

Risk Factors And Complications Of Perinatal Mortality In High-Risk Pregnancies: A Systematic Literature Review

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Abstrak

Latar belakang: Mortalitas perinatal masih menjadi masalah kesehatan global yang signifikan, terutama pada kehamilan risiko tinggi. Berbagai faktor maternal, plasenta, infeksi, dan obstetri berkontribusi terhadap peningkatan risiko kelahiran mati, kematian neonatal dini, serta luaran neonatal yang buruk. **Tujuan:** Penelitian ini bertujuan untuk mengidentifikasi dan mensintesis faktor risiko serta komplikasi yang berhubungan dengan mortalitas perinatal pada kehamilan risiko tinggi. **Metode:** Penelitian ini menggunakan desain Systematic Literature Review (SLR) yang mengikuti pedoman PRISMA 2020. Pertanyaan penelitian disusun menggunakan kerangka PICOS yang berfokus pada ibu hamil risiko tinggi, faktor risiko maternal dan obstetri, serta luaran mortalitas perinatal. Pencarian literatur dilakukan pada lima database, yaitu ProQuest, PubMed, SpringerLink, ScienceDirect, dan Semantic Scholar pada Maret–Mei 2026. Kata kunci yang digunakan meliputi “kehamilan risiko tinggi,” “mortalitas perinatal,” “kelahiran mati,” “kematian neonatal dini,” “faktor risiko,” dan “komplikasi kehamilan” dengan operator Boolean (“AND” dan “OR”). Kriteria inklusi meliputi artikel berbahasa Inggris, full-text, dipublikasikan antara Mei 2025–Mei 2026, serta menggunakan desain cohort, case-control, cross-sectional, prospective, dan retrospective study. Seleksi studi dilakukan melalui tahapan PRISMA yaitu identifikasi, skrining, kelayakan, dan inklusi. Dari 21.401 artikel yang teridentifikasi, sebanyak 14 artikel memenuhi kriteria inklusi dan dianalisis dalam studi ini. **Hasil** kajian menunjukkan bahwa infeksi COVID-19 pada ibu hamil, trombofilia hereditas, gangguan hipertensi dalam kehamilan, disfungsi plasenta, malnutrisi maternal, indeks massa tubuh abnormal, usia ibu ekstrem, serta komplikasi obstetri meningkatkan risiko kelahiran prematur, pertumbuhan janin terhambat, berat badan lahir rendah, kelahiran mati, dan kematian neonatal. Gangguan plasenta seperti abrupsi plasenta dan malperfusi vaskular berhubungan kuat dengan luaran neonatal yang buruk. Intervensi seperti pelayanan antenatal spesialisasi, stratifikasi risiko maternal, penggunaan tromboprolifaksis pada kasus tertentu, serta perencanaan persalinan pada usia gestasi optimal menunjukkan perbaikan luaran maternal dan neonatal. **Kesimpulan:** Mortalitas perinatal pada kehamilan risiko tinggi dipengaruhi oleh berbagai faktor maternal dan obstetri. Deteksi dini, pelayanan antenatal terintegrasi, serta manajemen kehamilan yang terindividualisasi sangat penting untuk menurunkan angka kematian maternal dan neonatal yang dapat dicegah.

Kata Kunci: Kehamilan Risiko Tinggi; Mortalitas Perinatal; Kelahiran Mati (Stillbirth); Kematian Neonatal Dini; Faktor Risiko Kehamilan.

Abstract

Background: Perinatal mortality remains a major public health problem, particularly among women with high-risk pregnancies. Maternal, placental, infectious, and obstetric complications contribute significantly to stillbirth, early neonatal death, and other adverse neonatal outcomes. Objective: This study aimed to identify risk factors and complications associated with perinatal mortality in high-risk pregnancies. Methods: This study used a Systematic Literature Review (SLR) design following the PRISMA 2020 guidelines. The research question was developed using the PICOS framework, focusing on pregnant women with high-risk pregnancies, maternal and obstetric risk factors, and perinatal mortality outcomes. Literature searches were conducted in ProQuest, PubMed, SpringerLink, ScienceDirect, and Semantic Scholar between March and May 2026. Keywords included “high-risk pregnancy,” “perinatal mortality,” “stillbirth,” “early neonatal death,” “risk factors,” and “pregnancy complications,” combined using Boolean operators (“AND” and “OR”). Inclusion criteria were English-language full-text studies published between May 2025 and May 2026 using cohort, case-control, cross-sectional, prospective, or retrospective designs. Study selection followed the PRISMA flowchart through identification, screening, eligibility, and inclusion stages. From 21,401 identified articles, 14 studies met the eligibility criteria and were included in the review. Results: The reviewed studies showed that maternal COVID-19 infection, inherited thrombophilia, hypertensive disorders, placental dysfunction, maternal undernutrition, abnormal body mass index, advanced maternal age, and obstetric complications significantly increased the risk of stillbirth, preterm birth, fetal growth restriction, low birth weight,

and neonatal death. Placental abnormalities and placental abruption were strongly associated with adverse neonatal outcomes. Specialized antenatal services, maternal risk stratification, thromboprophylaxis in selected patients, and planned birth at optimal gestational age were associated with improved maternal and neonatal outcomes. Conclusion: Perinatal mortality in high-risk pregnancies is influenced by multiple maternal and obstetric factors. Early identification, specialized antenatal care, and individualized management are essential to reduce preventable maternal and neonatal mortality.

Keywords: High-Risk Pregnancy; Perinatal Mortality; Stillbirth; Pregnancy Complications; Neonatal Outcomes.

1. INTRODUCTION

Perinatal mortality remains one of the most significant global public health problems and continues to reflect the quality of maternal and neonatal healthcare services worldwide (Behboudi-gandevani, Bidhendi-yarandi and Panahi, 2022). Perinatal mortality includes stillbirths occurring after 28 weeks of gestation and early neonatal deaths within the first seven days of life. Despite global improvements in maternal and child health, the reduction in perinatal deaths has progressed more slowly in many low- and middle-income countries, particularly among women experiencing high-risk pregnancies (Gutman *et al.*, 2022). According to the World Health Organization (WHO), approximately 2.3 million newborn deaths occurred globally in 2023, with neonatal deaths accounting for nearly half of all deaths among children under five years of age (WHO, UNICEF, UNFPA, 2023). Prematurity, birth asphyxia, infections, congenital anomalies, and complications during pregnancy and childbirth remain the leading contributors to perinatal mortality worldwide (Makasa *et al.*, 2025).

