Factors relating caesarean section to persistent pulmonary hypertension of the newborn

Niralee Babooa, Wen-Jing Shi, Chao Chen
Shanghai, China

Background: **Several studies have clearly demonstrated a significantly higher incidence of persistent pulmonary hypertension of the newborn (PPHN) in neonates delivered by caesarean section (CS) compared to those delivered vaginally. The pathophysiological factors underlying the link between CS and PPHN are still poorly understood. In this review, we describe the mechanisms that could explain the association between CS delivery and subsequent PPHN, as well as potential preventive measures.**

Data sources: **A literature search was conducted by electronic scanning of databases such as PubMed and Web of Science using the key words "persistent pulmonary hypertension of the newborn", "caesarean section", "iatrogenic prematurity", "oxidative stress", "late preterm", "labor" and "vasoactive agents".**

Results: **Iatrogenic prematurity, higher rates of late preterm delivery and lack of physiological changes of labor play an important role in the association between CS and PPHN. CS delivery also results in limited endogenous pulmonary vasodilator synthesis and lower levels of protective anti-oxidants in the neonates. In addition, CS delivery exposes infants to a higher risk of respiratory distress syndrome and its concomitant increase in endothelin-1 levels, which might indirectly lead to a higher risk of developing PPHN. We believe that neonates delivered by CS are exposed to a combination of these pathophysiological events, culminating in an endpoint of respiratory distress, hypoxia, acidosis, and delayed transition and thereby increased risks of PPHN. The use of antenatal corticosteroids prior to elective CS in late preterm deliveries, promoting accurate informed-consent process, delaying elective CS to 39 weeks of gestation or beyond and antenatal maternal anti-oxidant supplementation could potentially mitigate the effects of CS delivery and minimize CS-related PPHN.**

Conclusions: **The link between CS delivery and PPHN is complex. In view of the rising rates of CS worldwide, there is an urgent need to further explore the mechanisms linking CS to PPHN and experimentally test therapeutic options in order to allow effective targeted interventions.**

World J Pediatr 2017;13(6):517-527

Key words: **caesarean section;**
iatrogenic prematurity;
oxidative stress;
persistent pulmonary hypertension of the newborn;
vasoactive agents

Review article

Introduction

Persistent pulmonary hypertension of the newborn (PPHN), also known as "persistent fetal circulation", is defined as the failure of normal pulmonary vascular adaptation at or soon after birth, resulting in persistent high pulmonary vascular resistance (PVR) with diminished pulmonary blood flow and right to left shunting of unoxygenated blood to the systemic circulation through an open foramen ovale and/or a ductus arteriosus.[1]

Numerous publications have reported higher rates of PPHN in neonates delivered by caesarean section (CS) compared to those born by vaginal delivery (VD).[2-7] Caesarean deliveries have been reported to carry an approximately fivefold higher risk for PPHN when compared to VDs.[4,6] While the incidence of PPHN in general is 1-2 per 1000 live births,[3] caesarean deliveries have been reported to elevate this incidence to 6.9 per 1000 deliveries.[2] Of concern, caesarean births have been rising globally. CS rates have risen from about 5% in developed countries in the early 1970s to more than 50% in some regions of the world in the late 1990s.[8,9]

PPHN is also a risk factor for pulmonary arterial hypertension (PAH) later on in life.[10,11] The pathobiology of pediatric pulmonary vascular disease (PVD) often includes impaired or dysregulated growth of the

Author Affiliations: Department of Neonatology, Children Hospital of Fudan University, Shanghai, China (Babooa N, Shi WJ, Chen C)

Corresponding Author: Chao Chen, Department of Neonatology, Children Hospital of Fudan University, Shanghai 201102, China (Email: chen6010@163.com)

doi: 10.1007/s12519-017-0056-z

developing lung circulation, which plays an especially critical role in pediatric disorders such as PPHN. Disruption of normal angiocrine signaling between endothelial and epithelial cells decreases lung airspace growth and surface area for gas exchange and increases the risk of PAH. These changes may further play a role in determining risk of or susceptibility to PVD and PAH throughout adulthood.[12]

In order to optimize neonatal and long-term outcomes in caesarean births, it is crucial that we understand the contribution of caesarean delivery in the pathogenesis of respiratory morbidities in the newborn, including PPHN. Even though much progress has been made in recent years with respect to understanding the complex pathogenesis of PPHN, the role played by caesarean delivery is still not clear. In this review, we aim to discuss the various mechanisms through which caesarean delivery could potentially increase the risk of PPHN and explore preventive measures to minimize CS-related PPHN.

Pathogenesis of PPHN

At birth the pulmonary circulation must undergo a marked fall from its high resistance state *in utero* to a low resistance circuit within minutes after delivery to ensure survival of the newborn. This postnatal fall in pulmonary vascular resistance allows for the 8-fold increase in pulmonary blood flow, and allows the lung to become an organ for gas exchange. Several mechanisms contribute to the normal fall in PVR at birth, including increased oxygen tension, ventilation, and shear stress. These physiologic stimuli lower PVR directly and through changes in the production of several vasoactive products, including increased release of potent endogenous dilators, such as nitric oxide (NO) and prostacyclin, and decreased activity of vasoconstrictors, such as endothelin-1 (ET-1). Some infants fail to achieve or sustain the normal decrease in PVR at birth, leading to severe respiratory distress and hypoxemia, which is referred to as PPHN.[13,14]

Factors linking PPHN to CS

Interpreting the association between CS and PPHN is made challenging by the fact that certain antecedents (e.g., fetal distress) might serve both as indications for CS and as underlying causes, consequences, or markers for PPHN.[3] Hernandez-Diaz et al[3] suggested that the increased incidence of PPHN after CS might be largely attributable to underlying fetal conditions that triggered the intervention and ultimately resulted in PPHN, rather than to a direct causal effect of the CS (or lack of VD) per se. However, several other studies showed a consistently higher incidence of PPHN in infants born by elective CS (ECS) prior to onset of labor compared to those born by VD, thereby confirming that caesarean delivery is in itself a significant risk factor for PPHN.[2-4,7]

Lack of physiological changes of labor

A likely hypothesis for persistent pulmonary hypertension after CS is that there might be an advantage to labor and VD for the pulmonary vascular bed of the neonate.[4] Makihara et al[15] supported this hypothesis through echocardiography findings showing that transient pulmonary hypertension after delivery is prolonged in neonates delivered by ECS compared to vaginally delivered neonates.

