Chapter 12

Premature infants

Martijn JJ Finken

Introduction

Among preterm infants, three maturity levels are distinguished by the World Health Organization (WHO) [1] according to gestational age:

- preterm (<37 weeks);
- very preterm (<32 weeks);
- extremely preterm (<28 weeks).

However, a classification according to birth weight is often adopted in countries where a reliable estimate of gestational age is not always available [1]. Low birth weight (LBW) infants are those with a birth weight under 2500 g, which may be due to prematurity, being born small for gestational age (SGA), or both [1]. Those with a birth weight under 1500 g are labeled very low-birth-weight (VLBW) infants, while those with a birth weight under 1000 g are considered extremely low-birth-weight (ELBW) infants [1]. In general, there is an over-representation of infants born SGA in VLBW and ELBW study populations [2]. Therefore, caution must be exercised in extrapolating findings from study populations to general groups of preterm infants.

In most industrialized countries, there is a rising incidence in the number of preterm births, which is attributed to an older maternal age at first birth and the increased application of assisted reproductive technologies (leading to more twin gestations) [3,4]. Owing to improvements in perinatal management (eg, widespread use of antenatal

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glucocorticoids and synthetic surfactant), neonatal mortality of very preterm infants has declined from approximately 30% in the early 1980s to an estimated 10% by the mid-1990s [3,4]. The past decade has been characterized by advances in neonatal resuscitation techniques [5], ventilatory strategies [6], and nutrition [7], resulting in a greater number of infants born at the border of viability (23–24 weeks) that go on to survive, although often with chronic conditions and handicaps [8,9]. Therefore, results from studies in older populations of preterm infants cannot be automatically generalized and applied to the current generation of preterm survivors.

Recent evidence suggests that, from mid-childhood onwards, the endocrine-metabolic state of preterm individuals resembles that of subjects born SGA [10,11]. The first evidence for an elevated type 2 diabetes risk in survivors of preterm birth came from a small study which showed that prepubertal children born very preterm had reduced insulin sensitivity during an intravenous glucose tolerance test [10]. Similar findings were subsequently reported in adult populations [11].

Evidence for an association between preterm birth and type 2 diabetes was provided by several population-based studies in middle-aged subjects whose birth data (eg, weight, length, gestational age) were known [12–14]. The risk of diabetes doubled in subjects who were born preterm [12], whereas another study found that the relative risk (RR) for developing type 2 diabetes was 1.67 (95% CI, 1.33–2.11) after very preterm birth [13]. Another study found that preterm birth was associated with type 2 diabetes and with higher glucose and insulin levels during an oral glucose tolerance test [14]. The associations found in these studies were irrespective of the size at birth [10,11,13,14]. In addition, individuals born preterm were found to have higher blood pressure in adolescence/young adulthood [15–20].

Growth

Early growth

After an initial weight loss, birth weight is usually regained somewhere between the end of the first and third week of life, depending on the infant's gestational age, birth weight, morbidity, and nutrition [7,21].

Once birth weight is regained, the growth velocity increases to a level which approaches the intrauterine growth rate. However, the rate of weight gain during hospital stay was shown to be slower in infants with acute illnesses and chronic lung disease [21–23]. Postnatal growth failure has also been associated with shorter gestational age, lower birth weight standard deviation score (SDS), longer duration of respiratory support, and postnatal dexamethasone therapy [23].

A likely explanation for these associations relates to increased energy expenditure. However, the importance of practice decisions in nutritional support should not be overlooked, since it has been suggested that the perceived health status plays a crucial role in these decisions, with healthier infants receiving more nutritional support during the first weeks of life than those who are ill [24]. In comparisons between neonatal intensive care units, differences in the postnatal weight gain were often explained by variations in neonatal nutrition practices [25,26].

Evidence from randomized trials and observational studies has shown that strategies providing early nutritional support increased energy levels, reduced nutritional deficits, and improved neonatal growth and neurodevelopmental outcomes, without increasing the risk of adverse clinical outcomes [7].

Childhood growth

A considerable proportion of very preterm infants have a weight and/or length under –2 standard deviations (SD) from the mean at 40 weeks postmenstrual age [27–29]. As soon as their clinical condition improves, catch-up growth in weight, length, and head circumference is initiated and is often achieved within the first 2 years of life. Continuing catch-up growth throughout childhood and adolescence is not unusual [30–33].