High-risk pregnancy is defined as a pregnancy associated with increased risks to the mother, fetus, or newborn due to medical, obstetric, socioeconomic, or environmental factors. Conditions such as hypertensive disorders of pregnancy, gestational diabetes mellitus, maternal anemia, obesity, infections, multiple pregnancies, preterm labor, and previous adverse obstetric history substantially increase the likelihood of unfavorable perinatal outcomes. Recent systematic reviews have demonstrated that maternal complications and inadequate antenatal care are strongly associated with neonatal and perinatal mortality. Furthermore, pregnancies complicated by prematurity, low birth weight, and congenital anomalies are consistently identified as having significantly higher mortality risks (Nabila *et al.*, 2024).

Globally (Kasa *et al.*, 2023), disparities in healthcare access and quality contribute significantly to persistent perinatal mortality rates. Women living in low-resource settings frequently encounter barriers such as inadequate antenatal care, delayed referral systems, shortages of skilled birth attendants, and limited access to emergency obstetric and neonatal services. A systematic review conducted in Sub-Saharan Africa identified poor maternal healthcare utilization, obstructed labor, preterm birth, and low birth weight as major determinants of stillbirth and neonatal mortality. Additionally, women living in socioeconomically deprived areas were found to experience significantly worse perinatal outcomes compared to those in higher-income regions.

Maternal medical conditions and obstetric complications also play a crucial role in increasing perinatal mortality (Rocha *et al.*, 2022). A recent systematic review and meta-analysis reported that potentially life-threatening maternal conditions, including severe hemorrhage, hypertensive disorders, sepsis, and organ dysfunction, remain major contributors to maternal and neonatal morbidity and mortality globally. These complications frequently result in fetal distress, preterm birth, intrauterine growth restriction, and neonatal death. (Baykemagn, Abreha and Zelelow, 2024) In addition, evidence suggests that inflammatory conditions such as periodontitis may contribute to adverse pregnancy outcomes, including preeclampsia, which subsequently increases the risk of perinatal mortality (Le, Q. A., Akhter, R., Coulton, K. M., Vo, N. T. N., Duong, L. T. Y., Nong, H. V., Yaacoub, A., Condous, G., Eberhard, J., & Nanan, 2021).

Several recent studies have also emphasized the importance of accurate identification and classification of perinatal deaths to support effective prevention strategies (Connor *et al.*, 2024). The International Classification of Diseases for Perinatal Mortality (ICD-PM), developed by WHO, aims to standardize reporting and improve understanding of causes of perinatal deaths globally. However, inconsistencies in classification systems and reporting practices remain common across healthcare settings. A recent systematic review revealed that congenital malformations, prematurity, acute intrapartum events, and maternal complications related to the placenta, membranes, and labor were among the leading causes of perinatal mortality. The review also highlighted that unexplained perinatal deaths remain substantially high, especially in low-income countries (Kumsa, 2024).

Although many primary studies have investigated risk factors associated with perinatal mortality, the findings remain heterogeneous due to differences in study populations, healthcare systems, and methodological approaches. Furthermore, evidence specifically synthesizing risk factors and complications of perinatal mortality among high-risk pregnancies remains limited (Mar *et al.*, 2021). Therefore, a comprehensive systematic literature review is needed to critically evaluate and synthesize the current evidence regarding the major risk factors and complications contributing to perinatal mortality in high-risk pregnancies.

This systematic literature review aims to identify, analyze, and synthesize evidence related to the risk factors and complications associated with perinatal mortality in high-risk pregnancies. The findings of this review are expected to contribute to evidence-based clinical practice, improve maternal and neonatal healthcare strategies, and support preventive interventions to reduce preventable perinatal deaths globally.

2. METHODOLOGY

Study Design

This study employed a Systematic Literature Review (SLR) design to identify, evaluate, and synthesize evidence regarding risk factors and complications associated with perinatal mortality in high-risk pregnancies. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and methodological rigor.

Research Question

The review was guided by the following research question: “What risk factors and complications are associated with perinatal mortality among women with high-risk pregnancies?”

For a Systematic Literature Review (SLR), it is recommended to use a framework such as PICOS or PICOT to ensure that the research question and search strategy are developed in a structured and systematic manner. Since this study focuses on risk factors and complications rather than specific clinical interventions, the PICOS framework is considered the most appropriate approach. PICOT is more commonly used for intervention-based studies or clinical trials. The research question was developed using the PEOS framework (Population, Exposure, Outcome, and Study Design):

Component		Description
P	Population/Problem (P)	Pregnant women with high-risk pregnancies
I	Intervention/Exposure (I/E)	Maternal, fetal, obstetric, and socioeconomic risk factors and pregnancy complications
C	Comparison (C)	Pregnant women without identified risk factors or complications (when applicable)

Component		Description
O	Outcome (O)	Perinatal mortality, including stillbirth and early neonatal death
S	Study Design (S)	Cohort study, case-control, cross-sectional, prospective study, retrospective study

Search Strategy

A comprehensive literature search was conducted using several electronic databases, including:

- ProQuest
- PubMed
- SpringerLink
- ScienceDirect
- Semantic Scholar

The search process was conducted between March and Mei 2026. Articles published within the last 12 month (Mei 2025–Mei 2026) were included to ensure the use of current and relevant evidence.

The search strategy was developed based on the PICOS framework to identify studies relevant to the research question. Keywords and Medical Subject Headings (MeSH) terms related to population, exposure, and outcomes were combined using Boolean operators (“AND” and “OR”).

The keywords included: “High-risk pregnancy”, “Pregnancy complications”, “Risk factors”, “Perinatal mortality”, “Stillbirth”, “Early neonatal death”, “Maternal complications” dan “Neonatal outcomes”.

Search string used in ProQuest and ScienceDirect was:

("perinatal mortality" OR "perinatal death" OR stillbirth OR "fetal death" OR "neonatal death")
AND
("high-risk pregnancy" OR "high risk pregnancy" OR "high-risk pregnancies")
AND
("risk factors" OR complications OR determinants OR predictors OR "maternal complications")

Search string used in Pubmed was:

("perinatal mortality" OR "perinatal death" OR stillbirth OR "fetal death" OR "neonatal death")
AND
("high-risk pregnancy" OR "high risk pregnancy" OR "high-risk pregnancies")
AND
("risk factors" OR complications OR determinants OR predictors OR "maternal complications")

Search string used in ScienceDirect and Semantic Scholar was:

("stillbirth" OR "early neonatal death")
AND ("high risk pregnancy")
AND ("maternal complications" OR "obstetric complications")

Inclusion and Exclusion Criteria

The eligibility criteria for study selection were established prior to the review process. Inclusion Criteria

Studies were included if they met the following criteria: Published between Mei 2025 and 2026; Written in English; Focused on perinatal mortality in high-risk pregnancies; Examined risk factors or complications associated with perinatal mortality; Used Cohort, case-control, cross-sectional, prospective, retrospective study designs; Scholarly Journals/open access/Full-text articles available.