The etiology of PPHN delivered by ECS is unclear. Most infants begin as being normal or have mild transient tachypnea of the newborn (TTN) with minimal oxygen requirement and chest X-rays suggestive of retained lung fluid. However, in a subset of infants, there is a gradual increase in oxygen requirement and subsequent evidence of PPHN. Prematurity is not a significant issue in these neonates.[16] Thus, although TTN is usually benign, it can result in delay in normal newborn transition, which occasionally causes severe hypoxemia with a considerable oxygen requirement, and ultimately, PPHN necessitating mechanical ventilation, inhaled nitric oxide, or extracorporeal membrane oxygenation.[2]

Delayed resorption of fetal lung fluid after delivery is considered the main pathophysiological factor in TTN.[17] Pulmonary hypertension with right-to-left shunting across the ductus or foramen ovale may be present in these infants because of possible elevation in the PVR associated with retained fetal lung fluid.[18]

Several studies have documented higher incidence of TTN in infants born by CS before the onset of spontaneous labor compared to infants born by VD.[4,17,19,20] Levine et al[4] and Hook et al[19] both demonstrated that infants born by ECS were at least 2.5 times more likely to suffer from TTN compared to neonates delivered by VD. A large study further demonstrated that the duration of labor before birth positively influences the course of TTN, with the duration of oxygen supplementation inversely associated with the duration of labor.[17] Labor therefore appears to exert an influence on the postnatal adaptation of the respiratory system.[21] Just how the experience of labor brings about this respiratory adaptation is not known, but several mechanisms could be proposed:

1) Labor appears to play an important role in fetal lung fluid clearance. Rapid removal of liquid from potential airspaces is a key step in establishing the timely switch from placental to pulmonary gas exchange at birth.[22] For effective gas exchange to occur in the neonate at birth, alveolar spaces must be cleared of excess fluid and pulmonary blood flow

increased to match ventilation with perfusion. Failure of either of these events can jeopardize neonatal transition and cause the infant to develop respiratory distress.[16]

Fetal lungs are filled with liquid in the airspaces. In comparison to neonatal lungs, fetal lungs are hyperexpanded. This probably results in greater extraluminal pressures surrounding the pulmonary vasculature which contributes importantly to high PVR in the fetus.[14] Rapid fluid clearance at birth is therefore very important as it leads to a drop in the extraluminal pressure with a subsequent decrease in PVR and thus an increase in the pulmonary blood flow, as demonstrated in animal models.[14,23]

It is now known that traditional explanations, which relied on "starling forces" and "vaginal squeeze" only account for a fraction of the fluid absorbed.[16,22] Alveolar fluid clearance is a process which starts before birth and continues postnatally.[16] The fetus in fact begins its preparation for a smooth neonatal transition long before the onset of labor by changing its hormonal milieu and by reducing lung fluid secretion.[24] Animal studies have demonstrated that in the days leading up to labor the rate of production of lung liquid is reduced[25] and the volume of liquid contained in the fetal lungs declines.[26,27] A further decline in lung liquid volume occurs during labor itself.[28]

The lung epithelium is believed to undergo a switch, mediated by B-adrenergic receptors, from a predominantly chloride secreting membrane at birth to a predominantly sodium absorbing membrane after birth.[22,24] Epithelial Na channels (ENaC) are rate limiting in this process and developmentally timed for maximum expression only in late gestation.[29] Studies have shown that alveolar expression of these highly selective sodium channels in the lung epithelia is regulated by factors in the lung microenvironment such as steroids, catecholamines, and oxygen.[16,30-32] Higher levels of epinephrine, nor-epinephrine and cortisol have been found in neonates delivered by VD than in those delivered by CS without labor.[33] The increasing concentration of cortisol and thyroid hormones in the last days of gestation and during labor itself may accelerate maturation of the lung and play a key role in lung liquid reabsorption.[21,34]

The above sequence of events highlights the importance of labor in fetal lung fluid clearance, which leads to a decrease in the PVR and subsequent establishment of the neonatal pulmonary circulation, failure of which leads to PPHN.

2) Surfactant synthesis and release are increased during labor, by mechanisms that may partly depend upon β-stimulation.[21] CS-delivered neonates have in fact been observed to be at a higher risk for respiratory distress syndrome (RDS), a condition characterized by immaturity and insufficient production of pulmonary surfactant, as compared to their vaginally delivered counterparts.[20,35,36] Gerten et al[36] identified CS delivery as an independent risk factor for RDS when compared to neonates delivered vaginally (adjusted odds ratio: 2.3, (95% confidence interval: 2.1-2.6). RDS is recognised as one of the variety of perinatal and postnatal conditions that can cause secondary PPHN.[37]

3) The adrenaline surge that occurs in labor, in addition to promoting lung liquid reabsorption, might have other effects that improve respiratory performance after birth, for example by arousing the newborn and thereby adding a powerful wakefulness drive to breathe.[21]

4) Stress hormones can promote normal circulatory adaptation at birth. Several experimental and clinical studies have shown that norepinephrine improves circulation in the perinatal lung. In fetal lambs, norepinephrine has been shown to increase lung blood flow and reduce PVR.[38] Norepinephrine induces a NO-dependent pulmonary vasodilation in the ovine fetus through activation of α_2-adrenoceptors.[39,40] Jaillard et al[41] suggested that high incidence of PPHN delivered by ECS is related to lower levels of circulating norepinephrine in neonates after CS than after VD. Infants delivered through ECS often are deprived of these labor-related physiological stress response pattern at birth and consequently experience failure of postnatal respiratory transition.[42]

Role of iatrogenic prematurity

Studies evaluating large series of patients have shown a higher rate of prematurity and surfactant deficiency in neonates delivered by ECS.[16] Delivery by CS appears to expose neonates to higher risks of iatrogenic prematurity in the following ways:

Rising rates of CS: contribution to increasing rates of late preterms

Since ECS is commonly performed between 37 and 40 weeks gestation, it was believed that at least some of the respiratory morbidity in newborns delivered by ECS was secondary to iatrogenic prematurity. i.e., inadvertent delivery prior to 37 completed weeks of gestation.[16]

Delivery by CS could expose infants to iatrogenic prematurity and its associated respiratory morbidities through its contribution to increased rates of late preterm births. Analyses of the 1996 and 2004 US natality files showed that among preterm births, the largest percentage increase in CS rates occurred in the late preterm group, which is the largest and fastest growing segment of preterm births.[43]

Inaccurate gestational age assessment during elective deliveries, presumption of fetal maturity at 34

weeks' gestation and maternal autonomy with regards to route and timing of delivery have been proposed as some of the factors explaining the increase in late preterm births. Indeed, if gestational age estimates vary by even 1 or 2 weeks, elective induction of labor or ECS may be associated with premature delivery of a late preterm or early term infant.[44]

In obstetric practice, 34 completed weeks is considered a maturational milestone for the fetus.[45] Yet a large amount of evidence now show that compared with term infants, late-preterm infants, defined by birth at 34 0/7 through 36 6/7 weeks' gestation,[46] are in fact less physiologically and metabolically mature[46] and suffer from higher rates of morbidity and mortality.[47,48]

The relatively immature lung structure may be associated with delayed intrapulmonary fluid absorption, surfactant insufficiency, and inefficient gas exchange.[49,50] Little is known about cardiovascular physiology and pathobiology in late-preterm infants; it is however generally believed that structural and functional immaturity restricts the amount of cardiovascular reserve that is available during times of stress.[46] Immature cardiovascular function also may complicate recovery of the late-preterm infant with respiratory distress because of delayed ductus arteriosus closure and persistent pulmonary hypertension.[51] These features of relative overall immaturity, combined with limited compensatory responses to the extra-uterine environment[46] all predispose these infants to respiratory problems related to delayed transition and overall immaturity.[52]

Late preterm infants have been reported to be at higher risk for respiratory complications such as delayed lung fluid clearance, RDS and pulmonary hypertension as compared to term infants.[53-56] Hernandez Diaz et al[3] reported that the risk of PPHN was at least 3 times higher for neonates born between 34 and 37 completed weeks compared to those who were born within 37 to 41 gestational weeks.

