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The Association of Using Cooling Therapy Post Asphyxia among Newborns in NICU at Palestinian Hospitals: A Retrospective Study

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Thesis Approval

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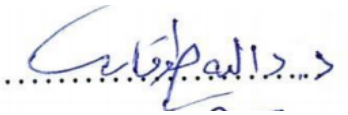
1. Dr. Dalia Toqan: Supervisor	
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Declaration

I declare that the work in this study titled “The Impact of Using Cooling Therapy (Hypothermia Therapy) Post Asphyxia among Newborns in NICU at Palestinian Hospitals: Retrospective” was carried out by me under the supervision of Dr. Dalia Toqan in the Department of Nursing .

In addition, I understand the nature of plagiarism and am aware of the University's policy on this .

Unless otherwise referenced, the work provided in this thesis is the researcher's work and has not been submitted by others elsewhere for any other degree or qualification.

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Abstract

Background: Perinatal hypoxia produces hypoxic-ischaemic encephalopathy (HIE), a primary lead to neonatal complications. Long-period neurological sequelae occur in one to two instances per 1,000 live term-born infants in affluent nations. Research suggests that starting whole-body moderate hypothermia (33-34°C) within six hours of delivery reduces mortality and neurodevelopmental impairment at 18 months and beyond. Hypothermia is most helpful when initiated during the latent phase of HIE before secondary energy failure leads to cell death (preclinical and clinical investigations confirm this).

Purpose: To investigate the impact of using cooling therapy for neonatal post-asphyxia in the NICU at Privet Hospitals in West Bank.

Methods: A retrospective, descriptive, quantitative study design was conducted, was conducted in the NICU Department at Privet Hospitals which contains a Neonate Intensive Care Unit. The target population was Newborns with Asphyxia and using cooling therapy, who met the inclusion criteria. A convincing sample was composed of 45 patients.

Results: The gender distribution was nearly equal between male (51.1%) and female (48.9%) infants. Major adverse events were hypotension (26.7%), abnormal renal function (4.4%), and metabolic acidosis (22.2%). Death occurred in 4.9% of patients during the 72-hour intervention and 4.7% during the hospitalization. Primary results showed that 71.1% had no intermediate disability, 82.2% had no severe disability, and 91.1% survived. Significant connections were found, with gestational age inversely related to death ($p=0.005$) and blood gas indicators having variable associations. Chi-square testing found a significant correlation

($p<0.05$) between 5-minute Apgar ratings, severe encephalopathy, adverse events during intervention and hospitalization, and mortality.

Conclusion: The study's conclusion provides a thorough understanding of prenatal therapies and their effects on mother and newborn health outcomes. The study sheds light on the varied nature of neonatal care and the obstacles that come with dealing with prenatal insults by meticulously analyzing maternal and neonatal features, major adverse events, postnatal issues, and primary outcomes.

Keywords: Asphyxia, Cooling Therapy, hypoxic-ischaemic encephalopathy, Hypothermia Treatment

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List of Abbreviations

aEEG: amplitude-integrated electroencephalography

AKI: Acute kidney damage

BA: Birth asphyxia

CS: Cesarean Section

DOL: Day of Life

ECG: Electrocardiogram

EEG: electroencephalography

GFAP: glial fibrillary acidic protein

HIE: Hypoxic-Ischaemic Encephalopathy

HICs: high-income countries

IL: Interleukin

IRB: Institutional Review Board

LMICs: low and middle-income countries

mCRT: Meta Register of Current Controlled Trials

NICHD: National Institute of Child Health and Human Development

NICU: neonatal intensive care unit

NVD: Normal Vaginal Delivery

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

RCT: randomized controlled trials

SCr: serum creatinine

SHC: selective head cooling

SPSS: Statistical Package for the Social Sciences

TH: therapeutic hypothermia

WBC: whole-body cooling

Chapter One

Introduction

1.1 Introduction

Perinatal hypoxia produces hypoxic-ischaemic encephalopathy (HIE), a primary lead to neonatal complications. Long-period neurological sequelae occur in one to two instances per 1,000 live term-born infants in affluent nations. Research suggests that starting whole-body moderate hypothermia (33-34°C) within six hours of delivery reduces mortality and neurodevelopmental impairment at 18 months and beyond (Thoresen et al., 2013; Wincoop et al., 2021; Tanigasalam et al., 2015).

Large research networks cannot run a definitive study to determine the benefit or harm of this uncommon ailment due to insufficient patient numbers to reach high statistical power within a reasonable timeframe. Over 8 years, a multicenter, randomized clinical trial compared infants with moderate or severe hypoxic-ischemic encephalopathy treated with hypothermia initiated at or after 6 hours but before 24 hours of age to no cooled infants to provide the most accurate estimate of treatment effect. Bayesian analyses were used to determine whether hypothermia reduced the chance of mortality or impairment at 18 months (Wassink et al., 2019).

Cooling the body to 33.5°C for 3 days has profound effects on both normal and pathological systems. Some effects are beneficial and neuroprotective, while others are not. Thomas Wood and I outlined how temperature affects normal organ function, including drug metabolism (Laptook et al., 2017).

Monitoring electroencephalography (EEG) and/or amplitude-integrated EEG and seizure activity is crucial in managing neonates with hypoxic-ischemic injury, as seizures are a key indicator of lesion severity (Sabir et al., 2020).

Hypothermia is most helpful when initiated during the latent phase of HIE before secondary energy failure leads to cell death (preclinical and clinical investigations confirm this). A retrospective study found that initiating hypothermia within three hours, rather than three to six hours after delivery, was related to better motor outcomes in surviving patients. These findings confirm the emerging trend of initiating hypothermia immediately after a hypoxia insult (Szakmar et al., 2019).

Cooling may not be effective in an asphyxiated infant due to circumstances such as unintentional hypocapnia, which can exacerbate brain injury. Retrospective research shows a significant incidence of hypocapnia (up to 88%) within the first 12 hours of postnatal life. In a mixed group of cooled and non-cooled HIE newborns, there was a dose-dependent link between hypocapnia and a negative neurodevelopmental outcome, such as mortality or disability at 18-22 months (Davidson et al., 2015).

Despite advancements in perinatal and neonatal care, the prevalence of long-term neurological outcomes like cerebral palsy has remained stable. Previously, resuscitative and post-resuscitative management was limited to supportive intensive care, including correction of hemodynamic and pulmonary disturbances (hypotension and hypoventilation), metabolic disturbances (glucose, calcium, magnesium, and electrolytes), seizure treatment, and monitoring for organ system dysfunction (Thoresen, 2015).

Intravenous pharmacological neuroprotective treatment is popular because of its quick and easy delivery. Pharmacological therapy may be limited by the need for quick delivery of therapeutic concentrations to brain tissue. The blood-brain barrier can impair the efficiency of neuroprotective pharmacological therapies (Cornette, 2012).

MRI brain scanning, particularly diffusion-weighted imaging, is being used to validate hypothermia and identify injuries early on. The treatment leads to less severe cortical and deep gray nuclear injuries. Many countries and institutions now use hypothermia as a standard of care for term asphyxiated newborns (Hakobyan et al., 2019).

Therapeutic hypothermia (TH) should be administered following a published procedure, the procedure has been shown to have neuroprotective properties by modifying cells that are programmed for apoptosis. This reduces the metabolic rate of the brain, attenuates the release of excitatory amino acids (glutamate, dopamine), improves ischemic damage through glutamate uptake, and decreases nitric oxide and free radical production, ultimately reducing neuronal death. Other techniques include reducing reactive oxygen species, slowing metabolic rate, and enhancing neuroprotection through endogenous mechanisms. Based on available data and knowledge gaps. Treatment with TH should begin within the first 6 hours of life and last for 72 hours, as the shift from recovery to the second phase of the injury provides a window for neuroprotection or decrease. Some requirements should be observed when applying TH. This guideline states that active cooling to 33.5-34°C should begin before 6 hours following birth (Souza et al., 2021).

The criteria for newborns with fetal distress and newborn depression include a pH of ≤ 7.0, indicating acidosis that causes end-organ failure. An isolated pathologic fetal distress

may not accurately identify newborns with high-income countries (HIE), as unsuspected academia in stable neonates can lead to the inducement of labor (Shankaran et al., 2014).

Following acute asphyxia in term newborns, neurological findings can indicate mild (grade I), moderate (grade II), or severe (grade III) encephalopathy. Grade I encephalopathy in neonates has a normal fate, while grade II encephalopathy has a 25% bad outcome and grade III has a 50-100% poor outcome. This grading method applies 24 hours after birth and takes into account EEG changes. The Thompson score is one of the new clinical scoring systems used to measure the severity of newborn encephalopathy. A Thompson score of ≥7 indicates moderate to severe clinical encephalopathy (Cornette, 2012).

Cerebral function monitoring, such as a single channel amplitude-integrated EEG (aEEG), can identify newborns at high risk of severe outcomes from prenatal hypoxia and detect subclinical convulsions. Pharmacological treatment of subclinical status epilepticus in per partum hypoxia may enhance patient prognosis (Joy et al., 2014).

The burden in low and middle-income countries (LMICs) is far higher than in high-income countries, and it accounts for approximately one million deaths annually. If not treated, 62% of infants with perinatal hypoxic brain injury will die or have moderate to severe disabilities by the age of 18 to 22 months; treatment reduces this rate to 41%. Survivors also develop long-term neurologic disabilities as follows: 45% have cognitive and developmental delay or learning difficulties, 29%, have some degree of cerebral palsy, 26%, have blindness or vision defects, 17%, have gross motor and coordination problems, epilepsy, 9%, hearing loss or deafness, and 1%, behavioral issues (Abate et al., 2021).

1.2 Problem Statement

Perinatal asphyxia is still a major concern in the neonatal intensive care unit (NICU). Perinatal asphyxia can cause multiorgan dysfunction in newborns, impacting almost all organ systems. Therapeutic hypothermia is now used to treat prenatal asphyxia, leading to better patient outcomes.

Acute kidney damage (AKI) is frequently seen in newborns suffering from prenatal hypoxia. Before therapeutic hypothermia, neonates with prenatal asphyxia had a significant rate of AKI (47-72%). Previous research used arbitrary serum creatinine (SCr) thresholds of >1.5 mg/dL to define AKI, making it difficult to compare investigations. In addition, no studies have included individuals who have had TH (David et al., 2013).

High-income countries deaths 60% of infants and leaves at least 25% with long-term neurological problems. The intensity of the insult varies with gestational age, with the most severe babies having a high level of cerebral vascular immaturity and experiencing extended periods of hostility (Souza et al., 2021).

50 million of the 53 million children under 5 with developmental disabilities reside in poor and middle-income nations. Perinatal brain injuries, particularly newborn encephalopathy (NE), account for over 80% of these impairments. Every year, around 1.2 million newborns worldwide suffer from NE, with a considerable number dying or experiencing permanent neuro disability. LMICs (5-20 per 1000 live births) account for approximately 90% of the illness burden, which is 5-20 times higher than in high-income nations (1-2 per 1000 live births). International emphasis has mostly concentrated on

neuroprotection in high-income countries (HICs) and, appropriately, community-based settings in LMICs (Krishnan et al., 2021).

While TH as well as early active cooling are helpful, there is still potential for improvement in neonatal critical care with HIE, particularly in terms of appropriate ventilation.

Despite increasing adoption, we need more comprehensive research to determine the efficacy of cooling therapy in neurological sequelae of birth asphyxia. Challenges in clinical practice, while cooling therapy holds promise, challenges in its seamless integration into routine clinical practice within NICU persist. Factors such as training, resource allocation, and standardized protocol must be addressed to facilitate widespread adoption and consistent application.

In light of these challenges, knowledge gaps, and no study of this related topic in Palestine, we need to conduct this approach of study.

1.3 Significant of the study

Therapeutic hypothermia has a major impact on neonatal encephalopathy outcomes. Pre-cooling outcome predictions are no longer as reliable in the cooling era.

The importance of investigating the impact of cooling therapy post-asphyxia among newborns in NICUs lies in its potential to save lives, enhance neurological outcomes, and transform the landscape of neonatal care. By offering a focused and innovative approach to address the challenges posed by birth asphyxia, cooling therapy can reshape the trajectories

of newborns affected by this condition, thereby realizing a future where neonatal health is optimized, and the burden of birth asphyxia is significantly diminished.

