Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2025.50

ORIGINAL ARTICLE

ANTICIPATING THE NEED FOR ADVANCED RESUSCITATION IN NEWBORNS: A 10-YEAR RETROSPECTIVE CASE-CONTROL STUDY

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ABSTRACT

Transition to extrauterine life involves significant physiological changes for every newborn. Although most neonates begin breathing on their own, about 10% require assistance at birth and approximately 1% need advanced resuscitation measures. Anticipation and preparation are the first and most important steps in delivering effective care.

A retrospective case-control study conducted over 10 years at a level 2 hospital was carried out by selecting newborns requiring advanced resuscitation measures (intubation, chest compressions and/or epinephrine) as cases. The control group included randomly selected newborns without the need for advanced resuscitation, matched for gestational ages. Extreme premature newborns were excluded. Twenty-nine potentially predictive antepartum, intrapartum and neonatal characteristics, based on the risk factors described in the 2020 American Heart Association guidelines, were analyzed.

The study sample included 90 cases and 90 controls (n=180). The case group predominantly consisted of males (52.2%), very premature (median gestational age of 32 weeks) and low birth weight newborns (median birth weight of 1917 g). Four characteristics were identified as independently predictive of the need for advanced neonatal resuscitation, such as history of previous stillbirth, oligohydramnios, need for urgent or emergent cesarean section and significant intrapartum bleeding.

Knowledge and assessment of risk factors are essential for effective neonatal resuscitation. The findings of this study reinforce previous research and underscore the importance of anticipating and identifying newborns at higher risk, enabling a specialized team to assist these births and improve neonatal outcomes.

ARTICLE HISTORY

Received 05 September 2024

Accepted 22 October 2024

KEYWORDS

Neonatology, Neonatal Resuscitation, Neonatal Intensive Care, Risk Factors, Perinatal Outcomes, Case-Control Study.

ABBREVIATIONS

ANR - Advanced Neonatal Resuscitation

ACGO - American College of Gynecology and Obstetrics

AHA - American Heart Association

AFI - Amniotic Fluid Index

BW - Birth Weight

GA - Gestational Age

HELLP - Hemolysis, Elevated Liver enzymes and Low Platelets

NICE - National Institute for Health and Care Excellence

NICU - Neonatal Intensive Care Unit

SPSS - Statistical Package for the Social Sciences.

Introduction

Transition to extrauterine life involves significant physiological changes for every newborn.[1,2] Although most neonates begin breathing on their own, about 10% require assistance at birth and approximately 1% need advanced resuscitation measures, such as intubation, chest compressions and/or epinephrine.[1,2] Successful advanced resuscitation resulting in good neonatal outcomes depends on critical timely and effectively taken actions.[1,2,3,4]

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Anticipation and preparation are the first and most important steps in delivering effective neonatal resuscitation.[2] When the need for advanced neonatal resuscitation (ANR) is not anticipated, the resulting delay in newborn birth assistance may worsen the prognosis.[1,2] Identification of risk factors for the need for ANR measures can indicate the need for more specialized personnel and equipment.[1,2] Without this risk stratification, up to 50% of neonates needing birth assistance may not be identified before delivery.[1,2]

In its most recent guidelines for neonatal resuscitation, the American Heart Association (AHA) recommends risk factors assessment before every birth so that a qualified team can be assembled based on that risk.[2] The study of Berazategui et al. identified ten risk factors for ANR in near-term and term neonates: gestational age (GA) 34-37 weeks; intrauterine growth restriction; gestational

diabetes; fetal bradycardia; clinical chorioamnionitis; placental abruption; forceps or vacuum delivery; emergency cesarean section; general anesthesia; and meconium-stained amniotic fluid.[3] A more extensive list of risk variables is published in the Textbook of Neonatal Resuscitation by the American Academy of Pediatrics and the AHA.[1] Based on these risk factors, Zarkesh et al. even proposed an algorithm to help predict the need for ANR.[4]

This study aims to identify predictive antepartum, intrapartum, and neonatal factors for ANR, enabling birth assistance teams to adequately anticipate and prepare.

