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**Review Article**

# Prevalence, Aetiology and Underlying Mechanism of Stillbirth: A Review

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**Abstract**

**Introduction:** Stillbirth is a global issue. The major factors linked to stillbirth include maternal age, parity (number of prior pregnancies), ethnicity, and pre-existing medical conditions such as diabetes or hypertension. Substance abuse like smoking, drug and alcohol consumption are strongly associated with low birth weight and/or stillbirth. Other factors like demographic profile and genetic variations, multiple gestation, nutritional deficiencies, and access to prenatal care and prior unfavourable pregnancy outcomes may also be associated to stillbirth.

**Methods:** We utilized several digital resources like, PubMed, World Health Organization (WHO) and United Nations (UN) databases to prepare this review article.

**Results:** Approximately one out of every 72 babies worldwide pass away before delivery, leading to almost 3 million stillbirths annually. Demographic factors that have a significant impact on stillbirth-rates include poverty, low socioeconomic status and limited access to necessary medical interventions. Some aetiology and mechanistic layouts associated with stillbirth events including the physiological, biochemical and molecular processes have been extensively reviewed in this article.

**Conclusion:** Conclusively, early record of stillbirth, hypertension, and multiple gestations were important determinants for stillbirth. Maternal age, BMI and several biochemical markers (PAPP-A, PIGF), other maternal factors like stress, haematological profile, and foetal factors like shorter gestation period and intra-uterine growth retardation may attribute to large number of stillbirth cases. Several preventive measures to avoid the above-mentioned factors could be beneficial to minimize stillbirth incidence.

**Keywords:** Stillbirth, Low birth weight, Aetiology of genetic and biological factors, Global issue

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## Introduction

Stillbirth is one of the worst outcomes of pregnancy.[1]A baby born dead at 28 weeks or more of pregnancy and weighing at least 1000 g or measuring at least 35 cm in length is considered a stillbirth, according to the World Health Organization (WHO).[2] The International Classification of Diseases (ICD) defines a stillbirth as a baby born at least 22 weeks of gestation or with no signs of life and a birthweight of at least 500g.[3] In some cases, assisted reproductive technology might also result in stillbirth. Mothers who are nulliparous, members of ethnic minority groups, from socioeconomically disadvantaged, and obese may result low birth weight and stillbirth. Moreover, delayed or absence of prenatal care is known risk factors for stillbirth.

Instead of using the WHO's 28-week standard, the majority of research presenting these risks describe stillbirth as occurring after 20 weeks of gestation.[4] Stillbirth may occur intrapartum or antepartum. Macerated or intra-uterine stillbirths, often referred to as antepartum stillbirths, happen when the infant passes away in the womb before labour begins, typically more than 12 hours before delivery. If the infant passes away after labour begins, typically less than 12 hours before delivery, this is known as an intrapartum stillbirth, or fresh stillbirth.[5] A significant public health concern is stillbirth, which is thought to cause 2.6 million fatalities globally each year, with 98% of those deaths taking place in low- and middle-income (LMIC) nations.

Compared to high-income nations, many LMIC have stillbirth rates of above 30 per 1,000 births, which is at least three times higher.[6]The WHO recommends that all stillbirths be counted, however caution should be used when comparing teens with birth weights of 1000g or gestational ages of 28 weeks to other nations to prevent selection of biased data.[3] In the current review the prevalence and the major mechanistic factors of stillbirth have been focused .The rationale of the current review is to screen the major confounding factors of stillbirth and epidemiological mapping of its prevalence. That would help to lower its occurrence and create a focused interventions enhancing perinatal care, and comprehending risk factors. It will also help to direct clinical care in future pregnancies and provide improved assistance. Determining the aetiology of a stillbirth might help doctors pinpoint the specific factors that contributed to the death. If a genetic problem is discovered, prenatal testing and genetic counselling can be offered for future pregnancies.