On average, very preterm subjects attain an adult stature that lies 0.5 SD below the population-specific reference mean [31,33–36] (Table 12.1). There is controversy as to whether this reduction could be explained by earlier pubertal development. Earlier menarche, bone-age advancement, and younger age at initiation of the pubertal growth spurt have been reported [33,37,38], while in other studies markers of pubertal timing did not deviate from control populations [31,32,36,39].

In a large study of 1320 VLBW children, height at 6 years of age was best predicted by their length at 1 year of age [40]; parental height, gestational age, and birth weight SDS were found to be less important predictors of childhood growth. Very preterm infants who were born appropriate for gestational age (AGA) with a length and/or weight under –2 SD at the age of 3 months post-term were found to grow in a similar way to children born SGA after a similar pregnancy duration, reaching a final height of approximately 1 SD below the population reference mean (Figure 12.1) [41]. Those with a height under –2 SD at 5 years of age were unlikely to catch up subsequently.

Body composition

Compared to term children, children born very preterm were found to have increased fat mass and abdominal fat deposition at term, in spite of a lower body weight and length [42,43]. Children who had experienced either intrauterine growth restriction (IUGR) or extrauterine growth retardation

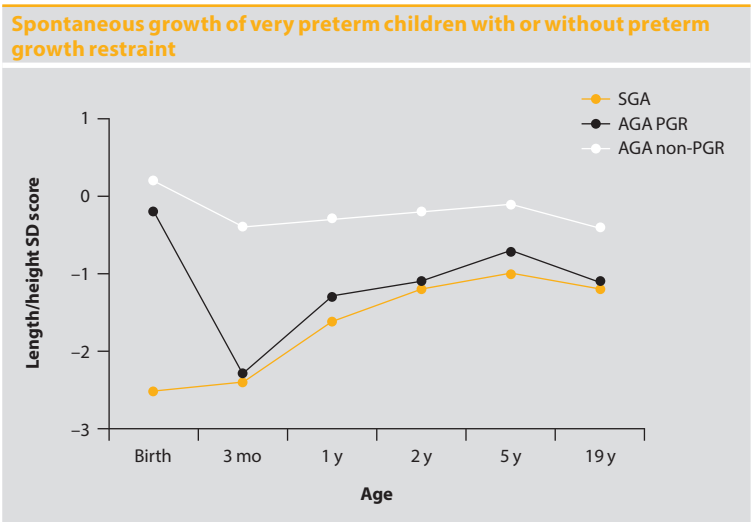

Figure 12.1 Spontaneous growth of very preterm children with or without preterm growth restraint. Growth patterns of 27 children born SGA (birth weight and/or length under –2 SD), 79 children born AGA with PGR (birth weight and length at or above -2 SD followed by a weight and/or length under –2 SD at the age of 3 months post-term), and 274 children born AGA without PGR. AGA, appropriate for gestational age; PGR, preterm growth restraint; SGA, small for gestational age; SD, standard deviation. Adapted from Finken et al [41].

(EUGR) had a lower fat-mass percentage at term than non-growth-retarded infants, but had a greater fat mass accretion in the period thereafter, so that these differences had disappeared by the age of 3 months post-term [44]. At the age of 1 year, the body composition of preterm children was still different from that of infants born at term [45].

Despite these differences in fat mass accretion after birth, preterm infants (especially those born SGA) were found to be lighter and thinner during infancy and childhood [40,46]. From mid-childhood onwards, a gradual increase in weight that exceeded increases in height was demonstrated (Table 12.1) [32,33,35,47]. There is a tendency towards a higher adult body mass index (BMI) with increasing prematurity (Table 12.1). Even with a relatively normal BMI, lower lean mass and centralization of fat distribution have been observed in young adults that were born preterm [11,34].

Growth hormone therapy

In the current SGA indication for growth hormone (GH) therapy, the nature and timing of the growth-restraining insult that has led to the SGA condition are thought to be irrelevant for determining whether or not to commence GH therapy. Regardless of whether the child's growth is retarded at birth, many very preterm infants have a weight and/or length under 2 SD at term age. It has been argued that it is illogical to exclude preterm AGA infants with EUGR from GH therapy if their small size at term evolves to a short stature in childhood [48].