Exclusion Criteria

Studies were excluded if they: Were duplicate publications; Were editorials, conference abstracts, letters, or commentaries; Focused solely on maternal mortality without neonatal or perinatal outcomes; Did not specifically address high-risk pregnancies; Had incomplete data or unavailable full text; Used quantitative, observational, or systematic review and other study designs.

Study Selection Process

All articles identified through database searching were exported into reference management software to remove duplicate studies. Titles and abstracts were screened independently based on the inclusion and exclusion criteria. Subsequently, full-text articles were assessed for eligibility. The study selection process followed the PRISMA 2020 flow diagram, consisting of four stages:

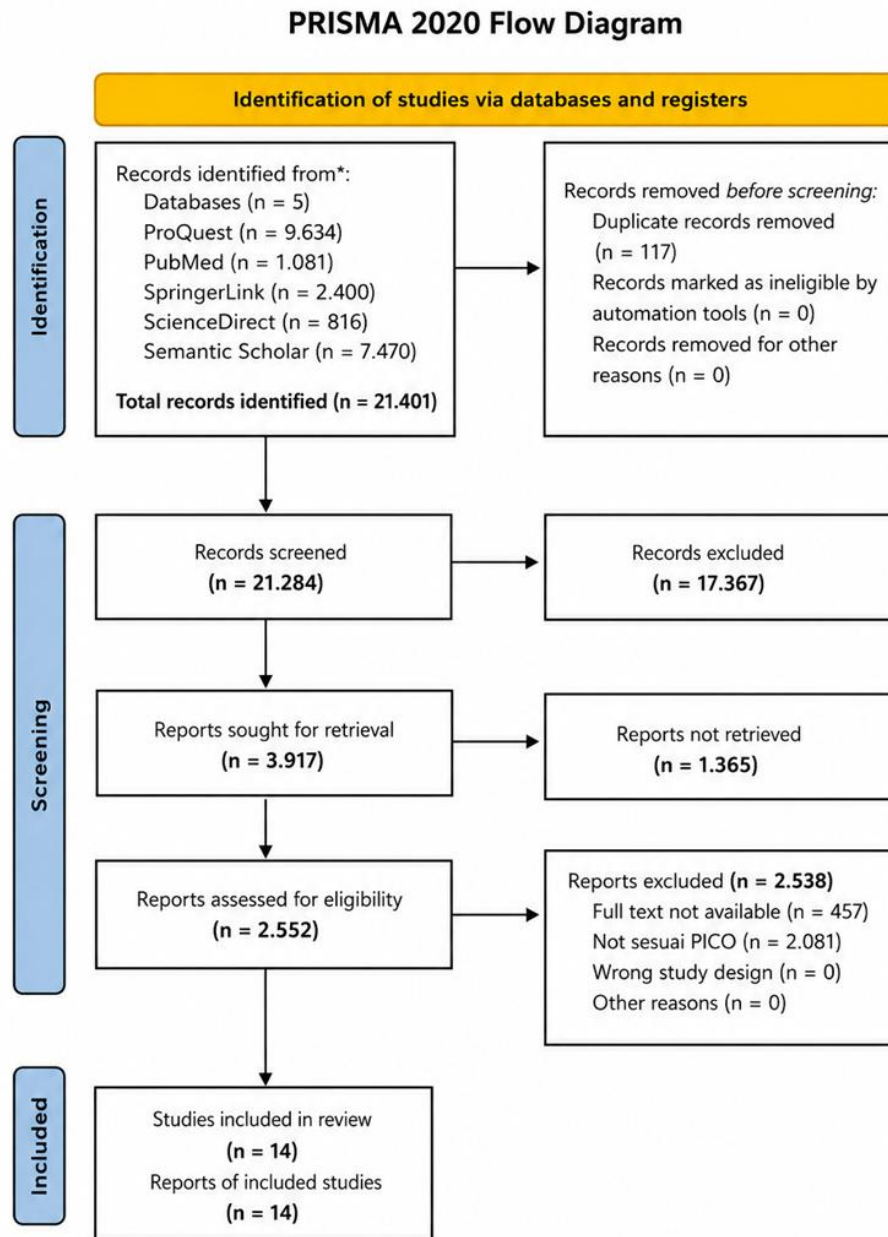
1. Identification
2. Screening
3. Eligibility
4. Included studies

Disagreements during the screening process were resolved through discussion and consensus.

Study Eligibility Results

From the initial search across five databases, a total of 21,401 articles were identified, of which 457 articles met the first inclusion criteria. After removing duplicates, screening titles and abstracts, and conducting full-text evaluations, 14 articles met the eligibility criteria and were included for further analysis.

Prisma Flowchart



* Databases include ProQuest, PubMed, SpringerLink, ScienceDirect, and Semantic Scholar.

Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al.
The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.
BMJ 2021;372:n71. doi: [10.1136/bmj.n71](https://doi.org/10.1136/bmj.n71)

3. RESULT

A total of 14 studies related to perinatal mortality, adverse neonatal outcomes, and high-risk pregnancies were reviewed. The studies included retrospective cohort studies, case-control studies, cross-sectional studies, and case series conducted in various countries including Brazil, Somalia, Germany, Thailand, South Africa, Australia, and the United Kingdom. Overall, the findings demonstrated that maternal comorbidities, placental abnormalities, infectious diseases, thrombophilia, obstetric complications, and inadequate maternal conditions significantly contributed to adverse neonatal and perinatal outcomes.

Several studies identified maternal infection and placental dysfunction as major contributors to poor neonatal outcomes. Pregnant women infected with COVID-19 showed a higher incidence of small for gestational age (SGA) newborns compared with non-infected women (22.4% vs 14.8%), and SGA infants born to infected mothers had significantly increased risks of prematurity, stillbirth, neonatal death, and neonatal intensive care unit (NICU) admission. Similarly, placental dysfunction was strongly associated with clinically unanticipated stillbirths, with abnormal birthweight-to-placental-weight ratios identified in more than 70% of cases. Histopathological examination revealed maternal and fetal vascular malperfusion as important contributors to stillbirth.

