) of full enteral nutrition (>100 ml/kg/d), delayed recovery to birth weight (>Day 13), and a prolonged requirement (beyond Day 6) for a high-humidity (>70%) environment.

Postnatal procedures and treatments were recorded, as was the time when they occurred and/or commenced. These items included the insertion of umbilical catheters, intravenous corticosteroids, morphine, dopamine and/or dobutamine, amino acid supplementation, indomethacin, levothyroxine, exogenous pulmonary surfactant, iodine-containing gastro-enteral contrast medium (amidotrizoic acid), surgical procedures, and the requirement for additional fluid intake (>100 ml/kg/d and >150 ml/kg/d for average water quotients between Days 0 and 6, and between Days 0 and 27, respectively). Short-term outcomes such as prolonged demand

for mechanical ventilation (>32 weeks corrected age), survival discharge to home and prolonged hospital stay (>44 weeks corrected age) were also assessed.

Criteria for levothyroxine replacement therapy

For all infants, as a part of neonatal blood screening tests, whole-blood samples were collected on filter paper on Days 7 and 28 for the measurement of TSH using enzyme-linked immunosorbent assay; for infants with TSH values >10 mI U/l, additional blood samples were obtained to determine serum TSH and free thyroxine levels using electrochemiluminescence immunoassay. Serum TSH and free thyroxine were also assessed at any timing when symptoms suggestive of hypothyroidism (e.g. delayed establishment of enteral feeding, poor weight gain and prolonged jaundice) were observed. Based on the finding that low free thyroxine levels of less than 12·5 PM/l (0·97 ng/dl) were associated with adverse neurodevelopmental outcome,[26] we start oral or gastro-enteral levothyroxine (Thyradin-S; Takeda Ltd, Osaka, Japan, 5 μg/kg/d, once daily) with free thyroxine levels <1·0 ng/dl. Blood tests were repeated with the interval of approximately 10 days until serum-free thyroxine levels normalized.

Other procedures potentially affecting thyroid function

Exposure to povidone iodine and amidotrizoic acid may lead to excessive iodine intake, potentially increasing the incidence of iatrogenic hypothyroidism and thus, subsequent prescription of levothyroxine.[27] In our unit, for infants <26 weeks GA, we initially try to insert umbilical catheters; prior to catheter placement, 10% povidone iodine is painted over an area of approximately 30 cm^2 (equivalent with approximately 3 mg of iodine). If meconium plug syndrome is suspected, we perform intestinal infusion of up to 2 ml/kg amidotrizoic acid (Gastrographin; Bayer AG, Leverkusen, Germany, diluted fivefold with sterile water, equivalent with 100–200 mg of iodine). In addition, for extremely preterm infants, morphine chloride, which may also influence the thyroid function,[28] is routinely infused at a rate of 7 μg/kg/min continuously until Day 5. Inotropes which activate dopamine D2 receptors are also known to suppress hypothalamic-pituitary-adrenal axis;[29] we use dopamine and/or dobutamine only as clinically indicated for treatment (see the next paragraph for the detail).

Definition and treatment of refractory hypotension

In our unit, hypotension with oliguria is initially treated by standard cares such as volume expanders (intravenous normal saline, 10 ml/kg/dose, up to three times within 8 h) and inotropes (continuous intravenous infusion of dopamine with/without dobutamine, initially started at 3–10 μg/kg/min) aiming to maintain the mean blood pressure (MBP) of 30 mmHg (25 mmHg before Day 7) and subsequent urine output of 2·5 ml/kg/h (1·5 ml/kg/h before Day 7). Blood pressure is measured either through an arterial (umbilical or peripheral) catheter or a cuff with an automated oscillometric device; abnormal values are confirmed by repeating

measurements three times, and the median values are recorded. Refractory hypotension was defined as a status of persistent circulatory compromise, which is resistant to standard treatments and is likely to progress into critical systemic hypoperfusion unless efficient treatments are promptly administered. The diagnosis of refractory hypotension is confirmed with at least one of following conditions despite ongoing standard cares: (i) MBP <30 mmHg (25 mmHg before Day 7) or progressive hypotension by >25% within 24 h, and (ii) oliguria <1 ml/kg/h for at least 8 h. For infants with refractory hypotension, a single dose of hydrocortisone is injected intravenously (2 mg/kg) after excluding the possibility of serious systemic infection and symptomatic patent ductus arteriosus.

Recurrent episodes of refractory hypotension with intervals ≤72 h were regarded as a single event. On the basis of our preliminary data and other reports,[1,8,9] which suggested that the incidence of refractory hypotension was biphasic with its first peak shortly after birth and the second persistent phase thereafter, episodes of refractory hypotension were subgrouped into early- and late-onset refractory hypotension, which developed before Day 7 and thereafter, respectively; as potential causes of early- and late-onset refractory hypotension, only clinical events and procedures which commenced/occurred before Days 7 and 28, respectively, were considered.

Statistical analysis

Physiological variables at the timing of or immediately before the administration of intravenous hydrocortisone were compared with ones after the treatment using repeated measure ANOVA with Dunnett's test. Univariate logistic regression analysis was used to assess the relationship between various causative agents/ triggers and the development of refractory hypotension. Scale and rank-ordinal variables were dichotomized for convenience at clinically relevant thresholds. Because of the limited number of subjects, we aimed to include 2–3 candidate variables for each multivariate model according to the number of events. The selection of variables was based on (i) our hypothesis that refractory hypotension is associated with extreme immaturity (GA <26 weeks) and levothyroxine supplementation (late-onset refractory hypotension only) and (ii) the result of univariate analysis; independent variables with P-values <0·05 were considered after evaluating collinearity using Spearman's rank correlation coefficient. To investigate the outcome related with refractory hypotension, the mortality rate was first assessed for the infants who did or did not develop refractory hypotension. Because the timing of death affects the incidence of refractory hypotension, comparisons with other short-term outcomes were performed within infants who survived to discharge. To address the relationship between levothyroxine supplementation and late-onset refractory hypotension, a subgroup analysis was performed within the infants who were prescribed levothyroxine before Day 28; serum-free thyroxine and TSH levels before and after the commencement of levothyroxine were compared between infants who did and did not develop late-onset refractory hypotension, using ANOVA.

Results

Data were presented as the mean ± SD unless stated otherwise.

Patient profile

Of 70 infants (26·8 ± 2·1 weeks gestation), 11 infants (25·1 ± 1·9 weeks gestation) died at 9·0 ± 11·6 days of life as a result of severe infection ($n = 5$), cerebral haemorrhage ($n = 4$), pulmonary haemorrhage ($n = 1$) or pneumothorax ($n = 1$; Table 1). In comparison with early- and late-onset refractory hypotension, only infants who survived over 7 ($n = 62$) and 28 ($n = 60$) days, respectively, were considered.

Requirement for levothyroxine replacement therapy

Levothyroxine replacement was commenced in 27 infants on Day 11·8 ± 6·2 (not including five infants who were given levothyroxine after Day 27) (Table 1). Elevated TSH levels >10 mI U/l were found in 10 infants; the timing of the diagnosis and treatment of hypothyroxinaemia were similar between infants with high and normal TSH levels. The use of povidone iodine or amidotrizoic acid was not associated with the increased use of levothyroxine.