To increase the knowledge about hypothermia by adding courses in the university's curriculum and workshops, protocol, policies… etc.

1.4 Study Objective

1.4.1 General Objective

- To investigate the impact of using cooling therapy for neonatal post-asphyxia in the NICU at Privet Hospitals in West Bank.

1.4.2 Specific Objectives

1. To evaluate the impact of cooling therapy in reducing mortality rate, improving short-term outcomes, and enhancing long-term neurodevelopmental among newborns.
2. To investigate the optimal timing, duration, and degree of hypothermia required for effective neuroprotection when using cooling therapy in the NICU.

1.5 Study Questions

1. Is there a significant difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and Neurological outcomes?
2. Is there a significant difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and the mortality rate?
3. Is there a significant difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and gestational age?

4. Is there a significant difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and gender?
5. Is there a significant difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and birth weight?
6. Is there a significant difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and the severity of asphyxia?

1.6 Study Hypothesis

1. There is no statistically significance difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and Neurological outcomes.
2. There is no statistically significance difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and the mortality rate.
3. There is no statistically significance difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and gestational age.
4. There is no statistically significance difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and gender.
5. There is no statistically significance difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and birth weight.

6. There is no statistically significance difference at ($\alpha \leq 0.05$) in the impact of using cooling therapy post asphyxia among newborns in NICU in West Bank and the severity of asphyxia.

1.7 Study Variables

1.7.1 Dependant Variables: Cooling Therapy post Neonatal Asphyxia

1.7.2 Independent Variables: Neurological outcomes, Mortality Rate, gestational age, gender, birth weight, severity of asphyxia.

Chapter Two

Literature Review

2-1 Introduction

This chapter provides a synthesis of recent research found concerning Neonatal Cooling Therapy. Concepts that are critical to the study of this phenomenon include demographic data, clinical presentation, Asphyxia, hypoxic-ischaemic encephalopathy, and Cooling Therapy. Each concept is individually discussed.

The collection of literature was conducted utilizing a computerized search of databases. Databases including Pub Med, Google Scholar, and MEDLINE were used for relevant articles and journals. The studies reviewed were published from 2012 to 2023. Keywords used during the search hypoxic-ischemic encephalopathy, Cooling Therapy, and Asphyxia.

2.2 Review of the Study

A study conducted by Shankaran et al (2023), the objective of this study was to determine whether a longer duration of cooling (120 hours), a deeper level of cooling (32.0°C), or both could be more effective than the standard cooling at 33.5°C for 72 hours in full-term neonates with moderate or severe hypoxic-ischemic encephalopathy. The study employed a randomized 2 × 2 factorial design clinical trial conducted across 18 US centers within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network from October 2010 to November 2013. Neonates were divided into four hypothermia groups: 33.5°C for 72 hours, 32.0°C for 72 hours, 33.5°C for

120 hours, and 32.0°C for 120 hours. The primary outcome of death or disability at 18 to 22 months is still under analysis. The independent data and safety monitoring committee halted the trial multiple times to assess safety concerns, including cardiac arrhythmia, persistent acidosis, and major vessel thrombosis and bleeding, and deaths in the neonatal intensive care unit (NICU) after specific enrollment milestones. The trial was ultimately terminated due to emerging safety issues and futility analysis after enrolling 364 neonates out of the planned 726. Regarding NICU deaths, rates were 7% for the 33.5°C for 72 hours group, 14% for the 32.0°C for 72 hours group, 16% for the 33.5°C for 120 hours group, and 17% for the 32.0°C for 120 hours group. The adjusted risk ratios for NICU deaths comparing 120 hours to 72 hours cooling and 32.0°C to 33.5°C depth did not show statistically significant differences. Safety outcomes were generally comparable between groups, except for a lower incidence of major bleeding in the 120-hour group compared to the 72-hour group. The futility analysis concluded that the likelihood of identifying a significant benefit for longer cooling, deeper cooling, or both in reducing NICU deaths was less than 2%.

In a study conducted by Souza et al (2021), Experimental evidence, along with enhanced clinical studies, This study aimed to assess the potential of hypothermic therapy for HIE in cases of neonatal asphyxia, by comparing the advantages between selective head cooling (SHC) and whole-body cooling (WBC). Methods involved conducting a search in PubMed and SciELO databases for human studies using keywords such as "Therapeutic Hypothermia," "Induced Hypothermia," "Hypoxic-Ischemic Encephalopathy," "Selective cooling of the head," "Total body cooling," and their respective variations. Results derived from a thorough reading led to the selection of eleven articles for the review. The consensus

in these studies indicates that the reduction in the risk of death or disability within 18 months of life in neonates experiencing moderate to severe HIE is attributed to TH via either WBC or SHC techniques.

Systematic Review and Meta-Analysis conducted by Abate et al (2021), this comprehensive review and meta-analysis aimed to determine the combined relative risk of mortality among neonates affected by hypoxic-ischemic encephalopathy globally. The researcher followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, searching randomized control trials across various electronic databases. These databases included PubMed, Cochrane Library, Google Scholar, MEDLINE, Embase, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Meta Register of Current Controlled Trials (mCRT). The researcher examined 28 randomized control trials involving a total sample of 35, 92 patients (1832 treated with hypothermia and 1760 without). The pooled relative risk of mortality following therapeutic hypothermia was determined as 0.74 (95% CI; 0.67, 0.80; I2 = 0.0%; p<0.996). Cooling devices such as cooling caps and blankets demonstrated comparable mortality risk (0.74), with a slightly lower risk observed with cold gel packs (0.73). Therapeutic hypothermia showcases a reduction in mortality risk for neonates affected by moderate to severe hypoxic-ischemic encephalopathy. Both selective head cooling and whole-body cooling methods prove effective in reducing mortality rates among infants with this condition.

A study conducted by Sabir et al (2021), to examine the available evidence to determine the optimal candidates, timing, and methodology for delivering TH. Despite the successful

application of TH in treating neonates with NE, its routine clinical use in the past decade has brought forth numerous new inquiries. Overall, the assessment suggests a high likelihood that cooling could be beneficial for late preterm infants with NE and for term or near-term infants presenting mild NE. There is insufficient evidence supporting the effectiveness of delayed cooling initiated more than 6–24 hours after birth. The effectiveness of cooling in NE cases sensitized by inflammation remains uncertain and could potentially be dependent on the specific pathogen involved. As numerous researchers worldwide are concluding clinical studies, the researcher anticipates gaining further insights in the forthcoming years. These insights hold promise for improving both survival rates and clinical outcomes among infants affected by NE.

A study conducted by n Wincoop et al (2021), this study aims to delineate the immediate and enduring consequences of TH on renal and myocardial functions in (near) term asphyxiated newborns. Using MeSH terms and specific keywords, an electronic search was conducted in October 2019 and updated in June 2020 through PubMed and Cochrane databases. The inclusion criteria encompassed randomized controlled trials (RCT) or observational cohort studies involving TH intervention following perinatal asphyxia, with available long-term data on renal and myocardial functions. A meta-analysis, heterogeneity assessment, and sensitivity analyses were conducted employing a random effects model. Subgroup analysis was performed based on the cooling method used. Out of 107 studies focused on renal function, 9 met the criteria for inclusion. None of these studies investigated the prolonged impact of TH on renal function post-perinatal asphyxia. Instead, these nine studies primarily examined the influence of TH on the occurrence of acute kidney injury

(AKI) following perinatal asphyxia. The meta-analysis revealed a notable contrast in AKI incidence between neonates treated with TH and the control group (RR = 0.81; 95% CI 0.67–0.98; p = 0.03). No studies were found exploring the enduring effects of TH on myocardial function after neonatal asphyxia. However, short-term beneficial effects were observed in 4 out of 5 identified studies, showcasing significant reductions in cardiac biomarkers and fewer instances of myocardial dysfunction observed through ECG and cardiac ultrasound.

A study conducted by Rosario et al (2020) Developmental delay affects approximately 15% of children worldwide. This is particularly common in clinical populations, including children with issues during prenatal, neonatal, or early infancy. Identifying developmental delays early is crucial for effective intervention and reducing impairment. Assessing a child's development strengths and shortcomings might help identify areas for support. The Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III) is a commonly used standard tool for assessing neurodevelopment in early childhood. The Bayley-III assessment for children aged 1 month to 42 months involves play tasks and parent questionnaires to evaluate cognitive, language, motor, social-emotional, and adaptive behavior. The language and motor scales are separated into subscales. The language scale analyzes receptive and expressive language ability, while the motor scale evaluates fine and gross motor capabilities. The Bayley-III ability test assesses global development. Cognitive, language, and motor domains are tested by behavioral assessments, whereas social, emotional, and adaptive behaviors are evaluated through parent reports. Play tasks for infants typically take 1 hour, while toddlers and preschoolers may require up to 1.5 hours. Each behavioral area can take up to 30 minutes to complete, starting with easier tasks and progressing to more challenging

ones that exceed the child's expected ability. To administer the Bayley Scale, individuals must be trained and experienced in developmental evaluation and interpretation. Individuals familiar with the assessment can demonstrate training administered through the guidebook. Healthcare personnel trained to conduct assessments include clinical psychologists, occupational therapists, and researchers. Domain-specific professionals include physiotherapists and speech/language therapists.

A study conducted by Bel & Groenendaal (2020), although moderate hypothermia (HT) is the only proven treatment for reducing birth asphyxia-induced brain injury in near-term neonates, pharmaceutical interventions during or after HT may further minimize brain damage. This report reviews pharmacological interventions with putative neuroprotective effects. Finally, we discuss the possible use of autologous and allogenic mesenchymal stem cell treatment to repair birth asphyxia-related brain injuries.

A retrospective cohort study conducted by Szakmar et al (2019), examined the correlation between active hypothermia and hypocapnia in neonates diagnosed with moderate to severe hypoxic-ischaemic encephalopathy (HIE) who were transported after birth. This retrospective cohort study focused on neonates born between 2007-2011 and transferred to Semmelweis University, Hungary, for hypothermia treatment, both before and after the implementation of active cooling during transport in 2009. Out of these, 71 neonates underwent intensive care with controlled active hypothermia during transport, while 46 controls received standard intensive care. The results indicated a higher occurrence of incident hypocapnia in the group undergoing actively cooled transport (36.6%) compared to the control group (17.4%; $p=0.025$). In the intervention group, pCO_2 decreased significantly

from a median of 45 to 35 mmHg ($p<0.0001$), whereas it remained unchanged in the control group. Following adjustment for potential confounders, hypothermia emerged as an independent risk factor for hypocapnia, displaying an odds ratio (OR) of 4.23 and a 95% confidence interval (95% CI) of 1.30-13.79. Notably, the administration of sedation was associated with a decrease in the odds ratio for hypocapnia, registering at 0.35 (95% CI 0.12-0.98).

A study conducted by Wassink et al (2019), Reviewed therapeutic hypothermia has proven effective in reducing death or disability among term and near-term infants with moderate to severe hypoxic-ischemic encephalopathy. Recent clinical trials and experimental studies have provided more refined insights into critical parameters for achieving neuroprotection through hypothermia. These parameters include the timing of initiation, depth, and duration of hypothermia, as well as the subsequent rate of rewarming. However, significant knowledge gaps persist. Promising but preliminary clinical evidence from a limited phase II trial suggests that combining hypothermia with recombinant erythropoietin may further decrease the risk of disability. Nevertheless, definitive studies are required to confirm these findings. Current evidence from recent studies indicates that existing protocols for therapeutic hypothermia are approaching optimality, highlighting the crucial aspect of early diagnosis and initiation of hypothermia post-birth for improved neurodevelopmental outcomes. Further research is imperative to identify and evaluate strategies aimed at advancing outcomes following hypoxic-ischemic encephalopathy. This includes exploring supplementary therapies in conjunction with therapeutic hypothermia and methods to prevent elevated body temperature during labor and delivery. Therapeutic hypothermia has

established itself as the standard care for enhancing neurological recovery in infants with moderate to severe hypoxic-ischemic encephalopathy.

