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NEONATAL AND EARLY CHILDHOOD OUTCOMES OF CESAREAN

Yusra Waheed Abdul Hasan* and Shaymaa Mohammed Arrar

Ministry of Health - Baghdad Medical Office - Al-Russafa, - Fatima Al-Zahraa Maternity Hospital for Women and Children, Baghdad, Iraq.

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***Corresponding Author**
Yusra Waheed Abdul Hasan
Ministry of Health - Baghdad Medical Office - Al-Russafa, - Fatima Al-Zahraa Maternity Hospital for Women and Children, Baghdad, Iraq.

ABSTRACT

There have been three major theoretical mechanisms proposed to explain why higher rates of morbidity are seen among neonates delivered by cesarean. The first, which primarily attempts to address short-term outcomes, involves ECD disrupting or pre-empting a process that involves the endogenous hormones associated with active labor triggering fetal lung fluid to be actively reabsorbed by the fetus. The second, iatrogenic prematurity, which attempts to address both short-term and long-term outcomes, involves the potential inaccuracy of determining gestational age combined with attempting to deliver prior to the onset of spontaneous labor. The third, which attempts to address long-term outcomes, is based on cesarean delivery causing the neonate's intestinal tract to be initially colonized with the "wrong" types of bacteria, which causes subtle changes in the child's immune and metabolic systems.

KEYWORDS: Neonatal, early childhood, cesarean delivery.

INTRODUCTION

Neonatal encephalopathy (NE) is the third leading cause of under 5- year mortality and contributes substantially to long-term neurological morbidity worldwide. Neonates affected by a perinatal insult typically present with NE, a descriptive term for a clinical constellation of neurological dysfunctions in the term infant.[1]

Long-term sequelae amongst NE survivors include cerebral palsy (CP), global developmental delay (GDD), vision and hearing impairments and seizure disorders. A systematic review of follow-up amongst high-risk newborns showed that one in five infants were at risk of severe impairment in at least one domain; however, few contributing data came from low and middle-income countries (LMICs) and in particular sub-Saharan Africa.[2] A common limitation of outcome studies amongst high-risk neonates is following to ≤1 year of age when neurodevelopmental impairment may be missed and diagnosis and classification of CP not possible. Worldwide, 80% of the estimated 200 million children with physical and intellectual disability live in LMICs where implications for the health, wellbeing and life chances of affected individuals, families and communities are far-reaching.[3]

Early childhood development has been recognized as one of the pillars of the Global Strategy for Women's, Children's and Adolescents' Health, to ensure that children not only survive but also thrive.[4] Children with GDD and other disabilities are vulnerable to health inequalities[8] and the social, emotional and financial impact on caregivers and other family members are high.[5] A focus on early child development is crucial to achieving the Sustainable Development Goals, to ensure that all children have the opportunity to maximize their full developmental potential and to improve life chances for themselves and their families.[6]

BACKGROUND

The rate of preterm birth (PTB, delivery prior to 37 weeks gestation) in the United States has recently begun to decline slightly but remains unacceptably high at 11.5% of all deliveries. Preterm premature rupture of membranes (PPROM) is the leading identifiable cause of preterm birth and accounts for approximately one-third of cases.[7]

The etiology of PPROM is multifactorial and likely related to factors including overt or subclinical infection/inflammation, abruption, uterine over-distension, smoking, and cervical insufficiency. However, many cases of PPROM occur without a clearly identifiable etiology.