Incidence of refractory hypotension

The incidence of refractory hypotension was highest during the first week of age, which was followed by a persistent phase (Fig. 1). Early-onset refractory hypotension was observed in seven infants (Day 3·1 ± 2·0), whereas 14 infants developed late-onset refractory hypotension (Day 21·9 ± 8·6). Symptoms of early- and late-onset refractory hypotension were reversed within 24 h following the administration of hydrocortisone in all cases (Fig. 2). However, of seven infants who developed early-onset refractory hypotension, six infants experienced recurrent refractory hypotension with either short (2–3 days, $n = 4$) or long (15 and 26 days, $n = 2$) intervals. Similarly, of 14 infants who developed late-onset refractory hypotension, five infants developed recurrent refractory hypotension at intervals of 2–3 days, which required additional cortisol supplementation. Four of these five infants required a further third dose of hydrocortisone, followed by gradual weaning. In infants with late-onset (but not early-onset) refractory hypotension, an increase in serum sodium levels and a decrease in potassium levels were observed simultaneously with the recovery in blood pressure and urine output; there were no significant changes in ventilator settings (Table 2). Intravenous cortisol rescue was also required in 14 infants with severe lung disease (0·3 mg/kg/d dexamethasone tapered over 9 days; one infant before Day 7 and 13 infants between Days 7 and 27; of these, four infants had developed early-onset refractory hypotension before the treatment of lung disease, whereas 10 other infants never developed refractory hypotension) and in four infants with critical hypotension associated with severe systemic infection (a single dose of 10 mg/kg hydrocortisone; these events were not regarded as refractory hypotension because of the evidence of severe systemic infection; two infants before Day 7 and 2 infants between Days 7 and 27; all of these infants died shortly

Table 1. Clinical background of infants with or without refractory hypotension

	A: Early-onset refractory hypotension (*n* = 7)	B: Late-onset refractory hypotension (*n* = 14)[†]	C: Did not develop refractory hypotension (*n* = 51)[††]
Gestational age (weeks)	25·4 (23·9, 26·9)	25·5 (24·4, 26·7)	27·0 (26·5, 27·6)
Birth weight (g)	693 (543, 843)	689 (597, 781)[a]	899 (825, 974)
Cord blood pH	7·34 (7·22, 7·46)	7·32 (7·27, 7·37)	7·27 (7·22, 7·32)
Cord blood base excess	-3·4 (-9·2, 2·3)	-5·6 (-9·0, -2·1)	-7·2 (-9·3, -5·0)
Apgar score (1 min)	2·6 (0·6, 4·5)	4·1 (3·0, 5·2)	4·8 (4·1, 5·4)
Apgar score (5 min)	5·7 (4·1, 7·3)	6·4 (5·5, 7·4)	7·2 (6·7, 7·7)
Levothyroxine replacement therapy			
Number (elevated TSH)	3 (1)	12 (4)	12 (5)
Age at commencement (days)*	11·3 (3·3, 19·4)	12·1 (7·8, 16·4)	11·6 (8·2, 14·9)
TSH at commencement (mIU/L)*	6·2 (3·5, 8·9)	8·8 (3·8, 13·9)	10·8 (5·9, 15·7)
Free thyroxine at commencement (ng/dL)*	0·72 (0·50, 0·94)	0·56 (0·46, 0·66)[a]	0·81 (0·69, 0·93)
Mortality			
Number	0	1	10
Postnatal age at death (days)*	–	39	6·0 (2·0, 10·0)
Weaning from mechanical ventilation			
Postnatal age (days)**	49·3 (33·5, 65·1)[a]	46·1 (33·4, 58·8)[‡b]	25·6 (20·2, 31·0)
Corrected age (weeks)**	32·7 (31·4, 34·0)	32·3 (30·0, 33·6)[‡]	31·1 (30·5, 31·7)
Hospital discharge			
Postnatal age (days)**	134·5 (104·2, 164·8)[b]	126·2 (114·2, 138·2)[b]	96·8 (90·8, 102·8)
Corrected age (weeks)**	44·9 (42·1, 47·7)[b]	43·8 (42·3, 45·3)[b]	41·3 (40·6, 42·0)

Values are mean (95% confidence interval) unless otherwise stated.
*Data presented only for affected infants.
**Excluding infants who died before weaning from mechanical ventilation or discharge, respectively.
[†]Including two infants who developed both early- and late-onset refractory hypotension.
[††]Including eight infants who died before Day 7.
[‡]Excluding one infant who had not discharged the unit because of the prolonged demand for mechanical ventilation at 50 weeks corrected age.
[a]$P < 0.05$ and [b]$P < 0.01$, one-way ANOVA and Tukey test, vs. group C.
Abbreviations: TSH, thyroid-stimulating hormone. NA, not available.
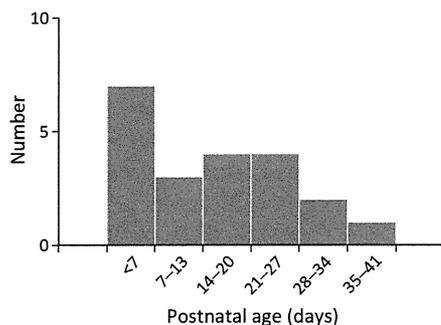

Fig. 1 Timing of onset of refractory hypotension. The incidence of refractory hypotension was biphasic with its first peak shortly after birth and the second phase lasting until the fifth week of life. Data do not include recurrent episodes within 72 h.

after the cortisol administration without developing early- or late-onset refractory hypotension).

Determinants of refractory hypotension

Univariate analysis indicated an association between the incidence of early-onset refractory hypotension and severe intraventricular haemorrhage (*P* = 0·003), the use of umbilical catheters

($P = 0.011$), GA < 26 weeks ($P = 0.013$) and the use of morphine ($P = 0.029$). Eventually, multivariate analysis was not performed because of high collinearity between GA < 26 weeks and other variables.

The incidence of late-onset refractory hypotension was related with levothyroxine replacement therapy ($P = 0.002$), birth weight <750 g ($P = 0.004$), GA < 26 weeks ($P = 0.005$), umbilical catheters ($P = 0.005$), delayed establishment of enteral nutrition ($P = 0.010$), amidotrizoic acid ($P = 0.014$) and requirement for additional fluid intake before Day 7 ($P = 0.016$; Table 3). In addition to levothyroxine replacement and GA < 26 weeks, amidotrizoic acid was examined using multivariate analysis (other variables were not considered because they showed high collinearity with one of the mandatory variables); levothyroxine replacement and GA < 26 weeks were recognized as significant contributors to an increased risk of late-onset refractory hypotension ($P = 0.004$ and 0·014, respectively).

