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Prematurity: present and future

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Abstract

The study of preterm labor and prematurity, as with any medical science, has undergone a major transformation in its approach from an inevitable part of obstetrics with few answers to one in which science has led to knowledge and clinical intervention. Despite these advancements, understanding of preterm labor and prevention of prematurity is still limited. In the current review, we begin the discussion with fetal viability, first from a historical perspective and then from the understanding of this issue from a prospective of various professional organizations. We then present the scope of the problem of preterm birth from various countries including the discrepancy between the US and Europe. We continue with updates on extreme prematurity and outcomes with two longitudinal studies from the past 2 years. We further review available interventions for prematurity and discuss the use of antenatal corticosteroids. First, we examine their use in the context of professional recommendations and then examine the trajectory of their continued use in the late preterm period. We focus on a European-based trial with preliminary results and an ongoing American counterpart. The current knowledge of molecular mechanisms behind preterm labor is presented with a focus on the multiple etiologies of preterm labor, both known and presumed, with updates in the basic science realm. Furthermore, up-to-date studies on prediction of preterm birth and prematurity-related morbidity are presented.

Keywords

Obstetric labor; premature - Infant; premature - Fetal viability; Adrenal cortex hormones

The study of preterm labor has been dominated by inconsistencies in defining fetal viability. Inherent in the problem are genetic, cultural, social, and technological variables that can cause misunderstanding between us providers and our patients. The ramifications of an inadequate definition go beyond obstetrics and can impact not only legislation, but also vital statistics and data collection.[1]

Traditionally, preterm deliveries are defined as those occurring between the point of fetal viability and 37 weeks of gestation.[2] Historically, the threshold of 500 grams has defined the lower limit of viability but this distinction is fraught with intrauterine growth restriction

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(IUGR) and inaccuracies in estimation of gestational age. In fact, the National Institute of Child Health and Human Development Neonatal Research Institute prospectively followed neonates born between 22 and 25 weeks estimated gestational age (EGA), the so-called period of extreme prematurity. The study determined that four additional factors influenced the likelihood of a favorable outcome of neonatal intensive care: neonatal sex, exposure to antenatal corticosteroids, presence of multi-fetal gestation, and birth weight.[3]

Updates on fetal viability

Despite the uncertainty, many professional organizations have made attempts to concretely define fetal viability. Table I presents a comparison between the United Kingdom's Nuffield Council on Bioethics in 2006 and the American Academy of Pediatrics Committee on Fetus and Newborn in 2009.[4, 5]

Prevalence of preterm birth

On a global level, preterm birth rates experience a wide variation with multifaceted causes. In the United States (US), the rate of preterm births had steadily risen from 10.6%. in 1990 to peak at 12.8% in 2006, which consistently ranks in the top 10 amongst nations with the highest preterm birth rate annually. As the pendulum has swung, the US recently witnessed a modest decline of preterm birth rates for the fifth straight year to 11.73% in 2011. In contrast, Italy saw a modest increase from 5.8% in 1990 to 6.5% in 2010, consistent with other European countries.[6, 7]

Consequences of preterm birth

The impact of preterm births has been well documented and related to the prematurity of developing organ systems as well as consequences related to intrauterine inflammation. Complications can include respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, late-onset infection, and adverse neurological outcomes; the latter involving varying degrees of cerebral palsy (CP), motor, and neurosensory deficits.[3] The EPI Cure Study Group tracked newborns born before 25 weeks gestation at a median of 30 months and 6 years of age. In the first time point, a cohort of 283 surviving infants was formally assessed using the Bayley Scales of Infant Development and found that 19% had severely delayed development eliciting mean scores >3 SD below mean, while 11% had scores from 2 SD to 3 SD below mean.[8] The follow-up study reassessed the neonates at 6 years of age and found the following breakdown of results: 22% had severe neurocognitive disabilities (CP, IQ >3 SD below mean, blindness, deafness), 24% had moderate disabilities, and 34% had mild disabilities. Nearly 86% of neonates with severe disability at 30 months continued to have moderate-to-severe deficiencies at 6 years of age.[9]