In a study conducted by Igboanugo, Chen, and Mielke (2019), Birth asphyxia (BA) affects millions of babies each year, particularly in low-income countries. The researcher identified maternal risk variables to inform primary prevention efforts for BA in resource-limited settings, as previous research has focused on secondary prevention. A comprehensive review of MEDLINE, PsychInfo, and EMBASE databases, identifying 38 relevant studies. The researcher identified 12 maternal variables linked to BA and classified them into three categories: sociodemographic factors (age, literacy, gravidity, parity), health care factors (antenatal care, delivery location), and health status (hypertension, pre-eclampsia, eclampsia, anemia, antepartum hemorrhage, pyrexia). Young maternal age (<20 years), poor literacy, insufficient prenatal care, non-hospital delivery, maternal hypertension, and anemia were the most consistent predictors of BA.

A study was conducted by Wood et al (2019), to examine this across all hospitals in Alberta, a Canadian province. A retrospective cohort research was conducted in Alberta from 2002 to 2016 on all singleton births at 35 weeks gestation documented in a perinatal database. Asphyxia was defined as intrapartum stillbirth, newborn death due to asphyxia, or admission to the newborn Intensive Care Unit with at least two of the following: a. An Apgar score of 5 within 10 minutes; b. Mechanical respiration or chest compressions for resuscitation within 10 minutes; c. Cord pH < 7.00 (venous or arterial), or arterial base excess ~ 12 at birth. Urban hospitals serve populations of around 50,000. During the research period, the overall rate of newborn asphyxia was 2.28 per 1000 births, with rates of 2.5/1000 in urban hospitals and

1.35/1000 in rural hospitals (OR: 1.86, 95% CI (1.58, 2.19). The risk of moderate or severe neonatal hypoxic-ischemic encephalopathy was 0.9/1000, with no association with urban hospital birth (OR: 1.12, 95% CI (0.82, 1.53)). Hospital volume did not correlate with asphyxia or mild or severe infant hypoxic-ischemic encephalopathy.

A randomized clinical trial conducted by Laptook et al (2017), to determine the likelihood that hypothermia initiated between 6 to 24 hours after birth reduces the risk of death or disability at 18 months among infants with hypoxic-ischemic encephalopathy. A randomized clinical trial was conducted from April 2008 to June 2016 involving infants at 36 weeks gestation or later with moderate or severe hypoxic-ischemic encephalopathy enrolled between 6 to 24 hours post-birth. Among the 168 infants, targeted esophageal temperature was maintained. Eighty-three received hypothermia at 33.5°C for 96 hours followed by rewarming, while 85 infants were not cooled and maintained at 37.0°C. The primary outcome was a composite of death or disability (moderate or severe) at 18 to 22 months, adjusted for the level of encephalopathy and age at randomization. The hypothermic and noncooled infants were term and predominantly presented with moderate encephalopathy, with similar characteristics between the groups. The primary outcome occurred in 19 of 78 hypothermic infants (24.4%) and 22 of 79 noncooled infants (27.9%). Bayesian analysis using a neutral prior suggested a 76% posterior probability of reduced death or disability with hypothermia compared to none cooling (adjusted posterior risk ratio, 0.86; 95% credible interval, 0.58-1.29). The probability that cooled infants experienced at least 1%, 2%, or 3% less death or disability than noncooled infants was estimated at 71%, 64%, and 56%, respectively. In term infants with hypoxic-ischemic encephalopathy, initiating hypothermia between 6 to 24 hours

after birth demonstrated a 76% likelihood of any reduction in death or disability, with a 64% chance of at least 2% less death or disability at 18 to 22 months. While there might be a potential benefit, the effectiveness of hypothermia initiated within 6 to 24 hours after birth remains uncertain."

A randomized controlled trial conducted by Tanigasalam et al (2015), this study aimed to assess whether therapeutic hypothermia reduces the occurrence of acute kidney injury (AKI) among full-term neonates experiencing perinatal asphyxia. Conducted at a tertiary care teaching hospital in South India, this randomized controlled trial involved 120 full-term neonates with perinatal asphyxia. They were randomly assigned to receive either therapeutic hypothermia or standard supportive care. Renal parameters of neonates in both groups were monitored, and AKI was determined based on the criteria set by the Acute Kidney Injury Network. The occurrence of AKI was lower in the therapeutic hypothermia group compared to the standard treatment group (32% versus 60%, $p<0.05$). Specifically, the incidence of Stages 1, 2, and 3 AKI was 22%, 5%, and 5% in the therapeutic hypothermia group, while it was 52%, 5%, and 3%, respectively, in the standard treatment group. Mortality was also lower in the therapeutic hypothermia group than in the standard treatment group (26% versus 50%, $p<0.05$). Therapeutic hypothermia demonstrates a reduction in both the frequency and severity of AKI among full-term neonates with perinatal asphyxia.

In a study conducted by Davidson et al (2015), while therapeutic hypothermia is now a widely accepted standard treatment for infants with moderate to severe hypoxic-ischemic encephalopathy (HIE), its effectiveness is only partial. Compelling evidence from both preclinical and clinical studies indicates that hypothermia provides the most protection when

initiated promptly after the occurrence of hypoxic-ischemic events. Enhancements in the outcomes of therapeutic hypothermia are highly likely to emerge from strategies aimed at reducing the delay in commencing treatment for affected infants. This review delves into evidence suggesting that existing protocols closely approximate the optimal depth and duration of cooling but remain uncertain regarding the ideal rate of rewarming post-hypothermia. Combining treatments to amplify hypothermic neuroprotection holds promise, particularly when targeting endogenous elements such as melatonin and erythropoietin, as well as inert gases like xenon. It underscores the crucial role of preclinical studies incorporating realistic treatment delays and clinically relevant cooling protocols when evaluating combined therapies.

In a study conducted by Thoresen (2015), this review examines the criteria for initiating TH, addressing concerns related to patient selection and TH management. This encompasses cooling strategies for cases ranging from mild to very severe perinatal asphyxia, exploring options such as extended or deeper cooling and delayed initiation. This involves contemplating TH for patients not meeting standard trial entry criteria, such as those experiencing postnatal collapse, premature infants, infections, and infants with metabolic, chromosomal, or surgical conditions alongside perinatal asphyxia. The initial TH protocol for term infants with perinatal asphyxia was established based on robust preclinical studies across various species. Remarkably, after 17 years, this protocol remains largely unchanged: commencing TH within 6 hours of birth, cooling to 33.5°C for 72 hours, followed by a 4-hour rewarming period. Assessing encephalopathy without utilizing aEEG/EEG or the strict neurological criteria developed by Shankaran is challenging. There is uncertainty regarding

the potential harm caused by cooling infants without encephalopathy. Recent trials investigating deeper (to 32.0°C) and/or longer (5 days) cooling were halted prematurely due to a lack of demonstrated efficacy. Moreover, experimental evidence indicating TH protection against extremely severe insults is scarce.

In a prospective cohort conducted by Chalak et al (2014), the aim was to assess if certain biomarkers found in the umbilical cords of newborns could help categorize the severity of hypoxic-ischemic encephalopathy (HIE), specifically evaluating neuronal and inflammatory markers. This study also examined whether these measurements changed during hypothermia-rewarming and if they were linked to neurological outcomes. The research design involved a prospective study of full-term newborns with varying degrees of HIE based on neurological evaluations. Serum levels of neuronal-glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase L1, and inflammatory cytokines were measured at different time points—6-24, 48, 72, and 78 hours after birth—from umbilical artery samples. Neurodevelopmental assessments using the Bayley Scales of Infant and Toddler Development-III were conducted at 15-18 months. Key findings revealed that 20 neonates had moderate (n = 17) or severe (n = 3) HIE and underwent hypothermia treatment, while 7 had mild HIE and were not treated with cooling. The levels of serum GFAP and ubiquitin carboxyl-terminal hydrolase L1 were higher with increased severity of HIE at birth ($P < .001$), and GFAP levels remained elevated in those with moderate to severe HIE over time. Additionally, certain inflammatory markers—Interleukin (IL)-6, IL-8, and vascular endothelial growth factor—were notably higher at 6-24 hours in moderate to severe cases compared to mild HIE ($P < .05$). These markers were not significantly affected by

hypothermia-rewarming. Elevated levels of GFAP, IL-1, IL-6, IL-8, tumor necrosis factor, interferon, and vascular endothelial growth factor at 6-24 hours were associated with abnormal neurological outcomes.

A study conducted by Selewsk et al (2013), Aimed to investigate whether acute kidney injury (AKI) was independently linked to increased illness severity and mortality. A retrospective review was conducted on 96 consecutively treated infants. The study employed Modified Acute Kidney Injury Network criteria to categorize AKI based on the absolute rise in serum creatinine (SCr) levels from a previous low point (stage I: SCr rise of 0.3 mg/dL or SCr 150-<200%; stage II: SCr rise of 200-<300%; stage III: SCr rise of ≥300%, SCr 2.5 mg/dL, or need for dialysis). The study assessed outcomes including mortality, duration of stay in the neonatal intensive care unit (NICU), and length of mechanical ventilation. AKI was identified in 36 out of 96 infants (38%). Although overall mortality was 7%, it was notably higher among those with AKI, approaching statistical significance (14% compared to 3% in those without AKI; P = .099). Infants with AKI had extended NICU stays (mean of 15.4 ± 9.3 days compared to 11 ± 5.9 days for those without AKI; P = .014) and required longer durations of mechanical ventilation (mean of 9.7 ± 5.9 days compared to 4.8 ± 3.7 days for those without AKI; P < .001).

In a study conducted by Cornette (2012), Hypoxic ischemic encephalopathy (HIE) is a severe condition affecting newborns, potentially leading to death or disability. Current robust clinical evidence supports the use of moderate total body cooling or hypothermia in full-term neonates following asphyxiation, providing long-term protection for the brain. This innovative therapy is now considered the standard of care. It's crucial to initiate treatment

within 6 hours after the injury, demanding efficient coordination among local hospitals, transport teams, and the nearest neonatal intensive care unit. The procedure is safe only when implemented according to established clinical trial protocols and in a neonatal intensive care unit setting. With hypothermia established as standard therapy for moderate-to-severe HIE in full-term infants, there's newfound optimism for brain protection. As the therapeutic window for hypothermia is brief (6 hours), its success relies on the early identification of high-risk term infants and prompt referral to a specialized cooling center.

A Randomized Controlled Trial was conducted by Jacobs et al (2011), to assess the efficacy and safety of moderate whole-body hypothermia in newborns diagnosed with hypoxic-ischemic encephalopathy (HIE). Conducted a multicenter, international, randomized controlled trial involving neonatal intensive care units across Australia, New Zealand, Canada, and the United States (N=28) from February 2001 to July 2007. Newborns born at 35 weeks gestation or later, displaying signs of peripartum hypoxia-ischemia and moderate to severe clinical encephalopathy, were randomly divided into hypothermia (n=110) or standard care (n=111) groups. Administered whole-body hypothermia maintaining the body temperature at 33.5°C for 72 hours or provided standard care at 37°C. The hypothermia-treated infants were cooled at room temperature by deactivating the radiant warmer and using refrigerated gel packs to sustain rectal temperature at 33°C to 34°C. Main Outcome Measures to Evaluate Death or significant sensorineural disability at the age of 2 years. Therapeutic hypothermia decreased the risk of death or major sensorineural disability at 2 years of age: 55 out of 107 infants (51.4%) in the hypothermia group and 67 out of 101 infants (66.3%) in the control group experienced death or a significant sensorineural

disability at 2 years (risk ratio, 0.77 [95% confidence interval, 0.62-0.98]; P=.03). The mortality rate declined, and survival without sensorineural disability increased. Minimal adverse effects were observed with hypothermia treatment. Whole-body hypothermia initiated within 6 hours of birth in term and near-term newborns diagnosed with hypoxic-ischemic encephalopathy has shown to be effective and safe.

In a study conducted by Wintermark et al (2011), this study aimed to evaluate brain perfusion during the initial week of life in these neonates. This prospective cohort study utilized MR imaging and ASL-PI to assess brain perfusion in the affected neonates. The study enrolled 18 asphyxiated and 4 control-term neonates, with 11 of the asphyxiated neonates receiving hypothermia treatment. Among those who developed brain injury despite hypothermia treatment, there was often a pattern of reduced perfusion on Day of Life (DOL) 1 followed by increased perfusion on DOL 2–3 in brain areas that later displayed injury. Asphyxiated neonates not receiving hypothermia but who developed brain injury also exhibited increased perfusion on DOL 1–6 in areas that later showed injury. The findings suggest that ASL-PI could be valuable in identifying at-risk asphyxiated neonates prone to developing brain injury, regardless of whether hypothermia treatment is administered. Since standard hypothermia for 72 hours might not prevent brain injury when increased perfusion is detected early in neonatal hypoxic-ischemic encephalopathy, such neonates may benefit from adjustments in their hypothermia therapy or additional neuroprotective interventions.