Subgroup analysis in infants with levothyroxine supplementation

Of 27 infants who were prescribed levothyroxine before Day 28, 12 infants developed late-onset refractory hypotension, and in all cases, the commencement of levothyroxine replacement therapy
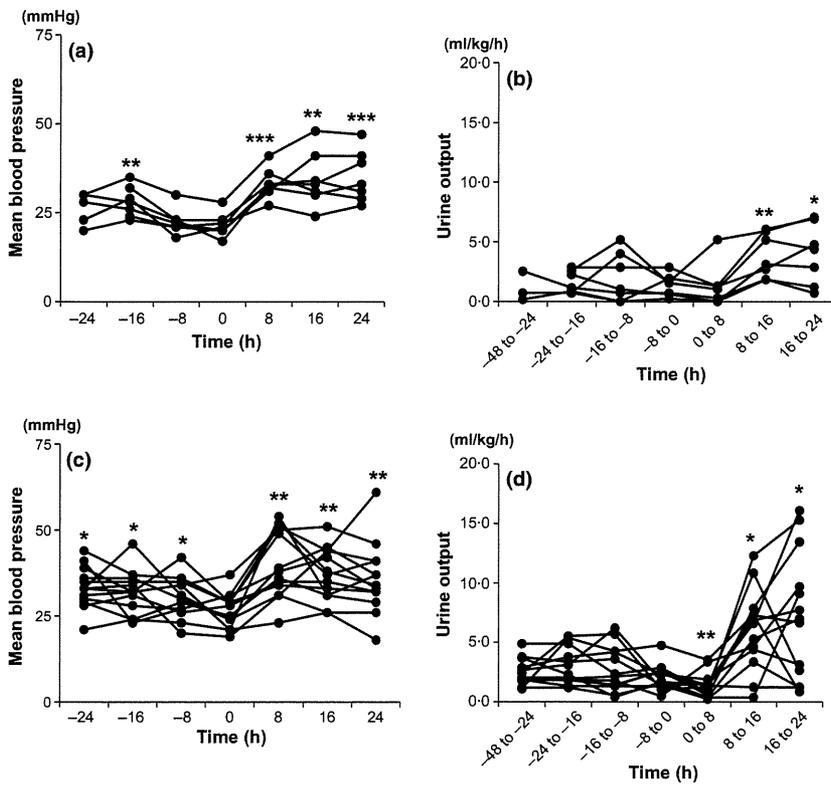
Fig. 2 Trajectories of blood pressure and urine output for infants who developed refractory hypotension. Changes in mean blood pressure (a, c) and urine output (b, d) of infants with early-onset (a–b) and late-onset (c–d) refractory hypotension. For both early-onset and late-onset refractory hypotension, blood pressure was swiftly reversed by an injection of intravenous hydrocortisone, which was followed by the recovery in urine output. Time zero represents the timing of the initial hydrocortisone administration. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$, repeated measure ANOVA, compared with time zero (a, c) or the period between -3 h and time zero (b, d).

Table 2. Changes in physiological variables following hydrocortisone administration for infants with refractory hypotension. (A) Early-onset refractory hypotension. (B) Late-onset refractory hypotension

	Time after hydrocortisone administration		
	−8 to 0 h	16 to 24 h	40 to 48 h
(A)			
Heart rate (beats per min)	151 (131, 171)	157 (145, 169)	161 (151, 171)
Mean airway pressure (cm H_2O)	10·1 (7·9, 12·3)	9·8 (7·9, 11·7)	9·6 (8·3, 10·9)
Fraction of inspired oxygen (%)	29 (23, 32)	27 (19, 35)	28 (23, 33)
Serum sodium (m Eq/l)	140 (131, 149)	140 (133, 147)	145 (139, 151)
Serum potassium (m Eq/l)	5·1 (4·5, 5·7)	5·9 (5·2, 6·6)	4·5 (3·6, 5·4)
(B)			
Heart rate (beats per min)	157 (150, 164)	149 (141, 157)	156 (149, 163)
Mean airway pressure (cm H2O)	9·9 (8·7, 11·1)	10·0 (8·6, 11·4)	9·3 (8·2, 10·4)
Fraction of inspired oxygen (%)	36 (30, 42)	31 (26, 36)	34 (27, 41)
Serum sodium (m Eq/l)	135 (131, 139)	137 (133, 141)	143 (140, 146)*
Serum potassium (m Eq/l)	6·0 (5·2, 6·8)	5·4 (4·7, 6·1)	4·5 (3·9, 5·1)*

Values are mean (95% confidence interval). Time zero is set at the timing when the first dose of hydrocortisone was given.
*$P < 0.05$, repeated measure ANOVA, compared with the period between −8 h and time zero.

preceded the development of late-onset refractory hypotension by 10·8 ± 9·2 days; these 12 infants had significantly lower pretreatment free thyroxine levels compared with 15 other infants who did not develop late-onset refractory hypotension (0·56 ± 0·18 and 0·77 ± 0·30, respectively, $P = 0.021$), pretreatment TSH (8·87 ± 9·00 and 10·20 ± 8·56, respectively), post-treatment free thyroxine (1·12 ± 0·37 and 1·02 ± 0·30, respectively) and TSH

(5·98 ± 13·60 and 3·79 ± 4·50, respectively) were invariant between each other.

Short-term outcome related to refractory hypotension

All seven infants who developed early-onset refractory hypotension survived to discharge. Of 14 infants who suffered late-onset

Table 3. Clinical variables related with the development of refractory hypotension (A). Early-onset refractory hypotension. (B) Late-onset refractory hypotension

	Incidence of early-onset refractory hypotension							
	No (n = 55)		Yes (n = 7)			95%CI		
	n	%	n	%	Odds ratio	Lower	Upper	P-value
(A)								
Univariate logistic regression analysis								
Antenatal steroid	22	40·0	5	71·4	3·75	0·67	21·07	0·133
Premature rupture of membrane	16	29·1	4	57·1	3·25	0·65	16·20	0·150
Chorioamnionitis	20	39·2	2	33·3	0·78	0·13	4·63	0·780
Tocolysis (ritodrine hydrochloride and/or magnesium sulphate)	50	90·9	6	85·7	0·60	0·06	6·03	0·664
Caesarean section	45	81·8	7	100·0	Complete separation			
Single pregnancy	43	78·2	5	71·4	0·70	0·12	4·06	0·689
Multiple pregnancy	12	21·8	2	28·6	1	Reference		
Gender								
Male	24	43·6	3	42·9	0·97	0·20	4·75	0·969
Female	31	56·4	4	57·1	1	Reference		
Gestational age (weeks)								
<26	15	27·3	6	85·7	1	Reference		
26≤	40	72·7	1	14·3	0·06	0·01	0·56	0·013
Birth weight (g)								
<750	19	34·5	5	71·4	4·74	0·84	26·76	0·078
750≤	36	65·5	2	28·6	1	Reference		
Cord blood pH								
<7·0	3	6·2	1	14	2·50	0·22	28·06	0·458
7·0≤	45	93·8	6	86	1	Reference		
Cord blood base excess								
<−10	12	25·5	1	14·3	0·49	0·05	4·46	0·524
−10≤	35	74·5	6	85·7	1	Reference		
Apgar score (1 min)								
<6	33	60·0	6	85·7	4·00	0·45	35·55	0·214
6≤	22	40·0	1	14·3	1	Reference		
Apgar score (5 min)								
<6	10	18·2	3	42·9	3·38	0·65	17·51	0·148
6≤	45	81·8	4	57·1	1	Reference		
Levothyroxine replacement between Days 0 and 6	3	5·5	1	14·3	2·89	0·26	32·35	0·389
Cortisol for lung disease between Days 0 and 6	1	1·8	0	0	Complete separation			
Amidotrizoic acid	4	7·3	1	14·3	2·13	0·20	22·26	0·529
Umbilical catheters	14	25·5	6	85·7	17·57	1·94	158·94	0·011
Surfactant replacement	47	85·5	7	100·0	Complete separation			
Morphine	19	34·5	6	85·7	11·37	1·27	101·45	0·029
Amino acid supplementation	32	58·2	7	100·0	Complete separation			
Exclusive breast milk feeding	24	43·6	2	28·6	0·52	0·09	2·90	0·453
Indomethacin	40	72·7	6	85·7	2·25	0·25	20·28	0·470
Dopamine/dobutamine	22	40·0	5	71·4	3·75	0·67	21·07	0·133
High-humidity environment over 7 days	27	49·1	6	85·7	6·22	0·70	55·16	0·101
Requirement for additional fluid (>100 ml/kg/d) between Days 0 and 6	28	50·9	6	85·7	5·79	0·65	51·29	0·115
Grade 3 or 4 intraventricular haemorrhage	1	1·8	3	42·9	40·50	3·39	483·92	0·003