The purpose of this study is to determine the factors associated with stillbirth in mothers from different income nations. We assessed the environmental and physiological factors that potentially impact a pregnant woman .The main aim of determining the cause of stillbirth is to uncover underlying variables, such as maternal, placental, and foetal disorders, in order to create and execute measures for preventing stillbirths.

## Methods

We have collected relevant data from different databases like PubMed, Google Scholar, World Health Organization (WHO) and United Nations (UN). We have procured date from the year 2009 to 2024. Inclusion criteria: If a baby born dead at 28 weeks or later in pregnancy. If the weight of the dead baby is at least 1000g and if the baby is at least 35 cm. long. Except to the above-mentioned criteria all other criteria were considered as exclusion criteria.

## Results

### *Epidemiology and global burden of stillbirth*

Approximately one out of every 72 babies worldwide pass away before delivery, leading to almost 3 million stillbirths annually. Even so, the stillbirth rate has only decreased by 2.3% annually over the last 20 years, which is less than the 2.9 percent annual decrease in neonatal mortality, the 4.3 percent annual decrease in child mortality for children aged 1 to 59 months, and the 2.9 percent annual decrease in maternal mortality.[7] The Inter Agency Group estimates that India had the largest number of stillbirths in 2019—340,600—with a stillbirth rate of 13.9 per 1000 births (Figure 1).

However, 2020 research claims that there are three stillbirths per 1,000 people in India, which is 4.6 times fewer than the previous estimate.[8] Stillbirth is an equality and equity concern because 98% of stillbirths occur in lower middle-income countries (LMICs), and the rates are highest in vulnerable populations.[9] The epidemiological study indicated with almost 2.6 million deaths each year, predominantly in low- and middle-income nations, and 60% occurring in rural areas. Stillbirths are a worldwide tragedy that is frequently disregarded.[10] Stillbirths, which account for 98% of instances globally, are frequently referred to as the "silent epidemic" in low-income nations. This illustrates how urgently these areas require improved maternal healthcare and assistance.[11] A concentration of cases in particular regions is shown by the fact that more than one-third of these happened in South East Asian and African countries. Other instances are also not rare in different parts of the globe.[12]

There are large numbers of issues and factors related to stillbirth (fig. 2). Major factors are explained here.

### *Factors associated with stillbirth*

*Maternal Factors:* These include high blood pressure, anemia, maternal stress and age. In case of high blood pressure PUFA, DHA and Omega-3 fatty acid levels in the blood may be elevated to protect against pregnancy-induced hypertension (PIH) and with a higher ratio of Omega-6 to Omega-3 fatty acids, the risk of PIH may increase.[11]Placental issues, obstetric compatibility to childhood development disorders lications (preterm labor, cervical incompetence), genetic issues, fetoplacental have also been important in this regard. Maternal infections (acute or chronic), medical conditions (diabetics, anti-phospholipid syndrome), hypersensitive disorders, abnormalities of the cord, and other conditions (hydrops, early amnion rupture), higher body mass index and black race are also considered as important factors.[13],[14]Intra-hepatic cholestasis of pregnancy (ICP)-related deliveries are also responsible for stillbirth.[15] Ante partum hemorrhage (in pregnant women who have a four-year or longer birth gap) and pregnant women with asthma may cause stillbirth.[4,16]

Foetal or Neonatal thrombocytopenia can be considered as a strong factor for stillbirth. Foetal platelets are

