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Review Article

Investigating the Causes of Neonatal Mortality: An Umbrella Review

*Elham Amini [1], Mohammad Heidarzadeh [2], Leila Ahmadian [3], Shahram Ariafar [4], *Mohammadreza Amiresmaili [5]*

1. *Student Research Committee, Kerman University of Medical Sciences, Kerman, Iran*
2. *Department of Pediatrics, School of Medicine, Zahedan University of Medical Science, Zahedan, Iran*
3. *Department of Health Information Sciences, Faculty of Management and Medical Information Sciences, Kerman University of Medical Sciences, Kerman, Iran*
4. *Department of Industrial Engineering, Faculty of Engineering, Shahid Bahonar University of Kerman, Kerman, Iran*
5. *Health in Disasters and Emergencies Research Center, Kerman University of Medical Sciences, Kerman, Iran*

***Corresponding Author:** Email: mohammadreza.amiresmaili@gmail.com

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Abstract

Background: Neonatal mortality remains a critical global challenge, with preventable instances prevailing. The initial stride in mitigating neonatal mortality involves elucidating its underlying causes.

Methods: This study utilized an umbrella review approach to discern factors associated with neonatal mortality. Five international databases, namely Pub Med, Web of Science, Scopus, CINAHL, and EMBASE, were meticulously searched to achieve this.

Results: The initial search yielded 12,631 articles using a search strategy centered on keywords related to factors contributing to neonatal mortality. Ultimately, 95 articles met the criteria incorporated into this study.

Conclusion: This study endeavors to identify the primary risk factors contributing to neonatal mortality. The discerned risk factors have been systematically categorized into four groups: maternal factors, neonatal factors, aspects linked to healthcare systems, and socio-economic factors. As such, it is imperative for policymakers to take heed of these identified risk factors and formulate comprehensive strategies encompassing both long-term and short-term initiatives. Effective interventions spanning various sectors are crucial for the prevention of neonatal mortality.

Keywords: Causes; Neonatal; Mortality; Umbrella review

Introduction

As per the Millennium Development Goals (MDGs), the objective was to diminish the mortality rate of children under the age of 5 between 2000 and 2015(1). During that timeframe, an average of approximately 2.5 million newborn deaths and 2.6 million stillbirths occurred annually (2). Undoubtedly, a paramount objective of the United Nations' Sustainable Development Goals

(SDGs) is to eradicate preventable neonatal mortality across the globe, with a particular emphasis on developing nations, by the year 2030 (3).

The IMR is categorized into three distinct sections: early neonatal (spanning the first 7 d of life), late neonatal (encompassing the period from the 8th to the 27th day of life), and post-neonatal (ranging from the 28th day to the 365th day of life) (4).

In developing nations, the Neonatal Mortality Rate (NMR) constitutes around 60% of the overall Infant Mortality Rate (IMR) (5, 6).

Furthermore, it's concerning to note that 37% of neonatal deaths are considered preventable, while the remaining cases are potentially preventable (7). Numerous reviews have demonstrated correlations between neonatal mortality and the life circumstances of both mothers and neonates (8). Additionally, investigations have revealed that factors such as low quality of care, limited maternal education, and instances of maternal or neonatal exposure to infections hold significant prominence as primary contributors to neonatal mortality (9). During the neonatal period, studies have underscored that neonatal infection, birth weight, asphyxia, and preterm birth are the foremost factors associated with mortality. Notably, research has highlighted those severe neonatal infections, particularly within the initial 7 d of life, stand out as the most significant cause of neonatal mortality (10, 11). Prematurity accounts for approximately one-tenth of instances of neonatal mortality (12).

To effectively develop interventions and prevention strategies targeting neonatal mortality, it is imperative to thoroughly review and assess the evidence linked to neonatal death (13). The initial step towards reducing the Neonatal Mortality Rate (NMR) involves identifying the causes and risk factors associated with neonatal death (14). In systematic reviews, it is common for researchers to focus on specific or limited causes of neonatal mortality.

However, this umbrella review in question was designed to go beyond this approach. Its primary objective was to compile comprehensively the most crucial risk factors associated with perinatal death, neonatal mortality, and stillbirth. This was achieved by meticulously reviewing all relevant systematic reviews that exhibited medium to high-quality scores.