Delivery by CS: an additional level of risk for respiratory morbidity both in late preterm and term newborns

As compared to infants born vaginally, delivery by CS appears to add another level of risk for an adverse respiratory outcome in this already vulnerable population.[54,56,57] This increased risk persists even in infants who are delivered by CS at full term (i.e., at or beyond 37 completed weeks of gestation).[4,35,58-60] Morrison et al[61] showed that respiratory morbidity in ECS is inversely related to gestational age at the time of ECS in term infants. A large prospective cohort study demonstrated an increased risk of respiratory morbidity (TTN, RDS and PPHN) for infants delivered by ECS at 37, 38 and 39 weeks' gestation (adjusted odds ratios: 7.0, 3.5 and 1.4, respectively) when compared with newborns intended for VD.[60]

A particularly high risk for respiratory distress was observed when ECS was performed before 39 weeks of gestation; therefore, CS may increase the risk of PPHN through delivery of infants who have significant pulmonary immaturity, which sets the stage for a maladaptive perinatal circulatory transition.[3] As mentioned previously, CS-delivered infants are deprived of the physiological changes associated with labor, which include an increase in surfactant synthesis and release.[21]

We believe that CS-born infants are exposed to varying extents of the pathophysiological events experienced in TTN and RDS, a combination of which could possibly lead to a common endpoint of respiratory distress, hypoxia and acidosis, thus leading to high PVR and higher risk of developing PPHN.

Role of vasoactive agents

Role of NO, carbon monoxide (CO) and cyclic guanosine 3', 5'-monophosphate (cGMP)

The NO-cGMP cascade involves production of NO primarily by vascular endothelium during the conversion of L-arginine to L-citrulline by the enzyme NO synthase (NOS). Once produced, NO rapidly diffuses to underlying smooth muscle cells and causes vasodilation by stimulating soluble guanylate cyclase and increasing cGMP production. Elevated cGMP levels stimulate cGMP kinase, which then opens calcium-activated K^+ channels and causes membrane hyperpolarization. This lowers intracellular calcium in the smooth muscle cell by decreasing calcium entry through L-type channels and causes vasodilation. In some experimental settings, NO has been shown to stimulate K^+ channels or voltage gated Ca^{2+} channels directly independent of increased cGMP.[62] Studies over the past two decades have clearly shown the critical role of NO-cGMP signalling in the regulation of the fetal and neonatal pulmonary circulation, and that disruption of the NO-cGMP cascade during the perinatal period leads to PPHN.[13] Decreased endothelial NOS (eNOS) expression,[63,64] reduced release of endothelium-derived NO[14] and decreased plasma cGMP levels[65] have all been documented in PPHN in human infants and in a number of animal models.

Reactive oxygen species (ROS) and NO have been shown to play a major role in the regulation of pulmonary vascular tone. The production of cGMP, the intracellular second messenger of NO, also influences the tone of pulmonary vessels during the first weeks of life.[66] CO has been found to induce vasodilation, increasing intracellular levels of cGMP in vascular smooth muscle cells similarly to NO[66] although the vasorelaxant potency of CO is markedly less than that of NO.[67]

Dani et al[66] investigated the levels of NO, CO and cGMP in healthy term infants born by VD compared to those delivered by ECS. The study showed that NO,

CO and cGMP concentrations were significantly lower in infants born by ECS than in vaginally born infants and decreased from birth to 48-72 hours of life in both groups. The authors of the study speculated that this occurs because fetuses experience many stresses during parturition, such as hypoxia, ischemia-reperfusion and tissue shear stress, which can strongly stimulate the expression of genes encoding inducible NOS (iNOS) and inducible enzyme heme oxygenase-1 (HO-1). They therefore suggested that an increase in activity of iNOS and HO-1 occurs at delivery which promotes the synthesis of NO, CO and in turn, cGMP.[66] NO and CO, acting as modulators of pulmonary vasculature tone, likely play a physiologic role in the transition from fetal to neonatal circulation by lowering the PVR. Accordingly, the lower level of NO and CO observed in the infants born by ECS could represent one of the causes for the increased risk of respiratory disorders (through the inadequate decrease of PVR) which these infants exhibit in comparison with vaginally delivered infants.[66]

We therefore suspect that inadequate decrease of PVR resulting from limited endogenous NO, cGMP and CO synthesis observed in CS-born infants could possibly place them at higher risk for delayed transition and PPHN. Further studies are however needed to determine the exact causal relationship between mode of delivery and secretion of vasoactive mediators in the fetal and neonatal lung.

Role of ET

ETs are a family of bicyclic 21-amino acid peptides composed of three isoforms: ET-1, ET-2, and ET-3. ET-1 is the major isoform with vasoactive properties. Endothelial cells are the major source of ET-1. When subjected to various stimuli such as shear stress, hypoxia or ischemia, ET-1 is transcripted, synthesized, and secreted within minutes.[14] ET-1 has potent vasoconstrictor and smooth-muscle cell mitogenic properties, as well as dose- and receptor-dependent vasodilator properties.[65]

Newborn infants with persistent pulmonary hypertension have been shown to have elevated plasma ET-1 levels,[65,68,69] which correlate with disease severity and decline with clinical improvement.[70] Experimental studies suggest that elevated ET-1 levels in PPHN contribute to the disease process by bringing about increased pulmonary vascular remodeling and downregulation of eNOS expression.[14,71,72]

CS per se does not appear to expose newborns to higher ET levels compared to those born by VD.[73-75] CS has however been shown to be a risk factor for the development of RDS[20,35,36] which is one of the secondary causes of PPHN.[37]

An experimental model of RDS in the newborn lamb showed that plasma ET-1 concentration increases concomitant with the development of pulmonary hypertension, from an early time point onward, and correlates with the severity of pulmonary hypertension.[76]

To determine whether ET-1 activity contributes to high PVR in the premature fetal lung with severe RDS or is simply a marker of disease activity, selective ET A receptor blockade was done in an ovine model of RDS. The selective ET A receptor blockade lowered PVR in experimental RDS, thereby suggesting that ET-1 contributes to pulmonary hypertension in an ovine model of severe RDS.[77]

Neonates with RDS were found to have significantly higher ET-1 concentrations in the acute phase of RDS compared to controls. ET levels also showed correlation with the clinical severity and radiological degree of RDS, suggesting that ET-1 plays a role in the natural course of RDS in newborns.[75,78-81]

We thereby conclude that CS delivery might indirectly lead to higher risks of developing PPHN by exposing infants to a higher risk of RDS and its concomitant increase in ET-1 levels. The contribution of high plasma ET-1 levels in the acute phase of RDS to the elevation of the PVR in neonates with RDS is however uncertain and remains to be confirmed.[81]

Role of oxidative stress

Several lines of evidence indicate that oxidative stress plays an important role in the pathogenesis of PPHN.[82-85] Animal models of PPHN have demonstrated an increase in ROS in the pulmonary vasculature which led to blunting of vascular relaxation to exogenous NO, stimulation of smooth muscle cell growth[82] and impaired angiogenesis of pulmonary artery endothelial cells which then contributed to elevated PVR seen in PPHN.[83]

Extracellular superoxide dismutase (ecSOD) is the only known enzymatic scavenger of extracellular superoxide and is highly expressed within the lungs and vascular smooth muscles. Superoxide scavenging in the vascular extracellular space by ecSOD plays an important role in regulating vasodilatation.[85] Brennan et al[82] showed that superoxide levels were increased and SOD activity was decreased in the pulmonary arteries of fetal PPHN lambs, and thus concluded that PPHN is associated with an overproduction of the oxidant superoxide without a simultaneous increase in cellular antioxidant capacity.