In a study conducted by Rutherford et al (2010), to better understand the impact of therapeutic hypothermia on neonatal brain injury, the researcher examined MRI scans of infants involved in the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial.

A total of 325 infants participated in the TOBY trial between 2002 and 2006. Among them, 131 infants had available images for analysis. Therapeutic hypothermia demonstrated an association with reduced lesions in the basal ganglia or thalamus, white matter, and abnormal posterior limb of the internal capsule. Cooled infants, in comparison to non-cooled infants, showed a lower likelihood of scans predictive of later neuromotor abnormalities and a higher probability of having normal scans. The predictive accuracy of MRI for death or disability up to 18 months of age was 0.84 (0.74–0.94) in the cooled group and 0.81 (0.71–0.91) in the non-cooled group.

A study was conducted by Zhou et al (2010), to examine the effectiveness and safety of selective head cooling in conjunction with mild systemic hypothermia in treating hypoxic-ischemic encephalopathy (HIE) among newborn infants. Newborns diagnosed with HIE were randomly divided into either the selective head cooling group or the control group. Selective head cooling was initiated within 6 hours after birth, aiming to reach a nasopharyngeal temperature of 34 ± 0.2°C and a rectal temperature between 34.5 to 35.0°C for 72 hours. Meanwhile, the control group maintained rectal temperatures between 36.0 to 37.5°C. Neurodevelopmental assessments were conducted at 18 months of age. The primary endpoint encompassed a combination of death and severe disability. The analysis comprised 194 infants, with 100 in the selective head cooling group and 94 in the control group. In the selective head cooling group compared to the control group, the combined outcome of death and severe disability was 31% versus 49% (OR: 0.47; 95% CI: 0.26-0.84; P = .01), the mortality rate was 20% versus 29% (OR: 0.62; 95% CI: 0.32-1.20; P = .16), and the incidence of severe disability was 14% (11/80) versus 28% (19/67) (OR: 0.40; 95% CI: 0.17-0.92; P =

.01). The application of selective head cooling combined with mild systemic hypothermia over 72 hours appears to notably reduce the combined outcome of severe disability and death, as well as the occurrence of severe disability in infants diagnosed with hypoxic-ischemic encephalopathy.

A retrospective review conducted by Fairchild et al (2010), aimed to assess how our center's experience with therapeutic hypothermia influenced neonatal transport. A retrospective review encompassing all instances of therapeutic hypothermia administered at a single neonatal intensive care unit from 2005 to 2009. Out of 50 infants treated with hypothermia for HIE, 40 were born outside our center, and 35 underwent cooling during transport. Referring clinicians passively cooled most patients, with subsequent active cooling by our transport team. About 34% of patients experienced overcooling to <32.1°C, yet there were no significant differences in admission vital signs or laboratory values between overcooled and appropriately cooled infants. On average, passive cooling was initiated 1.4 hours after birth, and active cooling began after 2.7 hours, compared to admission to our unit occurring at 5.9 hours.

2.3 Summery

The research presented focuses on therapeutic hypothermia (TH) for infant hypoxic-ischemic encephalopathy (HIE). They investigate a variety of topics, including chilling duration and depth, comparing whole-body versus selective head cooling, and determining mortality risk. While some studies show benefits in terms of lowering death and disability, others raise concerns about therapy effectiveness and safety. Despite positive outcomes in lowering acute kidney injury (AKI) and mortality rates, questions remain about AKI's link to increased

severity and death. The efficacy of TH, particularly when began shortly after delivery, is accepted, but further study is needed to optimize protocols and outcomes for infants with HIE.

Chapter Three

Research Methodology

3.1 Introduction

This chapter aims to provide an overview of the research methods used in this thesis. It covers the following elements: research design, study sample, study environment, study duration, data source, inclusion and exclusion criteria, sample size, sample and sampling procedure, validity, instrument, ethical consideration, and analysis strategy.

The design allows the researcher to efficiently collect a large amount of data without the need for additional interventions or data collection process, so this design can facilitate the collection of samples with time-consuming.

3.2 Research Design

It is defined as a process plan to conduct the research. A retrospective, descriptive, quantitative study design was conducted to describe the impact of using cooling therapy (hypothermia therapy) post Asphyxia among Newborns in NICU in West Bank.

3.3 Research Setting

The research was conducted in the NICU Department at Privet Hospitals which contains a Neonate Intensive Care Unit. (Specialized Alesraa Hospital in Tulkarem which contains 14 incubators; Alrazi Hospital in Jenin which contains 10 incubators; Specialized Arab Hospital in Nablus which contains 25 incubators; Specialized Nablus Hospital in Nablus which contains 18 incubators; Women's Union Hospital in Nablus which contain 21 incubators;

Istishary Arab Hospital In Ramallah which contain 32 incubators; Alahli hospital in Hebron which contain 24 incubators)

3.4 Population

A research population is a collection of subjects or departments who have certain traits and meet the inclusion requirements, and from whom data can be collected. (Polit& Beck 2014).

In this study, the target population was Newborns with Asphyxia and using cooling therapy, who met the inclusion criteria.

The accessible populations are those neonates who were admitted to the NICU at this hospital From January/ 2023 until December/2023.

3.5 Sample and Sampling

Convenience sampling was used, which a type of non-probability is a sampling method that is also used in quantitative approaches.

This form of sampling was used for the study because it was convenient for respondents; however. The researcher uses this strategy to choose the appropriate sample while keeping in mind the need to include certain criteria and elements inside the study.

A convincing sample was composed of 45 patients.

3.6 Inclusion criteria

1. Newborns admitted to the NICU in West Bank
2. Newborns diagnosed with asphyxia

3. Age group within 0-28 days
4. Newborn who received cooling therapy as a post-asphyxia intervention
5. Evidence of intrapartum hypoxia

3.7 Exclusion criteria

1. Preterm newborns
2. Newborns with other co-morbidity
3. Newborn with insufficient medical records
4. Newborns that incomplete full course of cooling therapy.
5. Weight less than 2Kg

3.8 Sample size

Based on alpha 0.05, and power of 0.80, and medium effect size, and the estimated sample size using G power, the total sample size was 45 newborns.

3.9 Study Instrumentation

The data abstraction sheet constructed based on the literature review, contains three parts.

Part one contains a maternal and neonatal characteristic, where the maternal contains gestational age, maternal age, gravida number, parity number, and other complications and some special points related to maternal information, while the neonatal contains the birth weight, length, blood gas, and other characteristics related to neonatal.

Part Two contains Major adverse events and postnatal complications which mention all risk factors that affect the maternal and neonatal.

Part Three contains the primary outcome related to cooling therapy and its effect.

3.10 Validity

The data instrument was validated for included 3 pediatricians and 3 experts in Neonatal cases and management.

3.11 Ethical considering

Ethical approval was obtained from the Arab American University Ethical Committee Institutional Review Board (IRB) before data collection, and then permission for conducting the study in private hospitals was taken from their administrative department. Upon approval, all data will kept confidential and only for the use of research purposes, no names of any neonates will be mentioned or used, and no other information will be used in any context other than this research.

3.12 Analysis plan

The Statistical Package for the Social Sciences (SPSS) version 23 was used to analyze the acquired data in this study. SPSS is a software package used for statistical analysis, data manipulation, and the generation of tables and graphs utilizing descriptive and inferential statistics. Data is summarized using means and standard deviations, ANOV test, and Correlation.

As a result, the survey results were instantly loaded into the database, and data cleaning was performed. This allowed the existence of potentially statistically significant correlations between the relevant variables to be identified.

Chapter Four

Result

4.1 Introduction

A total of 45participants achieved the previously mentioned inclusion criteria in the chosen timeline, the data were tested for normality using the Kolmogorov normality test, the data were normally distributed, and parametric analysis will be used to answer our research questions.

4.2 Maternal and Neonatal Characteristics

Table 1 provides a comprehensive overview of maternal and neonatal characteristics, shedding light on various aspects of pregnancy and delivery. Noteworthy findings include a prevalence of chronic hypertension (42.2%) as a complication during pregnancy, with antepartum hemorrhage (13.3%), thyroid disease (8.9%), and diabetes (17.8%) also reported. Intrapartum complications highlight instances of fetus heart rate decelerations (35.6%) and cord prolapse (40.0%), while uterine rupture is fortunately absent. The mode of delivery indicates a majority of normal vaginal deliveries (60.0%), followed by emergency Cesarean sections (33.3%). Gender distribution shows a nearly equal split between male (51.1%) and female (48.9%) newborns. Apgar scores at 5 minutes reveal a predominance of scores in the 4–6 range (62.2%). Notably, intubation in the delivery room is required in 71.1% of cases. Other parameters such as continued resuscitation at 10 minutes, time to spontaneous respiration, the occurrence of seizures, and the need for inotropic support and anticonvulsants provide insights into neonatal outcomes. The table concludes with pre-randomization aEEG

categories, indicating the prevalence of normal/mildly abnormal (31.0%), moderately abnormal (27.6%), and seizures present (41.4%).

Table 1, Maternal and Neonatal Characteristics

		Count	Column N %
Complications of pregnancy	Chronic hypertension	19	42.2%
	Antepartum haemorrhage	6	13.3%
	Thyroid disease	4	8.9%
	Diabetes	8	17.8%
	None	8	17.8%
Intrapartum complications	Fetal heart rate decelerations	16	35.6%
	Cord prolapse	18	40.0%
	Uterine rupture	0	0.0%
	Maternal pyrexia	2	4.4%
	Shoulder dystocia	2	4.4%
	Maternal haemorrhage	2	4.4%
	None	5	11.1%
Mode of delivery	NVD	27	60.0%
	EMERGENCY CS	15	33.3%

	ELECTIVE CS	3	6.7%
Gender	Male	23	51.1%
	Female	22	48.9%
5 min Apgar score	0–3	13	28.9%
	4–6	28	62.2%
	7–10	4	8.9%
Intubation in the delivery room	No	13	28.9%
	Yes	32	71.1%
Continued resuscitation at 10 min	No	18	43.9%
	Yes	23	56.1%
Time to spontaneous respiration ≥10 min	No	20	44.4%
	Yes	25	55.6%
Seizures	No	18	40.0%
	Yes	27	60.0%
Moderate encephalopathy	No	27	60.0%
	Yes	18	40.0%
Severe encephalopathy	No	33	73.3%
	Yes	12	26.7%
Inotropic support	No	25	55.6%
	Yes	20	44.4%
Anticonvulsants	No	16	35.6%

	Yes	29	64.4%
Pre-randomization aEEG	Normal/mildly abnormal	9	31.0%
	moderately abnormal	8	27.6%
	Seizures present	12	41.4%

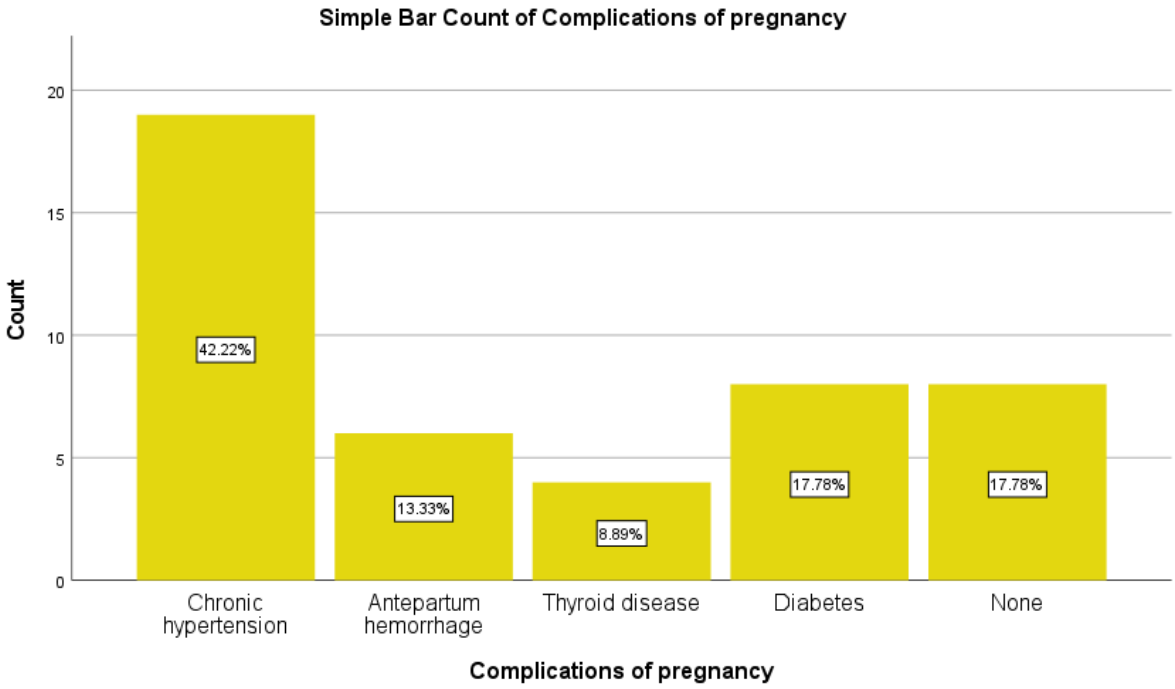

Figure 1, mothers with complications distributions.