Materials and Methods

Umbrella reviews systematically search and evaluate evidence from several systematic reviews and/or meta-analyses on all health outcomes related to a special subject (15). This umbrella review was undertaken with the purpose of identifying factors linked to neonatal mortality. The methodology followed the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions, ensuring a systematic and rigorous approach to the review process (16). Furthermore, this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a standardized and transparent reporting approach. The review protocol was registered on PROSPERO under Registration No CRD42022300532. All the stages of the review process have been meticulously documented and presented in a PRISMA chart in Appendix 1. The population under study encompasses individuals from all corners of the world.

Searching strategy

Five international databases including Pub Med, Web of Science, Scopus, CINAHL, and EMBASE were searched. Keywords were selected based on the PICO question formulation. For search terms two categories were used, including: "Neonat*" OR "Infant" OR "Perinatal" OR "newborn" searched in title. 2."Mortality" OR "death" OR "decease" in title-abstract. Other search strategy synonyms in each category were related with an "OR" and then two categories were related with "AND". The search filter was set to limit results to systematic reviews. Keyword synonyms were identified using the Medical Subject Heading (MESH) and through a scoping search. The obtained keywords were presented to and confirmed by an expert panel (clinicians, li-

brarians, and experts who had searched on related subjects). The scoping search included search terms for the neonatal period including perinatal and neonatal, and death. Moreover, synonyms for "death", such as mortality and stillbirth, were also added to identify relevant reproductive risk factors. This search strategy has been employed to retrieve all systematic reviews published from 1/1/2000 to 12/30/2021.

Eligibility criteria

The following are the inclusion criteria:

- Systematic reviews
- Causes of neonatal mortality
- English language articles
- Neonatal period

The following are the exclusion criteria:

- Reviews on interventions and clinical technics
- Reviews with low and very low quality according to AMSTAR2
- Review on effect of COVID-19

Quality assessment

The Quality of each study was evaluated by two independent authors (EA & MA) using AMSTAR2. AMSTAR2 is a valid, critical and reliable tool developed by AMSTAR in 2017. Any disagreement was resolved by the third author (LA). AMSTAR2 is a tool used for qualitatively evaluating reviews consist on a 16-item checklist (17).

Overlapping reviews

When two or more reviews assessed the same exposure and outcomes, they were categorized as overlapping reviews. Overlapping reviews are prone to biased findings and estimations due to the inclusion of primary studies multiple times from the same sources (18-20). The included articles displayed a significant degree of diversity, resulting in notable heterogeneity. To assess the occurrence of review overlaps, a process was undertaken. Initially, articles focusing on the same subject and yielding similar results were identified. Subsequently, the references of these articles were thoroughly examined. Finally, all instances of overlaps were meticulously documented and reported.

Data collection and analysis

The standard methodological protocols established by the Cochrane Collaboration were employed for both data collection and analysis. However, due to the observed heterogeneity among the studies, conducting a meta-analysis was not feasible. Consequently, the results are presented using a narrative approach, providing a descriptive overview of the findings. Upon thorough assessment of the predefined inclusion and exclusion criteria, 95 reviews were deemed suitable for inclusion in this umbrella review.

Results

Reviewing and extracting the articles in the PRISMA chart is presented in summary (Fig. 1).