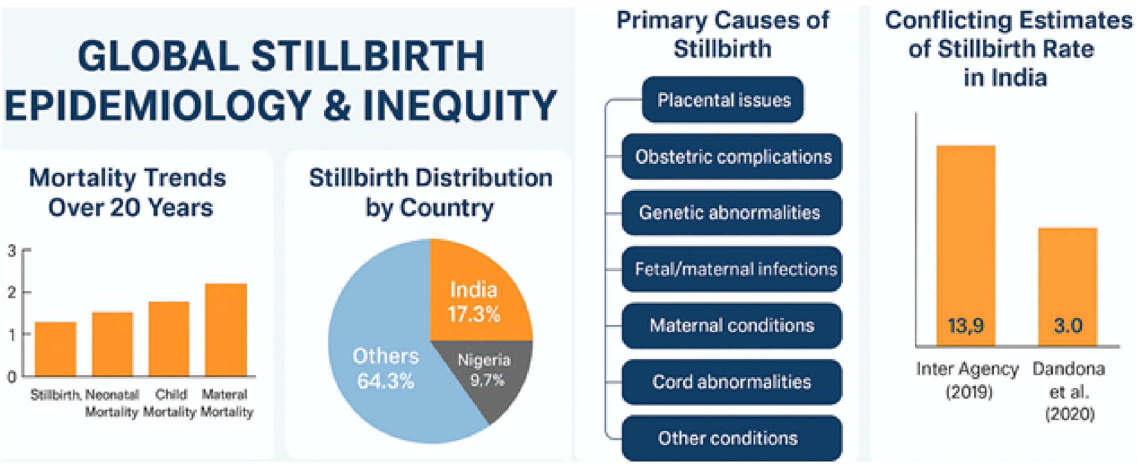


**Figure 1** Global stillbirth epidemiology and its major causes

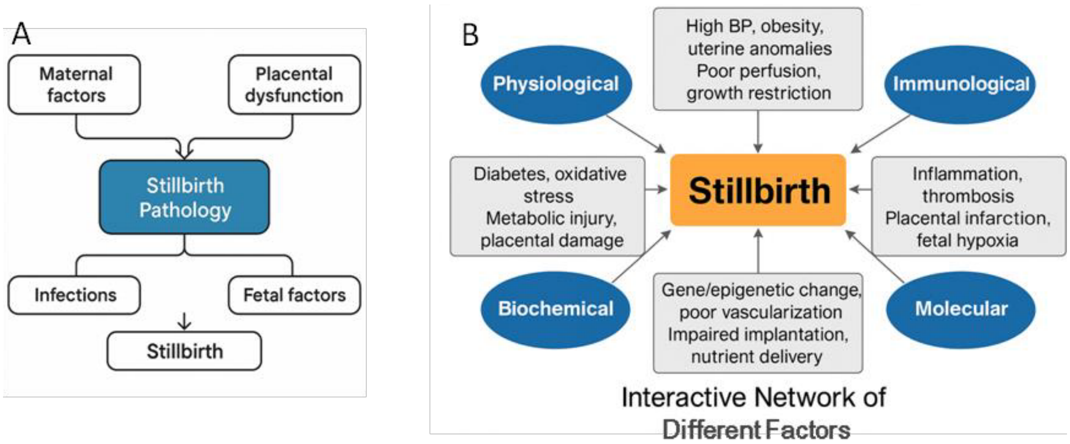


**Figure 2** Different causes of maternal, fetal and placental contribution and their interactive roles in stillbirth events

damaged by maternal antibodies in neonatal alloimmune thrombocytopenia (NAIT). This is a fatal immunological disorder that actually causes thrombocytopenia. Additionally, it poses a significant risk to the foetus and may result in birth defects, irreversible harm to the cranial nerves and result in neonatal death.[17,18] Non-cephalic fetal presentation increases the risk of stillbirth. Separately, stillbirth was associated with breech, complex, and shoulder presentations.[19] All these factors are potential threat for stillbirth and several of those can be prevented in advanced clinical treatments and proper scientific management.

*Socio-demographic Factors:* Age, place of residence (rural or urban) are some factors which can be responsible for stillbirth.[10]Divorced, widowed and single women are more likely to deliver stillbirth. Additionally, women who live alone are more likely to feel depressed and have fewer social support system, which can raise the chance of stillbirth.[20] It has been discovered that teenage moms (over 20) are more likely to experience stillbirth than mothers in other age groups (Table 1). Young moms are susceptible to a variety of health hazards that stem from both their illnesses and societal influences. These factors may include illiteracy, and poor health-seeking behaviors.[5]

