BIOLOGICAL REVIEWS
Cambridge Philosophical Society
Biol. Rev. (2011), pp. 000–000.
doi: 10.1111/j.1469-185X.2011.00195.x

The health implications of birth by Caesarean section

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ABSTRACT

Since the first mention of fetal programming of adult health and disease, a plethora of programming events in early life has been suggested. These have included intrauterine and postnatal events, but limited attention has been given to the potential contribution of the birth process to normal physiology and long-term health. Over the last 30 years a growing number of studies have demonstrated that babies born at term by vaginal delivery (VD) have significantly different physiology at birth to those born by Caesarean section (CS), particularly when there has been no exposure to labour, i.e. pre-labour CS (PLCS). This literature is reviewed here and the processes involved in VD that might programme post-natal development are discussed. Some of the effects of CS are short term, but longer term problems are also apparent. We suggest that VD initiates important physiological trajectories and the absence of this stimulus in CS has implications for adult health. There are a number of factors that might plausibly contribute to this programming, one of which is the hormonal surge or "stress response" of VD. Given the increasing incidence of elective PLCS, an understanding of the effects of VD on normal development is crucial.

Key words: early life programming, vaginal delivery, Caesarean section, stress response, catecholamines, birth, labour, neonate, microflora, allergy.

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I. INTRODUCTION

The hypothesis that the intrauterine environment impacts upon health in later life (Barker, 1998) has gained wide acceptance and significant support from epidemiology and experimentation. There are numerous reports linking intrauterine conditions to compromised adult health, including hypertension (Alexander, 2006), cardiac disease (Meyer & Lubo, 2007), obesity (Wild & Byrne, 2004) and the metabolic syndrome (McMillen & Robinson, 2005). The process by which the intrauterine environment modifies the phenotype of the neonate, altering disease susceptibility, has been termed 'programming'. The trimester of pregnancy in which the programming event occurs appears key to the long-term outcomes for the offspring. It seems likely that this dependence on timing is a consequence of differences in the temporal trajectories of organogenesis. One example of this mechanism is the development of the endocrine pancreas in rats, as reviewed by (Fowden & Hill, 2001).

One time point, the process of birth itself, has received little attention as a possible programming point. During the last 30 years a number of studies have shown that babies born at term by pre-labour Caesarian section (PLCS) have altered postnatal responses and physiology immediately after birth when compared to those born by vaginal delivery (VD) and that these responses are associated with long-term effects. An example of such a response is the association of cord cortisol concentration at birth and the stress response to immunisation at two months of age, that led the authors to hypothesise that mode of delivery may have long-term programming effects (Miller *et al.*, 2005). Evidence has also been accumulating that differences in physiology between PLCS and VD infants persist and may lead to disease in later life. Two large meta-analyses published recently have associated CS with increased susceptibility to type-I diabetes and asthma (Cardwell *et al.*, 2008; Thavagnanam *et al.*, 2008).

In this review we identify some of the changes that are required at birth to allow the infant to adapt to the postnatal environment, then describe the short- and medium-term medical consequences for babies born at term by CS and the systems involved in these adaptations. We briefly describe the processes thought to contribute to these adaptations at birth, and the contribution of VD and the process of labour to normal development. The rate of CS delivery is potentially highest for preterm deliveries in some countries [over 50% in babies born at less than 32 weeks gestational age in the USA (Malloy, 2008)]. However, as preterm birth introduces a large number of confounding influences upon long-term health, we have confined this review to studies comparing mode of delivery at term, and where no significant difference in the gestational age at birth between CS and VD groups is reported. Finally we discuss the components of these responses that are plausible determinants of increased disease susceptibility in individuals born at term by CS and PLCS.

II. ADAPTATIONS TO POSTNATAL LIFE

In utero, the fetus is provided with nutrients and oxygen *via* the placenta and the umbilical cord, maintained at a constant temperature and protected from the majority of pathogens. Following birth the surrounding temperature falls dramatically, pulmonary oxygen uptake is required instantly, food supply becomes irregular, waste products must be eliminated, exposure to pathogens increases and the surrounding environment is no longer constant. As a consequence the baby must be able to regulate thermal and respiratory homeostasis, respond to orexigenic signals (appetite stimulating) and regulate blood glucose within narrow limits. To combat the increased exposure to pathogens and entry of pathogens through the gastrointestinal and respiratory tracts, adaptations are necessary by the infant immune system. Finally the baby must be able to respond to environmental fluctuations, although in humans the extent of this requirement is reduced compared to other precocial mammalian species. These adaptations [reviewed extensively elsewhere (Leone & Finer, 2006; Ward Platt & Deshpande, 2005)] require modifications to the respiratory, metabolic, immune and central nervous systems. In each case, analysis of offspring born by CS indicates that the process of labour is crucial to the initiation of adaptation and that failure to adapt appropriately increases the risk of compromised health in the immediate newborn period.

III. SHORT-TERM PHYSIOLOGICAL CHANGES IN RESPONSE TO CAESAREAN SECTION

The short-term physiological differences between CS and VD babies include impaired lung function, reduced

thermogenic response, and alterations to metabolism, feeding, immune phenotype and blood pressure.

(1) Impaired lung function

Lung function is significantly compromised in infants born by CS compared to VD with significant differences in tidal volume and minute ventilation up to 2 h post-partum (Faxelius *et al.*, 1983). Mean thoracic gas volume 6 h after birth is reduced in PLCS compared to VD babies (Lee *et al.*, 1999; Milner, Saunders & Hopkin, 1978).

In a retrospective review of almost 30,000 births between 1992 and 1999 in Illinois, USA, including 4301 CS deliveries, there was an almost fivefold increase in the incidence of persistent pulmonary hypertension and a threefold increase in the risk of transient tachypnoea (Levine *et al.*, 2001). Similar data are found in studies of babies requiring extracorporeal membrane oxygenation for respiratory distress or persistent pulmonary hypertension; consistently babies born by CS are over-represented in these groups (Keszler *et al.*, 1992).

This widely reported impairment of lung function is consequent upon delayed clearance of lung liquid (Lee *et al.*, 1999; Milner *et al.*, 1978), pulmonary hypertension (Keszler *et al.*, 1992; Levine *et al.*, 2001), and surfactant insufficiency. The association between increased respiratory morbidity and PLCS remains even after allowing for complications of pregnancy (e.g. type-II diabetes, hypertension, intrauterine growth restriction) and maternal life style factors (e.g. alcohol consumption, smoking, maternal body mass index) (Hansen *et al.*, 2008).

Studies in sheep demonstrated that a catecholamine surge at delivery inhibits the secretion of, and drives absorption of, lung fluid (Brown *et al.*, 1983; Walters & Olver, 1978). This mechanism appears to be mediated by increased sodium ion uptake by the lung epithelium, driving liquid from the lumen into the interstitium where it is absorbed into the circulation (Bland *et al.*, 1982). The mechanism also appears to be driven by dibutyryl-cAMP (Walters, Ramsden & Olver, 1990), cortisol and aldosterone (Kindler, Chuang & Perks, 1993). The absorption of lung fluid in response to both adrenaline and dibutyryl-cAMP can be attenuated by thyroidectomy (Barker *et al.*, 1988) implying an important role for thyroid hormones.

(2) Reduced thermogenic response

Significantly lower axillary and skin temperatures 90 min after birth have been reported in babies delivered by CS, compared to VD babies, indicative of an impairment of the thermogenic response (Christensson *et al.*, 1993). Lower rectal temperatures have also been reported in calves born experimentally by CS prior to labour compared to CS performed during labour (Uystepruyst *et al.*, 2002). Consistent with this suggestion, PLCS delivery reduces the capacity for non-shivering thermogenesis in animal models (Clarke *et al.*, 1997; Symonds & Clarke, 1996) partially due to reduced levels of uncoupling protein-1 (UCP1) in the brown adipose tissue and altered plasma thyroid hormone concentrations (Symonds & Clarke, 1996). Such a reduction in plasma thyroid hormones may also be associated with reduced plasma cortisol levels, an additional regulator of UCP1 expression and activity (Mostyn *et al.*, 2003).

(3) Altered metabolism

Several studies in humans and animals have noted differences in plasma glucose levels following birth by PLCS compared with VD. A number of studies have shown hypoglycaemia in babies born by CS (Dobric *et al.*, 1998; Hagnevik *et al.*, 1984) or have identified CS as a significant risk factor for hypoglycaemia in the neonate (Zanardo *et al.*, 1999). In piglets (Hyde *et al.*, 2010) and rats similar changes have been found (Sodoyez-Goffaux, Sodoyez & De Vos, 1979). However, some human studies describe no effect of birth method on plasma glucose levels (Bird *et al.*, 1996; Diwakar & Sasidhar, 2002), the reason for this discrepancy is unclear, although *post-partum* plasma glucose concentrations are known to be very sensitive to different nutritional intakes and handling/storage methods (Ward Platt & Deshpande, 2005).

Similarly, concentrations of plasma glycerol and non-esterified fatty acids (NEFA) are reduced in PLCS compared to VD neonates, probably due to lower rates of lipolysis (Bahnsen *et al.*, 1984; Bird *et al.*, 1996; Comline & Silver, 1972; Hagnevik *et al.*, 1984). Possible mechanisms for this reduction in levels of plasma metabolites include reduced adrenergic stimulation (Jones & Ritchie, 1978), and lower plasma prolactin (Lorenzo, Roncero & Benito, 1986; McNabb, 2003) and thyroid-stimulating hormone (TSH) concentrations (Miyamoto *et al.*, 1991). These effects have been reported in CS-delivered infants and are associated with reduced lipolysis in the neonate (Marchini *et al.*, 1995; Pearce *et al.*, 2005).

(4) Altered feeding

Initiation of breastfeeding is reduced in mothers who deliver by CS, although once breastfeeding has started, mode of delivery is generally not a factor influencing duration (Kearney, Cronenwett & Reinhardt, 1990; Tamminen *et al.*, 1983). We have confirmed this in a meta-analysis which demonstrated a pooled unadjusted odds ratio (OR) for breastfeeding initiation comparing all CS with all VD babies was 0.66 (95% CI = 0.58, 0.75; $P < 0.001$; 20 studies; CS $N = 67177$, VD $N = 222812$) (Prior *et al.*, 2010). The failure of CS-delivered babies to initiate suckling as quickly as VD babies results in reduced breast milk intake in the immediate *post-partum* period, delaying *post-partum* body mass gain (Vestermark *et al.*, 1991). Babies born by CS (both elective and emergency) have significantly ($P< 0.05$) lower milk intake on days 2 to 5 *post partum* compared to VD babies, and consequently, by day 6 only 20% of CS babies had regained their birth mass compared to 40% of the VD neonates (Evans *et al.*, 2003). Failure to gain mass may also be due to reduced insulin-like growth factor 1 (IGF-1) levels in breast milk following CS compared to VD (Pawlus *et al.*,

2004) and to reduced IGF-1 production by the neonate (Kearney *et al.*, 1990; Tamminen *et al.*, 1983).

An altered pattern of breastfeeding following CS in comparison to VD may also be due to differences in maternal hormones (Nissen *et al.*, 1996; Zanardo *et al.*, 2001). In particular, decreased oxytocin secretion in CS mothers during breastfeeding may not only reduce milk ejection, but also interfere with mother–infant bonding (Nissen *et al.*, 1996). Furthermore, maternal circulating dopamine concentration is increased following CS (Jones & Greiss, 1982). Dopamine is an inhibitor of prolactin secretion, and may thereby limit lactogenesis (Ben-Jonathan & Hnasko, 2001).

In a rat model, pups exposed to simulated VD (by applying pressure to one uterine horn, similar to the pressure experienced during labour) before delivery by CS, were significantly ($P < 0.01$) more likely to be suckling 2 h *post partum* than pups from the same litter delivered without simulated VD (from the other uterine horn, without application of pressure). This suggests a role for the mechanical stimulus of VD in the initiation of suckling (Abel, Ronca & Alberts, 1998), or possibly a catecholamine response to mechanical stimulation. The anorexigenic hormone leptin may also be an important stimulus initiating suckling in neonates. A *post-partum* reduction in circulating leptin levels, stimulating appetite and increasing the drive to suckle, has been observed in ovine studies; notably this decline is delayed in PLCS offspring (Bispham *et al.*, 2002).