4.3 Major adverse events and postnatal complications

Table 2 outlines major adverse events and postnatal complications, providing a comprehensive snapshot of the health outcomes following the intervention. Notably, no instances of minor cardiac arrhythmia or coagulopathy are reported. Hypotension is observed in 26.7% of cases, while abnormal renal function and hyponatremia are noted in 4.4% each. Metabolic acidosis affects 22.2% of cases, and respiratory distress is observed in 17.8%. Hypoglycemia, difficulties in temperature control, and clinically diagnosed seizures are reported in 8.9% each. During the 72-hour intervention period, persistent acidosis is prevalent in 46.3% of cases, while skin changes are noted in 29.3%. Major adverse events include bleeding (4.9%), severe hypotension despite full support (14.6%), and, notably, no major cardiac arrhythmias or venous thrombosis. Throughout the hospital course, hypotension treated with vasopressors (18.6%), bloodstream infections (20.9%), and hypoglycemia (18.6%) emerged as significant concerns. The table concludes with instances of death, occurring in 4.9% during the 72-hour intervention and 4.7% during the hospital course, underlining the gravity of certain adverse outcomes.

Table 2, Major adverse events and postnatal complications

		Count	Column N %
Postnatal complications	Minor cardiac arrhythmia	0	0.0%
	Hypotension	12	26.7%
	Coagulopathy	0	0.0%

	Prolonged coagulation times	0	0.0%
	Abnormal renal function	2	4.4%
	Hyponatremia	2	4.4%
	Hypokalemia	0	0.0%
	Platelet count 100 000 per L	1	2.2%
	Raised liver enzymes concentrations	0	0.0%
	Metabolic acidosis	10	22.2%
	Respiratory distress	8	17.8%
	Systemic infection	0	0.0%
	Haemoconcentration	0	0.0%
	Hypoglycemia	4	8.9%
	Hypocalcaemia	0	0.0%
	Difficulties in temperature control	2	4.4%
	Clinically diagnosed seizures	4	8.9%

Adverse events during 72hr intervention	Major cardiac arrhythmia	0	0.0%
	Major venous thrombosis	0	0.0%
	Persistent acidosis	19	46.3%
	Bleeding	2	4.9%
	Severe hypotension despite full support	6	14.6%
	Unanticipated serious adverse event	0	0.0%
	skin changes	12	29.3%
	Death	2	4.9%
Adverse events during hospital course	Hypotension treated with vasopressors	8	18.6%
	Cardiac arrhythmia	2	4.7%
	Oliguria	6	14.0%
	Anuria	0	0.0%
	Persistent pulmonary hypertension	6	14.0%
	Hepatic dysfunction	0	0.0%
	Bloodstream infection	9	20.9%

	Disseminated intravascular coagulopathy	0	0.0%
	Hypoglycemia	8	18.6%
	Hypocalcemia	2	4.7%
	Death	2	4.7%

4.4 Primary Outcome

Table 3 presents the primary outcomes, providing insights into the occurrence of moderate disability, severe disability, and death. A majority of cases exhibit no moderate disability (71.1%), no severe disability (82.2%), and no death (91.1%). However, in instances where severe disability is present, it accounts for 28.9%, and in cases of death, it comprises 8.9% of the total. The table further delves into the major causes of death, with persistent pulmonary hypertension (44.4%), proven sepsis (33.3%), and intractable hypotension (22.2%) identified as significant contributors.

Table 3, Primary Outcome

		Count	Column N %
Moderate Disability	No	32	71.1%
	Yes	13	28.9%
Severe Disability	No	37	82.2%
	Yes	8	17.8%
Death?	No	41	91.1%
	Yes	4	8.9%
If Yes, major causes of death	Persistent pulmonary hypertension	4	44.4%
	Sepsis (proven)	3	33.3%
	Intractable hypotension	2	22.2%

Table 4 provides a detailed set of numerical data, capturing various aspects related to gestation, maternal characteristics, labor, and neonatal outcomes. The mean gestational age is 37 weeks, with a narrow standard deviation of 1 week, indicating a relatively homogeneous group in terms of fetal development? Maternal age, with a mean of 30 years and a standard deviation of 6 years, reflects a moderate spread in maternal age within the study cohort. Gravida number (mean: 2, standard deviation: 2) and parity number (mean: 2, standard deviation: 1) suggest a diverse range in the number of pregnancies and childbirths. Labor duration, with a mean of 6 hours and a higher standard deviation of 7 hours, highlights

significant variability in the duration of labor. Neonatal characteristics include mean birth weight (3210g, standard deviation: 615g), length (52cm, standard deviation: 3cm), and head circumference (33.7cm, standard deviation: 1.5cm), indicating variability in newborn size. Blood gas parameters within 60 minutes of birth, including pH (7.05, standard deviation: 0.25), CO2 levels (27.90, standard deviation: 6.38), HCO3 levels (17.08, standard deviation: 2.48), and base deficit (-12.3, standard deviation: 3.6), provide insights into neonatal acid-base balance, The mean age at randomization is 4 hours, with a standard deviation of 4 hours, suggesting a relatively early involvement in the study for participants, while the variability in this timeframe indicates differing onset times. Days receiving oxygen exhibit a mean of 6 days, accompanied by a standard deviation of 4 days, highlighting the duration of oxygen support required and the notable variability among individuals. The length of stay, with a mean of 12 days and a standard deviation of 8 days, underscores the diversity in the duration of hospitalization. The cooling start age, averaging at 4 hours with a standard deviation of 4 hours, provides information on the initiation time for cooling interventions, indicating a consistent practice within the study group.

Table 4, numerical data

	Mean	Standard Deviation
Gestational age/ week	37	1
Maternal age/ Years	30	6
Gravida no.	2	2
Parity no.	2	1
Labor/hr	6	7
Rupture of membranes/hr	9	10
Birth weight (g)	3210	615
Length/cm	52	3
Head circumference (cm)	33.7	1.5
Blood gas within 60 min of birth (PH)	7.05	.25
CO2 within 60 min of birth	27.90	6.38
HCO3 within 60 min of birth	17.08	2.48
Base Deficit within 60 min of birth	-12.3	3.6
Age at randomization/hr	4	4
Days receiving oxygen/ day	6	4
Length of stay/ Day	12	8
Colling start ate age (H)	4	4

Correlations

Table 5 below shows the correlations of cooling with maternal and fetus variables, the age at randomization shows a negative correlation with adverse events during the 72-hour intervention, suggesting that those randomized earlier may experience fewer complications during this period. Days receiving oxygen demonstrates a negative correlation with the age at randomization, indicating that participants involved earlier may require less oxygen support. The length of stay exhibits a positive correlation with the age at randomization, suggesting that earlier engagement in the study might be associated with a longer hospital stay.

Cooling start age shows interesting correlations with other variables. It correlates positively with birth weight, length, head circumference, and gestational age, implying that a later start of cooling interventions is associated with favorable neonatal characteristics. Moderate disability is positively correlated with gestational age, suggesting a potential connection between a longer gestation period and the occurrence of moderate disability. Severe disability shows positive correlations with gestational age, maternal age, and complications of pregnancy, indicating that these factors may contribute to more severe disabilities. Death is negatively correlated with gestational age, suggesting a potential protective effect of a longer gestation period. However, death is positively correlated with the rupture of membranes per hour, indicating a potential association between a higher frequency of membrane rupture and an increased risk of mortality.

Table 5, Correlations of outcomes after cooling with other variables

Correlations

		Postnatal complications	Adverse events during 72hr intervention	Adverse events during hospital course	Days receiving oxygen/ day	Length of stay/ Day	Colling start age (H)	Moderate Disability	Severe Disability	Death?
Gestational age/ week	Pearson	-.232	-.112	.208	-.070	-.048	-.004	.100	.238	-.415
	sig	.125	.486	.182	.650	.754	.982	.512	.116	.005
	N	45	41	43	45	45	41	45	45	45
Maternal age/ Years	Pearson	-.251	-.146	.053	-.466	-.423	.334	-.299	.285	-.062
	sig	.096	.363	.735	.001	.004	.033	.046	.058	.686
Gravida no.	Pearson	-.010	.216	-.055	-.375	-.347	.258	-.508	.053	.131
	sig	.947	.176	.727	.011	.020	.104	.000	.727	.391
Parity no.	Pearson	.082	.407	-.017	-.272	-.244	.326	-.380	.043	-.079
	sig	.591	.008	.912	.071	.106	.038	.010	.781	.607

Complications of pregnancy	Pearson	.159	-.349	-.245	.009	.178	.575	-.131	.130	-.208
	sig	.297	.025	.113	.951	.243	.000	.393	.393	.170
Intrapartum complications	Pearson	.143	-.070	-.134	-.227	-.120	.338	.078	-.254	-.093
	sig	.348	.663	.390	.134	.432	.030	.611	.093	.544
Mode of delivery	Pearson	.174	-.404	-.171	-.003	-.096	-.084	.471	-.351	.017
	sig	.254	.009	.273	.986	.530	.599	.001	.018	.913
Labor/hr	Pearson	-.284	.142	.142	.117	.114	.087	-.417	.076	-.078
	sig	.058	.377	.362	.444	.456	.586	.004	.620	.612
Rupture of membranes/hr	Pearson	.079	.495	.493	-.595	-.564	-.182	-.252	-.318	.741
	sig	.677	.010	.008	.001	.001	.372	.180	.087	.000
Birth weight (g)	Pearson	-.277	.312	-.032	.214	.287	.347	-.156	.212	-.190
	sig	.065	.047	.839	.158	.056	.026	.305	.162	.211
Length/cm	Pearson	.247	.185	.162	-.206	-.097	.101	-.095	.023	-.193
	sig	.102	.246	.300	.175	.526	.528	.535	.883	.204

Head circumference (cm)	Pearson	-.028	-.058	-.122	.305	.263	.054	-.172	.390	-.301
	sig	.853	.720	.436	.042	.081	.736	.257	.008	.044
Gender	Pearson	.048	-.122	.069	-.366	-.290	-.221	-.329	.010	.319
	sig	.754	.447	.662	.014	.053	.166	.027	.946	.032
5 min Apgar score	Pearson	.317	.226	-.017	-.059	.071	.278	.051	-.240	-.430
	sig	.034	.156	.914	.703	.642	.078	.741	.112	.003
Blood gas within 60 min of birth (PH)	Pearson	-.005	-.002	.249	-.011	-.052	-.373	.059	-.129	-.368
	sig	.974	.991	.107	.945	.736	.016	.701	.399	.013
CO2 within 60 min of birth	Pearson	-.094	-.370	-.171	.196	.108	.002	.150	.061	-.292
	sig	.539	.017	.272	.197	.482	.989	.325	.691	.052
HCO3 within 60 min of birth	Pearson	.149	-.137	.014	.088	.032	-.148	.161	-.174	-.360
	sig	.329	.392	.930	.564	.835	.355	.291	.253	.015
Base Deficit within 60 min of birth	Pearson	.449	.272	.233	.084	.062	-.309	.074	-.271	-.153
	sig	.002	.086	.132	.581	.686	.049	.628	.071	.314