Updates on extreme prematurity and outcomes

Herber-Jonat and colleagues showed that when compared to neonates born at 24 weeks, children born at 22–23 completed weeks showed no impairment in cognitive and neurological outcomes in a 7–10 year follow-up of 105 neonates. In addition, brith weight was also not significantly associated with poor neurologic outcome. In contrast, the risk

factors that were found predictive of an adverse outcome were an intraventricular hemorrhage greater than 2nd degree, periventricular leukomalacia, and retinopathy of prematurity greater than 2nd degree.[10]

The EXPRESS Group from Sweden conducted a prospective 2.5-year neurodevelopmental follow-up in extremely preterm infants (less than 27 weeks) all receiving active perinatal care. Extreme prematurity resulted in significantly lower composite Bayley scores of Infant and Toddler Development in cognition, language, and motor development when compared to matched controls neonates born at term. Also notable for extreme prematurity, were significant increases in cerebral palsy, blindness, and hearing impairment. Despite these results, 73% of extremely premature neonates had minimal or no disability and neurodevelopmental outcomes incrementally improved for each week of gestation.[11]

The extremely low gestational age newborns (ELGAN) studies suggested that extreme prematurity poses the same set of challenges that all preterm infants encounter but can often be more acute or severe.

In a 2-year follow-up study, neonates born before 28 weeks are observed to have a higher incidence of impaired visual fixation.[12] In addition, the same cohort of infants who had IUGR also had a higher risk for retinopathy of prematurity[13] Sriram *et al*. concluded that ventilation for 14 of more days for newborns born before 28 weeks tended to attenuate the severity of bronchopulmonary dysplasia (BPD) associated with hypoxemia and hypercapnia.[14] Erythropoietin, a pluripotent glycoprotein and thyroid stimulating hormone, both essential for fetal growth and development, were also studied. They concluded that erythropoietin and TSH levels correlate with circulating inflammatory markers in the developing gestation.[15, 16]

The use of antenatal corticosteroids: historical perspective

In 1972, Liggins and Howie were the first to note that antenatal steroids (ANS) reduced the incidence of respiratory distress syndrome (RDS) relative to controls (9% *versus* 26%). The neonates that showed such an effect presented earlier than 32 weeks and were treated for at least 24 hours.[17] This novel finding ushered an optimistic new era of administering corticosteroids to mothers who presented in threatened preterm labor. More than 40 years have passed and as a scientific community, we are still ironing out the details of ANS to define the extent of its utility.

In 1995, the NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes reviewed the available literature to provide a consensus on the use of antenatal steroids for fetal maturity. The main outcomes that complicated preterm birth were RDS, intraventricular hemorrhage (IVH), and overall neonatal morbidity and mortality. The Panel concluded that at 29–34 weeks' gestation, administration of ANS reduces the incidence of RDS and overall mortality. In contrast, at 24–28 weeks' gestation, the extent of RDS was observed to be less severe. At this same gestational age, reductions in IVH incidence and mortality were noted. Given the favorable neonatal profile, any fetus between 24–34 weeks at risk of preterm delivery, was a candidate for antenatal steroids administered as two doses 24 hours to 7 days before birth. Beyond 34 weeks, the risk of

RDS, IVH, and neonatal mortality was relatively low and the use of corticosteroids was not recommended after this gestational age except in cases of pulmonary immaturity. Similarly, due to the low incidence of neonates before 24 weeks, it was unclear whether antenatal corticosteroids would confer a benefit to these neonates.[13] This seminal statement paved the way for the use of antenatal steroids in modern obstetrics. As more studies emerged, two meta-analyses by Crowley and then by Roberts and Dalziel suggested that corticosteroid administration prior to 34 weeks was associated with a substantial reduction of neonatal problems including RDS, IVH, necrotizing enterocolitis, and neonatal mortality but no conclusion could be gleaned to recommend ANS use beyond 34 weeks gestation.[19, 20]