(5) Altered immune phenotype

Babies born by PLCS have a significantly reduced cord blood leucocyte count (Nikischin, Peter & Oldigs, 1997). This reduction is not limited to any specific immune cell type and includes reduced neutrophil, monocyte, and natural killer (NK) cell populations (Gronlund *et al.*, 1999b; Thilaganathan, Meher-Homji & Nicolaides, 1994). Additionally the activity of these immune cells differs following PLCS. For example, the apoptotic response to Fas ligand antibody stimulation, interleukin-8 (IL-8)-induced neutrophil chemotaxis and the expression of complement receptor-3 (CD11b) are lower following PLCS (Gessler & Dahinden, 2003; Yektaei-Karin *et al.*, 2007). The effects of mode of delivery on NK cell activity and on phagocytotic activity are less clear. Additional to changes in immune cell populations following CS in comparison to VD, is the change in the concentration of a number of cytokines. For example, the circulating concentrations of soluble IL-2 receptor (sIL-4r), IL-1β, IL-6 and tumour necrosis factor α (TNF-α), are significantly reduced in PLCS compared to VD infants (Malamitsi-Puchner *et al.*, 2005) (Zanardo, Solda & Trevisanuto, 2006). There is a twofold decrease in interferon-γ (INF-γ) gene expression seven days after birth in the liver of PLCS piglets compared to VD animals (Hyde *et al.*, 2010) with a similar trend persisting for up to 14 days after birth (Daniel *et al.*, 2008). Furthermore, the livers of PLCS piglets have reduced expression of a number of genes related to the innate immune system and the INF-γ response (e.g. NKp80, C-reactive protein, inflammatory response 6) seven days *post partum* compared to their VD counterparts (Hyde *et al.*, 2010).

(6) Altered blood pressure

At least four studies have demonstrated significantly reduced systolic and diastolic blood pressure in CS compared to VD infants up to three days of age (Gemelli *et al.*, 1992; Holland & Young, 1956; O'Sullivan, Kearney & Crowley, 1996; Sedaghat *et al.*, 2008). In one study, these differences were noticeable up to three months *post partum* (although not significant beyond three weeks) (Holland & Young, 1956). However in another study no difference was found in blood pressure on the basis of mode of delivery (Uhari, 1980). In a further study, though blood pressure at birth was the same, during the first 24 h *post partum* the blood pressure of the VD infants increased to a greater extent than that of the CS infants, producing a significant difference in blood pressure at 24 h *post partum* (Gemelli *et al.*, 1992). This finding may be attributable to differences in the renin-angiotensin-aldosterone system (Broughton Pipkin *et al.*, 1974; Fujimura *et al.*, 1990; Oliveira Filho & Procianoy, 1995).

Additionally, there are two reports of a reduced haematocrit in CS compared to VD infants during the first 24 h of life (Gemelli *et al.*, 1992; Martin & Norman, 1997). Possible explanations are a reduced placental transfusion following CS, or delayed loss of extracellular fluid (Martin & Norman, 1997).

IV. LONGER TERM EFFECTS OF DELIVERY BY CAESAREAN SECTION

More recently, it has become apparent that mode of delivery may have long-term effects on health, mediated by changes in the immune system, metabolism and the central nervous system. These longer term consequences may well arise from the alterations in metabolism and in the immune system that underpin short-term effects.

(1) Immune-related conditions

A significant number of studies indicate a marked increase in the susceptibility of children who were born by PLCS to a range of immune-related conditions. One relatively early manifestation of this outcome is a significant increase in the number of cells secreting immunoglobulins A and G (IgA and IgG), one year *post partum* (Huurre *et al.*, 2008). Further, a retrospective study of data from the Swedish medical service registers found that CS led to increased risk of hospitalisation after one year of age due to asthma (OR = 1.31; 95% CI = 1.23–1.40) and gastroenteritis (OR = 1.31; 95% CI = 1.24–1.38) (Hakansson & Kallen, 2003). Similarly, a retrospective study of 9,000 American children showed a significant increase in the risk of developing atopic rhinitis following CS delivery (OR = 1.37; 95% CI = 1.14–1.63)

(Renz-Polster *et al.*, 2005). A prospective cohort study of nearly two million Norwegians showed an increased hazard ratio for asthma in children born by CS compared to VD (adjusted hazard ratio = 1.52; 95% CI = 1.42–1.62) (Tollånes *et al.*, 2008). A meta-analysis of 23 studies showed a 20% increase in the risk of developing childhood asthma following CS *versus* VD (OR = 1.22; 95% CI = 1.14–1.29) (Thavagnanam *et al.*, 2008). A further large cohort study published after this meta-analysis from the Oxford Record Linkage study also found an increased incidence of asthma following CS *versus* VD birth (Davidson *et al.*, 2010). While it is conceivable that the increased risk of immune-related conditions following CS birth may be linked to the differences seen in immune components of the blood immediately after delivery, it is possible that the differences seen in lung function at birth between CS and VD neonates may also impact on development of later respiratory complications.

The effect of delivery by CS in other allergic disorders is less clear. A study of 865 one-year-old German children showed that infants born by CS ($N = 147$) had an increased risk of food allergy (adjusted OR = 2.06; 95% CI = 1.123–3.80) (Laubereau *et al.*, 2004). A separate study confirmed this effect of CS if the mother had a history of atopy (OR = 7.0; 95% CI = 1.8–28.0; $P = 0.001$) but not if there was no maternal history of atopy (OR = 1.9; 95% CI = 0.6–6.0) (Eggesbø *et al.*, 2003). A similar association of parental history with increased asthma in babies delivered by CS was shown by (Roduit *et al.*, 2009). This pattern is repeated for cow's milk intolerance in children born by CS (Eggesbo *et al.*, 2005). Together these data suggest that there is an additive effect of delivery by CS on genetically determined immune sensitivity.

A potential mechanism for the effect on the immune system is altered bacterial colonisation. Children with either atopic dermatitis or a positive skin prick test have decreased colonization of the intestinal tract with bifidobacteria ($P < 0.05$) and *Bacteroides* spp. ($P < 0.05$) and increased levels of clostridia ($P < 0.05$) (Bjorksten *et al.*, 2001). A similar pattern of colonization has been found in children born by CS when compared to VD infants (Bennet & Nord, 1987; Gronlund *et al.*, 1999a; Neut *et al.*, 1987).

In addition to allergy, CS delivery is implicated in the development of type-I diabetes, another immune-related disease. Meta-analysis indicates a 20% increase in the risk of developing type-I diabetes in childhood when delivered by CS compared to VD, even when controlling for gestational age, birth mass, maternal age, birth order, breastfeeding and maternal diabetes (adjusted OR = 1.19; 95% CI = 1.04–1.36; $P = 0.01$) (Cardwell *et al.*, 2008).

(2) Body mass

A recent, large population study, of children aged 7, found no difference in body mass between offspring born by CS or VD (Ajslev *et al.*, 2011). However, it is conceivable that differences in body mass may not be observable until after puberty, when most metabolic disturbances become apparent or until a sufficient time has elapsed for relatively small differences in appetite regulation or metabolic control to lead to a significant increase in body mass. In agreement with this, an increased risk of being overweight associated with CS has been reported in two studies of young adults. An epidemiological study of 179,414 adolescents in Utah, USA between 1998 and 2007 evaluated body mass and mode of delivery at the time of application for a driver's license at age 15–19 (Utz, 2008). The study sample represented approximately 60% of live births during 1983–1990, of which 19.8% were born by CS. Young adults born by CS were 1.4 times more likely to be overweight than children born by VD (Utz, 2008). A second study, utilising a prospective cohort of 2057 subjects in Brazil, recruited during 1978 and studied at the age of 23–25 years showed an adjusted risk of obesity 58% higher in CS-born adults, than in VD adults [prevalence ratio = 1.58; 95% CI = 1.23–2.02; adjusted for sex, birth mass, income, smoking status, education, physical activity and maternal factors (education and smoking status during pregnancy)] (Goldani *et al.*, 2011). The mechanism leading to this difference is unknown. It is possible that the difference arises from altered appetite regulation, as concentration of ghrelin, an appetite-controlling orexigenic peptide, is reduced in babies born by CS (Bellone *et al.*, 2003). We have noted reduced hepatic mRNA expression for two other orexigenic peptides, galanin-like peptide and angiopoietin-like 4 in PLCS piglets, seven days *post partum* (Hyde *et al.*, 2010). These data implicate VD in initiating *post partum* appetite regulation. Additionally, in piglets, plasma gastrin levels and increased gastric pH have also been shown to depend on mode of delivery (Sangild *et al.*, 1995), possibly suggesting a role for delivery in the generation of the appropriate environment for digestion.

(3) Hepatic consequences

Hepatic metabolism is a significant contributor to glucose regulation in adult life (Nordlie, Foster & Lange, 1999). Indeed increased hepatic lipid concentration (non-alcoholic fatty liver disease) contributes to the metabolic syndrome (Rafiq & Younossi, 2008). Alterations in hepatic metabolism may well therefore contribute to obesity. We have recently reported approximately twofold higher intra-hepatic lipid levels seven days after birth in piglets born by PLCS, irrespective of feeding regimen (in parentally fed animals PLCS resulted in lipid levels compatible with non-alcoholic fatty liver disease) (Hyde *et al.*, 2010). The effect of mode of delivery was not restricted to a single genotype of piglets as it was observed in both commercial and Meishan breeds (M. J. Hyde, P. Kemp and L. Clarke). The cause of the higher liver lipid concentration appeared to be failure of PLCS animals to activate gluconeogenesis from glycerol, (PLCS animals had higher hepatic glycerol and reduced glycerolphosphate dehydrogenase levels), rather than altered *de novo* synthesis of lipid. PLCS piglets also had a lower plasma glucose concentration at birth. In PLCS animals that were fed enterally, plasma glucose levels remained lower seven days *post partum* (Hyde *et al.*, 2010).

(4) Neurological and stress-related problems

CS delivery is associated with altered biochemical and behavioural responses to stress in humans and animal models. In the first two days after delivery PLCS infants are less excitable and show a reduction in the number of optimal responses to neurological tests (Otamiri *et al.*, 1991). At the time of immunisation at eight weeks of age, salivary cortisol concentration was significantly ($P = 0.001$) reduced in PLCS *versus* VD infants (Miller *et al.*, 2005), and the length of time the baby cried was significantly less (Taylor, Fisk & Glover, 2000). These data indicate persistence of the effects of mode of delivery.

Animal studies demonstrate an association between PLCS and dopamine metabolism in the brain. In two-month *post-partum* rats PLCS is associated with altered spatial dopamine concentrations (El-Khodor & Boksa, 1997): a 53% decrease in the prefrontal cortex ($P = 0.008$) and a 40% increase in the nucleus accumbens ($P = 0.011$) and striatum ($P = 0.003$) (El-Khodor & Boksa, 1997). When PLCS was accompanied by 15 min of anoxia the differences in dopamine concentration between PLCS and VD rats were totally ameliorated (El-Khodor & Boksa, 1997). The authors concluded that these results may be due to circulating concentrations of adrenaline, which were high in the VD and PLCS accompanied by anoxia groups, but low in the PLCS-alone group. These limited data indicate that transient hypoxaemia associated with compression of the umbilical cord during passage through the vaginal canal is a stimulus that may be of importance in neurological development.

V. HOW MIGHT PLCS ACCOUNT FOR THESE PHYSIOLOGICAL DIFFERENCES?

Given that some of the longer term changes associated with CS in contrast to VD are associated with the short-term responses, it is reasonable to consider if they might be driven by the same mechanisms. The process of VD is associated with several distinct stimuli and responses that are absent during PLCS. In order to understand the mechanisms potentially programming the differences in long-term physiology, it is necessary to discuss briefly the stimuli and physiological responses associated with the birth process.