In the United States, women with PPROM prior to 32-34 weeks gestation are typically given an antibiotic regimen such as erythromycin and ampicillin; antibiotic 66 administration in this setting has been shown to increase the latency period between membrane rupture and delivery and reduce neonatal morbidity and mortality.[8] The majority of women are also administered antenatal corticosteroids to accelerate fetal lung maturity.[9] Given the high risk of secondary complications such as placental abruption, cord prolapse, preterm labor, and intra-amniotic infection, women with PPROM are typically managed as inpatients until delivery. In the absence of one of these complications, the majority of women are delivered at or by 32-34 weeks gestation.[10]

The duration of latency between the timing of membrane rupture and delivery appears to be inversely related to the gestational age at PPROM; those women experiencing PPROM earlier in gestation tend to have the longest latency periods.[11] Traditionally, when PPROM occurs prior to fetal viability (23-25 weeks gestation),[12] neonatal outcomes have been poor. However, contemporary studies have demonstrated that in an era of advanced neonatal care, outcomes for neonates delivered following very early PPROM may be better than previously expected.

Despite advances in neonatal care and apparent improved neonatal outcomes, longer-term outcomes of children delivered following early PPROM are largely unknown. One small study examined early childhood outcomes among neonates who were expectantly managed following spontaneous PPROM.

Preterm delivery <37 weeks' gestation remains the leading cause of neonatal and childhood morbidity among nonanomalous infants in the United States and the developed world. Recent advances in perinatal and neonatal medicine over the last 2 decades have resulted in substantial increases in survival among premature infants. However, this survival increase may be accompanied by an increase in survival with subsequent major morbidities, resulting in sicker children who require intensive postnatal medical care and costly developmental services.4 Among the most premature, those children born <1000 g, approximately 10-15% develop moderate to severe cerebral palsy and 30% have deficits in cognitive development.

Frequently, obstetric and pediatric researchers use neonatal morbidity as a surrogate outcome for longer-term, childhood outcomes when studying pregnancy exposures and/or interventions. While risks factors such as extremely low birth weight (<750 g), early gestational age (<28 weeks' gestation), chorioamnionitis, intracranial hemorrhage, and fetal sex have been identified, the correlation between neonatal and childhood outcomes is imprecisely defined.

Additionally, many preterm infants acquire multiple neonatal morbidities, but it remains uncertain if this confers an additive risk for adverse childhood neurodevelopment. Previous studies have been limited.

Schmidt et al recently examined neonatal diagnoses: bronchopulmonary dysplasia (BPD), brain injury (defined as intraventricular hemorrhage, ventriculomegaly, and/or periventricular leukomalacia), and severe retinopathy of prematurity (ROP), diagnosed singly or in combination, with adverse neurodevelopmental outcomes at 18 months among infants delivered very prematurely (birthweight 500-999 g).[13]

These researchers found a correlation between the number of neonatal diagnoses and 18-month outcomes. Babies with all 3 of the studied diagnoses had an 88% chance of adverse childhood outcomes compared to an 18% chance if the infant had none of these diagnoses. The impact of other factors, including another major neonatal morbidity such as necrotizing enterocolitis, and pregnancy or antenatal characteristics such as chorioamnionitis, could not be assessed. Furthermore, it is unknown if these results are applicable to a wider range of the preterm population or are limited to the extremely low birth weight neonate.[14]

Cesarean section (CS) rates in the US have risen by nearly 60% since 1996, increasing from 21% to nearly 33% in 2009.[15] The primary CS rate is now above 20%, and the repeat CS rate is now above 90%. CS without indication, a proxy for CS on maternal request, also appears to be rising. CS is now the most common surgical procedure performed on women in the US with over 1.3 million CSs performed in the US every year.

There has been a growing concern by healthcare providers and policymakers over the rising cesarean section rate due to concerns of overuse and associated increased risk of infant and maternal morbidity. This concern is reflected in the Healthy People 2010 and 2020 goal of reducing the primary and repeat CS rates.[16]