Updates on antenatal corticosteroid administration

As the limits of viability shift to earlier gestational ages, it was inevitable that the question of beneficial effects of corticosteroid administration would be extended to the periviable period. Carlo *et al*. from the NICHHD Neonatal Research Network published the largest cohort study exploring the relationship between antenatal corticosteroid use at 22 to 25 weeks and two outcomes: neonatal mortality and neurodevelopmental outcomes at 18–22 months' corrected age. All the neonates included, weighed between 401–1000 grams and neonates who passed within 12 hours of delivery without resuscitation were excluded. A total of 10541 infants were included born between 1993–2008 and of those, 7808 of those received antenatal steroids. For each gestational age, the total infants in the study were:

- 22 weeks: 402 (119 with ANS);
- 23 weeks: 1978 (1147 with ANS);
- 24 weeks: 3793 (2979 with ANS);
- 25 weeks: 4368 (3563 with ANS);
- Total: 10541 (7808 with ANS).

The 18–22-month follow-up data are summarized in Table II, combining all gestational ages. Death or neurodevelopmental impairment was significantly lower in the ANS group for gestational ages 23, 24, and 25 weeks but not for the 22 weeks' gestation group even when confounders were taken into account. These promising results suggest drawing the line of ANS administration to begin at 23 weeks' gestation and beyond. The first study of its kind with such robust numbers, it has made major inroads in the clinical utility of antenatal corticosteroids and has unveiled insight into the management of extreme prematurity.[21]

The introduction of antenatal corticosteroids, no doubt, has provided an integral piece to our armamentarium against threatened preterm labor. Fraught with controversy, however, is the use of ANS in the late preterm (34–36 completed weeks gestation) neonate as the NIH consensus of 1995 stopped short of making recommendations beyond 34 weeks gestation. Since the majority of preterm infants are known to fall within this late preterm category, the optimum approach has been met with formidable differing opinions. The notion that late preterm infants were as mature as term infants has largely been abandoned and we now acknowledge that late preterm neonates suffer greater mortality and morbidity[22–25]

Respiratory issues (29% *versus* 4%) included transient tachypnea of newborn, RDS, pneumonia, and pulmonary hypertension.[24]

Porto *et al*. set out to solve the mystery in a randomized clinical trial. The study included 320 Brazilian women between 34–$36^{6/7}$weeks gestational age in which 163 were assigned to receive ANS. The primary outcome was the proportion of respiratory disorders including RDS and transient tachypnea of the newborn. Secondary outcomes were need for ventilator support, neonatal morbidity, and duration of hospital stay. While the overall incidence of RDS was low in the ANS (1.4%) and control group (0.8%), transient tachypnea was high but saw no significant difference in ANS versus controls (24% *versus* 22%). This trend was not altered when women were subdivided by gestational age.

With respect to their secondary outcomes, the incidences were, (ANS *versus* controls):

- need for ventilator support (20% *versus* 19%, P=0.81);
- neonatal morbidity (62% *versus* 72%, P=0.08);
- duration of hospital stay (5.12 *versus* 5.22 days, P=0.87).

The only neonatal benefit gleaned from the study was a reduction in the need for phototherapy. The ANS group saw a 24% rate of phototherapy treatment *versus* 38% in the control group (P=0.01).[26]

In contrast, Gazquez Serrano and her group from Spain performed a prospective observational study for women who presented in threatened preterm labor during the late preterm from October 2011 until September 2012. The group looked at ANS administration to gauge neonatal morbidity and mortality. From their results, 247 of the 332 preterm infants were considered born in the late preterm period. Admission to the NICU, transient tachypnea of the newborn, need for oxygen supplementation, hypoglycemia, feeding difficulties, and jaundice requiring phototherapy all underwent significant increases in the cohort that did not receive ANS (P<0.05).[27] From an economic perspective, Bastek *et al*. concluded that a full course of ANS at 34, 35, and 36 completed weeks for women at high risk for imminent delivery was incrementally more cost-effective to reduce the overall burden of cost and acute morbidity of late preterm deliveries.[28]