(1) Hormonal responses at delivery

VD elicits a stress response in mother and baby, and plasma catecholamine and cortisol levels are markedly increased in the neonate (Table 1). Catecholamine concentrations in the VD newborn are higher than in many adults with myocardial infarction or pheochromocytoma (Lagercrantz, 1996). During labour, contraction reduces the volume of the uterus forcing the baby through the vaginal canal, and compressing the infant and umbilical cord in the process. Increased cranial pressure and transient hypoxaemia are also likely to contribute to the changes in stress hormones (Smolich & Esler, 1999).

(a) *Catecholamines*

A number of authors describe up to fourfold lower plasma adrenaline and sixfold lower noradrenaline levels in neonates following PLCS compared to VD (Agata *et al.*, 1995; Falconer & Lake, 1982; Faxelius, Lagercrantz & Yao, 1984; Hagnevik *et al.*, 1984; Irestedt *et al.*, 1989; Jones & Greiss, 1982; Otamiri *et al.*, 1991; Zanardo *et al.*, 2006) (see Table 1). The elevated levels of plasma catecholamines in the fetus during labour are known to be of fetal origin, as this effect is not found in adrenalectomised fetuses (Padbury *et al.*, 1987). Furthermore, maternal analgesia during labour (that reduces levels of maternal catecholamines; (Shnider *et al.*, 1983), does not diminish the plasma catecholamine concentrations of the fetus, supporting the conclusion that the stress responses of the fetus and mother are independent (Bistoletti *et al.*, 1983).

The rise in fetal plasma catecholamines is in response to compression and occlusion of the umbilical cord during passage through the vaginal canal. This may only be momentary: a 5 min partial occlusion increases adrenaline concentration in the fetus tenfold (Gu, Jones & Parer, 1985). Furthermore, permanent cessation of umbilical blood flow following cord severance will also increase catecholamine secretion (Padbury *et al.*, 1981).

(b) *Cortisol*

Cortisol concentration increases in the fetal circulation several days prior to onset of labour, probably due to increased output from the maturing adrenal glands. During passage through the vaginal canal there is a further marked rise in cortisol levels indicative of a fetal stress response (Mears *et al.*, 2004). In keeping with the reduced catecholamine response to CS, cortisol is also reduced in babies born by PLCS when compared with VD (Bird *et al.*, 1996; Zanardo *et al.*, 2006), although there is no difference between emergency CS and VD, suggesting that the process of labour increases cortisol concentration. The difference in circulating cortisol levels can persist in rats up to 14 days *post partum* (Boksa, 1997). Given the physiological impacts of cortisol, this rise in concentration is a plausible candidate effector of short- and long-term effects.

(c) *Profile of other hormones*

Adrenaline and cortisol are not the only hormones known to be altered by mode of delivery. There is a transient increase in thyroxine (T_4) and triiodothyronine (T_3) in CS compared with VD babies at birth (Bird *et al.*, 1996; Ramezani Tehrani, Aghaee & Asefzadeh, 2003), that does not persist beyond 24 h *post partum* (Bagnoli *et al.*, 1993, cited in (Bird *et al.*, 1996). Other studies report an increase in cord blood thyroglobin levels (Ericsson, Ivarsson & Persson, 1987). Two studies report an increase in plasma TSH concentration (Bird *et al.*, 1996; Ramezani Tehrani *et al.*, 2003), although one study found the reverse (Miyamoto *et al.*, 1991); the reason for this discrepancy is unclear and further work is required to establish the dynamics of TSH after different

Table 1. Impact of method of birth [elective caesarean section (CS) or vaginal delivery (VD)] on the concentration of plasma catecholamines, hormones and metabolites in the neonate immediately *post partum*. NS, no significant difference

Parameter	Plasma concentration		*P*	Reference
	CS neonates	VD neonates		
Noradrenaline (nmol l^{-1})	9.9	33.5	<0.05	(Otamiri *et al.*, 1991)
	13.9	21.4	NS	(Faxelius *et al.*, 1984)
	5.24	21.88	<0.01	(Falconer & Lake, 1982)
	3.4	14.1	<0.01	(Faxelius *et al.*, 1983)
	5.8	31.0	<0.01	(Hagnevik *et al.*, 1984)
	12.8	22.7	<0.01	(Jones & Greiss, 1982)
	8.8	34.2	<0.01	(Irestedt *et al.*, 1989)
	2.7	5.8	<0.01	(Zanardo *et al.*, 2006)
	30.4	69.93	<0.05	(Agata *et al.*, 1995)
Adrenaline (nmol l^{-1})	3.6	4.7	NS	(Otamiri *et al.*, 1991)
	1.3	4.3	<0.05	(Faxelius *et al.*, 1984)
	0.6	2.6	NS	(Faxelius *et al.*, 1983)
	1.1	4.2	<0.05	(Hagnevik *et al.*, 1984)
	1.3	4.2	<0.01	(Irestedt *et al.*, 1989)
	4.2	10.8	<0.01	(Jones & Greiss, 1982)
	3.2	6.5	<0.05	(Agata *et al.*, 1995)
Cortisol (nmol l^{-1})	196	663	<0.01	(Faxelius *et al.*, 1983)
	271	512	<0.05	(Bird *et al.*, 1996)
	435	629	<0.05	(Dobric *et al.*, 1998)
	125	393	<0.001	(Zanardo *et al.*, 2006)
Prolactin (nmol l^{-1})	6.09	9.56	<0.01	(Heasman, Spencer & Symonds, 1997)
Thyroid-stimulating hormone (TSH) (IU ml^{-1})	6.5	9.5	<0.005	(Miyamoto *et al.*, 1991)
	12.1	3.3	<0.001	(Ramezani Tehrani *et al.*, 2003)
	7.8	4.9	<0.01	(Bird *et al.*, 1996)
Thyroxine (T_4) (nmol l^{-1})	97	66	<0.05	(Ramezani Tehrani *et al.*, 2003)
	109	92	<0.05	(Bird *et al.*, 1996)
Triiodothyronine (T_3) (nmol l^{-1})	1.39	1.13	<0.05	(Ramezani Tehrani *et al.*, 2003)
	1.11	0.68	<0.01	(Bird *et al.*, 1996)
Interleukin-6 (pg l^{-1})	1.32	7.58	<0.01	(Zanardo *et al.*, 2006)
Glucose (mmol l^{-1})	2.8	4.4	<0.01	(Hagnevik *et al.*, 1984)
	2.5	3.7	NS	(Bird *et al.*, 1996)
	3.2	4.6	<0.001	(Dobric *et al.*, 1998)
Non-esterified fatty acids (NEFA) (mmol l^{-1})	0.10	0.15	<0.05	(Hagnevik *et al.*, 1984)
	0.61	0.72	NS	(Bird *et al.*, 1996)
Glycerol (mmol l^{-1})	0.030	0.054	<0.01	(Hagnevik *et al.*, 1984)

modes of delivery. The plasma concentration of biologically active renin is reduced in CS neonates (Fujimura *et al.*, 1990), possibly as a result of the increase in cord blood pH (Tetlow & Broughton Pipkin, 1983). Consistent with this finding, plasma angiotensin II concentration is reduced ($P = 0.03$) in CS neonates (Broughton Pipkin *et al.*, 1974; Kingdom *et al.*, 1993; Lumbers & Reid, 1977). Cord blood aldosterone concentration is elevated by labour (Oliveira Filho & Procianoy, 1995). As mentioned previously, the *post-partum* decline in leptin levels is delayed after PLCS in an ovine model, resulting in significantly higher neonatal plasma leptin concentration 1 h after birth when compared to VD offspring (Bispham *et al.*, 2002). Conversely, in human studies plasma leptin concentration in umbilical venous and arterial blood from PLCS neonates is reduced compared to VD neonates and maternal leptin concentrations are also lower up to 24 h following CS delivery compared to VD (Nuamah *et al.*, 2004; Yoshimitsu *et al.*, 2000). It is therefore difficult to assess the biological consequences of altered leptin levels in response to PLCS delivery.

(2) Colonisation of the intestinal tract

Bacterial colonisation of the intestinal tract is an important postnatal phenomenon. In animal and human studies differences are found in the intestinal microbiota following CS (Hall *et al.*, 1990). In particular, colonisation of the intestinal tract with bacterial species is delayed in CS infants. This may affect the maturation of innate immunity. Bacterial cell counts per 1 g faeces remain lower in CS infants one month after birth ($P = 0.001$) (Huurre *et al.*, 2008) and the accumulation of *Bifidiobacterium*-like and *Lactobacillus*-like bacteria takes more than one month to reach that found in VD infants at birth (Gronlund *et al.*, 1999a). Similarly, reduced populations of *Bacteroides* spp. (Bennet & Nord, 1987; Neut *et al.*, 1987), and increased *C. difficile* colonisation (Penders *et al.*, 2006), have been shown in the

faeces of one-month-old CS babies compared to VD babies. Following antibiotic treatment during the perinatal period, the microflora was slower to regenerate in the CS compared with VD subjects with alterations in profile between the two groups (Bennet & Nord, 1987).

It is not known exactly how the microflora is altered by mode of delivery. It is widely believed that this is attributable to contact with maternal perineal bacterial flora during VD (Bezirtzoglou, 1997; Li *et al.*, 2005). However, there is now evidence that bacterial colonisation of the infant may begin *in utero*. Firstly it has been possible to isolate *Lactobacillus* species from umbilical blood samples (Jimenez *et al.*, 2005) and meconium (Jiménez *et al.*, 2008) of infants born by CS. Furthermore there may also be some transfer of bacteria from the maternal gut to the fetus as it is possible to isolate genetically modified bacteria from the amniotic fluid of pregnant mice orally inoculated with such an identifiable bacterium (Jimenez *et al.*, 2005). Finally, comparison of the bacterial composition of the baby's stool with that of the mother's vagina and milk demonstrated that five days *post partum* only 23% of babies showed the presence of bacterial species isolated from the perineum at delivery and less than 2% still had these bacterial species in their stools at one month of age (Matsumiya *et al.*, 2002). Consequently it may appear that the process of VD plays a smaller role in the colonisation of the newborn microflora than previously thought.

One alternative possibility is that the major source of microflora species acquired after birth is breast milk (Balmer & Wharton, 1989; Martín *et al.*, 2007), particularly as VD-born babies are breastfed earlier and are more likely to be breastfed than their CS-born counterparts (Leung, Lam & Ho, 2002; Prior *et al.*, 2010; Rowe-Murray & Fisher, 2002). Additionally, the maternal hormonal milieu during and following labour and VD (Nissen *et al.*, 1996) may also alter breast milk composition, in turn impacting upon bacterial species; indeed differences in milk hormone content have been reported between mothers giving birth by CS compared with VD (Pawlus *et al.*, 2004). It is also conceivable that differences in the immune system of babies born by CS and VD (see Section III.5) allow different patterns of colonisation, with altered immune responses immediately after CS birth predisposing to colonisation by different bacterial species. Alterations in metabolism in the CS baby (see Section III.3) may also mediate differences in the gastrointestinal environment.

VI. HOW DO THE PHYSIOLOGICAL CHANGES AROUND BIRTH PROGRAMME HEALTH?

The detailed mechanisms by which catecholamines, cortisol and mechanical factors contribute to the immediate adaptation of the newborn to postnatal life have been extensively reviewed (Aynsley-Green, 1985; Bassett, 1989; Bland, 2001; Duee *et al.*, 1996; Fowden, Apatu & Silver, 1995; Sangild, Fowden & Trahair, 2000). However, these reviews have not addressed longer term effects. Below we summarise aspects that appear relevant to altered adaptation that occurs in PLCS infants and are likely to contribute to the increased susceptibility to disease in later life. We confine our discussion to effects on metabolism, the immune system and the central nervous system.

(1) Adaptation to intermittent feeding

In utero the fetus receives a constant supply of nutrients and in late gestation accumulates energy stores. Following cessation of blood flow between mother and baby, the supply of nutrients to the baby stops but the requirement for energy by the neonate remains resulting very quickly in hypoglycaemia. This is corrected by: (*i*) a shift from predominant anabolism to catabolism releasing the energy stored in late gestation, including glucose from hepatic glycogen and NEFA from lipid stored in the adipose depots and the liver; (*ii*) the intake of enteral nutrition, generally in the form of milk.