Maternal thrombophilia and coagulation disorders were also associated with adverse pregnancy outcomes. Women with inherited thrombophilia had increased risks of preterm delivery, fetal growth restriction (FGR), recurrent pregnancy loss, and gestational hypertension. The use of low-molecular-weight heparin (LMWH) reduced adverse outcomes particularly among women with high-risk thrombophilia genotypes, including factor V Leiden carriers and antithrombin deficiency subtypes. Untreated women with antithrombin deficiency experienced significantly higher rates of preeclampsia and intrauterine fetal death.

Several obstetric complications were strongly associated with increased maternal and neonatal morbidity and mortality. Preterm placental abruption significantly increased risks of uterus-placenta apoplexy, fetal growth restriction, ICU admission, and stillbirth. Pregnancies complicated by fetal hemoglobin Bart's disease demonstrated extremely high rates of pregnancy-induced hypertension (83.8%) and mirror syndrome (49.3%), with substantially increased maternal morbidity and mortality. Advanced abdominal pregnancy was associated with severe maternal complications and neonatal morbidity; however, favorable outcomes were possible when early diagnosis and tertiary care management were available.

Studies assessing healthcare interventions demonstrated improved outcomes with specialized antenatal management. The Rainbow Clinic, a dedicated antenatal service for women with previous stillbirth, significantly reduced composite adverse perinatal outcomes and decreased rates of recurrent stillbirth and extreme preterm birth. Likewise, maternal risk stratification and planned delivery at 38–39 weeks gestation were associated with lower risks of severe maternal outcomes, neonatal neurologic morbidity, and perinatal mortality, especially among high-risk pregnancies.

Neonatal mortality and poor neonatal outcomes were also influenced by maternal nutritional and demographic factors. In rural populations, maternal undernutrition, low birth weight, pregnancy complications, intrapartum complications, and neonatal complications were significant predictors of neonatal mortality. A population-based predictive model for small vulnerable newborns identified multiple pregnancy, abnormal maternal BMI, maternal age extremes, hypertensive disorders, and placental disorders as major risk factors for preterm birth, low birth weight, and SGA.

Overall, the reviewed studies consistently demonstrated that high-risk maternal conditions, placental abnormalities, infectious diseases, thrombophilia, and obstetric complications substantially increased the risk of perinatal mortality and neonatal morbidity. Early risk identification, specialized antenatal care, individualized management, and timely obstetric intervention were repeatedly highlighted as key strategies to improve maternal and neonatal outcomes.

Table 1. Summary Of Articles Risk Factors And Complications Of Perinatal Mortality In High-Risk Pregnancies Systematic Review

No	Author(s)/ Year	Article	Location	Research Methods	Sampling	Number of Samples	Data Source	Quality Assessment (0-12 point)
1	(Raupp and Costa, 2025)	Incidence of small-for-gestational-age newborns in pregnant women with COVID-19	hospitals in Brazil	prospective cohort study conducted	Purposive sampling	15 maternity before the introduction of COVID-19 vaccination (February 2020 to February 2021)	Study data were collected and managed using REDCap®15 (Research Electronic Data Capture) tools hosted at CAISM/UNICAMP server, the coordinating center	12 (High Quality)
2	(Maglic <i>et al.</i> , 2025)	Impact of Inherited Thrombophilia on Pregnancy Complications and the Role of Low-Molecular-Weight Heparin Therapy: A Case-Control Study	at the University Clinic for Gynecology and Obstetrics “Narodni Front” in Belgrade, Serbia.	retrospective case-control study	Purposive sampling	552 participants, divided into two groups: 276 pregnant women diagnosed with inherited thrombophilia (IT) and with at least one prior pregnancy and 276 healthy pregnant women with at least one previous uncomplicated pregnancy and no known risk factors for IT, serving as the control group. The IT group was further subdivided into two cohorts: 108 patients who received low-molecular-weight heparin (LMWH) therapy from the first trimester until 14 days postpartum and 168 patients who did not receive LMWH during pregnancy.	selected based on the absence of personal or family history of thrombophilia or other established risk factors. This group was used exclusively for evaluating pregnancy outcomes such as gestational age at delivery, birth weight, Apgar scores, and mode of delivery in order to compare clinical outcomes between IT patients and a low-risk obstetric population.	11 (High Quality)
3	(Zhang <i>et al.</i> , 2025)	Preterm placental abruption and its association with adverse maternal and neonatal outcomes: a retrospective study	in the Maternal and Child Health Hospital of Hubei Province.	retrospective study	Purposive sampling	757 singleton pregnant women with confirmed PA who were classified into the preterm group (n = 300) and the full-term group (n = 457) based on their gestational age of PA onset, between June 2020 to March 2024.	All data were continuously collected from June 2020 to March 2024 in the Maternal and Child Health Hospital of Hubei Province.	12 (High Quality)
4	(Bremme, 2026)	Risk stratification according to genotype and effect of thromboprophylaxis on obstetric outcomes in women with antithrombin deficiency.	at Karolinska University Hospital	retrospective cohort study	Purposive sampling	43 women with AT deficiency with 106 (61 treated, 40 untreated, 5 unknown) pregnancies between 1990 and 2022	Data was gathered on maternal characteristics, heredity and history of VTE, thrombophilias, treatment during pregnancy, and maternal and neonatal outcome.	11 (High Quality)

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5	(Lens <i>et al.</i> , 2026)	Birthweight to placental weight ratio and placental pathology in clinically unanticipated stillbirths: a retrospective cohort study	e Amsterdam consensus	retrospective cohort study	Purposive sampling	placentas from 295 stillbirths at ≥24 weeks' gestation (2000–2017)	at a tertiary referral centre. Placental pathology reports were retrieved from a national registry and re-evaluated according	11 (High Quality)
6	(Hussein <i>et al.</i> , 2025)	Perinatal mortality rate and associated risk factors in Mogadishu, Somalia: A hospital-based cross-sectional study	two public hospitals in Mogadishu, Somalia: Benadir Hospital and Yardimeli Hospital	cross-sectional study with a seven-day prospective follow-up from January to April 2020	Purposive sampling	including 352 mother-newborn dyads from January to April 2020	conducted a hospital-based. Data on maternal demographics, antenatal care, delivery mode, and neonatal outcomes were collected via structured questionnaires and medical records.	12 (High Quality)
7	(Kriegs <i>et al.</i> , 2025)	Comparative analysis of maternal and neonatal outcomes in cases of vaginal breech births versus cases of vaginal cephalic births:	German Institute	retrospective cohort	Purposive sampling	2021 German population dataset compared 1435 VBBs to 422,019 VCBs. Maternal and neonatal short-term outcomes	Data were sourced from the German Institute for Quality Assurance and Transparency in Health Care (IQTIG), which, as part of the mandatory cross-institutional quality assurance program, collects predefined	11 (High Quality)