The study reaffirmed that neonates born in the late preterm range are more vulnerable to poor respiratory outcomes relative to term infants, most notably with respect to the incidence of transient tachypnea of the newborn. Despite the healthcare concern surrounding late preterm neonates, the data remains inconsistent to recommend routine ANS in the late preterm at this time. In the US, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) has initiated the Antenatal Late Preterm Steroids (ALPS), a randomized placebo-controlled trial in phase 3 at the time of this submission. The primary outcome will be neonatal oxygen support after ANS administration in the late preterm mother and the estimated primary completion is scheduled for October 2014.[29]

Molecular mechanisms of preterm labor: the common pathway

Of all preterm births, spontaneous preterm labor, approximately 45% occur with intact membranes and about 30% present in the context of premature rupture of membranes (PROM).[30, 31] The tripartite model comprising the common pathway of parturition includes uterine contractility, cervical ripening, and rupture of chorioamniotic membranes. The traditional view of preterm labor is the activation of the common pathway identical to term labor, albeit at an earlier gestational age.[32] This line of reasoning assumes the same underlying physiologic process when in reality, there is an elegantly regulated system delineating that preterm labor represents a pathologic activation of the various components of the common pathway.

The quiescence of the myometrium during pregnancy is predominantly determined by the increased presence of circulating progesterone, acting through the nuclear progesterone receptor.[33] Progesterone acts through a variety of downstream effects. The underlying mechanism of progesterone is that of inhibition of the transcription factors, NF-κB and AP-1 to prevent the expression of proinflammatory cytokines, including IL-1, IL-6, and IL-8 and the chemokine CCL2.[34–37] In addition, the progesterone receptor upregulates the zinc finger E-box binding homeobox 1 transcription factor (ZEB1), which in turn inhibits the expression of contraction-associated proteins: the oxytocin receptor, connexin 43, and a precursor of prostaglandin $F_2\alpha$.[38, 39] These selective downregulations act together to maintain myometrial inactivity.

The transition to labor (term or preterm) involves an untangling of the aforementioned molecular signaling ultimately leading to an increased inflammatory response. The combination of uterine wall mechanical stretch and hormonal factors derived from the fetus provides inflammatory stimuli. [37, 40, 41–45] As a result, the proinflammatory cytokines, IL-6 and IL-1(3 accumulate in the amniotic fluid while neutrophils and macrophages infiltrate the myometrium, the cervix, and the fetal membranes.[41] In the preterm labor model, the proinflammatory cytokines result from microbial invasion of the amniotic cavity (MIAC) to provide the proinflammatory signal switch.[47] The proinflammatory milieu activates NF-κB and AP-1, whose activated forms inhibit the progesterone receptor. More recently, the discovery of microRNA-200 (miRNA-200) has led to new inroads into the study of gene expression regulation in labor. These non-coding RNA sequences are evolutionarily conserved, which serve as post-transcriptional regulators of gene expression. The miRNA-200 has been found to down-regulate the ZEB genes, which allows the translation of contraction-associated proteins.[38, 39, 48] The decline in progesterone causes an expression of the contraction-associated proteins and leads to labor.

Molecular mechanisms of preterm labor: past and present

The causes of preterm labor involve multiple pathophysiologic mechanisms including intra-amniotic infection, vascular disorders, decidual senescence, uterine overdistention, decline in progesterone action, cervical disease, breakdown of maternal-fetal tolerance, stress, and other unknown factors to this day. Of these causes, only infection has been linked as a cause to spontaneous preterm labor.[49, 50]

Intra-amniotic infection and inflammation

Evidence for infection causing preterm labor has been well established. In fact, MIAC can be found in 12.8% of women with preterm labor with intact membranes, 32% with PROM, and 51% with cervical insufficiency[51] The mechanism by which microorganisms elicit an inflammatory immune response is via toll-like receptors (TLRs), which can produce chemokines (*e.g.*, IL-8), cytokines (*e.g.*, IL-1β and TNFα), prostaglandins and proteases eventually activating the common pathway[50] The inflammatory milieu of the amniotic cavity is not isolated and can inevitably enter the fetal circulation and dose so 30% of the time, leading to a fetal systemic inflammatory response (FIRS). The consequences of FIRS can involve multi-organ dysgenesis and dysfunction of the neurologic system (*e.g.*, cerebral palsy) and the pulmonary system (*e.g.*, chronic lung disease).[52, 53] The evidence suggests that one must view the problem of prematurity as not just one of pure immaturity of various organ systems but also in the context of infection.[54]