The fetus is protected from oxidative stress in several ways. The human placenta has been described as being protective against oxidative stress.[86,87] Moreover, intracellular ROS levels are maintained by enzymatic and non-enzymatic antioxidant defenses within a physiological range to prevent their harmful effects.[14]

Many factors may interact or independently influence oxidative stress during fetal neonatal transition, including the mode of delivery.[88] The process of birth can

potentially induce oxidative stress in the newborn. The transition from fetal to neonatal environment exposes the newborn to a more oxidative environment. High oxygen concentration could be toxic to fetal tissues, via mechanisms mediated by free radicals.[89]

Several studies have been carried out to determine which mode of delivery exposes the neonate to higher levels of oxidative stress[66,88-98] and hence determine which mode of delivery is most advantageous to the newborn in terms of oxidative stress. The results of these studies are however largely inconsistent with each other. Some authors reported similar levels of oxidative stress in infants irrespective of the mode of delivery[66,93] while others reported that the mode of delivery influences the level of exposure to oxidants as well as the protective anti-oxidant mechanisms in the neonate.[88-90,92,94-98]

Studies investigating the effect of mode of delivery on the levels of different markers of oxidation in the newborn have also yielded inconclusive results. Mutlu et al[94] and Nabhan et al[88] reported higher oxidant and lower anti-oxidant levels in neonates delivered by CS than those delivered by VD. Mutlu et al[94] thereby concluded that newborns delivered by CS are exposed to higher oxidative stress compared to vaginally delivered newborns, and the anti-oxidant mechanisms are insufficient to cope with this stress during CS, indicating that normal delivery through the physiological route is healthier for infants.

In contrast, several studies demonstrated higher oxidant levels in newborns delivered by VD compared to those delivered by CS.[91,92,95,97] The authors suggested that these results support a role of ROS in the initiation of labor, which is associated with an increased production of pro-inflammatory mediators, which in turn might induce an increase in the production of free radicals.[92,95,96]

An alternative explanation is that the high levels of free oxygen radical activity in the fetus delivered by VD are produced as a function of the labor process.[91,92,95,96] Uterine contractions during labor result in diminution of the arterial inflow to, and cessation of venous drainage from the placenta. This situation is reversed during the relaxation phase, leading to recurrent ischemia-reperfusion, free radical production and a rise in lipid peroxidation.[91]

The observation of higher levels of oxidants in vaginally delivered neonates led Vakilian et al[95] to conclude that VD neonates are under more oxidative stress than those delivered by ECS and that ECS thereby has advantages for newborns in terms of lowering oxidative stress. Rogers et al[91] however countered that, as all the infants in these studies ultimately had a satisfactory outcome, it can be assumed that the levels of lipid peroxidation observed in neonates delivered by VD indicate cellular damage that is within the scope of the neonate to repair without significant long term sequelae. They thus concluded that the low levels of peroxidation associated with ECS should therefore not be used to construe any benefit associated with this approach.

Studies investigating the effect of mode of delivery on the levels of anti-oxidants in newborns have likewise demonstrated conflicting results, though to a lesser degree.[86,88-90,94-99] While Inanc et al[97] reported higher levels of anti-oxidant activity in neonates delivered by ECS compared to those born by VD, numerous other authors have, on the contrary, demonstrated higher levels of anti-oxidants in neonates born by VD compared to those delivered by CS.[88-90,94-96,98,99]

Georgeson et al[96] proposed that increased free radical production during labor suggests that the oxidative burden of infants born via ECS might be lower, thus perhaps resulting in lower antioxidant enzyme expression and lower activity levels as well. On the other hand, infants born via VD might be exposed to higher levels of ROS and antioxidant defense systems of these newborns might therefore show higher total antioxidant power to overcome free radicals.[95] Buhimschi et al[90] further suggested that term labor triggers a compensatory up-regulation of non-enzymatic antioxidant reserve in the fetal red blood cell compartment that may act to protect against the relative hyperoxia that is experienced by the newborn infant at birth.

Georgeson et al[96] concluded that delivery by CS may cause a deficiency of antioxidant defense in the human newborn and suggested that neonates born via CS might therefore be predisposed to pathological conditions in which ROS may play a pathogenic role, such as PPHN[82,83] and RDS[100] among others. However, because of the large disparity in the results described above, additional studies are needed to determine more precisely the effect of mode of labor on the oxidant-anti-oxidant balance in neonates and the repercussions on the neonatal outcome.

Potential preventive and therapeutic interventions to minimize CS-related PPHN

Antenatal corticosteroids

Antenatal corticosteroids reduce the incidence of respiratory distress in preterm neonates[101] and their routine use is recommended when delivery is expected before 34 weeks' gestation.[102] Mechanisms of steroid-induced lung maturation include increased surfactant production, altered parenchymal lung structure, induction of lung ENaC channels and up-regulation of eNOS.[31,103] Animal experiments have moreover shown that antenatal glucocorticoids enhance pulmonary vasodilatation

induced by alveolar ventilation at birth, leading the authors to speculate that antenatal steroids exposure improves adaptation at birth through acceleration of both parenchymal and vascular lung maturation.[104]

The benefits of antenatal corticosteroids are not limited to preterm neonates. The well-established benefits of antenatal corticosteroids prompted the Antenatal Steroids for Term Elective Caesarean Section study which demonstrated a non-significant decreased risk of TTN [0.040 *vs*. 0.021; relative risk (RR)=0.54, 95% confidence interval (CI)=0.26-1.12] and RDS (0.011 *vs*. 0.002; RR=0.21, 95% CI=0.03-1.32).[105] Follow up studies did not show any adverse effect on health, behavior and academic achievement of children born following a single course of antenatal betamethasone at term.[106] Antenatal corticosteroids have also been shown to confer benefits to late preterm neonates through lowered incidence of transient tachypnea, need for respiratory support and admission to the neonatology unit.[107] The use of antenatal corticosteroids in late preterm births and in ECS carried out prior to 39 weeks of gestation could therefore potentially decrease rates of PPHN through diminished respiratory morbidity in these neonates.

The informed-consent process

Cesarean births in low risk or "no risk" mothers where no medical indication can be identified are on the rise and are often referred to as Cesarean Delivery at Maternal Request (CDMR).[16] Based on a number of reported series, it was estimated in 2004 that CDMR accounted for nearly 4% to 18% of all cesarean deliveries[108] and that figure was estimated to be as high as 28.43% in a large multicenter study in China in 2011.[109]

Every pregnant woman justifiably wishes a short labor and an uneventful delivery without complications, which explains the growing number of mothers tending toward ECS.[17] However in view of the neonatal respiratory morbidities associated with ECS, pregnant women should be given reliable information about the risks and benefits related to ECS in order to avoid unnecessary CS deliveries. Gestational age-specific risk estimates for neonatal morbidity are lowest between 38 and 40 weeks and should be included in the informed-consent process.[110]

Potential role of antenatal anti-oxidants

Prenatal maternal anti-oxidant supplementation has been investigated in relation to neonatal outcomes