Despite these recommendations, cesarean section rates continue to rise. The aim of reducing the overall CS rate would be accomplished most efficiently by making reductions in the primary CS rate, although with the repeat CS rate at over 90% it might prove more feasible to increase the proportion of women who attempt a trial of labor after cesarean (TOLAC). Some progress toward this goal was made in the mid1990s when the vaginal birth after cesarean rate reached its peak of approximately 28% and the overall CS rate reached a decade low of approximately 21%.[17] Subsequently, concerns have been raised over the safety of attempting a TOLAC, owing primarily to the risk of uterine rupture and the resultant negative consequences for the fetus,[18] resulting in rates of vaginal birth after cesarean delivery falling to current levels. Infants born by CS, especially CS without labor, have a birth experience that differs from those infants born by spontaneous vaginal delivery and differs in ways that could negatively impact these infants' health in both the short and long term.[19]

Labor exposes the fetus to a cascade of hormone changes that appear to aid in the clearance of fetal lung fluid. Infants born by CS without labor do not experience this surge of endogenous hormones, which could result in higher rates of respiratory morbidity and even mortality.[20]

Also, prior to birth, the fetuses' digestive tract is sterile and is first colonized by bacteria during delivery. The digestive tracts of infants born vaginally are first colonized by flora similar to the flora of the mother's digestive tract. The digestive tracts of infants born by CS are first colonized by surface bacteria in the delivery room and on the mother's skin. Infant gut flora has a significant impact on the maturation and development of the immune system.[21] Initial colonization with flora from the delivery room environment rather than the mother's digestive tract could lead to increased susceptibility to atopic diseases, such as asthma.

In addition, higher rates of iatrogenic prematurity are found in infants delivered by elective CS compared to spontaneous vaginal delivery. This is in large part because the determination of gestational age based on either the date of the mothers last menstrual period or a second-trimester ultrasound is only accurate within one to two weeks, and most elective CS deliveries occur at or before 39 weeks gestational age, with many of these deliveries as early as 37 weeks. With iatrogenic prematurity come increased rates of respiratory morbidity as well as any morbidity associated with late preterm and early term infants.

Neonatal outcomes of elective primary cesarean delivery compared to a trial of labor

At birth, the fetus has a number of rather remarkable challenges to overcome, including making the transition from having oxygen and nutrients provided through the maternal blood supply to relying on its own lungs and digestive tract for these needs. Infants that are born by cesarean, especially ECD, have a very different birth experience than infants that are delivered by a spontaneous vaginal birth. These differences may affect the infant's respiratory and metabolic systems in negative ways that result in increased short term and long-term morbidity.[22]

Labor exposes the fetus to a cascade of hormone changes thought to be important for a successful transition from the womb to the external environment. In particular, increased levels of catecholamine's and glucocorticoids are thought to help activate sodium ion channels in the pulmonary epithelium responsible for clearance of the majority of the fetal lung fluid. Infants born by ECD do not experience this surge of endogenous hormones. This is thought to lead to less fluid cleared from the lungs at birth, which could result in higher rates of respiratory morbidity in the neonatal period that could potentially extend into childhood.[23] The above transitional challenges could be made more difficult for the infant born by ECD due to higher rates of iatrogenic prematurity compared to spontaneous vaginal deliveries. Most ECDs occur at or before 39 weeks gestational age, with many as early as 37 weeks. It can be difficult to accurately determine gestational age, with errors of one to two weeks being common.

There have been a number of observational studies that have documented poorer outcomes for infants born by cesarean section compared to vaginal delivery. Outcomes that could be related to either lung fluid clearance or iatrogenic prematurity include perinatal mortality, respiratory morbidity, and neonatal intensive care unit admission. Outcomes that are more likely related to iatrogenic prematurity include jaundice and hypoglycemia.65 And several outcomes have been evaluated in the literature that is thought to be effects of the physical forces and the environment surrounding mode of delivery such as birth injury, seizures, and sepsis.[24]

Only three studies have been reported in the literature in which women were randomized to either planned vaginal delivery or planned cesarean delivery. Although individually these randomized studies were small, a meta-analysis of these three trials indicated a decreased risk of neonatal mortality for infants delivered by ECD.[25]