	Incidence of early-onset refractory hypotension							
	No (n = 46)		Yes (n = 14)			95%CI		
	n	%	n	%	Odds ratio	Lower	Upper	P-value
(B)								
(a) Univariate logistic regression analysis								
Antenatal steroid	20	43·5	7	50·0	1·30	0·39	4·31	0·668
Premature rupture of membrane	14	30·4	5	35·7	1·27	0·36	4·48	0·710

Table 3. (Continued)

| | Incidence of early-onset refractory hypotension | | | | | | | |
| | No (n = 46) | | Yes (n = 14) | | | 95%CI | | |
	n	%	n	%	Odds ratio	Lower	Upper	P-value
Chorioamnionitis	14	32·6	6	50·0	2·07	0·57	7·59	0·272
Tocolysis (ritodrine hydrochloride and/or magnesium sulphate)	41	89·1	13	92·9	1·59	0·17	14·83	0·686
Caesarean section	40	87·0	11	78·6	0·55	0·12	2·56	0·446
Single pregnancy	36	78·3	10	71·4	0·69	0·18	2·69	0·598
Multiple pregnancy	10	21·7	4	28·6	1	Reference		
Gender								
Male	22	47·8	5	35·7	0·61	0·18	2·09	0·427
Female	24	52·2	9	64·3	1	Reference		
Gestational age (weeks)								
<26	10	21·7	9	64·3	1	Reference		
26≤	36	78·3	5	35·7	0·15	0·04	0·57	0·005
Birth weight (g)								
<750	12	26·1	10	71·4	7·08	1·87	26·87	0·004
750≤	34	73·9	4	28·6	1	Reference		
Cord blood pH								
<7·0	4	9·3	0	0	Complete separation			
7·0≤	39	90·7	11	100				
Cord blood base excess								
<−10	10	23·3	3	30·0	1·41	0·31	6·51	0·656
−10≤	33	76·7	7	70·0	1	Reference		
Apgar score (1 min)								
<6	27	58·7	10	71·4	1·76	0·48	6·45	0·394
6≤	19	41·3	4	28·6	1	Reference		
Apgar score (5 min)								
<6	8	17·4	5	35·7	2·64	0·70	10·01	0·154
6≤	38	82·6	9	64·3	1	Reference		
Levothyroxine replacement between Days 0 and 28	15	32·6	12	85·7	12·40	2·46	62·59	0·002
Cortisol for lung disease between Days 0 and 28	13	28·3	1	7·1	0·20	0·02	1·65	0·133
Amidotrizoic acid	1	2·2	4	28·6	18·00	1·81	178·81	0·014
Umbilical catheters	10	21·7	9	64·3	6·48	1·77	23·74	0·005
Surgical procedures	5	10·9	2	14·3	1·37	0·24	7·96	0·728
Surfactant replacement	40	87·0	12	85·7	0·90	0·16	5·01	0·905
Morphine	14	30·4	10	71·4	5·71	1·53	21·36	0·010
Amino acid supplementation	27	58·7	11	78·6	2·58	0·63	10·52	0·186
Exclusive breast milk feeding	17	37·0	7	50·0	1·71	0·51	5·70	0·386
Patent ductus arteriosus over 7 days	11	23·9	7	50·0	3·18	0·91	11·08	0·069
Indomethacin	33	71·7	12	85·7	2·36	0·46	12·05	0·301
Dopamine/dobutamine	18	39·1	7	50·0	1·56	0·47	5·18	0·472
High-humidity environment over 7 days	21	45·7	10	71·4	2·98	0·81	10·88	0·099
Delayed recovery to birth weight after Day 14	40	87·0	10	71·4	0·38	0·09	1·59	0·183
Delayed establishment of enteral nutrition (>100 ml/kg/day) after Day 14	14	30·4	10	71·4	5·71	1·53	21·36	0·010
Requirement for additional fluid (>100 ml/kg/d) before Day 7	21	45·7	12	85·7	7·14	1·43	35·57	0·016
Requirement for additional fluid (>150 ml/kg/d) between Days 0 and 27	1	2·2	1	7·1	3·46	0·20	59·23	0·391
Grade 3 or 4 intraventricular haemorrhage	2	4·3	1	7·1	1·69	0·14	20·19	0·677
(b) Final multivariate logistic model								
Levothyroxine replacement					12·34	2·22	68·64	0·004
Gestational age (weeks) <26					6·45	1·46	28·57	0·014

Treatments and procedures are for the period between Days 0 and 27 unless otherwise stated.
Abbreviation: CI, confidence interval.

refractory hypotension, 13 infants survived to discharge, and one infant died on Day 39. Of remaining 51 infants, eight infants died before Day 7, two infants died thereafter, and 41 infants discharged home without developing refractory hypotension. In infants who survived to discharge, the incidence of early-onset refractory hypo-

tension was associated with an increased risk of prolonged hospital stay (P = 0·003; Table 4). The incidence of late-onset refractory hypotension was associated with increased risks of both prolonged mechanical ventilation and hospital stay (P = 0·0011 and 0·012 respectively; Table 4). When the relationship between adverse