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		a retrospective cohort study					outcome measures from all births in hospitals in Germany, covering approximately 98.5% of all births and thus representing a near-complete survey.	
8	(Harries <i>et al.</i> , 2025)	Advanced abdominal pregnancy at a tertiary hospital in South Africa: a case series	Groote Schuur Hospital in Cape Town, South Africa.	case series retrospectively	Purposive sampling	17 extrauterine pregnancies at Groote Schuur Hospital in Cape Town, South Africa. Seventeen mothers and 18 babies were included in the analysis	Data analysis focused on maternal history, risk factors, delivery complications, intraoperative findings, and neonatal outcomes. Microsoft StatPlus was used for statistical calculations.	11 (High Quality)
9	(Bouma and Rooshesslink, 2026)	Pregnancy in women with vascular Ehlers-Danlos syndrome: a case series from the registry of pregnancy and cardiac disease (ROPAC) III	Registry of Pregnancy and Cardiac disease (ROPAC),	prospective case series reports	Purposive sampling	Six women with confirmed or suspected Vascular Ehlers-Danlos syndrome (vEDS) enrolled in the ROPAC III registry. Pregnancies were prospectively included until April 2023	ROPAC III registry initiated in 2007 by the ESC as a part of the EORP to study pregnant women with structural heart disease	12 (High Quality)

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10	(Wanapirak <i>et al.</i> , 2026)	Pregnancy induced hypertension and mirror syndrome associated with fetal hemoglobin Bart's disease in Thailand: a retrospective cohort study	obstetric database maintained by the Department of Obstetrics and Gynecology, Chiang Mai University.	retrospective cohort study	Purposive sampling	The consecutive singleton pregnancies with fetal Hb Bart's disease diagnosed at ≥ 24 weeks, considered as delayed diagnosis were recruited into the study group (between 1992 and 2022)	This database has systematically recorded information on pregnant women who delivered at the center from the time of discharge, beginning in 1992 and continuing to the present. All data were digitally entered by the maternal-fetal medicine team.	12 (High Quality)
11	(Mbbs <i>et al.</i> , 2026)	Maternal risk stratification and planned birth improve pregnancy outcomes at term: a population-based cohort study	Queensland, Australia.	retrospective cohort study	Purposive sampling	1,167,372 singleton births at $\geq 37+0$ weeks' gestation, conducted from 2000 to 2021	Queensland Perinatal Data Collection, 46 with ethics approval granted by the Metro North Hospital and Health Service Human Research Ethics Committee (Reference number: LNR/219/QRBC/53154). The Queensland Perinatal Data Collection 46 is a statutory population-based data set maintained by the Queensland Department of Health.	11 (High Quality)

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12	(Nurdin; and Ahmad, 2026)	Determinant of Neonatal Mortality in Rural Gorontalo: A Population-Based Case Control Study	Gorontalo	Case-control design	Purposive sampling	224 participants (56 neonatal deaths and 168 surviving controls) March and September 2023	Medical records and structured questionnaires.	12 (High Quality)
13	(Vance <i>et al.</i> , 2025)	Impact of a dedicated antenatal specialist service for women with a history of stillbirth: the rainbow clinic	the Rainbow Clinic at the Birmingham Women’s Hospital, United Kingdom.	retrospective case-control study	Purposive sampling	comparing women with a history of previous stillbirth prior to and following the inception Case records were reviewed from 2017 to August 2024.	Individual maternal and fetal outcome data were collected from case records.	12 (High Quality)
14	(Xiao, 2025)	Establishment and validation of a prediction model for small vulnerable newborns: a retrospective study	Shanghai, China,	Retrospective cohort study	Purposive sampling	129554 pregnant women who met inclusion criteria between January 2015 and December 2023 and divided them into training and validation cohorts.	Gini index to screen for potential risk factors.	12 (High Quality)

Tabel 2. Attributes of studies evaluating Risk Factors And Complications Of Perinatal Mortality In High-Risk Pregnancies

No	Author(s)/ Year	Title	Risk Factors And Complications	Perinatal Mortality	High-Risk Pregnancies	Results	Conclusion	Recommendation
1	(Raupp and Costa, 2025)	Incidence of small-for-gestational-age newborns in pregnant women with COVID-19 (REBRACO Network, Brazil)	Maternal COVID-19 infection; comparison between COVID-19 positive vs negative pregnant women	Increased neonatal adverse outcomes (prematurity, stillbirth, neonatal death, NICU admission) in SGA infants	Pregnant women with confirmed COVID-19 infection	Incidence of SGA: 22.4% in COVID-19 positive vs 14.8% in negative group. SGA newborns had higher risk of adverse outcomes [OR = 1.655; 95% CI 1.145–2.394; P=0.017]. Mechanical ventilation associated in SGA newborns [OR = 0.692; P=0.002].	COVID-19 infection in pregnancy is associated with higher incidence of SGA and increased neonatal morbidity and mortality, especially prematurity-related complications.	Not explicitly stated; suggests need for close monitoring of pregnant women with COVID-19
2		Impact of Inherited Thrombophilia on Pregnancy Complications and the Role of Low-Molecular-Weight Heparin Therapy	Inherited thrombophilia; prior pregnancy complications; comparison LMWH vs no LMWH; pregnancy complications include preterm rupture of membranes, oligohydramnios, FGR, preterm delivery, stillbirth, HELLP syndrome, gestational hypertension, DVT, recurrent pregnancy loss	Included complications affecting perinatal outcomes such as preterm delivery, stillbirth, recurrent pregnancy loss	Pregnant women with inherited thrombophilia (276 cases vs 276 controls)	Women with IT had higher age, higher BMI, earlier delivery, and lower birth weight infants. LMWH reduced preterm delivery, FGR, gestational hypertension, and recurrent pregnancy loss, especially in factor V Leiden carriers. No significant benefit in low-risk genotypes.	LMWH is beneficial mainly in high-risk thrombophilia cases, but not effective across all genotypes; routine use is not supported.	LMWH should be reserved for high-risk inherited thrombophilia; emphasize risk stratification, early screening, and individualized treatment
3	Zhang L, Yang H, Sun Y, Liu S (2020–2024)	Preterm placental abruption and its association with adverse maternal and neonatal outcomes	Placental abruption (preterm vs term onset); complications include fetal growth restriction, uterus-placenta apoplexy, ICU admission	Increased stillbirth risk in preterm PA (aOR 9.38, 95% CI 1.10–79.68, P<0.01)	Pregnancies with placental abruption (n=757; 300 preterm, 457 term)	Preterm PA increased risk of uterus-placenta apoplexy (aOR 2.93), FGR (aOR 3.47), ICU admission (aOR 3.28). Neonates had higher stillbirth risk and reduced forceps use	Preterm placental abruption is associated with significantly higher maternal and neonatal adverse outcomes, especially stillbirth and severe maternal morbidity.	Requires enhanced clinical surveillance, timely intervention, and further research on prevention and long-term outcomes