However, all of these studies were restricted to breech deliveries, and therefore could be of limited generalizability. Visco et al. (2006) conducted a systematic review in which they examined the effect of EPCD on neonatal mortality.[26] They excluded studies that only examined subpopulations and studies with less than 100 subjects. They found that the evidence was inconclusive at that time due to small sample sizes and lack of control variables in the available studies. Since then, several additional observational studies have been published. MacDorman et al., (2006) examined the effect of cesarean delivery with no indicated risk on neonatal mortality in a population of the term, singleton deliveries.38 The no indicated risk group was used as a proxy for cesarean delivery on maternal request.[27]

They used national vital records data consisting of linked birth and infant death certificates for years 1998-2001. Their most conservative multivariate models excluded women with a previous cesarean delivery, deliveries with any evidence of congenital anomalies, any reported labor complications, any reported medical risk factors, and infants with 5-minute APGAR scores are less than. They found an increased risk of neonatal mortality for infants delivered by cesarean delivery with no indicated risk, with an adjusted odds ratio (AOR) of 2.0 (95% CI, 1.6-2.6).[28] In this study, all remaining cesarean deliveries after exclusions, including cesarean deliveries in which there was evidence that the woman labored prior to delivery, were combined and compared with all vaginal deliveries. In a later study, MacDorman et al. (2008) repeated the above analysis, using data from 1999-2002, with an intent to treat design.[29]

Neonatal outcomes of primary elective cesarean delivery

The above transitional challenges could be made more difficult for the infant born by ECD due to higher rates of iatrogenic prematurity compared to spontaneous vaginal deliveries. Most ECD occurs at or before 39 weeks gestational age, with many as early as 37 weeks. It can be difficult to accurately determine gestational age, with errors of one to two weeks being common. This degree of error in estimating gestational age, combined with the desire in many cases to deliver prior to the onset of spontaneous labor, result in higher rates of post-delivery determined prematurity in ECD.[30]

Potentially, these increased rates of iatrogenic prematurity in infants delivered by ECD 43 could expose them to increased rates of any morbidity associated with late preterm infants. There have been a number of observational studies that have documented poorer outcomes for infants born by cesarean section compared to vaginal delivery.[31] Outcomes that could be related to either lung fluid clearance or iatrogenic prematurity include perinatal mortality, respiratory morbidity,[32] and neonatal intensive care unit admission. Outcomes that are more likely related to iatrogenic prematurity include jaundice44 and hypoglycemia.65 And several outcomes have been evaluated in the literature that is thought to be effects of the physical forces and the environment surrounding mode of delivery such as birth injury, seizures, 35;46;68 and sepsis. 46;65;68 Only three studies have been reported in the literature in which women were randomized to either planned vaginal delivery or planned cesarean delivery.33-35 Although individually these randomized studies were small, a meta-analysis of these three trials indicated a decreased risk of neonatal mortality for infants delivered by ECD.36 However, all of these studies were restricted to breech deliveries, and therefore could be of limited generalizability. The evidence from the sizeable literature of observational studies, which largely indicates that infants delivered by ECD are at increased risk of morbidity and mortality, are at odds with the evidence from the few trials that randomized mode of delivery. Although these randomized controlled trials were limited to the non-vertex presenting subpopulation of term deliveries, the lack of a randomized controlled trial in the larger population of deliveries in the vertex presentation has left the question of generalizability unanswered. The most definitive method of answering this question would be to conduct a randomized controlled trial of mode of delivery in a population of term, vertex, singleton pregnancies. Conducting such a trial could prove problematic due to both ethical concerns and the high cost of enrolling a large enough sample to adequately study rare outcomes such as neonatal mortality. Even the most well designed prospective, registry-based studies, if not randomized, can be subject to selection bias and other forms of omitted variable bias. In such situations, quasi-experimental research designs, such as instrumental variable analysis, can fill in the gaps by providing causal estimates of treatment effects without incurring the high cost or ethical concerns associated with prospective clinical trials.[33]

RESULTS AND DISCUSSION

Overall cesarean delivery rates have been steadily increasing since 2000, reaching an all-time high of nearly 55% in 2010, while the repeat cesarean delivery rate is now above 90%.