*Environmental Factors*: Toxicity due to environmental factors are going to an increasing order that caused maternal exposure and several disorders. Even early age exposure at young ages, might have residual effects in adult women causing abnormal pregnancy. Most of the time that may affect different signaling process at cellular and transcription level. Consequently, neonatal development and growth are impaired. As for example, serotonin transporter gene (SLC 64A) and other stress-related genes may have altered DNA methylation in pregnant women exposed to PM 2.5 (fine airborne particles with a diameter of 2.5 micrometers or less) pollution and maternal stress.[21]Early exposure to Pb during pregnancy is associated with an increased risk of Childhood Development Disorders (CDD) if the unborn child has a high genetic vulnerability to CDD.[22]

### *Mechanism underlying the event of stillbirth*

There are different mechanistic pathways for different factors causing stillbirth. Maternal hypertensive disorders have been linked to high risk of stillbirth. Recent report suggests that pregnancy-induced hypertension (PIH) risk may rise with a larger ratio of omega-6 to omega-3 fatty acids and that can be protected by specific fatty acids (PUFA, DHA, and Omega-3).[11] Their lower ratio is associated with the higher risk. Maternal anemia can also cause stillbirth due to several reason e.g. hypoxia, oxidative stress etc. which frequently generate free radicals. Eventually, free radicals can trigger eryptosis, which can change cell integrity and cause anemia. Through processes like Fenton and Haber-Weiss reactions, newborn RBC produces free radicals and become targets of those highly reactive substances. This event feeds an oxidative stress loop.[23]Oxidative stress can develop inflammatory components. In this regard, maternal stress is the potential cause for increasing pro-inflammatory cytokines. It might cause dysregulated metabolic processes, and an increased risk of chronic diseases in the infant.[24] The gut and human milk microbiome are important components of the microbiome-gut-brain axis, a mechanism for transferring stress from mother to infant. Maternal microbial choline metabolism may influence the offspring's long-term health and development by influencing epigenetics during pregnancy. Because choline forms cell membranes and serves as a precursor to the neurotransmitter acetylcholine, choline is essential for the development of the brain and spinal cord in a developing fetus.[25] Pregnancy-related vitamin D (VD) levels decline throughout tenure as a result of fetal needs. Preventing pre-eclampsia, gestational diabetes, low birth weight and low bone mass in the fetus, as well as an increased risk of bronchiolitis, asthma, multiple sclerosis, and autism.[26,27] A high-fat diet (HFD) during pregnancy causes inflammation and decreases blood flow to the placenta, which results in placental malfunction. It deteriorates placental function when coupled with obesity, which lowers fetal blood flow and may result in stillbirth.[28]

**Table 1.** Causal factors and underlying mechanism of stillbirth

| Chronic Stress Exposure | Related causes |
|---|---|
| High blood pressure/Hypertension | I Blood PUFA levels, Omega-6 and Omega-3 fatty acids |
| Anemia | Eryptosis, cellular self- destruction by oxidative stress. |
| Thrombocytopenia | Neonatal alloimmune thrombocytopenia (NAIT). |
| Maternal Stress and Physiological stress | The maternal microbiota (gut and milk)and fetal relationship.<br>Pregnancy-related mal regulation of vitamin D<br>Maternal high fat dies (HFD) during pregnancy. |
| Environmental stress | Maternal exposure to per- and polyfluoroalkyl substances (PFAS),DNA methylation due to lead exposure. |
| Effect of microbial choline metabolism | Maternal microbiota and choline metabolic disorder. |
| Maternal age(>35yearsofage) | Higher maternal age is related to fetal several metabolic disorder. |

Some reports reveal the association of few health-disorders with risk of stillbirth.