4	(Hussein <i>et al.</i> , 2025)	Perinatal mortality rate and associated risk factors in Mogadishu, Somalia: A hospital-based cross-sectional study	Maternal age, education level, mode of delivery (cesarean section), history of stillbirth	High perinatal mortality rate (PMR 173 per 1,000 births); stillbirths accounted for 82% of deaths	Pregnant women delivering at two referral hospitals in Mogadishu (n=358 deliveries)	Significant protective factors against perinatal mortality included maternal age 22–29 years (AOR 0.44), primary/secondary education (AOR 0.40), and cesarean delivery (AOR 0.33). Previous stillbirth was a risk factor in univariate analysis.	Perinatal mortality remains extremely high in Mogadishu, largely driven by stillbirths, with maternal education and access to obstetric care acting as protective factors.	Strengthening antenatal care, improving intrapartum services, and expanding access to emergency obstetric care are essential to reduce preventable perinatal deaths.
5	(Kriegs <i>et al.</i> , 2025)	Comparative analysis of maternal and neonatal outcomes in vaginal breech birth vs vaginal cephalic birth: a retrospective cohort study	Mode of delivery (vaginal breech birth vs vaginal cephalic birth); neonatal condition differences including APGAR score, arterial blood gases, need for resuscitation	No significant difference in perinatal mortality (up to 7 days postpartum) between VBB and VCB	Vaginal breech births (n=1435) vs vaginal cephalic births (n=422,019) in Germany	VBB showed lower APGAR scores and arterial blood gas levels, with higher need for resuscitation and neonatal transfer. Maternal outcomes showed higher labor augmentation and episiotomy rates, but lower perineal tears.	With proper risk stratification and expert management, perinatal mortality in vaginal breech birth is comparable to cephalic birth, though neonatal intervention needs are higher.	Requires adequate risk selection, interdisciplinary management, and preparedness for neonatal resuscitation in vaginal breech deliveries.
6	(Bremme, 2026)	Risk stratification according to genotype and effect of thromboprophylaxis on obstetric outcomes in women with antithrombin deficiency	Antithrombin deficiency (genotype-based risk stratification); thromboprophylaxis (treated vs untreated); obstetric complications including preeclampsia, intrauterine fetal death (IUFD), VTE	Increased intrauterine fetal death in untreated low-risk group (20%); no difference reported in overall perinatal mortality	Pregnant women with antithrombin deficiency (n=43; 106 pregnancies)	In low-risk genotype group, untreated women had higher preeclampsia (24%) and IUFD (20%) compared to treated women (0% for both; p=0.005 and p=0.014). No significant differences in VTE or complications between high- and low-risk groups overall.	Untreated women with certain antithrombin deficiency subtypes (especially IIHBS) have high risk of adverse pregnancy outcomes; thromboprophylaxis may be beneficial regardless of VTE risk.	Thromboprophylaxis should be considered based on genotype-specific risk stratification, not only VTE risk.
7	(Harries <i>et al.</i> , 2025)	Advanced abdominal pregnancy at a tertiary hospital in South Africa: a case serie	Advanced abdominal pregnancy (extrauterine implantation >20 weeks); missed diagnosis on ultrasound; complex placental implantation sites; surgical delivery via laparotomy	Neonatal death rate included 2 deaths (1 early, 1 late); maternal mortality 2 cases	Advanced abdominal pregnancy cases (n=17 pregnancies; 18 neonates)	82.4% missed diagnosis initially. 94.1% delivered within 48 hours after diagnosis. 66.7% live births. Median Apgar 5 (1 min) and 7 (5 min). Median birth weight 1313 g. All cases had maternal complications.	Advanced abdominal pregnancy is a rare high-risk condition with significant maternal and neonatal morbidity, but outcomes can be favorable in well-resourced tertiary centers with early detection and management.	Early detection and referral to tertiary care facilities are essential to improve maternal and neonatal outcomes in advanced abdominal pregnancy.