Post partum, glucose metabolism changes rapidly to meet the needs of the baby. Plasma glucose concentration drops after birth, reaching a nadir about 1 h *post partum* (Hoseth *et al.*, 2000; Srinivasan *et al.*, 1986). The rise in plasma glucagon levels (Sperling *et al.*, 1974) at delivery drives glycogenolysis providing glucose for up to 10 h *post partum* (Shelley, 1961). When glycogen stores are depleted the neonate becomes dependent on endogenous glucose production or alternative substrates such as ketones, as glucose supplied by milk intake falls short of requirements to maintain euglycaemia and energy balance. Glucose production starts within 2 h of birth and has been estimated at 4–5 mg kg^{-1} min^{-1} (Kalhan *et al.*, 1980), 2–3 times more, per unit body mass, than in older children (Ward Platt & Deshpande, 2005). Gluconeogenesis in the newborn uses both amino acids and glycerol as important substrates with both pathways significantly up-regulated following birth. The increase in amino acid usage is mediated primarily by increased expression and activity of phosphoenolpyruvate carboxykinase (PEPCK) (Duee *et al.*, 1996; El Manoubi *et al.*, 1983; Mitanchez, 2007). Expression of gluconeogenic enzymes increases (e.g. glucose-6-phosphatase and fructose-1,6-bisphosphatase; (Mersmann, 1971). PEPCK expression increases over 1000-fold in the rat (Lyonnet *et al.*, 1988) and fourfold in piglets (Grun *et al.*, 1982) during the first day of postnatal life. Gluconeogenesis from glycerol, both from lipolysis of adipose stores and milk, is increased by a 10-fold rise in glycerol kinase and glycerol-3-phosphate dehydrogenase activity in the rat (Vernon & Walker, 1970).

To maintain gluconeogenesis in the neonate, the onset of lipid oxidation is essential in order to provide adenosine triphosphate (ATP) and reducing equivalents (Mitanchez, 2007). In particular, a high rate of β-oxidation is a prerequisite for the elevated ratio of reduced/non-reduced nicotinamide adenine dinucleotide NADH/NAD ratio essential for shifting the glyceraldehyde 3-phosphate dehydrogenase reaction in the direction of glucose synthesis (Bohme, Sparmann & Hofmann, 1983). Birth also marks a shift from a low-fat diet *pre partum* to a high-fat diet *post partum* (in human milk lipid supplies 40–60% of the calories;

(Hamosh, 1987; Jensen, 1999). This fat, together with initial mobilisation of lipid from adipose tissue *post partum*, driven by high plasma catecholamine concentrations following VD and a favourable insulin/glucagon ratio (Bahnsen *et al.*, 1984; Herrera & Amusquivar, 2000; Kimura & Warshaw, 1983), results in high concentrations of circulating NEFA and triacylglycerol (TAG) in the neonate (Van Aerde *et al.*, 2003). In response to increased circulating NEFA concentrations, the VD neonate commences β-oxidation and ketogenesis within the liver and peripheral tissues e.g. the heart (Duee *et al.*, 1994). The increased lipid catabolism is probably due to increased carnitine palmitoyltransferase (CPT1) expression, mediated by enteral feeding (Gu & Li, 2003) and increased concentrations of circulating glucagon and T_3 (Louet *et al.*, 2001). Furthermore, increased levels of circulating long-chain fatty acids, possibly from the first enteral feed, also increase gene expression associated with fatty acid oxidation (Pegorier, 1998; Pegorier *et al.*, 1998). Additionally glucagon and cyclic adenosine monophosphate (cAMP) mediate a decrease in the half maximal inhibitory concentration (IC_{50}) of carnitine palmitoyltransferase for malonyl-CoA, also inducing β-oxidation *post partum* (Girard *et al.*, 1992; Prip-Buus *et al.*, 1990).

While changes in metabolism at birth are mediated to a large extent by the first intake of enteral nutrition, they are also driven by increased circulating glucagon and T_3 levels at delivery in the neonate. Given that there appears to be no difference of mode of delivery on plasma glucagon levels in humans (Johnston & Bloom, 1973), although we have reported reduced plasma glucagon concentration in PLCS compared with VD piglets at birth (Hyde *et al.*, 2010), it seems unlikely that either of these hormones, or the onset of enteral feeding is responsible for the differences seen in metabolism between CS and VD neonates (see Section III.3). Treatment of mothers prior to PLCS with terbutaline increases cord blood glucose level to concentrations similar to those in VD babies suggesting that reduced exposure to adrenaline contributes to the relative hypoglycaemia in PLCS babies (Eisler, Hjertberg & Lagercrantz, 1999).

Changes in hepatic metabolism are likely to reflect alterations in hepatocyte differentiation. Cortisol is known to be important in the maturation of hepatocytes, in particular in the expression of genes associated with gluconeogeneisis (Fowden *et al.*, 1995). It is also worth noting that cAMP is an important regulator of hepatocyte differentiation in combination with glucocorticoids. For example, both the cAMP and glucocorticoid response elements of the tyrosine aminotransferase (TAT) promoter are activated *in vivo* in the perinatal period in transgenic mice (Boshart *et al.*, 1990; Ruppert *et al.*, 1990). Furthermore, a tissue-specific extinguisher (TSE1) that suppresses TAT expression in other cell types was identified as the RIα subunit of cAMP-dependent protein kinase (Boshart *et al.*, 1991). We found that the expression of a number of markers of hepatic stem cells persisted in the liver of CS-delivered piglets seven days after birth (Hyde *et al.*, 2010). However, the contribution of cAMP or TSE1 to the expression of these markers remains to be established.

(2) Adaptation to increased exposure to pathogens

Additional to microbial exposure at birth, fetal catecholamines released during VD appear to play a major role in modulating the neonate's immune response and CS delivery is associated with a different cytokine pattern compared to VD. Parturition itself is associated with a marked increase in levels of inflammatory markers and leucocytes in the myometrium (Norman *et al.*, 2007), and although leucocyte populations in the fetal membranes are not increased, there is a marked acute inflammatory gene expression signature (Haddad *et al.*, 2006).

Although there is inconsistency in available data, differences have been noted in concentrations of IL-6, IL-2, IL-13, INF-γ and TNF-α in the first week of life between CS and VD infants (Bessler *et al.*, 1998; Ly *et al.*, 2006; Malamitsi-Puchner *et al.*, 2005; Zanardo *et al.*, 2006). The increase in sIL-2R and sIL-4R levels following VD has been hypothesised as regulating the immune response to VD (Malamitsi-Puchner *et al.*, 2005). These changes in concentrations of cytokines in CS compared with VD babies are in keeping with data from both human and animal studies suggesting differences in the production of cytokines by monocytes in response to lipopolysaccharide exposure, dependent on mode of delivery (Brown, Rad & Halonen, 2003; Daniel *et al.*, 2008).

Immune cells have receptors for a number of stress hormones including cortisol and the catacholamines indicating that these hormones are likely to play an important part in the change of immune system function (Padgett & Glaser, 2003). However, the role for stress hormones is not entirely clear. For example, increased stress is associated with a suppression of immune function and cortisol has been implicated in the regression of lymphoid tissue near to birth (Liggins, 1994). Cortisol is known to suppress the production of IL-12 by monocytes an effect that would suppress leucocyte proliferation (Elenkov *et al.*, 2001; Visser *et al.*, 1998). Furthermore in adults cortisol suppresses the expression of INF-γ, a result that contradicts the increase in INF-γ levels that is seen following VD both immediately and over the subsequent 1–2 weeks (Malamitsi-Puchner *et al.*, 2005).

In contrast to this suppression of immune function as described earlier there is a direct association between the magnitude of the stress response and the number and types of leucocytes present in cord blood (Yektaei-Karin *et al.*, 2007). Furthermore both the number of leucocytes and levels of stress hormones are higher in babies born by assisted VD compared to both CS and unassisted VD. Similarly there is a direct relation between the amount of INF-γ in cord blood at birth and the stress response that the baby experiences during the birth process (Miller *et al.*, 1990). The type of anaesthesia used during CS delivery appears to have no role in modulating the immune response in the neonate (Dermitzaki *et al.*, 2009).

There are at least three possible explanations for these differences. Firstly, the increase in levels of stress hormones and immunological markers are not causally related. Secondly, the changes seen in response to birth reflect different stages

of maturity of the system, and thirdly there is a different effect of a large acute stress response and a chronic response on the immune system.

In support of a direct role for the stress hormones in increasing immune activity at birth, increased numbers of NK cells have been found in response to both cortisol and norepinephrine (Li & Diehl, 2003; Sanders & Straub, 2002). In the case of cortisol this increase probably results from augmentation of the activity of IL-21 in stimulating NK cell proliferation (Ly *et al.*, 2006). While the length of time required to increase cell numbers in response to mitogens probably precludes such mitogenic effects increasing leucocyte number in cord blood, increased cell division may well contribute to the persistent increase in the expression of the NK receptor that we observed. Similarly norepinephrine has been shown to increase the number of NK-T cells in the liver of adult leptin-deficient mice (Li *et al.*, 2004). It is of note that the increase in hepatic NK cells in the leptin-deficient mice was associated with a reduction in hepatic lipid levels in common with our study in piglets (Hyde *et al.*, 2010).

(3) Central nervous system

A number of studies imply a role for the stress of birth on the development of the nervous system. For example, in babies, cord blood catecholamine concentration is significantly correlated with muscle tone and excitability (Otamiri *et al.*, 1991). Comparison of adrenocorticotropic hormone receptor mRNA expression two weeks *post partum* also shows a significant difference ($P < 0.016$) in PLCS *versus* VD piglets (Daniel *et al.*, 1999), suggesting that birth may programme the hypothalamic-pituitary-adrenal stress axis function long term. Adult rats born by PLCS show significantly different responses to repeated mild stress compared with VD rats. In particular they showed increased tyrosine hydroxylase activity in the nucleus accumbens and increased dopamine transporter binding in dorsal striatum and accumbens, following repeated brief periods of isolation (Boksa & Zhang, 2008). These differences were ameliorated by administration of adrenaline to the PLCS animals at birth, supporting a role for the catecholamine surge at birth in long-term programming of the central nervous system (Boksa & Zhang, 2008).

Differences in dopamine concentration in the brain of PLCS rats are accompanied by a differential response to amphetamine intake compared to VD rats. Animals born by PLCS showed increased locomotor activity following amphetamine administration compared to VD controls (El-Khodor & Boksa, 1998; Vaillancourt & Boksa, 2000). Differences in dopamine concentrations were associated with lower catecholamine concentrations immediately following birth in the PLCS *versus* VD rat pups (El-Khodor & Boksa, 1997; El-Khodor & Boksa, 1998). Although anaesthetic administration during PLCS alters the *post-natal* neurocognitive responses (Vaillancourt, Berger & Boksa, 1999), the same differences in locomotor activity are found in rats undergoing PLCS without anaesthetic immediately following maternal decapitation (Vaillancourt & Boksa, 1998), suggesting that it is an absence of neonatal stress in PLCS and not anaesthesia which drives the differences.

VII. DOES THE ABSENCE OF STRESS AT BIRTH PROGRAMME LATER DISEASE RISK?

It is clear that the process of normal parturition at term is a significant stimulus to the neonate at a point in time when the respiratory, metabolic and immunological systems in the infant need to change markedly to adapt to the outside world. The stimulus of vaginal birth is also extremely strong, resulting in levels of adrenaline in the neonate that exceed those found in response to myocardial infarction and phaeochromocytoma in adults (Lagercrantz, 1996). The hormones that are increased in response to parturition are known to drive the differentiation of numerous cell types and commence multiple physiological processes. It therefore seems likely that this surge in maternal biochemical responses triggers the differentiation of cells necessary for the adaptation of biological systems to the postnatal environment. There is perhaps a significant requirement in setting the hormonal threshold for these differentiation processes at such high concentrations, so as to prevent premature differentiation of the cells *in utero*, whether in response to maternal stress from starvation and predation, or fetal distress.

We therefore hypothesise that the stress response to birth is a key mechanism that modifies the differentiation of a number of cell types, preparing the baby not only for the challenges of extra-uterine life but also long-term health and well-being. In the absence of the hormonal milieu created by the process of labour and/or the mechanical process of VD, the maturation of these cells is altered leading to an increased susceptibility to a number of diseases in later life including asthma, type-I diabetes and perhaps an increased propensity to adiposity and to fatty liver disease.