Intubation in the delivery room	Pearson	-.069	-.316	-.305	-.165	-.254	.073	.190	.296	.199
	sig	.654	.044	.047	.279	.093	.648	.211	.048	.190
resuscitation at 10 min	Pearson	-.399	.006	-.347	.136	-.058	-.016	.274	.436	.291
	sig	.010	.970	.030	.396	.718	.925	.084	.004	.065
spontaneous respiration ≥10 min	Pearson	-.259	-.213	-.217	.152	.049	-.296	.274	.182	-.035
	sig	.085	.182	.163	.319	.750	.060	.068	.232	.820
Seizures	Pearson	-.061	-.482	-.626	.531	.329	.034	.520	.142	-.064
	sig	.688	.001	.000	.000	.027	.831	.000	.351	.677
Moderate encephalopathy	Pearson	-.137	-.148	-.194	.536	.460	.048	.580	-.142	-.255
	sig	.368	.355	.213	.000	.001	.764	.000	.351	.091
Severe encephalopathy	Pearson	-.182	-.089	-.196	-.163	-.345	.142	.059	.508	.518
	sig	.233	.581	.208	.285	.020	.375	.700	.000	.000
Inotropic support	Pearson	-.240	-.082	-.467	-.030	-.094	.359	.022	.286	.035
	sig	.113	.610	.002	.846	.539	.021	.886	.057	.820

Anticonvulsants	Pearson	-.042	-.604	-.785	.497	.378	.192	.473	.103	-.094
	sig	.787	.000	.000	.001	.011	.230	.001	.503	.538
Pre-randomization aEEG	Pearson	.334	.009	-.362	-.125	-.321	.103	-.038	.189	.310
	sig	.077	.963	.053	.517	.090	.594	.846	.326	.102
Age at randomization/hr	Pearson	-.142	-.489	-.378	-.111	-.028	.493	-.109	.307	-.218
	sig	.353	.001	.012	.469	.854	.001	.475	.040	.150

Table 6 below shows ANOVA by death, Gestational age exhibits a significant F-value of 8.962 with a corresponding significance level of .005, suggesting that differences in gestational age are associated with variations in the occurrence of death. Maternal age, gravida number, parity number, labor duration, birth weight, length, and base deficit within 60 minutes of birth do not show significant differences with death. However, rupture of membranes per hour, head circumference, and blood gas parameters within 60 minutes of birth (PH, CO2, HCO3) reveal significant F-values of 34.028, 4.291, 6.725, 4.006, and 6.413, respectively, with associated significance levels of .000, .044, .013, .052, and .015, suggesting that these factors may play a role in the occurrence of death. Age at randomization, days receiving oxygen, length of stay, and cooling start age do not exhibit significant differences concerning the death variable

ANOVA

Table 6, ANOVA testing by Death variable.

	F	Sig.
Gestational age/ week	8.962	.005
Maternal age/ Years	.166	.686
Gravida no.	.749	.391
Parity no.	.268	.607
Labor/hr	.261	.612
Rupture of membranes/hr	34.028	.000
Birth weight (g)	1.609	.211
Length/cm	1.661	.204
Head circumference (cm)	4.291	.044
Blood gas within 60 min of birth (PH)	6.725	.013
CO2 within 60 min of birth	4.006	.052
HCO3 within 60 min of birth	6.413	.015
Base Deficit within 60 min of birth	1.036	.314
Age at randomization/hr	2.153	.150
Days receiving oxygen/ day	5.122	.029
Length of stay/ Day	7.048	.011
Colling start ate age (H)	1.717	.198

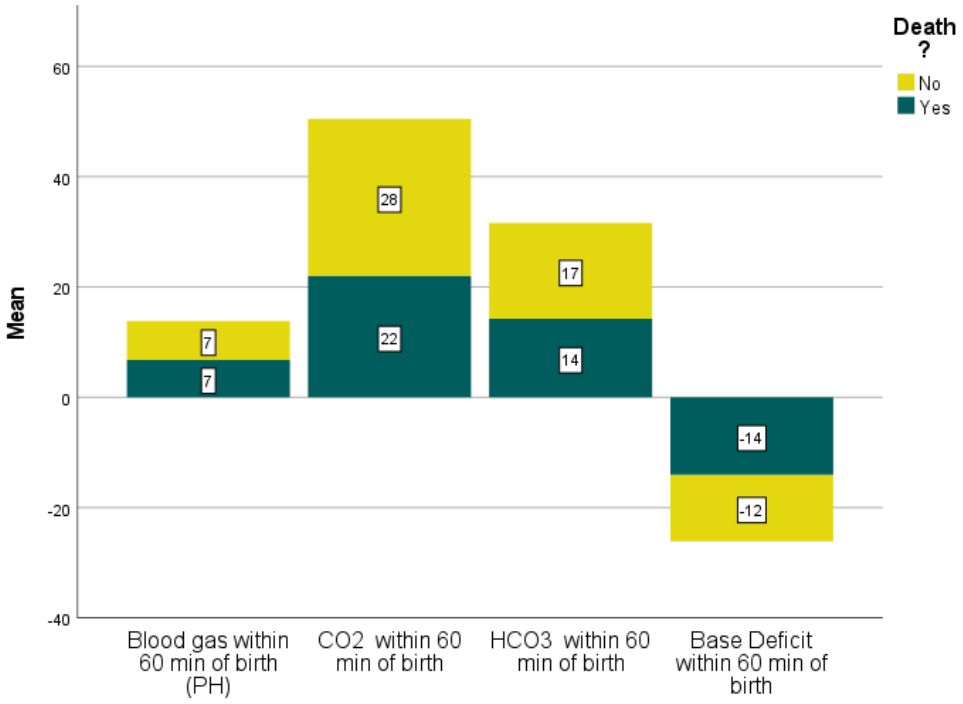

Figure 2, Blood gases reading mean by Death.

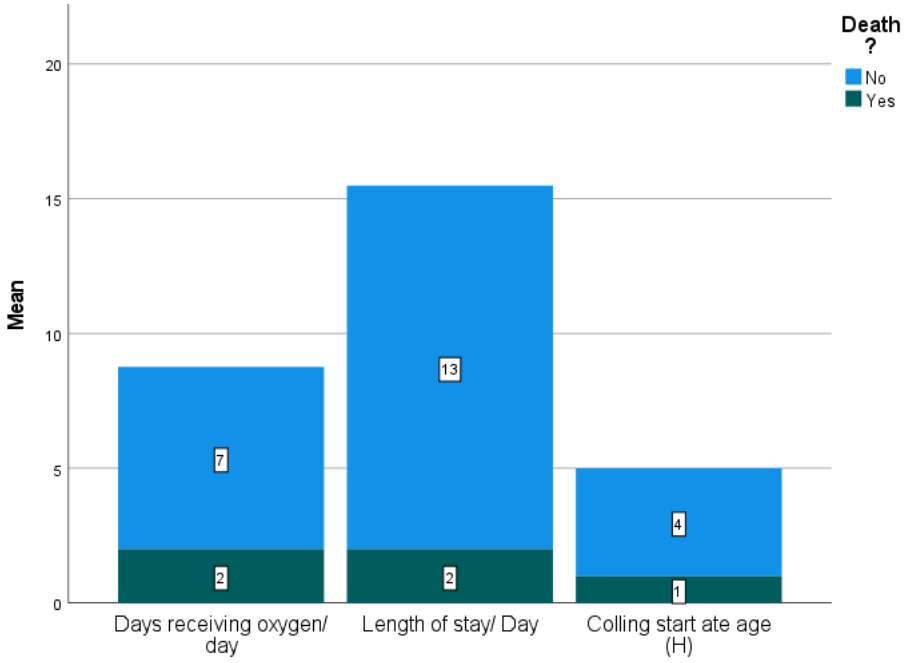

Figure 3, Days on O2, LOS and cooling start means by Death.

Table 7, titled "Chi-square testing by death variable," presents significance levels (Sig) for various categorical variables to explore potential associations with the death outcome. Complications of pregnancy, intrapartum complications, mode of delivery, and gender exhibit relatively high significance levels of 0.169, 0.253, 0.649, and 0.49, respectively, indicating that these factors may not be significantly associated with death. The 5-minute Apgar score, severe encephalopathy, adverse events during the 72-hour intervention, and adverse events during the hospital course also show relatively high significance levels of 0.005, 0.003, 0.001, and 0.001, respectively. The previous results mean that higher Apgar score results in the first 5 minutes had lower death rates among babies on cooling, babies with severe encephalopathy had higher death rates, and babies with adverse events during the hospital course or in the first 72 hours had higher rates of death.

Table 7, Chi-square testing by death variable.

	Sig
Complications of pregnancy	0.169
Intrapartum complications	0.253
Mode of delivery	0.649
Gender	0.49
5 min Apgar score	0.005
Intubation in the delivery room	0.241
Continued resuscitation at 10 min	0.087
Time to spontaneous respiration ≥10 min	0.677
Seizures	0.529

Moderate encephalopathy	0.118
Severe encephalopathy	0.003
Inotropic support	0.606
Anticonvulsants	0.448
Pre-randomization aEEG	0.218
Postnatal complications	0.148
Adverse events during 72hr intervention	0.001
Adverse events during hospital course	0.001
Moderate Disability	0.241
Severe Disability	0.443

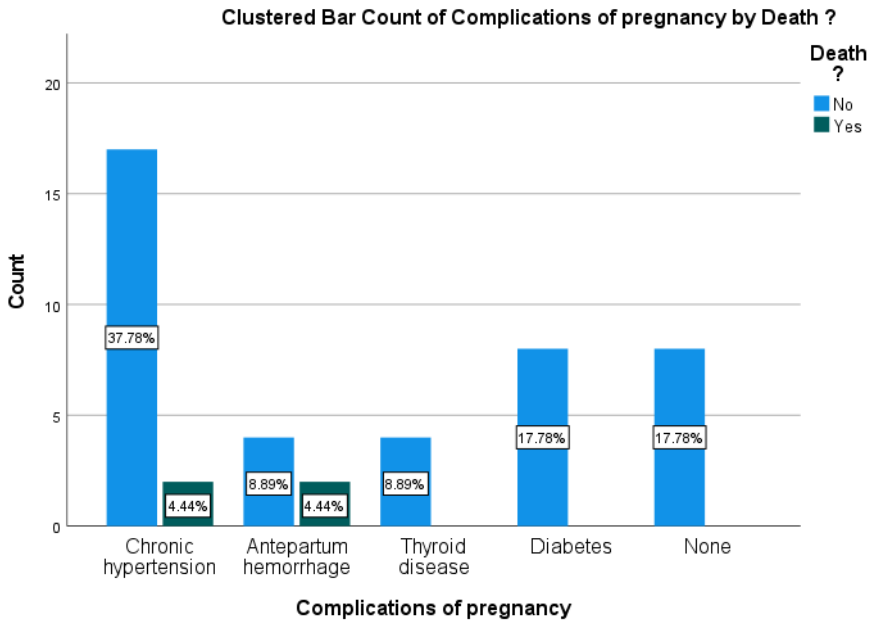

Figure 4, complications during pregnancy by death.