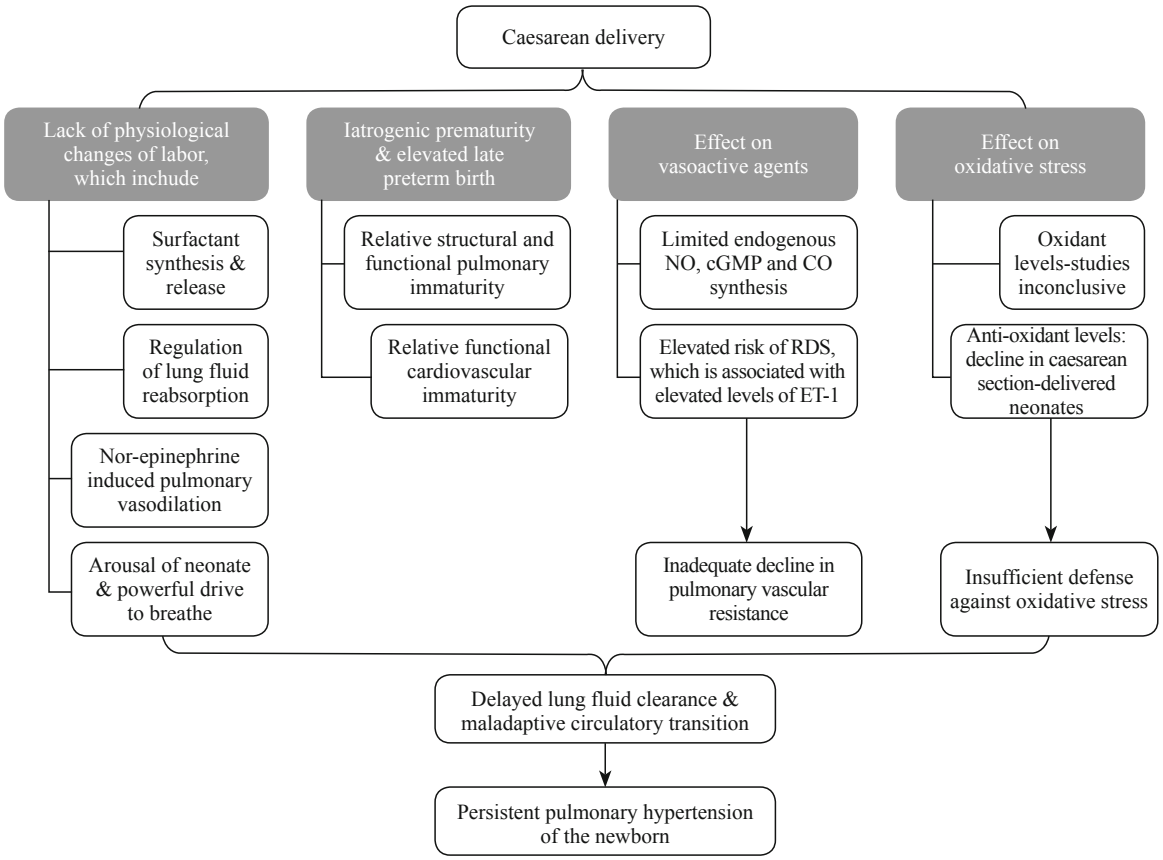

Fig. Schematic overview of the proposed mechanisms underlying the link between delivery by caesarean section and persistent pulmonary hypertension of the newborn. NO: nitric oxide; cGMP: cyclic guanosine 3', 5'-monophosphate; CO: carbon monoxide; RDS: respiratory distress syndrome; ET-1: endothelin-1.

for diseases in which oxidative stress is known to be implicated. For instance, a study showed that maternal docosahexaenoic acid-enriched diet during pregnancy provided neuroprotection to a murine model of neonatal hypoxic-ischemic encephalopathy by inhibiting oxidative stress and apoptotic neuronal death.[111]

In view of the observations linking oxidative stress to PPHN[82,83] and of the finding that delivery by CS may cause a deficiency of antioxidant defense in human newborn,[96] it may be reasonable to assess whether antioxidant supplementation during pregnancy may be beneficial to neonates delivered by ECS.

Delaying ECS to at least 39 weeks of gestation

A large body of evidence indicates that ECS before 39 weeks of gestation is associated with increased risks of respiratory morbidity, compared with delivery at 39 or 40 weeks.[35,55,59,112-114]

The American College of Obstetrics and Gynecology therefore recommends scheduling ECS at 39 weeks' gestation or later on the basis of menstrual dates or waiting for the onset of spontaneous labor, which is a step toward minimizing the occurrence of iatrogenic prematurity.[16] One of the causes cited for the rise in CS rates is the changing practice standards of medical professionals and their willingness to perform CS either due to their perceived safety or fear of malpractice litigation.[16] However, given that delivery by CS is a predictor for infants with high risk for PPHN and other respiratory morbidities, obstetricians should consider this added morbidity when performing elective cesareans and ECS should only be undertaken before 39 weeks gestation for established medical reasons.[55]

Conclusions

In view of the rising rates of CS worldwide, there is an urgent need for better understanding of the mechanisms linking CS and PPHN. Iatrogenic prematurity and lack of physiological changes of labour have since long been described as factors linking CS to PPHN. Delivery by CS could also result in limited endogenous NO, cGMP and CO synthesis and lower levels of anti-oxidants in the neonate. In addition, delivery by CS exposes infants to a higher risk of RDS and its concomitant increase in ET-1 levels, and might therefore indirectly lead to higher risks of developing PPHN. We believe that neonates born via CS might be exposed to varying extents of the pathophysiological events described above, a combination of which could possibly lead to a common endpoint of respiratory distress, hypoxia and acidosis, thus leading to high pulmonary vascular resistance, delayed transition and higher risks of developing PPHN (Fig.).

Further experimental studies should be carried out to determine the exact causal relationship between CS and PPHN followed by testing of therapeutic options to allow effective targeted interventions. There are still many gaps in our knowledge regarding the long-term consequences of PPHN. Experimental studies and follow up of PPHN patients should therefore be encouraged to explore the long term impact of PPHN on the pulmonary circulation such as the occurrence of PAH later on in these patients. Further studies are also necessary to assess other therapeutic options such as the impact of maternal anti-oxidant supplementation and antenatal corticosteroids in late preterm neonates and in ECS on the incidence of PPHN.

Given that cesarean delivery at maternal request accounts for a considerable proportion of CS deliveries, pregnant women should be provided with reliable data regarding the neonatal risks of ECS to prevent unnecessary CS deliveries. ECS should ideally be delayed till 39 weeks or later where such an option is medically safe.

Funding: None.
Ethical approval: As this work is a review article, approval was not required from the institutional ethics committee.
Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.
Contributors: All authors contributed to the conception and design of the article and the collection of articles for review. Chen C proposed the study. Babooa N performed the literature review and wrote the manuscript. Both Chen C and Shi WJ contributed to revisions of the manuscript for intellectual content. All authors approved the final version of the article.