Thus far, a randomized trial aimed at the long-term efficacy and safety of GH therapy in short children who had experienced EUGR after a preterm birth has not been conducted. The short-term response to GH therapy in short children born prematurely has been evaluated by a few observational studies [49–51], which have shown an average height-gain of 0.6–0.9 SD in the first year of treatment [49,50]. It is unclear whether the short-term response to GH therapy is indicative of the long-term growth response.

Assessing size at preterm birth

The use of neonatal anthropometric charts for assessing the preterm newborn's size deserves special attention. Firstly, many charts are based

Growth of very preterm or very low birth weight infants

First author	Population	Year of birth	Sex	*n*	Length/height (SDS)				Weight (SDS)			
					Infancy	Childhood	Adolescence	Adulthood	Infancy	Childhood	Adolescence	Adulthood
Brandt [36]	ELBW and SGA (1) with catch-up growth	1967-1978	M+F	21	–	–	–	22.8 y: +0.03 (2)	3.5 y: -0.72	5 y: -0.64	–	–
	ELBW and SGA (1) without catch-up growth	1967-1978	M+F	26	–	–	–	22.8 y: -1.89 (2)	3.5 y: -1.12	5 y: -0.98	–	–
Hack [31]	VLBW	1977-1979	M	103	8 mo.: -0.94 20 mo.: -0.55	8 y: -0.45	–	20 y: -0.44	8 mo: -1.70 20 mo.: -1.16	8 y: -0.46	–	20 y: -0.35
			F	92	8 mo.: -0.51 20 mo.: -0.16	8 y: -0.20	–	20 y: -0.26	8 mo. -1.09; 20 mo.: -0.82	8 y: -0.23	–	20 y: +0.26
Ford [32] and Doyle [35]	ELBW	1977-1982	M+F	86	2 y: -0.98	5 y: -0.67 8 y: -0.78	14 y: -0.43	20 y: -0.52 (3)	2 y: -1.27	5 y: -1.01 8 y: -0.89	14 y: -0.14	20 y: +0.14 (3)
	VLBW, not ELBW	1977-1982	M+F	120	2 y: -0.59	5 y: -0.35 8 y: -0.46	14 y: -0.11	–	2 y: -0.45	5 y: -0.43 8 y: -0.43	14 y: +0.10	–

First author	Population	Year of birth	Sex	*n*	Length/height (SDS)				Weight (SDS)			
					Infancy	Childhood	Adolescence	Adulthood	Infancy	Childhood	Adolescence	Adulthood
Saigal [33]	ELBW	1977-1982	M	65	1 y: -1.59 2 y: -0.92 3 y: -0.72	8 y: -0.84	11-16 y: -0.46	21.5-26.5 y: -0.86	1 y: -2.49 2 y: -1.90 3 y: -1.44	8 y: -1.05	11-16 y: -0.53	21.5-26.5 y: -0.25
			F	82	1 y: -1.04 2 y: -0.77 3 y: -0.58	8 y: -0.94	11-16 y: -0.59	21.5-26.5y: -0.77	1 y: -1.96 2 y: -1.68 3 y: -1.16	8 y: -1.05	11-16 y: -0.24	21.5-26.5 y: -0.13
Euser [34]	Very preterm	1983	M	187	–	–	–	19 y: -0.55	3 mo.: -0.94 (M+F) 1 y: -0.98 (M+F)	–	–	19 y: -0.41
			F	216	–	–	–	19 y: -0.60	3 mo.: -0.94 (M+F) 1 y: -0.98 (M+F)	–	–	19 y: -0.48

Table 12.1 Growth of very preterm or very low birth weight infants. (1) SGA (small for gestational age) = birth weight < 10th percentile; (2) Mean adult height of the entire group:= –1.02 SDS; (3) Data at 20 years of age are provided for only 43 subjects. Only studies that provided a longitudinal follow-up into adulthood are listed in the table. ELBW, extremely low birth weight; F, female; M, male; SDS, standard deviation score; VLBW, very low birth weight; y, year-of-age. Data taken from [31–36].

upon relatively small numbers of extremely preterm infants, which makes them less accurate in the lower range of gestational ages. For instance, the widely adopted Usher and McLean curve is derived from the data of 300 infants, among whom there were 33 born at a gestational age of 28 weeks or less [52].