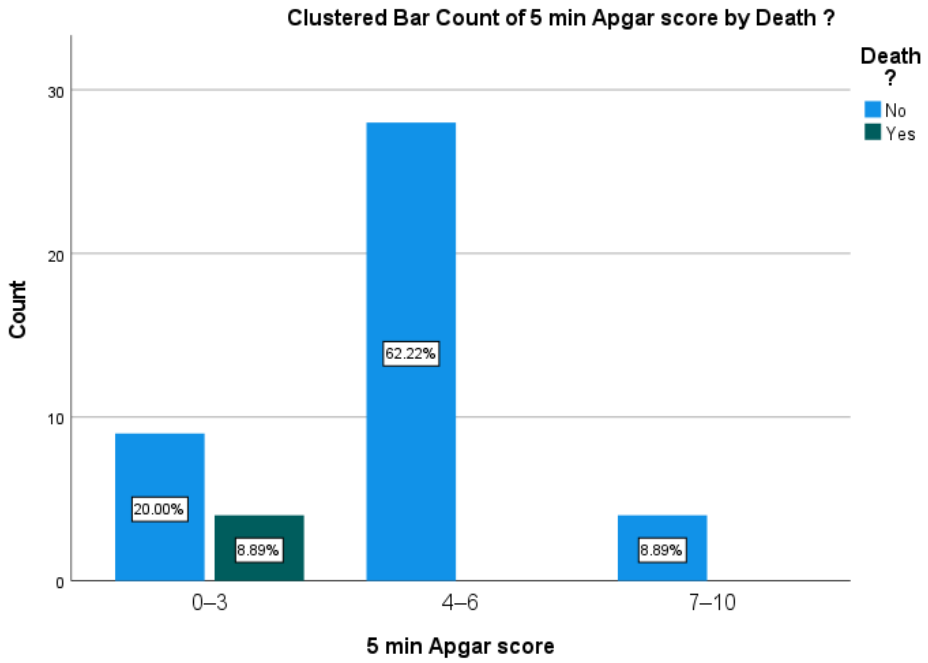

Figure 5, 5min Apgar by Death

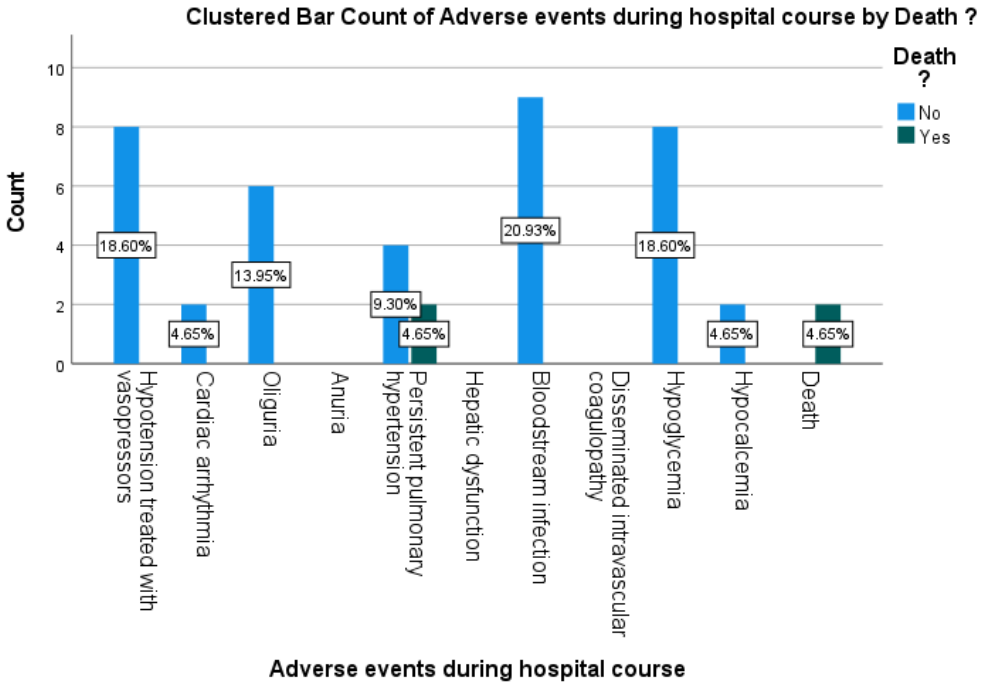

Figure 6, adverse events by Death.

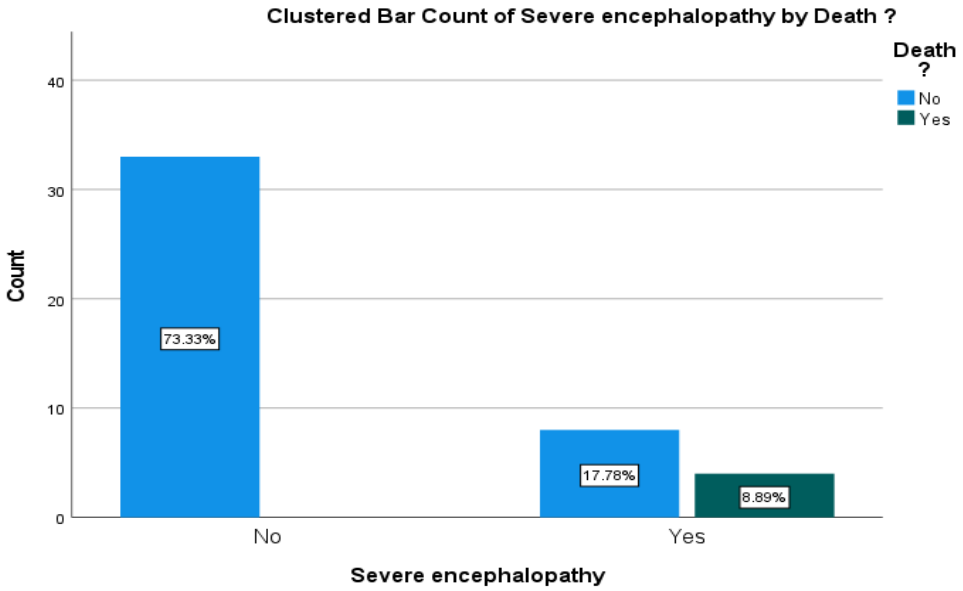

Figure 7, sever encephalopathy by death.

Chapter Five

Discussion

5.1 Discussion

5.1.1 Complications of Pregnancy

The incidence of pregnancy problems such as persistent hypertension, antepartum hemorrhage, and diabetes highlights the various issues that expectant women face. Chronic hypertension affects 42.2% of the study group, this result is similar to the study conducted by Chalak et al., 2014 and shows the prevalence of chronic hypertension is (40%) which is identified as a significant risk factor that necessitates close monitoring and specialist care during pregnancy to reduce related risks for both mother and baby. While antepartum hemorrhage has a lower prevalence of 13.3%, which contradicts Joy et al., 2014 (3.45%), its potential influence on mother and fetal health necessitates vigilant monitoring and proactive management techniques to avoid negative outcomes. Similarly, the diabetes prevalence of 17.8%, which is constant to study by Joy et al., 2014 (13.79%) emphasizes the significance of strict glucose management measures to reduce risks and improve maternal and newborn health. These numbers highlight the complicated terrain of maternal problems during pregnancy, stressing the important need for personalized care approaches that meet individual risk profiles and assure the best results for both mother and baby.

5.1.2 Intrapartum Complications

The incidence of intrapartum problems, particularly cord prolapse at 40.0% and fetal heart rate decelerations at 35.6%, this result is contradict with the study by Shankaran et al., 2014 (32%, 26% respectively) highlights the complexities of labor and delivery, the need for more awareness and prompt intervention to ensure the best results for both mother and baby. Cord prolapse, which occurs in a considerable number of cases, highlights the importance of constant monitoring during labor and prompt obstetric measures to avoid fetal compromise and severe birth outcomes. Similarly, the prevalence of fetal heart rate decelerations underlines the difficulties encountered throughout labor, emphasizing the crucial significance of continuous fetal monitoring and timely obstetric treatments to reduce risks and improve infant well-being. These statistics serve as a stark reminder of the complexities and risks inherent in the intrapartum period, emphasizing the critical role of skilled obstetric care and preparedness in addressing and managing potential complications to ensure the mother's and baby's safety and health throughout the birth.

5.1.3 Mode of Delivery

Emergency Caesarean sections (CS) account for 33.3% of deliveries that require rapid surgical intervention, which may be precipitated by obstetric crises or fetal distress. This result is similar to Chalak et al., 2014 that the prevalence of CS is (25%), and this statistic sheds light on the complicated dynamics of birthing, in which unforeseen conditions may develop, prompting immediate intervention to protect the health and well-being of both mother and child. The high frequency of emergency CS emphasizes the importance of healthcare personnel remaining prepared to properly manage obstetric crises, ensuring access

to urgent surgical care when necessary. Furthermore, it emphasizes the significance of complete birth planning and continuous fetal monitoring during labor to detect signals of distress early and make timely decisions about the mode of delivery. Finally, the incidence of emergency CS emphasizes the importance of obstetric teams in managing unexpected obstacles during labor to improve mother and newborn outcomes.

5.1.4 Neonatal outcomes

The high prevalence of neonatal outcomes such as intubation in the delivery room (71.1%) and seizures (60.0%) highlights neonates' vulnerability to immediate health issues and neurological problems, this result is contradicted by the study by Thoresen, 2014 (64%, 52.3% respectively). The high rate of intubation indicates that a significant proportion of babies are having respiratory distress or birth asphyxia, demanding rapid respiratory support to ensure adequate oxygenation and ventilation. Similarly, the high prevalence of seizures emphasizes neonates' vulnerability to neurological disorders, which necessitate constant monitoring and prompt management to avoid long-term negative effects. These findings highlight the crucial need for specialist neonatal care that is suited to meet babies' particular health concerns, such as breathing assistance and the management of neurological disorders. Furthermore, they emphasize the need for early detection and management in decreasing neonatal health risks, assuring optimal outcomes, and lowering the possibility of long-term difficulties for neonates in critical care settings.

5.1.6 Major Adverse Events and Postnatal Complications

The study's investigation of Major Adverse Events and Postnatal Complications revealed two common issues: hypotension (26.7% of cases) and metabolic acidosis (22.2% of newborns), this does not agree with a study by Thoresen, 2015 that show (55%, 61% respectively). These issues highlight the importance of continuous monitoring and prompt action to avoid undesirable outcomes such as organ malfunction or hypoxic-ischemic injury. Despite their presence, fatality rates over the 72-hour intervention and hospitalization period were low. Nonetheless, these deaths serve as sobering reminders of the possible severity of outcomes even with medical interventions, emphasizing the continued need for continuous improvement in newborn care standards. The discovered adverse events highlight the vital nature of newborn care and the importance of early detection and therapy to successfully limit unfavorable outcomes.

5.1.7 Primary Outcome

When the Primary Outcome was assessed, it became clear that moderate disability affected 28.9% of the investigated population that’s constant with Thoresen et al., 2014 that’s show the moderate diabiltity is (22.5%). Whereas severe disability as shown in our study affected 17.8% of persons this constant with Gluckman et al., 2010 (19%). These results shed light on the significant burden of neurodevelopmental sequelae caused by prenatal insults, underlining the important need for early intervention and ongoing neurodevelopmental follow-up. The incidence of moderate and severe deficits highlights the long-term influence of prenatal injuries on the neurological health and well-being of those affected. These findings serve as a sharp reminder of the importance of preventive methods and early

interventions to improve neurodevelopmental outcomes and mitigate the long-term effects of prenatal insults. Effective preventative approaches and timely interventions can reduce the severity of disabilities and improve the overall quality of life for newborns suffering from perinatal injuries.

In summary, the statistical analyses provide useful information on the maternal and neonatal features, major adverse events, and primary outcomes in the study population. These findings can be used to identify high-risk groups, optimize clinical management regimens, and guide future research to improve maternal and newborn health outcomes.

5.2 Conclusion

The study's conclusion provides a thorough understanding of prenatal therapies and their effects on mother and newborn health outcomes. The study sheds light on the varied nature of neonatal care and the obstacles that come with dealing with prenatal insults by meticulously analyzing maternal and neonatal features, major adverse events, postnatal issues, and primary outcomes.

Key findings emphasize the incidence of maternal problems during pregnancy and after birth, emphasizing the urgent need for comprehensive prenatal and intrapartum care programs. Neonatal outcomes, including significant adverse events and postnatal difficulties, highlight the significance of close monitoring and timely intervention to reduce negative outcomes and improve neurodevelopmental outcomes. The study's primary outcomes, which include moderate disability, severe disability, and mortality, highlight the long-term impact of prenatal insults on neonates.

5.3 Recommendation

1. Emphasize the importance of comprehensive antenatal and intrapartum care to monitor and manage maternal complications effectively.
2. Adopt protocol for monitoring neonates during the perinatal period with particular attention to hemodynamic status.
3. Enhance early recognition and management of neurodevelopmental sequelae following perinatal insults.
4. Establish a mechanism for continuous quality improvement in neonatal care protocol and practice.
5. Encourage ongoing education and training for health care professionals to provide opportunities for professional development knowledge and skills.

5.4 Limitation

1. Movement between cities due to the obstacles of the Israeli occupation and thus the difficulty of reaching the areas of the central and southern West Bank, which increases wasted time and financial costs.
2. Some hospitals refused to take samples from them for administrative matters

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Appendices

Appendix 1: Consent Form

أنا ..... (اسم المشارك / اختياري) أوافق بموجبه على المشاركة في البحث السريري (الدراسة السريرية / دراسة الاستبيان / تجربة الأدوية) المحددة أدناه:

استخدام العلاج بالتبريد (علاج انخفاض حرارة الجسم) بعد الاختناق بين الأطفال حديثي الولادة في وحدة العناية المركزة لحديثي الولادة في المستشفيات الفلسطينية: بأثر رجعي

لتحقيق درجة: ....الماجستير.....، في برنامج: ..... حديثي الولادة.....في الجامعة العربية الامريكية.