There are plenty reports on maternal environmental stress. Maternal age has been long time regarded as a determining factor for fetus health. Higher (≥35 years) age is associated with increased 13% of the metabolic indicators in the newborn. As for example higher age is linked with higher levels of malonylcarnitine (C3DC), that exerts detrimental effects on fetal growth.[29] Maternal exposure to per- and polyfluoroalkyl substances (PFAS) can reduce prenatal brain development and a higher likelihood of sleep problems in newborns.[30]Neonatal alloimmune thrombocytopenia (NAIT) is a serious immune condition in which fetal platelets are destroyed by maternal antibodies, resulting in thrombocytopenia. It cause serious problems, such as cerebral bleeding in the newborn, irreparable damage to the cranial nerves, and neonatal mortality.[17,18]

### *Some important factors in under-privileged communities*

Numerous important factors that contribute to stillbirths are identified by research conductedin low- and middle-income nations. Maternal infections, low access to obstetric care, insufficient healthcare services, and problems such as ante-partum hemorrhage, pregnancy-related hypertension, inadequate labor and delivery care, fetal growth restriction, and congenital abnormalities are major determinants (Figure 3). A medical history of diabetes, chronic hypertension, and prior stillbirths are additional risk factors for stillbirth (Figure 3).

### *Probabilistic prediction and prevention of stillbirth*

Probabilistic prediction means estimating the likelihood of an event happening, rather than giving a single “yes” or “no” answer. Output is a probability – usually within a range of numerical values (or 0% and 100%). These are categorized in some points. Accounts for uncertainty – reflects the model’s confidence level, uses statistical or machine learning models – like logistic regression, Bayesian networks, or random forests, Inputs are risk factors or predictors – e.g., age, gender, lab results, comorbidities. It can produce probability distributions – not just a single point estimate, showing the full range of possible outcomes. Here in Figure 4 we demonstrate the risk of possible outcome of stillbirth by three different approaches. These highlight major intervening factors as high risk for stillbirth. Amongst those, early record of stillbirth, hypertension, and multiple gestations are important. Maternal age, BMI and several biochemical markers are found to be important.

Biochemical markers are associated to some risk factors which are ubiquitous. In that sense, climate change, global warming and heat wave is universal risk factor. Compared to birth weight, heat appears to be more strongly and consistently linked to stillbirth and premature birth. Higher temperatures were associated with stillbirths in male fetuses. So, it can be included as a potential factor for the assessment of the probabilistic risk calculation, which is mentioned in the previous section. Increased ambient temperatures may increase the risk of newborn sepsis by encouraging the establishment of Group B streptococcus colonization in the cervix and vagina of pregnant women.[31]Compared to women born in resettlement countries, pregnant women from African refugee backgrounds are reportedly more likely to have unfavorable pregnancy outcomes.[32] Sub-Saharan African women experienced higher rates of mortality and stillbirth than other migrants. Special information and instructions may be needed for specific groups of migrants, such as those who have undergone infibulations (traditional female genital cutting/female genital mutilation), are terrified of cesarean sections, or restrict their diet during pregnancy in order to avoid large fetuses.[33]Stillbirth can be predicted early using maternal, foetal, and biochemical factors. Three main scoring systems aid in prediction: (1) Clinical risk scoring systems (normalized), (2) Machine learning/predictive modelling (advanced), and (3) Integrated scoring systems. These are detailed in Figure 4.

## Discussion

Even with better prenatal and postpartum care, stillbirth is still a common and underreported obstetric complication that accounts for almost half of perinatal mortality rates today.[34] Preventing pregnancy complications from major obstetrical syndromes, such as pre-eclampsia, foetal growth restriction, preterm labour, and stillbirth, should