Studies comparing outcomes on the basis of mode of delivery, and the mechanisms which may underlie differences in outcomes, involve several potential confounders. These include a lower mean gestational age at birth in CS deliveries (whether the data are from human or animal studies), reduced breastfeeding following CS, and other factors relating to maternal and fetal health which drive elective pre-labour, and more commonly, emergency in-labour, CS deliveries. All of these factors are difficult to exclude in observational studies of mode of delivery and may obscure the real picture. However, given the range of studies that have been carried out it seems more likely that they are interacting factors that contribute to physiological differences arising from PLCS and VD, rather than the determinants of the differences.

VIII. THE FUTURE—THE EPIDEMIOLOGICAL IMPACT OF CAESAREAN DELIVERY

Today Caesarean section is the most common surgical procedure in young women. In 2010, delivery by CS

accounted for 24.8% of all births in England and Wales; in 1985 it accounted for just 10% (HES Online & NHS: The Information Centre, 2010). In the USA the Caesarean section rate in 2007 was 31.8% (Martin *et al.*, 2007) and in China and parts of South America the rate was between 40 and 50% (Belizan *et al.*, 1999; Lumbiganon *et al.*, 2010). These figures are far in excess of the World Health Organization (WHO) recommended national rate of 15% (WHO, 1985). In the UK the number of elective PLCS deliveries has risen by 250% between 1980 and 2010, and currently accounts for 40% of all CS deliveries (HES Online & NHS: The Information Centre, 2010). In Australia, there has been a similar increase in elective CS rate but this has not been accompanied by increases in maternal health factors which are normally linked with CS (e.g. maternal obesity) (Janssens, Wallace & Chang, 2008). In 2001, the majority of obstetricians in England & Wales suggested that they were prepared to agree to maternal request for CS in the absence of medical indications (Cotzias, Paterson-Brown & Fisk, 2001). Choosing the best mode of delivery on a case-by-case basis remains an area of particular ethical difficulty, in which the physician's duty to promote patient well-being may conflict with the mother's right to choose. Furthermore, the rights of the infant may be at variance with those of the mother (Kalish, McCullough & Chervenak, 2008).

Given the increasing number of births by PLCS, both for medical indications and (Department of Health, Medical Directorate & Respiratory Team, 2010) maternal choice, further work on the present hypothesis is essential. This fact is underscored by the burden that PLCS places on healthcare providers. Epidemiological evidence shows a 20% increase in the likelihood of asthma (Thavagnanam *et al.*, 2008) and type-I diabetes (Cardwell *et al.*, 2008) in offspring born by CS delivery. Given that asthma costs the UK National Health Service (NHS) an estimated £1 billion (Department of Health *et al.*, 2010), and diabetes costs the NHS £649 million annually (The NHS Information Centre—July 2010), the potential cost of PLCS to the national budget is significant. Furthermore, with an increasing number of births by PLCS this cost is only likely to increase.

IX. THE FUTURE—A RESEARCH GAP

Carefully designed animal studies will remain an important part of the study of the physiological mechanisms driving differentiation at birth and long-term programming. The emergence of an increasing repertoire of non-invasive, safe *in vivo* techniques is advancing study in human neonates.

An exciting prospect for the future is the possibility of modulating programming events to improve human health. For example maternal terbutaline administered prior to PLCS, increases the respiratory response and offspring blood glucose levels, similar to those found in VD babies (Eisler *et al.*, 1999). In animals, administration of adrenaline to CS offspring at birth, normalises parameters to those of VD offspring (Boksa & Zhang, 2008). Simulated VD by passing the neonate through a rubber ring normalises respiratory rate and suckling behaviour in CS animals (Abel *et al.*, 1998; Ronca & Alberts, 1995). These data indicate that as CS will continue to be required for medical indications, ways of ameliorating adverse short- and long-term effects should be a focus of clinical research endeavour.

X. CONCLUSIONS

(1) We propose that birth is a defining moment for later life health. Studies addressing the impact of mode of delivery on short-term adaptations are plentiful. We suggest that normal vaginal delivery is an important programming event with life-long health consequences.

(2) Understanding the mechanisms by which this programming occurs will allow us to ameliorate the effects of operative delivery in the future. With the rising number of pre-labour Caesarean deliveries each year, this is an area that requires research attention.

XI. REFERENCES

Abel, R. A., Ronca, A. E. & Alberts, J. R. (1998). Perinatal stimulation facilitates suckling onset in newborn rats. *Developmental Psychobiology* **32**, 91–9.

Agata, Y., Hiraishi, S., Misawa, H., Han, J. H., Oguchi, K., Horiguchi, Y., Fujino, N., Takeda, N. & Padbury, J. F. (1995). Hemodynamic adaptations at birth and neonates delivered vaginally and by Cesarean section. *Biology of the Neonate* **68**, 404–11.

Ajslev, T. A., Andersen, C. S., Gamborg, M., Sorensen, T. I. & Jess, T. (2011). Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *International Journal of Obesity (Lond)* **35**, 522–9.

Alexander, B. T. (2006). Fetal programming of hypertension. *American Journal of Physiology* **290**, R1–R10.

Aynsley-Green, A. (1985). Metabolic and endocrine interrelations in the human fetus and neonate. *American Journal of Clinical Nutrition* **41**, 399–417.

Bahnsen, M., Burrin, J. M., Johnston, D. G., Pernet, A., Walker, M. & Alberti, K. G. (1984). Mechanisms of catecholamine effects on ketogenesis. *American Journal of Physiology* **247**, E173–80.

Balmer, S. E. & Wharton, B. A. (1989). Diet and faecal flora in the newborn: breast milk and infant formula. *Archives of Disease in Childhood* **64**, 1672–7.

Barker, D. J. P. (1998). *Mothers, Babies and Health in Later Life*, Second edition. Churchill Livingstone, Edinburgh.

Barker, P. M., Brown, M. J., Ramsden, C. A., Strang, L. B. & Walters, D. V. (1988). The effect of thyroidectomy in the fetal sheep on lung liquid reabsorption induced by adrenaline or cyclic AMP. *Journal of Physiology* **407**, 373–83.

Bassett, J. M. (1989). Hormones and metabolic adaptation in the newborn. *Proceedings of the Nutrition Society* **48**, 263–9.

Belizan, J. M., Althabe, F., Barros, F. C. & Alexander, S. (1999). Rates and implications of caesarean sections in Latin America: ecological study. *British Medical Journal* **319**, 1397–1402.

Bellone, S., Rapa, A., Vivenza, D., Vercellotti, A., Petri, A., Radetti, G., Bellone, J., Broglio, F., Ghigo, E. & Bona, G. (2003). Circulating ghrelin levels in newborns are not associated to gender, body weight and hormonal parameters but depend on the type of delivery. *Journal of Endocrinological Investigation* **26**, RC9–11.

Ben-Jonathan, N. & Hnasko, R. (2001). Dopamine as a prolactin (PRL) inhibitor. *Endocrine Reviews* **22**, 724–63.

Bennet, R. & Nord, C. E. (1987). Development of the faecal anaerobic microflora after caesarean section and treatment with antibiotics in newborn infants. *Infection* **15**, 332–6.

Bessler, H., Kuperman, A., Beilin, B., Klinger, G., Gurary, N., Mozes, C. & Sirota, L. (1998). Labor affects cytokine production in newborns. *American Journal of Reproductive Immunology* **39**, 27–32.

Bezirtzoglou, E. (1997). The intestinal microflora during the first weeks of life. *Anaerobe* **3**, 173–7.

Bird, J. A., Spencer, J. A., Mould, T. & Symonds, M. E. (1996). Endocrine and metabolic adaptation following caesarean section or vaginal delivery. *Archives of Disease in Childhood* **74**, F132–4.

Bispham, J., Budge, H., Mostyn, A., Dandrea, J., Clarke, L., Keisler, D. H., Symonds, M. E. & Stephenson, T. (2002). Ambient temperature, maternal dexamethasone, and postnatal ontogeny of leptin in the neonatal lamb. *Pediatric Research* **52**, 85–90.

Bistoletti, P., Nylund, L., Lagercrantz, H., Hjemdahl, P. & Strom, H. (1983). Fetal scalp catecholamines during labor. *American Journal of Obstetrics & Gynecology* **147**, 785–8.

Bjorksten, B., Sepp, E., Julge, K., Voor, T. & Mikelsaar, M. (2001). Allergy development and the intestinal microflora during the first year of life. *Journal of Allergy and Clinical Immunology* **108**, 516–20.

Bland, R. D. (2001). Loss of liquid from the lung lumen in labor: more than a simple "squeeze". *American Journal of Physiology* **280**, L602–5.

Bland, R. D., Hansen, T. N., Haberkern, C. M., Bressack, M. A., Hazinski, T. A., Raj, J. U. & Goldberg, R. B. (1982). Lung fluid balance in lambs before and after birth. *Journal of Applied Physiology* **53**, 992–1004.

Bohme, H. J., Sparmann, G. & Hofmann, E. (1983). Biochemistry of liver development in the perinatal period. *Experientia* **39**, 473–83.

Boksa, P. (1997). Early developmental profiles of plasma corticosterone are altered by birth condition in the rat: a comparison of vaginal birth, cesarean section, and cesarean section with added anoxia. *Pediatric Research* **41**, 34–43.

Boksa, P. & Zhang, Y. (2008). Epinephrine administration at birth prevents long-term changes in dopaminergic parameters caused by Cesarean section birth in the rat. *Psychopharmacology (Berl)* **200**, 381–91.

Boshart, M., Weih, F., Nichols, M. & Schutz, G. (1991). The tissue-specific extinguisher locus TSE1 encodes a regulatory subunit of cAMP-dependent protein kinase. *Cell* **66**, 849–59.

Boshart, M., Weih, F., Schmidt, A., Fournier, R. E. & Schutz, G. (1990). A cyclic AMP response element mediates repression of tyrosine aminotransferase gene transcription by the tissue-specific extinguisher locus Tse-1. *Cell* **61**, 905–16.

Broughton Pipkin, F., Kirkpatrick, S. M., Lumbers, E. R. & Mott, J. C. (1974). Renin and angiotensin-like levels in foetal, new-born and adult sheep. *Journal of Physiology* **241**, 575–88.

Brown, M. A., Rad, P. Y. & Halonen, M. J. (2003). Method of birth alters interferon-gamma and interleukin-12 production by cord blood mononuclear cells. *Pediatric Allergy and Immunology* **14**, 106–11.

Brown, M. J., Olver, R. E., Ramsden, C. A., Strang, L. B. & Walters, D. V. (1983). Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. *Journal of Physiology* **344**, 137–152.

Cardwell, C. R., Stene, L. C., Joner, G., Cinek, O., Svensson, J., Goldacre, M. J., Parslow, R. C., Pozzilli, P., Brigis, G., Stoyanov, D., Urbonaite, B., Sipetic, S., Schober, E., Ionescu-Tirgoviste, C., Devoti, G., de Beaufort, C. E., Buschard, K. & Patterson, C. C. (2008). Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* **51**, 726–35.

Christensson, K., Siles, C., Cabrera, T., Belaustequi, A., Fuente, P., Lagercrantz, H., Puyol, P. & Winberg, J. (1993). Lower body temperatures in infants delivered by caesarean section than in vaginally delivered infants. *Acta Paediatrica* **82**, 128–131.

Clarke, L., Heasman, L., Firth, K. & Symonds, M. E. (1997). Influence of route of delivery and ambient temperature on thermoregulation in newborn lambs. *American Journal of Physiology* **272**, R1931–9.

Comline, R. S. & Silver, M. (1972). The composition of foetal and maternal blood during parturition in the ewe. *Journal of Physiology* **222**, 233–56.

Cotzias, C. S., Paterson-Brown, S. & Fisk, N. M. (2001). Obstetricians say yes to maternal request for elective caesarean section: a survey of current opinion. *European Journal of Obstetrics & Gynecology and Reproductive Biology* **97**, 15–6.

Daniel, J. A., Carroll, J. A., Keisler, D. H. & Kojima, C. J. (2008). Evaluation of immune system function in neonatal pigs born vaginally or by Cesarean section. *Domestic Animal Endocrinology* **35**, 81–7.