References

1 Roofthooft MT, Elema A, Bergman KA, Berger RM. Patient characteristics in persistent pulmonary hypertension of the newborn. Pulm Med 2011;2011:858154.
2 Winovitch KC, Padilla L, Ghamsary M, Lagrew DC, Wing DA. Persistent pulmonary hypertension of the newborn following elective cesarean delivery at term. J Matern Fetal Neonatal Med 2011;24:1398-1402.
3 Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Mitchell AA. Risk factors for persistent pulmonary hypertension of the newborn. Pediatrics 2007;120:E272-E282.
4 Levine EM, Ghai V, Barton JJ, Strom CM. Mode of delivery and risk of respiratory diseases in newborns. Obstet Gynecol 2001;97:439-442.
5 Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Elective caesarean section and respiratory morbidity in the term and near-term neonate. Acta Obstet Gynecol Scand 2007;86:389-394.
6 Araujo OR, Albertoni AD, Lopes VA, Louzada ME, Lopes AO, Cabral EA, et al. Cesarean deliveries and other risks for persistent pulmonary hypertension of the newborn. Rev Bras Ter Intensiva 2008;20:394-397.
7 Wilson KL, Zelig CM, Harvey JP, Cunningham BS, Dolinsky BM, Napolitano PG. Persistent pulmonary hypertension of

the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. Am J Perinatol 2011;28:19-24.
8 Villar J, Valladares E, Wojdyla D, Zavaleta N, Carroli G, Velazco A, et al. Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. Lancet 2006;367:1819-1829.
9 Menacker F, Declercq E, Macdorman MF. Cesarean delivery: background, trends, and epidemiology. Semin Perinatol 2006;30:235-241.
10 Haworth SG. Pulmonary hypertension in the young. Heart 2002;88:658-664.
11 Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U. Augmented vasoreactivity in adult life associated with perinatal vascular insult. Lancet 1999;353:2205-2207.
12 Abman SH, Baker C, Gien J, Mourani P, Galambos C. The Robyn Barst Memorial Lecture: differences between the fetal, newborn, and adult pulmonary circulations: relevance for age-specific therapies (2013 Grover Conference series). Pulm Circ 2014;4:424-440.
13 Abman SH. Recent advances in the pathogenesis and treatment of persistent pulmonary hypertension of the newborn. Neonatology 2007;91:283-290.
14 Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. Physiol Rev 2010;90:1291-1335.
15 Makihara K, Hata T, Hata K, Kitao M. Echocardiographic assessment of systolic time intervals in vaginal and cesarean delivered neonates. Am J Perinatol 1993;10:53-57.
16 Ramachandrappa A, Jain L. Elective cesarean section: its impact on neonatal respiratory outcome. Clin Perinatol 2008;35:373-393, vii.
17 Tutdibi E, Gries K, Bucheler M, Misselwitz B, Schlosser RL, Gortner L. Impact of labor on outcomes in transient tachypnea of the newborn: population-based study. Pediatrics 2010;125:e577-e583.
18 Guglani L, Lakshminrusimha S, Ryan RM. Transient tachypnea of the newborn. Pediatr Rev 2008;29:e59-e65.
19 Hook B, Kiwi R, Amini SB, Fanaroff A, Hack M. Neonatal morbidity after elective repeat cesarean section and trial of labor. Pediatrics 1997;100:348-353.
20 Dani C, Reali MF, Bertini G, Wiechmann L, Spagnolo A, Tangucci M, et al. Risk factors for the development of respiratory distress syndrome and transient tachypnoea in newborn infants. Italian Group of Neonatal Pneumology. Eur Respir J 1999;14:155-159.
21 Berger PJ, Smolich JJ, Ramsden CA, Walker AM. Effect of lung liquid volume on respiratory performance after caesarean delivery in the lamb. J Physiol 1996;492:905-912.
22 Bland RD. Loss of liquid from the lung lumen in labor: more than a simple "squeeze". Am J Physiol Lung Cell Mol Physiol 2001;280:L602-L605.
23 Hooper SB. Role of luminal volume changes in the increase in pulmonary blood flow at birth in sheep. Exp Physiol 1998;83:833-842.
24 Jain L. Alveolar fluid clearance in developing lungs and its role in neonatal transition. Clin Perinatol 1999;26:585-599.
25 Kitterman JA, Ballard PL, Clements JA, Mescher EJ, Tooley WH. Tracheal fluid in fetal lambs: spontaneous decrease prior to birth. J Appl Physiol Respir Environ Exerc Physiol 1979;47:985-989.
26 Dickson KA, Maloney JE, Berger PJ. Decline in lung liquid volume before labor in fetal lambs. J Appl Physiol (1985) 1986;61:2266-2272.
27 Berger PJ, Kyriakides MA, Smolich JJ, Ramsden CA, Walker AM. Massive decline in lung liquid before vaginal delivery at term in the fetal lamb. Am J Obstet Gynecol 1998;178:223-227.
28 Bland RD, Hansen TN, Haberkern CM, Bressack MA, Hazinski TA, Raj JU, et al. Lung fluid balance in lambs before and after birth. J Appl Physiol Respir Environ Exerc Physiol 1982;53:992-1004.
29 Jain L. Respiratory morbidity in late-preterm infants: prevention is better than cure! Am J Perinatol 2008;25:75-78.
30 Finley N, Norlin A, Baines DL, Folkesson HG. Alveolar epithelial fluid clearance is mediated by endogenous catecholamines at birth in guinea pigs. J Clin Invest 1998;101:972-981.
31 Venkatesh VC, Katzberg HD. Glucocorticoid regulation of epithelial sodium channel genes in human fetal lung. Am J Physiol 1997;273:L227-L233.
32 Jesse NM, McCartney J, Feng X, Richards EM, Wood CE, Keller-Wood M. Expression of ENaC subunits, chloride channels, and aquaporins in ovine fetal lung: ontogeny of expression and effects of altered fetal cortisol concentrations. Am J Physiol Regul Integr Comp Physiol 2009;297:R453-R461.
33 Vogl SE, Worda C, Egarter C, Bieglmayer C, Szekeres T, Huber J, et al. Mode of delivery is associated with maternal and fetal endocrine stress response. BJOG 2006;113:441-445.
34 Barker PM, Olver RE. Invited review: clearance of lung liquid during the perinatal period. J Appl Physiol (1985) 2002;93:1542-1548.
35 Zanardo V, Simbi AK, Franzoi M, Solda G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective caesarean delivery. Acta Paediatrica 2004;93:643-647.
36 Gerten KA, Coonrod DV, Bay RC, Chambliss LR. Cesarean delivery and respiratory distress syndrome: does labor make a difference? Am J Obstet Gynecol 2005;193:1061-1064.
37 Razzaq A, Iqbal Quddusi A, Nizami N. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pak J Med Sci 2013;29:1099-1104.
38 Jaillard S, Houfflin-Debarge V, Riou Y, Rakza T, Klosowski S, Lequien P, et al. Effects of catecholamines on the pulmonary circulation in the ovine fetus. Am J Physiol Regul Integr Comp Physiol 2001;281:R607-R614.
39 Storme L, Aubry E, Rakza T, Houeijeh A, Debarge V, Tourneux P, et al. Pathophysiology of persistent pulmonary hypertension of the newborn: impact of the perinatal environment. Arch Cardiovasc Dis 2013;106:169-177.
40 Magnenant E, Jaillard S, Deruelle P, Houfflin-Debarge V, Riou Y, Klosowski S, et al. Role of the alpha2-adrenoceptors on the pulmonary circulation in the ovine fetus. Pediatr Res 2003;54:44-51.
41 Jaillard S, Houfflin-Debarge V, Storme L. Higher risk of persistent pulmonary hypertension of the newborn after cesarean. J Perinat Med 2003;31:538-539.
42 Jain L, Dudell GG. Respiratory transition in infants delivered by cesarean section. Semin Perinatol 2006;30:296-304.
43 Bettegowda VR, Dias T, Davidoff MJ, Damus K, Callaghan WM, Petrini JR. The relationship between cesarean delivery and gestational age among US singleton births. Clin Perinatol 2008;35:309-323, v-vi.
44 Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. Clin Perinatol 2008;35:325-341, vi.
45 Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006;118:1207-1214.