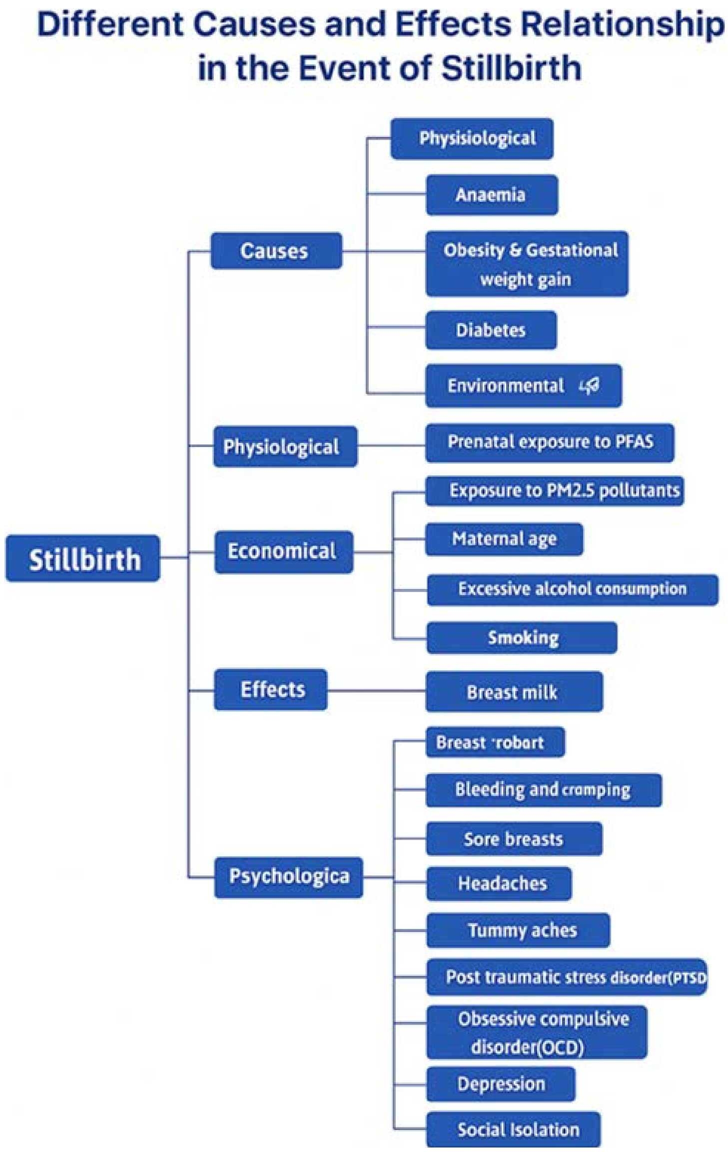


**Figure 3.** Detailed causes of and effects relationship in different categories

be the focus of worldwide research and clinical interest.[35] By spotting symptoms like foetal hypoxemia and acidosis, antenatal foetal surveillance can reduce the chance of stillbirth linked to high-risk pregnancies (Table 1). These include the foetal heart rate characteristics, amniotic fluid content, contraction stress, non-stress, and biophysical profile tests, as well as the mother's assessment of the foetal movements.[36] Maternal, biophysical, and biochemical markers are used to correct new preeclampsia screening markers during weeks 11–14 of pregnancy. However, there is a widespread belief that additional prenatal care, such as several ultrasounds, is provided, but that parents' psychological needs are typically not sufficiently taken into account (Figure 5). Despite having underlying mental health conditions like depression, anxiety, PTSD, and relationship issues that make future pregnancies more difficult, just 10% of parents seek bereavement therapy.

Therefore, both parents and preventive and psychological care should be involved in future pregnancies.[37] Because it allows for prompt intervention in high-risk scenarios, the widespread use of cardiotocography (CTG) during delivery, together with the capability of performing caesarean sections for non-reassuring foetal heart tones, has been instrumental in lowering stillbirth rates in industrialized nations.[38] Key interventions include regular educational sessions at prenatal care (ANC) to raise awareness and thorough evaluations and follow-up for moms with pregnancy-related issues. Additionally, partograph use during labour is essential for early problem detection, which lowers the risk of avoidable stillbirth.[39]Provision to provide accurate information on family care and is helpful in developing health care preventative strategies. As a result, pathologists and healthcare professionals still need to accurately identify the causes of stillbirth.[40] According to research, stillbirths can be avoided and controlled by managing risk factors and providing appropriate care during the preconception, antepartum, and intrapartum phases (Figure 4).