Methods & Materials

A single-center retrospective case-control study was conducted after approval by the Institutional Research Ethics Committee of the Unidade Local de Saúde de Matosinhos.

The study case group consisted of all neonates born in our hospital, Hospital Pedro Hispano, Porto, between January 2010 and December 2020, requiring ANR, defined as the need for intubation, chest compressions and/or epinephrine. We then divided these neonates in terms of their GA into 8 groups: extremely preterm (<28 weeks); very preterm (≥28 and <32 weeks); moderately preterm (≥32 and <34 weeks); late preterm (≥34 and <37 weeks); early term (≥37 and <39 weeks); full term (≥39 and <41 weeks); late term (≥41 and <42 weeks); and post term (≥42 weeks).[4,5] The control group was composed of randomly selected patients born in the same period with matched GA for a case/control rate of 1:1.

In both groups, clinical maternal, gestational, and neonatal data were recorded, using information available on the electronic platform SClínico Hospitalar. We used the list of risk factors described by Kattwinkel J. and the 2020 AHA guidelines as predictive of the need for neonatal resuscitation.[1,2] We classified these variables into antepartum, intrapartum, and neonatal. Accordingly to their birth weight (BW), newborns are classified as: macrosomic if BW >4000 g; normal BW if ≥2500 g and ≤4000 g; low BW if ≥1500 g and <2500 g; very low BW if ≥ 1000g and <1500 g; and extremely low BW if <1000 g.[7] A newborn is described as small for GA if his BW is lower than the 3rd percentile and large for GA if his BW is higher than the 97th percentile, according to Fenton curves if premature or INTERGROWTH-21st charts if term.[8] Good adaptation to extrauterine life is defined as an Apgar score of ≥7 at the first (1st) minute of life and an Apgar score of <7 at the fifth (5th) minute reflects an inadequate response to resuscitation measures.[1] Maternal chronic diabetes is defined as diabetes predating pregnancy and gestational diabetes as glucose intolerance with onset during pregnancy.[6] Maternal chronic hypertension is defined as hypertension preceding pregnancy or diagnosed before 20 weeks of gestation, while gestation hypertension is the one diagnosed after this timeline.[6] Preeclampsia is defined as hypertension plus significant end-organ dysfunction with or without proteinuria, HELLP (hemolysis, elevated liver enzymes and low platelets) as a severe form of preeclampsia with hemolytic anemia, thrombocytopenia and liver dysfunction and eclampsia as new onset of seizures or coma in a woman with preeclampsia.[9] Maternal substance use was considered positive if cannabinoids, cocaine, or opioid use. A nulliparous woman is someone who has never had a pregnancy beyond 20 weeks of gestation, regardless of the outcome.[6] Previous stillbirth, following the American College of Gynecology and Obstetrics (ACGO) definition, is a previous fetal death after 20 weeks of gestation.[10] Unsupervised pregnancy was defined as less than 3 obstetric appointments. A multiple gestation is a pregnancy with more than one fetus.[6] Oligohydramnios is defined as amniotic fluid index (AFI) ≤5 cm and polyhydramnios as AFI ≥ 24 cm.[10] Structural birth defects were classified as fetal malformation. Fetal malpresentation refers to a fetus with a fetal part other than the head engaging the maternal pelvis.[6] Premature rupture of membranes refers to the breaking of the amniotic sac before the beginning of labor.[6] Pathological cardiotocography was categorized according to the International Federation of Gynecology and Obstetrics guidelines on intrapartum fetal monitoring.[12] Urgent or emergent cesarean sections were defined according to the Portuguese General Directorate of Health guidelines.[12] Chorioamnionitis is the acute inflammation of the membranes and chorion of the placenta and its diagnosis was made after the presumptive criteria of the ACGO.[6] Placenta previa is the complete or partial covering of the internal os of the cervix with the placenta.[14] Placental abruption occurs when the placenta separates from your uterus before delivery.[6] Umbilical cord prolapse occurs when the umbilical cord exits the cervical opening before the fetus.[15] Significant intrapartum bleeding was defined as bleeding that caused maternal hemodynamic instability.[6]