8	(Lens <i>et al.</i> , 2026)	Birthweight to placental weight ratio and placental pathology in clinically unanticipated stillbirths: a retrospective cohort study	Placental dysfunction (abnormal birthweight-to-placental-weight ratio, maternal and fetal vascular malperfusion); classification of stillbirth causes	All cases were stillbirths ≥ 24 weeks (n=295); 43.7% clinically unanticipated stillbirths	Stillbirth cases at ≥ 24 weeks gestation in a tertiary referral center (n=295)	Abnormal BWPW ratios occurred in 71.3% of clinically unanticipated stillbirths, similar to placental cause stillbirths (70.6%). Fetal vascular malperfusion was more frequent in unanticipated stillbirths (16.9% vs 5.7%).	Clinically unanticipated stillbirths are strongly associated with underlying placental dysfunction, often comparable to known placental causes, indicating underdiagnosis during pregnancy.	Routine placental examination (macroscopic and histopathological) is recommended to improve diagnosis and future pregnancy risk assessment.
9	(Bouma and Roos-hesselink, 2026)	Pregnancy in women with vascular Ehlers-Danlos syndrome: a case series from the registry of pregnancy and cardiac disease (ROPAC) III	Vascular Ehlers-Danlos syndrome (vEDS); pregnancy-related complications including preterm birth, hemorrhage, cesarean delivery	One fetal death reported; no maternal deaths	Pregnant women with confirmed or suspected vEDS (n=6)	No maternal deaths or aortic dissections occurred. Obstetric complications (preterm birth, hemorrhage) were frequent. Most deliveries were cesarean. No significant aortic enlargement during pregnancy.	Pregnancy in women with vEDS may have better outcomes than previously assumed when carefully managed, with no life-threatening vascular events observed in this small cohort.	Supports individualized counseling, careful monitoring, and further prospective research in vEDS pregnancies.
10	(Wanapirak <i>et al.</i> , 2026)	Pregnancy induced hypertension and mirror syndrome associated with fetal hemoglobin Bart's disease in Thailand: a retrospective cohort study	Fetal hemoglobin Bart's disease; pregnancy-induced hypertension (gestational hypertension, preeclampsia); mirror syndrome; severe maternal complications	High maternal mortality reported (2.8%); severe adverse pregnancy outcomes associated with condition	Pregnancies complicated by fetal Hb Bart's disease (n=142) vs controls (n=2840)	PIH incidence 83.8% (RR 11.33). Mirror syndrome markedly higher (49.3% vs 0.1%, RR 700). Earlier onset and more severe hypertension in affected group. Increased maternal morbidity and mortality.	Hb Bart's disease is strongly associated with severe PIH, mirror syndrome, and increased maternal morbidity and mortality.	Requires early detection, close monitoring, and high-risk obstetric management to reduce severe outcomes.
11	(Mbbs <i>et al.</i> , 2026)	Maternal risk stratification and planned birth improve pregnancy outcomes at term: a population-based cohort study	Maternal risk stratification (low, intermediate, high risk); pregnancy complications including severe maternal outcomes, neonatal neurologic morbidity, maternal-infant separation	Included perinatal mortality (antepartum stillbirth, intrapartum stillbirth, neonatal death); risk increased with higher maternal risk category	Singleton pregnancies ≥ 37 weeks (n=1,167,372); stratified into low, intermediate, and high-risk groups	High-risk group had highest odds of severe maternal and perinatal outcomes, including perinatal mortality. Planned birth at 38–39+6 weeks was associated with lowest odds of adverse outcomes, especially in high-risk pregnancies.	Maternal risk stratification is strongly associated with perinatal outcomes, and planned birth at 38–39+6 weeks may reduce adverse outcomes, particularly in high-risk women.	Supports individualized antenatal risk stratification and consideration of planned delivery at 38–39+6 weeks to optimize outcomes.
12	(Rohmah, Fitriyati and Ido, no date)	Determinant of Neonatal Mortality in Rural Gorontalo:	Maternal undernutrition, low birth weight, pregnancy complications,	Neonatal mortality (56 deaths vs 168 controls); high	Rural pregnant women and neonates (n=224)	Significant risk factors for neonatal mortality: undernutrition (AOR 3.54), low birth weight (AOR 6.77),	Neonatal mortality is strongly influenced by maternal nutritional status and pregnancy-	Improve maternal nutrition, strengthen early detection of complications, and

		A Population-Based Case Control Study	intrapartum complications, neonatal complications	mortality risk associated with multiple maternal/neonatal factors		pregnancy complications (AOR 8.04), intrapartum complications (AOR 7.39), neonatal complications (AOR 9.17). ANC attendance and socioeconomic factors were not significant.	related complications.	enhance neonatal care to reduce mortality.
13	(Vance <i>et al.</i> , 2025)	Impact of a dedicated antenatal specialist service for women with a history of stillbirth: the rainbow clinic	Previous stillbirth; risk of recurrent stillbirth and adverse perinatal outcomes; specialist antenatal care intervention	Composite adverse perinatal outcomes included perinatal mortality, NICU admission, neonatal sepsis, respiratory distress syndrome, HIE, and others	Women with previous stillbirth receiving specialist antenatal care (Rainbow Clinic) vs standard care	Composite adverse perinatal outcomes were significantly lower in the Rainbow Clinic group (OR 0.46; 95% CI 0.22–0.98). Aspirin use was higher (91% vs 70%). Gestational age at delivery was longer, with reduced very/extreme preterm births. Further stillbirth or miscarriage reduced from 8% to 2%.	Specialist antenatal services for women with previous stillbirth improve maternal-fetal outcomes and reduce adverse perinatal complications.	Dedicated pregnancy-after-loss clinics should be considered to improve outcomes in women with prior stillbirth; further evaluation of these specialist services is recommended.
14	(Xiao, 2025)	Establishment and validation of a prediction model for small vulnerable newborns: a retrospective study	Multiple pregnancy, abnormal pre-pregnancy BMI (<18.5 or ≥25), maternal age (<25 or ≥35), hypertensive disorders of pregnancy, placental disorders, assisted reproductive technology, infections (mycoplasma/chlamydia), elevated bile acids	Composite adverse perinatal outcomes included perinatal mortality, NICU admission, neonatal sepsis, respiratory distress syndrome, HIE, and others	Women with previous stillbirth receiving specialist antenatal care (Rainbow Clinic) vs standard care	Composite adverse perinatal outcomes were significantly lower in the Rainbow Clinic group (OR 0.46; 95% CI 0.22–0.98). Aspirin use was higher (91% vs 70%). Gestational age at delivery was longer, with reduced very/extreme preterm births. Further stillbirth or miscarriage reduced from 8% to 2%.	Specialist antenatal services for women with previous stillbirth improve maternal-fetal outcomes and reduce adverse perinatal complications.	Dedicated pregnancy-after-loss clinics should be considered to improve outcomes in women with prior stillbirth; further evaluation of these specialist services is recommended.

4. DISCUSSION

The findings from the reviewed studies demonstrate that perinatal mortality and adverse neonatal outcomes are multifactorial conditions influenced by maternal diseases, placental dysfunction, infectious conditions, obstetric complications, and healthcare access. Across the reviewed literature, high-risk pregnancies consistently showed significantly increased risks of stillbirth, neonatal death, prematurity, fetal growth restriction (FGR), and neonatal intensive care unit (NICU) admission.

Maternal infectious diseases were shown to contribute substantially to adverse neonatal outcomes. Raupp et al. found that pregnant women with confirmed COVID-19 infection had a higher incidence of small for gestational age (SGA) newborns compared with noninfected women, and these newborns experienced higher rates of prematurity, stillbirth, neonatal death, and NICU admission (Raupp et al., 2020–2021). These findings support previous evidence suggesting that maternal viral infection can impair placental perfusion and fetal growth, ultimately increasing neonatal morbidity and mortality. COVID-19-related inflammation and vascular dysfunction may explain the increased frequency of placental insufficiency and adverse fetal outcomes observed in infected pregnancies.