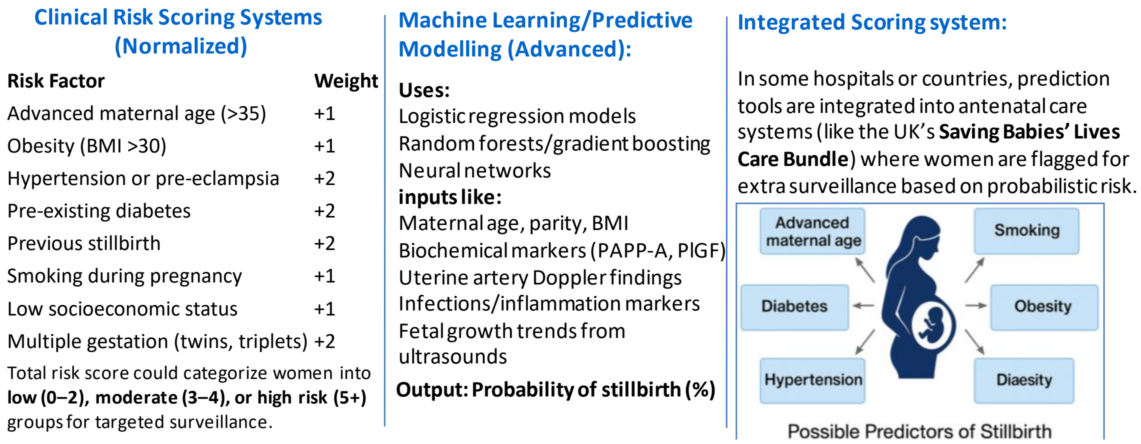


**Figure 4** Probabilistic prediction value/score of possible stillbirth event

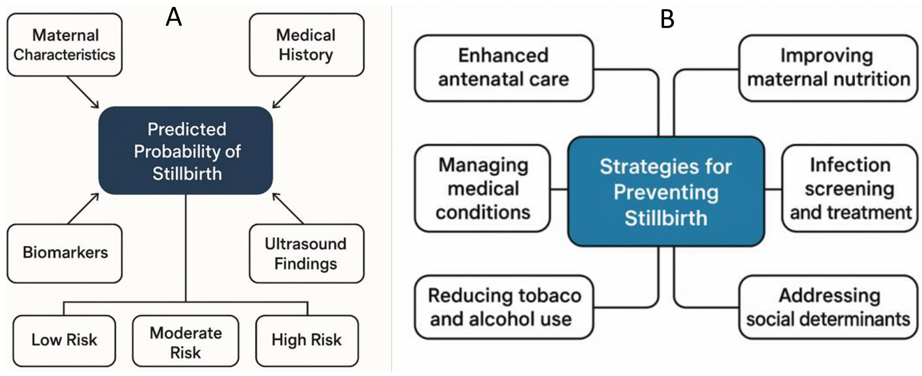


**Figure 5** Possible strategies for prevention and management of stillbirth

## Conclusion

As fewer prenatal care visits occur, infant mortality at birth is likely to increase. In low- and middle-income countries, a trained traditional birth attendant is likely to lower stillbirth rates in rural communities when compared to an untrained one. Low birth weight can lead to stillbirth. Being overweight or obese, smoking, drinking alcohol, and taking drugs can all increase the risk of stillbirth. Vaccination and folic acid supplementation prior to and during the first 12 weeks of pregnancy are examples of preventive measures. All prenatal appointments should be attended by expectant women in order to monitor the baby's progress in advance.

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### Authors' Contribution

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**Formal analysis:** Smarajit Maiti, Pikash Pratim Maity.
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**Supervision:** Smarajit Maiti.
**Validation:** Smarajit Maiti and Pikash Pratim Maity.
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**Writing review & editing:** Sanchaita Bera, Arunima Ghosh, Biswajit Chakraborty, Pikash Pratim Maity, Smarajit Maiti.

### Competing Interests

None.

### Ethical Approval

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