46 Engle WA, Tomashek KM, Wallman C. "Late-preterm" infants: a population at risk. Pediatrics 2007;120:1390-1401.
47 Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 2004;114:372-376.
48 Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284:843-849.
49 Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. Semin Perinatol 2006;30:28-33.
50 Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of Labor. Semin Perinatol 2006;30:34-43.
51 Randala M, Eronen M, Andersson S, Pohjavuori M, Pesonen E. Pulmonary artery pressure in term and preterm neonates. Acta Paediatr 1996;85:1344-1347.
52 Jain L. Morbidity and mortality in late-preterm infants: more than just transient tachypnea! J Pediatr 2007;151:445-446.
53 Hibbard JU, Wilkins I, Sun L, Gregory K, Haberman S, Hoffman M, et al. Respiratory morbidity in late preterm births. JAMA 2010;304:419-425.
54 Anadkat JS, Kuzniewicz MW, Chaudhari BP, Cole FS, Hamvas A. Increased risk for respiratory distress among white, male, late preterm and term infants. J Perinatol 2012;32:780-785.
55 Madar J, Richmond S, Hey E. Surfactant-deficient respiratory distress after elective delivery at "term". Acta Paediatr 1999;88:1244-1248.
56 Yoder BA, Gordon MC, Barth WH Jr. Late-preterm birth: does the changing obstetric paradigm alter the epidemiology of respiratory complications? Obstet Gynecol 2008;111:814-822.
57 Malloy MH. Impact of cesarean section on intermediate and late preterm births: United States, 2000-2003. Birth 2009;36:26-33.
58 Fogelson NS, Menard MK, Hulsey T, Ebeling M. Neonatal impact of elective repeat cesarean delivery at term: a comment on patient choice cesarean delivery. Am J Obstet Gynecol 2005;192:1433-1436.
59 Tita AT, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med 2009;360:111-120.
60 Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. BMJ 2008;336:85-87.
61 Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Br J Obstet Gynaecol 1995;102:101-106.
62 Abman SH. Abnormal vasoreactivity in the pathophysiology of persistent pulmonary hypertension of the newborn. Pediatr Rev 1999;20:e103-e109.
63 Villanueva ME, Zaher FM, Svinarich DM, Konduri GG. Decreased gene expression of endothelial nitric oxide synthase in newborns with persistent pulmonary hypertension. Pediatr Res 1998;44:338-343.
64 Black SM, Johengen MJ, Soifer SJ. Coordinated regulation of genes of the nitric oxide and endothelin pathways during the development of pulmonary hypertension in fetal lambs. Pediatr Res 1998;44:821-830.
65 Christou H, Adatia I, Van Marter LJ, Kane JW, Thompson JE, Stark AR, et al. Effect of inhaled nitric oxide on endothelin-1 and cyclic guanosine 5'-monophosphate plasma concentrations in newborn infants with persistent pulmonary hypertension. J Pediatr 1997;130:603-611.
66 Dani C, Giannini L, Bertini G, Pratesi S, Corsini I, Longini M, et al. Changes of nitric oxide, carbon monoxide and oxidative stress in term infants at birth. Free Radic Res 2007;41:1358-1363.
67 Villamor E, Perez-Vizcaino F, Cogolludo AL, Conde-Oviedo J, Zaragoza-Arnaez F, Lopez-Lopez JG, et al. Relaxant effects of carbon monoxide compared with nitric oxide in pulmonary and systemic vessels of newborn piglets. Pediatr Res 2000;48:546-553.
68 Kumar P, Kazzi NJ, Shankaran S. Plasma immunoreactive endothelin-1 concentrations in infants with persistent pulmonary hypertension of the newborn. Am J Perinatol 1996;13:335-341.
69 Endo A, Ayusawa M, Minato M, Takada M, Takahashi S, Harada K. Endogenous nitric oxide and endothelin-1 in persistent pulmonary hypertension of the newborn. Eur J Pediatr 2001;160:217-222.
70 Rosenberg AA, Kennaugh J, Koppenhafer SL, Loomis M, Chatfield BA, Abman SH. Elevated immunoreactive endothelin-1 levels in newborn infants with persistent pulmonary hypertension. J Pediatr 1993;123:109-114.
71 Wedgwood S, Black SM. Endothelin-1 decreases endothelial NOS expression and activity through ETA receptor-mediated generation of hydrogen peroxide. Am J Physiol Lung Cell Mol Physiol 2005;288:L480-L487.
72 Sud N, Black SM. Endothelin-1 impairs nitric oxide signaling in endothelial cells through a protein kinase Cdelta-dependent activation of STAT3 and decreased endothelial nitric oxide synthase expression. DNA Cell Biol 2009;28:543-553.
73 Malamitsi-Puchner A, Economou E, Sevastiadou S, Efstathopoulos T, Nicolopoulos D. Endothelin 1-21 plasma levels on the first and fourth postpartum day in normal full-term neonates. Dev Pharmacol Ther 1993;20:195-198.
74 Kumar P, Kazzi NJ, Shankaran S. Plasma immunoreactive endothelin-1 concentration in cord blood of normal term neonates. Am J Perinatol 1995;12:113-115.
75 Benzing J, Stabile O, Szinnai G, Morgenthaler NG, Schulzke SM, Buhrer C, et al. Plasma pro-endothelin-1 and respiratory distress in newborn infants. J Pediatr 2012;160:517-519.
76 de Vroomen M, Lopes Cardozo RH, Steendijk P, Frolich M, Baan J, van Bel F. Endothelin-1 plasma concentration increases in the early phase of pulmonary hypertension development during respiratory distress syndrome: a study in newborn lambs. Early Hum Dev 2001;63:9-21.
77 Ivy DD, Parker TA, Kinsella JP, Abman SH. Endothelin A receptor blockade decreases pulmonary vascular resistance in premature lambs with hyaline membrane disease. Pediatr Res 1998;44:175-180.
78 El Sayed M, Sherif L, Said RN, El-Wakkad AS, El-Refay A, Aly H. Endothelin-1 and L-arginine in preterm infants with respiratory distress. Am J Perinatol 2011;28:129-136.
79 Benjamin AC, Silveira RC, Procianoy RS. Umbilical cord blood and neonatal endothelin-1 levels in preterm newborns with and without respiratory distress syndrome. Braz J Med Biol Res 2005;38:1417-1422.
80 Benzer D, Aygun AD, Godekmerdan A, Kurt AN, Akarsu S, Yilmaz E. Serum endothelin-1 and transforming growth factor-beta levels in the newborns with respiratory distress. Mediators Inflamm 2006;2006:85432.
81 Kaapa P, Kero P, Ekblad H, Erkkola R, Arjamaa O. Plasma endothelin-1 in the neonatal respiratory distress syndrome. Ann Chir Gynaecol Suppl 1994;208:110-112.
82 Brennan LA, Steinhorn RH, Wedgwood S, Mata-Greenwood E, Roark EA, Russell JA, et al. Increased superoxide generation is associated with pulmonary hypertension in fetal lambs: a role for NADPH oxidase. Circ Res 2003;92:683-691.
83 Teng RJ, Eis A, Bakhutashvili I, Arul N, Konduri GG.