Placental pathology also emerged as one of the strongest contributors to stillbirth and neonatal complications. Lens et al. demonstrated that clinically unanticipated stillbirths had placental abnormalities comparable to stillbirths directly attributed to placental causes, with abnormal birthweight-to-placental-weight (BWPW) ratios and vascular malperfusion highly prevalent among these cases (Lens et al., 2000–2017). Similarly, Zhang et al. reported that preterm placental abruption significantly increased risks of fetal growth restriction, ICU admission, and stillbirth (Zhang et al., 2020–2024). These findings reinforce the importance of placental health in maintaining fetal well-being and suggest that earlier detection of placental insufficiency could potentially reduce preventable stillbirths.

Several studies highlighted the important role of maternal thrombophilia in adverse pregnancy outcomes. Maglić et al. reported that inherited thrombophilia increased risks of preterm birth, fetal growth restriction, recurrent pregnancy loss, and gestational hypertension (Maglić et al., 2020–2024). Likewise, Diemer et al. demonstrated that untreated women with antithrombin deficiency experienced significantly higher rates of preeclampsia and intrauterine fetal death, while thromboprophylaxis reduced these complications (Diemer et al., 1990–2022). These findings suggest that thrombophilia-associated placental thrombosis and impaired uteroplacental circulation contribute significantly to fetal compromise. However, both studies emphasized that routine prophylaxis for all thrombophilia cases may not be justified and that individualized risk stratification remains essential.

Hypertensive disorders during pregnancy were another major determinant of poor outcomes. Wanapirak et al. demonstrated that pregnancies complicated by fetal hemoglobin Bart's disease had markedly elevated rates of pregnancy-induced hypertension (PIH) and mirror syndrome, with severe maternal morbidity and mortality (Wanapirak et al., 1992–2022). The study reported a relative risk of 700 for mirror syndrome compared with controls, indicating the extreme severity of this condition. Hypertensive disorders are known to impair placental perfusion and increase risks of fetal hypoxia, growth restriction, and stillbirth, which explains the severe outcomes observed in affected pregnancies.

Maternal nutritional and demographic factors were also associated with neonatal mortality. Rohmah et al. identified maternal undernutrition, low birth weight, pregnancy complications, intrapartum complications, and neonatal complications as significant predictors of neonatal death in rural settings (Rohmah et al., 2024). Additionally, Xiao et al. reported that abnormal maternal body mass index (BMI), maternal age extremes, multiple pregnancy, hypertensive disorders, and placental abnormalities were strong predictors of small vulnerable newborns, including preterm birth, low birth weight, and SGA (Xiao et al., 2015–2023). These

findings indicate that maternal nutritional optimization and monitoring of high-risk maternal characteristics are essential components of perinatal mortality prevention strategies.

The reviewed studies also demonstrated the positive impact of specialized antenatal care services. Le Vance et al. found that women managed through the Rainbow Clinic, a dedicated pregnancy-after-loss service, had significantly lower composite adverse perinatal outcomes compared with standard care (Le Vance et al., 2017–2024). Similarly, Wong et al. showed that maternal risk stratification and planned birth at 38–39 weeks gestation were associated with lower rates of severe maternal outcomes, neonatal neurologic morbidity, and perinatal mortality, especially in high-risk pregnancies (Wong et al., 2000–2021). These findings support the importance of individualized antenatal surveillance and multidisciplinary management in improving maternal and neonatal outcomes.

Rare but severe obstetric conditions also contributed substantially to maternal and neonatal morbidity. Harries et al. reported that advanced abdominal pregnancy carried high maternal complication rates and neonatal morbidity; however, outcomes improved considerably when cases were managed in tertiary care hospitals with adequate resources (Harries et al., 2024). Likewise, Kriegs et al. demonstrated that vaginal breech birth could achieve comparable perinatal mortality rates to cephalic birth when strict risk stratification and expert interdisciplinary management were implemented (Kriegs et al., 2021). Furthermore, Peters et al. found that pregnancies in women with vascular Ehlers-Danlos syndrome could have relatively favorable outcomes under close monitoring despite the traditionally high-risk classification of the condition (Peters et al., 2024). These findings underscore the importance of healthcare infrastructure, specialist expertise, and timely intervention in reducing mortality associated with complex pregnancies.

In low-resource settings, healthcare access and quality remained important determinants of perinatal mortality. Hussein et al. reported an extremely high perinatal mortality rate in Mogadishu, Somalia, with stillbirths accounting for most deaths, while maternal education and cesarean delivery were identified as protective factors (Hussein et al., 2020). This finding highlights the continuing disparities in maternal and neonatal healthcare between resource-limited and high-income settings.

Overall, the reviewed studies consistently indicate that adverse neonatal outcomes and perinatal mortality are closely linked to maternal health status, placental pathology, hypertensive disorders, thrombophilia, infectious diseases, and healthcare quality. Early identification of high-risk pregnancies through risk stratification, specialized antenatal care, placental monitoring, and individualized obstetric management are essential strategies to reduce preventable maternal and neonatal morbidity and mortality.

5. CONCLUSION

Based on the reviewed studies, perinatal mortality and adverse neonatal outcomes are strongly associated with multiple maternal, placental, and obstetric factors. Maternal conditions such as COVID-19 infection, inherited thrombophilia, hypertensive disorders, undernutrition, abnormal body mass index, and advanced maternal age significantly increased the risk of preterm birth, fetal growth restriction, low birth weight, stillbirth, and neonatal death. Placental dysfunction, including placental abruption and vascular malperfusion, also played a major role in clinically unanticipated stillbirths and poor neonatal outcomes. High-risk pregnancies consistently demonstrated higher rates of maternal morbidity, neonatal complications, NICU admission, and perinatal mortality. However, several studies showed that early identification of risk factors, individualized antenatal surveillance, thromboprophylaxis in selected patients, specialist antenatal services, and planned delivery at optimal gestational age could significantly improve maternal and neonatal outcomes. Specialized pregnancy care services, such as dedicated clinics for women with previous stillbirth and comprehensive maternal risk

stratification, were associated with reductions in adverse perinatal outcomes and recurrent pregnancy loss. In addition, tertiary-level management and multidisciplinary care improved outcomes in rare but severe obstetric conditions such as advanced abdominal pregnancy and vascular Ehlers-Danlos syndrome. Overall, the evidence emphasizes the importance of strengthening antenatal care, improving early detection of maternal and placental complications, implementing individualized risk-based management, and ensuring access to high-quality obstetric and neonatal services. These strategies are essential to reduce preventable perinatal mortality and improve neonatal survival and long-term outcomes.

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