Table 4. Refractory hypotension and short-term outcomes

	Prolonged mechanical ventilation >32 weeks corrected age					
	Incidence of adverse outcome		Odds ratio			
	No (n = 37)	Yes (n = 22)		95% CI		
	n (%)	n (%)		Lower	Upper	P-value
Early-onset refractory hypotension	2 (5.4)	5 (20.0)	5.15	0.90	24.30	0.065
Late-onset refractory hypotension	4 (10.5)	9 (45.5)	5.71	1.49	21.84	0.011
Levothyroxine replacement < Day 28	11 (28.9)	15 (72.7)	5.07	1.62	15.85	0.005
Gestational age < 26 weeks	7 (18.9)	11 (50.0)	4.29	1.33	13.89	0.015
	Prolonged hospital stay >44 weeks corrected age					
	Incidence of adverse outcome		Odds ratio			
	No (n = 44)	Yes (n = 15)		95% CI		
	n (%)	n (%)		Lower	Upper	P-value
Early-onset refractory hypotension	1 (6.8)	6 (22.2)	28.67	3.07	268.09	0.003
Late-onset refractory hypotension	6 (13.6)	7 (50.0)	5.54	1.47	20.96	0.012
Levothyroxine replacement < Day 28	16 (34.1)	10 (75.0)	3.50	1.02	12.07	0.047
Gestational age < 26 weeks	10 (22.7)	8 (53.3)	3.89	1.13	13.33	0.031

Abbreviation: CI, confidence interval.

short-term outcomes and independent variables which increased the incidence of late-onset refractory hypotension were assessed, both levothyroxine replacement (P = 0·005 and 0·022 respectively) and birth weight <750 g (P = 0·047 and 0·027 respectively) were related to increased risks of prolonged mechanical ventilation and hospital stay (Table 4).

Discussion

Levothyroxine supplementation and extreme immaturity were associated with refractory hypotension in preterm infants out of the transitional period. To our knowledge, this is the first observational study to warn of the potential risk of levothyroxine in stable preterm infants. Preterm infants should be monitored carefully after the commencement of levothyroxine supplementation. Although all cases responded to exogenous cortisol, refractory hypotension was associated with short-term adverse outcomes such as prolonged mechanical ventilation and hospital stay; further follow-up studies are required to elucidate the related long-term neurodevelopmental outcome of infants who developed refractory hypotension.

Immature hypothalamic-pituitary-adrenal axis and refractory hypotension

In our study population, refractory hypotension was effectively reversed by intravenous hydrocortisone, suggesting that insufficient adrenal response relative to systemic demand was one of underlying causes. Foetal hypothalamus, pituitary and adrenal glands are already activated by the end of the first trimester; however, the rapid growth of the adrenal cortex occurs during the second trimester; sufficient upregulation of intrinsic corticosteroid release in response to external stress requires further maturation.[30] Given that the incidence of refractory hypotension increased with younger GA, an immature hypothalamic-pituitary-adrenal axis may render immature infants unable to respond properly to external stressors.

Potential triggers precipitating late-onset refractory hypotension

An immature hypothalamic-pituitary-adrenal axis may best explain the development of early-onset refractory hypotension; after the successful transition to the extra-uterine life, additional triggers may be required to precipitate relatively stable preterm infants into refractory hypotension. In our current study, levothyroxine replacement was identified as the principal factor associated with the incidence of late-onset refractory hypotension. Recently, the potential benefit of thyroid hormone supplementation for infants with THOP has rigorously been investigated.[31] Although THOP may represent the adaptation of the thyroid system to unfavourable conditions following preterm birth, restricted availability of thyroid hormone at tissue level may be deleterious for the normal development of the brain. Indeed, the incidence of THOP is associated with an increased risk of neurodevelopmental deficits;[32,33] a study has demonstrated favourable effects of

prophylactic thyroid hormone supplementation on the neurodevelopmental outcome of infants <27 weeks gestation.[34] Given the fact that approximately a third of neonatologists in the United States had already prescribed thyroid hormone to infants with THOP in 2001,[19] it is important to share the knowledge about potential adverse events related with levothyroxine supplementation regardless of the verdict on the treatment for THOP. In our study population, the incidence of late-onset refractory hypotension was unrelated with pretreatment TSH levels, suggesting that infants with congenital hypothyroidism may similarly be at risk of refractory hypotension after hormonal supplementation.

Although levothyroxine has been prescribed for infants without any particular attention, in adult patients, hormone replacement for hypothyroidism is suspended until adrenal deficiency has either been excluded or treated because, in patients with secondary or tertiary hypothyroidism, levothyroxine monotherapy increases the demand for cortisol as a consequence of increased metabolism, inducing acute adrenal insufficiency.[35] Our current findings suggest that even in preterm infants, exogenous levothyroxine may induce acute adrenal insufficiency. Given the relatively long "latent periods" between the commencement of levothyroxine and the development of refractory hypotension observed in our study, these two variables might merely be the consequences of common backgrounds associated with extreme immaturity. However, levothyroxine replacement remained as a prominent independent variable even when its effect was adjusted for GA. One big difference between newborn and adult patients would be the efficacy of oral (or gastro-enteral) hormonal replacement: in sick preterm infants, especially when enteral feeding is not fully established, serum thyroxine levels are often normalized only after weeks of dose titration. Indeed nine of the 27 infants who were prescribed levothyroxine in our study eventually required higher doses at the second prescription; of these, three infants developed refractory hypotension shortly after the prescription of increased doses. However, other pharmacological effects of levothyroxine might also be involved in the development of late-onset refractory hypotension; levothyroxine downregulates vascular angiotensin type one receptors, which mediate smooth muscle contraction and play an important role in fluid and electrolyte regulation.[36]

Univariate analysis also identified birth weight <750 g, umbilical catheters, amidotrizoic acid, morphine and delayed establishment of enteral feeding as independent variables related with the increased incidence of late-onset refractory hypotension. Some of these procedures may lead to additional iodine intake; however, extremely immature infants may require relatively more intensive cares such as the use of umbilical catheters, morphine and amidotrizoic acid, suggesting that the observed associations are most likely to be a consequence of the highly immature status of the infant rather than a specific cause of refractory hypotension. It was of interest that a requirement for additional fluid intake <7 days of life was correlated with late-onset refractory hypotension, because preliminary studies have suggested the relationships between inappropriate fluid intake, insufficient aldosterone secretion and late-onset refractory hypotension.[13,37]

Refractory hypotension and outcome of infants

In our study population, only one mortality case was observed in infants who suffered refractory hypotension. However, the incidence of refractory hypotension was associated with adverse short-term outcomes, such as prolonged requirement for mechanical ventilation and increased duration for hospital stay. Consequences could have been more serious if there had been delays in the diagnosis and treatment. It was of note that in our current study, potential triggers of late-onset refractory hypotension (i.e. levothyroxine supplementation and younger gestational age) were also associated with higher risks of short-term adverse outcomes. Further studies are required to delineate direct associations between these variables and long-term neurodevelopmental outcomes.

Study limitations

This was a retrospective observational study with a limited number of subjects. We were able to assess only a few candidate variables for the multivariate model because of the limited number of infants who developed refractory hypotension. For ethical reasons, we were unable to follow temporal hormonal changes during the evolution of refractory hypotension; thus, changes in thyroid and adrenal function related to the development of refractory hypotension were only assumed on the basis of the clinical events and the infants' responses to cortisol replacement therapy. In addition, our strategy to check free thyroxine levels for infants with symptoms of hypothyroidism may introduce another bias for the diagnosis and treatment of THOP. Prospective studies are required to address these issues.