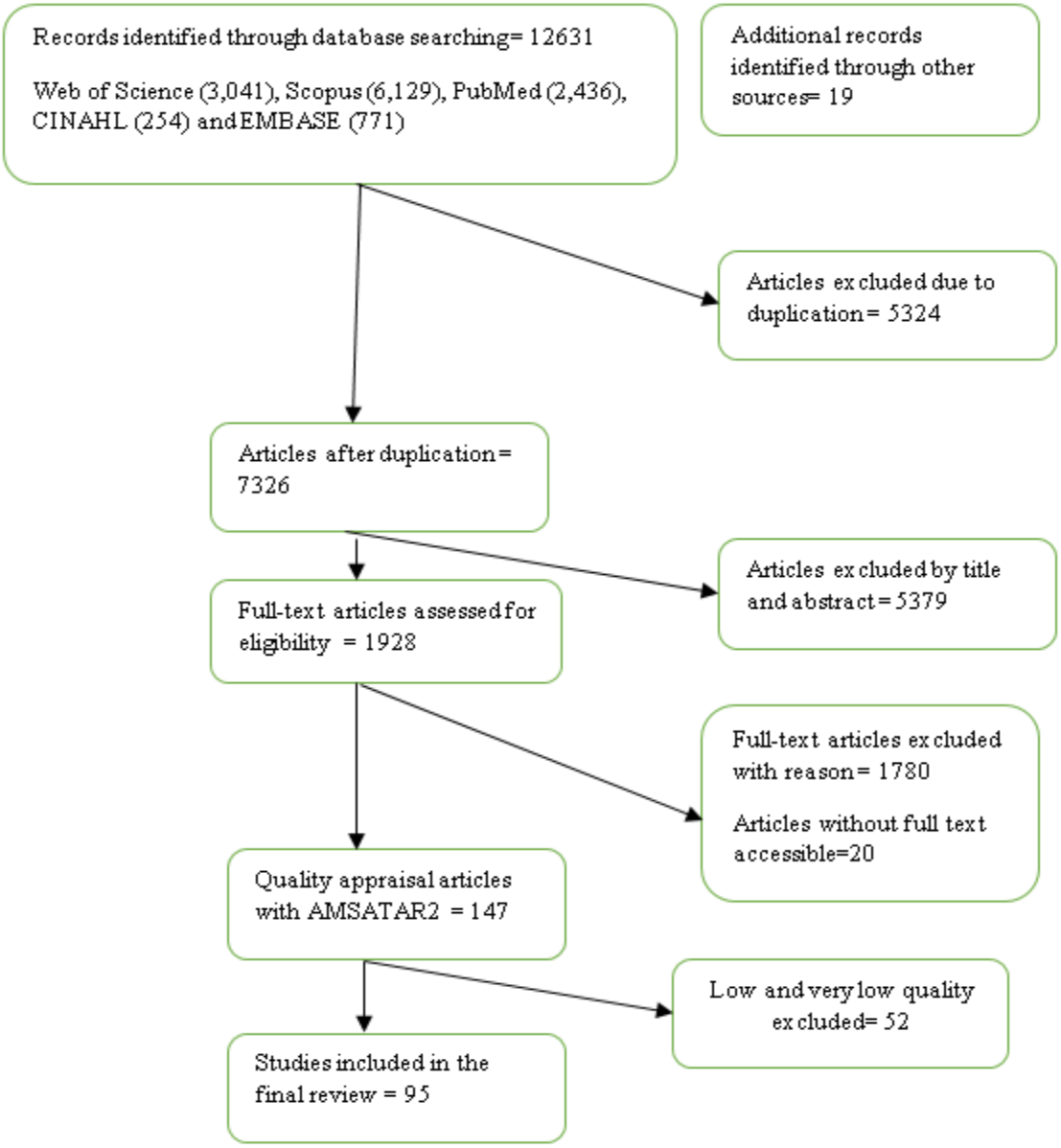

Fig. 1: PRISMA Chart of retrieving studies

The results have been succinctly summarized and organized into four tables in Supplementary files (Not published).

Factors contributing to neonatal mortality were divided into four categories:

Maternal factors
Neonatal factors
Factors related to healthcare systems
Socio-economic factors

Maternal factors affected neonatal mortality

Various lifestyle factors can contribute to adverse pregnancy outcomes. These encompass aspects like advanced maternal age, young maternal age, alcohol consumption, smoking, inadequate diets, exposure to intimate partner violence, maternal obesity, improper birth spacing, and infections such as Parvovirus B19. Furthermore, specific maternal diseases wield considerable influence on perinatal, neonatal, and infant mortality. Some of

these include preexisting diabetes, polycystic ovary syndrome during pregnancy, rubella infection while pregnant, maternal anemia, low maternal hemoglobin levels, high maternal hemoglobin levels, epilepsy, hepatitis E during pregnancy, chlamydia infection during pregnancy, hypertensive disorders of pregnancy, Lyme disease, ZIKA infection during pregnancy, Neisseria gonorrhea infection, Ebola virus disease during pregnancy, Lassa fever, and maternal anti-phospholipid syndrome. Furthermore, medical interventions like In Vitro Fertilization and cesarean section have been associated with adverse pregnancy outcomes. Multiple gestations and gestational age of 37 wk or less have also been linked to increased neonatal mortality (21).