Vascular disease—Vaginal bleeding experienced during preterm labor has its origins in a defective decidual hemostatic mechanism. The bleeding that occurs at the decidual-placental interface generates thrombin. Thrombin has two consequences: stimulation of myometrial contractions and inhibition of expansion of uterine spiral arteries, essential to increase perfusion and the growing demand of the fetus. Failure of these arteries to expand their lumen may lead to pre-eclampsia.[55] In this model, we see a possible link between preterm labor and the etiology of preeclampsia but to date, it is unclear why a certain subset develop one condition over the other.

decidual senescence—The process of decidualization is necessary for blastocyst implantation, pregnancy continuation and delivery. At a molecular level, there is a proliferation and differentiation of the stromal cells at the implantation interface to become decidual cells. Of interest, the signaling pathway for tumorigenesis appears to be the same as that of a normal pregnancy with the exception that the p53 gene is unregulated in tumor growth. Hirota *et al*. showed that a conditional deletion of Trp53 increased the incidence of preterm birth to 50%, which was corrected when a COX2 inhibitor was administered. The study exemplified that decidual maintenance, regulated by p53, is paramount in pregnancy continuation and adds a novel pathway to the pathogenesis of preterm labor.[56]

The maternal-fetal immunologic tolerance

The maternal immune system during pregnancy experiences a physiologic silencing in which immune effector cells with fetal specificity are attenuated by T regulatory cells. This process is key for pregnancy progression insofar as the fetus and placenta can coexist in the host mother as partial allografts.[57, 58] There have been reports of allograft rejection in cases of immune dysfunction. For example, chronic chorioamnionitis causes a T cell infiltration of the chorioamnion leading to trophoblast apoptois, reminiscent of graft-*versus*-host disease.[59] The results suggested that immune tolerance has a role in preterm labor, albeit by some unknown mechanism.

Preterm birth prediction and prevention

Biomarkers as a predictive tool

It is well-recognized that spontaneous preterm birth (PTB) is a major public health issue. However, to date, it has been difficult to predict various biomarkers to act as predictors of PTB in women who do not have overt clinical signs of threatened preterm labor. Brou *et al*. have reported on the differential expression of 36 biomarkers expressed in maternal plasma, fetal plasma, and amniotic fluid between cases and controls in an attempt to decipher a biomarker with predictive capacity of PTB. They also stratified each marker based upon race between African Americans (AA) and Caucasians. They concluded that with respect to European Americans, the dysregulation of fetal plasma biomarkers contribute to PTB, whereas with AA, the maternal plasma biomarker concentration was more predictive.[60]

Recently, the concept of biomarker interaction has emerged whereby one dys-regulated biomarker in conjunction with another can have a better predictive value. Menon *et al*., from the same institution, took the same cohort of samples and performed multivariate adaptive regression splines (MARS) modeling to ascertain if biomarker interplay was a significant predictor of PTB.[61] They generated receiver operating characteristics for maternal plasma, fetal plasma, and amniotic fluid and then subdivided each compartment by race. Important variables for each compartment were determined. In maternal plasma, IL-1RA, TNF-β, angiopoietin 2, TNFRI, IL-5, MIP1α, IL-1β, and TGF-α modeled preterm birth in AA. In contrast, for Caucasians, TNFR1, ICAM-1, and ILR-A contribute to the PTB model. In the fetal cord plasma group, AA produced IL-12P70 and IL-8, while Caucasians showed IGF-II, PDGFBB, TGF-β1, IL-12P70, and TIMP1. Lastly, amniotic fluid saw AA changes in FasL, TNFRII, RANTES, KGF, IGFI and with Caucasians TNF-α, MCP3, TGF-β_3, TNFR1 and angiopoietin 2 were strong predictors of PTB. The study was able to validate MARS as a potential methodological tool whereby biomarker concentrations can influence and reliably predict PTB.[61]