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), version 28.0.1. Normal distribution was checked using Shapiro-Wilk test. Qualitative variables were analyzed by X2 and Fisher's tests, as appropriate. Categorical variables are presented as frequencies and percentages and continuous variables as means and standard deviations for variables with normal distribution or medians and interquartile ranges for variables with skewed distributions. A logistic regression analysis was conducted to identify independent predictors of ANR. All reported p-values are two-tailed, with a p-value of less than 0.05 indicating statistical significance.

Results and Discussion

Between January 2010 and December 2020, a total of 134 newborns at Hospital Pedro Hispano required ANR. When selecting the control sample, it was found that the extremely preterm control group (n=19) had significantly fewer individuals compared to the case group (n=44) due to their particular vulnerability (p=0.008). Therefore, this GA group of newborns was excluded from the inferential analysis. The final sample included 90 newborns who needed ANR (case group) and 90 who did not (control group), with reported gestational ages between 28 and 41 weeks.

Neonatal characteristics are presented in Table 1. Regarding GA, the distribution was as follows: 40% (n=36) were very preterm; 24.4% (n=22) were full term; 16.7% (n=15) were moderately preterm; 10.0% (n=9) were early term; 4.4% (n=4) were

Table 1. Characteristics of the study population.

Variables	Total (n=180)	Cases (n=90)	Controls (n=90)	p-value
Male sex (%)	98 (54.4)	47 (52.2)	51 (56.7)	0.549
GA (weeks) median	32 [30-39]	32 [29-39]	33 [30-39]	
BW (g) median	1900 [1350-3050]	1917 [1365-3060]	1747 [1307-3116]	
Normal BW (%)	71 (39.4)	35 (38.9)	36 (40.0)	0.879
Low BW (%)	53 (29.4)	28 (31.1)	25 (27.8)	0.624
Very low BW (%)	39 (21.7)	18 (20.0)	21 (23.3)	0.587
Extremely low BW (%)	16 (8.9)	9 (10.0)	7 (7.8)	0.600
Macrosomia (%)	1 (0.6)	0	1 (1.1)	1
Appropriate for GA (%)	162 (90.0)	83 (92.2)	79 (87.8)	0.320
Small for GA (%)	13 (7.2)	7 (7.8)	6 (6.7)	0.773
Large for GA (%)	5 (2.8)	0	5 (5.6)	0.059
Apgar score				
<7 at 1st minute	86 (47.8)	61 (67.8)	25 (27.8)	<0.001
<7 at 5th minute	33 (18.3)	33 (36.7)	0	<0.001
Destination at discharge				
Rooming-in (%)	165 (91.7)	75 (83.3)	90 (100.0)	<0.001
Transference to another NICU (%)	10 (5.6)	10 (11.1)	0	0.001
Dead (%)	5 (2.8)	5 (5.6)	0	0.059

Table 2. Characteristics of the worst outcome group of newborns.

Variables	Cases (n=15)
Male sex (%)	7 (46.7)
GA (weeks) median	36 [28-41]
BW (g) median	2040 [630-3540]
Apgar score <7 at 1st and 5th minutes (%)	15 (100.0)
Maternal chronic hypertension (%)	4 (26.7)
Previous stillbirth (%)	5 (33.3)
Nulliparity (%)	11 (73.3)
Oligohydramnios (%)	6 (40.0)
Pathological cardiotocography (%)	9 (60.0)
Need for urgent or emergent cesarean section (%)	9 (60.0)
Placental abruption (%)	6 (40.0)
Significant intrapartum bleeding (%)	2 (13.3)

late preterm; and 4.4% (n=4) were late term. The male sex predominated in both the case and control groups (52.2%, n=47 and 56.7%, n=51, respectively; p=0.549). The median BW for both groups fell within the low BW range, but most neonates were appropriate for GA (92.2%, n=83 and 87.8%, n=79, respectively; p=0.320). The percentage of infants with an Apgar score <7 at the 1st and 5th minutes was significantly higher in the case group (67.8%, n=61 and 36.7%, n=33, respectively; p<0.001).