Furthermore, neonatal anthropometric charts differ from fetal growth charts that are used in obstetrics, the latter being based upon ultrasound measurements obtained during healthy pregnancies continued until term [53]. The exclusion of preterm neonates born after pathological pregnancies does not imply that the reference data rely exclusively on completely healthy pregnancies. Even in the absence of clear pathology, a preterm birth is often preceded by a variable degree of IUGR. In other words, in the preterm range, anthropometric charts tend to underestimate the level of IUGR.

Blood pressure

Hypotension (low blood pressure) is diagnosed in up to 50% of preterm infants during the first days of life. Several definitions have been implemented in clinical practice, including a mean arterial blood pressure (MABP) of less than 30 mmHg, below the infant's gestational age in weeks and in the lower range of distribution (eg, if below the 10th percentile of MABP for birth weight and postnatal age based on normative data) [54].

In extremely preterm infants, myocardial dysfunction is thought to play a role in hypotension in the first hours after birth, during which period the immature myocardium is confronted with an abrupt increase in afterload [55]. Of greater importance is a low systemic vascular resistance, due to either a hemodynamically active shunt or abnormalities in the regulation of the vascular tone (eg, adrenocortical dysfunction).

In very preterm newborns, systemic hypotension was found to be a predictor of intraventricular hemorrhage and periventricular leukomalacia [56,57]. It has also been associated with a poorer neurological outcome [58,59]. However, many studies have failed to confirm these relations and the causality of these statistical associations has therefore been questioned [60]. An alternative explanation for these associations is confounding by factors associated with both systemic hypotension and cerebral injury (eg, asphyxia or respiratory distress syndrome).

Treatment for neonatal hypotension should be based upon the cardiovascular status and not merely on blood pressure [60]. Assessment of the heart rate, peripheral perfusion, urinary output, and other factors that limit oxygen delivery (eg, hypoxemia or anemia) should therefore not be overlooked.

Glucose availability

Because of a continuous transplacental delivery of nutrients, the endocrine milieu of the growing fetus is characterized by constantly high levels of insulin and low levels of glucagon. The situation in postnatal life is characterized by alternating periods of enteral feeding and fasting. During fasting, glucose, gluconeogenic substrates, and alternative fuels are released from energy stores, the development of which is generally confined to the third trimester of pregnancy. In the last month of gestation, there is a rapid increase in hepatic glycogen content, reaching a concentration of approximately 50 mg/g tissue at the time of birth [61].

Hypoglycemia

Hypoxia, asphyxia, hypothermia, and illness are common in preterm infants and these consequently increase the glucose demands in tissues. This, in combination with a lack of energy stores and immature responses to declining glucose concentrations, results in hypoglycemia being almost inevitable in the early postnatal course of preterm infants.

In the first week of life, circulating levels of the gluconeogenic substrates lactate and pyruvate are similar to those of full-term newborns, contrasting with the lower circulating levels of glycerol and alanine [62].

Very preterm newborns in their first week of life can only partly compensate for a sudden decline in the intravenous glucose supply with an increase in their glucose production rate [63]. In ELBW infants receiving total parenteral nutrition, the glucose production rate did not increase at all in response to a reduction in the infusion rate, and consequently the circulating level, of glucose [64]. This could be attributed to a decreased activity of glucose-6-phosphatase [65], the final step in both glycogenolysis and gluconeogenesis. Intravenous administration of glycerol was found to enhance gluconeogenesis [66], especially in

conjunction with polyunsaturated free fatty acids [67]. Preterm infants are also compromised in their ability to respond adequately to declining glucose levels with an increase in counter-regulatory hormones such as catecholamines and cortisol [63,68].

Lipolysis and ketogenesis are severely impaired in preterm infants in their first week of life, even at low blood glucose levels [62,63]. The lack of ketone bodies is not explained solely by small fat deposits, as it has been demonstrated in preterm infants that, for a given level of free fatty acids, the hepatic ketone production was two to three times lower than in full-term infants [69].

Hyperglycemia

Glucose disposal is dependent on the action of insulin. It has been observed that hyperglycemic preterm infants require insulin infusion at higher rates to achieve euglycemia, which is indicative of insulin resistance or lack of insulin-sensitive targets such as hepatic glucokinase, adipose tissue, and skeletal muscle [61]. In line with these observations, hepatic glucose production was not switched off during a euglycemic-hyperinsulinemic clamp [70] or glucose infusion at high rates [71,72]. There is some evidence for a partial defect in the processing of proinsulin in very preterm infants, given the high proinsulin/insulin ratio that was observed in those who became hyperglycemic [73]. Lack of insulin action leads to hyperglycemia (and if profound, to osmotic diuresis), and promotes catabolism.