MicroRNA in cervical cells

MicroRNA (miRNA) was previously described as a transcriptional regulator of gene expression in the common pathway of labor. More recent studies have shown that these highly conserved single-stranded noncoding RNAs have a quintessential role in disease states. Elovitz *et al*. performed a case-control study and compared cervical cells in women who had PTB and women who delivered at term. They then mapped miRNA expression profiles using microar d ray to compare 5640 different miRNA sequences. The group was able to differentiate 99 miRNA sequences that were unique to the women with a PTB. The utility of this miRNA profiling is the ability to predict PTB months before the outcome and suggest that miRNA effects somehow program the fetomaternal environment with respect to cervical remodeling. This can subsequently. lead to therapeutic targets at the molecular level.[62]

Cervical length as a preventative tool for spontaneous preterm birth

The two most important predictors of spontaneous preterm birth detection are: sonographic evidence of a short cervix in the midtrimester,[63] and a previous history of spontaneous

preterm birth. Approximately 2 to 5% of women will demonsrate a cervical length of 20 mm or less and should be offered vaginal progesterone. The utilization of this is linked with a reduction in the rate of preterm birth by 45% and neonatal benefits such as reduced incidence of respiratory distress syndrome.[64] In women with a history of PTB, the administration of 17-alpha hydroxyprogesterone caproate can reduce the rate of preterm birth by 34% and reduces the need for oxygen supplementation.[65]

Neurologic perinatal biomarkers of prematurity

With the increased survival of extremely premature infants, comes a demand to identify various perinatal biomarkers to predict prognosis for brain injury in these high-risk infants. The most common forms of CNS injury are intraventricular hemorrhage (IVH), posthemorrhagic hydrocephalus (PHH), and periventricular leukomalacia (PVL).

Intraventricular hemorrhage

The etiology of IVH is multifactorial but is a combination of the inherent sensitivity of nascent germinal matrix capillaries to hypoxic insult and the dysfunctional cerebral autoregulation. In approximately half of cases, the clinical onset can be asymptomatic and recent interest has shifted to predict and diagnose IVH before the manifestations appear.[67]

Activin is a growth factor that regulates a variety of biologic processes whose origin is cerebral and as such, its receptor and binding proteins are widely distributed in various brain regions.[68] Specifically, the physiologic response to acute brain injury is mediated by activin A. Florio *et al*. looked at activin A concentrations in preterm neonates who eventually developed grade I or II IVH exalting activin A as a potential early biomarker of IVH in neonates at high-risk of hypoxic brain injury[69]

The S100b protein is synthesized by astrocytes and regulates neurotrophic as well as neurotoxic activity. The role of S100b in perinatal brain injury has also been promising as an early biomarker leading to IVH in preterm neonates. Gazzolo *et al*. saw higher serum concentration levels of S100b in infants who later went on to develop IVH within 24 hours after delivery[70]

The proinflammatory cytokine, IL-6 has been investigated as an early marker of perinatal neurologic disease in preterm infants. Heep *et al*. correlated increased IL-6 levels with severe IVH in the first 12 hours of life in neonates born before 28 weeks. The group reported that IL-6 is an independent risk factor for IVH and can serve as a formidable biomarker in early perinatal neurologic injury.[71] More recently Poralla *et al*. similarly showed that IL-6 elevations are closely entwined with a diminished coagulation profile and development of IVH supporting a role for IL-6 as a marker of inflammation and IVH as a neonatal outcome.[72] In addition, erythropoietin,[73] the chemokine CCL18 [74] and adrenomedullin [75] have also been correlated with the presence of IVH.