Neonatal factors affected neonatal mortality

Neonatal factors that contribute to neonatal mortality primarily revolve around neonatal diseases. These encompass conditions such as birth asphyxia, sepsis, severe infections (including pneumonia), respiratory distress syndrome, and meningitis. Other factors include infants with necrotizing enterocolitis, fetal urachal sinthrombosisis, hyperglycemia in very preterm infants, and echogenic bowel. Notably, fetuses with severe bilateral ventriculomegaly and fetuses with severe fetal hydrops are also associated with neonatal mortality. Several factors have been highlighted as significant contributors to neonatal mortality. These include preterm birth, male gender, Apgar score below 7 at the fifth minute after birth, low and very low birth weight, prematurity, marginal association with primigravity, and fetal heterodoxy. In cases of fetal heterodoxy, cardiac anomalies are often observed (22). Certainly, the presence of fetal meconium peritonitis and a 10%elevation in stillbirth rates are outlined as neonatal factors influencing neonatal mortality.

Healthcare systems factors affecting neonatal mortality

These factors encompass various dimensions. Lower nurse-to-patient ratios and the presence of 31%beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units identified as elements associated with neonatal mortality (23). The quality of care for neonatal females is notably lower compared to males (24). Inadequate or completely lacking prenatal care are underlying causes of neonatal mortality (21).

Socio-economic factors affecting neonatal mortality

Residing in underprivileged neighborhoods, experiencing socioeconomic disparities, and encountering income inequality have been linked to elevated IMR, higher occurrences of stillbirths, increased perinatal mortality, preterm births, and neonatal mortality (25-27). Ethnic minority women and migrant populations in Western industrialized countries often confront a higher prevalence of adverse pregnancy outcomes and complications (28).

Overlapping reviews

For maternal body mass, 5 articles have overlaps including articles (29-33). Authors were overlapping articles in two studies (34, 35).

For maternal smoking, 2 articles have some overlaps including articles from Wisborg (36) and Froen (37) in two studies of Zhang (38) and Marufu (39) been overlapped.

For maternal hypertensive disorders, 9 articles had overlaps including (40-48) are taken by Gemechu (49) and Noubiap (50).

Discussion

Within this umbrella review, the primary objective was to diligently search for and identify the most critical risk factors associated with neonatal mortality. These identified risk factors were thoughtfully categorized into four distinct groups. Notably, articles that highlighted a combination of factors spanning various categories were categorized under the fourth group, encompassing maternal factors, neonatal factors, healthcare system-related factors, and socioeconomic factors. This comprehensive approach ensured a thorough understanding of the multifaceted nature of neonatal mortality risk factors.

Reviews focusing on maternal risk factors were allocated to the first category. The WHO publication, known as the International Classification of Diseases – Perinatal Mortality, classifies perinatal mortality risk factors. Notably, maternal conditions are a pivotal contributor to PM. As highlighted in our review, maternal age emerges as a crucial factor in this context. Specifically, there is a significantly elevated risk associated with maternal ages between 35 to 39 yr and particularly beyond 45 yr, as well as maternal ages below 15 yr (51-53).

Our findings indicate that maternal diseases including Lyme disease, ZIKA infection, Neisseria gonorrhea infection, Ebola virus disease, Lassa fever, and maternal anti-phospholipid syndrome are associated with an elevated risk of neonatal mortality (54-56). In a review, maternal exposure to Ebola virus was linked to adverse outcomes such as neonatal mortality, stillbirths, and miscarriages (57). A knowledge gap was explained for management of mothers with Ebola virus (58).

Within this umbrella review, multiple studies have investigated the implications of maternal obesity on infant mortality. Notably, a Body Mass Index exceeding 25, particularly levels surpassing 30 and 35, has been associated with a range of serious complications for mothers and is linked to adverse pregnancy outcomes (59-61). Maternal overweight is correlated with an increased risk of neonatal mortality (62).

Conversely, specific maternal circumstances such as unintended pregnancies and inappropriate birth spacing play a pivotal role in influencing pregnancy outcomes (63, 64). Low birth space led to neonatal mortality (65). Furthermore, our review identified specific maternal conditions such as maternal smoking, maternal diabetes, and hypertensive disorders as contributing factors to neonatal mortality (49, 50, 66,67). Specific maternal conditions contribute to the occurrence of stillbirths. These conditions encompass abnormal labor, maternal hypertension, maternal infections, chorioamnionitis, maternal diabetes, antepartum hemorrhage, maternal pre-existing disorders, and spontaneous preterm labor (68).