Hyperglycemia is common in VLBW infants, especially in the most immature children [74]. Glucose intake should be kept between 6–12 mcg/kg/min, depending on the clinical condition, with sick infants requiring higher rates than their healthier counterparts. Insulin therapy should be considered when the blood glucose level remains greater than 10 mmol/L after the glucose intake has been optimized, and started at a relatively low rate (eg, 0.025 U/kg/hr). To avoid hypoglycemia, it is recommended to keep the glucose level at the upper range of normal [75,76].

Adrenocortical function

During the third trimester of pregnancy, the adrenal cortex changes substantially. While the fetal zone involutes, the adult zone increases

in size [77]. The main product of the fetal zone is dehydroepiandrosterone sulfate (DHEAS), which serves as a precursor for the placental hormone, estriol.

Cortisol is the principal steroid from the adult zone and is necessary for the maintenance of blood pressure and glucose homeostasis. It plays a role in setting the sensitivity of the peripheral tissues to insulin, glucagon, and catecholamines. In preterm newborns, the cortisol level and the cortisol:DHEAS ratio in cord blood increase with gestational age [78,79].

The greatest impairment in adrenocortical function is observed in very preterm newborns at 1 week of age, particularly in those who require mechanical ventilation and/or inotropic support [80–82]. This is followed by a rapid adaptation of the hypothalamus-pituitary-adrenal (HPA) axis by the end of the second week, with the largest improvement in adrenocortical function being observed in ill preterm infants [80,81]. The most important rate-limiting step is probably impaired 11β-hydroxylase activity [83–85].

Antenatal glucocorticoid therapy

A single treatment course of antenatal glucocorticoids to mothers with impending preterm delivery has been shown to improve neonatal survival [86]. This is attributed to a lower incidence of the respiratory distress syndrome and complications related to hemodynamic instability, such as intraventricular hemorrhage and necrotizing enterocolitis.

Repeated treatment courses of antenatal glucocorticoids (mostly given every 7–14 days until weeks 32–34) seem to increase the risk for IUGR [87,88]. Infants exposed to at least four treatment courses were found to have a reduction of 1 SD in birth weight and length [89]. Head circumference was less affected. Rates of neurological impairment among infants aged 18–24 months who had been treated with repeated courses (74% of whom were exposed to three courses or less) did not differ from those treated only once [90]. Long-term follow-up data are not available yet.

Betamethasone and dexamethasone are used for the induction of fetal lung maturation, since these glucocorticoids are able to escape inactivation by placental 11β-hydroxysteroid dehydrogenase type 2 activity.

Betamethasone readily crosses the placenta, resulting in a high cord vein glucocorticoid bioactivity that returns to the reference level within 1 or 2 days following the last steroid dose [91,92].

In preterm newborns, the effects of antenatal glucocorticoids are likely to be more pleiotropic, at least shortly after exposure, than merely reflected in a lower incidence of the respiratory distress syndrome.

In ELBW infants, antenatal betamethasone treatment was associated with a reduced need for blood pressure support during the first 48 hours after birth [93]. Preterm newborns exposed antenatally to betamethasone had an elevation of proinsulin, insulin, and C-peptide levels in cord blood up to 48 hours after the last steroid dose, in spite of a normal glucose concentration, indicative of insulin resistance [94]. There is some preliminary evidence suggesting that betamethasone suppresses aldosterone production [95], an effect that might be mediated through inhibition of P450 side-chain cleavage.

Postnatal glucocorticoid therapy

In two placebo-controlled randomized trials in preterm infants on vasopressor support, hydrocortisone (1 mg/kg every 8 hours for 5 days) or a single dose of dexamethasone (0.25 mg/kg) successfully enabled the discontinuation of inotropics [96,97]. Comparable results were reached in case series of preterm infants with refractory hypotension and/or adrenocortical insufficiency [98–100]. Dosages of hydrocortisone of up to 6 mg/kg per day were used in these studies.