To define refractory hypotension, we used cut-off MBP values of 25–30 mmHg under maximum conventional support, together with progressive hypotension and severe oliguria; for some infants, MBP of this level would be sufficient to maintain the normal brain perfusion.[2] However, given that more than 90% of preterm infants of 23–26 weeks GA are reported to have blood pressure ≥30 mmHg by the third day of life[38] and that cerebrovascular autoregulation is likely to be lost with MBP of less than approximately 30 mmHg in extremely low-birth-weight infants,[39] the current cut-off level may be reasonable. Indeed, in our current study, the infants who suffered refractory hypotension had nadir urine output of 1·3 ± 1·3 ml/kg/h and MBP of 25 ± 5 mmHg despite ongoing standard treatments, suggesting the critically ill status of the infants.

Conclusions

In preterm infants, the incidence of early-onset refractory hypotension was associated with clinical variables characteristic to highly immature infants, whereas the risk of late-onset refractory hypotension was associated with levothyroxine replacement and GA <26 weeks. Following the commencement of levothyroxine replacement therapy, preterm infants should be monitored carefully for sudden manifestations of symptoms of refractory hypotension even after the transitional period. Future prospective studies need to provide direct evidence, supporting a role for a

pathological hormonal imbalance associated with refractory hypotension.

Category of study

Clinical investigation.

Details of ethical approval

This study was conducted with the approval of the ethics committee of Kurume University School of Medicine.

Authors' contribution

J Okada, S Iwata, A Hirose, H Kanda, Y Maeno, M Yoshino, T Matsuishi and O Iwata contributed to the study design and manuscript writing. J Okada, S Iwata and O Iwata participated in the statistical analysis. J Okada, S Iwata, Y Maeno, T Matsuishi and O Iwata contributed to the interpretation of the results. J Okada, S Iwata, A Hirose, H Kanda, and O Iwata participated in the data collection. All authors have seen and approved the final version of this manuscript.

Competing interest statement

All authors declare that there is no financial or other competing interest and therefore have nothing to declare.

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Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2011 edition

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Abstract

Clinical guidelines for obstetrical practice were first published by the Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Association of Obstetricians and Gynecologists (JAOG) in 2008, and a revised version was published in 2011. The aims of this publication include the determination of current standard care practices for pregnant women in Japan, the widespread use of standard care practices, the enhancement of safety in obstetrical practice, the reduction in burdens associated with medico-legal and medico-economical problems, and a better understanding between pregnant women and maternity-service providers. These guidelines include a total of 87 Clinical Questions followed by several Answers (CQ&A), a Discussion, a List of References, and some Tables and Figures covering common problems and questions encountered in obstetrical practice. Each answer with a recommendation level of A, B or C has been prepared based principally on 'evidence' or a consensus among Japanese obstetricians in situations where 'evidence' is weak or lacking. Answers with a recommendation level of A or B represent current standard care practices in Japan. All 87 CQ&A are presented herein to promote a better understanding of the current standard care practices for pregnant women in Japan.

Key words: clinical question, complicated pregnancy, guideline, obstetrical practice, recommendation, standard care practice.

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Introduction

In Japan, approximately 1 100 000 women give birth annually at 2800 facilities, at which approximately 8000 obstetricians are employed. Because guidelines for obstetrical practice were not previously available in Japan, remarkable diversity exists among these facilities, particularly with regard to the screening and treatment of fetal/pregnancy abnormalities. This diversity in practice may partly explain the increased number of malpractice lawsuits. The Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Association of Obstetricians and Gynecologists (JAOG) decided to publish guidelines describing standard care practices for pregnant women in 2005. The aims of this guideline are to encourage the widespread use of standard care practices, to enhance the safety of obstetrical practice, to reduce burdens associated with medico-legal and medico-economical problems, and to promote a better understanding between pregnant women and maternity-service providers.

The authors of this article have contributed greatly to the preparation of this draft. The draft was frequently revised as a result of frequent audits and opinions gathered after the publication of the draft in the official Journal of JSOG and on the JSOG and JAOG websites. Then, the first edition, 'Guidelines for Obstetrical Practice in Japan 2008,' consisting of 63 Clinical Questions and 254 Answers (CQ&A), was published in April 2008. The second edition, 'Guidelines for Obstetrical Practice in Japan 2011', containing the revised 63 CQ&A as well as 24 new CQ&A, was published in April 2011.

As these guidelines were originally written in Japanese, non-Japanese speakers have been somewhat inconvenienced; this English version may overcome this problem. The original version of 'Guidelines for Obstetrical Practice in Japan 2011' contains a Discussion, a List of References, and some Tables and Figures. However, these sections have been omitted here because of space limitations.

Implications of 'A', 'B', and 'C' Recommendation Levels

Several tests and/or treatments for pregnant women are presented as answers with a recommendation level of 'A', 'B' or 'C' to each clinical question. The answers and recommendation levels are principally based on evidence or a consensus among Japanese obstetricians when the evidence is considered to be weak or lacking.

Thus, the answers are not necessarily based on 'evidence'. The answers usually begin with a verb, which may promote changes in behavior among maternity-service providers in clinical practice. Answers with a recommendation level of A or B are regarded as current standard care practices in Japan. Level A indicates a stronger recommendation than level B. Consequently, informed consent is required when maternity-service providers do not provide care corresponding to an answer with a level of A or B. Answers with a recommendation level of C are possible options that may favorably affect the outcome but for which some uncertainty remains regarding whether the possible benefits outweigh the possible risks. Thus, care corresponding to answers with a recommendation level of C does not necessarily need to be provided. Some answers with a recommendation level of A or B include examinations and treatments that may be difficult for general maternity-service providers to perform. In such cases, the maternity-service providers must refer the patient to an appropriate institution.

Contents

Chapter A. General practice

CQ001: How should uncomplicated healthy pregnant women be cared for prenatally?
   Answer

1 Provide antenatal care regularly and try to detect early premature labor, gestational diabetes, pregnancy-induced hypertension, low-lying placenta and placenta previa, fetal abnormalities (fetal growth restriction, abnormal position, oligohydramnios, and polyhydramnios), and placental insufficiency. (A)
2 Measure maternal weight, fundal height of the uterus, and blood pressure; semiquantify glucose

and protein concentrations in the urine; and assess fetal heartbeat and maternal edema at each antenatal visit. (B)

3 Provide antenatal care according to the following schedule: three times until the end of 11 gestational weeks (GW); every 4 weeks between 12 GW and the end of 23 GW; every 2 weeks between 24 GW and the end of 35 GW; and once a week thereafter. (C)

4 Regularly assess the fetal well-being at ≥41 GW. (B)

5 Consider the possibility that midwife-managed care for healthy women, together with existing services (see CQ414), may be clinically effective and may enhance the pregnant woman's satisfaction. (C)

CQ002: What information should be obtained from women during an early stage of pregnancy?
Answer

1 Ask women to complete the questionnaire form (see sample in Discussion). (B)

2 Measure bodyweight and blood pressure and semi-quantify glucose and protein concentrations in the urine. (B)

3 Screen for cancer of the uterine cervix using a cytological examination. (C)

CQ003: What blood tests should be performed during the first trimester?
Answer

1 The following blood tests are recommended: blood typing including ABO and Rh (A), atypical antibody against erythrocyte (indirect Coombs test) (A), complete blood count (A), HBs antigen (A), hepatitis C virus (HCV) antibody (A), rubella antibody using HI (A), screening tests for syphilis (A), human T-cell leukemia virus type 1 (HTLV-1) antibody (A, before the end of the second trimester), screening test for HIV (B), glucose concentration (B), and toxoplasma antibody (C).