Prematurity and BW less than 2500 grams are established risk factors for poor adaptation to extrauterine life.[1] Although our study population predominantly comprised very preterm and low BW newborns, a significant strength of our research lies in the use of a broad GA sample. Our 1:1 GA-matched sample with a comparable BW distribution across the case and control groups makes the influence of these factors negligible. This contrasts with other studies, which often select populations based on specific GA or BW criteria, thereby limiting the generalizability of their conclusions.[16,17]

Regarding the destination at discharge (Table 1), there were 5 deaths (2.8%), including 2 in the delivery room, and 10 hospital transfers (5.6%) for treatment escalation, all within the case group. All newborns in the control group were sent to rooming-in with their mothers.

In Table 2, we thoroughly examine the unfavorable outcome group of newborns (n=15). Eight newborns were premature (53.3%), with a median GA of 32 weeks, and 7 were born at term (46.7%), with a median GA of 39 weeks. Thirteen of the neonates had a BW appropriate for GA (86.7%), while 2 were small for GA (13.3%). All exhibited poor adaptation to extrauterine life and an inadequate response to resuscitation measures, reflected by Apgar scores of less than 7 at the 1st and 5th minutes. Every newborn in this group had at least one of the risk factors analyzed in the study, including those found to be significantly associated with the need for ANR.

The two deaths in the delivery room were as follows: a 40-week GA full-term newborn with an appropriate BW, born with an Apgar score of 0-0-0 after an emergent cesarean section due to placental abruption; and a 28-week GA very preterm newborn with an extremely low BW, born to a nulliparous, chronically diabetic, and hypertensive mother, with a pregnancy complicated by oligohydramnios, and an Apgar score of 2-1-0. Eight of the ten hospital transfers (80.0%) were due to hypoxic-ischemic encephalopathy, eligible for therapeutic hypothermia, while two (20.0%) were due to surgical pathologies.

We analyzed 29 antepartum and intrapartum characteristics, as described and correlated with the need for ANR in Table 3. Group comparison analysis revealed significant associations with the need for ANR for the following factors: maternal chronic hypertension; previous stillbirth; nulliparity; oligohydramnios; pathological cardiotocography; need for urgent or emergent cesarean section; placental abruption; and significant intrapartum bleeding.

Maternal chronic hypertension, affecting 1-5% of pregnancies, has long been associated with adverse outcomes. Consistent with our findings, a recent systematic review and meta-analysis highlighted that chronic hypertension is linked to a higher incidence of stillbirth, preterm birth, need for cesarean section, perinatal and neonatal death, NICU admission and newborns small for GA and low BW. Our study confirms these associations, emphasizing the critical role of hypertension in predicting the need for ANR.[18]

Our results regarding the history of previous stillbirth align with existing literature, which reports that such a history is associated with a two-fold increased risk of recurrence and significant neonatal morbidity. Specifically, women with a prior stillbirth face a 25% higher risk of neonatal morbidity, a 50% increased likelihood of NICU admission, and nearly a seven-fold increased risk of neonatal death.[19] This finding underscores the importance of monitoring and preparing for high-risk deliveries in this population.

The association between nulliparity and adverse outcomes in our study mirrors findings from other research. Despite some controversy, nulliparous women have been shown to be at higher risk for complications such as intrauterine growth retardation, oligohydramnios, preterm labor, need for emergency cesarean section, newborns small for GA and low BW and neonatal death.[20,21]

Our analysis also confirmed the well-documented risks associated with oligohydramnios, supporting the need for careful management of these pregnancies and deliveries. This condition has been consistently linked to adverse maternal and neonatal outcomes, including intrauterine demise, low Apgar scores and neonatal death.[11]

The significance of pathological cardiotocography in predicting fetal distress and the need for ANR is also supported by existing literature. Pathological cardiotocography indicates a high probability of fetal hypoxia and acidosis, with associated innumerous morbidities, ensuring the need for expedite delivery.[11] This is consistent with our results, highlighting the critical role of timely intervention.