There is less experience with prophylactic glucocorticoid treatment for preterm hypotension. Both a single dose of dexamethasone (0.2 mg/kg) and hydrocortisone for 5 days (2 mg/kg/day on day 1 and day 2 and 0.6 mg/kg/day on days 3–5) seems to be effective [101,102]. A review of postnatal glucocorticoid therapy for respiratory conditions is beyond the scope of this chapter.

Thyroid function

When comparing term and preterm infants, the thyroid function of preterm newborns is characterized by a lower thyroid stimulating hormone (TSH) surge immediately after delivery and a thyroxin (T4) concentration

that falls, after a smaller initial increase, over the subsequent 1 to 2 weeks (Figure 12.2). The T4 nadir on day 7 is deeper with increasing prematurity [103,104]. The triiodothyronine (T3) concentration does not decrease in parallel with T4, which is probably the result of an increase in the availability of type 1 deiodinase, as well as the loss of placental type 3 deiodinase activity.

Apparently, the causes of the decrease in T4 observed postnatally in preterm infants are multifactorial and include clearance of maternal T4 from the neonatal circulation, decreased thyroidal iodide stores, an increased vulnerability to the thyroid-suppressive effects of excess iodide, medical treatment (eg, dopamine and glucocorticoids), and differences in the availability of thyroid-binding globulin (TBG) [105]. TBG is produced in the liver and its plasma concentration increases with maturity levels and decreases during critical illnesses, thereby influencing the total T4 concentration [103]. The free T4 concentration usually remains constant in spite of fluctuations in the concentrations of TBG and total T4.

Despite a low serum T4, the TSH level usually remains within the normal range. Elevated TSH levels may be seen in the recovery phase of critically ill children, or early in the course of healthy infants in the extremely preterm range [103,106]. In the latter group, this could reflect insensitivity to TSH associated with maturity-related differences in its glycosylation [107].

Lower levels of T4 and T3 throughout the neonatal phase have been associated with increased mortality and short- and long-term morbidity, including the respiratory distress syndrome, intraventricular hemorrhage, and neuromotor and cognitive deficits [108–111]. Several trials have studied the effects of thyroid hormone supplementation in preterm infants [112]. Different treatment protocols have been used in these trials, including T4 or T3 alone, and T4 and T3 combined, as continuous or bolus injections. Overall, no effect on mortality or respiratory outcomes was observed. A trend towards a lower occurrence of patent ductus arteriosus was observed. Only one trial in infants born before 30 weeks gestation has focused on neurodevelopmental outcomes up to 10 years of age, which were improved in the most premature ones but worse in those of 29 weeks gestation [113–115].