CQ004: How should pregnant women with an increased risk of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) be screened and managed?
Answer

1 Recommend the use of elastic stockings for women with risk factors such as dehydration during emesis, long-term bed rest, obesity, and an older age. (C)

2 Consider the use of unfractionated heparin for women with the highest risk according to the 2004 guidelines for the prophylaxis of DVT/PTE. (C)

3 Do not administer warfarin to pregnant women because of its teratogenicity. As an exception to the rule, warfarin may be considered in pregnant women who have undergone a heart valve replacement. (A)

4 Assess PT, APTT, platelet count, and liver function at appropriate intervals during anti-coagulation with heparin. Measure the platelet count 5–7 days after the initiation of heparin for the early detection of heparin-induced thrombocytopenia (HIT). (B)

5 Try to prevent perinatal DVT/PTE according to the 2004 guidelines for the prophylaxis of DVT/PTE. (B)

6 Rule out DVT prenatally based on symptoms and palpation of both the legs before the postnatal prophylactic use of the intermittent pulse-pressure method. (C)

7 Avoid placing the patient in a 'lithotomy' position when performing a cesarean section. (C)

8 Initiate heparin calcium at a dose of 5000 units twice daily (s.c.) after confirming hemostasis and continue for 3 to 5 days for the prophylaxis of DVT/PTE when anti-coagulation is indicated after a cesarean section. (B)

CQ005: How should patients with hyperglycemic disorders during pregnancy be screened?
Answer

1 Screen all pregnant women for 'gestational diabetes mellitus (GDM)' and 'overt diabetes in pregnancy'. (B)

2 Screen using the following stepwise method: (B)
 1) Measure random blood glucose level at an early stage of pregnancy (each hospital should determine its own cut-off value). Check items ①–③ in Answer 4 before planning a 75-g oral glucose tolerance test (OGTT) in women with a random blood glucose level of ≥200 mg/dL.
 2) Give the pregnant woman a 50-g glucose challenge test (GCT; cut-off value ≥140 mg/dL) or measure the random blood glucose level a second time (cut-off value ≥100 mg/dL) between 24 and 28 GW in women not diagnosed as having 'GDM' or 'overt diabetes in pregnancy'.

3 Give a 75-g OGTT to all women with a positive screening test result except women diagnosed as having 'overt diabetes in pregnancy'. Diagnose the pregnant woman as having 'GDM' if one or more threshold values of a 75-g OGTT are fulfilled. Check items ①–③ in Answer 4 in women with a 2-h plasma glucose (PG) ≥ 200 mg/dL. (A)

Threshold values for 75-g OGTT

① Fasting plasma glucose (FPG) ≥92 mg/dL (5.1 mmol/L)
② 1-h PG ≥ 180 mg/dL (10.0 mmol/L)
③ 2-h PG ≥ 153 mg/dL (8.5 mmol/L)

4 Diagnose the pregnant woman as having 'overt diabetes in pregnancy' if any of the following three criteria are fulfilled. (A)

① FPG ≥ 126 mg/dL
② HbA1c ≥ 6.5%, expressed as National Glycohemoglobin Standardization Program (NGSP) value (HbA1c ≥ 6.1% according to Japan Diabetes Society [JDS])*
③ Definite diabetic retinopathy
④ Random blood glucose ≥200 mg/dL with any of ①–③, or 2-h PG ≥ 200 mg/dL with any of ①–③.

*The HbA1c value (%) according to the NGSP criteria corresponds to the same value plus 0.4 according to the JDS criteria.

5 Give a 75-g OGTT to all women with 'GDM' at 6–12 weeks postpartum. Assess the degree of glucose intolerance once again in all postpartum women diagnosed as having 'overt diabetes in pregnancy'. (C)

CQ006: How should patients with thyroid dysfunction during pregnancy be screened?
Answer

1 Determine the TSH, free T3, and free T4 levels in the blood of women with suspicious clinical signs and/or a medical history of thyroid dysfunction. (B)
2 Try to normalize the thyroid function of patients with thyroid dysfunction. Consult appropriate specialists or other appropriate experts if any difficulty is encountered while treating the patient. (A)

CQ007: How should women visiting a clinic and complaining of decreased fetal movements be dealt with?
Answer

1 Tell the patient, 'Some investigators have suggested that decreased fetal movements are associated with fetal jeopardy.' (C)
2 Assess the fetal well-being in an appropriate manner, such as a non-stress test (NST). (B)

CQ008: How should women with an atypical antibody against red blood cells be treated? (see CQ302 for women with ant-Rh [D] antibody)

Answer

1 Identify the antibody when a screening test, such as the indirect Coombs test, suggests the presence of an atypical antibody against red blood cells. (B)
2 Assess the titer of the antibody if the antibody belongs to an immunoglobulin (Ig) G that may cause hemolysis in the fetus. (B)
3 Monitor the fetal well-being, paying special attention to anemia and hydrops, in women with an elevated titer of an IgG antibody that may cause hemolysis in the fetus. (B)
4 Be prepared to administer un-crossmatched packed red blood cells compatible with an ABO blood type if the pregnant woman develops unexpected massive bleeding. (B)

CQ009: How should the expected date of confinement (EDC) be determined?
Answer

1 Determine the EDC based on the last menstrual period (LMP) in principle, but use the date of ovulation or fertilization if available. (A)
2 Use the EDC based on the crown–rump length (CRL) in cases with a CRL of 14–41 mm if the difference in the EDC is ≥7 days from the EDC based on the LMP. (B)
3 Use the EDC based on the biparietal diameter (BPD) and the femur length (FL) in cases with an estimated 12–19 GW and/or a CRL of >50 mm if the difference in the EDC is ≥10 days from the EDC based on the LMP. (C)
4 Estimate the EDC according to Answer 3, with careful consideration of fetal growth restriction (FGR) and post-term pregnancy, after taking possible deviations into account in cases with an estimated GW of ≥20. (C)
5 Determine the EDC based on findings of the early neonate if no relevant information is available prenatally. (C)

CQ010: What guidance regarding maternal body composition and weight gain during pregnancy should be provided?
Answer

1 Provide the following information when asked about the association between maternal body composition and pregnancy outcome. (C)
1) Lean women (body mass index [BMI] < 18.5 before pregnancy) are at an increased risk for preterm labor, preterm delivery, and low birthweight newborns.

2) Obese women (BMI ≥ 25 before pregnancy) are at an increased risk for pregnancy-induced hypertension, gestational diabetes mellitus, stillbirth, fetal macrosomia, and fetal neural tube defects.