The definition of an urgent or emergent cesarean section foresees a clinical situation that requires quick resolution, implicating danger to the fetus or the mother's life in the case of the need for an emergent procedure, therefore the association between urgent or emergent cesarean sections and the likelihood of ANR is well-established.[13] Our study highlights the importance of establishing well-prepared birth assistance teams to effectively manage such critical scenarios.

Placental abruption, a life-threatening obstetric emergency, is linked with stillbirth, growth restriction, and asphyxia, which aligns with our findings. This condition's association with low birth weight and NICU admission underscores the necessity for careful monitoring and preparation in at-risk pregnancies.

Finally, our study supports the NICE (National Institute for Health and Care Excellence) guidelines, which recognize the severe neonatal morbidities associated with intrapartum hemorrhage, including hypoxic-ischemic encephalopathy, neonatal anemia, cerebral

Table 3. Characteristics associated with the need for advanced neonatal resuscitation.

Variables	Total (n=180)	Cases (n=90)	Controls (n=90)	p-value
Antepartum				
Maternal age >35 years	63 (35.0)	36 (40.0)	27 (30.0)	0.160
Chronic diabetes	4 (2.2)	0	4 (4.4)	0.121
Chronic hypertension	35 (19.4)	24 (26.7)	11 (12.2)	0.014
Maternal substance use	18 (10.0)	12 (13.3)	6 (6.7)	0.136
Previous stillbirth	39 (21.7)	32 (35.6)	7 (7.8)	<0.001
Nulliparity	117 (65.0)	65 (72.2)	52 (57.8)	0.042
Unsupervised pregnancy	8 (4.4)	2 (2.2)	6 (6.7)	0.278
Gestational diabetes	18 (10.0)	9 (10.0)	9 (10.0)	1
Gestational hypertension	6 (3.3)	2 (2.2)	4 (4.4)	0.682
Pre-eclampsia	25 (13.9)	11 (12.2)	14 (15.6)	0.537
Eclampsia	2 (1.1)	2 (2.2)	0	0.497
HELLP	7 (3.9)	6 (6.7)	1 (1.1)	0.054
Multiple gestation	37 (20.6)	21 (23.3)	16 (17.8)	0.356
Oligohydramnios	20 (11.1)	16 (17.8)	4 (4.4)	0.004
Polihydramnios	1 (0.6)	0	1 (1.1)	0.497
Fetal malformation	2 (1.1)	0	2 (2.2)	0.497
Breech or transverse presentation	33 (18.3)	15 (16.7)	18 (20.0)	0.563
Premature rupture of membranes	19 (10.6)	8 (8.9)	11 (12.2)	0.467
Intrapartum				
Pathological cardiotocography	49 (27.2)	33 (36.7)	16 (17.8)	0.004
>24 hours labour	7 (3.9)	2 (2.2)	5 (5.6)	0.247
General anesthesia	18 (10.0)	12 (13.3)	6 (6.7)	0.136
Vaccum or forceps delivery	26 (14.4)	15 (16.7)	11 (12.2)	0.396
Urgent or emergent cesarean section	85 (47.2)	63 (70.0)	22 (24.4)	<0.001
Chorioamnionitis	7 (3.9)	5 (5.6)	2 (2.2)	0.444
Placenta previa	6 (3.3)	3 (3.3)	3 (3.3)	1
Placental abruption	23 (12.8)	20 (22.2)	3 (3.3)	<0.001
Prolapse cord	2 (1.1)	2 (2.2)	0	0.497
Significant intrapartum bleeding	19 (10.6)	18 (20.0)	1 (1.1)	<0.001
Meconium or hematic-stained amniotic fluid	14 (7.8)	4 (4.4)	10 (11.1)	0.095

Table 4. Antepartum, intrapartum and neonatal factors associated to ANR.