These changes in practice are in contrast to national health policy evidenced by Healthy People 2010 and 2020 advocates for reducing both the primary and the repeat cesarean delivery rates.[34] Although many of these observational studies were well designed prospective studies with high-quality clinical data, even the highest quality non-randomized studies can suffer from selection bias if such bias is not specifically modeled and accounted for. In the current study, we estimated the causal effects of EPCD on neonatal outcomes using IV analysis, a quasi-experimental method designed to account for forms of omitted variable bias, such as selection bias. Although the data used in the current study, vital records data and hospital discharge data, are not as accurate or clinically in depth as many of the registry-based studies previously conducted, the limitations of the current data set are the type of limitations that IV analysis is well suited to accommodate.[35]

Results from the current study, specifically the results from the IV analyses, differ significantly from those previously reported in the literature for both primary outcomes, neonatal mortality and the composite measure of respiratory morbidity. Increased rates of neonatal mortality and respiratory morbidity for infants delivered by EPCD compared to those delivered vaginally has become a well-recognized phenomenon.

And indeed, the majority of published studies concerning either neonatal mortality or respiratory morbidity, have reported higher rates in neonates born by EPCD. The current study, when employing traditional bivariate and multivariate methods of analysis, also found significantly higher rates of both neonatal mortality and overall respiratory morbidity in infants delivered by EPCD. However, when selection bias was taken into account by the IV analysis, presumably estimating a less biased result from which causal inferences can be drawn, infants delivered by EPCD had a lower risk of both neonatal mortality and respiratory morbidity.[36]

The only published study the authors are aware of that reported a reduced risk of both neonatal mortality and respiratory morbidity for those delivered by elective cesarean, is the Term Breech Trial. Though limited to breech deliveries, the Term Breech Trial is by far the largest of only three published RCT for the mode of delivery.[37] When an RCT has been limited to a specific population, such as breech deliveries, the generalizability of results is potentially limited to that specific population. Although there may be no direct evidence of this limited generalizability, especially in the absence of any other RCT in the greater population, there is also no evidence that the results are not generalizable to the greater population. Results from the current study lend support to the idea that at least some of the outcomes from the Term Breech Trial could be generalizable to the population of low-risk, vertex presenting deliveries. The multivariable results of the current study seem to indicate that there is some mechanism that causes neonates born by EPCD to be at higher risk of mortality and respiratory morbidity. The results from the instrumental variable analyses seem to indicate that bypassing labor with an elective cesarean is likely not that mechanism.[38]

There are two commonly accepted theories as to why neonates delivered by EPCD are at greater risk of morbidity, especially respiratory morbidity, than neonates experiencing a TOL. The first states that the labor process itself is involved in triggering fluid in the fetal lung to be reabsorbed in preparation for the conversion to air breathing. The second states that neonates delivered by EPCD, suffer from a greater degree of iatrogenic prematurity than neonates delivered vaginally, in large part because the delivering physician is often attempting to deliver before the onset of spontaneous labor. The former theory is dependent upon cesarean delivery disrupting the natural process of allowing labor to trigger the absorption of significant amounts of fetal lung fluid prior to delivery. In this scenario, cesarean delivery prior to the onset of labor is the mechanism that disrupts a biological process that aids in the transition to breathing air. The latter theory is dependent upon measurement error; the physician incorrectly judges the fetus to be more mature than it actually is. In this scenario timing of delivery is the mechanism which exposes immature lungs to demands that the fetus might not be prepared to meet. If the majority of the morbidity seen in the multivariate analyses was due to a disruption of fetal lung fluid clearance, then the instrumental variable analyses would have also shown this morbidity because delivery prior to the onset of labor is by definition a part EPCD.[39] If the majority of the morbidity seen in the standard multivariable analyses is due to misjudging the gestational age of the fetus, a type of measurement error that is not intrinsic to EPCD, then the instrumental variable analysis, with its ability to essentially balance measurement error and other forms of omitted variable bias across groups, would control for this and show little or no morbidity differential between groups. Based on the results of the current study, it seems more likely that the increased morbidity seen in EPCD is due more to iatrogenic prematurity than issues with fetal lung fluid clearance. This is not to suggest that fetal lung fluid absorption is not triggered by spontaneous labor or even that this might not be harmful in itself, but rather than having this process disrupted is likely not the underlying cause of the majority of respiratory morbidity seen in EPCD.[40]