2 Provide the following information when asked about weight gain during pregnancy. (B)

1) Japanese women of normal body composition (18.5 ≤ BMI < 25) are estimated to require a weight gain of 11 kg as of the 40th GW to have a singleton newborn weighing 3 kg, according to the 'Dietary Reference Intakes for Japanese' published by the Ministry of Health, Labour, and Welfare, Japan (2010). However, considerable individual differences exist.

2) Maternal weight gain during pregnancy is correlated with the birthweight of the newborn. However, this correlation becomes weaker as the pre-pregnancy maternal BMI increases. In cases of obese women, the pre-pregnancy BMI, rather than the weight gain during pregnancy, tends to affect the birthweight of the newborns more strongly.

3 Consider the following items when providing nutritional advice.

1) Recommend a balanced intake of nutrients. (A)

2) Use the pre-pregnancy BMI. (B)

3) Note that maternal weight gain is one of the parameters for assessing the maternal nutritional condition, and several different guidelines for maternal weight gain during pregnancy exist in Japan. (B)

4) Moderate nutritional guidance for pregnant women is preferred because high-quality evidence is not available. (C)

Chapter B. Consultation

CQ101: Which vaccines are safe for pregnant and lactating women?
Answer

1 Viable vaccines are contraindicated, in principle, for pregnant women. (A)

2 Non-viable vaccines can be given to pregnant women. (B)

3 Both viable and non-viable vaccines can be given to lactating women. (B)

CQ102: What considerations are necessary regarding the administration of vaccines against influenza and antiviral drugs to pregnant women?

Answer

1 Administer vaccines after explaining that the benefit of vaccination outweighs the risk derived from infection with influenza when women want to be vaccinated. (B)

2 Consider that the benefit outweighs the risk of using antiviral drugs, such as oseltamivir and zanamivir, for the treatment of influenza in pregnant and lactating women. (C)

3 Consider that the benefit outweighs the risk of using antiviral drugs, such as oseltamivir and zanamivir, for the prophylaxis of influenza in pregnant and lactating women after they have come in close contact with an infected person. (C)

CQ103: How should women anxious about the adverse effects of radiation exposure during pregnancy be treated?
Answer

1 Before counseling, determine the dose of the exposure and the stage of pregnancy (GW) when the exposure occurred using the last menstrual period, measurement of the conceptus by ultrasonography, or the date of a positive pregnancy test result. (A)

2 Explain that the risk of a fetal anomaly does not increase in cases with exposure within 10 days after conception. (B)

3 Explain that an embryo at stages ranging from 11 days after conception until 10 GW is vulnerable but does not have an increased risk of malformation at doses of <50 mGy. (B)

4 Explain that the central nervous system of a fetus at 10–27 GW may be affected unfavorably at doses of ≥100 mGy. (B)

5 Explain that a dose of 10 mGy is associated with a subtle, but negligible, increase in the risk of childhood cancer. (B)

CQ104: How should women who ask questions regarding the effects of a drug on the fetus be answered?
Answer

1 First determine the date on which the drug was taken and the corresponding GW. Use the last menstrual period, the date of a positive pregnancy test (urinary human chorionic gonadotrophin [hCG] level), and an ultrasound measurement to estimate the GW accurately. (A)

2 Refer to Table 1, a textbook such as 'Drugs in Pregnancy and Lactation,' by Briggs *et al.* (Lippincott Williams and Wilkins) or information on the

Internet. Inform the woman of the service provided by the Japan National Center for Child Health and Development. (B)

CQ105: How should one respond when asked about the association between folic acid and the occurrence of neural tube defects (NTD) in the fetus?
Answer

1 Explain as follows. (B)
   1) A reduction in the risk of an NTD is expected if 0.4 mg of folic acid is taken as a daily supplement prior to the establishment of pregnancy.
   2) A reduction in the recurrent risk of an NTD is expected when a woman who has previously given birth to an infant with an NTD takes 4.0–5.0 mg of folic acid daily under the supervision of a physician.

CQ106: How should women in whom a thickened nuchal translucency (NT) is incidentally found be treated?
Answer

1 Remember that the accurate measurement of an NT requires the following:
   1) A stage of pregnancy between 10 and 14 GW. (C)
   2) Sufficient magnification of the upper trunk of the fetus. (C)
   3) Measurement on a sagittal section as shown in the figure. (C)
2 Explain the implications of a thickened NT to women who have agreed to be informed of the results of antenatal diagnosis using ultrasonographic testing. (B)
3 Remember that some women do not wish to know the results of antenatal diagnosis. (A)
4 Consider the ethical problems involved in both situations described in Answers 2 and 3. (A)
5 Explain that the implications of a thickened NT are as follows: (C)
   1) A fetus with an NT of ≥3 mm, 4 mm, 5 mm, or 6 mm has a 3-times, 18-times, 28-times, and 36-times higher risk than the risk based on maternal age, respectively, of having 21-trisomy, 18-trisomy, or 13-trisomy, as shown in Figure 2.
   2) More than 90% of fetuses with a normal karyotype but with an NT of ≥3.5 mm survive without developing any congenital diseases.
   3) Approximately 70% of fetuses with a chromosomal aberration have an NT that is ≥95th percentile value and that increases from 2.1 mm to 2.7 mm with advancing gestation during the 11th

to 14th GW. The 99th percentile value for NT is 3.5 mm, independently of the GW.
   4) Chromosomal analysis using amniotic fluid is needed for a definite diagnosis of chromosomal aberration.

CQ107: How should one respond when asked about the effects of a drug during lactation on neonates/infants?
Answer

1 Assure the patient that most drugs, with a few exceptions, are not harmful to neonates/infants when taken while a woman is lactating. (B)
2 Recommend that the condition of the child, such as the speed of suckling, sleep status, mood and activity, and weight gain, be observed when a lactating woman decides to take a drug for which some concern over possible unfavorable effects exists. (C)
3 Refer to a textbook such as 'Drugs in Pregnancy and Lactation,' by Briggs *et al.* (Lippincott Williams and Wilkins) or visit the website of the Japan National Center for Child Health and Development. (C)

CQ108: How should one respond to questions regarding exercise during pregnancy?
Answer

1 Exercises to develop adequate strength may contribute to the maintenance and promotion of a healthy lifestyle. (B)
2 No evidence exists supporting any favorable effects of exercise on the prevention of pregnancy-induced hypertension, gestational diabetes mellitus, or prolonged labor. (C)
3 Women with the following complications should refrain from regular exercise. (A)
   1) Serious diseases of the heart and lung.
   2) Threatened preterm labor, cervical incompetency, shortened uterine cervix, or premature rupture of the membranes.
   3) Genital bleeding, placenta previa, or a low-lying placenta.
   4) Pregnancy-induced hypertension.
4 Women should refrain from the following exercises. (B)
   1) Exercises requiring a supine or standing position with minimal movement for long periods of time.
   2) Activities with an inherent increased risk of falling or traumatic injuries.
   3) Scuba diving.
5 Women with the following symptoms should discontinue all exercise: dizziness, headache, chest