Increased superoxide production contributes to the impaired angiogenesis of fetal pulmonary arteries with in utero pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2009;297:L184-L195.
84 Lakshminrusimha S, Russell JA, Wedgwood S, Gugino SF, Kazzaz JA, Davis JM, et al. Superoxide dismutase improves oxygenation and reduces oxidation in neonatal pulmonary hypertension. Am J Respir Crit Care Med 2006;174:1370-1377.
85 Wedgwood S, Lakshminrusimha S, Fukai T, Russell JA, Schumacker PT, Steinhorn RH. Hydrogen peroxide regulates extracellular superoxide dismutase activity and expression in neonatal pulmonary hypertension. Antioxid Redox Signal 2011;15:1497-1506.
86 Schulpis KH, Lazaropoulou C, Vlachos GD, Partsinevelos GA, Michalakakou K, Gavrili S, et al. Maternal-neonatal 8-hydroxy-deoxyguanosine serum concentrations as an index of DNA oxidation in association with the mode of labour and delivery. Acta Obstet Gynecol Scand 2007;86:320-326.
87 Lista G, Castoldi F, Compagnoni G, Maggioni C, Cornelissen G, Halberg F. Neonatal and maternal concentrations of hydroxil radical and total antioxidant system: protective role of placenta against fetal oxidative stress. Neuro Endocrinol Lett 2010;31:319-324.
88 Nabhan AF, El-Din LB, Rabie AH, Fahmy GM. Impact of intrapartum factors on oxidative stress in newborns. J Matern Fetal Neonatal Med 2009;22:867-872.
89 Paamoni-Keren O, Silberstein T, Burg A, Raz I, Mazor M, Saphier O, et al. Oxidative stress as determined by glutathione (GSH) concentrations in venous cord blood in elective cesarean delivery versus uncomplicated vaginal delivery. Arch Gynecol Obstet 2007;276:43-46.
90 Buhimschi IA, Buhimschi CS, Pupkin M, Weiner CP. Beneficial impact of term labor: nonenzymatic antioxidant reserve in the human fetus. Am J Obstet Gynecol 2003;189:181-188.
91 Rogers MS, Mongelli JM, Tsang KH, Wang CC, Law KP. Lipid peroxidation in cord blood at birth: the effect of labour. Br J Obstet Gynaecol 1998;105:739-744.
92 Yaacobi N, Ohel G, Hochman A. Reactive oxygen species in the process of labor. Arch Gynecol Obstet 1999;263:23-24.
93 Fogel I, Pinchuk I, Kupferminc MJ, Lichtenberg D, Fainaru O. Oxidative stress in the fetal circulation does not depend on mode of delivery. Am J Obstet Gynecol 2005;193:241-246.
94 Mutlu B, Aksoy N, Cakir H, Celik H, Erel O. The effects of the mode of delivery on oxidative-antioxidative balance. J Matern Fetal Neonatal Med 2011;24:1367-1370.
95 Vakilian K, Ranjbar A, Zarganjfard A, Mortazavi M, Vosough-Ghanbari S, Mashaiee S, et al. On the relation of oxidative stress in delivery mode in pregnant women; a toxicological concern. Toxicol Mech Methods 2009;19:94-99.
96 Georgeson GD, Szony BJ, Streitman K, Varga IS, Kovacs A, Kovacs L, et al. Antioxidant enzyme activities are decreased in preterm infants and in neonates born via caesarean section. Eur J Obstet Gynecol Reprod Biol 2002;103:136-139.
97 Inanc F, Kilinc M, Kiran G, Guven A, Kurutas EB, Cikim IG, et al. Relationship between oxidative stress in cord blood and route of delivery. Fetal Diagn Ther 2005;20:450-453.
98 Hracsko Z, Safar Z, Orvos H, Novak Z, Pal A, Varga IS. Evaluation of oxidative stress markers after vaginal delivery or caesarean section. In Vivo 2007;21:703-706.
99 Raijmakers MT, Roes EM, Steegers EA, van der Wildt B, Peters WH. Umbilical glutathione levels are higher after vaginal birth than after cesarean section. J Perinat Med 2003;31:520-522.
100 El-Masry HM, Nasr AA, Al Kabeer AM, Amin HH, Eldeeb HM. Nitric oxide and antioxidant enzyme levels in blood of respiratory distress syndrome-Egyptian preterms and their mothers. J Matern Fetal Neonatal Med 2015;28:41-45.
101 Crowley P. Prophylactic corticosteroids for preterm birth. Cochrane Database Syst Rev 2000:Cd000065.
102 Surbek D, Drack G, Irion O, Nelle M, Huang D, Hoesli I. Antenatal corticosteroids for fetal lung maturation in threatened preterm delivery: indications and administration. Arch Gynecol Obstet 2012;286:277-281.
103 Grover TR, Ackerman KG, Le Cras TD, Jobe AH, Abman SH. Repetitive prenatal glucocorticoids increase lung endothelial nitric oxide synthase expression in ovine fetuses delivered at term. Pediatr Res 2000;48:75-83.
104 Houfflin-Debarge V, Deruelle P, Jaillard S, Magnenant E, Riou Y, Devisme L, et al. Effects of antenatal glucocorticoids on circulatory adaptation at birth in the ovine fetus. Biol Neonate 2005;88:73-78.
105 Stutchfield P1, Whitaker R, Russell I, Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ 2005;331:662.
106 Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJ. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed 2013;98:F195-F200.
107 Gazquez Serrano IM, Arroyos Plana A, Diaz Morales O, Herraiz Perea C, Holgueras Bragado A. Antenatal corticosteroid therapy and late preterm infant morbidity and mortality. An Pediatr (Barc) 2014;81:374-382. [In Spanish]
108 Wax JR, Cartin A, Pinette MG, Blackstone J. Patient choice cesarean: an evidence-based review. Obstet Gynecol Surv 2004;59:601-616.
109 Liu Y, Li G, Chen Y, Wang X, Ruan Y, Zou L, et al. A descriptive analysis of the indications for caesarean section in mainland China. BMC Pregnancy Childbirth 2014;14:410.
110 De Luca R, Boulvain M, Irion O, Berner M, Pfister RE. Incidence of early neonatal mortality and morbidity after late-preterm and term cesarean delivery. Pediatrics 2009;123:e1064-e1071.
111 Suganuma H, Arai Y, Kitamura Y, Hayashi M, Okumura A, Shimizu T. Maternal docosahexaenoic acid-enriched diet prevents neonatal brain injury. Neuropathology 2010;30:597-605.
112 Chiossi G, Lai Y, Landon MB, Spong CY, Rouse DJ, Varner MW, et al. Timing of delivery and adverse outcomes in term singleton repeat cesarean deliveries. Obstet Gynecol 2013;121:561-569.
113 Ertugrul S, Gun I, Mungen E, Muhcu M, Kilic S, Atay V. Evaluation of neonatal outcomes in elective repeat cesarean delivery at term according to weeks of gestation. J Obstet Gynaecol Res 2013;39:105-112.
114 Ben Hamida Nouaili E, Bouziri A, Ben Miled A, Chaouachi S, Sfar R, Ben Jaballah N. Neonatal respiratory morbidity after elective cesarean section at term. Tunis Med 2010;88:924-927. [In French]

Received March 18, 2015
Accepted after revision September 5, 2016