Periventricular leukomalacia

The predominant manifestation in premature infants of white matter injury is periventricular leukomalacia (PVL). At a cellular -level, it shows a focal necrosis and gliosis of the

periventricular white matter and can be a precursor to cerebral palsy in preterm neonates.[76] Two predominant animal models that are used to recreate periventricular white matter injury are the hypoxia/ischemia with carotid artery occlusion and the administration of bacterial lipopolysaccharide (LPS). Through these models, glial fibrillary acidic protein (GFAP) is an intermediate filament protein localized to the cerebral cytoskeletal structure, acting as a marker for differentiated astrocytes. Bembea *et al*. have observed high levels of GFAP during extracorporeal membrane oxygenation associated with the potential development of PVL.[77] Building on this study, Stewart *et al*. demonstrated that cord blood levels of GFAP were significantly higher for 4 consecutive days in neonates that had PVL *versus* controls.[78] These studies suggest that GFAP is emerging as a potential biomarker for predicting PVL in preterm neonates. There is also an implication that proinflammatory cytokines have a role in PVL[79] but these results have not been reproduced.[80]

Posthemorrhagic hydrocephalus

Posthemorrhagic hydrocephalus (PHH) is a late complication of IVH whereby the ventricular system becomes progressively occluded by blood clots. Typically the severity of IVH (grade III-IV) will portend a higher incidence of PHH.[81] Most studies have focused on the cytokine transforming growth factor β (TGF-β). Whitelaw and Aquilina showed that the introduction of TGF-β can convert a potentially reversible CSF obstruction with a permanent one by inducing the production of extracellular matrix proteins.[82] Similarly, Heep *et al*. found that persistently high levels of TGF-β1 CSF concentrations and white matter injury[83] In summary, no biomarker to this date has been validated for widespread clinical use to predict perinatal brain injury.

Cell-free fetal DNA

The concept of cell-free fetal DNA (cffDNA) is most notably known in modern-day obstetrics for its use as a screening test for fetal aneuploidies and genetic mutations and is widely accepted. Its non-invasive nature and its low false negative rate have allowed it to become commonplace for most couples with known or possible genetic syndromes. Recently, however, cffDNA has been put forth as a potential marker for preterm labor.[84] The cffDNA has the ability to induce an inflammatory response, which activates the common pathway. Indeed, elevations of cffDNA midtrimester are also at increased risk of spontaneous preterm delivery later in that gestation.[85] Conversely, mothers with a previous episode of PTL and high plasma levels of cffDNA are at higher risk for PTB.[86, 87]

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Table I

Comparison between United Kingdom's Nuffield Council on Bioethics and AAP's Committee on fetus and newborn.

	UK (2006)	**AAP (2009)**
EGA ≤22–$22^{6/7}$	Routine resuscitation is not provided unless requested by informed parents or clinician deems intervention is in child's best interests.	Resuscitation is offered to parents if there is at least a small chance of survival based on available information (eg, the NICHHD outcome estimator for patients receiving mechanical ventilation) and is then provided only if requested by informed parents.
EGA $23^{0/7}$-$23^{6/7}$ weeks	Resuscitation is left to the discretion of informed parents, but a clinician need not provide interventions that offer no benefit to neonate.	Resuscitation is offered to parents, but provided or withheld based on the preference of informed parents
EGA $24^{0/7}$-$24^{6/7}$ weeks	Resuscitation should generally be provided but may be withheld based on child's condition and agreement between clinician and informed parents.	Resuscitation is offered to parents and may be provided or withheld based on the preference of informed parents. However, if the newborn is predicted to have greater than 50 percent chance of survival without neurodevelopmental impairment, resuscitation is provided.
EGA ≥25 weeks	Intensive care should be initiated.	Resuscitation is provided.

Table II

Primary outcomes and their adjusted odds ratio at 18–22-month follow-up of neonates receiving antenatal corticosteroids at 22–25 weeks gestation.

Primary outcome	Adjusted odds ratio (AOR) [95% CI]
Death	0.59 [0.53–0.65]
Neurodevelopmental impairment	0.83 [0.70–0.99]
Moderate to severe cerebral palsy	0.76 [0.59–0.98]
Psychomotor developmental index <70	0.79 [0.65–0.96]