تم شرح وتفسير طبيعة الدراسة وهدفها عن طريق الباحث: .....حنين المصري .....

لقد تم إخباري عن طبيعة البحث من حيث المنهجية والآثار السلبية المحتملة والمضاعفات (حسب ورقة معلومات المشارك).

بعد معرفة وفهم جميع المزايا والعيوب المحتملة لهذا البحث، أوافق طواعية بمحض إرادتي على المشاركة في البحث السريري المحدد أعلاه.

أفهم أنه يمكنني الانسحاب من هذا البحث في أي وقت دون إبداء أي سبب على الإطلاق.

التاريخ: ..... إمضاء المشارك: .....

في حضور:-

اسم: .....

التسمية / اللقب: . ..... إمضاء:

.....

(شاهد على توقيع المشارك)

أؤكد أنني أوضحت للمشارك طبيعة وهدف البحث المذكور أعلاه.

تاريخ: ..... إمضاء: .....حنين المصري .....

Appendix 2: Instrument

Maternal and Neonatal Characteristics.

Maternal

Gestational age: ……. week

Maternal age: …….. Years

Gravida no. : ……..

Parity no. : ……..

Complications of pregnancy: ( ) Chronic hypertension ( ) Antepartum hemorrhage
( ) Thyroid disease ( ) Diabetes

Intrapartum complications: ( ) Fetal heart rate decelerations ( ) Cord prolapse
( ) Uterine rupture ( ) Maternal pyrexia
( ) Maternal pyrexia ( ) Shoulder dystocia
( ) Maternal hemorrhage

Mode of delivery: ( ) NVD ( ) EMERGENCY CS ( ) ELECTIVE CS

Labor: …….. Hr.

Rupture of membranes: …… hr.

Neonatal

Birth weight (g): ……

Length: ……. Cm

Head circumference (cm): ……

Gender: ( ) male ( ) Female

5 min Apgar score: ( ) 0–3 ( ) 4–6 ( ) 7–10

Blood gas within 60 min of birth

PH: …….. CO2: ……. Base deficit: ……

Intubation in the delivery room: ( ) Yes ( ) No

Continued resuscitation at 10 min: ( ) Yes ( ) No ( ) Not applicable

Time to spontaneous respiration ≥10 min: ( ) Yes ( ) No

Seizures: ( ) Yes ( ) No

Moderate encephalopathy: ( ) Yes ( ) No

Severe encephalopathy: ( ) Yes ( ) No

Inotropic support: ( ) Yes ( ) No

Anticonvulsants: ( ) Yes ( ) No

Pre-randomization aEEG: ( ) Normal/mildly abnormal ( ) moderately abnormal

( ) Severely abnormal ( ) Seizures present

Age at randomization: …… hr.

Major adverse events and postnatal complications

Postnatal complications ( ) Minor cardiac arrhythmia ( ) Hypotension

( ) Coagulopathy ( ) Prolonged coagulation times

( ) Abnormal renal function ( ) Hyponatremia

( ) Hypokalemia ( ) Platelet count 100 000 per L

( ) Raised liver enzymes concentrations ( ) Metabolic acidosis

( ) Respiratory distress ( ) Systemic infection

( ) Systemic infection ( ) Haemoconcentration

( ) Hypoglycemia ( ) Hypocalcaemia

( ) Difficulties in temperature control

( ) Clinically diagnosed seizures

Adverse events during 72hr intervention: ( ) Major cardiac arrhythmia

( ) Major venous thrombosis

( ) Persistent acidosis ( ) Bleeding

( ) Severe hypotension despite full support

( ) Unanticipated serious adverse event

( ) skin changes ( ) Death

Adverse events during hospital course: ( ) Hypotension treated with vasopressors

( ) Cardiac arrhythmia ( ) Oliguria ( ) Anuria

( ) Persistent pulmonary hypertension

( ) Hepatic dysfunction ( ) Bloodstream infection

( ) Disseminated intravascular coagulopathy

( ) Hypoglycemia ( ) Hypocalcemia ( ) Death

Days receiving oxygen: …… Day

Length of stay: ……. Day

Primary Outcome

Colling start time: ……

Moderate Disability: ( ) Yes ( ) No

Severe Disability: ( ) yes ( ) No

Death: ( ) Yes ( ) No

If Yes, major causes of death: ( ) Encephalopathy

( ) Persistent pulmonary hypertension

( ) Sepsis (proven) ( ) Renal failure

( ) Intractable hypotension ( ) other ……

Appendix 3: IRP Approval

Arab American University
Institutional Review Board - Ramallah

الجامعة العربية الأمريكية
مجلس اخلاقيات البحث العلمي – رام الله

IRB Approval Letter

Study Title: "The Association of Using Cooling Therapy (Hypothermia Therapy) Post Asphyxia among New-borns in NICU at Palestinian Hospitals: A Retrospective Study"

Submitted by: Haneen Tahseen Masri

Date received: 15th December 2023

Date reviewed: 4th January 2024

Date approved: 6th January 2024

Your study titled **"The Association of Using Cooling Therapy (Hypothermia Therapy) Post Asphyxia among New-borns in NICU at Palestinian Hospitals: A Retrospective Study"** with code number **"R-2024/A/8/N"** was reviewed by the Arab American University (IRB-R) committee and was approved on the 6th January 2024.

Sajed Ghawadra, PhD
IRB-R Chairman
Arab American University-Palestine

الجامعة العربية الأمريكية - فلسطين
مجلس اخلاقيات البحث العلمي - رام الله
IRB-R
ARAB AMERICAN UNIVERSITY-PALESTINE
INSTITUTIONAL REVIEW BOARD - RAMALLAH

General Conditions:
1. Valid for 6 months from the date of approval.
2. It is important to inform the IRB-R with any modification of the approved study protocol.
3. The Bord appreciates a copy of the research when accomplished.

رام الله – فلسطين
Tel: 02-294-1999 **E-Email:** IRB-R@aaup.edu **Website:** www.aaup.edu

Appendix 4: تسهيل المهمة

Arab American University
Faculty of Graduate Studies

الجامعة العربية الأمريكية
كلية الدراسات العليا

2023/9/16

الى من يهمه الأمر

تسهيل مهمة بحثية

تحية طيبة وبعد،،

تهديكم كلية الدراسات العليا في الجامعة العربية الأمريكية أطيب التحيات، وبالإشارة إلى الموضوع أعلاه، تشهد كلية الدراسات العليا في الجامعة أن الطالبة حنين تحسين "يوسف عمران" المصري والتي تحمل الرقم الجامعي (202112541) هي طالبة في برنامج ماجستير تمريض حديثي الولادة وتعمل على أطروحة الماجستير الخاصة بها بعنوان:

"The Impact of Using Cooling therapy (Hypothermia Therapy) post Asphyxia among Newborn in NICU at Palestinian Hospitals: Retrospective Study"

تحت إشراف الدكتورة داليا طوقان، نأمل من حضرتكم الإيعاز لمن يلزم لمساعدتها للحصول على المعلومات اللازمة للدراسة، علماً أن المعلومات ستستخدم لغاية البحث فقط وسيتم التعامل معها بغاية السرية، وقد أعطيت هذه الرسالة بناءً على طلبها.

مع فائق الشكر والتقدير

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الملخص

المقدمة: نقص الأكسجة في الفترة المحيطة بالولادة يؤدي إلى اعتلال الدماغ الإقفاري بنقص التأكسج (HIE)، وهو السبب الرئيسي لمضاعفات الأطفال حديثي الولادة. تحدث العواقب العصبية طويلة الأمد في حالة أو حالتين لكل 1000 طفل مولود حيًا في الدول الغنية. تشير الأبحاث إلى أن بدء انخفاض حرارة الجسم بشكل معتدل (33-34 درجة مئوية) في غضون ست ساعات من الولادة يقلل من معدل الوفيات وضعف النمو العصبي عند 18 شهرًا وما بعده. يكون انخفاض حرارة الجسم مفيدًا للغاية عندما يبدأ خلال المرحلة الكامنة من HIE قبل أن يؤدي فشل الطاقة الثانوي إلى موت الخلايا (تؤكد التحقيقات قبل السريرية والسريرية ذلك). وجدت دراسة بأثر رجعي أن بدء انخفاض حرارة الجسم خلال ثلاث ساعات، بدلاً من ثلاث إلى ست ساعات بعد الولادة، كان مرتبطًا بنتائج حركية أفضل لدى المرضى الباقين على قيد الحياة.

الهدف: دراسة تأثير استخدام العلاج بالتبريد على الأطفال حديثي الولادة بعد الاختناق في وحدة العناية المركزة لحديثي الولادة في المستشفيات الخاصة في الضفة الغربية.

منهدية البحث: تم إجراء تصميم دراسة وصفية وكمية بأثر رجعي في قسم NICU في المستشفيات الخاصة والذي يحتوي على وحدة العناية المركزة لحديثي الولادة. كان السكان المستهدفون هم الأطفال حديثي الولادة الذين يعانون من الاختناق والذين يستخدمون العلاج بالتبريد، والذين استوفوا معايير الاشتمال. وتألفت عينة مقنعة من 45 مريضا.

النتائج: فحصت الدراسة 45 مشاركًا استوفوا متطلبات التضمين خلال إطار زمني محدد، وأكدت البيانات التوزيع الطبيعي باستخدام اختبار كولموغوروف الطبيعي، مما يسمح بالتحليل البارامتري لاستفسارات البحث. قدمت ميزات الأم والوليد نظرة ثاقبة لصعوبات الحمل، مثل ارتفاع ضغط الدم المزمن (42.2٪)، ونزيف ما قبل الولادة (13.3٪)، وأمراض الغدة الدرقية (8.9٪)، والسكري (17.8٪). وشملت المشاكل أثناء الولادة تباطؤ معدل ضربات قلب الجنين (35.6%) وهبوط الحبل السري (40.0%)، وكانت معظم الولادات ولادة مهبلية طبيعية (60.0%). كان التوزيع بين الجنسين متساويًا تقريبًا بين الذكور (51.1%) والإناث (48.9%) من الرضع، وكانت غالبية درجات أبغار في 5 دقائق تقع بين النطاق 4-6 (62.2). كان التنبيب في غرفة الولادة مطلوبًا في 71.1% من

الحالات. وكانت الأحداث السلبية الرئيسية انخفاض ضغط الدم (26.7٪)، وظائف الكلى غير طبيعية (4.4٪)، والحماض الأيضي (22.2٪). حدثت الوفاة لدى 4.9% من المرضى أثناء التدخل الذي استمر 72 ساعة و4.7% أثناء العلاج في المستشفى. وأظهرت النتائج الأولية أن 71.1% ليس لديهم إعاقة متوسطة، و82.2% ليس لديهم إعاقة شديدة، و91.1% نجوا. تم العثور على اتصالات مهمة، حيث يرتبط عمر الحمل عكسيا بالوفاة (قيمة الاحتمال = 0.005) ومؤشرات غازات الدم لها ارتباطات متغيرة. وجد اختبار مربع كاي وجود علاقة ذات دلالة إحصائية ($P<0.05$) بين تقييمات أبغار لمدة 5 دقائق، والاعتلال الدماغي الوخيم، والأحداث الضائرة أثناء التدخل والاستشفاء، والوفيات. توفر هذه النتائج رؤى كاملة حول النتائج الصحية للأمهات والأطفال حديثي الولادة بعد التدخل، مما يسمح بفهم أفضل وتحسين الممارسات السريرية.

الاستنتاج: توفر نتيجة الدراسة فهمًا شاملاً لعلاجات ما قبل الولادة وتأثيراتها على النتائج الصحية للأم والوليد. تلقي الدراسة الضوء على الطبيعة المتنوعة لرعاية الأطفال حديثي الولادة والعقبات التي تصاحب التعامل مع الإهانات السابقة للولادة من خلال التحليل الدقيق لسمات الأم والوليد، والأحداث السلبية الكبرى، وقضايا ما بعد الولادة، والنتائج الأولية.