Daniel, J. A., Keisler, D. H., Sterle, J. A., Matteri, R. L. & Carroll, J. A. (1999). Birth by caesarian section alters postnatal function of the hypothalamic-pituitary-adrenal axis in young pigs. *Journal of Animal Science* **77**, 742–9.

Davidson, R., Roberts, S. E., Wotton, C. J. & Goldacre, M. J. (2010). Influence of maternal and perinatal factors on subsequent hospitalisation for asthma in children: evidence from the Oxford record linkage study. *BMC Pulmonary Medicine* **10**, 14.

Department of Health, Medical Directorate & Respiratory Team. (2010). Consultation on a strategy for services for chronic obstructive pulmonary disease (COPD) in England (ed. D. O. Health), pp. 15. Department of Health, London.

Dermitzaki, E., Staikou, C., Petropoulos, G., Rizos, D., Siafaka, I. & Fassoulaki, A. (2009). A randomized study of maternal serum cytokine levels following cesarean section under general or neuraxial anesthesia. *International Journal of Obstetric Anesthesia* **18**, 33–7.

Diwakar, K. K. & Sasidhar, M. V. (2002). Plasma glucose levels in term infants who are appropriate size for gestation and exclusively breast fed. *Archives of Disease in Childhood* **87**, F46–48.

Dobric, L., Vuleta, P., Milasinovic, L., Vejnovic, T., Djordjevec, A., Kopitovic, V., Ristivojevic, A. & Kapamadzija, A. (1998). The labor: stress for mother and the newborn infant. In *Labor and Delivery* (ed. E. V. Cosmi), pp. 411–414. The Parthenon Publishing Group, London.

Duee, P. H., Pegorier, J. P., Darcy-Vrillon, B. & Girard, J. (1996). Glucose and fatty acid metabolism in the newborn pig. In *Advances in Swine Biomedical Research*, vol. **2** (eds M. E. Tumbleson and L. B. Schook), pp. 865–884. Plenum Press, New York.

Duee, P. H., Pegorier, J. P., Quant, P. A., Herbin, C., Kohl, C. & Girard, J. (1994). Hepatic ketogenesis in newborn pigs is limited by low mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase activity. *Biochemical Journal* **298**, 207–12.

Eggesbø, M., Botten, G., Stigum, H., Nafstad, P. & Magnus, P. (2003). Is delivery by cesarean section a risk factor for food allergy? *Journal of Allergy and Clinical Immunology* **112**, 420–426.

Eggesbo, M., Botten, G., Stigum, H., Samuelsen, S. O., Brunekreef, B. & Magnus, P. (2005). Cesarean delivery and cow milk allergy/intolerance. *Allergy* **60**, 1172–3.

Eisler, G., Hjertberg, R. & Lagercrantz, H. (1999). Randomised controlled trial of effect of terbutaline before elective caesarean section on postnatal respiration and glucose homeostasis. *Archives of Disease in Childhood* **80**, F88–92.

El-Khodor, B. F. & Boksa, P. (1997). Long-term reciprocal changes in dopamine levels in prefrontal cortex versus nucleus accumbens in rats born by Caesarean section compared to vaginal birth. *Experimental Neurology* **145**, 118–29.

El-Khodor, B. F. & Boksa, P. (1998). Birth insult increases amphetamine-induced behavioral responses in the adult rat. *Neuroscience* **87**, 893–904.

El Manoubi, L., Callikan, S., Duee, P. H., Ferre, P. & Girard, J. (1983). Development of gluconeogenesis in isolated hepatocytes from the rabbit. *American Journal of Physiology* **244**, E24–30.

Elenkov, I. J., Wilder, R. L., Bakalov, V. K., Link, A. A., Dimitrov, M. A., Fisher, S., Crane, M., Kanik, K. S. & Chrousos, G. P. (2001). IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. *The Journal of Clinical Endocrinology & Metabolism* **86**, 4933–8.

Ericsson, U. B., Ivarsson, S. A. & Persson, P. H. (1987). Thyroglobulin in cord blood. The influence of the mode of delivery and the smoking habits of the mother. *European Journal of Pediatrics* **146**, 44–7.

Evans, K. C., Evans, R. G., Royal, R., Esterman, A. J. & James, S. L. (2003). Effect of caesarean section on breast milk transfer to the normal term newborn over the first week of life. *Archives of Disease in Childhood* **88**, F380–382.

Falconer, A. D. & Lake, D. M. (1982). Circumstances influencing umbilical-cord plasma catecholamines at delivery. *British Journal of Obstetrics and Gynaecology* **89**, 44–9.

Faxelius, G., Hagnevik, K., Lagercrantz, H., Lundell, B. & Irestedt, L. (1983). Catecholamine surge and lung function after delivery. *Archives of Disease in Childhood* **58**, 262–6.

Faxelius, G., Lagercrantz, H. & Yao, A. (1984). Sympathoadrenal activity and peripheral blood flow after birth: comparison in infants delivered vaginally and by cesarean section. *Journal of Pediatrics* **105**, 144–8.

Fowden, A. L., Apatu, R. S. & Silver, M. (1995). The glucogenic capacity of the fetal pig: developmental regulation by cortisol. *Experimental Physiology* **80**, 457–67.

Fowden, A. L. & Hill, D. J. (2001). Intra-uterine programming of the endocrine pancreas. *British Medical Bulletin* **60**, 123–42.

Fujimura, A., Morimoto, S., Uchida, K., Takeda, R., Ohshita, M. & Ebihara, A. (1990). The influence of delivery mode on biological inactive renin level in umbilical cord blood. *American Journal of Hypertension* **3**, 23–6.

Gemelli, M., Mami, C., Manganaro, R., Stelitano, L., Bonaccorsi, P. & Martino, F. (1992). Effects of the mode of delivery on ANP and renin-aldosterone system in the fetus and the neonate. *European Journal of Obstetrics & Gynecology and Reproductive Biology* **43**, 181–4.

Gessler, P. & Dahinden, C. (2003). Increased respiratory burst and increased expression of complement receptor-3 (CD11b/CD18) and of IL-8 receptor-A in neutrophil granulocytes from newborns after vaginal delivery. *Biology of the Neonate* **83**, 107–12.

Girard, J., Ferre, P., Pegorier, J. P. & Duee, P. H. (1992). Adaptations of glucose and fatty acid metabolism during perinatal period and suckling-weaning transition. *Physiological Reviews* **72**, 507–62.

Goldani, H. A., Bettiol, H., Barbieri, M. A., Silva, A. A., Agranonik, M., Morais, M. B. & Goldani, M. Z. (2011). Cesarean delivery is associated with an increased risk of obesity in adulthood in a Brazilian birth cohort study. *American Journal of Clinical Nutrition* **93**, 1344–7.

Gronlund, M. M., Lehtonen, O. P., Eerola, E. & Kero, P. (1999a). Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. *Journal of Pediatric Gastroenterology and Nutrition* **28**, 19–25.

Gronlund, M. M., Nuutila, J., Pelto, L., Lilius, E. M., Isolauri, E., Salminen, S., Kero, P. & Lehtonen, O. P. (1999b). Mode of delivery directs

the phagocyte functions of infants for the first 6 months of life. *Clinical & Experimental Immunology* **116**, 521–6.

Grun, E., Pfuller, K., Heyne, D. & Weber, C. (1982). [Activity of gluconeogenetic enzymes in the kidney of pigs during pre- and post-natal development]. *Acta biologica et medica Germanica* **41**, 861–71.

Gu, W., Jones, C. T. & Parer, J. T. (1985). Metabolic and cardiovascular effects on fetal sheep of sustained reduction of uterine blood flow. *Journal of Physiology* **368**, 109–29.

Gu, X. & Li, D. (2003). Fat nutrition and metabolism in piglets: a review. *Animal Feed Science and Technology* **109,** 151–170.

Haddad, R., Tromp, G., Kuivaniemi, H., Chaiworapongsa, T., Kim, Y. M., Mazor, M. & Romero, R. (2006). Human spontaneous labor without histologic chorioamnionitis is characterized by an acute inflammation gene expression signature. *American Journal of Obstetrics & Gynecology* **195**, 394 e1–24.

Hagnevik, K., Faxelius, G., Irestedt, L., Lagercrantz, H., Lundell, B. & Persson, B. (1984). Catecholamine surge and metabolic adaptation in the newborn after vaginal delivery and caesarean section. *Acta paediatrica Scandinavica* **73**, 602–9.

Hakansson, S. & Kallen, K. (2003). Caesarean section increases the risk of hospital care in childhood for asthma and gastroenteritis. *Clinical & Experimental Allergy* **33**, 757–64.

Hall, M. A., Cole, C. B., Smith, S. L., Fuller, R. & Rolles, C. J. (1990). Factors influencing the presence of faecal lactobacilli in early infancy. *Archives of Disease in Childhood* **65**, 185–8.

Hamosh, M. (1987). Lipid metabolism in premature infants. *Biology of the Neonate* **52** (**Suppl. 1**), 50–64.

Hansen, A. K., Wisborg, K., Uldbjerg, N. & Henriksen, T. B. (2008). Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *British Medical Journal* **336**, 85–7.

Heasman, L., Spencer, J. A. & Symonds, M. E. (1997). Plasma prolactin concentrations after caesarean section or vaginal delivery. *Archives of Disease in Childhood* **77**, F237–8.

Herrera, E. & Amusquivar, E. (2000). Lipid metabolism in the fetus and the newborn. *Diabetes/Metabolism Research and Reviews* **16**, 202–10.

Hes Online & NHS: The Information Centre. (2010). NHS Maternity Statistics 2009–2010.

Holland, W. W. & Young, I. M. (1956). Neonatal blood pressure in relation to maturity, mode of delivery, and condition at birth. *British Medical Journal* **2**, 1331–3.

Hoseth, E., Joergensen, A., Ebbesen, F. & Moeller, M. (2000). Blood glucose levels in a population of healthy, breast fed, term infants of appropriate size for gestational age. *Archives of Disease in Childhood* **83**, F117–9.

Huurre, A., Kalliomaki, M., Rautava, S., Rinne, M., Salminen, S. & Isolauri, E. (2008). Mode of delivery—effects on gut microbiota and humoral immunity. *Neonatology* **93**, 236–40.

Hyde, M. J., Griffin, J. L., Herrera, E., Byrne, C. D., Clarke, L. & Kemp, P. R. (2010). Delivery by Caesarean section, rather than vaginal delivery, promotes hepatic steatosis in piglets. *Clinical Science (Lond)* **118**, 47–59.

Irestedt, L., Dahlin, I., Hertzberg, T., Sollevi, A. & Lagercrantz, H. (1989). Adenosine concentration in umbilical cord blood of newborn infants after vaginal delivery and cesarean section. *Pediatric Research* **26**, 106–8.

Janssens, S., Wallace, K. L. & Chang, A. M. (2008). Prepartum and intrapartum caesarean section rates at Mater Mothers' Hospital Brisbane 1997–2005. *The Australian and New Zealand Journal of Obstetrics and Gynaecology* **48**, 564–9.

Jensen, R. G. (1999). Lipids in human milk. *Lipids* **34**, 1243–71.

Jimenez, E., Fernandez, L., Marin, M. L., Martin, R., Odriozola, J. M., Nueno-Palop, C., Narbad, A., Olivares, M., Xaus, J. & Rodriguez, J. M. (2005). Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. *Current Microbiology* **51**, 270–4.

Jiménez, E., Marín, M. L., Martín, R., Odriozola, J. M., Olivares, M., Xaus, J., Fernández, L. & Rodríguez, J. M. (2008). Is meconium from healthy newborns actually sterile? *Research in Microbiology* **159**, 187–193.

Johnston, D. I. & Bloom, S. R. (1973). Plasma glucagon levels in the term human infant and effect of hypoxia. *Archives of Disease in Childhood* **48**, 451–4.

Jones, C. M., 3rd & Greiss, F. C., Jr. (1982). The effect of labor on maternal and fetal circulating catecholamines. *American Journal of Obstetrics & Gynecology* **144**, 149–53.