Certain systematic reviews have indicated that In Vitro Fertilization (IVF) is associated with an elevated risk of neonatal mortality (69-73). IVF is linked to twin pregnancies, low birth weight, preterm birth, preeclampsia, congenital anomalies, and placental abnormalities (74). The escalated rates of Caesarean section, particularly in developing countries, have been associated with an increased risk of neonatal mortality (75).

The second category within this review pertained to neonatal risk factors. Noteworthy neonatal risk factors contributing to neonatal mortality, as identified in this umbrella review, encompass low birth weight, birth asphyxia, sepsis, severe infections, pneumonia, respiratory distress syndrome, meningitis, echogenic bowel, bilateral ventriculomegaly, preterm birth, fetal heterodoxy, and fetal meconium peritonitis. These factors collectively contribute to the understanding of neonatal mortality risk within this study (76-80). Additionally, within this review, several other neonatal risk factors were highlighted. These include Apgar scores below 7 at the fifth minute after birth, low and very low birth weight, prematurity, and marginal association with primigravity (81).

Furthermore, the prevalence of stillbirths in male infants was approximately 10% higher compared to female infants (82). Neonatal mortality causes were ranked. Notably, low birth weight and premature birth emerged as the leading risk factors in this ranking (83).

The third category within the review was associated with healthcare factors. Notably, lower nurse-to-patient ratios were found to have a direct correlation with increased neonatal mortality rates (84). Implementing policies to enhance nurse-to-patient ratios can lead to favorable outcomes, including a positive return on investment, reduced mortality rates, and decreased readmissions (85).

Quality improvement efforts within NICUs have a pivotal role in effectively reducing neonatal mortality rates. The significance of NICUs were underscores in mitigating preterm deaths (86, 87). The provision of low-quality care poses a multitude of challenges for healthcare systems, directly contributing to issues such as neonatal mortality

(24). The quality of care during the antenatal, intrapartum, and postnatal periods could potentially reduce 21%-32% of neonatal mortality instances (88).

Indeed, the lack of antenatal care and insufficient or absent prenatal care have been identified as contributing factors to neonatal mortality (81, 89). Group care models for antenatal and prenatal care have demonstrated positive impacts on neonatal health in high-income countries. Given these positive outcomes, these group care models are recommended for adoption in low and middle-income countries (90).

The fourth category within the review focused on socio-economic factors. Notably, living in a deprived neighborhood has been linked to an increased risk of neonatal mortality. Residing in deprived neighborhoods is associated with an elevated risk of neonatal mortality (91).

Having a low socioeconomic status, income inequality and being part of an ethnic minority are associated with neonatal mortality. Many confounding factors are in these variables (25-27). The impact of structural racism on infant mortality in the United States was explored (92). A study that highlighted the correlation between inequalities in access to healthcare facilities, family income, and certain social determinants such as the literacy of women, with an elevated risk of neonatal mortality (93).

Migrant women in western industrialized countries faced many pregnancy complications (28). Migrant women experienced higher rates of maternal and neonatal complications compared to local women (94). Finally, a systematic review found that wildfire exposure during late pregnancy is linked to low birth weight, preterm birth and infant mortality (95).

Limitations

Our review was the first umbrella review to summarize systematically broad causes of neonatal mortality. Moreover, this umbrella review assessed the overlapping and appraised the quality of previous systematic reviews using the AMSTAR2 checklist.

As a limitation of the review, since we wanted to gather all causes of neonatal mortality, a large number of articles were retrieved using our search strategy. A great amount of time was spent screening the articles and excluding those discussing clinical causes and their interventions. Screening all the retrieved articles was an arduous task three authors participated in.

Conclusion

A multitude of factors contributes to infant mortality, which have been systematically categorized into four distinct groups. Analyzing these factors collectively reveals that certain interventions can lead to immediate reductions in infant mortality, such as enhancing routine maternal care and improving access to healthcare services. However, other factors necessitate more comprehensive and sustained efforts, particularly those related to socio-economic aspects. Thus, to effectively enhance conditions and curtail infant mortality rates, a well-rounded strategy is essential. This strategy should encompass both short-term interventions and long-term initiatives, fostering cross-sector collaboration and effective communication among various departments. By adopting such a multifaceted approach, meaningful progress in reducing infant mortality can be achieved.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare no conflicts of interest.

Data availability

All supplementary files will be sent to respected readers in case of reasonable apply from the corresponding author.

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