Thyroid function in very preterm newborns

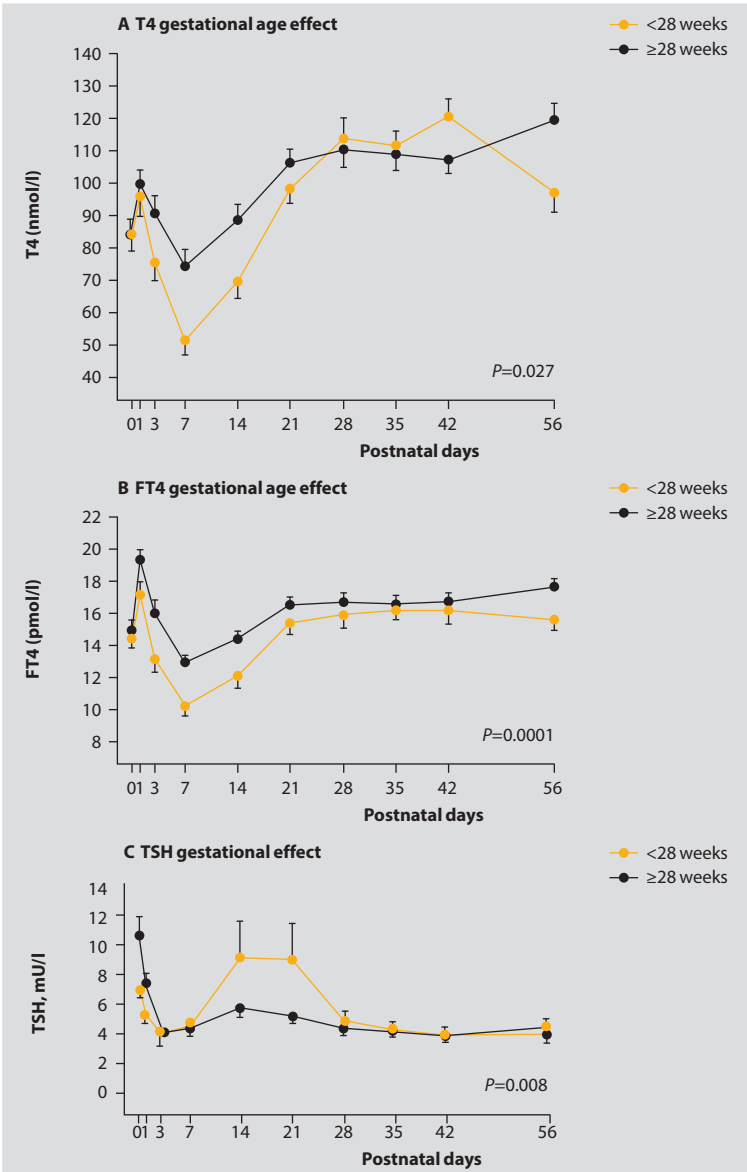

Figure 12.2 A-C Thyroid function in very preterm newborns. Thyroid function during the first 8 weeks after birth: effects of gestational age on T4 (Figure 12.2A), FT4 (Figure 12.2B), and TSH (Figure 12.2C). Adapted from Van Wassenaer et al [103].

The optimal treatment protocol remains to be defined. There are some pharmacokinetic arguments, related to TSH depression and immature tissue metabolism by deiodinases, that recommend continuous supplementation with T4 and T3, or T4 alone, rather than bolus injections or treatment with T3 alone [116–118]. Given all these uncertainties, routine treatment with thyroid hormone is not recommended in preterm infants.

Bone metabolism

Very preterm newborns carry a risk of developing metabolic bone disease with undermineralized bones, as bone mineralization, along with calcium and phosphorus accretion, mainly occurs during the third trimester of pregnancy. Although frank radiological rickets with fractures has been described, the condition is often asymptomatic and is generally detected biochemically (eg, by an elevation of serum alkaline phosphatase).

After infancy, most preterm individuals show an improvement in bone mineralization, so that their bone mass in childhood is in proportion to their body size. Some have suggested that the adverse effects of neonatal dexamethasone therapy on the bone-mass accrual in infancy [119,120] are still present in childhood [121].

Several studies have shown that once adulthood is reached, the bone mineral density (BMD) is no different to that of non-preterm individuals [122–124]. Only one study has found a decreased BMD in young adulthood [125], with the subjects in the study born at a lower gestational age (mean=29.3 weeks) than those included in the other studies. It is possible that BMD cannot be fully restored in the most immature subjects.

Long-term endocrine sequelae

It can be assumed that very preterm infants with enhanced cardiovascular responses and who mobilize their fuels more efficiently are offered short-term benefits. Traits associated with blood pressure regulation and glucose availability that predispose to later hypertension and type 2 diabetes possibly contribute to these benefits.

There is some evidence for a permanent activation of the HPA axis in survivors of very preterm births [126,127]. Whether this is a reflection of selective survival of particular sets of genotypes is hard to prove. Survivors

aged 19 years old who had been treated with glucocorticoids as neonates were found to have altered allele frequencies of glucocorticoid receptor (GR) polymorphisms [128], which suggests that genotype selection by life-threatening conditions is possible.

An alternative explanation for the enhanced stress responsiveness is an environmentally-driven hypermethylation at the GR gene promoter in the brain, leading to decreased central feedback suppression. This has been demonstrated in the offspring of low-grooming rat mothers [129] and in humans who were abused as children and later committed suicide [130]. Whether this also occurs in the preterm newborn is unknown.

There is no compelling evidence for long-lasting metabolic side effects in subjects born to mothers who had been treated with a single treatment course of betamethasone [131–134]. The long-term effects of multiple courses of antenatal glucocorticoids remain to be explored.

From epidemiological data, it has been speculated that accelerated fat mass accretion in infancy and childhood, which is commonly observed after a period with suboptimal neonatal nutrition and EUGR, produces alterations in metabolic set points predisposing to insulin resistance and raised blood pressure [44,135,136]. The impact of recent improvements in early feeding upon adult metabolic health outcomes has yet to be determined.

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