	Multivariable Probit Models		Bivariate Probit with Instrumental Variables		Test of Endogeneity		Test of Weak Instruments	
Outcome	ARR	95% CI	ARR	95% CI	F-Statistics	p-value	F-Statistics	p-value
Neonatal Mortality	0.86	0.49-1.52	0.67	0.09-5.18	0.1	0.8019	6,159	<0.0001
Composite Respiratory Morbidity*	1.28	1.23-1.34	0.92	0.74-1.15	8.0	0.0048	1,968	<0.0001
Mechanical Ventilation	0.78	0.72-0.85	0.28	0.21-0.38	32.8	<0.001	2,300	<0.0001
Respiratory Distress Syndrome	1.40	1.22-1.60	1.02	0.63-1.66	1.7	0.1918	5,725	<0.0001
Transitory Tachypnea of Newborn	1.62	1.53-1.71	1.67	1.30-2.14	0.1	0.7941	3,273	<0.0001
Birth Asphyxia	0.50	0.39-0.65	0.09	0.04-0.23	12.5	0.0004	3,809	<0.0001
Seizures	0.87	0.61-1.22	0.31	0.09-1.10	2.8	0.0959	6,538	<0.0001
Sepsis	0.89	0.81-0.98	1.00	0.64-1.57	0.3	0.5742	2,455	<0.0001
Treated Jaundice	1.06	0.99-1.14	1.12	0.82-1.53	0.1	0.7233	2,872	<0.0001
Hypoglycemia	1.25	1.12-1.39	0.68	0.43-1.08	6.6	0.0103	6,017	<0.0001
Birth Injury	0.32	0.27-0.37	0.19	0.11-0.31	4.3	0.0389	5,611	<0.0001

*Composite respiratory morbidity defined as mechanical ventilation, RDS, or TTN.

Approximately 1 in 4 children delivered preterm 2 specific diagnoses are considered, are limited by the small sample size and small numbers of babies with these combinations of multiple diagnoses. We attempted to address this issue by also separately examining the relationship between the absolute number of diagnoses (regardless of which specific ones) and outcomes.[41] Although there was a higher chance of adverse childhood neurodevelopmental outcomes with each additional neonatal diagnosis through 4 total diagnoses, the majority of babies with multiple neonatal diagnoses did not meet criteria for severe neurodevelopmental impairment at age 2 years. These data are useful when counseling patients regarding anticipated long-term outcomes following premature delivery. Although there was a definite relationship between the number of neonatal diagnoses and neurodevelopmental impairment in early childhood, this correlation was imperfect and remained imperfect even among the highest-risk subset, those delivered 2 SD below the mean when evaluated at age 2 years.[42]

In contrast, >40% of infants carrying up to 4 neonatal diagnoses did not have adverse outcomes at age 2 years. Our study had several strengths. This was a large, prospectively collected cohort. All children were evaluated in a standardized fashion by trained research nurses and physicians. Outcomes were determined, in part, by using an objective, previously validated assessment tool (Bayley II Scales of Infant Development). Other outcomes were obtained by trained pediatricians.[43]

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