Jones, C. T. & Ritchie, J. W. (1978). The metabolic and endocrine effects of circulating catecholamines in fetal sheep. *Journal of Physiology* **285**, 395–408.

Kalhan, S. C., Bier, D. M., Savin, S. M. & Adam, P. A. (1980). Estimation of glucose turnover and 13C recycling in the human newborn by simultaneous [1-13C]glucose and [6,6-1H2]glucose tracers. *The Journal of Clinical Endocrinology & Metabolism* **50**, 456–60.

Kalish, R. B., McCullough, L. B. & Chervenak, F. A. (2008). Patient choice cesarean delivery: ethical issues. *Current Opinion in Obstetrics and Gynecology* **20**, 116–9.

Kearney, M. H., Cronenwett, L. R. & Reinhardt, R. (1990). Cesarean delivery and breastfeeding outcomes. *Birth* **17**, 97–103.

Keszler, M., Carbone, M. T., Cox, C. & Schumacher, R. E. (1992). Severe respiratory failure after elective repeat cesarean delivery: a potentially preventable condition leading to extracorporeal membrane oxygenation. *Pediatrics* **89**, 670–2.

Kimura, R. E. & Warshaw, J. B. (1983). Metabolic adaptations of the fetus and newborn. *Journal of Pediatric Gastroenterology and Nutrition* **2**, S12–5.

Kindler, P. M., Chuang, D. C. & Perks, A. M. (1993). Fluid production by in vitro lungs from near-term fetal guinea pigs: effects of cortisol and aldosterone. *Acta Endocrinologica (Copenhagen)* **129**, 169–77.

Kingdom, J. C., McQueen, J., Connell, J. M. & Whittle, M. J. (1993). Fetal angiotensin II levels and vascular (type I) angiotensin receptors in pregnancies complicated by intrauterine growth retardation. *British Journal of Obstetrics and Gynaecology* **100**, 476–82.

Lagercrantz, H. (1996). Stress, arousal and gene activation at birth. *News in Physiological Science* **11**, 214–218.

Laubereau, B., Filipiak-Pittroff, B., von Berg, A., Grubl, A., Reinhardt, D., Wichmann, H. E., Koletzko, S. & for the GINI Study Group. (2004). Caesarean section and gastrointestinal symptoms, atopic dermatitis, and sensitisation during the first year of life. *Archives of Disease in Childhood* **89**, 993–997.

Lee, S., Hassan, A., Ingram, D. & Milner, A. D. (1999). Effects of different modes of delivery on lung volumes of newborn infants. *Pediatric Pulmonology* **27**, 318–21.

Leone, T. A. & Finer, N. N. (2006). Foetal adaptation at birth. *Current Paediatrics* **16**, 373–378

Leung, G. M., Lam, T. H. & Ho, L. M. (2002). Breast-feeding and its relation to smoking and mode of delivery. *Obstetrics & Gynecology* **99**, 785.

Levine, E. M., Ghai, V., Barton, J. J. & Strom, C. M. (2001). Mode of delivery and risk of respiratory diseases in newborns. *Obstetrics & Gynecology* **97**, 439–42.

Li, Y., Caufield, P. W., Dasanayake, A. P., Wiener, H. W. & Vermund, S. H. (2005). Mode of delivery and other maternal factors influence the acquisition of Streptococcus mutans in infants. *Journal of Dental Research* **84**, 806–11.

Li, Z. & Diehl, A. M. (2003). Innate immunity in the liver. *Current Opinion in Obstetrics and Gynecology* **19**, 565–71.

Li, Z., Oben, J. A., Yang, S., Lin, H., Stafford, E. A., Soloski, M. J., Thomas, S. A. & Diehl, A. M. (2004). Norepinephrine regulates hepatic innate immune system in leptin-deficient mice with nonalcoholic steatohepatitis. *Hepatology* **40**, 434–41.

Liggins, G. C. (1994). The role of cortisol in preparing the fetus for birth. *Reproduction, fertility, and development* **6**, 141–50.

Lorenzo, M., Roncero, C. & Benito, M. (1986). The role of prolactin and progesterone in the regulation of lipogenesis in maternal and foetal rat liver in vivo and in isolated hepatocytes during the last day of gestation. *Biochemical Journal* **239**, 135–9.

Louet, J. F., Chatelain, F., Decaux, J. F., Park, E. A., Kohl, C., Pineau, T., Girard, J. & Pegorier, J. P. (2001). Long-chain fatty acids regulate liver carnitine palmitoyltransferase I gene (L-CPT I) expression through a peroxisome-proliferator-activated receptor alpha (PPARalpha)-independent pathway. *Biochemical Journal* **354**, 189–97.

Lumbers, E. R. & Reid, G. C. (1977). Effects of vaginal delivery and caesarian section on plasma renin activity and angiotensin II levels in human umbilical cord blood. *Biology of the Neonate* **31**, 127–33.

Lumbiganon, P., Laopaiboon, M., Gulmezoglu, A. M., Souza, J. P., Taneepanichskul, S., Ruyan, P., Attygalle, D. E., Shrestha, N., Mori, R., Nguyen, D. H., Hoang, T. B., Rathavy, T., Chuyun, K., Cheang, K., Festin, M., Udomprasertgul, V., Germar, M. J., Yanqiu, G., Roy, M., Carroli, G., Ba-Thike, K., Filatova, E. & Villar, J. (2010). Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007-08. *The Lancet* **375**, 490–9.

Ly, N. P., Ruiz-Perez, B., Onderdonk, A. B., Tzianabos, A. O., Litonjua, A. A., Liang, C., Laskey, D., Delaney, M. L., DuBois, A. M., Levy, H., Gold, D. R., Ryan, L. M., Weiss, S. T. & Celedon, J. C. (2006). Mode of delivery and cord blood cytokines: a birth cohort study. *Clinical and Molecular Allergy* **4**, 13.

Lyonnet, S., Coupe, C., Girard, J., Kahn, A. & Munnich, A. (1988). In vivo regulation of glycolytic and gluconeogenic enzyme gene expression in newborn rat liver. *Journal of Clinical Investigation* **81**, 1682–9.

Malamitsi-Puchner, A., Protonotariou, E., Boutsikou, T., Makrakis, E., Sarandakou, A. & Creatsas, G. (2005). The influence of the mode of delivery on circulating cytokine concentrations in the perinatal period. *Early Human Development* **81**, 387–92.

Malloy, M. H. (2008). Impact of cesarean section on neonatal mortality rates among very preterm infants in the United States, 2000-2003. *Pediatrics* **122**, 285–92.

Marchini, G., Persson, B., Jonsson, N. & Marcus, C. (1995). Influence of body temperature on thyrotropic hormone release and lipolysis in the newborn infant. *Acta Paediatrica* **84**, 1284–8.

Martin, H. & Norman, M. (1997). Skin microcirculation before and after local warming in infants delivered vaginally or by caesarean section. *Acta Paediatrica* **86**, 261–7.

Martin, J. A., Hamilton, B. E., Sutton, P. D., Ventura, S. J., Mathews, T. J., Kirmeyer, S. & Osterman, M. J. (2007). Births: final data for 2007. *National Vital Statistics Reports* **58**, 1–85.

Martín, R., Heilig, G. H. J., Zoetendal, E. G., Smidt, H. & Rodríguez, J. M. (2007). Diversity of the Lactobacillus group in breast milk and vagina of healthy

women and potential role in the colonization of the infant gut. *Journal of Applied Microbiology* **103**, 2638–2644.

Matsumiya, Y., Kato, N., Watanabe, K. & Kato, H. (2002). Molecular epidemiological study of vertical transmission of vaginal Lactobacillus species from mothers to newborn infants in Japanese, by arbitrarily primed polymerase chain reaction. *Journal of Infection and Chemotherapy* **8**, 43–9.

McMillen, I. C. & Robinson, J. S. (2005). Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiological Reviews* **85**, 571–633.

McNabb, M. (2003). The foetus at birth: maternal and fetal preparations for postnatal development In *Nutrition in early life* (eds J. B. Morgan and J. W. T. Dickerson), pp. 145–177 Wiley, Chichester.

Mears, K., McAuliffe, F., Grimes, H. & Morrison, J. J. (2004). Fetal cortisol in relation to labour, intrapartum events and mode of delivery. *Journal of Obstetrics and Gynaecology* **24**, 129–32.

Mersmann, H. J. (1971). Glycolytic and gluconeogenic enzyme levels in pre- and postnatal pigs. *American Journal of Physiology* **220**, 1297–302.

Meyer, K. & Lubo, Z. (2007). Fetal programming of cardiac function and disease. *Reproductive Sciences* **14**, 209–16.

Miller, L. C., Isa, S., LoPreste, G., Schaller, J. G. & Dinarello, C. A. (1990). Neonatal interleukin-1 beta, interleukin-6, and tumor necrosis factor: cord blood levels and cellular production. *Journal of Pediatrics* **117**, 961–5.

Miller, N. M., Fisk, N. M., Modi, N. & Glover, V. (2005). Stress responses at birth: determinants of cord arterial cortisol and links with cortisol response in infancy. *British Journal of Obstetrics and Gynaecology* **112**, 921–6.

Milner, A. D., Saunders, R. A. & Hopkin, I. E. (1978). Effects of delivery by caesarean section on lung mechanics and lung volume in the human neonate. *Archives of Disease in Childhood* **53**, 545–8.

Mitanchez, D. (2007). Glucose regulation in preterm newborn infants. *Hormone Research* **68**, 265–71.

Miyamoto, N., Tsuji, M., Imataki, T., Nagamachi, N., Hirose, S. & Hamada, Y. (1991). Influence of mode of delivery on fetal pituitary-thyroid axis. *Acta paediatrica Japonica* **33**, 363–8.

Mostyn, A., Pearce, S., Budge, H., Elmes, M., Forhead, A. J., Fowden, A. L., Stephenson, T. & Symonds, M. E. (2003). Influence of cortisol on adipose tissue development in the fetal sheep during late gestation. *Journal of Endocrinology* **176**, 23–30.

Neut, C., Bezirtzoglou, E., Romond, C., Beerens, H., Delcroix, M. & Noel, A. M. (1987). Bacterial colonization of the large intestine in newborns delivered by cesarean section. *Zentralbl Bakteriol Mikrobiol Hyg [A]* **266**, 330–7.

Nikischin, W., Peter, M. & Oldigs, H. D. (1997). The influence of mode of delivery on hematologic values in the umbilical vein. *Gynecologic and Obstetric Investigation* **43**, 104–7.

Nissen, E., Uvnas-Moberg, K., Svensson, K., Stock, S., Widstrom, A. M. & Winberg, J. (1996). Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route. *Early Human Development* **45**, 103–18.

Nordlie, R. C., Foster, J. D. & Lange, A. J. (1999). Regulation of glucose production by the liver. *Annual Review of Nutrition* **19**, 379–406.

Norman, J. E., Bollapragada, S., Yuan, M. & Nelson, S. M. (2007). Inflammatory pathways in the mechanism of parturition. *BMC Pregnancy Childbirth* **7 (Suppl. 1)**, S7.

Nuamah, M. A., Yura, S., Sagawa, N., Itoh, H., Mise, H., Korita, D., Kakui, K., Takemura, M., Ogawa, Y., Nakao, K. & Fujii, S. (2004). Significant increase in maternal plasma leptin concentration in induced delivery: a possible contribution of pro-inflammatory cytokines to placental leptin secretion. *Endocrine Journal* **51**, 177–87.

O'Sullivan, M. J., Kearney, P. J. & Crowley, M. J. (1996). The influence of some perinatal variables on neonatal blood pressure. *Acta Paediatrica* **85**, 849–53.

Oliveira Filho, E. A. & Procianoy, R. S. (1995). [The influence of the mode of delivery on the umbilical cord serum aldosterone levels in preterm newborn infants]. *Jornal de Pediatria (Rio J)* **71**, 331–6.

Otamiri, G., Berg, G., Ledin, T., Leijon, I. & Lagercrantz, H. (1991). Delayed neurological adaptation in infants delivered by elective cesarean section and the relation to catecholamine levels. *Early Human Development* **26**, 51–60.