Variables		Odds Ratio (CI 95.0%)
Chronic hypertension	No	1
	Yes	0.40 (0.06 - 2.73)
Previous stillbirth	No	1
	Yes	6.00 (2.43 - 14.81)
Nulliparity	No	1
	Yes	1.69 (0.86 - 3.32)
Oligohydramnios	No	1
	Yes	4.52 (1.35 - 15.05)
Urgent or emergent cesarean section	No	1
	Yes	5.94 (2.94 - 11.99)
Pathological cardiotocography	No	1
	Yes	2.04 (0.89 - 4.68)
Placental abruption	No	1
	Yes	3.70 (0.90 - 15.28)
Significant intrapartum bleeding	No	1
	Yes	14.54 (1.74 - 121.26)

palsy and long-term neurodevelopmental disabilities.[23]

Table 4 presents the logistic regression analysis identifying the antepartum and intrapartum characteristics independently associated with the need for ANR. Four of the characteristics analyzed in the study were found to independently predict the need for ANR.

Regarding antepartum factors, newborns born to women with a history of previous stillbirths were six times more likely to require ANR (OR: 6.00, 95% CI: 2.43 - 14.81). Additionally, newborns from women who experienced oligohydramnios during pregnancy had a higher likelihood of needing ANR (OR: 4.52, 95% CI: 1.35 - 15.05).

In terms of intrapartum factors, the likelihood of ANR was 5.94 times higher when an urgent or emergent cesarean section was performed (OR: 5.94, 95% CI: 2.94 - 11.99), and significant intrapartum bleeding was associated with a markedly higher probability of requiring ANR (OR: 14.54, 95% CI: 1.74 - 121.26).

The loss of apparent significance for factors such as maternal chronic hypertension, nulliparity, pathological cardiotocography and placental abruption is likely due to the simultaneous adjustment for multiple factors in the logistic regression analysis. In group comparison analysis, each factor is considered independently, which may overestimate its significance. For example, while maternal chronic hypertension showed a significant association in the group comparison, its effect may be intertwined with other factors like the need for urgent or emergent cesarean section or significant intrapartum bleeding, which are accounted for in the logistic regression model. Similarly, pathological cardiotocography and placental abruption, which indicated a high risk in group comparison, may lose significance when the model adjusts for overlapping conditions like urgent cesarean sections and significant bleeding. Another explanation, and a limitation of the study, is the small sample size, which can reduce the power to detect significant effects in logistic regression, especially when controlling for multiple variables.

In summary, our study's findings are largely consistent with established literature, reinforcing the need for ongoing vigilance and preparedness in high-risk deliveries to optimize neonatal outcomes.

Conclusion

A comprehensive assessment of risk factors associated with the necessity for ANR was conducted in this study. Our analysis identified several characteristics independently predictive of the need for ANR, such as history of previous stillbirth, oligohydramnios, need for urgent or emergent cesarean section and significant intrapartum bleeding.

These findings align with previous studies and underscore the importance of early identification of newborns at higher risk for requiring advanced resuscitation, ensuring that a specialized team is available to assist these births, thereby improving neonatal outcomes.

Further research should delve deeper into the specific mechanisms underlying these identified risk factors and explore additional predictors to refine risk assessment models, ultimately contributing to more effective strategies for neonatal care and improving overall maternal and fetal health outcomes.

A strength of our study is that we included neonates above 28 weeks of gestation with a 1:1 GA-matched sample and a comparable BW distribution, enabling an accurate risk factor comparison. Furthermore, although not independently predictive, we highlight the possible role of nulliparity as an important risk factor to consider, which is not yet emphasized in neonatal resuscitation guidelines. Regarding its limitations, in addition to the small sample size already mentioned, it is a retrospective single-center study, making it necessary for larger multicenter studies to confirm our findings.

Compliance with Ethical Standards
Funding None
Conflict of Interest None

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