Padbury, J., Agata, Y., Ludlow, J., Ikegami, M., Baylen, B. & Humme, J. (1987). Effect of fetal adrenalectomy on catecholamine release and physiologic adaptation at birth in sheep. *Journal of Clinical Investigation* **80**, 1096–103.

Padbury, J. F., Diakomanolis, E. S., Hobel, C. J., Perelman, A. & Fisher, D. A. (1981). Neonatal adaptation: sympatho-adrenal response to umbilical cord cutting. *Pediatric Research* **15**, 1483–7.

Padgett, D. A. & Glaser, R. (2003). How stress influences the immune response. *Trends in Immunology* **24**, 444–8.

Pawlus, B., Walczak, M., Kordek, A., Gizewska, M. & Czajka, R. (2004). [Impact of delivery type on EGF and IGF-1 concentration in umbilical blood of newborns and their mothers' milk]. *Ginekologia Polska* **75**, 821–4.

Pearce, S., Budge, H., Mostyn, A., Genever, E., Webb, R., Ingleton, P., Walker, A. M., Symonds, M. E. & Stephenson, T. (2005). Prolactin, the prolactin receptor and uncoupling protein abundance and function in adipose tissue during development in young sheep. *Journal of Endocrinology* **184**, 351–9.

Pegorier, J. P. (1998). Regulation of gene expression by fatty acids. *Current Opinion in Clinical Nutrition & Metabolic Care* **1**, 329–34.

Pegorier, J. P., Chatelain, F., Thumelin, S. & Girard, J. (1998). Role of long-chain fatty acids in the postnatal induction of genes coding for liver mitochondrial beta-oxidative enzymes. *Biochemical Society Transactions* **26**, 113–20.

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., van den Brandt, P. A. & Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* **118**, 511–21.

Prior, E., Hyde, M., Santhakumaran, S., Philipps, L., Gale, C. & Modi, N. (2010). The effect of mode of delivery on breastfeeding success. In *The Neonatal Society Summer Meeting*, Nottingham.

Prip-Buus, C., Pegorier, J. P., Duee, P. H., Kohl, C. & Girard, J. (1990). Evidence that the sensitivity of carnitine palmitoyltransferase I to inhibition by malonyl-CoA is an important site of regulation of hepatic fatty acid oxidation in the fetal and newborn rabbit. Perinatal development and effects of pancreatic hormones in cultured rabbit hepatocytes. *Biochemical Journal* **269**, 409–15.

Rafiq, N. & Younossi, Z. M. (2008). Interaction of metabolic syndrome, nonalcoholic fatty liver disease and chronic hepatitis C. *Expert Review of Gastroenterology and Hepatology* **2**, 207–15.

Ramezani Tehrani, F., Aghaee, M. & Asefzadeh, S. (2003). The Comparison of Thyroid Function Tests in Cord Blood Following Cesarean Section or Vaginal Delivery. *European Journal of Endocrinology and Metabolism* **1**, 22–26.

Renz-Polster, H., David, M. R., Buist, A. S., Vollmer, W. M., O'Connor, E. A., Frazier, E. A. & Wall, M. A. (2005). Caesarean section delivery and the risk of allergic disorders in childhood. *Clinical & Experimental Allergy* **35**, 1466–72.

Roduit, C., Scholtens, S., de Jongste, J. C., Wijga, A. H., Gerritsen, J., Postma, D. S., Brunekreef, B., Hoekstra, M. O., Aalberse, R. & Smit, H. A. (2009). Asthma at 8 years of age in children born by caesarean section. *Thorax* **64**, 107–113.

Ronca, A. E. & Alberts, J. R. (1995). Simulated uterine contractions facilitate fetal and newborn respiratory behavior in rats. *Physiology & Behavior* **58**, 1035–41.

Rowe-Murray, H. J. & Fisher, J. R. (2002). Baby friendly hospital practices: cesarean section is a persistent barrier to early initiation of breastfeeding. *Birth* **29**, 124–31.

Ruppert, S., Boshart, M., Bosch, F. X., Schmid, W., Fournier, R. E. & Schutz, G. (1990). Two genetically defined trans-acting loci coordinately regulate overlapping sets of liver-specific genes. *Cell* **61**, 895–904.

Sanders, V. M. & Straub, R. H. (2002). Norepinephrine, the beta-adrenergic receptor, and immunity. *Brain, Behavior, and Immunity* **16**, 290–332.

Sangild, P. T., Fowden, A. L. & Trahair, J. F. (2000). How does the foetal gastrointestinal tract develop in preparation for enteral nutrition after birth? *Livestock Production Science* **66**, 141–150.

Sangild, P. T., Hilsted, L., Nexo, E., Fowden, A. L. & Silver, M. (1995). Vaginal birth versus elective caesarean section: effects on gastric function in the neonate. *Experimental Physiology* **80**, 147–57.

Sedaghat, N., Ellwood, D., Shadbolt, B., Kecskes, Z., Falk, M. C., Brussel, T. & Kent, A. L. (2008). The effect of mode of delivery and anaesthesia on neonatal blood pressure. *The Australian and New Zealand Journal of Obstetrics and Gynaecology* **48**, 172–8.

Shelley, H. J. (1961). Glycogen reserves and their changes at birth and in anoxia. *British Medical Bulletin* **17**, 137–143.

Shnider, S. M., Abboud, T. K., Artal, R., Henriksen, E. H., Stefani, S. J. & Levinson, G. (1983). Maternal catecholamines decrease during labor after lumbar epidural anesthesia. *American Journal of Obstetrics & Gynecology* **147**, 13–5.

Smolich, J. J. & Esler, M. D. (1999). Total body catecholamine kinetics before and after birth in spontaneously hypoxemic fetal lambs. *American Journal of Physiology* **277**, R1313–20.

Sodoyez-Goffaux, F. R., Sodoyez, J. C. & De Vos, C. J. (1979). Insulin secretion and metabolism during the perinatal period in the rat. Evidence for a placental role in fetal hyperinsulinemia. *Journal of Clinical Investigation* **63**, 1095–102.

Sperling, M. A., DeLamater, P. V., Phelps, D., Fiser, R. H., Oh, W. & Fisher, D. A. (1974). Spontaneous and amino acid-stimulated glucagon secretion in the immediate postnatal period. Relation to glucose and insulin. *Journal of Clinical Investigation* **53**, 1159–66.

Srinivasan, G., Pildes, R. S., Cattamanchi, G., Voora, S. & Lilien, L. D. (1986). Plasma glucose values in normal neonates: a new look. *Journal of Pediatrics* **109**, 114–7.

Symonds, M. E. & Clarke, L. (1996). Influence of thyroid hormones and temperature on adipose tissue development and lung maturation. *Proceedings of the Nutrition Society* **55**, 561–9.

Tamminen, T., Verronen, P., Saarikoski, S., Goransson, A. & Tuomiranta, H. (1983). The influence of perinatal factors on breast feeding. *Acta paediatrica Scandinavica* **72**, 9–12.

Taylor, A., Fisk, N. M. & Glover, V. (2000). Mode of delivery and subsequent stress response. *The Lancet* **355**, 120.

Tetlow, H. J. & Broughton Pipkin, F. (1983). The effect of changes in blood gas tension upon the renin-angiotensin system of the newborn infant. *British Journal of Obstetrics and Gynaecology* **90**, 898–903.

Thavagnanam, S., Fleming, J., Bromley, A., Shields, M. D. & Cardwell, C. R. (2008). A meta-analysis of the association between Caesarean section and childhood asthma. *Clinical & Experimental Allergy* **38**, 629–33.

Thilaganathan, B., Meher-Homji, N. & Nicolaides, K. H. (1994). Labor: an immunologically beneficial process for the neonate. *American Journal of Obstetrics & Gynecology* **171**, 1271–2.

Tollånes, M. C., Moster, D., Daltveit, A. K. & Irgens, L. M. (2008). Cesarean Section and Risk of Severe Childhood Asthma: A Population-Based Cohort Study. *Journal of Pediatrics* **153**, 112–116.e1.

Uhari, M. (1980). Changes in blood pressure during the first year of life. *Acta paediatrica Scandinavica* **69**, 613–7.

Utz, R. L. (2008). *Can Prenatal Care Prevent Childhood Obesity? In Policy Perspectives*, vol. **4.** University of Utah, Utah.

Uystepruyst, C., Coghe, J., Dorts, T., Harmegnies, N., Delsemme, M. H., Art, T. & Lekeux, P. (2002). Optimal timing of elective caesarean section in Belgian White and Blue breed of cattle: the calf's point of view. *The Veterinary Journal* **163**, 267–82.

Vaillancourt, C., Berger, N. & Boksa, P. (1999). Effects of vaginal birth versus caesarean section birth with general anesthesia on blood gases and brain energy metabolism in neonatal rats. *Experimental Neurology* **160**, 142–50.

Vaillancourt, C. & Boksa, P. (1998). Caesarean section birth with general anesthesia increases dopamine-mediated behavior in the adult rat. *Neuroreport* **9**, 2953–9.

Vaillancourt, C. & Boksa, P. (2000). Birth insult alters dopamine-mediated behavior in a precocial species, the guinea pig. Implications for schizophrenia. *Neuropsychopharmacology* **23**, 654–66.

Van Aerde, J. E., Wilke, M. S., Feldman, M. & Clandinin, M. T. (2003). Accretion of lipid in the fetus and newborn. In *Fetal and Neonatal Physiology*, vol. 1 (eds R. A. Polin, W. W. Fox and S. H. Abman), pp. 388–404. Saunders, London.

Vernon, R. G. & Walker, D. G. (1970). Glycerol metabolism in the neonatal rat. *Biochemical Journal* **118**, 531–6.

Vestermark, V., Hogdall, C. K., Birch, M., Plenov, G. & Toftager-Larsen, K. (1991). Influence of the mode of delivery on initiation of breast-feeding. *European Journal of Obstetrics & Gynecology and Reproductive Biology* **38**, 33–8.

Visser, J., van Boxel-Dezaire, A., Methorst, D., Brunt, T., de Kloet, E. R. & Nagelkerken, L. (1998). Differential regulation of interleukin-10 (IL-10) and IL-12 by glucocorticoids in vitro. *Blood* **91**, 4255–64.

Walters, D. V. & Olver, R. E. (1978). The role of catecholamines in lung liquid absorption at birth. *Pediatric Research* **12**, 239–42.

Walters, D. V., Ramsden, C. A. & Olver, R. E. (1990). Dibutyryl cAMP induces a gestation-dependent absorption of fetal lung liquid. *Journal of Applied Physiology* **68**, 2054–9.

Ward Platt, M. & Deshpande, S. (2005). Metabolic adaptation at birth. *Seminars in Fetal and Neonatal Medicine* **10**, 341–50.

WHO. (1985). Appropriate technology for birth. *The Lancet* **2**, 436–7.

Wild, S. H. & Byrne, C. D. (2004). Evidence for fetal programming of obesity with a focus on putative mechanisms. *Nutrition Research Reviews* **17**, 153–62.

Yektaei-Karin, E., Moshfegh, A., Lundahl, J., Berggren, V., Hansson, L. O. & Marchini, G. (2007). The stress of birth enhances in vitro spontaneous and IL-8-induced neutrophil chemotaxis in the human newborn. *Pediatric Allergy and Immunology* **18**, 643–51.

Yoshimitsu, N., Douchi, T., Kamio, M. & Nagata, Y. (2000). Differences in umbilical venous and arterial leptin levels by mode of delivery. *Obstetrics & Gynecology* **96**, 342–5.

Zanardo, V., Cagdas, S., Golin, R., Trevisanuto, D., Marzari, F. & Rizzo, L. (1999). Risk factors of hypoglycemia in premature infants. *Fetal Diagnosis and Therapy* **14**, 63–7.

Zanardo, V., Nicolussi, S., Giacomin, C., Faggian, D., Favaro, F. & Plebani, M. (2001). Labor pain effects on colostral milk beta-endorphin concentrations of lactating mothers. *Biology of the Neonate* **79**, 87–90.

Zanardo, V., Solda, G. & Trevisanuto, D. (2006). Elective cesarean section and fetal immune-endocrine response. *International Journal of Gynecology & Obstetrics* **95**, 52–3.

(*Received 9 February 2011; revised 4 July 2011; accepted 8 July 2011*)